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Quanjun Cui, MD, Professor; Bao-Gan Peng, MD, PhD, Chief Doctor, Director, Professor; Melanie Jane Franklyn, PhD, Academic Fellow, Academic Research; Florian M Kovar, MD, Doctor; Gerold Labek, MD, Assistant Professor, Doctor, Senior Scientist, Surgeon; Klemens Trieb, MD, Chief Doctor, Director, Professor; Tom Van Leemput, MD, Chief Doctor, Surgeon; Wei-Min Pan, PhD, Doctor, Professor; and Pauline Po Yee Lui, PhD, Academic Research, Manager.

EDITORS FOR THIS BOOK

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Quanjun Cui, MD, Professor, Department of Orthopaedic Surgery, School of Medicine, University of Virginia, Charlottesville, VA 22908, United States

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8226 Regency Drive, Pleasanton, CA 94588, United States
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
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PREFACE

Core progresses of clinical orthopedics in 2014

I am honored and delighted to write a preface for this first online, open-access book by the *World Clinical Orthopedics* (*WCO*, ISBN 978-0-9861420-1-7). Although this is a collection of high impact manuscripts published by the journal in 2014, virtually every aspect of orthopedics has been covered in this book. I am certain that the information will be extremely useful for and well received by the Journal's loyal readers. I am certain the information provided will help both practicing orthopedic surgeons and internists, who treat patients with musculoskeletal diseases, and scientists who conduct basic and translational orthopedic research.

In the advances in bone diseases section, this book highlighted osteoporosis, osteoarthritis (OA), psoriatic arthritis, vanishing bone disease (Gorham-Stout syndrome), imaging of multiple myeloma, and major orthopedic conditions associated with systemic lupus erythematosus. A review by Andrea Montagnani indicated that antagonists of Wnt-inhibitors, such as sclerostin antibodies and dickkopf-1 antagonists, present greater potential as therapeutic agents for osteoporosis. In another article, Colaianni *et al* stated that Wnt family members are key molecules regulating differentiation of multipotent mesenchymal stem cells (MSCs) into osteoblasts and adipocytes. Therefore, modulation of Wnt signaling pathway can potentially enhance osteogenesis while inhibiting adipogenesis by MSCs. In terms of OA, Poonpet and Honsawek summarized the current knowledge on the role of adipokines (including leptin, adiponectin, visfatin and resistin) in OA and their potential to be used as biomarkers for earlier diagnosis, monitoring disease progression, and testing pharmacological interventions for OA. Most interestingly Nikolaou *et al* summarized the theories regarding the etiology, clinical presentation, diagnostic approaches and treatment options of a rare disease, vanishing bone disease (Gorham-Stout syndrome).

Technological innovations in joint replacement, with respects to surgical techniques, prosthesis design and materials, are the beneficial news in orthopedics. Total knee and hip arthroplasty have proven to be the best surgeries in human history that provide effective pain relief, improved function and stability. However, challenges remain which call for critical analysis of current researches to improve the longevity of implant and prevention of peri-prosthetic infection and other peri-operative complications. The advances in hip and knee section of this book provided publications that review the current state of art treatment options and evidences that support the current clinical practice for joint replacement. In addition, the readers will enjoy reading through a cumulative body of literature in the diagnosis and management of cartilage injury, joint deformities and diseases, including the current state of cartilage tissue engineering through MSCs and biomaterials, osteotomies around the hip, meniscal and cruciate ligament surgery, hip fractures, as well as, rehabilitation after ligament and cartilage repair procedures in knee.

Reverse total shoulder replacement can provide excellent pain relief and restore shoulder motion. However, it is a complex procedure associated with significant risks. It is important to understand the biomechanics, principles of surgery, extended indications, pitfalls associated with the procedure and the available literature. The review, by Lee and Desai, summarizes the concept of this procedure and the most recent available biomechanical and clinical evidence to aid clinicians' practice. In the section of Advances in Shoulder, we also included treatment options to manage the proximal humerus fractures in adults and rotator cuff tear, one of the most common shoulder problems.

Under the section of advances in foot and ankle, Baums *et al* summarized different options for treating chondral and osteochondral defects of the talus and reviewed the available literature, while Shabtai *et al* reported the worldwide spread of the Ponseti method for clubfoot. Another excellent review by Sims and Kurup discussed painful sesamoid of the great toe.

The book also covered, in detail, advances in spine and in rheumatic diseases. Readers will find chapters under these two sections derived from a broad base of backgrounds including the basic science, translational and clinical studies that led to better implants, instrumentations, therapies and treatment outcomes.

I hope the information in this open-access book will help scientists and physicians in their research and clinical practice.

We thank the authors for dedicating their time and expertise in creating this excellent text book. We also thank Lian-Sheng Ma, President and Company Editor-in-Chief, Fang-Fang Ji, science editor, for their hard work and editorial expertise.

Quanjun Cui, MD, Professor

Quanjun Cui, Department of Orthopaedic Surgery, School of Medicine, University of Virginia, Charlottesville, VA 22908, United States

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WJO 5th Anniversary Special Issues (6): Osteoporosis

Osteoporosis and obesity: Role of Wnt pathway in human and murine models

Graziana Colaianni, Giacomina Brunetti, Maria Felicia Faienza, Silvia Colucci, Maria Grano

Graziana Colaianni, Giacomina Brunetti, Silvia Colucci, Maria Grano, Department of Basic Medical Science, Neuroscience and Sense Organs, Section of Human Anatomy and Histology, University of Bari, 70124 Bari, Italy
Maria Felicia Faienza, Department of Biomedical Sciences and Human Oncology, University of Bari, 70124 Bari, Italy
Author contributions: Colaianni G, Brunetti G, Faienza MF, Colucci S and Grano M wrote the paper.
Correspondence to: Graziana Colaianni, PhD, Department of Basic Medical Science, Neuroscience and Sense Organs, Section of Human Anatomy and Histology, University of Bari, Piazza Giulio Cesare 11, 70124 Bari, Italy. graziana.colaianni@libero.it
Telephone: +39-080-5478306 Fax: +39-080-5478308
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Abstract

Studies concerning the pathophysiological connection between obesity and osteoporosis are currently an intriguing area of research. Although the onset of these two diseases can occur in a different way, recent studies have shown that obesity and osteoporosis share common genetic and environmental factors. Despite being a risk factor for health, obesity has traditionally been considered positive to bone because of beneficial effect of mechanical loading, exerted by high body mass, on bone formation. However, contrasting studies have not achieved a clear consensus, suggesting instead that excessive fat mass derived from obesity condition may not protect against osteoporosis or, even worse, could be rather detrimental to bone. On the other hand, it is hitherto better established that, since adipocytes and osteoblasts are derived from a common mesenchymal stem cell precursor, molecules that lead to osteoblastogenesis inhibit adipogenesis and vice versa. Here we will discuss the role of the key molecules regulating adipocytes and osteoblasts differentiation, which are peroxisome proliferators activated receptor-γ and Wnts, respectively. In particular, we will focus on the role of both canonical and non-canonical Wnt signalling, involved in mesenchymal cell fate regulation. Moreover, at present there are no experimental data that relate any influence of the Wnt inhibitor Sclerostin to adipogenesis, although it is well known its role on bone metabolism. In addition, the most common pathological condition in which there is a simultaneous increase of adiposity and decrease of bone mass is menopause. Given that postmenopausal women have high Sclerostin level inversely associated with circulating estradiol level and since the sex hormone replacement therapy has proved to be effective in attenuating bone loss and reversing menopause-related obesity, we hypothesize that Sclerostin contribution in adipogenesis could be an active focus of research in the coming years.

Key words: Osteoporosis; Obesity; Bone; Fat; Wnt; Peroxisome proliferators activated receptor-γ; Dickkopf; Sclerostin

Core tip: Here we will discuss the role of the key molecules influencing adipocytes and osteoblasts differentiation, which are peroxisome proliferators activated receptor-γ and Wnts, respectively. Besides these proteins, the Wnt inhibitor molecules are also necessary to control the Wnt signalling balance from active to inactive state, in favour of osteogenesis or adipogenesis. It seems remarkably important a deepen analysis of these molecules, not only for their involvement in the regulation of the differentiation processes but also in coordinating the switch toward osteo- or adipo-genesis fate within bone marrow.

Original sources: Colaianni G, Brunetti G, Faienza MF, Colucci S, Grano M. Osteoporosis and obesity: Role of Wnt pathway in human and murine models. *World J Orthop* 2014; 5(3): 242-246 Available from: URL: http://www.wjgnet.com/2218-5836/full/v5/i3/242.htm DOI: http://dx.doi.org/10.5312/wjo.v5.i3.242

INTRODUCTION

Bone and fat connection: The loss and gain of a relationship

Several lines of evidence have largely supported the tight relationship between the adipose tissue and the skeleton. In particular, thorough molecular examination of the fat-bone connection, similarities between obesity and osteoporosis, the most important diseases affecting these two tissues, have been identified[1]. For instance, aging is associated with high incidence to develop both obesity and osteoporosis[1], which are often simultaneous pathological conditions deriving from an altered balance between fat and bone cells in bone marrow. Moreover, the finding that pharmacologic strategies have opposite effects on fat versus bone mass further supports the inverse correlation between these two tissues. In particular, in aged women affected by menopause, the sex hormone replacement therapy has proved to be effective in attenuating bone loss[2,3] and reversing menopause-related obesity[4]. For example, in postmenopausal women, because ovaries no longer secrete estrogens, replacement therapy with estrogen and progestogen or estrogen alone or with selective estrogen receptor modulators (SERMS) has been, for long time, the treatment of choice for prevention and treatment of bone loss. Likewise, the effect of postmenopausal hormone replacement therapy has also been linked to the reversal of both obesity and loss of lean mass[3,4].

Furthermore, the clinical use of glucocorticoids has been shown to affect bone remodelling[5-7] and increase obesity[8] or bone-marrow infiltration by adipocytes[1]. The ongoing researches, studying the balance of adipose and bone cells differentiation in bone marrow, have established a negative relationship between fat and bone mass. Thus, adipocytes and osteoblasts originate from a common mesenchymal precursor that can also differentiate into other cell types, but among the various fates, differentiate in adipocyte or osteoblast becomes of particular relevance because factors that enable osteoblastogenesis inhibit adipogenesis and vice versa. For example, activation of peroxisome proliferators activated receptor-γ (PPAR-γ) promotes the differentiation of mesenchymal stem cells into adipocytes over osteoblasts[9]. In contrast, the wingless-type MMTV integration site (Wnt) signaling pathway inhibits adipogenesis[10] while supporting osteogenesis[11]. These two pathways can also influence each other. Indeed, it has been demonstrated that Wnt signaling negatively regulates adipogenesis through β-catenin, which inhibits PPAR-γ-induced genes[12]. Moreover, Kang *et al*[13] reported that induction of osteogenesis mediated by Wnt10b was also due to its ability in inhibiting PPAR-γ expression.

Fate of mesenchymal stem cells to become osteoblasts or adipocytes: Roles of the key regulators Wnt(s) and PPAR-γ

The relevance of the canonical Wnt signaling in bone is well acknowledged and several reports have unanimously established that Wnt/β-catenin activity is essential for bone development[14]. Wnts are a highly conserved family of proteins that can operate through two different signalling pathways. In the canonical pathway, when Wnt signalling is absent, a multiprotein complex, including adenomatous polyposis coli (APC), glycogen synthase kinase 3 (GSK3) and Axin, induces the degradation of β-catenin, thus reducing the free cytoplasmic pool of β-catenin. When Wnt signal is active through the Frizzled (FZD) receptor and low density lipoprotein receptor-related protein 5 and 6 (LRP5/6) receptor complex, it inactivates GSK3 and causes its dissociation from Axin preventing the phosphorylation of β-catenin. Hence, this pool of β-catenin in the cytoplasm increases and translocates to the nucleus where it binds members of the LEF/TCF family of transcription factors to provoke transcriptional induction of target genes[14]. In non-canonical pathway, Wnt signaling is induced through Frizzled independent of LPR5/6. This pathway causes cytoskeletal changes through activation of the small GTPases Rho and Rac[14].

Wnt10b, one of Wnt family member, plays a key role in bone formation. It is expressed by osteoblast progenitors in bone marrow[15] and, hence, its transgenic overexpression in mesenchymal cells enhances osteoblastogenesis and leads to increased bone density. Accordingly, Wnt10b deficient mice display reduced trabecular bone[16] by μCT analysis. Thus, the distal metaphyses of these mice showed a 30% reduction in bone volume/total volume and bone mineral density. This loss was ascribed to a decrease in trabecular number with a associated increase in trabecular spacing. In addition to decreased bone mass in the femur, Wnt10b deficient mice also displayed reduction in bone volume fraction in proximal tibia[16].

Furthermore, non-canonical Wnt members may also be involved in regulating osteogenesis. In particular, Wnt5a seems to be the most important Wnt member, acting through non canonical way, that is expressed during osteoblastic differentiation of mesenchymal stem cells[17]. Wnt-5a stimulates osteoblast differentiation through an autocrine loop[18] and haploinsufficient mice for Wnt-5a display a lower bone mass with decreased osteoblast number[19]. Another non-canonical Wnt member with a potential interest in bone accrual is Wnt4. Chang *et al*[20] reported that human mesenchymal stem cells, genetically engineered to express Wnt-4, have enhanced commitment toward osteogenesis. Moreover, the ectopic Wnt-4 expression was able to ameliorate craniofacial defects in two different models of craniofacial bone injury[20].

Regarding Wnts functions in adipogenesis, studies of Moldes *et al*[21], demonstrated that transgenic expression of Wnt1 in preadipocyte cell line strongly suppresses adipogenesis. This study also suggests a reciprocal relationship between PPARγ activity and β-catenin expression, since the concomitant over-expression of PPARγ and Wnt-1 in preadipocytes rescued the inhibition of adipogenesis by suppressing β-catenin expression, after the exposure to the PPARγ agonist, troglitazone. Based

on these observations, authors have proposed a model according to which, if Wnt signalling at the early stage of adipogenesis has been lowered to a level that permits induction of PPARγ, this latter, once activated, can further down-regulate β-catenin levels, leading differentiation of mature adipocytes. Likewise, pharmacological treatments that activate Wnt signaling and stabilize free cytosolic β-catenin are able to inhibit preadipocyte differentiation[22]. Conversely, by blocking Wnt signaling in preadipocytes, stimulates their differentiation[22], suggesting that preadipocytes might synthesize endogenous Wnt molecules. Indeed, it has been showed that Wnt10b is highly expressed in confluent preadipocytes and it is immediately downregulated after exposure to elevated cAMP occurring during adipocyte differentiation[22]. Accordingly, if Wnt-10b is constitutively expressed, it stabilizes cytosolic β-catenin leading to suppression of adipogenesis[22]. On the contrary, Wnt-5b is transiently induced during adipogenesis and destabilizes β-catenin to enhance adipocyte differentiation[23], indicating that preadipocytes could be targeted by opposite Wnt signals.

While mesenchymal stem cells activate their differentiation process toward adipo- or osteogenic cell fate, specific transcription factors become up-regulated. These include CCAAT/Enhancer binding protein (C/EBP) alpha and PPARγ for adipocytes[24] and core binding factor alpha 1 (Cbfal/Runx2) for osteoblasts[25]. The reciprocal relationship between adipogenesis and osteoblastogenesis is also dependent on the ability of these lineage-specific transcription factors to inhibit differentiation of other lineages. For example, PPARγ also inhibits terminal osteoblast differentiation by suppressing Runx2 expression[26].

Canonical vs non-canonical Wnt signalling: How this switch controls mesenchymal stem cell fate

A reversal process, from non-canonical Wnt signaling to canonical Wnt signaling or vice versa, drives the progression into the differentiation stage. Indeed, during early adipogenesis, a prompt activation-inactivation of the Wnt pathway is crucial for the induction of PPARγ[27]. Specifically, the non-canonical Wnt5a pathway induces a signalling, through PPARγ, that regulates differentiation and insulin sensitivity of mature adipocytes[28]. On the other hand, canonical Wnt signaling is responsible for promoting cell proliferation *via* activation of cyclin Dl and c-myc while inhibiting PPARγ. This accounts for the mechanism involved in keeping pre-adipocytes in an undifferentiated state. Thus, cyclin Dl and c-myc directly bind and inhibit PPARγ and the C/EBPα transcription factor, respectively[29]. At the same time, the expression of C/EBPα leads per se to the phosphorylation of β-catenin and its subsequent degradation. Therefore, nuclear β-catenin activity is down-regulated and non-canonical signaling is switched on in order to promote adipocyte differentiation[21]. Notably, the concomitant induction of PPARγ, after β-catenin proteasomal degradation, further suggests that β-catenin could suppress PPARγ expression, as vice versa[12].

Based on what has been described, it appears questionable how Wnts molecules are capable of exert different stimuli in mesenchymal stem cells. A reasonable explanation might be given considering other molecules involved in the Wnt signalling, that have inhibitory functions.

Wnt signaling inhibitors: Novel perspective in the control of adipogenesis

Wnt signaling can be blocked by secreted antagonists including Dickkopf (DKK)[10] and Sclerostin[30]. DKK1 and Sclerostin inhibit WNT signaling by binding to the co-receptors LDL receptor-related proteins (LRPs) 5 and 6, preventing formation of the active LRP/Frizzled complex. The involvement of DKK1 in adipocyte differentiation has been demonstrated in several experiments. Transfection of human mesenchymal stem cells with DKK1 small interfering RNA reduced adipogenesis[31]. Furthermore, Dkk1 was found to be highly expressed in differentiated 3T3-L1 adipocytes and its expression was enhanced by PPAR-γ agonists[32]. Therefore, secretion of DKK1 might be the mechanism whereby PPAR-γ promote adipogenesis, while inhibiting Wnt signalling[31].

Sclerostin is the other inhibitor of the powerful bone anabolic Wnt pathway[30]. Targeting deletion of Sclerostin in mice leads to high bone mass, due to a great increase in bone formation in both trabecular and cortical bone[33]. It has been demonstrated that antibody-based sclerostin inhibition increased bone mass and strength in healthy female rats and rescued ovariectomy-induced bone loss[34]. Furthermore, in a model of hindlimb disuse, antibody-based sclerostin inhibition was able to increase cortical and trabecular bone mass either in loaded upper limbs or in immobilized hind limb. This effect was characterized by coupling of high bone formation and decreased bone resorption, suggesting that inhibition of sclerostin might be useful for the treatment of immobilization-induced osteopenia[35].

Conversely, an important clinical study in the field of rehabilitation, performed enrolling 39 subjects with chronic spinal cord injury and 10 without spinal cord injury, demonstrated that greater total limb bone mineral content was significantly associated with greater circulating levels of Sclerostin. Thus, Sclerostin levels were reduced in subjects with spinal cord injury who use a wheelchair compared to those with spinal cord injury who walk normally. Likewise, Sclerostin levels were lower in patients with spinal cord injury who use a wheelchair compared to persons without spinal cord injury. These results showed that circulating Sclerostin can be used as biomarker of severe osteoporosis, but not as biomarker of bone loss, in long-term absence of mechanical loading[36].

However, to date it is well known about conditions where Sclerostin is genetically absent, such as in the disease known as Sclerostosis with bone mass markedly enhanced[37]. Conversely, there are currently few notions about the molecular mechanism involved in Sclerostin up-regulation, unless for the knowledge that postmeno-

pausal women have high serum Sclerostin level inversely associated with the circulating free estradiol (E2) index[38]. Furthermore, the reduction in Sclerostin circulating levels after E2 treatment[38] provides a meaning for addressing the key question about the involvement of sex steroid as regulators of Sclerostin expression.

The understanding of the molecular mechanism whereby Estrogen reduces the circulating Sclerostin levels might support the use of an anti-Sclerostin antibody in preventing bone loss, but also in avoiding fat mass augmentation, occurring at the decline of sex hormones. However, nowadays there are few data regarding the relationship between Sclerostin levels and obesity. Only one cross-sectional study, performed by Urano et colleagues[39] aimed to identify the relationship between serum sclerostin levels and markers of metabolic disease. Authors measured serum sclerostin levels in 352 Japanese postmenopausal women and analyzed the relationship of these levels with abdominal fat mass. Their result show that serum Sclerostin levels were positively correlated with percentages of abdominal and gynoid fat.

CONCLUSION

Recently, it has become evident that Wnt family members are key molecules regulating differentiation of multipotent mesenchymal stem cells into osteoblasts and adipocytes, as showed both by animal models and by several clinical studies in humans. Besides Wnt proteins, the Wnt inhibitor molecules are also necessary to control the Wnt signalling balance from active to inactive state, in favour of osteogenesis or adipogenesis. This molecular control could be evidently crucial in the pathogenesis of obesity, as it is established to be fundamental in osteoporosis. Finally, it seems remarkably important a deepen analysis of these bioactive molecules, not only for their involvement in the regulation of the differentiation processes but also in coordinating the switch toward osteo- or adipo- genesis fate within bone marrow.

Moreover, in the view of using the antibody-based sclerostin inhibition, as therapeutic approach to shift the balance in favor of osteogenesis at the expense of adipogenesis, further studies could be extremely relevant in the understanding the role of Sclerostin in regulating adipogenesis. These future studies could likely open an exciting avenue in osteoporosis and obesity research field, which may outcome in the development of novel therapeutic approaches to treat these burden diseases. Therefore, Sclerostin antibody will be extremely useful as skeletal anabolic agents to treat osteoporosis, but might also have potential utility in the therapy of obesity.

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Bone anabolics in osteoporosis: Actuality and perspectives

Andrea Montagnani

Andrea Montagnani, Metabolic Bone Diseases Area, Department of Internal Medicine, Misericordia Hospital, 58100 Grosseto, Italy
Author contributions: Montagnani A solely contributed to this paper.
Correspondence to: Andrea Montagnani, MD, PhD, Metabolic Bone Diseases Area, Department of Internal Medicine, Misericordia Hospital, Via Senese, 169, 58100 Grosseto, Italy. montagnaniand@gmail.com
Telephone: +39-564-483165 Fax: +39-564-485330
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Abstract

Vertebral and nonvertebral fractures prevention is the main goal for osteoporosis therapy by inhibiting bone resorption and/or stimulating bone formation. Antiresorptive drugs decrease the activation frequency, thereby determining a secondary decrease in bone formation rate and a low bone turnover. Bisphosphonates are today's mainstay among antiresorptive treatment of osteoporosis. Also, oral selective estrogen receptor modulators and recently denosumab have a negative effect on bone turnover. Agents active on bone formation are considered a better perspective in the treatment of severe osteoporosis. Recombinant-human parathyroid hormone (PTH) has showed to increase bone formation and significantly decrease vertebral fractures in severe patients, but with a modest effect on nonvertebral fractures. The study of Wnt signaling pathway, that induces prevalently an osteoblastic activity, opens large possibilities to antagonists of Wnt-inhibitors, such as sclerostin antibodies and dickkopf-1 antagonists, with potential effects not only on trabecular bone but also on cortical bone.

Key words: Anabolic therapy; Bone mass; Bone fracture; Osteoporosis

Core tip: The study of agents active on bone formation is the main objective in the treatment of severe osteoporosis. rhparathyroid hormone (rhPTH) decreases vertebral, but not nonvertebral, fractures. On the contrary, antagonists of Wnt-inhibitors, that exert their effects mostly through a bone remodeling-independent mechanism, open new perspectives to improve not only trabecular bone but also cortical bone, with potential positive effect also on nonvertebral fractures incidence. The perspective in osteoporosis treatment should be more effective and better tolerated therapies aimed at minimizing individually fractures risk.

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INTRODUCTION

Osteoporosis is an emerging medical and socioeconomic threat characterized by a systemic impairment of bone mass, strength and microarchitecture, which increases the propensity of fragility fractures[1]. Osteoporosis results by a dysfunction of physiological bone turnover and cells in bone by endocrine and/or autocrine/paracrine factors (Figure 1), negatively affecting peak bone mass and/or skeletal homeostasis. Patient with osteoporosis show a higher propensity to spine and femur fractures, even if other bones could be also involved.

Osteoporotic fractures of the hip and spine increase mortality and are related to important medical complications that, such as pneumonia or thromboembolic disease due to chronic immobilization with a negative economic impact on public health[2].

Osteoporosis is considered a global public health concern and result to have great socioeconomic burden[3], worthy to be addressed in an evidence-based and

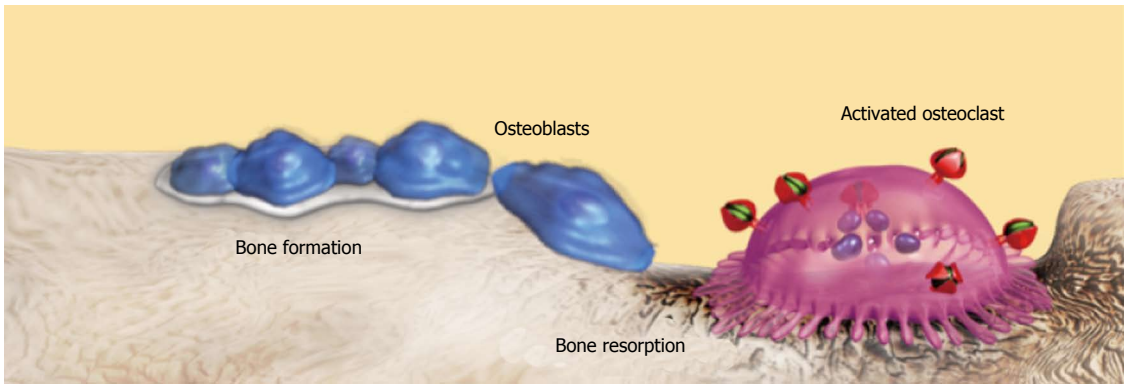

Figure 1 Osteoblasts and osteoclasts are close related in determining bone formation and bone resorption (bone turnover) that maintain the quantitative and qualitative characteristics of bone.

cost-effective manner[4-6], taking into account several risk factors[7]. Taking into account these preliminary considerations is resulting that osteoporosis therapy is considered an important field of study where to converge most of the efforts.

Osteoporosis therapy should prevent both vertebral (mostly dependent on trabecular bone density and architecture) and nonvertebral (mostly dependent on cortical thickness and porosity) fractures. This could be achieved by inhibiting bone resorption and/or by stimulating bone formation.

Bone remodeling or modeling activity is different between cortical and trabecular bone sites and this difference could mostly explain the relative lack of efficacy of antiresorptive drugs on nonvertebral fractures since their effect is higher on trabecular than cortical bone.

Bisphosphonates are the most prescribed drugs for osteoporosis treatment. They have a high affinity for bone and inhibit bone resorption reducing fracture risk. Alendronate, risedronate, and zoledronate were shown to reduce the risk of new vertebral, non-vertebral, and hip fractures[8-12], showing a prevalent effect on axial with respect to appendicular skeletal site, a relative risk reduction of 50% for spine *vs* 20%. Although, long term treatment with bisphosphonate has been associated with a potential risk of osteonecrosis of the jaw and of atypical subtrochanteric femoral fractures, their use for at least 10 years has shown good safety[13,14].

Raloxifene, bazedoxifene and subcutaneous denosumab, a human monoclonal antibody that inhibits RANKL, have showed convincing evidences to reduce osteoporotic fractures. Raloxifene have a positive effect on vertebral fracture and on breast cancer risk worsening the thrombotic risk[15,16]. Denosumab, instead, reduced vertebral, non-vertebral and hip fracture risk in postmenopausal women with osteoporosis by the same order of magnitude as bisphosphonates without significant adverse events[17]. A particular behavior seems to have strontium ranelate (SR), which has a double effect, anabolic, inducing an increase of osteoblast activity, and at the same time antiresorptive, inhibiting osteoclasts activity[18]. In a recent meta-analysis Kanis *et al*[19] reported positive effect on clinical and morphometric vertebral fractures. Since SR has shown to have a reduced safety in patients with venous thromboembolism and ischaemic heart diseases, such a drug should not be administered to patients with a higher risk of atherothrombotic events.

In synthesis, antiresorptive drugs reduce the activation frequency, acting mostly on osteoclast and only indirectly on osteoblast activity, with e final slight gain in trabecular bone mass.

Anabolic therapies, instead, directly stimulate bone formation through activation of bone modeling, independently of resorption activity, suggesting a potential positive effect on non-vertebral other than vertebral fractures.

In Figure 2 are reported the two main bone anabolic pathways: one linked to parathyroid hormone (PTH) signaling and the second dependent on canonical wingless-int (Wnt) signaling (Figure 2). The main difference between this two pathways is that Wnt-signaling acts increasing bone mass independently of bone remodeling, as it does PTH induces an increase of osteoblastic and osteoclastic activity. This could explain why PTH shows a closer therapeutic windows.

PTH

The secretion of human PTH, an 84-amino acid peptide, by parathyroid cells is closely controlled by serum calcium levels through the calcium-sensing receptors (CaSR). This hormone plays an important role in calcium homeostasis. PTH determines an increase of serum calcium by mobilization of skeletal stores, increasing intestinal and renal calcium absorption[20]. When PTH is administered by intermittent subcutaneous *via*, it has an anabolic effect on bone, influencing osteoblastic activity directly and indirectly with the regulation of some growth factors[21].

To date, injectable forms of recombinant-human PTH (rhPTH) are the only approved osteoanabolic drugs on the market for the treatment of osteoporosis. It exists an intact form (rhPTH 1-84) and an other bioactive N-terminal 34-amino acid fragment rhPTH 1-34 (teriparatide). rhPTH showed a higher effects on trabecular

bone reducing more the relative risk of vertebral than nonvertebral fractures, confirming that rhPTH has a prevalent effect on trabecular rather than on cortical bone[22].

Osteoblasts, activated by rhPTH, produce several paracrine factors, which in turn stimulate osteoclast activity. This, when the rhPTH intermittent treatment is prolonged, could enhance activation frequency and thereby increase bone resorption. Although the initial net effect is positive with a gain of trabecular bone mass, the anabolic effect could show a plateau curve when the treatment is prolonged beyond two years[22]. Such limit could be overcome by a co-administration of an antiresorptive drug able to limit the rhPTH-activated bone resorption. Some experiences did not report consistent evidence that confirm such hypothesis[23,24], however, a recent study has reported that one single administration of zoledronic acid combined with daily sc injections of rhPTH could reduced fracture risk in patients with a high risk profile[25]. On the other hand, sequential administration of antiresorptive drugs after rhPTH is already an established treatment protocol that limit bone resorption after withdraw of rhPTH treatment[26].

Although, rhPTH is usually well tolerated, some adverse effects, such as hypercalcemia, nausea, headache, dizziness, and leg cramps, could be associated to rhPTH treatment with a lower risk of hypercalcemia for the rhPTH 1-84[26].

To improve the rhPTH safety profile some attractive options for the alternative delivery have been tested. One is transdermal self-administration using coated microneedle patches[27] whereas other are inhaled and oral delivery[28]. In the first case PTH interestingly showed an increased of trabecular bone to the same extent whereas the gain of total hip BMD was much greater than those obtained with sc administered rhPTH 1-34[27]. Oral and inhaled administrations are being investigated in phase Ⅰ studies, showing interesting data.

Since rhPTH use is limited by a low effect on nonvertebral fractures, by the osteoclasts activation and by the loss of efficacy in a prolonged treatment, it seems to need to search new molecule which show a better profile.

PTH RELATED PEPTIDE

PTH related peptide (PTHrP) shows a similar sequence to PTH in its first 36 amino acids and activates PTH1R. In rats and in humans PTHrP has demonstrated similar effect to rhPTH on bone mass, improving mechanical strength of bone tissue in rats[29]. However, PTHrP appeared to stimulate only bone formation as a pure bone anabolic agent; as showed by bone turnover markers variations with an increase of bone formation markers, such as osteocalcin and P1NP associated to unchanged levels of bone resorption markers[30]. In a phase 2 study the administration of PTHrP in postmenopausal women determined an 4%-5%/year increase of BMD without serious adverse effects[31]. On this basis, some phase 3 studies are ongoing and could give further information on efficacy and safety of this interesting molecule, namely in comparison with PTH (www.clinicaltrials.gov).

CALCILYTIC AGENTS

PTH is synthesized and secreted by parathyroid glands cells expressing on their surface calcium-sensing receptor (CaSR). Serum low levels of Ca^{2+} determine a low bond with CaSR decreasing its activity, and in turn stimulating PTH release. On the contrary, activation of the CaSR decreases PTH synthesis and secretion[32].

Antagonists of the CaSR bind and inhibit the receptor determining a short pulse of PTH secretion. A rapid increase of PTH secretion followed by rapid normalization should cause an anabolic effect in bone. Unfortunately, calcilytics, considered a new class of bone-forming agents, have showed an unfavorable pharmacokinetics[33]. In fact, a close therapeutic window between the effect on bone and hypercalcemia, the fact that CaSR are also expressed in other organs besides the parathyroid glands and finally, that together to PTH other products, with potential negative effects on PTH secretion itself, represent actual limits to use of these new anabolic drugs[34]. Although the mechanism of action, calcilytics remain an interesting opportunity for treatment of a reduced bone mass. However, these drugs are worthy of furthers studies to clarify their role in osteoporosis therapy.

ANTAGONISTS OF WNT-INHIBITORS

In the last decade, some genetic study of the low-density lipoprotein receptor-related protein 5 (Lrp5) associated to low or high bone mass, suggested a potential role of the Wnt pathway as an important player influencing bone mass and as possible target to the PTH signaling pathway (Figure 2).

To date two endogenous inhibitors of the Wnt/β-catenin pathway specific to bone have been known: sclerostin (SOST) and dickkopf-1 (dkk1). These molecule inhibit Wnt signal stopping β-catenin degradation and osteoblast differentiation. When SOST and dkk1 are blocked by specific antibodies bone formation increases with an anabolic effect.

Binding of Wnt to Lrp5/6 prevents the phosphorylation and the proteasomal degradation of β-catenin, stimulates the production of osteoprotegerin (OPG), an osteoblast-derived inhibitor of osteoclast differentiation[35] that acts by binding to RANKL and preventing it from binding to its receptor, RANK.

The fact that Wnt signaling pathway is blocked by endogenous inhibitor factors, represents an important opportunity in the field of osteoporosis therapy.

Sclerostin antibodies

Sclerostin expression is prevalently restricted to late osteoblasts and osteocytes[36], and therefore could represent a favorable target of osteoporosis treatment. In studies in animals, SOST antibodies significantly improved the healing of fractures with an increase in bone formation,

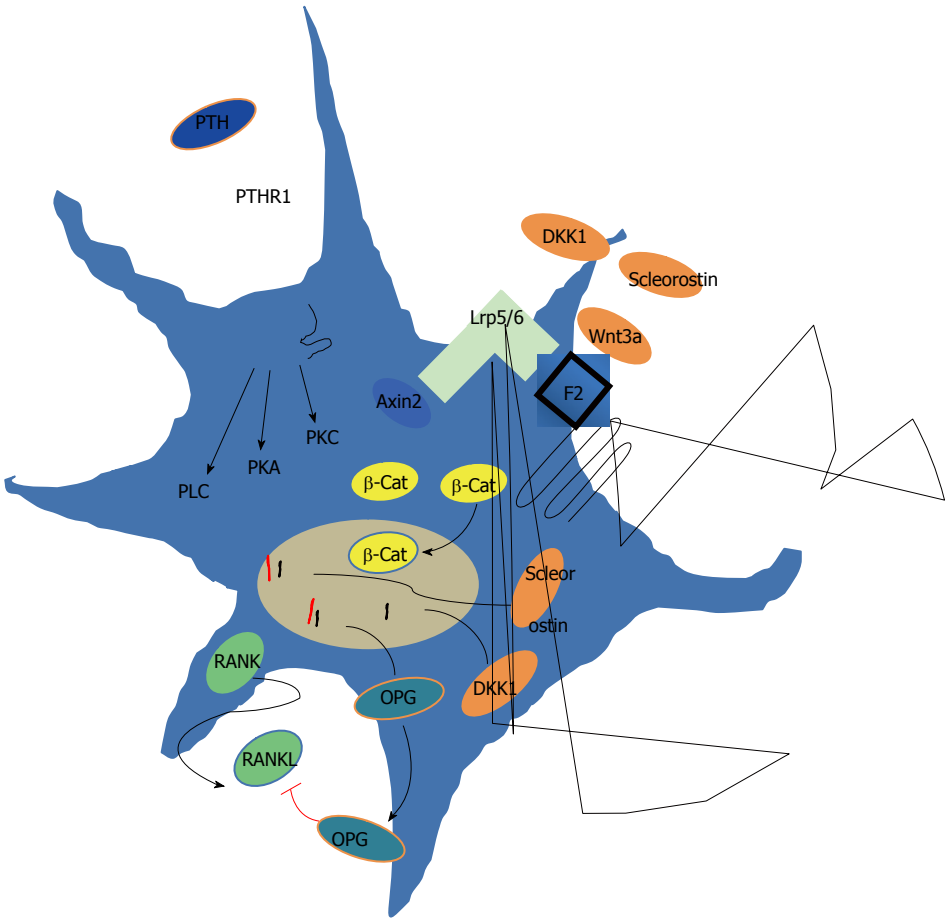

Figure 2 Signaling and cross talk of the parathyroid hormone and Wnt signaling pathways in the late osteoblast (osteocyte). Parathyroid hormone (PTH) binds to its seven-transmembrane-spanning receptor and activates phosphatidyl inositol-specific phospholipase C (PLC), cAMP-dependent protein kinase A (PKA), and the protein kinase C (PKC) downstream signaling cascades, all contributing to the bone anabolic effect of PTH. In the late osteoblast activation of the canonical Wnt signaling pathway occurs upon simultaneous binding of the secreted glycoprotein Wnt3a to the seven-helix-receptor frizzled (Fz) family and the coreceptors Lrp 5/6. Binding of Wnt3a to Lrp5/6 changes the conformation of the cytoplasmic receptor domain, causing the recruitment of Axin2. β-Catenin accumulates in the cytosol and translocates into the nucleus, thereby stimulating the expression of the Lrp5/6 antagonists dickkopf-1 and sclerostin, and the RANKL inhibitor osteoprotegerin.

bone mass, and bone strength[37]. Similar findings were made in sclerostin knockout mice and in ovariectomized rats treated with sclerostin antibodies[38].

The first human phase I clinical trial, studying a humanized monoclonal sclerostin antibody in healthy men and postmenopausal women, showed that this new compound had effects on bone formation and resorption after a single month similar to those showed by rhPTH after 6 months, but with greater effects on bone mass than rhPTH[39]. Such data are, then confirmed, in a phase II study in more than 400 postmenopausal osteoporotic women who showed a significantly increase in BMD at the lumbar spine compared with placebo and teriparatide[40].

Antagonists to inhibitors of the Wnt pathway have show to have positive effect on osteoblast activity regardless of osteoclasts and bone resorption. This their characteristic may be useful not only in osteoporosis but also in other pathologic conditions, such as bone repair after fracture and in low bone turnover diseases.

Dkk1 antagonists

Dkk1 is a further endogenous inhibitor of Wnt signaling. Its neutralization by antibodies is still limited to preclinical trials which have showed an inhibited bone loss in a model of rheumatoid[41] and the prevention of the formation of osteolytic lesions with an increased bone formation rate in a myeloma model[42].

These antibodies could also play a role in the treatment of diseases characterized by a low bone mass, first of all osteoporosis. Some concerns may exist about the possibility that Dkk1 is less selective for bone than SOST with possible more off-target effects.

The possibility to induce the Wnt signaling pathway is a very promising, however, some doubt exist regarding possible important adverse-effects, namely oncogenic effects and a possible uncontrolled process of bone formation with important neurological consequences at cranial and spine levels. Therefore, a particular attention must be taken in long-term use of Wnt antagonists inhibitors.

OTHER POTENTIAL ANABOLIC AGENTS

Activin antagonists

Activin A, a transforming growth factor-β (TGF-β) superfamily member, has showed to be an antagonist to hu-

man osteoblast differentiation[43] and to induce osteoclast formation and bone resorption[44]. On this basis, an antagonist of activin should shift the balance of bone turnover in favor of bone formation. In fact, as showed by a phase I trial, using an activin antagonist increased markers of bone formation[45] of similar extent determined by rhPTH or antagonists of Wnt signaling inhibitors.

Agonists of prostaglandin

Some evidence indicate that prostaglandin E2 (PGE2) play a role in bone metabolism by stimulating bone turnover with a prevalence of bone formation and thereby an increasing bone mass and bone strength[46]. A study in OVX rats animal models has showed that a subcutaneous administration of PGE2 E4 receptor agonist stimulates bone formation by increasing osteoblast recruitment activity on periosteal, endocortical, and trabecular surfaces[47]. The PGE2 effect seems to be present on both smooth and scalloped endocortical and trabecular surface, suggesting an effect both on bone modeling and remodeling-dependent bone formation.

Statins

Statins have a well-know hypocholesterolemic effect by reducing 3-hydroxy-3-glutaryl-coenzyme A (HMG-CoA) reductase activity. However, the blocking of such enzyme causes the depletion of farnesyl diphosphate or geranyl diphosphate synthesis and in turn the reduction of protein prenylation, which plays a role in bone cells activity by preventing the post-translational modifications of small GTPases.

However, the main proposed mechanism by which statins stimulate bone formation involves an increase in expression and synthesis of BMP-2[48] and osteocalcin[49].

Evidence regarding the effects of statins on BMD[50,51] and fracture risk are not completely consistent but do suggest the anabolic potential of these drugs. In fact, a meta-analysis conclude that statins reduce hip fracture risk and, to a lesser extent, nonspine fracture risk[52].

Unfortunately, statin shows a high affinity for the liver and only very low concentration reach the bone as potential target. Therefore, to overcome the liver first-pass effect, statins would be administered in a suitable delivery system aimed to allow the major concentration in fracture sites. In such sense, a perspective could be a different copolymerization with ethylene glycol that covalently incorporates into hydrogel networks[53] or a different administration route, as a transdermal application, which bypasses the first-pass liver effect[54].

Insulin-growth-factor I and proline-rich tyrosine kinase 2

Administration of insulin-growth-factor I (IGF-I) determines an increase of bone mass with an anabolic effect by inducing bone remodeling both in healthy and in subjects with GH deficiency or IGF-I deficiency[55]. Although, recombinant human IGF-I is used currently for the treatment of short stature genetic syndromes secondary to caused by mutations of the GH receptor or the IGF1 gene, the long-term efficacy and safety of IGF-I in patients with osteoporosis remain to be determined.

An interesting suggestion to identify a novel future anabolic therapy of osteoporosis seems to come from the study of marrow cultures from the proline-rich tyrosine kinase 2 (PYK2)-null mice, which showed enhanced osteogenesis[56]. Blocking PYK2 activity may be hypothesized to have an osteogenic effect also in humans. However, no evidence for such effect in humans has been reported and therefore up to date, this remains only an interesting field of study.

CONCLUSION

All antiresorptive drugs share a minor effect on nonvertebral fracture and this remains the biggest limit of severe osteoporosis therapy inducing an important research to identify an agent able to induce bone formation rather than block resorption[57].

To date, only some drugs have demonstrated to have an anabolic effect on bone; one of these, rhPTH, increases bone formation and significantly decreases vertebral fractures in severe patients, but it is less effective on nonvertebral fractures, probably because rhPTH action is mostly based on bone remodeling, that induces an increase both osteoblasts and osteoclasts activity. On the contrary, the agents influencing Wnt signaling pathway, mostly linked to a bone remodeling-independent mechanism (modeling-based), prevalently affect osteoblastic activity, thereby with a major improvement of trabecular than cortical bone. This action may be thought that Antagonists of Wnt-inhibitors may reduce the incidence of nonvertebral other than of vertebral fractures.

In the next years, several clinical trials could give further data making available more effective and better tolerated therapies allowing tailor-made approaches aimed at minimizing individually fractures risk.

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Imaging of multiple myeloma: Current concepts

Thorsten Derlin, Peter Bannas

Thorsten Derlin, Peter Bannas, Department of Diagnostic and Interventional Radiology, University Medical Center Hamburg-Eppendorf, DE-20246 Hamburg, Germany
Author contributions: Both Derlin T and Bannas P designed and wrote the article.
Correspondence to: Dr. Thorsten Derlin, MD, Department of Diagnostic and Interventional Radiology, University Medical Center Hamburg-Eppendorf, Martinistr 52, DE-20246 Hamburg, Germany. t.derlin@uke.de
Telephone: +49-40-741056146 Fax: +49-40-741055181
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Abstract

Medical imaging is of crucial importance for diagnosis and initial staging as well as for differentiation of multiple myeloma (MM) from other monoclonal plasma cell diseases. Conventional radiography represents the reference standard for diagnosis of MM due to its wide availability and low costs despite its known limitations such as low sensitivity, limited specificity and its inability to detect extraosseous lesions. Besides conventional radiography, newer cross-sectional imaging modalities such as whole-body low-dose computed tomography (CT), whole-body magnetic resonance imaging (MRI) and ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT are available for the diagnosis of osseous and extraosseous manifestations of MM. Whole-body low-dose CT is used increasingly, replacing conventional radiography at selected centers, due to its higher sensitivity for the detection of osseous lesions and its ability to diagnose extraosseous lesions. The highest sensitivity for both detection of bone marrow disease and extraosseous lesions can be achieved with whole-body MRI and ^{18}F-FDG PET/CT. According to current evidence, MRI is the most sensitive method for initial staging while ^{18}F-FDG PET/CT allows monitoring of treatment of MM. There is an evolving role for assessment of treatment response using newer MR imaging techniques. Future studies are needed to further define the exact role of the different imaging modalities for individual risk stratification and therapy monitoring.

Key words: Multiple myeloma; Plasmocytoma; X-Ray; Magnetic resonance imaging; Diffusion-weighted imaging; Positron emission tomography-computed tomography; Imaging

Core tip: A comprehensive review about state-of-the-art imaging of multiple myeloma with a focus on whole-body imaging techniques including computed tomography (CT), magnetic resonance imaging and positron emission tomography/CT which are increasingly used for detection and visualization of both osseous and extraosseous myeloma manifestations.

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INTRODUCTION

Multiple myeloma (MM) is the second most common (10%-15% of all) hematological malignancies and represents 1% of all malignant diseases[1,2]. It is responsible for 15%-20% of deaths from hematological malignancies and about 2% of all deaths from cancer[3-5]. The disease is characterized by clonal proliferation of plasma cells which may produce excessive amounts of monoclonal immunoglobulins that can be detected in serum and urine[2,3]. The proliferating plasma cells infiltrate the bone marrow leading to replacement of the normal myelopoiesis. Characteristic clinical symptoms include anemia and infections due to the progressive cytopenia, renal

Table 1 Monoclonal plasma cell disorders

Plasma cell disorder	Diagnostic criteria
Monoclonal gammopathy of undetermined significance	Monoclonal serum paraprotein ⩽ 3 g/dL and plasma cell infiltration of bone marrow ⩽ 10% and no end organ damage[1]
Asymptomatic smoldering multiple myeloma	Monoclonal serum paraprotein ⩾ 3 g/dL and/or plasma cell infiltration of bone marrow ⩾ 10% and no end organ damage[1]
Symptomatic multiple myeloma	Monoclonal paraprotein in serum or urine and/or plasma cell infiltration of bone marrow ⩾ 10% and end organ damage[1]

[1]End organ damage: Anemia, hypercalcaemia, renal insufficiency, or bone lesions.

insufficiency due the excessive monoclonal light chains in the blood, and hypercalcaemia due to activation of osteoclasts with consecutive demineralization of the bones and pathologic fractures[6]. Moreover, there are extraosseous manifestations of MM, which may affect soft tissues and organs in 10%-16% of patients that can be detected using various imaging methods[7,8].

Treatment of MM consists of conventional chemotherapy or high dose chemotherapy and subsequent allogeneic or autologous stem cell transplantation[6]. The introduction of novel agents, such as immunomodulatory drugs thalidomide and lenalidomide and proteasome inhibitor bortezomib, combined with conventional chemotherapy has radically changed the treatment paradigm of elderly patients and improved outcome[9]. Due to these new and partly more aggressive treatments the progression free survival time has dramatically increased and the 10-year survival rate may reach up to 30%-40%[10].

Differentiation of MM from other monoclonal plasma cell diseases, such as the monoclonal gammopathy of undetermined significance (MGUS) and the so-called smoldering multiple myeloma (SMM) (Table 1), is of significant importance[11,12]. MGUS is also characterized by monoclonal plasma cells in the bone marrow and monoclonal immunoglobulins in serum/urine, but to a lower extent as compared to MM[11]. In addition, MGUS is characterized by an obligatory lack of end organ damage (no hypercalcaemia, no renal insufficiency, no anemia, and no bone lesions). SMM is regarded as a precursor and intermediate stage of MM and is also characterized by a lack of end organ damage[12]. MGUS and SMM have different risks for progression to MM: MGUS has a risk of 1% per year and SMM has a risk of 10% per year[11,13]. Currently, neither MGUS nor SMM represent an indication for therapy. The solitary plasmacytoma, which is a localized plasma cell tumor, has to be differentiated from these systemic plasma cell diseases. Plasmocytoma may be treated curatively in some cases with local treatments such as radiation therapy.

Role of imaging in multiple myeloma

Diagnosis of symptomatic and hence treatment requiring MM, as a differential diagnosis of MGUS and SMM, is based on the detection of osseous lesions as defined by osteolysis, a diffuse severe osteopenia or pathologic fractures[1,6]. The consensus statement of the International Myeloma Working Group (IMWG) still recommends conventional projection radiography for the majority of patients[1]. According to the Durie-Salmon-Staging system, the presence and number of osseous lesions contribute directly to the staging of the disease and thereby to the risk stratification of MM[14].

The use of more sophisticated imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) may help to better define osteolytic lesions allowing for earlier detection of the disease[9,15]. Whole body low-dose CT has replaced conventional radiography at many centers. Newer staging systems like the Durie-Salmon-PLUS staging system take into account results from more sensitive methods such as whole body MRI or ^{18}F-fluorodeoxyglucose (FDG) PET/CT[16]. Two patterns of osseous involvement have to differentiated in MM[1]: On one hand, there are focal lesions with confirmed circumscriptive plasma cell infiltration of the bone marrow which may lead to destruction of the inner cortical bone (scalloping). On the other hand, there is diffuse bone marrow infiltration which leads to a mixture of monoclonal cells and physiologic hematopoietic cells while the spongiosa of the bone remains primarily intact.

These two involvement patterns of MM may occur isolated, synchronous or metachronous. Moreover, soft tissue and/or organ involvement can be observed, which may originate from primarily extraosseous lesions or arise secondarily from osseous lesions after destruction of the cortical bone. Therefore, the main role of imaging in MM is the reliable detection of osseous and extraosseous lesions, enabling exact staging and risk stratification of individual patients.

ROLE OF DIFFERENT IMAGING MODALITIES FOR MM

While the primary aim of this review is to provide a guideline-based overview of the currently recommended imaging modalities and their specific advantages and disadvantages (in the sometimes confusing context of numerous original studies, case reports and reviews), a number of other reviews with a different focus have recently been published including reviews addressing the specific role of imaging in the context of non-secretory myeloma[17] and the potential influence of newer imaging modalities on patient management[18-20]. In addition,

Table 2 Conventional radiographic status in multiple myeloma

Region
Skull in 2 views
Spine (cervical/thoracic/lumbar) in 2 views
Chest AP
Pelvis AP
Long proximal bones AP

AP: Anterior-posterior view.

other more pictorial reviews provide a good description of imaging features of both osseous and extraosseous myeloma[21-23].

Conventional projection radiography

Conventional projection radiography still represents the standard method for detection of bone lesions for initial staging and monitoring of MM. Lytic lesions in the plate bone of the skull and pelvis are typically characterized by stamped out lesions without a sclerotic rim (Figure 1). In the long bone various appearances may be detected: thinning of the inner cortical bone (scalloping), discrete small lytic lesions up to 1 cm, "moth-eaten" patterns deriving from multiple small lesions or large destructing osteolytic lesions[1]. All these lesions represent replacement of the physiological bone marrow by clonally expanding plasma cells with consecutive destruction of the bone[24]. According to the IMWG, a complete conventional radiographic status is recommended for each newly diagnosed patient with MM (Table 2)[1]. Nearly 80% of all newly diagnosed cases of MM reveal detectable changes using conventional radiography. The following sites are most commonly affected: vertebrae in 65% of patients, ribs in 45%, skull in 40%, shoulders in 40%, pelvis in 30% and long bones in 25%[1,25]. The detection of lytic bone lesions represents a criterion defining a symptomatic and treatment-requiring MM even in the absence of clinical symptoms[4,26]. The advantage of conventional radiography is its wide availability, low costs and coverage of almost the entire skeletal system.

The disadvantage of conventional radiography is its low sensitivity, which is explained by the fact that lytic lesions are only detectable if more than 30% of the trabecular bone is destroyed[27]. Hence, up to 20% of patients with normal skeletal status have non-detected osteolytic lesions[1,25]. In addition, conventional radiography can neither detect nor quantify a diffuse bone marrow infiltration nor extraosseous lesions. Another limitation of conventional radiography is the fact that it cannot be used for therapy monitoring, since lytic lesions rarely show radiographically detectable changes despite the presence of a therapy response[28]. Moreover, conventional radiography fails to differentiate benign reasons for focal lucent bone lesions, has a relatively high interobserver variability and certain regions can not be depicted free from superposition. Due to the aforementioned reasons, more sophisticated cross-sectional imaging methods are being established for diagnosis of MM[1].

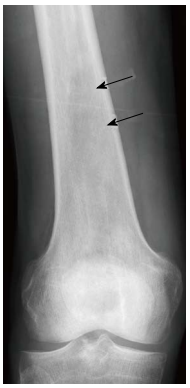

Figure 1 X-ray of an osseous myeloma lesion. Conventional X-ray of the right femoral bone showing an osteolytic lesion (arrows) representing an osseous myeloma manifestation.

CT

CT allows for detection of smaller osseous lesions that are not detectable by conventional radiography[3,5]. Early changes can be detected more reliably with CT. Another advantage of CT as compared to conventional radiography is its higher sensitivity, particularly in regions that are superimposed on conventional radiographs such as scapulae, ribs and sternum[3]. Importantly, potential instabilities and risk of fractures can be estimated better using cross-sectional CT (Figures 2 and 3)[2,29,30]. Another advantage of CT is short imaging times with modern multi-detector CT and complication free examinations of patients in the supine position without the need of repeated relocation, which might be of importance in anguished patients. Moreover, CT allows for detection of extraosseous manifestations of MM and the acquired 3D data sets can be used for radiation therapy if needed. In symptomatic patients with inconspicuous conventional radiographic imaging studies, a CT should be considered.

A known disadvantage of CT is its high radiation dose, which had led to the implementation of so called low-dose CT protocols, which are still highly specific for the detection of osteolytic bone lesions[4,5,31]. The dose of CT may be reduced even further in the future with newly developed iterative reconstruction techniques[2,32].

However, CT has limited sensitivity for detection of diffuse bone marrow infiltration, bone marrow lesions without lytic reaction and extraosseous lesions.

MRI

The use of MRI for imaging of MM has dramatically increased within the last decade[6,33]. MRI is clearly more sensitive than conventional radiography. Up to 50% of patients with inconspicuous conventional radiographic imaging reveal focal lesions detectable on a MRI (Figure 4)[7,8,33]. In particular, MRI offers improved detection of lesions in the spine, pelvis, sternum, skull and scapulae. Other advantages as compared to both conventional radiography and CT are the excellent depiction of the spinal

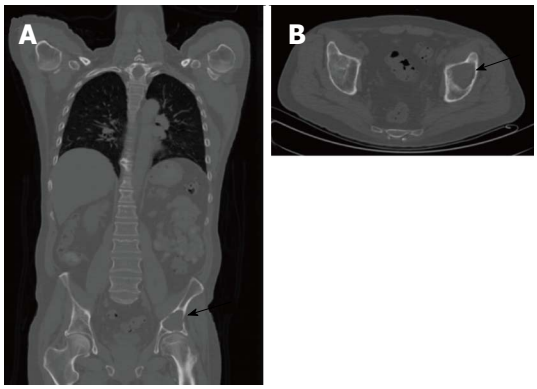

Figure 2 Computed tomography of an osseous myeloma lesion. Computed tomography in coronal (A) and transversal views (B) showing an osteolytic lesion in the left iliac bone (arrows) representing an osseous myeloma manifestation.

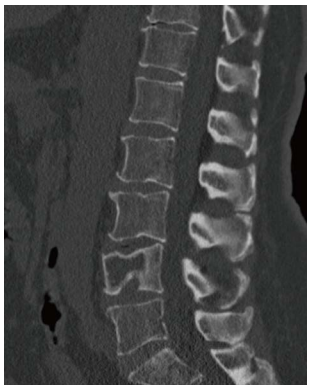

Figure 3 Computed tomography of an osseous myeloma lesion. Computed tomography in sagittal view showing an osteolytic lesion in L4 with associated pathologic fracture.

cord and nerve roots, detection of soft tissue manifestations and the ability to differentiate between physiological and myeloma-infiltrated bone marrow[6,33-35]. The involvement of the bone marrow is classified in three different patterns[9,36-38]: focal lesions, homogenous diffuse bone marrow infiltration and mixed "salt-and-pepper" pattern with remaining islets of fatty bone marrow. An excellent review containing a large number of imaging examples for the different involvement patterns before and after treatment has recently been published[23].

An inconspicuous MRI indicates very low tumor burden, while diffuse involvement and contrast enhancement correspond to high tumor burden[10,39]. Several studies have shown that asymptomatic patients with detectable lesions on MRI have a higher probability to become symptomatic earlier than patients without such lesions[11,12,40,41]. Future studies are needed to evaluate whether detectable lesions on MRI have to be included in the definition of symptomatic MM. However, MRI of the spine and pelvis is indicated when there is suspicion of solitary plasmacytoma to rule out additional lesions[11,42]. Also in patients with suspicion of spinal chord or nerve root compression MRI is indicated, as well

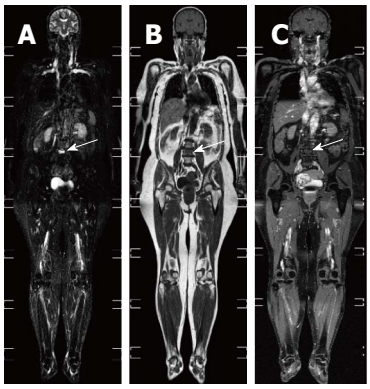

Figure 4 Whole-body magnetic resonance imaging of an osseous myeloma lesion. Whole-body magnetic resonance imaging: short-tau-inversion-recovery sequence (A), T1-weighted image (B) and T1-weighted image with fat suppression after contrast administration (C) showing an osseous lesion in L4 (arrows) representing an osseous myeloma manifestation.

as in patients with painful myeloma manifestations for evaluation of the extent of potential soft tissue masses. Moreover there is an indication for MRI in patients with non-secretory myeloma for initial staging as well as for monitoring of treatment[12,34].

MRI has several disadvantages: relatively high costs, relatively long scanning time which may be difficult in ill patients, and the risk of development of nephrogenic systemic fibrosis after intravenous administration of gadolinium-based contrast agents, particularly in patients suffering from renal insufficiency.

Besides the morphological MR imaging, there are newer functional MR techniques such as diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) MR imaging. However, published data particularly for DWI in the context of initial staging are very limited. A recent study has shown that diffusion-weighted imaging does not only allow for detection of myeloma manifestations, but also that the apparent diffusion coefficients significantly differ before and after initiation of therapy[43]. Concerning DCE imaging, data has been limited to several mainly small studies. In one such study on 24 patients with myeloma, DCI MRI reflected the degree of infiltration and vessel density in corresponding bone marrow biopsy specimens[44]. In another study, Hillengass *et al*[45] could demonstrate a prognostic significance of DCE-derived parameters for event-free survival ($P = 0.02$) in myeloma patients. DCE MRI may identify a subgroup of patients with asymptomatic monoclonal plasma cell disease and pathologic microcirculation. These patients show a significantly higher bone marrow plasmocytosis compared with patients with a low microcirculation pattern. However, the clinical significance of that finding is currently unclear[46]. Another study evaluating DCE MRI findings in patients with myeloma and metastases from non-haematological cancer has shown that characteristic DCE parameters, including the peak signal enhancement percentage (SE%), the steepest wash-in SE% during the ascending phase and the wash-out SE% may indicate if an unclear spinal lesion is of myelomatous origin or

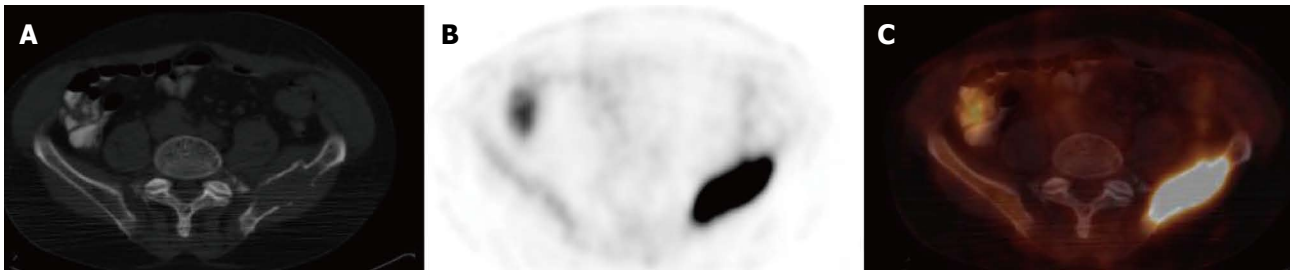

Figure 5 Positron emission tomography/computed tomography of an osseous myeloma lesion. Transversal computed tomography (CT) (A), ^{18}F-fluorodeoxyglucose positron emission tomography (PET) (B) and fused PET/CT (C) showing an osteolytic lesion in the left iliac bone with cortical destruction representing an osseous myeloma manifestation.

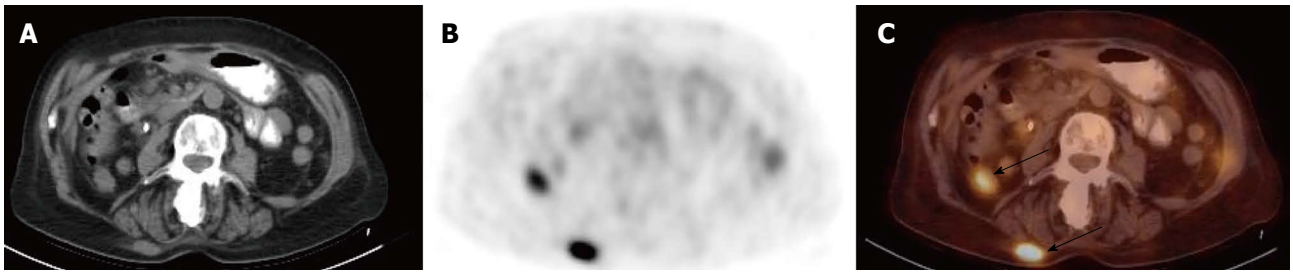

Figure 6 Positron emission tomography/computed tomography of extraosseous myeloma lesions. Transversal computed tomography (CT) (A), ^{18}F-fluorodeoxyglucose positron emission tomography (PET) (B) and fused PET/CT (C) showing extraosseous myeloma manifestations (arrows).

not[47]. In short, both DCE MRI and DWI are promising techniques particularly for response monitoring, but further prospective studies are needed to define their exact role.

The applied MR imaging protocols vary widely between different institutions, and may include standard non-enhanced T1- and T2-weighted imaging, STIR sequences and contrast-enhanced T1-weighted fat-saturated imaging[48-50]. The usefulness of contrast-enhanced MR imaging for the initial evaluation of multiple myeloma is debatable because it does not usually allow the identification of additional focal lesions compared to non-enhanced imaging protocols[49]. In addition, gadolinium-based contrast agents may cause nephrogenic systemic fibrosis, particularly in patients with impaired renal function.

Based on our experience, we recommend a whole-body MRI protocol containing a T1-weighted sequence without fat suppression, a STIR sequence and a contrast-enhanced T1-weighted sequence with fat suppression in all patients without contraindications to gadolinium-based contrast agents, particularly because contrast-enhanced imaging has been shown to predict diffuse bone marrow infiltration[51,52].

PET/CT

Combined PET/CT using ^{18}F-FDG as radiotracer allows for the simultaneous acquisition of several morphological and function parameters relevant to MM. The excellent depiction of osseous structures and lesions by CT is supplemented with the high sensitivity of PET for detection of isolated focal medullary lesions without destruction of the osseous substance as well as for detection of extraosseous manifestations (Figures 5 and 6)[1,6,18,34,53]. Moreover, PET/CT allows for initial staging and treatment monitoring of non-secretory myeloma[1,54]. In contrast to MM, the MGUS is typically PET negative[1,14,54].

The higher sensitivity of ^{18}F-FDG PET/CT for detection of focal osseous lesions as compared to conventional radiography has been shown in several prospective studies. PET/CT detects more osseous myeloma manifestations in 40%-60% of cases as compared to conventional radiography and detects lesions in patients with false negative conventional radiography results[9,15,55,56]. Several studies have shown that in up to 40% of patients with initially solitary plasmacytoma, additional and so far unknown lesions may be detected by PET/CT leading to an upstaging and change of therapeutic management[1,16,57]. When compared to MRI, the sensitivity for detection of focal osseous lesions seems to be comparable. However, MRI has a higher sensitivity for detection of diffuse bone marrow infiltration, which may remain particularly undetected by PET/CT in cases of low degree plasma cell infiltration[1,56,58,59]. However, some newer studies have demonstrated a high sensitivity of PET also for detection of diffuse bone marrow infiltration. In a study by Sager *et al*[60], bone marrow involvement on FDG PET/CT of patients with MM was compared with bone marrow biopsy. In that study, the sensitivity of FDG PET in detecting bone marrow involvement at initial diagnosis was 90%. There was a significant correlation between SUV_{max} values, bone marrow biopsy cellularity and plasma cell ratios (r = 0.54 and r = 0.74, $P < 0.01$). Another study by Ak *et al*[61] also found a statistically significant positive correlation be-

tween the percentage of CD38/CD138 expressing plasma cells in bone marrow and both mean qualitative ($r = 0.616$) and semiquantitative ($r = 0.755$) FDG uptake.

PET imaging allows estimation of the standardized uptake value (SUV), which represents a quantitative measurement of ^{18}F-fluorodeoxyglucose uptake and metabolic activity of a given lesion. Several studies have shown that a high SUV of lesions in MM patients correlates with faster disease progression and therefore with a worse prognosis[1,62,63]. A prospective study on 239 patients has shown that the presence of more than 3 PET-positive lesions represented the major independent parameter for predicting progression-free survival and overall survival[24,64]. In a study assessing the prognostic implications of serial FDG PET in 2 consecutive Total Therapy 3 trials for newly diagnosed myeloma, multivariate analysis showed that more than 3 focal lesions on day 7 of induction therapy imparted inferior overall survival and progression-free survival. Thus, the presence of > 3 focal lesions on day 7 PET follow-up may be exploited toward early therapy change[65]. In a study by Nanni *et al*[66], 107 patients had FDG PET 3 mo after therapy (autologous stem cell transplantation) and every 6 to 12 mo during the follow-up. In that series of patients, a negative posttherapy PET was predictive for nonrelapse or a long disease-free survival. In a study by Zamagni *et al*[62], 192 patients with newly diagnosed myeloma underwent FDG PET/CT at baseline and after autologous stem cell transplantation. In a multivariate analysis, both extramedullary disease detected by PET and SUV > 4.2 at baseline and persistence of FDG uptake after stem cell transplantation were independent variables adversely affecting progression-free survival. In addition to the parameters described above, the metabolic tumor volume, representing the metabolically active malignant tissue throughout the body has been shown to be useful for prediction of progression-free and overall survival in myeloma patients[67]. Future studies are required to further define the role of FDG PET/CT for individual risk stratification and therapy monitoring.

Apart from FDG, several other PET radiotracers have been evaluated for initial staging. In a study comparing FDG and ^{11}C-acetate for initial staging of myeloma, ^{11}C-acetate PET was able to detect diffuse bone marrow infiltration with a sensitivity of 100%, whereas FDG PET could establish a diagnosis of diffuse infiltration in only 40% of patients. In addition, the authors observed a positive correlation between bone marrow uptake values and percentages of plasma cell infiltrates ($r = +0.63$, $P = 0.01$) [68]. In a different study comparing the value of ^{11}C-choline PET and FDG PET in assessing bone involvement in patients with multiple myeloma, ^{11}C-Choline PET/CT scans detected 37 bone lesions, whereas ^{18}F-FDG PET/CT scans detected 22 bone lesions. The authors concluded that ^{11}C-Choline PET/CT appears to be more sensitive than ^{18}F-FDG PET/CT for the detection of bony myelomatous lesions[69]. In a study by Nakamoto *et al*[70] assessing the clinical value of ^{11}C-methionine (MET) as a radiolabelled amino acid tracer in plasma cell malignancies (which may also be useful because plasma cell malignancies are able to activate protein synthesis), MET PET revealed an equal or greater number of lesions than FDG (MET 156 lesions *vs* FDG 58 lesions) and tended to demonstrate higher uptake (maximum standardized uptake value 10.3 ± 5.6) than did FDG (3.4 ± 2.7, $P < 0.001$). The amino-acid tracer ^{18}F-alpha-methyltyrosine (FAMT) was evaluated in a small study including eleven patients with MM. Although FAMT PET detected all lesions seen on FDG PET, uptake was significantly higher on FDG PET ($P < 0.05$)[71]. However, these new tracers are not widely available yet, usually require an on-site cyclotron for isotope production and an on-site radiochemistry for tracer synthesis.

IMAGING FOR MONITORING OF TREATMENT OF MM

According to the IMWG criteria, currently none of the presented imaging methods are mandatory for monitoring treatment of MM, as long as the response can be assessed by serum and urine analyses[1,6,34]. Repeated imaging is only indicated if ailment is likely induced by osseous lesions or in cases of relapse to exclude extraosseous lesions[1,6,25,34].

A characteristic feature of osseous manifestations of MM is the fact that the lesions regress only slowly or not at all, even in patients with complete remission[4,26,72]. Hence conventional radiography and CT cannot be adequately used for treatment monitoring. Typically, successfully treated inactive osteolytic lesions may show a sclerotic rim. A recent study has addressed the value of MRI for monitoring treatment of MM after stem cell transplantation, but found no additional benefit as compared to routinely performed hematological and immunological tests[27,38]. In contrast, ^{18}F-FDG uptake represents a direct parameter of lesion activity (Figure 7), that enables detection of active myeloma lesions[1,16,25,54]. This allows ^{18}F-FDG PET/CT to detect specific lesions after stem cell transplantation, albeit with lower sensitivity as compared to the initial staging[28,53]. In a study analyzing 197 whole-body ^{18}F-FDG PET/CT scans performed in 99 patients with myeloma at different time points in the course of disease after autologous or allogeneic stem cell transplantation, PET/CT had a sensitivity of 54.6%, a specificity of 82.1%, a positive predictive value of 82.3%, a negative predictive value of 54.2% and an overall accuracy of 65.5%. The sensitivity of FDG PET/CT was shown to depend on the disease category according to the Uniform Response Criteria for myeloma. The authors concluded that FDG PET/CT may have a lower sensitivity for restaging after therapy compared to the pretreatment setting[53]. There are small PET studies on other tracers than FDG. In a recent prospective study, 13 patients underwent ^{11}C-acetate PET/CT before and after treatment. After treatment, the diffuse bone marrow ^{11}C-

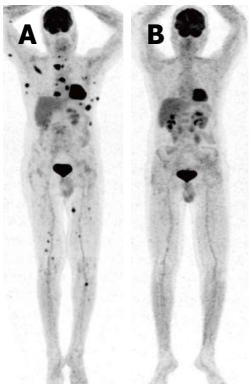

Figure 7 Positron emission tomography for therapy monitoring. Whole-body maximum-intensity-projection positron emission tomography (PET) images before and after stem cell transplantation showing extensive osseous and extraosseous myeloma manifestations before therapy (A) and complete resolution on PET after therapy (B).

acetate uptake showed a mean SUV_{max} reduction of 66 % in patients with at least a very good partial response versus 34 % in those with at most a partial response only (P = 0.01), indicating a potential role of ^{11}C-acetate PET for response assessment[68].

There are several mainly small studies demonstrating changes on DWI or dynamic contrast-enhanced MRI after therapy, indicating a potential role of newer MRI techniques for response monitoring. In a study by Hillengass *et al*[43] on 56 patients with myeloma or monoclonal gammopathy of undetermined significance, the DWI-parameter apparent diffusion coefficient (ADC) correlated with bone marrow cellularity and micro-vessel density (P < 0.001). ADC was significantly different in 15 patients which underwent systemic treatment before and after that therapy (P < 0.001). In a study by Horger *et al*[73], twelve consecutive patients with myeloma underwent whole-body DWI both at baseline and 3 wk after onset of therapy. All involved lesions showed restricted diffusion at baseline, and ADC quantification yielded an increase of 63.9% in responders and a decrease of 7.8% in the sole non-responding patient during therapy, indicating that whole-body DWI with ADC analysis represents a feasible diagnostic tool for assessment of short-term treatment response. In a study by Lin *et al*[74], post-treatment bone marrow changes at whole-body dynamic contrast material-enhanced MR imaging were compared with clinical response in patients with multiple myeloma. Maximal percentages of bone marrow [BME(max)] and focal lesion [FLE(max)] enhancement were assessed. After induction chemotherapy, mean BME(max) differed between good and poor responders (94.3% *vs* 138.4%, respectively, P = 0.02). Mean timing [*i.e.*, the number of post-contrast dynamic acquisitions where FLE(max) was observed] was significantly delayed in good responders compared with poor responders (4.7 *vs* 2.9, P < 0.0001). The authors concluded that whole-body dynamic contrast-enhanced MR imaging can be used to assess treatment response in patients with MM[74]. In another study comparing DWI and arterial spin labeling (ASL) perfusion in 10 patients, ASL showed a marked decrease in perfusion from baseline at 3 wk and at 8 wk (P = 0.01). In contrast, there was an increase in diffusion which was borderline significant (P = 0.0049). Both methods were able to correctly classify 9/10 patients as responder or non-responder. However, temporary changes in signal intensity between baseline and follow-up examinations were inconsistent on T1-weighted (w) and T2w images, indicating that standard MRI protocols may be of limited usefulness for response assessment[75]. This is in line with a whole-body MRI study on 66 patients after stem cell transplantation in which only moderate agreement was observed between MRI and routinely performed laboratory tests for the determination of remission[38]. Another study comparing ^{18}F-FDG PET/CT and whole-body MRI for determination of remission status in patients with multiple myeloma after stem cell transplantation found that MRI may often be false positive because of persistent non-viable lesions in the post-treatment setting, indicating that PET/CT might be more suitable than MRI for determination of remission status[76].

As for the initial staging, future studies are needed to further define the exact value of the presented imaging techniques for monitoring treatment of MM.

CONCLUSION

Medical imaging is of crucial importance for diagnosis and initial staging as well as for differentiation of MM from other monoclonal plasma cell diseases. Despite the known limitations such as low sensitivity, limited specificity and inability to detect extraosseous lesions, conventional radiography still represents the reference standard for diagnosis of MM due to its wide availability and low costs. Besides conventional radiography, newer cross-sectional imaging modalities such as whole-body low-dose CT, whole-body MRI and ^{18}F-FDG PET/CT are available for diagnosis of osseous and extraosseous manifestations of MM.

Among the cross-sectional imaging techniques, whole-body low-dose CT is currently replacing conventional radiography due to its high sensitivity for osseous lesions and the possibility to detect extraosseous lesions. Whole-body MRI and ^{18}F-FDG PET/CT feature the highest sensitivity for osseous lesions, soft tissue lesions and organ manifestations. For that matter, MRI has the highest sensitivity for detection of diffuse bone marrow involvement and ^{18}F-FDG PET/CT for detection of extraosseous lesions. Whole-body MRI should be considered in all patients with inconspicuous conventional radiography, all patients with apparently solitary plasmacytoma and patients with suspicion of spinal cord or nerve root compression.

Based on the results of recent studies and our experience, we recommend performing whole-body MRI for initial staging of MM due to its high sensitivity for detection of osseous and extraosseous lesions without the need for ionizing radiation. MRI allows for sensitive detection of both focal and diffuse bone marrow infiltra-

tion. A complementary CT may be indicated in case of conspicuous lesions to assess the presence of osteolytic lesions and to evaluate stability. For restaging of MM and detection of a possible relapse after initiation of treatment, we recommend performing ^{18}F-FDG PET/CT due to its ability to differentiate between active and inactive lesions, enabling monitoring of MM treatment. There is an evolving role for assessment of treatment response using newer MR imaging techniques.

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WJO 5th Anniversary Special Issues (6): Osteoporosis

Bone three-dimensional microstructural features of the common osteoporotic fracture sites

Huayue Chen, Kin-ya Kubo

Huayue Chen, Department of Anatomy, Gifu University Graduate School of Medicine, Gifu 501-1194, Japan
Kin-ya Kubo, Seijoh University Graduate School of Health Care Studies, Aichi 476-8588, Japan
Author contributions: Chen H and Kubo KY contributed to this work.
Correspondence to: Huayue Chen, MD, PhD, Department of Anatomy, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu 501-1194, Japan. huayue@gifu-u.ac.jp
Telephone: +81-58-2306295 Fax: +81-58-2306298
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Abstract

Osteoporosis is a common metabolic skeletal disorder characterized by decreased bone mass and deteriorated bone structure, leading to increased susceptibility to fractures. With aging population, osteoporotic fractures are of global health and socioeconomic importance. The three-dimensional microstructural information of the common osteoporosis-related fracture sites, including vertebra, femoral neck and distal radius, is a key for fully understanding osteoporosis pathogenesis and predicting the fracture risk. Low vertebral bone mineral density (BMD) is correlated with increased fracture of the spine. Vertebral BMD decreases from cervical to lumbar spine, with the lowest BMD at the third lumbar vertebra. Trabecular bone mass of the vertebrae is much lower than that of the peripheral bone. Cancellous bone of the vertebral body has a complex heterogeneous three-dimensional microstructure, with lower bone volume in the central and anterior superior regions. Trabecular bone quality is a key element to maintain the vertebral strength. The increased fragility of osteoporotic femoral neck is attributed to low cancellous bone volume and high compact porosity. Compared with age-matched controls, increased cortical porosity is observed at the femoral neck in osteoporotic fracture patients. Distal radius demonstrates spatial inhomogeneous characteristic in cortical microstructure. The medial region of the distal radius displays the highest cortical porosity compared with the lateral, anterior and posterior regions. Bone strength of the distal radius is mainly determined by cortical porosity, which deteriorates with advancing age.

Key words: Osteoporosis; Fracture; Microstructure; Trabecular bone; Cortical bone; Vertebra; Femoral neck; Distal radius

Core tip: The most common sites of the osteoporotic fractures include the vertebra, femoral neck and distal radius, where the microstructural information is a key for fully understanding osteoporosis pathogenesis and improving the prediction of fracture risk. Vertebral strength is mostly preserved by trabecular bone, which is microstructurally inhomogeneous, with lower bone volume in the central and anterior superior regions. Increased fragility of osteoporotic femoral neck is attributed to low cancellous bone volume and high compact porosity. Distal radius shows significant variations in cortical porosity, which is the major element attributed to bone strength of the distal radius.

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INTRODUCTION

Osteoporosis is a common metabolic skeletal disorder characterized by decreased bone mass and deteriorated

Table 1 The main bone histomorphometric parameters and their significance

Parameters	Meaning	Significance
BV/TV	Trabecular bone volume per total tissue volume	In osteoporotic patients, BV/TV significantly decreases, accompanied by low BMD
Tb.Th	Trabecular thickness	Trabeculae become thinner with the progression of osteoporosis for both women and men
Tb.N	Trabecular number	In osteoporotic patients, the decrease in Tb.N is usually greater in women than in men
Tb.Sp	Trabecular separation	Tb.Sp increases with the progression of osteoporosis
Co.Po	Cortical porosity	With the progression of osteoporosis, Co.Po increases, accompanied by low cortical BMD

BV/TV: Bone volume fraction; Tb.Th: Trabecular thickness; Tb.N: Trabecular number; Tb.Sp: Trabecular separation; BMD: Bone mineral density.

bone structure, resulting in an increased susceptibility to fractures[1,2]. With the rapid growth in the elderly population, osteoporotic fracture is a global public health problem with enormous socioeconomic consequences[3]. Osteoporosis is estimated to affect more than 200 million people around the world. Osteoporosis leads to approximately 9 million new fractures annually, 1.4 million being in the vertebra, 1.7 million in the forearm and 1.6 million in the femoral neck[4]. A key characteristic of osteoporosis is fracture that occurs with little or no injury. Osteoporotic fractures might affect functioning of body movement, which can lead to disability, limit daily activities and affect the quality of life.

Osteoporosis can affect any bone in the body. However, osteoporotic fractures are some skeletal sites are more easily fractured than would normally be the case. However, osteoporotic fractures are more easily and more likely to occur at some special skeletal sites. Consistent with current clinical experience, the most common sites of fractures in osteoporotic patients include bones that are under certain strain as they bear body weight such as vertebra and femoral neck or take the stress when a person falls on an outstretched hand such as distal radius[5]. To prevent fractures is the major purpose of osteoporosis screening. When the external force applied to a bone exceeds its strength, a fracture would occur. The ability of a bone to tolerate loading depends on the quantity and quality of the bone. The intrinsic material properties of bone are bone mineral density (BMD), bone size, geometry, bone mineralization, microstructure and bone turnover[6].

The decline in BMD is related to decreased bone strength, increased bone fragility and elevated fracture risk. BMD is a major important predictor of subsequent osteoporotic fracture risk. Many techniques are available to determine BMD value. Low BMD is correlated with increased fracture risk[6]. Clinical studies demonstrate that BMD only accounts for bone strength partially and that there is a limitation of BMD measurements in evaluating fracture risk[7,8]. Recent studies show that bone microstructural information can detect early changes in osteoporotic process. Knowledge of bone microstructure is important to fully understanding the pathogenesis of osteoporotic fracture[9-11]. The microstructural properties of vertebra, femoral neck and distal radius are critical for predicting the fracture risk of these sites. Bone microstructure typically refers to histomorphometric parameters originally obtained from two-dimensional (2D) stained sections. The sample preparation process of this 2D approach is tedious and destructive. Bone structure is three-dimensional (3D). Owing to the substantially improved spatial resolution, it has been possible recently to analyze quantitatively 3D bone microarchitectural properties. Micro-computed tomography (CT) can provide excellent 3D spatial resolution of 10 m. A High-resolution peripheral quantitative CT (HR-pQCT) technique has been implemented on the XtremeCT scanner. The scanner provides 3D images with isotropic voxel size of 41 m or 82 m, the latter resulting in isotropic spatial resolution of about 130-150 m[12]. With these newly developed techniques, many studies have been carried out to investigate the variations of 3D cancellous bone microstructure, such as bone volume fraction (BV/TV), trabecular thickness (Tb.Th), trabecular number (Tb.N) and trabecular separation (Tb.Sp). Cortical parameters such as BMD, thickness and porosity are also calculated[13]. All these parameters are important for evaluating bone quality (Table 1). This review article will discuss the bone microstructural parameters obtained from 3D work and newer technologies, especially the vertebra, femoral neck and distal radius, the common sites of the osteoporotic fractures according to the existing literature.

VERTEBRA

The vertebrae are made up of 24 individual bones to bear the weight of the upper body and withstand substantial loads. Vertebral body is a thick oval segment of bone, composed of internal cancellous bone and a thin coating of compact bone. Intervertebral disc is a massive pad of fibrocartilage, which is firmly attached to vertebral body above and below, forming a flexible column. This lightweight structure contains a minimal amount of material in its structure. Cancellous bone of vertebral body is crucial for the function of the whole spinal column[14,15]. Osteoporotic fractures most often occur in the vertebrae. Approximately 700000 new vertebral fractures occur in the United States annually[16]. They are nearly twofold as common as other fractures, such as osteoporosis-related femoral neck and radial fractures. When osteoporosis is involved, a vertebral compression fracture generally is a patient's earliest sign of a deteriorated skeleton from osteoporosis.

Cancellous bone of vertebra is metabolically more active than cortical bone and trabecular BMD may act as an initial predictor of spinal osteoporotic fracture[17].

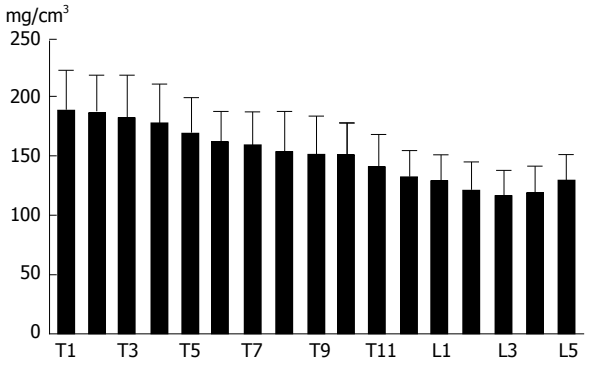

Figure 1 The trabecular bone mineral density of the thoracic and lumbar vertebrae[22]. The bone mineral density tends to decrease from the first thoracic to third lumbar vertebra.

There is a negative correlation between vertebral cancellous BMD and spinal fracture[14]. It is necessary to examine regional BMD separately in different levels, as osteoporosis-related spinal fractures occur frequently in the midthoracic region and thoracolumbar transitional area, as described by Wasnich[18]. Vertebral BMD can be explored using QCT-based BMD measurement approach[19-22]. Trabecular BMD of the cervical spine is significantly higher than that of the thoracic and lumbar one. Trabecular BMD of the first sacral vertebra is significantly higher than that of the lumbar vertebrae. In an age- and gender-stratified population-based non-invasive study, we examined trabecular volumetric BMD (vBMD) of thoracic and lumbar vertebrae[19-22]. Trabecular vBMD of vertebral body gradually decreased craniocaudally from the first thoracic (Th1) to third lumbar spine (L3) for both genders. Compared with Th1, vBMD at L3 declined around 30% (Figure 1). There was a very high correlation between adjacent vertebral BMD, though the BMD correlation became lower between vertebrae with increasing distance from each other. It might be suitable to use any vertebra for evaluating bone strength of spine. By using our knowledge available for BMD correlations, one can estimate the BMD of any vertebra, provided that one vertebral BMD is known.

The regional variation of vertebral microstructure has been examined extensively[23-25]. We studied 3D microstructure of L4 from Japanese cadaver donors by quantitative micro-CT and electron microscopic methods[25]. BV/TV and Tb.N of vertebral cancellous bone declined with advancing age. BV/TV decreased by 22%-24% from 60 to 90 years of age for both males and females. Age-dependent decreases of BV/TV were similar for males and females. Tb.N also decreased with age by 19% in males and 16% in females. Tb.Sp consistently increased with age. There was no significant decline of Tb.Th with advancing age. Thus, age-related decrease of BV/TV is mainly related to increased Tb.Sp and decreased Tb.N[17,23,25].

Cancellous bone of vertebra is complicated morphologically that contains numerous plate-like and rod-like trabeculae[24-27]. Trabecular plate-like or rod-like characteristic might be assessed by determining the structure model index (SMI). SMI is a crucial morphometric parameter which effects intensely on bone intrinsic properties. Vertebral cancellous bone has a more rod-like than plate-like structure. SMI of the vertebral cancellous bone increases by about 20% from 60 and 90 years of age. Vertebral trabeculae are gradually converted from plate-like to rod-like and consequently are more fragile and are especially prone to fracture. Cancellous connectivity density (Conn.D) is a basic characteristic of 3D network and is critical for the preservation of bone strength. When the amount of cancellous bone declines, the value of Conn.D would decrease correspondently, perhaps attributable to the small trabecular bone loss[25,26,28]. Vertebral trabecular Conn.D decreases significantly with advancing age. Age-dependent change of Conn.D is almost identical for males and females[25,28].

Determination of BMD locally is achievable using QCT owing to its high spatial resolution. However, clinical assessment is limited to just a few thin slices and QCT is commonly carried out in the central area of the vertebral body. As cancellous bone is heterogeneous microarchitecturally in the vertebral body[19,22,25], localization of low BMD value within the vertebral body is beneficial clinically and may play a role in clarifying pathophysiology of spinal osteoporosis-related fracture. QCT and micro-CT studies show that BV/TV is lower in central and anterior superior regions, compared with the posterior region of the vertebral body (Figure 2). The cancellous regional differences of the microarchitectural characteristic within the vertebrae is important for assessing the bone quality of vertebra and may also contribute to the pathogenesis of osteoporosis-related spinal fracture.

By using scanning electron microscopy, it is easy to examine the trabecular resorption state, that is critical for cancellous structural integrity, possibly deciding if the bone strength is sustained or declined[25,29,30]. The decrease of spinal cancellous bone with advancing age is predominantly through trabecular perforation rather than trabecular general thinning[25,28]. It is demonstrated that osteoclasts resorb some perforated trabecular bone and the trabecular connectivity is destroyed. When the newly formed bone is insufficient adequately to replace missing bone, the trabecular connectivity will reduce and the bone will become more brittle and fragile[25,29,30]. Microcallus is a nodular aggregation of woven bone, which is often found predominantly on the thin vertical trabeculae (Figure 3A). Microcallus acts to preserve or repair a trabecula[25,31-33]. However, what triggers the microcallus formation is still subject to debate.

The conventional view is that a compressive load on vertebrae is mainly carried by the vertical trabeculae, whereas the horizontal trabeculae serve to prevent buckling of the vertical trabeculae[34,35]. This view is reinforced by finite element analyses of human vertebral bone specimens, which demonstrates that vertical trabeculae are more highly strained than horizontal ones under normal compressive loading, the[14,36]. Consequently, it is important to quantify the trabecular thickness as well as bone volume fraction for horizontal and vertical trabecular bone

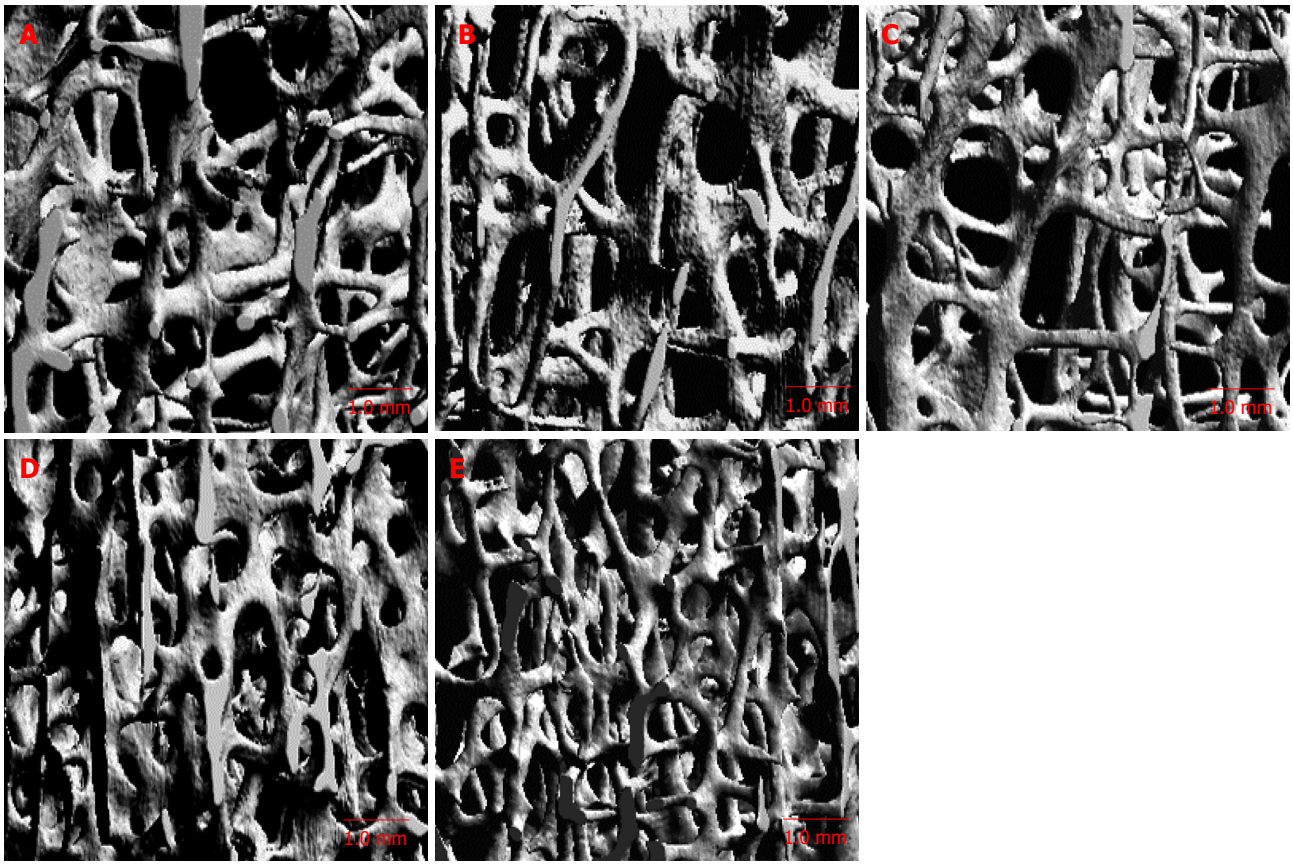

Figure 2 Micro-computed tomography image in different regions of vertebral body[25]. A: Anterosuperior; B: Anteroinferior; C: Central; D: Posterosuperior; E: Posteroinferior regions. The trabecular bone is lower in the anterosuperior and central regions.

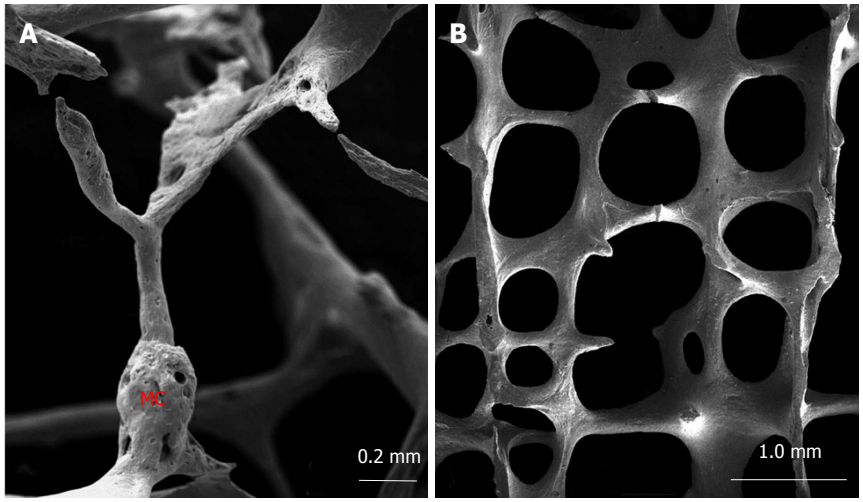

Figure 3 Scanning electron microscopic image of vertebral trabecular bone[25]. The microcallus (MC) is seen on the vertical trabecula (A). Tertical trabeculae are relatively thicker than the horizontal ones (B).

independently. Recently, a 3D approach was introduced to segment a trabecular network into vertical and horizontal trabeculae of the vertebral body[37-39]. Fields *et al*[37,38] found that vertical trabeculae played a particular important role for the compressive bone strength of vertebrae with low BMD and presumed that vertebral bone strength is better explained by the vertical trabecular bone volume fraction alone, than by the total trabecular bone volume fraction. The scanning electron microscopic images confirmed that the horizontal trabeculae were thinner, whereas the vertical ones were relatively thicker (Figure 3B). Both vertical and horizontal trabeculae decreased with age and vertical trabeculae were lost more rapidly in females than in males. Furthermore, the vertical as well as horizontal trabecular thickness were independent of age, however the ratio of horizontal/vertical trabecular thickness declined significantly with age suggesting a more pronounced thinning of horizontal trabeculae[39]. Age-related bone loss of trabecular elements results in compensatory hypertrophy of vertical trabeculae in females, but not in males[40].

Vertebral trabecular bone is inhomogeneous micro-

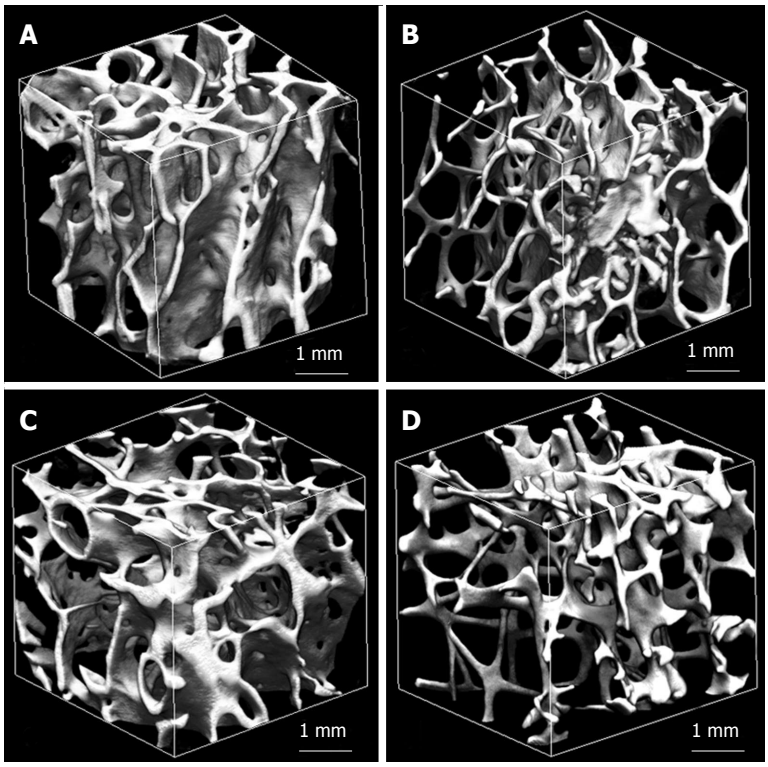

Figure 4 Trabecular microstructure of femoral neck from a man aged 62 years (A), a man aged 92 years (B), a woman aged 62 years (C), and a woman aged 92 years (D)[49]. The trabecular bone is higher in a man aged 62 years and is lower in a woman aged 92 years.

structurally. Age-dependent declines of BV/TV and Conn.D are similar in males and females. There are significant differences of some morphometric parameters between males and females. Age-dependent bone loss of vertebral trabeculae may be induced by elevated bone resorption activity. These findings elucidate the possible mechanisms of vertebral fractures[17,25].

Highly porous cortical bone of the spine is very thin. Therefore, it is difficult to sort out the role of cortical bone, especially in aged individuals. It is difficult to determine the cortical thinness accurately with non-destructive methods. It is unclear whether the compact bone significantly contributes to biomechanical strength of whole vertebral bone. Cortical thickness of vertebral body ranges from 180 to 600 m, with a mean thickness of 380 m[40-43]. The compact bone of the cervical and lumbar vertebrae is relatively thicker than that of the thoracic one. The dorsal cortex is generally thinner than that of the ventral one. There is no significant gender difference in vertebral cortical thickness. There is a slight age-related decline in vertebral cortical thickness. Most studies highlight the importance of trabecular bone for maintaining bone strength of vertebrae, however recent studies indicate a crucial role of the cortical bone, especially in elderly individuals whose cancellous bone is lower[40-43].

FEMORAL NECK

Femoral neck has to bear high compressive and shear forces continually. These forces are approximately 1 × body weight (BW) during standing, but they are much higher during physical activities[44]. Femoral neck fracture is generally induced by a fall, but may be caused by impact to the hip. When the bone becomes weak due to osteoporosis, only a slight external force is enough to make femoral neck more susceptible to fracture. This type of fracture is very serious and debilitating osteoporotic fracture. Osteoporosis-related femoral neck fractures are a major cause of mortality and morbidity in elderly people worldwide[45,46]. Gullberg *et al*[47] estimated that there were 1.25 million new femoral neck fractures occurred in the world annually and that the fracture number will increase by 310% in males and 240% in females by 2025. There have been many studies conducted to investigate the underlying causes of femoral neck fracture. It is suggested that 3D microstructures play a significant role in assessing the bone quality and provide compelling evidence to explain the bone strength[48-50].

The proximal femur was isolated by cutting at the base of femoral head and femoral neck. Cancellous bone specimen of 8 mm × 8 mm × 8 mm cube was prepared from the central part of femoral neck for quantitative micro-CT examination. Alterations of the femoral neck cancellous bone with advancing age include a decline in BV/TV and Tb.N, and an increase in Tb.Sp[49,51,52]. BV/TV decreases by around 20% from 60 to 90 years of age (Figure 4). Tb.N and Tb.Th decline, while Tb.Sp increases in males and females. The decrease of BV/TV with age is related to decreases in Tb.N and Tb.Th, and increases in Tb.Sp[49,50]. There are a few studies regarding SMI of femoral neck trabeculae[49,50,53]. It is found that SMI increases with age. Trabecular structure of the femoral neck becomes more rod-like with advancing age. Therefore it is more brittle and more likely to fracture. Conn.D decreases significantly with age[49,50]. When the trabecular bone volume fraction declines, Conn.D will decline concomitantly, probably because of small trabecular bone loss[25,49]. Ciarelli *et al*[48] examined 3D micro-

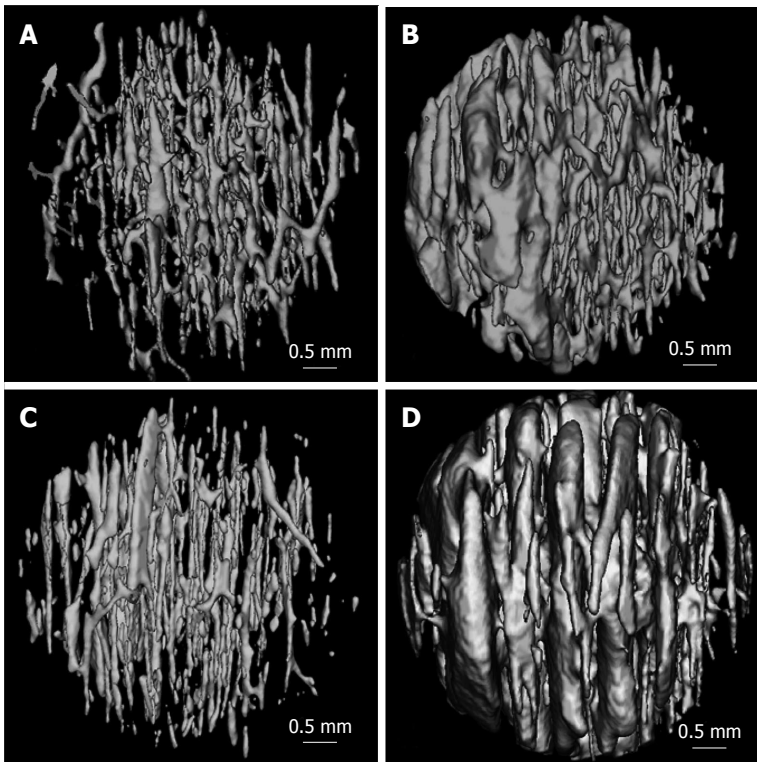

Figure 5 Three D reconstructed images of the canal networks in the inferior femoral neck cortex from a man aged 62 years (A), a man aged 92 years (B), a woman aged 62 years (C), and a woman aged 92 years (D)[49]. There are more enlarged canals in the 92 years than those of the 62 years.

architecture of femoral neck in hip fracture patients and nonfracture controls. There were more anisotropic 3D microstructures and relatively fewer cancellous elements transverse to the primary load axis in fracture cases. The changed 3D microstructures would be supposed to influence bone biomechanical characteristics. Relatively fewer transverse cancellous bones in fracture patients might produce diminished cross bracing and a high susceptibility to buckling of cancellous bone oriented along the loading axis, and the decreased resistance of transverse loads. This changed microstructure may distinguish between patients of high fracture risk and low fracture risk with identical trabecular bone volume[48].

The femoral neck displays noted regional heterogeneity morphologically[49,54-56]. When the hip joint bears entire body weight vertically, compact bone of the inferior region is thicker than that of the superior region. Compact bone of the aged subjects is very thin in the upper region, while that of the lower region remain relatively thicker[54-56]. Cortical thickness of the superior posterior region decreases by 6.4% per decade in females between the ages 60 to 90 years. Similar but a significantly lesser effect is evident in males. The thinning of femoral cortex compromises the functional capacity of femoral neck to absorb energy independent of osteoporosis[49,55]. Cortical porosity (Ct.Po) of femoral neck varies from 5% to 13%[49,55-57]. With advancing age, the diameter of cortical pores increases and some pores adjacent to the endosteum coalesce, leaving the remnant cortexes that resemble to cancellous bone. The remained cortical bone close to the periosteum is kept with normal appearance including several enlarged pores. In elderly female individuals, enlarged cortical pores are present at the endosteal surface, as well as at the periosteal surface. Figure 5 indicates the age-dependent variations of cortical porosity in the inferior region of femoral neck. Cortical thickness (Ct.Th) declines by 3% to 5% and Ct.Po increases by 31% to 33% per decade between ages of 60 to 90 years[49]. The number of cortical pores has no marked age-related changes, whereas the diameter of cortical pore increases significantly with age[49,55-57]. Accordingly, increase of cortical porosity with advancing age is predominantly attributable to enlarged cortical pores. Compared with males, females have a greater Ct.Po and larger cortical pore. Consequently, in addition to age, gender is also an important factor to influence cortical porosity. With advancing age, especially in females several intracortical pores coalesce into a giant pores larger than 385 m[46,52,55]. The giant intracortical pore formation might have a pivotal function in the process of local cortical bone loss during aging.

Osteoporotic fractures of femoral neck are considered to be caused by both cancellous bone loss and compact bone thinning. The relative contribution of compact bone and cancellous bone to whole bone strength of the femoral neck is still poorly understood. It has been shown that an increase in Ct.Po is the most noticeable age-dependent change of femoral neck. The decline in BV/TV with age is more apparent than that of Ct.Th. There is a statistically significant negative correlation between BV/TV and Ct.Po. Ct.Th and BV/TV are lower, and Ct.Po is higher in females, when compares with males. The above results might be used as reference for racial comparison with age and gender, and contribute to the pathogenesis of osteoporosis-related fracture at the femoral neck[49,55,58].

DISTAL RADIUS

Distal radius fractures are very common in osteoporosis patients[59]. The most common cause of the distal radial fracture is a fall on the outstretched hand in people with normal or low bone mineral density[60]. When people fall from standing position, the sudden external force can cause fracture of the distal radius. However, the severity of fall required to cause radial fracture in osteoporotic patients is much less than the subjects with normal BMD, because of the greater skeletal fragility.

Population-based cross-sectional studies by HR-pQCT imaging technique uncovered that BV/TV of the radial cancellous bone declines by 26% in males and 27% in females from 60 to 90 years of age[61]. Trabecular bone volume of distal radius remains relatively stable until midlife and thereafter decreases[61-63]. Trabecular bone volume is higher in males than in females of the same age. Age-dependent decreases in the trabecular BV/TV and BMD are similar for males and females from 20 to 90 years of age[61-63]. There is a different microstructural basis for the decline of cancellous bone volume with advancing age between males and females. Gender difference of cancellous bone loss with age is present at the distal radius. Decreases of Tb.N and increases of Tb.Sp are observed in females, whereas in males the decrease of BV/TV is primarily caused by trabecular thinning, leading to a substantial decline in Tb.Th and unchanged Tb.N[61-63].

Recent studies highlight the importance of the cortical microstructure in the maintenance of the radial strength[62,64]. Cortical bone at the distal radius can be analyzed structurally with HR-pQCT method[63]. Cortical porosity significantly increased with age. Cortical porosity parameters of the distal radius provided an important decade-wise discrimination for females in their fifties and sixties[62,63,65]. Cortical vBMD is dramatically decreased in older women than in younger women[66,67]. There is no significant alteration in the cortical vBMD with age in males. As compared with younger subjects, older men and women have elevated values of Ct.Po and cortical pore diameter. Bone strength of distal radial cortex strongly correlated inversely with Ct.Po, which has a major impact on bone quality[63-65]. Age-dependent increase of Ct.Po in females is more than twice as high as in males. Cortical bones have a tendency to become thinning more with age in females than in males. Compared with males, females have lower bone strength of the distal radius. The gender difference is perhaps attributable higher cortical porosity in females.

As compared with young subjects, older women and men had significantly worse microstructure of cortical bone, including increased Ct.Po, but generally similar trabecular bone parameters of the distal radius. The main effect of age independent of BMD is on cortical morphometric parameters[62]. The spatial inhomogeneous characteristic in cortical porosity is particularly noticeable at the distal radius. The anterior region exhibits the lowest Ct.Po, while the medial region shows the highest. Ct.Po is more than twofold higher in the medial region than in the anterior region. Ct.Th is lowest in the lateral region and highest in the anterior and posterior regions. Ct.BMD is lowest in the lateral region and highest in the posterior region. Increased Ct.Po is investigated in the medial region of the distal radius, which is adjacent to the ulna[66]. Assessment of region-dependent cortical parameters is critical for evaluating therapeutic effect and for understanding osteoporosis and its related fracture. Histomorphometric changes of the cortical bone display significant deficits in cortical structure at the distal radius with age as an important base for osteoporotic fracture mechanism[54,67]. Collectively, these findings suggest that cortical porosity is a crucial element of bone strength that deteriorates with advancing age.

CONCLUSION

Osteoporosis is a skeletal disorder with a decreased bone mass and a deteriorated bone microstructure, resulting in reduced bone strength, elevated bone fragility and increased fracture risk. Bone microstructural properties can detect early alterations in bone fragility process and are an important predictor of bone strength. The changes of bone microstructure with osteoporosis in the axial and peripheral bone are complex. Cancellous and compact bone work effectively together to preserve biomechanical competence of the skeleton. Cancellous bone microstructure is crucial to preserve bone quality of the axial skeleton, while cortical bone is critically important for maintaining skeletal integrity, especially at the appendicular sites where the cortical bone is a major contributor to bone strength[64]. The bone strength of vertebra is preserved predominantly by cancellous bone. Trabecular bone mass of vertebra is much lower than that of the peripheral bone. Trabecular bone of vertebral body has a complex heterogeneous microstructure, with reduced BMD in the central and anterior superior regions. Elevated fragility of femoral neck in osteoporotic subjects is attributed to decreased cancellous bone volume and increased compact porosity. The main microstructural characteristic of cortical bone is cortical porosity, which is significantly higher at femoral neck in osteoporotic fracture patients than that of the controls[68]. Distal radius demonstrates obvious differences in cortical microstructure. The medial region of the distal radius has the highest Ct.Po compared with the lateral, anterior and posterior regions. Cortical porosity of the distal radius plays an important role in maintaining local bone quality that deteriorates with advancing age. There has been remarkable progress in our understanding of the pathophysiology of osteoporosis and its related fracture. However, greater effort is needed to elucidate precise mechanism of the bone fragility at the common sites of osteoporotic fractures.

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Orthopedic surgery and its complication in systemic lupus erythematosus

Anselm Mak

Anselm Mak, Division of Rheumatology, Department of Medicine, University Medicine Cluster, Singapore 119228, Singapore
Anselm Mak, Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 119228, Singapore
Author contributions: Mak A solely wrote this manuscript.
Correspondence to: Anselm Mak, MMedSc, MBBS, MD, FRCP Edin, Division of Rheumatology, Department of Medicine, University Medicine Cluster, 1E Kent Ridge Road, Level 10, NUHS Tower Block, Singapore 119228, Singapore. mdcam@nus.edu.sg
Telephone: +65-67-795555 Fax: +65-67-724119
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Abstract

Systemic lupus erythematosus (SLE) is a multi-systemic immune-complex mediated autoimmune condition which chiefly affects women during their prime year. While the management of the condition falls into the specialty of internal medicine, patients with SLE often present with signs and symptoms pertaining to the territory of orthopedic surgery such as tendon rupture, carpal tunnel syndrome, osteonecrosis, osteoporotic fracture and infection including septic arthritis, osteomyelitis and spondylodiscitis. While these orthopedic-related conditions are often debilitating in patients with SLE which necessitate management by orthopedic specialists, a high index of suspicion is necessary in diagnosing these conditions early because lupus patients with potentially severe orthopedic conditions such as osteomyelitis frequently present with mild symptoms and subtle signs such as low grade fever, mild hip pain and back tenderness. Additionally, even if these orthopedic conditions can be recognized, complications as a result of surgical procedures are indeed not uncommon. SLE *per se* and its various associated pharmacological treatments may pose lupus patients to certain surgical risks if they are not properly attended to and managed prior to, during and after surgery. Concerted effort of management and effective communication among orthopedic specialists and rheumatologists play an integral part in enhancing favorable outcome and reduction in postoperative complications for patients with SLE through thorough pre-operative evaluation, careful peri-operative monitoring and treatment, as well as judicious postoperative care.

Key words: Orthopedics; Complications; Surgery; Systemic lupus erythematosus; Operation

Core tip: Systemic lupus erythematosus (SLE) is a complex autoimmune condition. Orthopedic specialists often encounter patients with SLE presenting with various orthopedic conditions which require surgical intervention but due to the complexity of SLE and its associated treatment, pre-operative preparation and post-operative care for these patients are often challenging. Concerted effort of management and effective communication between orthopedic specialists and rheumatologists play an integral part in enhancing favorable outcome and reduction in postoperative complications for patients with SLE through thorough pre-operative evaluation, careful peri-operative monitoring and treatment, as well as judicious postoperative care.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an immune-

complex mediated autoimmune disease characterized by protean clinical manifestation and fluctuating disease course[1]. The exact patho-aetiology of SLE is not fully understood but is believed to be multi-factorial, with environmental, neuroendocrine, genetic, hormonal and infectious factors participating in playing a role[2]. On the molecular level, failure in clearance of apoptotic bodies which contain a wide array of genetic materials exposes lupus-susceptible individuals to the formation of autoantibodies against these genetic materials. The pathogenic autoantibodies induce inflammatory reactions through complement deposition, leucocyte ingression and tissue damage due to the consequent formation of immune complexes[3]. The reason why SLE preferentially affects young females is not fully understood although high estrogen levels and increase in CD40L expression in lymphocytes have been postulated[4]. Thus far, SLE is an incurable and unpreventable disease. Treatment largely aims at suppressing inflammation and reducing the occurrence of chronic tissue and organ damage[5]. In general, patients with major organ involvement such as diffuse proliferative glomerulonephritis, severe systemic vasculitis and neuropsychiatric involvement including myelitis will require heavier immunosuppression such as high dose glucocorticoids and cytotoxic agents. In contrast, symptomatic therapy may be the sole treatment in those who present with mild symptoms such as arthralgia, photosensitive rash and mild depression.

While rheumatologists are amongst the chief healthcare providers for patients with SLE, these patients often present with common and potentially debilitating conditions which require attention by orthopedic specialists. These conditions include tendon rupture, carpal tunnel syndrome (CTS), osteonecrosis or avascular necrosis (AVN), osteoporotic fracture and infections such as osteomyelitis, septic arthritis and spondylodiscitis. While many of these conditions require surgical treatment, SLE *per se* and its medications may predispose patients to surgical risks[6]. Currently, strong literature and guideline with respect to pre-operative evaluation and post-operative care for patients with SLE are scarce. In this short review, individual diseases which are more commonly associated with the area of orthopedic surgery will be briefly discussed, followed by discussing how patients should be assessed pre-operatively and monitored peri-operatively and managed post-operatively with an aim to reduce the chance of post-operative complications.

COMMON ORTHOPEDIC CONDITIONS IN PATIENTS WITH SLE

CTS

CTS (or median entrapment neuropathy) is common, especially amongst middle-aged women. If severe, CTS can cause disturbing symptoms such as paresthesia, pain and numbness which can lead to sleep disturbance and poor quality of life especially if they occur nocturnally[7]. In a study of 436 patients reported in the 1990s, the prevalence of CTS was found to be around 11%[8]. In severe and prolonged cases, wasting of the thenar muscles and weakness of palmar adduction would be observed and hand function may be impaired. Since most patients experience satisfactory outcome with night splints and carpal tunnel release as day surgical procedures, most patients will not require specific pre-operative assessment unless patients have bleeding tendency which may need to be corrected before the procedure.

Fragility fracture

Observational studies have unanimously demonstrated a higher risk of osteoporotic fracture in patients with SLE[9]. One of the largest observational studies found that there was a five-fold increase in fragility fracture occurrence in women with SLE when compared with the general population[10]. Bone loss in patients with SLE is a result of a number of well-established factors such as glucocorticoid use, renal dysfunction, vitamin D deficiency, immobility, inflammation and premature menopause[11]. A recent case-control study has found that by using the FRAX® risk calculation model, the 10-year major fracture risk was estimated to be increased as a result of postmenopausal state and the use of glucocorticoids[11]. In fact, other medications which patients with SLE are taking may induce bone loss, such as anti-coagulants and cyclosporin. Apart from treatment, it appears that high SLE disease activity may predispose lupus patients to fracture[11]. Hip fractures are the most serious consequences of osteoporosis due to the associated disability and high mortality. It has been estimated that the mortality rate in the first year after fracture is up to 20%-30%[12]. Osteoporotic vertebral fractures, which are clinically silent in two thirds of cases, are also common, with reported prevalence between 9% and 20%[13,14]. An important point of note is, back pain *per se* is not a manifestation of lupus and uncomplicated osteoporosis. Lupus patients with back pain must be thoroughly investigated for pathological processes such as nerve entrapment, fragility fracture, infection and metastases in the vertebra and their associated structures. To date, the gold standard to diagnose osteoporosis is dual energy X-ray absorptiometry (DXA) of the hips and spine. According to the definition by the World Health Organization, a T-score (the number of standard deviation above or below the peak bone mass of young adult of the general population) of or below -2.5 is considered to be osteoporosis[15]. However, those who have history of fragility fracture are considered to have established osteoporosis even though their T-scores do not fall into the osteoporotic range. Indeed, many patients do fracture above the osteoporotic range of T-score, suggesting that DXA and the T-score are not perfect predictors for fractures[11]. Inferior bone quality due to damage of bone micro-architecture is detrimental to bone strength and cannot be assessed by routine DXA[16]. As for the treatment of osteoporotic fracture, hip fractures are largely managed by hip replacement or arthroplasty, while vertebral fractures are chiefly conservatively managed unless the fractures lead to neurological involvement, which is rare. Medical treatment of osteo-

porosis includes the use of anti-resorptive agents such as bisphosphonates and RANKL inhibitor (Denusumab)[17], or anabolic agents including strontium ranelate and intermittent subcutaneous parathyroid hormone injection (Teriparatide)[18,19]. While the risks and benefits regarding the use of these agents are beyond the scope of discussion of this review, the benefits of regular weight-bearing exercise and adequate intake of elementary calcium and vitamin D are paramount, in terms of prevention and reduction of the severity of osteoporosis[20].

AVN

AVN or osteonecrosis is not an uncommon phenomenon in SLE patients. Amongst all rheumatic diseases, the prevalence of AVN is the highest in patients with SLE, as compared with patients with other rheumatological conditions such as autoimmune myositis, vasculitides, rheumatoid arthritis (RA) and systemic sclerosis[21]. In one of the oldest studies, 4.6% of patients with SLE were found to develop AVN[22]. One of the main factors of predisposition to AVN is the presence of anti-phospholipid antibodies (APA) and/or anti-phospholipid syndrome. In a one-year prospective magnetic resonance imaging (MRI) study of 687 joints in patients with SLE, the risk factors for the increase in the incidence of AVN in comparison to patients with other autoimmune diseases such as myositis, medium- and large-vessel vasculitides, pemphigoid, RA, scleroderma and Behcet's disease were adult and adolescent patients (OR = 13.2), high glucocorticoid dose of more than 40 mg/d of prednisolone equivalent (OR = 4.2), patients with SLE (OR = 2.6) and the male sex (OR = 1.6)[21]. Treatment of AVN depends on the stage of the disease, the severity of the involvement of AVN, pain severity and the presence of co-morbidities which may pose patients to higher risks for major operation and anesthesia[23]. Patients with stage 0 and stage 1 AVN associated with mild symptoms warrant conservative treatment with rest and reduction in weight bearing. However, a randomized controlled trial of 36 patients demonstrated superiority of treatment success with surgical approach compared with conservative therapy (70% *vs* 20%)[24]. Free vascularized grafting for AVN of the femoral head appears to be promising in lupus patients although the concern of the health of the graft which might be compromised by SLE-related vasculitis will need to be addressed by further investigation[25]. Nevertheless, the best approach to manage AVN is prevention and early recognition so as to slow down disease progression and delay the need for hip replacement[26]. Judicious use of glucocorticoids, especially in patients who are positive for APA, is an important strategy to reduce the incidence of AVN.

Infection

Osteomyelitis and spondylodiscitis: Besides osteoporotic fracture, clinicians taking care of lupus patients with back pain should always carry a high index of suspicion of osteomyelitis of the vertebra and their associated structures. Patients with SLE are more prone to bacterial infection due to a number of reasons, for example, quantitative and qualitative deficiencies of complement proteins and immunoglobulins, renal dysfunction, impaired phagocytosis and chemotaxis, and obviously, the use of immunosuppressants[27]. Threshold of suspicion of infection should even be lower if these patients experience fever, night sweating, night pain without promising relieving factors and suboptimal response to painkillers. Apart from appropriate imaging studies such as computed tomography or MRI of the spine, patients suspicious of osteomyelitis should always have complete sepsis workup including blood, urine and stool cultures because aside from common bacterial infections such as those caused by *Staphylococcus aureus*, opportunistic infections such as those due to *Salmonella* should not be overlooked. In regions where tuberculosis (TB) is prevalent, a chest radiograph and sputum smear and culture, as well as TB molecular tests should be performed.

Septic arthritis and tenosynovitis: Only 1% to 2% of patients with SLE satisfy the American College of Rheumatology criteria for classical RA and have erosive arthropathy[28]. Most patients with SLE do not present with inflammatory arthritis with effusion although up to 90% of lupus patients experience arthralgia during the course of the disease. The "swan-neck" deformities and ulnar deviation observed in lupus patients are more likely due to tenosynovitis, or Jaccoud's deformities. Thus, a high index of suspicion of septic arthritis should always be exercised in lupus patients with joint inflammation and effusion. In sexually-active patients who present with polyarthritis, tenosynovitis and dermatitis, disseminated gonococcal infection (DGI) must be considered. In these patients, blood and extra-articular cultures of urethral, cervical, rectal and pharyngeal sites for *Neisseria gonorrhoeae* with a special medium (chocolate or Thayer-Martin medium) will be helpful. Similar to vertebral infections, TB needs to be excluded in patients with tenosynovitis which is highly suspicious of an infective process[29]. For the management of non-gonococcal septic arthritis, the prompt use of intravenous antibiotics should be accompanied by drainage of the affected joint, with continuation of antibiotics for at least 6 wk. DGI responds very well to intravenous or intramuscular third-generation cephalosporin, or intramuscular spectinomycin. Open drainage for joints affected by DGI is often unnecessary[30]. Importantly, patients who are confirmed to have DGI should undergo comprehensive screening for other potentially concomitant sexually transmitted diseases such as hepatitis B, hepatitis C, chlamydial infection and HIV.

Tendon rupture

Spontaneous rupture of tendons which has been reported in patients with chronic renal failure, RA, local glucocorticoid injection and hyperparathyroidism[31], occurs rarely in patients with SLE but it can be disabling[32,33]. While no large-scale study has been performed, high dose, prolonged and pulse glucocorticoid therapies, hypercoagulability state and APA positivity tend to be

reported more frequently in lupus patients who experienced tendon rupture[34]. Most reported sites of tendon rupture are weight-bearing areas such as Achilles' tendon, patellar tendon and extensor tendons of the hands[33,34]. While tendon rupture can be diagnosed based on physical examination, a definite diagnosis can be made with MRI. Tendon biopsy is not required in most cases unless infection is suspected, since biopsy specimens may yield non-specific findings such as mononuclear infiltration and neovascularization[35]. Most of the patients require tendon transfer and full recovery is often achieved.

IMPORTANT PRE-OPERATIVE ASSESSMENT FOR PATIENTS WITH SLE

Cardiovascular condition

Data from a number of observational studies of large cohorts invariably revealed a higher prevalence of cardiovascular disease in patients with SLE when compared with the age- and gender-matched general population[36]. While traditional cardiovascular risk factors such as hypertension, hyperlipidaemia and the use of glucocorticoids are more prevalent in patients with SLE, non-traditional risk factors such as inflammation are also operant in these patients. In fact, a recent study has found that inflammation exerts its impact very early on atherosclerosis by inducing endothelial dysfunction, which is the very first step of the atherogenic process[37]. Thus, based on the higher cardiovascular risk amongst patients with lupus, pre-operative assessment of the cardiovascular system is essential. Detailed personal and family history of cardiovascular disease and its risk factors should be obtained. A thorough cardiovascular examination including blood pressure, peripheral pulses, carotid bruit, position and character of the apex beat, added heart sounds and cardiac murmur, as well as signs of cardiac failure should be noted. Investigation should include a 12-lead electrocardiogram and chest radiograph at baseline. If possible, a cardiologist should always be consulted for further investigation such as an echocardiogram, Treadmill test or even coroangiogram in any suspected cases of heart disease before surgery.

Thrombophilia and thrombocytopenia

Patients with SLE are prone to thrombosis especially if they have history of vascular thrombosis, heart failure, pulmonary hypertension, or if they are positive for APA and/or lupus anticoagulant (LAC). On the other hand, lupus patients with positive APA and/or LAC, hypersplenism, anti-platelet antibodies and blood marrow suppression due to SLE *per se* or immunosuppressant may present with severe thrombocytopenia which may complicate invasive procedures due to an excessive bleeding risk. Management of patients with thrombotic risk will be discussed in subsequent section. Patients with thrombocytopenia may need to have their platelet count corrected before emergency surgery, an exception is thrombotic thrombocytopenic purpura (TTP) or microangiopathic hemolytic anemia (MAHA) which is associated with active SLE in some cases. In these cases, thrombocytopenia is often associated with hemolytic anemia with fragmentation of red cells in combination with any of the following including fever, acute renal impairment and altered conscious level. Surgery will need to be postponed in case of TTP or MAHA unless the procedure is an important option to remove the cause of TTP or MAHA, such as severe infection or disseminated malignancy. In elective surgery, thrombocytopenia is preferred to be corrected prior to the procedures, such as the use of intravenous immunoglobulins (IVIg) in patients with autoimmune thrombocytopenia. Prior exclusion of immunoglobulin A (IgA) deficiency which is present in between 2.6% and 5.2% of patients with SLE[38,39], is beneficial before IVIg infusion in order to avoid anaphylactic transfusion reaction upon subsequent encounter of IgA protein, although no guidance has been established at the time of writing. While there is no universal cut-off value for a safe level of platelet count, a platelet count of at least 80 $\times 10^9$/L is usually advised in major operation such as hip replacement and vertebral instrumentation. Table 1 summarizes the major tests that patients may require before operation, appended with associated main points.

POSTOPERATIVE CARE IN PATIENTS WITH SLE

Deep vein thrombosis and pulmonary embolism

Due to immobilization after operation, screening for deep vein thrombosis (DVT) between day 3 and 5 after operation are routinely carried out in patients with hip and knee surgery in our centre, even in lupus patients without obvious thrombotic risk and whose APA and LAC are negative. Prophylactic low molecular weight heparin and early mobilization are beneficial in preventing DVT until sonographic absence of DVT is proven[40].

SPECIAL ISSUES ON MEDICATIONS IN PATIENTS WITH SLE

Glucocorticoids

Glucocorticoids are the main immunosuppressants in patients with SLE. However, chronic glucocorticoid administration (*e.g.,* prednisolone 5 mg or equivalent and above for more than 2 wk) suppresses adrenal function. Adrenal suppression is detrimental in patients who are exposed to surgical stress, especially during the first 48 h peri-operatively when patients would develop circulatory shock and renal shutdown if adrenal suppression is not corrected before operation. To assess adrenal function, a physician should be consulted for performing a simple short synacthan test whereby 250 μg of intravenous synthetic adrenocorticotrophic hormone is injected and after 60 min a plasma level of cortisol of at least 550 nmol/L or a rise of 200 nmol/L is expected in individuals with normal adrenal response. However, since chronic glucocorticoid administration would affect the central component of

Table 1 Pre-operative workup for patients with systemic lupus erythematosus planned for orthopaedic surgery

Workup and test	Description
Baseline kidney and liver function tests, fasting glucose and lipid profile	Anaesthetists should be alerted to abnormalities of the renal and liver functions as they may have implications on anaesthetics use. Patients need to fast for at least 8 h for fasting glucose and lipid tests. Endocrinologists should ideally be referred to assess diabetic patients in order to maintain stable glucose levels before and after operation by adjusting existing or starting new hypoglycaemic agents and/or insulin. Poor glycaemic control is associated with poor wound healing
Full blood count, peripheral blood smear (if hemolysis is suspected or proven) and clotting profile. Type and match if transfusion is contemplated or expected. Thrombophilic screen if there is history or suspicion of vascular thrombosis: Blood protein C and protein S levels, lupus anticoagulant, serum anti-cardiolipin antibodies and serum IgA level if IVIg infusion is required	Haematology or rheumatology consultation is necessary in case of anaemia, hemolysis, thrombocytopenia and evidence of thrombophilia, especially if patients have history of severe bleeding and/or vascular thrombosis, and if patients are on anti-platelet agents and/or anticoagulants
Resting 12-lead ECG	Patient should be referred for formal CVS assessment if ECG abnormalities such as ST segment changes, heart block or arrhythmia is evident
Chest radiograph	A plain chest radiograph is considered baseline pre-operative assessment in case general anaesthesia is required. In patients with SLE, a chest radiograph allows a crude assessment for pulmonary lesions such as interstitial lung disease and serositis. Assessment by pulmonologists may be required if lung pathology is suspected
Radiograph of the cervical spine (flexion and extension views)	Rarely required unless lupus patients have features of bone erosion in the peripheral joints which might heighten the chance C1-C2 disease
Treadmill test and coroangiogram	Patients with suspected or confirmed ischaemic heart disease may require these tests after assessment by cardiologists on a case-by-case basis. These tests allow diagnosis of coronary artery disease and risk stratification

CVS: Cardiovascular; ECG: Electrocardiogram; SLE: Systemic lupus erythematosus; IgA: Immunoglobulin A; IVIg: Intravenous immunoglobulins.

the hypothalamic-pituitary-adrenal axis and tests for these central components are complex, most authorities recommend empirical glucocorticoid cover pre-operatively. While no strong data are available, in our centre, patients preparing for surgery who are on chronic glucocorticoid administration will be given hydrocortisone 100 mg intravenously on call to operation theatre. Then, hydrocortisone will be given 100 mg intravenously every 8 h on the first day after operation, followed by every 12 hourly and daily on the second and third day after operation. If patient is awake and stable, oral glucocorticoids of the usual dose will be re-commenced.

Methotrexate

A few lupus patients are on methotrexate (MTX) to control lupus arthritis. While traditionally MTX would be held off several weeks before surgery, there is indeed no evidence suggesting that stopping MTX is beneficial unless patients have clinically overt postoperative wound infection[41]. While wound healing might be affected by MTX, the risk of arthritis flare which may delay postoperative rehabilitation progress outweighs the benefit of continuation of the medication.

Aspirin and warfarin

Aspirin is mainly used in patients with ischaemic heart disease and history of cerebrovascular disease. However, aspirin inhibits cyclooxygenase-1 (COX-1) and impairs platelet aggregation, rendering an excessive risk of perioperative bleeding. If there is no major contraindication, aspirin can be stopped for 5 to 7 d prior to surgery, and should be restarted 3 to 4 d postoperatively. For patients who are on warfarin due to conditions such as anti-phospholipid antibody syndrome, the medication should be held off at least 5 d prior to surgery, and replaced by low molecular weight heparin, which should be held off in the morning of surgical procedure[42]. Anticoagulation should be re-commenced as soon as patients are hemodynamically stable with minimal bleeding risk.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in patients with SLE who present with joint pain, muscle aches and pleuritis. NSAIDs also inhibit COX-1 and they have been shown to be associated with a higher risk of gastrointestinal bleeding when given peri-operatively. Thus, it is encouraged to withhold NSAIDs preoperatively for a period equivalent to five half-lives of the drugs in order to restore normal platelet function while they can be re-started 2-3 d postoperatively. COX-2 NSAIDs do not affect platelet function and hence they are safe to be given peri-operatively. However, an important point of note is, COX-2 may be associated with cardiovascular disease and shall be discouraged in lupus patients who have high cardiovascular risk such as hypertension, diabetes and hyperlipidaemia, and in those patients who are thrombophilic, or those who have a history of vascular thrombosis[43].

CONCLUSION

The link between SLE and orthopedic surgery is increas-

ingly recognized. Based on the literature, the link is largely facilitated by the use of glucocorticoids and immunosuppressants, infection, bleeding and hypercoagulability states, leading to a number of conditions such as AVN, tendon rupture, vascular thrombosis and postoperative bleeding. Heightened awareness, meticulous pre-operative assessment and judicious monitoring peri-operatively and post-operatively will likely increase the successful outcome of surgery and reduce the post-operative risk in patients with SLE.

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Vanishing bone disease (Gorham-Stout syndrome): A review of a rare entity

Vasileios S Nikolaou, Dimitrios Chytas, Demitrios Korres, Nicolas Efstathopoulos

Vasileios S Nikolaou, Dimitrios Chytas, Nicolas Efstathopoulos, 2nd Orthopaedic Department, School of Medicine, Athens University, 15124 Athens, Greece
Demitrios Korres, Orthopaedic Department, Athens University, 15124 Athens, Greece
Author contributions: Nikolaou VS and Chytas D contributed equally to this work and performed the literature research and wrote the paper; Korres D provided the pictures and the history of the case example; Efstathopoulos N did the final proof reading of the paper and made final corrections.
Correspondence to: Vasileios S Nikolaou, MD, PhD, MSc, Orthopaedic Surgeon, Lecturer in Orthopaedics, 2nd Orthopaedic Department, School of Medicine, Athens University, Dimitriou Ralli 21 Street, Maroussi, 15124 Athens, Greece. vassilios.nikolaou@gmail.com
Telephone: +30-69-32543400 Fax: +30-21-08022142
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Core tip: Vanishing bone disease (Gorham-Stout syndrome) is a rare entity of unknown etiology, characterized by destruction of osseous matrix and proliferation of vascular structures, resulting in destruction and absorption of bone. The syndrome can affect one or multiple bones of the patient, including the skull, the upper and lower extremities, the spine and pelvis. Physicians should be aware of the existence of this rare entity and reliably direct affected patients to right diagnosis and therapeutic approach.

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Abstract

Vanishing bone disease (Gorham-Stout syndrome) is a rare entity of unknown etiology, characterized by destruction of osseous matrix and proliferation of vascular structures, resulting in destruction and absorption of bone. Despite the extensive investigation of the pathogenetic mechanisms of the disease, its etiology hasn't been clarified and several theories exist. The syndrome can affect one or multiple bones of the patient, including the skull, the upper and lower extremities, the spine and pelvis. The clinical presentation of a patient suffering from vanishing bone disease includes, pain, functional impairment and swelling of the affected region, although asymptomatic cases have been reported, as well as cases in which the diagnosis was made after a pathologic fracture. In this short review we summarize the theories regarding the etiology as well as the clinical presentation, the diagnostic approach and treatment options of this rare disease.

INTRODUCTION

Vanishing bone disease is a rare entity characterized by destruction of osseous matrix and proliferation of vascular structures with benign origin[1]. Despite the extensive investigation of the pathogenetic mechanisms of the disease, its etiology hasn't been clarified. The first that described this entity was Jackson in 1838, who reported the case of a young man with a gradually vanishing humerus[2]. Moreover, in 1955, Gorham and Stout published a paper, which correlated the massive osteolysis noted in the disease with hemangiomatosis[3], that seems to have played an important role in the fact that vanishing bone disease is also called "Gorham-Stout syndrome".

This syndrome is considered as the type Ⅳ of osteolysis, according to Hardegger *et al*[4], among five types: type Ⅰ is hereditary multicentric osteolysis with dominant transmission, type Ⅱ is hereditary multicentric osteoly-

sis with recessive transmission, type Ⅲ is nonhereditary multicentric osteolysis with nephropathy and type V is Winchester syndrome, defined as a monocentric disease of autosomal recessive inheritance[4].

Despite its previously mentioned benign character, its prognosis is unpredictable[5] and the presence of several serious complications in some cases cannot be ignored. Therefore, meticulous research has been done concerning the molecular mechanisms of the disease and possible pharmacological targets are systematically investigated.

ETIOPATHOLOGY

Principally, a reference to the molecular basis of the disease has to be done. Dickson *et al*[6] in 1987 were the first that approached Gorham-Stout syndrome from a cytochemical point of view. Investigating the cytochemistry of alkaline and acid phosphatase, they suggested that mononuclear phagocytes, multinuclear osteoclasts and the vascular endothelium participate in bone resorption in this disease[6]. Furthermore, in 1996, Devlin *et al*[7] attributed this massive osteolysis to the enhanced activity of the osteoclasts, in which Interleukin-6 seems to play a critical role, since its levels in the serum of patients suffering from Gorham-Stout syndrome in early stages, were elevated. Moreover, an interesting observation of Korsić *et al*[8], in 1998, was that the disease appeared in a person with agenesis of C-cells of the thyroid gland and subsequent lack of calcitonin, an hormone with antiosteoclastic activity. On the other hand, Möller *et al*[9] in 1999 referred to the increased number of stimulated osteoclasts as a factor that is involved in the pathogenesis of vanishing bone disease, while, in 2001, Hirayama *et al*[10] concluded that the increased number of the circulating osteoclasts is the consequence of the increased sensitivity of their precursors to humoral factors that lead to osteoclast formation. Another important point about the histopathology of Gorham-Stout syndrome was noted by Colucci *et al*[11] (in 2006), who found that the cells they isolated from a patient's lesion belonged to a monocyte-macrophage lineage and could release high amounts of osteoclastogenic and angiogenic molecules. Additionally, Hagendoorn *et al*[12] (in 2006) underlined the critical role that could play the signaling pathway of the PDGFR-b (receptor of the lymphangiogenic growth factor Platelet Derived Growth Factor BB) in the pathogenetic mechanism of the disease. Besides, in 2007, Bruch-Gerharz *et al*[5] tried to shed more light onto the pathogenesis of the syndrome, writing about lymphatic vascular malformations involving the skin and the soft tissues adjacent to the diseased bone. The character of Gorham-Stout syndrome as a disease of disordered lymphangiogenesis is also highlighted by Radhakrishnan *et al*[13] (in 2008), who supported that research should focus on the investigation of lymphangiogenic pathways.

CLINICAL FEATURES

The syndrome can affect one or multiple bones of the patient, whose age has been reported to be from 1 mo[14] to 75 years old[15]. As a general rule, the persons that suffer from the disease are younger than 40-year-old[16], while an epidemiologic correlation with race, gender and geography does not seem to exist[9,17-19]. However, some authors noticed a clear "predilection" of the disease in males[20].

Gorham-Stout syndrome is met in a large spectrum of bones, but the majority of case reports refer to the maxillofacial region and the upper extremity[16]. Nevertheless, Hu *et al*[20] recently reported a case series, in which the femur was the predominant affected bone.

Radiologicaly, initial x-rays reveal changes resembling patchy osteoporosis. At a later stage bone deformity occurs with bone mass loss and concentric shrinkage in the long bones of upper and lower extremities. Eventually, near complete resorption of the bone occurs, resulting in the appearance of the so-called "vanishing bone" disease[9,21].

The clinical presentation of a patient suffering from vanishing bone disease includes, most frequently, pain, functional impairment and swelling of the affected region, although asymptomatic cases have been reported, as well as cases in which the diagnosis was made after a pathologic fracture[20]. Furthermore, the complications of the syndrome can be potentially fatal. For example, pleural effusion and chylothorax (which has been reported to be a complication of Gorham-Stout syndrome in a percentage up to 17%)[22] can dramatically influence the respiratory function. Chylothorax may occur due to the affected thoracic skeleton by the extension of lymphangiectasia into the pleural cavity or by the invasion of the thoracic duct[23]. Also, hemangiomatosous cutaneous lesions[5,24], bone infection and subsequent septic shock[24], spinal cord involvement and paraplegia due to vertebral lesion[25] and cerebrospinal fluid leakage and meningitis due to diseased bones of the skull[26] have been rarely reported.

The differential diagnosis of the disease includes hereditary multicentric osteolysis, osteolysis with nephropathy, osteomyelitis, rheumatoid arthritis[27], osteolysis due to intraosseous malignacies, hyperparathyroidism, eosinophilic granuloma and osteolysis due to diseases of central nervous system, like syringomyelia and tabes dorsalis[28].

Figures 1 and 2 shows a case example of a massive Gorham-Stout syndrome of the Pelvis in a young female, treated in our institution. Only few similar cases of pelvic appearance of the disease have been described in the literature[17,29-31].

DIAGNOSIS

The diagnosis of the syndrome is challenging, demands a high grade of clinical suspicion and is assisted by several diagnostic examinations. Initially, blood tests are not indicative of the diagnosis, as they are usually normal, with the possible exception of alkaline phosphatase, which may be slightly elevated[23]. Additionally, a diagnostic role could be played by plain radiographs[32,33], bone scan[34], Computed tomography[35] and magnetic resonance imag-

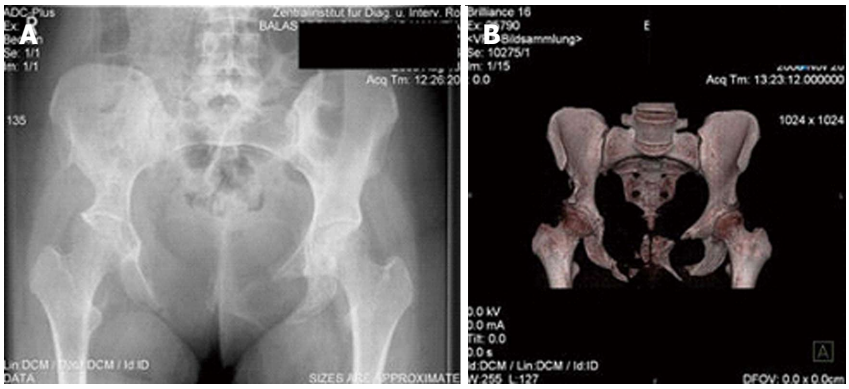

Figure 1 Case example: X-ray (A) and computed tomography scan (B), of a 26 years old female, with vanishing bone disease of the pelvis. She presented with mild groin pain without any further symptoms.

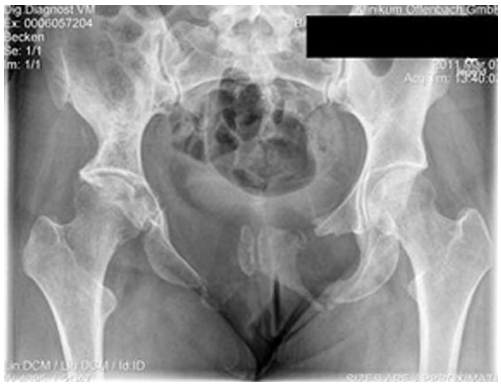

Figure 2 X-ray of the pelvis of the previous patient. Three years later she remained asymptomatic with only mild discomfort to the groin and no further symptoms.

ing (MRI)[36]. Plain X-rays, initially, show radiolucent foci in the intramedullary or subcortical regions and, later, slowly progressive atrophy, dissolution, fracture, fragmentation and disappearance of a part of a bone, with tapering or "pointing" of the remaining osseous tissue and atrophy of soft tissues[37]. On the other hand, the results from bone scan and MRI are variable[16,38].

Despite the usefulness of the previously reported diagnostic means, the disease is confirmed by the histopathological analysis of the lesions[39]; the biopsy shows nonmalignant hyperproliferation of small vessels[4,5,17]. So, Heffez *et al*[40] suggested the following 8 diagnostic criteria of Gorham-Stout syndrome: (1) positive biopsy findings in terms of angiomatous tissue presence; (2) absence of cellular atypia; (3) minimal or no osteoclastic response and absence of dystrophic calcifications; (4) evidence of local bone progressive resorption; (5) non-expansive, non-ulcerative lesion; (6) absence of visceral involvement; (7) osteolytic radiographic pattern; and (8) negative hereditary, metabolic, neoplastic, immunologic and infectious etiology[40]. Indeed, the diagnosis of vanishing bone disease should be suspected only after other causes of osteolysis, like infection, cancer, inflammatory and endocrine disorders are excluded[41].

TREATMENT

Vanishing bone disease, despite the fact that is considered as benign[42] and its natural progression is characterized by spontaneous resolution[4], has an unpredictable prognosis[5] and possible serious complications. Since its etiology remains unclear, its treatment is still an object of research, although several therapeutic options have been proposed with various results. The treatment of syndrome includes three major categories: medicine therapy, radiation and surgery[20]. In the first field, biphoshonates have been successfully used for the treatment of the syndrome, showing an antiosteolytic activity[43]. Besides, other pharmacologic agents, like vitamin D, a-2b interferon, calcium, adrenal extracts and androgens have been suggested[5,13,39,44]. However, current research about the molecular mechanisms of the disease promises encouraging results, focusing on pathways of receptors of lymphangiogenic growth factors, which may be proved useful therapeutic targets[4].

In patients with large symptomatic lesions with long-standing disabling functional instability, radiation and surgical treatment are preferred[23]. The therapeutic results from the use of radiation in moderate doses seem to be satisfactory, with few long-term complications[42]. However, radiation could provoke some serious side effects, like secondary malignancy and growth restriction in children and adolescents who receive a high-dose therapy[23]. Finally, the surgical management is performed by resection of the lesion and reconstruction by use of bone grafts and/or prostheses[16].

In the case of chylothorax, several therapeutic solutions, like chest drainage[20], thoracic duct ligation, pleurodesis, pleurectomy, radiation therapy, interferon and bleomycin have been suggested[23].

CONCLUSION

In conclusion, provided that the etiopathology of vanishing bone disease has not been fully clarified, further research is needed for more effective therapeutic interventions. Physicians should be aware of the existence of this rare entity and reliably direct affected patients to correct diagnosis and therapeutic approach.

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Adipokines: Biomarkers for osteoarthritis?

Thitiya Poonpet, Sittisak Honsawek

Thitiya Poonpet, Sittisak Honsawek, Department of Biochemistry and Orthopaedics, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Patumwan, Bangkok 10330, Thailand
Author contributions: Poonpet T and Honsawek S equally contributed to this paper.
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Correspondence to: Sittisak Honsawek, MD, PhD, Department of Biochemistry and Orthopaedics, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Rama IV road, Patumwan, Bangkok 10330, Thailand. sittisak.h@chula.ac.th
Telephone: +66-1-22564482 Fax: +66-1-22564482
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Abstract

Osteoarthritis (OA) is one of the most common degenerative joint diseases in aging population. Obesity is an important risk factor for initiation and progression of OA. It is accepted that excess body weight may lead to cartilage degeneration by increasing the mechanical forces across weight-bearing joints. However, emerging data suggest that additional metabolic factors released mainly by white adipose tissue may also be responsible for the high prevalence of OA among obese people. Adipocyte-derived molecules "adipokines" have prompt much interest in OA pathophysiological research over the past decade since they play an important role in cartilage and bone homeostasis. Therefore, the aim of this review is to summarize the current knowledge on the role of adipokines including leptin, adiponectin, visfatin and resistin in OA and their potential to be used as biomarkers for earlier diagnosis, classifying disease severity, monitoring disease progression, and testing pharmacological interventions for OA. In OA patients, leptin, visfatin and resistin showed increased production whereas adiponectin showed decreased production. Leptin and adiponectin are far more studied than visfatin and resistin. Importantly, altered adipokine levels also contribute to a wide range of diseases. Further experiments are still crucial for understanding the relationship between adipokines and OA.

Key words: Osteoarthritis; Adipokines; Biomarker; Obesity; Adipose tissue

Core tip: Osteoarthritis (OA) is one of the most common degenerative joint diseases in aging population. Obesity is an important risk factor for initiation and progression of OA. Adipokines have prompt much interest in OA pathophysiological research over the past decade since they play an important role in cartilage and bone homeostasis. Therefore, the aim of this review is to summarize the current knowledge on the role of adipokines including leptin, adiponectin, visfatin and resistin in OA and their potential to be used as biomarkers for earlier diagnosis, classifying disease severity, monitoring disease progression, and testing pharmacological interventions for OA.

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INTRODUCTION

The coexistence of obesity and osteoarthritis (OA) has increased remarkably nowadays. OA is the most common degenerative joint disease which affects more than 37% of people whose age are over 60 years[1]. Due to aging of the population, the prevalence of OA continues to

Table 1 Relationship of adipokines with osteoarthritis

Adipokines	Association with BMI	Plasma levels between genders	Plasma levels between groups	Levels in OA patients
Leptin	positive	women > men	OA > control	SF > plasma
Adiponectin	negative	women > men	control > OA	plasma > SF
Visfatin	positive	unclear	OA > control	SF > plasma
Resistin	unclear	women > men	OA > control	plasma > SF

BMI: Body mass index; OA: Osteoarthritis; SF: Synovial fluid.

increase in the near future[2]. Osteoarthritis is characterized by articular cartilage degradation, subchondral bone sclerosis, osteophyte formation, and synovial inflammation. The etiology of OA is largely complicated because it includes both genetic and non-genetic factors[3]. Obesity is considered as a worldwide health problem with low-grade inflammatory status. It has long been recognized as an important risk factor for initiation and progression of OA. Since obesity is a modifiable risk factor, it has received much interest in OA clinical study.

It is primarily accepted that excess body weight may leads to cartilage degeneration by increasing the mechanical forces across weight-bearing joints. However, several studies have revealed the association between obesity and OA in non-weight-bearing joints such as those in fingers and wrists. For example, a study reported a two-fold increase in hand OA risk in obese individuals[4]. Moreover, emerging data suggest that additional metabolic factors released mainly by white adipose tissue (WAT) may also be responsible for the high prevalence of OA among obese people[5].

In general, radiography is used to confirm the diagnosis of OA because it can reveal clinical changes at the joint margin, such as the bony outgrowth and joint space narrowing. However, these radiographic evidences are seen only after substantial cartilage loss has already taken place. To avoid severe joint pain or dysfunction, as well as total joint replacement surgery, early detection, especially in the preradiographic stage of the disease are required. Biomarkers offer a potential alternative mean for earlier diagnosis of nonsymptomatic OA. Nowadays, bone and cartilage biomarkers responsible for cartilage degradation are still frequently used in classifying disease severity, monitoring disease progression, and testing pharmacological interventions. Nevertheless, adipocyte-derived molecules "adipokines" have prompted much interest in OA pathophysiological research over the past decade due to the fact that they play an important role in cartilage and bone homeostasis. Moreover, the association of adipokines with obesity, together with its pro- or anti-inflammatory properties suggests that adipokines might be another crucial mediator that links inflammation with obesity and OA. Therefore, the aim of this review is to include the current knowledge of the role of adipokines including leptin, adiponectin, visfatin and resistin in OA and their potential to be used as biomarkers for OA.

ADIPOKINE LEVELS IN OA

The production of most adipokines is increased with obesity, except for adiponectin. Adipokine levels are gender dependent, which normally higher in women than in men even after adjusted for body mass index (BMI). This might contribute to higher prevalence of OA in females. Adipokines are produced in knee OA joints by infrapatellar fat pads (IPFPs), synovium, chondrocytes, osteoblasts, as well as osteoclasts[6,7]. It was suggested that systemic (plasma) and local (synovial fluid) adipokine levels would be related with cartilage degeneration and synovial inflammation[8]. The information regarding adipokine levels are summarized in Table 1.

Leptin

The leptin concentration in plasma was positively correlated with BMI, in both healthy controls and OA patients. Obese individuals generally display higher levels of circulating leptin than their non-obese counterparts[9,10]. Premenopausal women show about 3 times higher plasma leptin concentration than men[11]. It has been reported that higher leptin concentration in plasma was associated with higher odds ratio of having knee OA, after age, ethnicity and BMI adjustments[12]. Interestingly, synovial leptin levels were 3 to 11 times higher than those in matched plasma sample[6]. Therefore, local leptin may play more distinct roles in bone metabolism regulation than systemic leptin.

Adiponectin

Adiponectin circulates in high concentrations (0.01% of total plasma protein) in the blood exceeding those in the paired synovial fluid[7]. Plasma adiponectin levels are negatively correlated with BMI, lower in obese people and increase with weight loss[13,14]. Women have significantly higher plasma adiponectin levels than men[15]. Unlike other adipokines, plasma adiponectin levels were reported to be lower in OA patients than in healthy individuals[16]. In OA patients, adiponectin levels in plasma were almost 100 times higher than in synovial fluid, and these levels showed an inverse correlation[17]. However, Distel *et al*[18] have shown the increased adiponectin levels in the IPFPs of knee OA. It has been reported that the amount of HMW relative to total adiponectin in OA synovial fluid was lower than in OA plasma, whereas that of the hexamer was similar and that of the trimer was higher in OA synovial fluid than in OA plasma[19].

Visfatin

Visfatin levels are increased in obese individuals com-

Table 2 Effects of adipokines on osteoarthritis pathogenesis

Adipokines	Proteases	Cytokines	Inflammation	Cartilage	Bone
Leptin	↑MMP-1 ↑MMP-3 ↑MMP-9 ↑MMP-13 ↑Cysteine proteases ↑ADAMTS-4 ↑ADAMTS-5	↑IL-1β ↑IL-6 ↑IL-8 ↓FGF ↑TNF-α ↑IGF-1 ↑TGF-β ↑GRO ↑MCP-1	↑NOS2 ↑iNOS ↑PGE2 ↑COX-2	↓↑Chondrocyte proliferation ↑Proteoglycan synthesis ↑Collagen synthesis	↑Osteoblast proliferation ↑Ossification ↑ALP ↑OC
Adiponectin	↑MMP-1 ↑MMP-3 ↑MMP-9 ↑↓MMP-13 ↑TIMP-1 ↑TIMP-2	↑IL-6 ↑IL-8 ↑MCP-1 ↑VCAM-1	↑NOS2 ↑PGE2 ↑VEGF	↑Chondrocyte proliferation ↑Proteoglycan synthesis ↑Collagen synthesis ↑Matrix mineralization	↑Osteoblast proliferation ↑Osteoclast differentiation ↑RANKL ↓OPG
Visfatin	↑MMP-3, ↑MMP-13, ↑ADAMTS-4, ↑ADAMTS-5	↑IL-1β ↑IL-6 ↑TNF-α	↑NO ↑PGE2	↓Chondrocyte phenotype ↓Proteoglycan synthesis ↓Collagen synthesis	↑Osteoblast proliferation ↓Osteoclast differentiation
Resistin	↑MMP-1 ↑MMP-13 ↑ADAMTS-4	↑IL-6 ↑TNF-α	↑PGE2	↓Proteoglycan synthesis ↓Collagen synthesis	↑Osteoblast proliferation ↑Osteoclast differentiation

ADAMTS: A disintegrin and metalloproteinase with thrombospondin motifs; ALP: Alkaline phosphatase; COX-2: Cyclooxygenasse-2; FGF: Fibroblast growth factor; GRO: Growth-related oncogene; IGF-1: Insulin-like growth factor-1; IL: Interleukin; iNOS: Inducible nitric oxide synthase; MCP-1: Monocyte chemo-attractant protein-1; MMP: Metalloproteinases; NO: Nitric oxide; NOS2: Type 2 nitric oxide synthase; OC: Osteocalcin; OPG: Osteoprotegerin; PGE2: Prostaglandin E2; RANKL: Receptor activator of nuclear factor kappa-B ligand; TGF-β: Transforming growth factor-beta; TIMP: Tissue inhibitor of metalloproteinases; TNF-α: Tumor necrosis factor-alpha; VCAM-1: Vascular cell adhesion molecule-1; VEGF: Vascular endothelial growth factor.

pared with lean people[20], which can be reduced by weight loss[21]. Although very recent study reported no significant differences in plasma visfatin levels between genders, it seems to be higher in female than in male[22]. OA patients have higher circulating and local visfatin concentrations compared with controls, with levels in OA synovial fluid are greater than paired OA plasma[23]. It has been shown that OA cartilage and synovium release higher amounts of visfatin than control samples[24]. Moreover, the visfatin expression in OA IPFPs is also higher than in the matched subcutaneous adipose tissue[25].

Resistin

Plasma resistin levels were significantly higher than matched synovial levels and increased in obese individuals without direct association with BMI[26]. Resistin levels in females showed significantly higher than in males. It can be detected in inflamed synovium joints, such as rheumatoid arthritis (RA) and OA[6,27]. It was demonstrated that resistin levels in both plasma and synovial fluid were elevated after traumatic joint injuries[28]. In radiographic hand OA patients, plasma resistin levels were higher than in non-radiographic hand OA and controls[29]. Interestingly, leptin deficient (ob/ob and db/db) mouse models showed elevated levels of circulating resistin, suggesting that resistin levels are slightly dependent upon leptin levels[30].

ROLES OF ADIPOKINES IN OA

Adipokines exert both catabolic and anabolic roles in cartilage, chondrocytes, osteoblasts and osteoclasts as summarized in Table 2.

Leptin

In vivo injection of leptin into the rat knee joints shows catabolic effects in OA cartilage by increasing the production of metalloproteinases (MMPs) enzymes such as MMP-1, -3, -9 and -13, as well as cysteine proteases at both gene and protein levels[31,32]. In parallel, human OA cartilage treated with small interfering RNA (siRNA) targeted for leptin showed decreased MMP-13 expression[33]. Moreover, Bao *et al*[34] have demonstrated that the gene expression of two important aggrecanases, a disintegrin and metalloproteinase with thrombospondin motifs *(ADAMTS)-4* and *-5*, were considerably increased after treatment with leptin, whereas it decreases the anabolic factors such as basic fibroblast growth factors (FGF) production in mouse articular cartilage. These evidences suggest a prominent catabolic effect of leptin on cartilage metabolism in OA joints.

In cultured chondrocytes, OA chondrocytes produce higher leptin concentrations than normal chondrocytes. Leptin can stimulate chondrocytes to secrete higher levels of key mediators in cartilage degradation such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, IL-8, growth-related oncogene (GRO) and monocyte chemo-attractant protein-1 (MCP-1)[32,35-37]. It has been shown that leptin had proinflammatory and catabolic effects on chondrocyte proliferation. Leptin reduced proliferation of OA chondrocytes after the 48-hour treatment

and reduced chondrocyte proliferation in both control and OA after the 7-d treatment[38].

However, anabolic activities of leptin in cartilage metabolism have also been reported, suggesting that catabolic effects of leptin may trigger compensatory anabolic responses. Dumond *et al*[9] have showed that the production of insulin-like growth factor-1 (IGF-1) and transforming growth factor-β (TGF-β) can be induced by intra-articular injection of leptin. In addition, Figenschau *et al*[39] demonstrated increased chondrocyte proliferation and enhanced proteoglycans and collagen synthesis after leptin incubation. Recent studies revealed that leptin can also promote proliferation, differentiation, type X collagen production and cytoskeletal remodeling in chondrocytes[40-42]. The ob/ob mice showed reduced type X collagen synthesis in growth plates[43].

Leptin increases the proliferation and differentiation of osteoblasts by inhibiting adipogenic differentiation of bone marrow cells. It has been found that leptin acts as a regulator for bone growth by inducing collagen synthesis, osteoblast proliferation and differentiation, bone mineralization, as well as endochondral ossification[44-46]. The increased synthesis of leptin in OA subchondral osteoblasts is associated with the osteoblast dysfunction by increasing levels of alkaline phosphatase (ALP), osteocalcin (OC), collagen type Ⅰ, and TGF-β[47]. The results of immunohistological studies showed that osteophytes expressed high levels of leptin[5].

Nitric oxide (NO) is a proinflammatory mediator which promotes apoptosis, chondrocyte phenotype loss, as well as MMPs activation. The combination of leptin and interferon-γ can activate the production of type 2 nitric oxide synthase (NOS2) in cultured chondrocytes[48]. Leptin, alone or in synergy with IL-1β, has also been reported to enhance the production of inducible nitric oxide synthase (iNOS), prostaglandin E2 (PGE2) and cyclooxygenasse (COX)-2 in human OA cartilage and chondrocytes[49,50]. Surprisingly, the incidence of knee OA between leptin deficient (ob/ob) obese mice and leptin receptor deficient (db/db) obese mice was not different when compared with wild-type mice[51], suggesting that obesity alone was unable to induce knee OA and therefore leptin has a significant role in OA pathophysiology.

Adiponectin

Adiponectin seems to have both catabolic and anabolic effects on pathological changes of several tissues/cells involved in the initiation and progression of OA. Adiponectin and adiponectin receptors have been identified in human chondrocytes[6]. Adiponectin exert a proinflammatory function by stimulating NOS2, MCP-1, MMP-1, -3, -9 and-13, IL-6, IL-8, PGE2, and vascular endothelial growth factor (VEGF) production from chondrocytes and cartilage[36,52,53]. Adiponectin can induce vascular cell adhesion molecule 1 (VCAM-1) expression in murine and human chondrocytes, suggesting its role to perpetuate cartilage degradation by modulating molecules responsible for leukocyte infiltration at inflamed joints[54]. In addition, adiponectin levels in OA synovial fluid was correlated with aggrecan degradation[55].

Adiponectin enhances proliferation and mineralization of human osteoblasts[56]. The stimulation of osteoblasts with adiponectin increased the production of the inflammatory mediators IL-6, IL-8, and MCP-1. In grade 1 (non-ossified) osteophytes, adiponectin were detectable in connective tissue fibroblasts. In grade 2–5 (ossified osteophytes) a lower extent of adiponectin was expressed by osteoblasts, suggesting its involvement in early osteophyte formation[57]. By contrast, adiponectin stimulates receptor activator of nuclear factor kappa-B ligand (RANKL) and inhibits the production of osteoprotegerin (OPG) in osteoblasts, which in turn indirectly activates osteoclasts[58].

Interestingly, several studies have shown a protective effect of adiponectin in knee OA. Chen *et al*[17] demonstrated down-regulated IL-1β induced MMP-13 production and up-regulated tissue inhibitor of metalloproteinases (TIMP)-1 and -2 production in primary chondrocytes at both mRNA and protein levels. Moreover, adiponection can stimulate release of antiinflammatory molecules such as IL-10 and IL-1 receptor antagonist[59,60], suggesting the protective role against cartilage damage[17]. In addition, adiponectin has been shown to increase murine chondrocyte proliferation, aggrecan synthesis, matrix mineralization, and upregulated type Ⅱ and type X collagen expression[61].

Visfatin

Visfatin affects the expression of chondrocyte-specific genes involved in extracellular matrix (ECM) formation. For example, it was observed that visfatin plus IGF-1 reduces the production of proteoglycans and collagen type Ⅱ[62]. Similarly, visfatin-treated mouse articular chondrocytes showed increased MMP-3, MMP-13, ADAMTS-4, and ADAMTS-5 expression[24], suggesting a deleterious role of visfatin in articular cartilage. A recent study had shown that visfatin counteracted anabolic IGF-1 signaling, and therefore reduced IGF-1-mediated proteoglycan synthesis in human chondrocytes[62].

Moreover, elevated level of visfatin can reduce the expression of factors essential for the maintenance of the chondrocyte phenotype such as sex determining region Y)-box 9 (SOX-9) and type Ⅱ collagen[63]. On the other hand, visfatin has also showed some anabolic properties. It was demonstrated that the inhibition of visfatin by pharmacological or siRNA techniques decreased the production of human chondrocyte specific matrix genes such as *collagen type2 alpha1 (COL2A1)* and *aggrecan (ACAN)*[64]. Moreover, visfatin has been shown to induce the production of IL-1β, TNF-α, and IL-6 in lymphocytes[65].

It has been shown that visfatin is related to inflammation at the cartilage level by increasing MMP activity and NO production, as well as proteoglycan release in OA cartilage matrix[66]. To note, visfatin plus IL-1β stimulation is able to induce the synthesis of PGE2, a relevant

catabolic factor, in murine and human OA chondrocytes. The knockdown of visfatin expression by using a siRNA confirms this effect[24].

Visfatin could influence differentiation of mesenchymal stem cells to adipocytes or osteoblasts *in vitro*[67]. Visfatin is expressed in osteoblasts and osteoclasts in ossified osteophytes[57]. Apart from the effect of visfatin on osteoblast proliferation and collagen type I synthesis[68], it has been mentioned that visfatin also participates in osteoclast formation by inhibiting osteoclastogenesis[65], suggesting its role in osteophyte formation.

Resistin

Although the study regarding the role of resistin in OA is sparse, some studies showed its direct effect on cartilage matrix and cytokine production. In the weeks immediately after joint injury, both plasma and synovial fluid levels of resistin were elevated. Resistin increased expression of MMP-1,-13, and ADAMTS-4 in human articular chondrocytes. In addition, resistin can stimulate inflammatory cytokines, such as IL-6 and TNF-α, as well as PGE2 synthesis. Furthermore, resistin stimulates proteoglycan degradation, as well as inhibited the production of proteoglycan and type II collagen in mouse and human cartilage explants[69]. It is produced in osteoblasts and osteoclasts in ossified osteophytes. Recombinant mouse resistin stimulates osteoblast proliferation and osteoclast differentiation, indicating a role in osteophyte formation[70].

ASSOCIATIONS BETWEEN ADIPOKINES AND OA CLINICAL DATA

Leptin

In a 5-year cohort study, plasma leptin levels seemed to be positively associated with the occurrence of radiographic knee OA. Moreover, it showed a positive association with knee OA progression in subjects who have radiographic knee OA at baseline. However, the association disappeared after adjustment for BMI[71]. In addition, leptin expression has been reported to be associated with the radiographic severity of OA, suggesting a potential role of leptin as a possible biomarker for quantitative detection of OA[72]. In advanced grade OA cartilage, leptin and its long isoform receptor (Ob-Rb) levels in synovial fluid were significantly increased compared to healthy or adjacent mildly affected cartilage[38]. In addition, elevated plasma leptin levels have been detected in the end-stage knee OA patients compared with controls, independent of BMI, age and gender. On the contrary, no association was found between plasma leptin levels and cartilage damage or synovial inflammation parameters in OA patients[8]. In addition, Iwamoto's group did not find any association between plasma leptin levels and knee OA with grade 4 Kellgren-Lawrence (KL) scores, and Berry *et al*[71] found no association between baseline plasma leptin levels and 2-year alterations of cartilage volume and defects in knee OA patients.

Adiponectin

Plasma adiponectin levels were significantly increased in end-stage knee OA patients compared with healthy controls independent of age, gender and BMI[8]. Compared to less severely affected subjects, Koskinen *et al*[73] found increased plasma adiponectin levels in patients with the radiologically most severe OA, grade 4-5 Ahlback scores, compared with patients who have less severe disease. Likewise, a significant association between plasma adiponectin levels and the Lequesne index was found[74]. Filková *et al*[15] also found that plasma adiponectin levels were higher in erosive OA patients than in nonerosive OA patients. The study of Gandhi *et al*[75] showed an elevation in the adiponectin expression in IPFP from end-stage knee OA compared with that from early stage OA.

However, some clinical data support the protective roles of adiponectin as a molecule against cartilage damage in OA. Honsawek and Chayanupatkul showed an inverse correlation between plasma adiponectin and radiographic knee OA severity. They found increased adiponectin levels in grade 2 KL-scores knee OA patients compared with controls, but decreased levels in grade 4 KL-scores knee OA patients[76]. In addition, it has been reported that patients with high adiponectin levels had a decreased risk for hand OA progression[4]. However, another study showed no association between plasma adiponectin levels and radiographic hand OA severity[77]. In addition, Berry *et al*[71] did not find any association between baseline plasma adiponectin levels, cartilage volume changes and defects in knee OA subjects in a 2-year study. Interestingly, leptin/adiponectin ratio in synovial fluid was proposed to be a predictor of pain in knee OA patients. A lower leptin/adiponectin ratio correlated with lower knee OA pain when measured by the McGill Pain Questionnaire-Short Form (MPQ-SF) pain scale[78].

Visfatin

Levels of visfatin in plasma and synovial fluid appeared to be associated with lipid metabolism, inflammation and clinical disease activity. Plasma visfatin concentrations showed a positive correlation with C-reactive protein (CRP), an inflammatory marker, indicating that it may be related to lipid metabolism and inflammatory process[79,80]. Visfatin levels in synovial fluid were increased in OA patients with more radiographic damage compared with patients with less severe disease. Synovial visfatin levels in grade 4 KL-scores were significantly higher than those of grade 3 KL-scores[81].

Resistin

Gómez *et al*[49] found no association between baseline plasma resistin levels and cartilage volume loss. Plasma resistin concentrations were positively associated with the prevalence of radiographic knee OA, independently with BMI, but it was not associated with the disease progression. Interestingly, the association between resistin and the presence of radiographic knee OA was more obvious

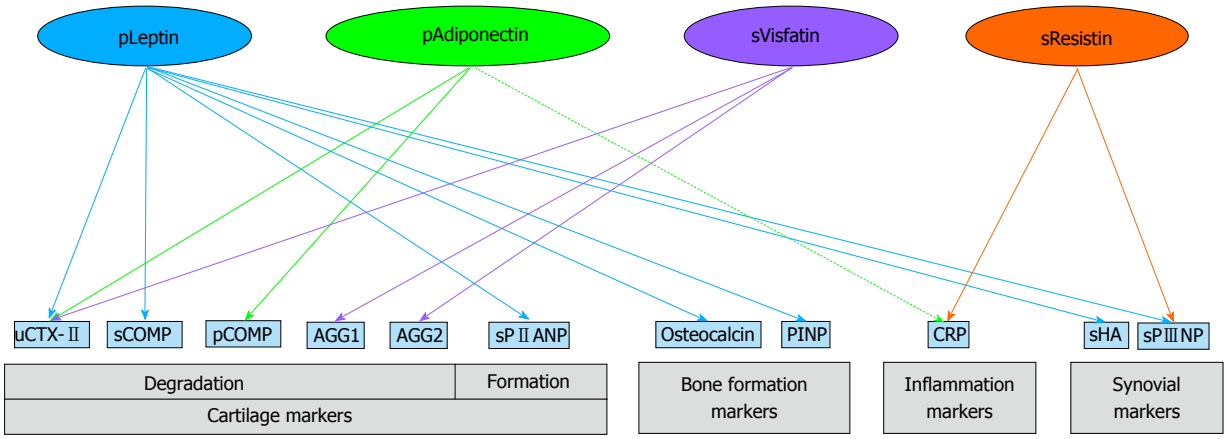

Figure 1 Association between adipokines and other osteoarthritis biomarkers. Solid lines represent positive association; dashed lines represent negative association. AGG: Aggrecan; PINP: N-terminal type Ⅰ procollagen propeptide; COMP: Cartilage oligomeric matrix protein; CRP: C-reactive protein; CTX-Ⅱ: C-terminal telopeptide of type Ⅱ collagen; HA: Hyaluronic acid; PⅡAN: N-terminal propeptide of type ⅡA procollagen; PⅢNP: N-terminal propeptide of type Ⅲ procollagen; p: Plasma; s: Synovial fluid; u: Urine.

in OA patients with higher adiponectin levels[74]. Moreover, plasma resistin levels were positively associated with histologically determined grades of synovial inflammation[27]. The presence of radiographic changes such as subchondral erosion in hand OA was shown to be related with plasma resistin levels[29].

ASSOCIATIONS BETWEEN ADIPOKINES AND OTHER OA BIOMARKERS

Leptin

Berry *et al*[71] have revealed that plasma leptin was significantly associated with the level of bone formation markers, such as osteocalcin and N-terminal type Ⅰ procollagen propeptide (PINP). In addition, leptin was positively associated with the cartilage biomarkers such as urine C-terminal telopeptide of type Ⅱ collagen (uCTX-Ⅱ), synovial cartilage oligomeric matrix protein (sCOMP), and synovial N-terminal propeptide of type ⅡA procollagen (sPⅡANP), as well as synovial markers such as synovial hyaluronic acid (sHA) and synovial N-terminal propeptide of type Ⅲ procollagen (sPⅢNP) after adjustment for gender and age. However, after additional adjustment for BMI, these associations disappeared except for sPⅡANP and sPⅢNP. In contrast, baseline expression levels of soluble leptin receptors OB-Rb were negatively associated with 2-year changes of the cartilage formation biomarkers PⅡANP and bone formation markers, osteocalcin levels.

Adiponectin

Plasma adiponectin levels showed positive associations with markers of cartilage degradation such as uCTX-Ⅱ and plasma COMP (pCOMP), but showed negative associations with plasma high sensitivity C-reactive protein (hsCRP) levels. These associations turned stronger after adjustments for BMI. In addition, Kang *et al*[53] reported increased levels of collagenase-cleaved type Ⅱ collagen neoepitope in supernatants of OA cartilage explants incubated with adiponectin.

Visfatin

Synovial visfatin concentrations also showed positive correlation with uCTX-Ⅱ, and two aggrecan degradation biomarkers: aggrecan (AGG)1 and AGG2[81]. In addition, visfatin increases the release of a marker of cartilage breakdown sulfated glycosaminoglycans (s-GAG), suggesting its involvement in cartilage matrix degradation[66].

Resistin

Plasma resistin concentrations were positively associated with sPⅢNP and hsCRP levels[74]. In addition, A positive correlation has been found between synovial resistin levels and systemic markers of inflammation[82]. Association between adipokines and other OA biomarkers are illustrated in Figure 1.

CONCLUSION

Prevention and early diagnosis are undoubtedly important for OA management. This review demonstrates that the levels of leptin, visfatin and resistin are elevated in OA patients, suggesting the catabolic role of these adipokines. In contrast, adiponectin is upregulated in OA patients and seems to play protective roles against OA. Adipokines might be also produced in other tissues and altered adipokine levels are also contributes to a wide range of obesity-related health problems such as autoimmune diseases, cardiovascular diseases and metabolic disorders. Therefore, the use of adipokines alone may not be enough for the prediction of OA risk. Nevertheless, adipokines exhibit prominent role in OA pathophysiology and show associations with OA progression. Thus it may become possible to use adipokines as biomarkers for monitoring disease progression and following the efficiency of therapeutic interventions. In addition, the ratio

of different adipokines levels or the ratio of adipokines and other biomarker levels might be used to better reflect the net effect of these molecules. Importantly, further experiments are needed to understand paradoxical relationship between adipokines and OA in both genders. However, uncertainty still remains whether adipokines could be utilized as biomarkers in clinical practice for OA.

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Psoriatic arthritis: Epidemiology, diagnosis, and treatment

Jung-Tai Liu, Horng-Ming Yeh, Shyun-Yeu Liu, Kow-Tong Chen

Jung-Tai Liu, Department of Physical Medicine and Rehabilitation, Chi-Mei Medical Center, Liouying, Tainan 736, Taiwan
Horng-Ming Yeh, Division of Rheumatology, Department of Internal Medicine, Tainan Municipal Hospital, Tainan 701, Taiwan
Shyun-Yeu Liu, Chi-Mei Medical Center, Tainan 710, Taiwan
Kow-Tong Chen, Department of Occupational Medicine, Tainan Municipal Hospital, Tainan 701, Taiwan
Kow-Tong Chen, Department of Public Health, College of Medicine, National Cheng Kung University, Tainan 701, Taiwan
Author contributions: Liu JT was contribution to conception, design, and drafting the article; Yeh HM was contribution to conception and design of this article; Liu SY was contribution to design of this article; Chen KT was contribution of conception, design, revising, supervision, and final approval of version of this article.
Correspondence to: Kow-Tong Chen, MD, PhD, Department of Occupational Medicine, Tainan Municipal Hospital, No. 670, Chongde Road, East District, Tainan 701, Taiwan. kowton@ms81.hinet.net
Telephone: +886-6-2609926 Fax: +886-6-2606351
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Abstract

Our understanding of psoriatic arthritis has evolved as new knowledge of the disease has emerged. However, the exact prevalence of psoriatic arthritis is unknown, and its pathogenesis has not been fully elucidated. Genetic, environmental, and immunologic factors have all been implicated in disease development. Early diagnosis and treatment have become primary objectives in clinical rheumatology. Psoriatic arthritis not only causes functional impairment, but also increases mortality risk of patients. The advent of new therapeutic agents capable of arresting the progression of joint damage is expected. However, early psoriatic arthritis assessment remains limited. The objectives of this article are to outline the epidemiology, diagnosis, and treatment of psoriatic arthritis and to suggest a paradigm for identifying early psoriatic arthritis patients.

Key words: Arthritis; Psoriasis; Psoriatic arthritis; Spondyloarthritis

Core tip: Psoriatic arthritis, usually seronegative for rheumatoid factor, involves the inflammation of synovial tissue, entheses, skin. Clinical manifestation of psoriatic arthritis varies and is under-diagnosed in psoriasis patients. This article presented the epidemiology, diagnosis, and treatment of psoriatic arthritis and to suggest a paradigm for use in standard clinical practice.

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INTRODUCTION

Psoriatic arthritis (PsA) is a chronic disease which involves the inflammation of synovial tissue, entheses, skin and usually seronegative for rheumatoid factor[1]. Spondyloarthritis complex includes ankylosing spondylitis, reactive arthritis, arthritis associated with inflammatory bowel disease, undifferentiated spondyloarthritis, and PsA[2,3]. PsA is belonged as one part of the spondyloarthritis complex. PsA patients have heterogeneous clinical presentations, with diverse articular and dermatological features and varied disease courses and outcomes. PsA was initially considered to be a mild disease, but in the past decade, 40%-60% of patients have developed erosive and deforming joint complications[4]. PsA-induced joint damaging complications not only lead to lower articular function and higher mortality but also affect patients' ability to work and affect their social relationships[4]. The remission of PsA symptoms has been attributed to early diagnosis and treatment in recent studies[5,6]. However, PsA is underdiagnosed in psoriasis patients, which may be due to under-recognition of PsA symptoms and a lack of effective screening tools. The aims of this article were

Table 1 The classification for psoriatic arthritis criteria[7] for diagnosing psoriatic arthritis-related inflammatory musculoskeletal disease (joint, spine or entheseal)

Evidence of psoriasis (any of three)
Current[1]: Psoriatic skin or scalp disease present, as judged by a dermatologist or rheumatologist (score of 2)
Personal history: May be obtained from the patient, family doctor, dermatologist, or rheumatologist (score of 1)
Family history: In a first- or second-degree relative, according to patient report (score of 1)
Psoriatic nail dystrophy
Typical psoriatic Nail dystrophy, including onycholysis, pitting, and hyperkeratosis, observed on current physical examination (score of 1)
Negative rheumatoid factor
By any method except latex, but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range (score of 1)
Dactylitis
Current: swelling of an entire digit (score of 1)
Personal history: recorded by a rheumatologist (score of 1)
Radiological evidence of juxta-articular new bone formation
Ill-defined ossification near the joint margins (but excluding osteophyte formation) on plain X-rays of the hand or foot (score of 1)

[1]Current: Psoriasis score of 2; others: 1. A PsA patient must have inflammatory articular disease with > 3 points from the following 5 categories.

to present the epidemiology, diagnosis, and treatment of PsA and to suggest a paradigm for use in standard clinical practice.

DATA COLLECTION

We collected all of the articles published from January 2005 through October 2013 that described patients who were affected by PsA. By searching MEDLINE (National Library of Medicine, Bethesda, Maryland, United States), we used the key words "psoriatic arthritis" and "epidemiology of psoriatic arthritis" or "diagnosis of psoriatic arthritis" or "management of psoriatic arthritis" to obtain these articles. Articles that were not published in English, manuscripts without an abstract (which were assumed to not be original), and opinion articles were excluded from the review. The relevant information was extracted from the selecting articles and classified based on the following: PsA epidemiology, PsA diagnosis, PsA management, the setting of study, and the methodology of study.

The article searches were conducted from August 2013 to September 2013. Using the search terms previously described, a total of 853 papers were collected. All selected articles were reviewed by the authors and 109 articles were considered to be relevant. The study settings mostly located in European countries, the United States, Australia and Japan. The region that produced the most original information was Europe, which accounted for 35% of the articles. After analyzing the abstracts, we found that 85% of the studies were case reports, and 10% were retrospective. Additionally, 5% referenced other designs.

EPIDEMIOLOGY

It is difficult to determine the epidemiology of PsA due to the absence of universally accepted criteria for its diagnosis. The first classification criteria for PsA were proposed by Moll *et al*[7]. However, the pattern of disease may change over time and, therefore, is not useful for classification. The classification for psoriatic arthritis (CASPAR) criteria were developed in 2006 (Table 1)[7]. The CASPAR criteria are easier to use in epidemiologic studies. The specificity and sensitivity of these criteria are 98.7% and 91.4%, respectively[7].

Table 2 Comparison of the incidence and prevalence of psoriatic arthritis among several countries

Country	Incidence (1/100000)	Ref.	Prevalence	Ref.
Asia				
China	NA		0.02%	[33]
Japan	0.1	[17]	0.001%	[32]
Europe	NA		NA	
Greece	3	[20]	0.17%	[29]
France	NA		0.19%	[23]
Italy	NA		0.42%	[25]
Germany	NA		0.29%	[24]
Finland	23.1	[18]	NA	
Sweden	8	[19]	0.02%-0.25%	[30]
Iceland	NA		0.14%	[28]
Norway	NA		0.2%	[27]
Russia	NA		0.3%	[31]
Americas				
United States	7.2	[22]	0.16%	[22]
Argentina	6.3	[92]	0.07%	[21]
Mexico	NA		0.02%	[26]

NA: Not available.

PsA usually occurs in the age of 40 to 50 years old, and the disease may occur in young children and elderly patients as well[8]. Psoriasis vulgaris is the most common type of psoriasis with PsA[9]. A few proportion (4%-5%) of PSA cases are related to guttate and pustular psoriasis[10]. One to two percent of cases involve single nail without skin involvement[11]. Male-to-female ratio is from 0.7:1 to 2.1:1[11]. Approximately 10%-37% of patients have skin and joint disease simultaneously, and 6%-18% of patients have arthritis preceding psoriasis[12,13]. Environmental factors, including infection (such as streptococcus, human immunodeficiency virus), drug use, and joint trauma (mainly in children), are known to contribute to PsA[14,15]. Emotional stress plays an important role as a trigger for both skin and joint psoriasis[15]. However, the neuroimmunoendocrine mechanisms involved in this phenomenon have not been elucidated. One population-based study suggested that pregnancy and steroid use might trigger PsA in patients with psoriasis[16].

Table 2 shows the incidence and prevalence of PsA worldwide. There is substantial variability in the incidence and prevalence of PsA by country. The incidence of PsA varies from 0.1/100000 in Japan to 23.1/100000 in Finland[17-22]. The prevalence of PsA in Europe and America varies from 0.02%-0.42%[22-30]. The prevalence in Japan is approximately at 0.001%[31]. In China, the disease prevalence is 0.02%[32]. Indians were found to have the highest prevalence of PsA among the multiethnic population in

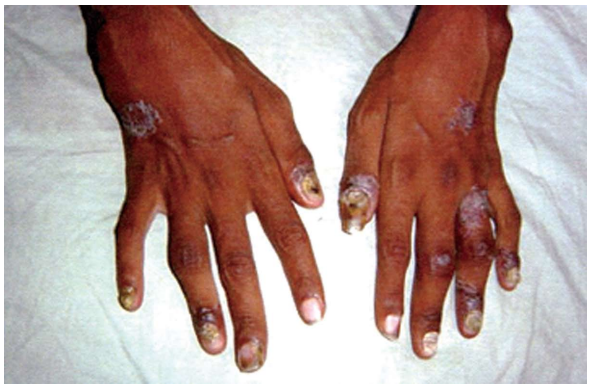

Figure 1 Peripheral hand joint involvement along with psoriatic skin lesion and nail changes. Reproduced with permission from Dhir *et al*[39].

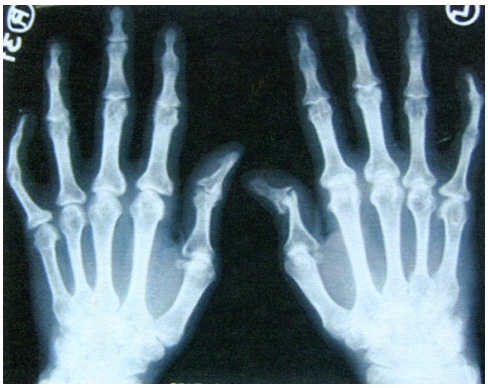

Figure 2 Ankylosis of distal interphalangeal joint on both hands, pencil in cup deformity in the first left interphalangeal joint on radiography. Reproduced with permission from Dhir *et al*[39].

Singapore[33].

Collectively, compared to Americas and Europe, Asia has lower incidence and prevalence of PsA. The reasons for the difference of PsA morbidity in different areas are unclear. However, different case definitions and clinical settings in the studies may be one of the reasons.

DIAGNOSIS

Clinical manifestations

The clinical spectrum of PsA is diverse in nature; psoriatic patients might have axial skeleton disorders, nail changes, peripheral joint inflammation, entheses, tenosynovitis, or dactylitis. Each of these conditions can be found in isolation or in combination with others. The major clinical features of the disease are spondylitis (18%-46%), inflammatory neck pain (23%-39%), thoracic inflammatory pain (13%-21%), and axial symptoms (25%-50%)[8,34]. Most of patients with axial involvement can be no clinical symptoms and maintain their spinal mobility with no reduction in spinal flexion or chest expansion for more than 10 years [34,35].

Sacroiliitis is a common symptom among PsA patients[8,11,12,34,36]. Usually, it occur unilaterally and then become bilaterally in the following years. A study conducted in an Italian patient population using bone scans to detect active sacroiliitis found that the prevalence of sacroiliitis was 32%[37]. A multicenter study from the United States found that the prevalence of sacroiliitis was 78%[38]. It was found that one-third of PsA patients developed sacroiliitis after 5 years of illness and that half of patients developed sacroiliitis by 10 years[35]. Longer period of disease may be the cause of higher prevalence of sacroiliitis. Males have a three-fold greater risk of developing sacroiliitis than females have[11]. The onset time of PsA at younger age has higher risk to hip joint disease, however, there is no significant association between occurrence of enthesitis, dactylitis, and peripheral arthritis with the occurrence of hip joint disease[36].

PsA can simulate rheumatoid arthritis to involve the knee or a large joint with some small joints in fingers or toes (Figure 1)[39]. Polyarthritis is generally symmetrical and has dactylitis and enthesitis[37,39]. Oligoarthritis can be associated with dactylitis[37]. It is also found a shortening of the fingers with pencil-in-cup deformity[40].

Dactylitis was present in 32%-48% of patients with PsA in various studies[37,40-45]. Seventy-five percent of patients have toes with dactylitis and 50% of patients have multiple digits involved simultaneously[43]. The morbidity of dactylitis increases as the duration of disease prolongs[40-45].

Twenty-five to fifty three percent of PsA patients present enthesitis[36,44]. One study in Canada demonstrated that only 15% of patients had enthesitis at the beginning of treatment, but the incidence increased to 36% as the disease progressed[44]. The Achilles tendon, plantar fascia, and greater trochanter are the most common sites affected[44,45].

From 4% to 18% of patients with PsA are found to have acute anterior uveitis[8,46,47]. Uveitis is more common in PsA patients with the spondylitis, with or without peripheral joint involvement[9]. However, uveitis is uncommonly clinical presentation in Spain and Israel. The prevalence of uveitis among PsA patients in these areas is only 1%-3%[11,41].

Imaging findings

Radiography, ultrasonography, magnetic resonance imaging (MRI), computed tomography (CT), and bone scintigraphy[48] are imaging techniques for diagnosis of PsA. In recent years, MRI and ultrasonography are increasingly used for assessment of PsA, providing additional information of the pathogenesis of the disease.

The most characteristic radiological finding indicative of PsA is bone destruction and proliferation[49]. Figure 2 shows the characteristics of radiological findings of peripheral PsA: an asymmetrical distribution, distal interphalangeal joints involvement, periostitis, bone density preservation, bone ankylosis, and pencil-in-cup deformity[39]. Axial involvement includes paravertebral ossification, syndesmophytes, interspinous or anterior ligament calcification, apophysis, sclerosis, and asymmetrical sacroiliitis[49]. Cervical intervertebral discs may be narrowed, and ankylosis may be present with atlantoaxial fusion or subluxation[50,51]. Bone erosion and condyle osteolysis

might be found in the temporomandibular joint[52].

Ultrasonography is a reliable method for investigating subclinical enthesopathy in the Achilles tendon and for confirming a diagnosis in symptomatic patients[53]. This method can be used to identify acute or degenerative tendinitis, rupture, peritendinitis, and retrocalcaneal or pre-Achilles bursitis[53]. Ultrasonography has been considered an important tool in the evaluation of PsA. Power Doppler ultrasonography is not only a useful tool to assess musculoskeletal and cutaneous involvement, but also a functional tool to monitor the efficacy of therapy and to guide steroid injections at the level of inflamed joints, tendon sheaths, and entheses[54].

MRI examination has improved our understanding of PsA by establishing that synovial inflammation is usually secondary to extrasynovial involvement, which helps to differentiate PsA from rheumatoid arthritis[55]. However, this diagnosis cannot always be precisely determined. The use of gadolinium contrast increases the odds of differentiation by calculating the relative enhancement and rate of early enhancement[55]. MRI has improved the quality of diagnosis and objective observation of the disease spectrum in PsA[55,56]. In addition, direct visualization of inflammation in the peripheral and axial joints and peripheral and axial entheses is the advantage of MRI. It may show the images among enthesitis, synovitis, and osteitis in PsA and support an spondyloarthritis (SpA) pattern of inflammation of enthuses, in which is the primary target of inflammation[56].

CT is another useful tool for diagnosis of PsA. CT plays a limited role in the diagnosis of peripheral joints, however, it may be useful in assessing spine disease[57]. The sensitivity of CT in the detection of erosions of sacroiliac joint is similar to that of MRI, but MRI is more effective in monitoring synovial inflammation. The specificity of bone scintigraphy for diagnosis of PsA has improved when supplanted with ultrasonography and MRI techniques[57].

Taken together, conventional radiography, ultrasonography, and MRI have similar diagnostic efficacy in the assessment of joint space width[48]. Radiology is less sensitive than ultrasonography and MRI in the assessment of other features of joint inflammation[48]. Radiography allows the detailed analysis of morphostructural and blood flow changes in multiple psoriasis-affected sites (skin, joints, tendons, entheses, and nails)[58]. Ultrasonography with power Doppler has shown that psoriasis patients without PsA more commonly exhibit synovitis and enthesopathy than do patients with other skin diseases. Additionally, ultrasonography has shown a significant prevalence of musculoskeletal asymptomatic involvement (3.2% synovitis and 11.6% enthesopathy)[59]. MRI is more sensitive in detecting small erosions and enthesitis[48].

TREATMENT

The basic goals of PsA treatment are helping patient to alleviate from the suffering of the disease, to preserve the joint structure, to improve patients' physical activities, and to reduce the risk of mortality. As a rule, all PsA patients must be informed of the characteristics of the disease and given psychological counseling and physiotherapy.

Corticosteroids

Mild forms of the disease may respond to nonsteroidal inflammatory agents, which are occasionally given in combination with intra-articular glucocorticoid injections[60]. Intra-articular corticosteroids may represent a therapeutic option in cases of mono- or oligoarticular joint involvement in PsA. The systemic use of corticosteroids is not recommended due to a lack of evidence regarding its efficacy and due to the risk of severe adverse events and relapse of skin psoriasis upon discontinuation[60].

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed as an initial therapy for both peripheral and axial disease[60]. For example, according to the measurement by the American College of Rheumatology Responders Index 20 (ACR20), the treatment of PsA patients with celecoxib at a dose of 200 or 400 mg over two weeks increased their rates of clinical response by 21% and 11%, respectively[61]. However, there was no difference in response between patients treated with celecoxib and untreated patients after 12 wk[61]. Treatment with NSAIDs represents an option for the short-term symptomatic treatment of PsA[60,62-64].

Conventional disease-modifying antirheumatic drugs

Disease-modifying antirheumatic drugs (DMARDs) include methotrexate, oral and parenteral gold, cyclosporine, leflunomide, azathioprine and 6-mercaptopurine, antimalarial agents, D-penicillamine, colchicines, retinoids, photochemotherapy, somatostatin, and sulfasalazine[60]. Moderate to severe forms of the disease are initially treated with the same therapy as in the mild form of the disease, but with the addition of DMARDs[61]. The efficacy of methotrexate in the treatment of PsA is controversial; although this drug is occasionally used in combination with NSAIDs, its use should be carefully monitored due to the possibility of hepatotoxicity[60,63,64]. Cyclosporine is an efficacious option for the treatment of PsA, and its results may be potentiated by combination with adalimumab. Leflunomide may be used in the treatment of PsA but should be carefully monitored due to its hepatotoxicity. Sulfasalazine can be used in PsA to afford pain relief[63,64].

Anti-tumor necrosis factor agents

Table 3 summarizes the current biological therapies for the treatment of moderate to severe psoriasis and PsA[63-65]. Adult patients who have had moderate to severe active PsA (at least three swollen and painful joints) for more than six months and those with psoriatic skin lesions or a history of psoriasis and an intolerance to NSAIDs or DMARDs over three months, whether combined or not combined with methotrexate, are the indi-

Table 3 Summary of current biologic therapies for the treatment of psoriasis and psoriatic arthritis[63-65]

Drug	Treatment
Anti-TNF	
Adalimumab	PsA: 40 mg *sc* every other week. Psoriasis: 80 mg *sc* at week 0, 40 mg *sc* every other week thereafter
Etanercept	PsA: 25 mg *sc* twice per week. Psoriasis: 50 mg *sc* twice weekly for 3 mo, 50 mg/wk thereafter
Golimumab	PsA: 50 mg *sc* every month
Infliximab	PsA and psoriasis: 5 mg/kg at week 0, 2, and 6, every 8 wk thereafter
Anti-IL-17	
Brodalumab	In clinical trials
Ixekizumab	In clinical trials
Secukinumab	In clinical trials
Anti-IL-12/IL-23	
Briakinumab	In clinical trials
Ustekinumab	Psoriasis: 45 mg (weight < 100 kg) or 90 mg (weight > 100 kg) *sc* at wk 0 and 4, followed by 45 mg or 90 mg every 12 wk
Anti-T cell activation	
Alefacept	Psoriasis: 15 mg IM weekly for 12 wk

PsA: Psoriatic arthritis; SC: Subcutaneous injection; IM: Intramuscular injection; TNF: Tumor necrosis factor; IL: Interleukin.

cations for the use of anti-tumor necrosis factor (TNF) agents (*e.g.*, infliximab, etanercept, adalimumab, and golimumab)[63,64]. Although it is difficult to quantify the occurrence of adverse effects, there are no statistically significant differences in the safety profiles among the various anti-TNF drugs using for treatment of PsA[63,64].

CONCLUSION

The incidence and prevalence of PsA vary worldwide. The incidence and prevalence of PsA in Asia are lower than in North American and European countries. Early diagnosis and treatment for PsA improve patient's outcomes. PsA is underdiagnosed among psoriasis patients. Physicians should be alert the possibility of PsA when a patient with preexisting psoriasis has arthritis. If needed, counsel a rheumatologist for help. The treatment of PsA should be considered all aspects of the disease, including clinical manifestations, mental problems, and maintenance of articular function.

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Use of demineralized bone matrix in spinal fusion

Konstantinos Tilkeridis, Panagiotis Touzopoulos, Athanasios Ververidis, Sotirios Christodoulou, Konstantinos Kazakos, Georgios I Drosos

Konstantinos Tilkeridis, Athanasios Ververidis, Sotirios Christodoulou, Konstantinos Kazakos, Georgios I Drosos, Department of Orthopaedic Surgery, Medical School, Democritus University of Thrace, University General Hospital of Alexandroupolis, 68100 Alexandroupolis, Greece
Panagiotis Touzopoulos, Department of Orthopaedic Surgery, General Hospital of Komotini, 69100 Komotini, Greece
Author contributions: Tilkeridis K, Touzopoulos P and Drosos GI contributed to conception and design of the study, acquisition, analysis and interpretation of data; Tilkeridis K, Touzopoulos P, Ververidis A and Christodoulou S contributed to drafting the article; Drosos GI, Ververidis A and Kazakos K contributed to revising the article; all the authors read and approved the final manuscript.
Correspondence to: Georgios I Drosos, MD, PhD, Assistant Professor of Orthopaedics, Department of Orthopaedic Surgery, Medical School, Democritus University of Thrace, University General Hospital of Alexandroupolis, Dragana, Farm Nea Makri, 68100 Alexandroupolis, Greece. drosos@otenet.gr
Telephone: +30-69-44380694 Fax: +30-25-51030339
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Abstract

Spinal fusion remains the gold-standard treatment for several pathological spine conditions. Although, autologous Iliac Crest Bone Grafting is considered the gold-standard graft choice to promote spinal fusion; however, it is associated with significant donor site morbidity and a limited graft quantity. Therefore, several bone graft alternatives have been developed, to augment arthrodesis. The purpose of this review is to present the results of clinical studies concerning the use of demineralized bone matrix (DBM), alone or as a composite graft, in the spinal fusion. A critical review of the English-language literature was conducted on Pubmed, using key word "demineralized bone matrix", "DBM", "spinal fusion", and "scoliosis". Results had been restricted to clinical studies. The majority of clinical trials demonstrate satisfactory fusion rates when DBM is employed as a graft extender or a graft enhancer. Limited number of prospective randomized controlled trials (4 studies), have been performed comparing DBM to autologous iliac crest bone graft in spine fusion. The majority of the clinical trials demonstrate comparable efficacy of DBM when it used as a graft extender in combination with autograft, but there is no clinical evidence to support its use as a standalone graft material. Additionally, high level of evidence studies are required, in order to optimize and clarify the indications of its use and the appropriate patient population that will benefit from DBM in spine arthrodesis.

Key words: Bone grafts; Demineralized bone matrix; Spinal fusion; Scoliosis

Core tip: It is widely accepted that autologous iliac crest bone graft (ICBG) is considered the gold-standard for spinal fusion surgery, although it is associated with a series of complications and a morbidity rate. Demineralized bone matrix (DBM) could be successfully used as a potential graft extender, enhancer or substitute. Spinal surgeons can take advance of DBMs osteoinductivity and osteoconductivity and achieve good results in spinal fusion, with a significantly lower complication rate and results similar to these of ICBG. The most significant drawbacks to DBM may be the difference between and within products so, it is important the surgeon to remain updated of the product properties to optimize the successful use of DBM, and the fact that it is not useful as a structural graft material because of its amorphous consistency, so it has to be used in combination with other type of grafts or scaffolds increasing the cost.

Original sources: Tilkeridis K, Touzopoulos P, Ververidis A, Christodoulou S, Kazakos K, Drosos GI. Use of demineralized bone matrix in spinal fusion. *World J Orthop* 2014; 5(1): 30-37 Available from: URL: http://www.wjgnet.com/2218-5836/full/v5/i1/30.htm DOI: http://dx.doi.org/10.5312/wjo.v5.i1.30

INTRODUCTION

Spinal fusion remains the gold-standard treatment for several pathological spine conditions, such as; spine trauma, tumors, degenerative disorders, and discogenic back pain. It is estimated that the number of spinal fusions performed in the United States, could be greater than 200000 per annum, with the majority of these being lumbar fusions[1,2]. Although spinal fusion is a widely accepted successful procedure, offering acceptable clinical results, pseudarthrosis following spine surgery remains a major clinical challenge. Rates of pseudarthrosis have been reported to be as high as 48% in posterolateral inter-transverse process lumbar fusions[3], with an increasing risk in multi-level fusions.

The high rate of non-union necessitates the use of various bone graft materials and substitutes, ceramics, and augmentation with growth factors such as bone morphogenetic protein-2 (BMP-2). It is widely accepted that autologous iliac crest bone graft (ICBG) is considered the gold-standard for spinal fusion surgery[4-7].

ICBG demonstrates a reliably high fusion rate, and additionally, being autologous, does not carry the risk of rejection or disease transmission[8].

However, harvesting bone from the iliac crest is associated with a series of complications and a morbidity rate[9], that have made spine surgeons to employ alternatives to ICBG such as bone graft substitutes or extenders[10-20]. Ideally these bone graft substitutes or extenders should have both osteoinductive and osteoconductive characteristics, in order to promote comparable fusion rates to autologous bone graft.

Demineralized bone matrix (DBM) is bone that has been acid treated to have the mineralized portion removed while maintaining the organic matrix and growth factors. Approximately 93% of DBM consists of collagen, whereas only 5% consists of other growth factors, a fraction of which are BMPs. It is weakly osteoconductive because the organic portions of bone, such as collagen, remain. The small quantity of BMPs provides osteoinductive capabilities[21-26] as well, but has no osteogenic capacity because of its processing. Osteoinductivity may be variable within a single manufacturer's product and between manufacturers, because the osteoinductive capacity of DBM can be affected by storage, demineralization process, washing procedure, sterilization method and the source of the bone, which depends on the individual donor and the site of harvest[27-33]. DBM has no immunological rejection as the antigenic surface structure of the bone is destroyed during demineralization by acid[34], but, in the other hand, various studies have shown that any allograft bone can induce host immune responses[35-38] despite its processing. Unfortunately, there are no studies, referred whether available DBM products could differ in immunogenicity issues, or whether immunogenicity issues would influence the osteoconductive and osteoinductive potentials of DBM.

Since DBM was found to be effective and safe as an option of bone grafting, it has been used to induce bone formation in various clinical applications.

The purpose of this review is to present the results of clinical studies concerning the use of DBM, alone or as a composite graft, in the spinal fusion, and the Grades of Recommendation[39] of use of DBM in different situations, like cervical fusion, lumbar fusion and at the treatment of scoliosis.

LITERATURE RESEARCH

A critical review of the English-language literature was conducted on MEDLINE using Pubmed. Various combinations of search key and MeSH terms including "demineralized bone matrix", "DBM", "spinal fusion", "scoliosis" and "cervical spine fusion" were employed to generate a broad literature base. The two senior authors K.T and D.G conducted the search independently, and there were not any discrepancies in their findings. Results had been restricted to clinical studies in English language. Abstracts, supplements, editorials, correspondence, book reviews, and articles on aspects of DBM unrelated to efficacy and outcome were excluded. Clinical studies of use of DBM in non-spinal surgery were excluded as well. Papers that were included were full-length original research articles in peer-reviewed journals that investigated fusion efficacy. The Grades of Recommendation and the levels of evidences (LOEs) are presented. The Oxford centre for evidence based medicine classification is used in order to classify LOEs of individual studies[40]. Clinical studies, authors, and their main outcomes presented in Table 1, and described by category of use.

Requirements of extensive bone grafting in spinal fusion and the subsequent morbidity of the donor site, are making iliac crest not the most accessible option for graft harvesting. This fact leads the spinal surgeons to employ different type of bone graft substitutes in order to cover their needs.

DBM has, performed successfully in long bones operative procedures requiring bone grafts, such as repairing segmental defects[41-44]. However, there are limited clinical data to support the efficacy of any DBMs in spinal arthrodesis.

The literature has supported the use of DBM as a potential graft extender, enhancer or substitute, but there was no clinical evidence to support its use as a standalone graft material. On top of that there are studies that demonstrate, that in younger and healthier patients, use of DBM may be unnecessary, since harvesting autograft from local sources, like laminae and spinous processes after destruction of facet joints and decortication, shows excellent results and a fusion rate of 94% without implant failure, infection or loss of correction[45]. It seems that spinal surgeons can take advance of DBMs osteoinductivity and osteoconductivity and achieve good results in spinal fusion but unfortunately, it is not useful as a structural graft material because of its amorphous consistency which is a draw back, since in has to be used in combination with other type of grafts or scaffolds which

Table 1 Clinical studies of demineralized bone matrix used in spinal fusion

Ref.	Study design	Diagnosis/procedures	Type of graft	Main outcomes	Level of evidence
Cervical spine					
An *et al*[48]	2-Center randomized prospective control trial	Patients undergone anterior cervical fusion for degenerative disc disease, *n* = 77	Freeze-dried allograft augmented with DBM (Grafton®), *n* = 39. Iliac Crest Autograft, *n* = 38	Pseudarthrosis rate was 46.2% in DBM-allograft Group *vs* 26.3% in autograft group, but with no significant differences. Graft collapse ⩾ 2 mm occurred in 39.7% in DBM-allograft group than 24.4% in autograft group (*P* = 0.09)	Ⅱ
Vaidya *et al*[49]	Retrospective comparative study	Patients treated with anterior cervical discectomy and fusion, *n* = 46	PEEK cages + morphogenetic protein-2 (rhBMP-2), *n* = 22 Allograft spacers + DBM, *n* = 24	No significant difference in pain scores between groups. Probable fusion at latest follow up in 23/24 of DBM group *vs* 22/22 in rhBMP-2 group. 85% of rhBMP-2 and 56% of DBM reported difficulty in swallowing. The cost of implants in patients treated with rhBMP-2 and PEEK spacers was more than three times the cost of the other group	Ⅲ
Park *et al*[52]	Prospective, case series study	Patients undergoing anterior cervical discectomy and fusion	PEEK cages and DBM (Grafton®), *n* = 31	97% fusion rate (41/42 levels), neck and arm pain improved after surgery and significanly improved in 12/12 follow-up, *P* < 0.05	Ⅳ
Topuz *et al*[50]	Retrospective, case series study	Patients underwent 2-level contiguousanterior cervical discectomy and fusion	PEEK cages and DBM (Grafton®) and autologous blood, *n* = 79	87.3% "excellent" and "good" clinical outcomes, final fusion rate 91.7% (145/158 levels)	Ⅳ
Moon *et al*[51]	Retrospective case series	Patients undergone 2-level, non-instrumented cervical fusion for degenerative disk disease, *n* = 27 (54 levels)	PEEK cages and DBM	Fusion rate was 88.9% of levels. All patients showed improvements in clinical outcomes (VAS score, neurologic pain and JOA myelopathy score)	Ⅳ
Demircan *et al*[53]	Prospective case series	Patients undergone non-instrumented anterior cervical fusion for degenerative disk disease, *n* = 16 (42 levels)	Polyetheretherketone cages packed with autologous blood, curettage microchip material, and DBM (Grafton®)	Fusion rate was 90.5% of levels, at 18 mo after surgery with improved clinical outcomes using JOA score (*P* = 0.004)	Ⅳ
Lumbar spine					
Kang *et al*[54]	Prospective multicenter randomized clinical trail	Patients undergoing single-level posterior lumbar fusion	DBM (Grafton®) + local bone, *n* = 30. Autologous iliac crest bone graft, *n* = 16	Fusion rates were 86% (Grafton®) *vs* 92% (autologous graft). Grafton showed consistently higher physical function scores at 24 mo. There was a greater mean intraoperative blood loss in the autologous group.	Ⅰ
Cammisa *et al*[3]	Prospective multicenter control trial	Patients undergone posterolateral lumbar, instrumented fusion, *n* = 120	Iliac Crest Autograft on one side DBM (Grafton®) + Iliac crest autograft on contralateral side of same patient	Radiographic fusion rates at 24 mo after surgery in Grafton DBM side was 52% and in Iliac Crest Bone Autograft side was 54%	Ⅱ
Vaccaro *et al*[55]	Prospective, comparative study	Patients undergone instrumented posterolateral lumbosacral spinal fusion	DBM (Grafton®) + Bone Marrow, *n* = 19, DBM + Iliac crest autograft, *n* = 27 Autograft, *n* = 27	Fusion rates were 63% with DBM + Bone Marrow, 70% DBM + autograft and 67% with autograft	Ⅲ
Sassard *et al*[56]	Retrospective comparative study	Instrumented posterolateral lumbar spinal fusion with rigid pedicle screw fixation (*n* = 108)	Iliac crest bone graft (*n* = 52). Local autograft-Grafton® (*n* = 56)	Fusion rates at 24 mo after surgery: In Iliac crest bone graft group: 56% and in local autograft-Grafton group: 60%	Ⅲ

Schizas *et al*[57]	Retrospective case control study	Patients undergone posterolateral, one or two-level, instrumented, lumbar fusion, *n* = 59 (78 levels)	DBM (Accell Connexus® putty) with Iliac crest autograft or local decompression material, *n* = 33 Iliac crest autograft or local decompression material, *n* = 26	Fusion rate was 69.7% with DBM *vs* 76.9% without DBM. There were no differences in complication rates, ODI or VAS pain score	Ⅲ
Epstein *et al*[58]	Prospective, clinical study	Patients undergone multilevel lumbar laminectomies, 1-level (*n* = 95) and 2-levels (*n* = 45)	Lamina autograft + DBM (Osteofil), *n* = 140	1-level fusion rates: 98%, 2-levels fusion rates: 96%. Revealed essentially comparable outcomes on 6 of 8 Health Scales of SF-36	Ⅳ
Thalgott *et al*[61]	Prospective case series study	Patients undergone lumbar interbody fusion (*n* = 50)	Titanium mesh cages filled with coralline hydroxyapatite (ProOsteon™ 500R) and DBM (Grafton®)	96% fusion rate, decrease in mean pain scores by 60% from baseline	Ⅳ
Girardi *et al*[60]	Retrospective case series study	Instrumented lumbar spinal fusion for various diagnoses (*n* = 65)	Combination of autologous bone graft and allograft DBM (AlloMatrix® Injectable Putty)	Gradual and constant improvement based on radiographic measurements taken 1, 3, 6 and 12 mo after surgery	Ⅳ
Thalgott *et al*[62]	Retrospective case series	Patients undergone instrumented posterolateral lumbar fusion, *n* = 40	Coralline hydroxyapatite (Pro Osteon™ 500) + DBM (Grafton®), *n* = 28 Pro Osteon™ 500 alone, *n* = 12.	Radiographic fusion rates was 100% with coralline hydroxyapatite alone, than 89.3% with Grafton added.	Ⅳ
Epstein[59]	Prospective case series	Geriatric patients undergone posterolateral non-instrumented lumbar fusion, *n* = 75	Lamina autograft mixed with DBM (Osteofil) in 1:1 ratio	Fusion rate was 82.7% of levels. Improved clinical outcomes using SF-36 score.	Ⅳ
Idiopathic scoliosis					
Weinzapfel *et al*[63]	Retrospective comparative study	Anterior thoracic discectomies with video Assisted thoracoscopic surgery in idiopathic scoliosis	Morselized allograft bone, *n* = 12. DBM (Grafton®), *n* = 28	Curve correction was similar for both groups (68% *vs* 67%). Radiological fusion fusion: 82% in allograft group *vs* 92% in DBM group	Ⅲ

DBM: Demineralized bone matrix; PEEK: Polyetheretherketone; JOA: Japanese-orthopaedic-association; BMP: Bone morphogenetic protein; ODI: Oswestry disability index; VAS: Visual analogue scale.

increases the cost.

The most significant drawback to DBM may be the difference between and within products. The osteoinductive potential of DBM may be variable within a single manufacturer's product and among manufacturers, because the osteoinductive capacity of DBM can be affected by storage, demineralization process, washing procedure, sterilization method and the source of the bone, which depends on the individual donor and the site of harvest and affects the quantity and type of BMPs preserved. There are numerous DBM composites in many forms, from gels, pastes, putties, and sheets available currently for clinical use.

Bae *et al*[27] have pointed out that the variability of BMP concentrations among different lots of the same DBM formulation was higher than the inter-product variability or concentrations of BMP among different DBM formulations.

Another important factor that could influence efficacy of DBMs is the choice of the carrier. As opposed to the neutral pH of hyaluronic acid (DBX) carriers, negative effects have been observed in relation to the use of glycerol carriers (Grafton), which generate a highly acidic environment for host tissues, especially when used in large quantities at the fusion site[46]. Moreover, the amount of DBM applied does not necessarily correlate with outcomes and efficacy as demineralization process, and sterilization method can also affect osteoinductivity, as mentioned before[21,47]. It is important the surgeon to remain updated of the product properties to optimize the successful use of DBM.

DBM USED IN CERVICAL FUSION

There are a few clinical trials in literature, which evaluated the use of DBM in fusion in cervical spine. In one of the first reports, An *et al*[48] in a two-center prospective randomized controlled clinical trial (Level 2), found that freeze-dried allograft with DBM (Grafton®) mixed, shown higher nonunion and graft collapse rates than iliac crest autograft. Thirty-nine patients undergoing anterior cervical fusion for degenerative disc disease had randomly selected to take freeze-dried allograft augmented with DBM (Grafton®), while 38 patients took autologous ICBG. Pseudarthrosis developed in 33.3% of levels (46.2% of patients) in the allograft-DBM group, than

22% of levels (26.3% of patients) in autograft group, but with no significant difference between groups ($P = 0.23$). In addition, graft collapse > 2 mm occurred in 39.7% of the allograft-DBM group compared with 24.4% of the autograft group ($P = 0.09$). Authors suggested the use of autograft in cervical fusion for better outcomes.

In a level 3 study, Vaidya *et al*[49], evaluated the use of polyetheretherketone (PEEK) cages and morphogenetic protein-2 (rhBMP-2) against allograft spacers and DBM, in patients treated with anterior cervical discectomy and fusion. There were no significant differences in pain scores between groups. Probable fusion occurred in 23 of 24 patients of DBM group *vs* 22 of 22 patients in rhBMP-2 group. 85% of patients in rhBMP-2 group and 56% of patients in DBM group reported difficulty in swallowing. The cost of implants in patients treated with rhBMP-2 and PEEK spacers was more than three times the cost of the other group. Authors concluded that despite providing good fusion rates, they have abandoned using rhBMP-2 and PEEK cages for anterior cervical fusion, due to the side effects, high cost, and the availability of a suitable alternative.

There are also 4 series of patients in literature, which studied the use of PEEK cages and DBM (Grafton®) in patients treated with cervical discectomy and fusion. Topuz *et al*[50] used PEEK cages packed with Grafton® DBM and autologous blood in 79 patients, who underwent 2-levels contiguous anterior cervical discectomy and fusion. Authors found "excellent" and "good" clinical results in 87.3% of patients, while final fusion had occurred in 145 of 158 levels (91.7%). In a same case series study, Moon *et al*[51] used PEEK cages packed with DBM, and found that fusion rate was 88.9% of levels. All patients had clinical improvement using visual analogue scale (VAS) score, neurological pain and Japanese-orthopaedic-association (JOA) myelopathy score. Park *et al*[52] also found high fusion rate, up to 97% using same methods in a prospective case series study. Similar main outcomes, found Demircan *et al*[53] in a case series of patients undergone non-instrumented anterior cervical fusion for degenerative disc disease. Authors used PEEK cages packed with Grafton®, autologous blood and curettage microchip material. Fusion rate was 90.5% with patients had improved clinical outcomes using JOA score ($P = 0.004$).

USE OF DBM IN LUMBAR FUSION

Despite the few published clinical trials about the use of DBM in cervical fusion, there are a few more about lumbar fusion. There are two level 1 and 2, three level 3 and five level 4 available clinical trials, since the preparation of this manuscript.

In a prospective multicenter randomized controlled clinical trial, Kang *et al*[54] reported the efficacy of a commercial DBM graft (Grafton®) compared with iliac crest autograft in patients undergone single-level posterior lumbar fusion. In this study 46 patients were randomly assigned to receive Grafton DBM Matrix with local bone (30 patients) or autologous ICBG (16 patients). Fifty-one patients completed the 2-year follow-up. Fusion rates were 86% for Grafton group than 92% for autologous group. Grafton showed consistently higher physical function scores at 24 mo, but this was not significant. There was a significant greater mean intraoperative blood loss in the autologous group ($P = 0.0031$). Authors concluded that fusion rate and improvement in clinical outcomes of use of Grafton in lumbar fusion were comparable with those in iliac crest autograft group.

Cammisa *et al*[3] investigated whether Grafton® might be able to serve the function of an autograft extender, in 120 patients undergone posterolateral instrumented lumbar fusion. In this level 2 study, Iliac crest autograft was implanted on one side of the spine and a Grafton® DBM and autograft composite was implanted on the contralateral side in the same patient. After 24-mo follow-up, Radiographic fusion rates in Grafton DBM side was 52% and in Iliac Crest Bone Autograft side was 54%, while overall percentage agreement for fusion status between sides was approximately 75% ($P < 0.001$). These results suggested that Grafton DBM gel in combination with autologous bone can provide a similar rate of successful fusion as autograft alone.

In a prospective series, Vaccaro *et al*[55] evaluated patients undergone instrumented posterolateral lumbosacral spinal fusion. Nineteen patients had supplemental bone grafting with DBM putty (Grafton®; Osteotech, Eatontown, NJ) enriched with aspirated bone marrow, 27 patients DBM putty combined with iliac crest autograft, and 27 patients had autograft. Fusion rate at 24 mo after surgery were 63% of levels in DBM and bone marrow group, 70% of levels in DBM and iliac crest group and 67% in ICBG group. Findings suggest that both DBM composites offer similar performance to autograft in posterolateral spinal fusion.

Sassard *et al*[56], in a level 3 clinical trial, examined the fusion rates of a local autograft-Grafton® construct against that of iliac crest autograft alone in one hundred and eight patients undergone instrumented posterolateral lumbar spinal fusion. Fusion rates were found not to vary between the two groups, with 60% in local autograft-DBM group and 56% in iliac crest autograft group. These findings prompted further evaluation of whether Grafton® might be able to serve as graft extender.

Schizas *et al*[57] found that DBM was useful as a graft extender for both local bone and ICBG. They compared 33 patients who had local bone or ICBG augmented with DBM with 26 patients who received ICBG or local bone alone, for posterolateral, one or two-level, instrumented, lumbar fusion. The groups were equivalent in radiographic fusion and clinical outcomes. Fusion rates were 69.7% with DBM augmented *vs* 76.9% without DBM. There were no differences in complication rates, oswestry disability index or VAS pain score.

There are also case series available in literature, which concluded that DBM is a useful graft extender for spinal fusions, when mixed with lamina autograft, or iliac crest autograft. Epstein *et al*[58] reported high fusion rates

(1-level fusion rate: 98%, 2-levels fusion rate: 96%) in 140 patients undergone multilevel lumbar laminectomies and had lamina autograft augmented with DBM (Osteofil) as a graft for fusion. Radiographic followed by clinical outcomes. Same authors, reported similar results in geriatric patients undergone posterolateral non-instrumented lumbar fusion, with fusion rate up to 82.7% of levels and improved clinical outcomes, using SF-36 surveys[59]. Girardi *et al*[60], in a series of 65 patients who undergone instrumented spinal fusion for various diagnoses, reported a gradual and constant improvement based on radiographic measurements taken 1, 3, 6, and 12 mo after surgery. Patients had combination of autologous bone graft and DBM (AlloMatrix® Injectable Putty).

Thalgott *et al*[61] retrospectively reviewed the radiographic and clinical results of 50 patients who had received titanium mesh cages filled with coralline hydroxyapatite (ProOsteon™ 500R) and DBM Grafton® preparation for anterior lumbar interbody fusion. The authors reported a 96% fusion rate, alongside with a decrease in mean pain scores by 60% from baseline. In the other hand, there are conflicting results on the efficacy of DBM as a graft extender by the same authors, who found a higher rate of pseudarthrosis (10.7% *vs* 0%) with the use of Grafton® gel and coralline hydroxyapatite (Pro Osteon™ 500R) as compared with coralline hydroxyapatite alone in a retrospective study of 40 patients who underwent instrumented posterolateral lumbar spinal fusion[62].

DBM USED FOR TREATMENT OF SCOLIOSIS

Because of the extensive fusion requirements for correction of scoliosis, DBM can be an available alternative to iliac crest. Weinzapfel *et al*[63] compared retrospectively the fusion rates between allograft bone and Grafton DBM Flex in video-assisted thoracoscopic surgery for idiopathic scoliosis. Forty patients with 1 year or more follow-up were evaluated-12 with morselized allograft bone and 28 with folded Grafton DBM Flex. Percent curve correction from before surgery to the most recent follow-up was very similar in both groups (68% in Allograft and 67% in DBM group). Sixty of 73 disc spaces (82%) in the Allograft group and 100 of 109 disc spaces (92%) in the DBM group were rated as radiographically fused.

CONCLUSION

This review demonstrates that DBM shows similar fusion rates with autologous bone graft in lumbar spine fusion, when used as a graft extender either with local autologous bone of ICBG. In addition in the only one level I study that was included in this review DBM group showed consistently higher physical function scores at 24 mo and there was a greater mean intraoperative blood loss in the autologous group.

Regarding use of DBM in cervical spine fusion, it is clear that when used as an extender with autologous bone graft in PEEK cages, shows good results, although in a level two study where Freeze-dried allograft augmented with DBM compared with ICBG, the autograft group showed superior non-union rates (Pseudarthrosis rate was 46.2% in DBM-allograft Group *vs* 26.3% in autograft group).

For correction of scoliosis due to the extensive fusion requirements DBM shows to be a reliable alternative to autograft, especially comparing with the use of other types of allografts.

Concluding, the majority of the clinical trials demonstrate comparable efficacy of DBM when it used as a graft extender in combination with autograft, but there is no clinical evidence to support its use as a standalone graft material. Additionally, studies of high methodological quality are required, in order to optimize and clarify the indications of its use and the appropriate patient population that will benefit from DBM in spine arthrodesis.

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Research in spinal surgery: Evaluation and practice of evidence-based medicine

Mark E Oppenlander, Christopher M Maulucci, George M Ghobrial, James S Harrop

Mark E Oppenlander, Christopher M Maulucci, George M Ghobrial, James S Harrop, Department of Neurological Surgery, Thomas Jefferson University Hospital, Philadelphia, PA 19107, United States
Mark E Oppenlander, Division of Neurological Surgery, Barrow Neurological Institute, St. Joseph Hospital and Medical Center, Phoenix, AZ 85003, United States
Author contributions: Oppenlander ME designed the research, contributed to data review, drafted the paper; Maulucci CM and Ghobrial GM contributed to data review and drafting of paper; Harrop JS was the consultant supervisor, contributed to review and approval of paper.
Correspondence to: James S Harrop, MD, Professor of Neurological Surgery, Department of Neurological Surgery, Thomas Jefferson University, 909 Walnut Street Second Floor, Philadelphia, PA 19107, United States. james.harrop@jefferson.edu
Telephone: +1-215-9557959 Fax: +1-215-5037007
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Abstract

Evidence-based medicine (EBM) is a common concept among medical practitioners, yet unique challenges arise when EBM is applied to spinal surgery. Due to the relative rarity of certain spinal disorders, and a lack of management equipoise, randomized controlled trials may be difficult to execute. Despite this, responsibility rests with spinal surgeons to design high quality studies in order to justify certain treatment modalities. The authors therefore review the tenets of implementing evidence-based research, through the lens of spinal disorders. The process of EBM begins with asking the correct question. An appropriate study is then designed based on the research question. Understanding study designs allows the spinal surgeon to assess the level of evidence provided. Validated outcome measurements allow clinicians to communicate the success of treatment strategies, and will increase the quality of a given study design. Importantly, one must recognize that the randomized controlled trial is not always the optimal study design for a given research question. Rather, prospective observational cohort studies may be more appropriate in certain circumstances, and would provide superior generalizability. Despite the challenges involved with EBM, it is the future of medicine. These issues surrounding EBM are important for spinal surgeons, as well as health policy makers and editorial boards, to have familiarity.

Key words: Evidence-based medicine; Spinal surgery; Trial design; Research; Methodology

Core tip: This paper highlights the intricacies of spinal research. The difficulties of conducting high quality research in spinal surgery are discussed, but the tools for success are outlined. Specifically, the tenets of implementing evidence-based research are provided, along with a discussion of validated outcome measures which will increase the quality of a given study design. Importantly, the randomized controlled trial should not always be considered the best study design for a given research question, and observational cohort studies may be more appropriate in certain circumstances. Ultimately, spinal surgeons are responsible for evidence-based research to justify treatment paradigms.

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INTRODUCTION

The concept of evidence-based medicine (EBM) assumes

that current medical research, along with individual clinician judgment, can optimally guide clinical decision making to result in the best possible patient outcomes[1,2]. While EBM requires the use of best available evidence, multiple challenges may arise in its practical application to spinal surgery. For instance, rare disorders result in small patient numbers and subsequent lower quality data. At the other extreme, randomized controlled trials (RCTs) attempt to generate high quality evidence, yet are hindered by expense and difficulties in study recruitment and conduct.

Despite the challenges involved with EBM, it is the future of medicine[3,4]. If spine surgeons do not want poor-quality studies to dictate and limit their clinical decisions, then responsibility rests with this group of practitioners to design high quality studies to justify certain treatment modalities.

This review therefore highlights the tenets of implementing evidence-based research, through the lens of spinal disorders. Techniques of conducting and evaluating EBM are first discussed, followed by a review of pertinent outcome measures in spinal surgery. It is the authors' goal that these basic tools will provide a basis of EBM for the practicing spinal surgeon.

TECHNIQUES OF EBM

Asking the correct question

Before a study is designed, a research question must be asked. The importance of the research question lies in the fact that it dictates a study's design. Often, the RCT is considered the gold standard of evidence-based medicine, yet the research question may exclude the RCT from feasibility or utility. For example, a question of superiority in treatment protocols, where each treatment has equipoise for the surgeon and patient, is suitable for a RCT. However, a question may best be answered with a prospective cohort design if there are subjective treatment preferences among surgeons, the presence of significant selection biases, or poor generalizability[3,5].

A well-designed and focused research question will not only dictate the study design, but will also aid in literature searches. Instead of turning up hundreds to thousands of citations, a well-defined question will limit the pertinent literature to a manageable number that allows a focused interpretation.

In addition, the research question will permeate through a central theme of the research manuscript. The question should be stated in the introduction of a manuscript, and contain the intervention of study and cohort of interest. Returning to the research question throughout the manuscript will allow reporting of more concise results and a more pertinent discussion.

Designing the study

Once a research question is proposed and a formal review of the literature is performed, the study design is implemented. Table 1 highlights the advantages and disadvantages of various study designs. A case series tracks patients with a known pathology given similar treatment, and allows assessment of a clinical course based on that treatment. Case series are often retrospective but may be prospective. They are often confounded by selection bias, limiting elucidations of causal relationships. Case series may be improved, however, with well-defined selection criteria and the use of validated outcome measures. For rare spinal disorders, a case series may be the best available evidence.

A case-control study design is a type of observational study, wherein two patient groups with differing outcomes are identified and compared for a supposed causal attribute. They are retrospective in nature and relatively inexpensive. Because of their retrospective nature, however, there is difficulty in obtaining reliable information about a patient's exposure over time. This effectively hinders the ability to make claims of causation.

A cohort study is also observational in nature. It follows a group of patients without a disease in order to determine risks of contracting that condition, or compares two treatment options. A cohort study may be retrospective or prospective in nature. It is beneficial for identifying the natural history of a disease, the risk factors of a disease, or the impact of an intervention. Cohort studies are more expensive and time consuming than a case-control design or a case series, with strict inclusion and exclusion criteria. Prospective cohort studies in particular are considered to yield the most reliable results in observational studies.

A RCT is considered the gold standard for a clinical trial. It is often used to test the effectiveness of a medical or surgical intervention within a well-defined patient population. The intervention is provided to the patient based on a process of randomization, in a blinded or unblinded manner. The RCT offers reliable evidence because it reduces bias and spurious causality. Nonetheless, RCTs are prone to high cost, administrative difficulties, and limited recruitment.

Spine surgeons in particular may struggle with obtaining a high quality RCT because of high crossover rates and low patient recruitment. In addition, it is relatively difficult for surgeons to design a study that randomizes patients to interventions that are typically used in sequence[3]. For example, a RCT may be designed to compare operative *vs* non-operative treatment of neck pain. Most surgeons, however, consider failure of non-operative measures as an indication for surgery. Therefore, a patient in this study would need to accept being randomized to a non-operative treatment modality that s/he has already failed. If the concept of equipoise is used in an attempt to circumvent this problem, then surgeons may be relegated to operating on patients without clear operative indications. In this example, a supposed state of equipoise could lead to a surgeon operating on a patient with neck pain who has not failed conservative measures, further confounding results and perhaps leading to poorer surgical outcomes.

Because practical and ethical reasons may prevent the initiation of a RCT, strong observational alternatives are

Table 1 Types of study design

Design type	Advantages	Disadvantages
Case series	Suitable for rare diseases or new treatments	No comparison group
		Retrospective nature
Case control	Small sample size	Presence of confounding
	Short duration	Retrospective nature
Cohort studies	Evaluates risk factors	Presence of confounding
	Compares two treatments	
	May be prospective	
Randomized controlled trials	Prospective in nature	Limited generalizability
	Reduce confounding and bias	Potential for low recruitment and high crossover
		High cost and administrative oversight
Systematic review	Provides summation of available literature	Dependent on quality of individual studies

Adapted from Fisher *et al*[5].

Table 2 Levels of evidence

Evidence level	Therapeutic studies: Evaluating results of treatment	Prognostic studies: Evaluating outcome of disease
Ⅰ	RCT	Prospective study (> 80% follow-up)
	Systematic review of level 1 RCTs	Systematic review of level Ⅰ studies
Ⅱ	Prospective cohort study	Retrospective study
	Poor quality RCT (*e.g.*, < 80% follow-up)	Systematic review of level Ⅱ studies
	Systematic review of level Ⅲ studies	
Ⅲ	Case control study	
	Retrospective cohort study	
	Systematic review of level Ⅲ studies	
Ⅳ	Case series	Case series
Ⅴ	Expert opinion	Expert opinion

Adapted from Wright *et al*[8]. RCT: Randomized controlled trial.

needed in spinal research[2]. This notion would circumvent the impossibility of randomizing every component of intervention.

Systematic, evidence-based literature reviews provide a summation of the available literature on a topic. This type of study is valuable as a synopsis of previously-reported data, aiding understanding of outcomes, safety, risk factors, and impact of spinal surgery intervention[6]. Systemic reviews should be transparent, so that data is presented in an unbiased manner, thus allowing the surgeon to make independent conclusions based on the data. A quantitative synthesis of high quality data is termed a meta-analysis, which may be useful when pooling studies which are individually under-powered to find conclusive results[7].

Assessing the level of evidence

Based on study design, the level of evidence for an intervention can be assessed (Table 2)[8]. RCTs are categorized as level Ⅰ or Ⅱ. Cohort studies are level Ⅱ or Ⅲ. Case-control studies are level Ⅲ, and case series are level Ⅳ. Expert opinion is considered level Ⅴ. The level of evidence correlates with certainty of risks and benefits of a given intervention, so that higher levels of evidence (and thus higher quality studies) provide more certainty in their conclusions, and therefore stronger recommendations for treatment.

Although a majority of studies in spinal surgery are of levels Ⅲ and Ⅳ, a select number of studies are of higher level evidence[9,10]. Certainly the level of evidence, however, is not the final answer in evaluating the literature. The lack of RCTs in spinal surgery research reflects the complexities and limitations of this study design. In addition, the current system of analyzing levels of evidence ignores whether the study asked the correct question or examined the relevant patient population[3].

OUTCOME MEASUREMENTS IN SPINE RESEARCH

The use of standardized outcome measurements is important for conducting evidence-based research. The quantification of patient symptoms, ability to perform activities of daily living, and overall health status is necessary to track patient progress as well as to conduct clinical studies. Outcome measurement tools allow clinicians to communicate, in a standardized manner, the success of treatment strategies. However, there is no standardized set of clinical outcome measures for all spine patients[11]. Outcome measurements for those with cervical pathology differ from those with lumbar pathology, for example. The questionnaires given to the patient must be carefully selected so as to elicit the most pertinent information in

Table 3 Outcome tools in spinal surgery

Topic	Tool	Notes
Pain	VAS	May be used for generalized or localized pain
Disability	ODI, NDI	Evaluates multiple life experiences
		The NDI is an adaptation of ODI for patients with neck disability
Myelopathy	JOA, mJOA	Evaluates motor function, sensation, and bladder function
Quality of life	SRS-22, EQ-5D-5L, SF-36	SRS-22 developed for patients with spinal deformity

VAS: Visual analog scale; NDI: Neck disability index; ODI: Oswestry disability index; JOA: Japanese Orthopaedic Association; mJOA: Modified JOA; SRS-22: Scoliosis Research Society-22; SF-36: Short Form-36.

the most efficient manner. It is important to recognize that providing an excessive number of questionnaires will decrease patient compliance. The aim of this section is to highlight the outcome measurement tools commonly used in spinal surgery research (Table 3).

The oswestry disability index (ODI) is the most common questionnaire utilized to evaluate the physical symptoms of patients with low back pain, with an emphasis on quality of life[12]. This questionnaire evaluates ten categories: pain, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and traveling. There are six answers available per question with point values of zero to five; the maximum score is fifty. A quantification of patient disability may be calculated by dividing the point total by fifty then multiplying by one hundred percent. Those with 0%-20% disability are considered minimally disabled. A score of 21%-40% is moderate disability, 41%-60% is severe, 61%-80% is crippled. Those with scores of 81%-100% are bed bound. A change of 4 points is the minimum difference that can be considered clinically significant. A 15 point change, though, is what is considered significant for patients undergoing spinal fusion.

The neck disability index (NDI) represents a modification of the ODI for patients with cervical spine pain[13]. The questions elicit information about activities such as concentration and reading which can be affected by cervical pain. Soft tissue injury can also lead to headache, which is also evaluated by the NDI. The scoring system is the same as that of the ODI.

The visual analog scale is a measurement instrument which quantifies patient subjective pain[14]. It consists of a 10 centimeter line with one end representing no pain and the other end the worst pain possible. The patient indicates where on the line his or her pain is in relation to these two extremes. This outcome measure can be used to quantify generalized pain or any specific type of pain (back, leg, *etc*.).

Patients with cervical myelopathy may suffer from a constellation of disabling symptoms, but pain may be a relatively minor issue. The Japanese Orthopaedic Association (JOA) scale is an objective assessment of upper and lower extremity motor function, sensation, and bladder function[15]. The highest possible score is 17. The JOA is specific for patients who utilize chopsticks to feed themselves. For those who do not, the modified JOA (mJOA) has been developed[16,17]; the questionnaire has replaced the word "chopsticks" with "knife and fork". The mJOA is therefore more often used in the United States compared to the JOA. In addition, the mJOA involves a highest score of 18, rather than the JOA's high score of 17[15,17].

Those with spinal deformities, in particular idiopathic scoliosis, have a slightly different set of concerns and health issues than those with degenerative conditions. These patients are typically adolescents or young adults. The Scoliosis Research Society-22 (SRS-22) questionnaire targets 5 domains: physical function, pain, self image, mental health, and satisfaction with management of scoliosis[18]. Each of the 22 questions contains 5 answers with point values from 1 to 5, with 5 being the best. The mean scores from each of the 5 categories are averaged to produce a single value. Studies indicate that significant point differences for the SRS-22 are: pain 0.6, function 0.8, self image 0.5, mental health 0.4, average sum score 0.5, and raw sum score 6.8.

The EQ-5D-5L is a questionnaire that investigates patient quality of life[19]. It consists of 2 forms. The first assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is associated with 5 statements; the patient selects the statement that most correlates with their condition. No point values are assigned to each statement. The second form consists of a 20 cm vertical line with endpoints labeled "the best health you can imagine" and "the worst health you can imagine." Patients are asked to indicate where on the line they believe their present state of health to be. Given that no numerical score is calculated from the 5 questions, the data can be presented in a variety of formats.

Similar to the EQ-5D-5L is the Short Form-36 (SF-36)[20,21]. This is a heath survey analyzing 2 general domains: physical health and mental health. There are 36 questions and 5 possible responses per question. Physical health is divided into physical functioning, physical role functioning, bodily pain, and general health. Mental health is divided into vitality, social functioning, emotional role functioning, and mental condition. The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in each section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight.

Ultimately, an outcome assessment tool must be reliable, reproducible, specific to the outcome of interest, yet brief enough to promote compliance. For these purposes, an array of well-validated standardized questionnaires is available.

CONCLUSION

Evidence-based research in spinal surgery has received a growing amount of attention, not only from surgeons and scientists, but from government regulators and the lay press. With continued pressure to produce high quality evidence for the success of spinal interventions, one must recognize that the RCT is not always the optimal study design for a given research question. Rather, prospective observational cohort studies may be more appropriate in certain circumstances, and would provide superior generalizability. In addition, case series and case-control study designs have their own utility, particularly in studying rare diseases and new treatment options. The use of validated outcome measurements will increase the quality of a given study design. Finally, evaluating spinal research with levels of evidence, I-V, allows for an objective measurement of study quality, yet this system does not account for whether the correct question was asked or if the correct patient population was studied. These issues surrounding EBM are important for spinal surgeons, as well as health policy makers and editorial boards, to have familiarity.

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Modern posterior screw techniques in the pediatric cervical spine

Daniel J Hedequist

Daniel J Hedequist, Department of Orthopedic Surgery, Children's Hospital Boston/Harvard Medical School, Boston, MA 02115, United States
Author contributions: Hedequist DJ solely contributed to this paper.
Correspondence to: Daniel J Hedequist, MD, Department of Orthopedic Surgery, Children's Hospital Boston/Harvard Medical School, 300 Longwood Avenue, Boston, MA 02115, United States. daniel.hedequist@childrens.harvard.edu
Telephone: +1-617-3554847 Fax: +1-617-3554847
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Abstract

Treatment of children with cervical spine disorders requiring fusion is a challenging endeavor for a variety of reasons. The size of the patients, the corresponding abnormal bony anatomy, the inherent ligamentous laxity of children, and the relative rarity of the disorders all play a part in difficulty of treatment. The benefits of modern posterior cervical instrumentation in children, defined as rigid screw-rod systems, have been shown to be many including: improved arthrodesis rates, diminished times in halo-vest immobilization, and improved reduction of deformities. The anatomy of children and the corresponding pathology seen frequently is at the upper cervical spine and craniocervical junction given the relatively large head size of children and the horizontal facets at these regions predisposing them to instability or deformity. Posterior screw fixation, while challenging, allows for a rigid base to allow for fusion in these upper cervical areas which are predisposed to pseudarthrosis with non-rigid fixation. A thorough understanding of the anatomy of the cervical spine, the morphology of the cervical spine, and the available screw options is paramount for placing posterior cervical screws in children. The purpose of this review is to discuss both the anatomical and clinical descriptions related to posterior screw placement in the cervical spine in children.

Key words: Pediatric cervical spine; Cervical screw fixation; Posterior cervical techniques

Core tip: This paper reviews the techniques used for modern posterior screw fixation of the pediatric cervical spine. The preoperative considerations, necessary studies, and surgical techniques are reviewed in order to educate the reader on the use of modern screw fixation in the pediatric cervical spine. Upper cervical fixation techniques as well as lateral mass screw fixation in the subaxial spine are discussed.

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PREOPERATIVE CONSIDERATIONS

The standard preoperative work-up of any child undergoing surgical treatment for a cervical spine problem will include plain radiographs, magnetic resonance imaging, and computed tomography scanning. Plain radiographs include anterior-posterior and lateral views, as well as flexion-extension lateral views of the cervical spine. The use of magnetic resonance imaging (MRI) is important as it gives detail oriented information regarding the spinal cord, neuroforamen, and position of the vertebral artery. Areas of compression are readily visualized as well as cord signal changes which are important to have as a

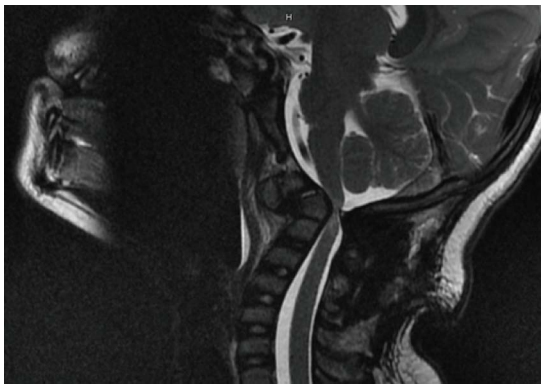

Figure 1 Magnetic resonance imaging showing severe cord compression at the craniocervical junction in a 6 year-old child with instability and myelopathy due to previous failed fusion for atlanto-axial instability.

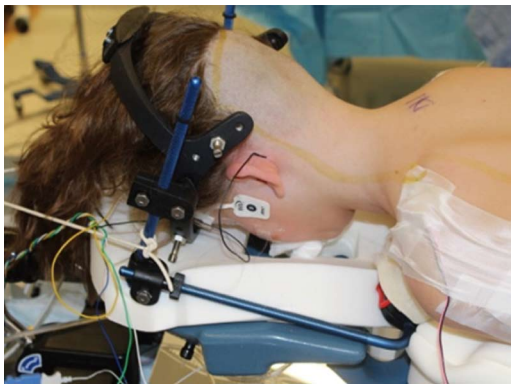

Figure 2 Clinical photo of a 10 year-old child in prone positioning with halo ring and anterior portion of vest attached. Note the alignment of the head and absence of pressure on the eyes or face.

baseline in patients with instability or neurologic findings (Figure 1).

Computed tomography (CT) scanning with fine cut images is important as it gives concrete information regarding the bony anatomy as well as the course of the vertebral artery. Three-dimensional reconstructions are of paramount importance in cases of upper cervical instrumentation as it gives the surgeon a complete understanding of the course of the vertebral artery which is mandatory with upper cervical screw placement. The standard use of CT angiography or MR angiography is not needed unless either significant congenital bony malformations are present or high grade instability is present with concern regarding the course of the vertebral artery. We have also found in some cases of tumor encasement that angiography is helpful to define the exact location of the vertebral artery as well as the patency of the vertebral artery.

ANESTHESIA AND POSITIONING CONSIDERATIONS

Depending on the reason that cervical surgery is performed fiberoptic techniques may be required for intubation or nasal intubation may be required. Frequently instability is present requiring immobilization during airway placement and having an anesthesiologist present who is experienced in difficult airways is paramount to patient safety. The use of a halo-vest for positioning or Gardner-wells tongs for positioning is of great importance to secure the cranium and allow for adequate fluoroscopic visualization. In the majority of patients I place the halo crown and attach it to a vest and then turn the patient to prone positioning. The posterior aspect of the vest can then be removed for the operation (Figure 2). This is important for a variety of reasons, the first being complete immobilization of the head and neck during positioning and turning which is the safest way to turn when a patient is completely relaxed under anesthesia. Second, placing the patient in a halo crown and vest also allows me to afford reduction of deformities and to place the skull in the appropriate position in order to avoid craniocervical fusions done in misalignment. Finally, if the patient is going to stay in a vest then at the end of the operation the posterior vest can be added and the patient safely turned and then extubated.

The use of neurologic monitoring is required for all pediatric patients undergoing cervical instrumentation and fusion. The standard for all patients is motor-evoked monitoring, sensory monitoring, as well as EMG monitoring of the upper limb. Anesthetic agents should be used which don't interfere with the ability to obtain stable and reliable monitoring.

C1 LATERAL MASS FIXATION

Fixation at C1 in the past has traditionally been with sublaminar wiring underneath the arch of the atlas, which is inherently not dangerous or technically difficult given the space available for the cord at this level. However, wiring or cable grafting is problematic both biomechanically and from a pathologic standpoint. C1 wiring is inherently not stable in rotation which is problematic given the articulation of C1 with both the occiput and C2 allows for the majority of cervical rotation. From a clinical standpoint, the posterior ring of C1 frequently requires removal in cases where decompression is required and then wiring is not an option. These factors have led to the anatomical studies of the lateral mass of C1 to determine if screw fixation is feasible, and if so then what are the anatomical constraints[1-3].

The lateral mass of C1 is a quadrilateral structure of bone lying anterolateral to the spinal cord and in close relationship to the vertebral artery, which lies in the anterolateral confines of the lateral mass. The surgical exposure of the lateral mass entry point is challenging for a variety of reasons. The entry point of the lateral mass screws requires following the posterior arch of C1 surgically down to the entry point into the lateral mass (Figure 3A). This can be done by electrocautery dissection staying on the inferior aspect of the posterior arch of C1 as the vertebral artery lies on the superior aspect of the ring of C1 as it exits from the skull base. Classically the teaching had

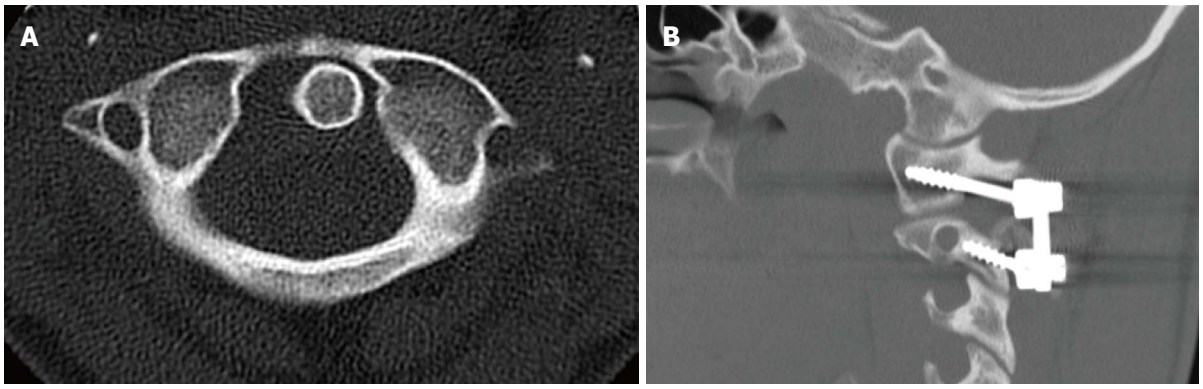

Figure 3 C1 lateral mass fixation. A: Axial computed tomography (CT) cut through the atlas. Note the lateral masses and the relationship of the C1 arch meeting the lateral masses which are landmarks for correct starting points for lateral mass screws; B: Sagittal cut of a CT scan in a 14 year-old patient who has underwent C1-C2 arthrodesis with C1-C2 screw rod construct for an odontoid non-union. Note the starting position of the C1 lateral mass screw inferior to the bony arch of C1. The outline of the vertebral artery can be seen on the superior aspect of the C1 arch.

been the vertebral artery is at risk 1.5 cm from the midline, this has never been validated in children and is not a reliable rule in pathologic cases. Nevertheless, the current recommendation would be to be aware of the position of the vertebral artery laterally on the superior aspect of C1 and if need be a preoperative CT angiography study is helpful, especially with congenital deformities. The ring of C1 gradually turns away and into the lateral mass of C1 and this region needs to be dissected out with meticulous attention to the venous plexus, which is diffuse and engulfs this region. Aggressive bipolar cautery of these venous bleeders prophylactically will make exposure of the entry point easier. The C2 nerve root also is encountered running below the arch of C1 and needs to be identified to find the lateral mass starting point. Variation exists in opinion regarding the need sacrifice the root of C2 for better exposure[4]. I have found this not to be required for adequate exposure or for safe screw placement.

The ideal starting point of C1 screws can be found by studying the preoperative CT scan of the patient, however in all cases the screw starting point remains underneath the arch of C1, although occasionally the undersurface of the arch where it meets the bony lateral mass needs to be burred away (Figure 3B). The starting point is usually in line where the arch meets the lateral mass, it is never lateral to the arch and the medial border is easily identified with a freer. The spinal cord is not at risk with this screw given the entry point is anterolateral and usually lies at the anterior-posterior midpoint of the cord.

The C1 lateral mass usually allows for screw placement even in the youngest of pediatric patients. In a recent series of patients as young as two years of age, CT evaluation revealed that the mean length available for the lateral mass screw was greater than 15 mm and the mean medial-lateral dimensions were greater than 7 mm which would allow for safe placement in all patients of a 3.5 mm screw[2]. The screw trajectory was evaluated in another series of pediatric patients with CT scans and confirmed from an optimal starting point the ideal screw trajectory would be medially angled 16 degrees and could be placed to a depth of 20 mm[1]. In that study, the placement of screws was deemed feasible in 151/152 lateral masses.

Clinically, the anatomic feasibility found in CT studies has been shown to be a reliable indicator of anatomy in children. Two recent series looking specifically at screw placement into C1 in pediatric patients documented successful screw placement with no intraoperative complications and uneventful fusion for a variety of pediatric pathologic conditions[5,6].

C2 SCREW FIXATION

The axis plays a significant role in the management of cervical spine problems in children requiring instrumentation and fusion. It can be either the base of a craniocervical fusion; it may be coupled with the atlas in cases of atlanto-axial instability, or may be the top of a mid-level fusion. Many screw options exists for the axis and are preferable to subaxial cabling as the space available for the cord is much less at the axis rendering sub laminar placement of wires dangerous and the inherent biomechanical weakness of cabling. Screw fixation into the axis may be divvied into three separate screw types: pedicle, pars, and intralaminar. The placement of which screw is dependent on a variety of factors which may be seen on the preoperative CT scanning, notably the width of the bony channels and the position of the vertebral artery[7].

The C2 spinouts process is used as a landmark in the upper cervical spine and can be used as the entry point for intralaminar screws. Intralaminar screws at C2 have been shown to be effective for rigidity of constructs in biomechanical studies[8]. The entry point for C2 laminar screws is on the contralateral side of the spinous process and needs to be placed either caudal or rostral in the spinous process so that crossing screws can be placed (Figure 4A). The dorsal aspect of the lamina is exposed the same for all cervical fusions involving the axis. A starting point on the contralateral side of the spinous process is made using a burr and then the lamina is annulated using an awl. Looking at the dorsal lamina easily sees the rostral-caudal orientation. The avoidance of penetrating the

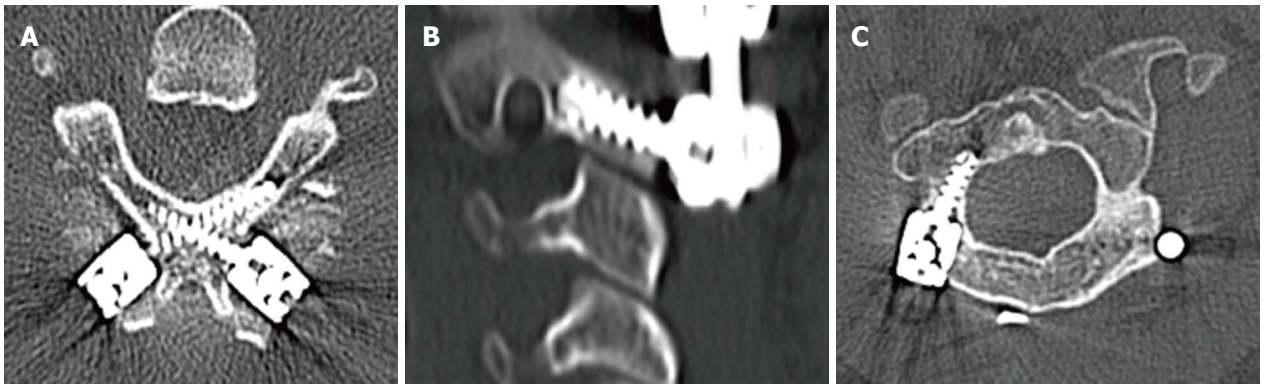

Figure 4 C2 screw fixation. A: Axial cut computed tomography (CT) scan of intralaminar screw placement at C2. The starting point on the spinous process can be seen as well as the space available for screws; B: Sagittal cut CT of a patient who underwent instrumentation with C2 pars screws. Note the relationship of the vertebral artery in this patient and the need for shorter screw placement; C: Axial CT demonstrating the medial orientation of a C2 pedicle screw with the spinal canal medial and the vertebral artery anterior and lateral.

ventral lamina and spinal canal can be done by placing a freer *via* blunt dissection under the ventral lamina as a landmark to avoid misguided trajectory. Screw length can be estimated by the preoperative studies of the presumed screw tract.

CT analysis of the upper cervical vertebra has shown that the lamina is able to accept 3.5 mm screws in most patients. A recent tomographic study of children revealed screw lengths measured on CT to be around a mean of 20 mm with the majority of lamina having a bony channel able to withstand screw placement[2]. Clinically, the placement of laminar screws has been shown to be safe and efficacious and the decision regarding intralaminar screw placement can be determined with preoperative CT in all patients[7,9,10]. The complication of canal breach has not been reported in multiple clinical studies regarding screw placement in children[5,7].

There is variability in the terminology of C2 screws placed in the pars/isthmus/pedicle. Two separate screw paths exist which have been described, each with different starting points and risks associated with their trajectory. The pars and pedicle are intertwined in a shared mass of bone in the atlas, which needs to be directly visualized during surgical dissection. During dissection as the lamina is followed down laterally the isthmus of C2 can then be followed going superiorly and medially. The dissection of the isthmus is paramount for defining safe screw trajectory as the dorsal and medial part of the isthmus is readily dissected aiding in direct visualization in screw path. The dissection of the isthmus must be done with bipolar cautery to avoid bleeding from the venous plexus, which engulfs the C1-C2 posterior bony complex. The medial aspect of isthmus once dissected can be used to guide screw trajectory and avoid unwanted canal penetration, placing a freer on the medial side will help directly visualize the screw path. Placement of C2 screws can be done with the determination of a pedicle screw or a pars screw. Pars screws are done with a starting point more caudal and just above the C2-C3 facet in the midline. The medial-lateral determination is done by using the medial dissected out isthmus as the landmark and the lateral trajectory is done under fluoroscopic guidance using the dorsal isthmus as a landmark as well. The length if the pars screw is directly determined by the course of the vertebral artery as well as by the C1-C2 articulation (Figure 4B). C2 pedicle screws share the same isthmus of bone but the starting point is more superior and lateral than the pars screws. The screw trajectory is more medially directed and headed into the C2 body, placing the canal at risk unless dissection has identified the medial pars (Figure 4C).

The morphometric studies regarding C2 screws are not entirely clear regarding the variation of pedicle versus pars, but can be interpreted regarding the shared isthmus of bone necessary for screw placement. In a morphometric study of children less than six years of age the mean width of the pedicle measured on CT scan was greater than 3.5 mm and the mean pedicle length was greater than 17 mm[2].

Multiple clinical studies exit regarding the use of pars/pedicle screws in children. While not entirely clear of the separation of pars/pedicle screws it is clear that screws can be place in the vast majority of patients without injury to the vertebral artery or malposition of screws[5-7]. These clinical studies show that rigid screw fixation either through pars/pedicle or intralaminar screws are possible in almost all patients and serves as an excellent and reliable fixation point in pediatric deformity surgery.

C1-C2 TRANSARTICULAR SCREWS

Placement of C1-C2 transarticular screws remains a powerful yet challenging technique of fixation. Classically, these screws are placed for C1-C2 instability but may be placed as a base for craniocervical constructs. The challenges of screw placement make dissection of the C2 isthmus as well as C1-C2 joint mandatory for safe screw placement.

The placement of transarticular screws demands a

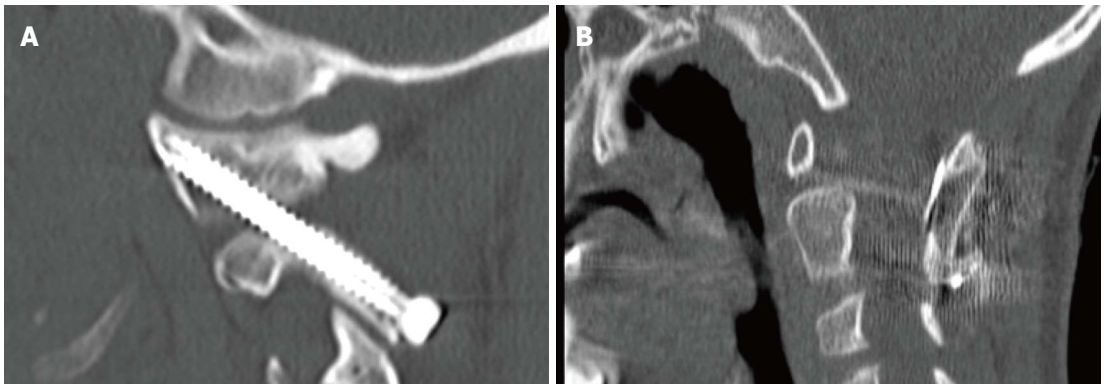

Figure 5 C1-C2 transarticular screws. A: Sagittal computed tomography (CT) of a fully contained and well placed transarticular screw in a 10 year-old male with Down's syndrome and os odontoideum; B: Sagittal CT cut demonstrating the placement of a structural iliac crest graft cable grafted in between C1 and C2 which supplemented transarticular screws in an 8 year-old patient with C1-C2 instability.

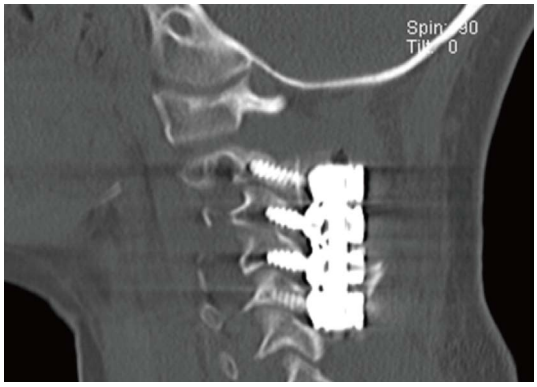

Figure 6 Sagittal computed tomography cut of a 5 year-old patient who underwent lateral mass screw fixation after tumor reconstruction.

complete understanding of the course of the vertebral artery both in its relationship to the axis and in its relationship to C1. The course of the vertebral artery is anomalous in up to 25% of patients in clinical studies where screw placement would be beneficial[11]. The most common problematic course in relationship to C2 is either a medially deviated course where the ideal trajectory of the screw from the isthmus of C2 into the C1 lateral mass does not exist or in a sagittal plane abnormality where the vertebral artery is high riding and lead to a small isthmus negating any potential screw placement[7]. The position of the vertebral artery in relationship to the C1 lateral mass is also of paramount importance screw placement must end up in the lateral mass after crossing the joint.

Morphometric studies of upper cervical anatomy suggest that a minority of patients less than six have anatomy suitable for transarticular screws given either the size of the C2 isthmus or the course of the vertebral artery[2]. Clinical studies have shown that even in younger patients screws may be safely placed if the preoperative imaging suggests anatomy, which allows for safe screw placement[12,13].

Adequate visualization of the C2 isthmus is paramount to safe screw placement and is done as described above for pars screws. The C1-C2 joint must also be in a reduced position and accessible by direct fell *via* a freer elevator. We have used a cannulated screw system at our institution and once the guide wire is placed thru C2 into the joint we have made it a step of the procedure then to adequately feel with a freer the guide wire in a good position as well as using confirmatory biplanar fluoroscopy. There is minimal room for error using transarticular screws so guide wire placement in a correct position and must be done by C2 pars visualization, palpation of the guide wire in the C1-C2 joint, and confirmation of correct guide wire placement on AP and lateral fluoroscopy. Once adequate guide wire placement has been done then screws can be placed after measuring, drilling, and tapping (Figure 5A).

Placement of a unilateral C1-C2 transarticular screw is occasionally needed if the anatomy of the vertebral artery on both sides is not symmetrical. Biomechanically his has been shown to be reasonable fixation[13]. We have made it a habit to placed autogenous structural iliac crest graft between C1 and C2 in cases where the ring of C1 is present in order to augment the posterolateral gutter fusion. Typically we have place a horseshoe shaped graft and secured it *via* cables placed underneath the ring of C1 and through the spinouts process of C2 (Figure 5B).

Clinically, transarticular screws have been safely used in children who have safe anatomy on preoperative CT scans. Brockmeyer reviewed his series of patients treated with transarticular screws and found safe screw placement in children younger than age four[13,14].

SUBAXIAL LATERAL MASS SCREWS

The use of lateral mass screws has been studied in children and shown to be safe and efficacious if the preoperative template on CT scanning is favorable[15,16]. The lateral mass is a quadrangular structure of bone, which has a medial border of the spinal canal and an anterior border the vertebral artery. Multiple techniques exist for placement of screws in the lateral mass with variation in the starting point and variation in both the laterally

directed and the cranially directed angle. I have used the modified technique of dividing the lateral mass into a box with the facet above and below being the cranial and caudal borders, the lateral edge of bone being the lateral border and the medial border being where the lamina meets the facet. The starting point for screw placement is 1 mm inferior and 1mm medial to the center of this box. The angulation is approximately 15 degrees laterally and the cranial angulation is dictated by the lateral fluoroscopic views. Fluoroscopy is necessary in children given the small size of the lateral mass does not allow for false drill passage given this will not allow for redirection.

At our institution we have studies the use in lateral mass screws for a variety of pathologic conditions in children. Post-operative computed tomography scanning has shown complete screw containment in all cases and there have been no vertebral artery injuries or post-operative nerve deficits[15,16]. Standard screw diameter is 3.5 mm and we have found it useful to have screws as low as 8 mm in length to avoid anterior penetration into the vertebral artery by a long screw. We have placed subaxial screws in children as young as four years of age, although the indications for this age group are rare given most pathologic conditions in younger children involve the craniocervical junction and the upper cervical spine (Figure 6). We have not used cervical pedicle screws in pediatric patients given the cadaveric anatomical studies showing the size of the pedicle is not adequate for screw placement in the majority of patients[17].

CONCLUSION

Surgeons taking care of children with cervical spine abnormalities will encounter a wide variety of pathologic conditions requiring fusion. Stability of the spine, reduction of deformities, protection of the spinal cord, and enhanced fusion all are aided by stability obtained with modern instrumentation using screw-rod constructs. These constructs have been shown to be both feasible in morphometric studies as well as safe in clinical studies. Placement of screws demands a complete understanding of the preoperative anatomy which can be done by adequate preoperative studies. Finally, given the small nature of the patients meticulous surgical dissection is paramount to safe screw placement. The modern techniques will lead to an improved rate of arthrodesis while minimizing any time needed in external immobilization which ultimately leads to better patient/family satisfaction.

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Perioperative visual loss after spine surgery

Travis J Nickels, Mariel R Manlapaz, Ehab Farag

Travis J Nickels, Mariel R Manlapaz, Ehab Farag, Department of General Anesthesia, Anesthesiology Institute, Cleveland Clinc, Cleveland, OH 44195, United States
Author contributions: Nickels TJ, Manlapaz MR and Farag E performed research, analyzed the data, and wrote the paper.
Correspondence to: Ehab Farag, MD, Department of General Anesthesia, Anesthesiology Institute, Cleveland Clinc, 9500 Euclid Avenue; E-30, Cleveland, OH 44195, United States. farage@ccf.org
Telephone: +1-216-4447550 Fax: +1-216-4449247
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Abstract

Perioperative visual loss (POVL) is an uncommon, but devastating complication that remains primarily associated with spine and cardiac surgery. The incidence and mechanisms of visual loss after surgery remain difficult to determine. According to the American Society of Anesthesiologists Postoperative Visual Loss Registry, the most common causes of POVL in spine procedures are the two different forms of ischemic optic neuropathy: anterior ischemic optic neuropathy and posterior ischemic optic neuropathy, accounting for 89% of the cases. Retinal ischemia, cortical blindness, and posterior reversible encephalopathy are also observed, but in a small minority of cases. A recent multicenter case control study has identified risk factors associated with ischemic optic neuropathy for patients undergoing prone spinal fusion surgery. These include obesity, male sex, Wilson frame use, longer anesthetic duration, greater estimated blood loss, and decreased percent colloid administration. These risk factors are thought to contribute to the elevation of venous pressure and interstitial edema, resulting in damage to the optic nerve by compression of the vessels that feed the optic nerve, venous infarction or direct mechanical compression. This review will expand on these findings as well as the recently updated American Society of Anesthesiologists practice advisory on POVL. There are no effective treatment options for POVL and the diagnosis is often irreversible, so efforts must focus on prevention and risk factor modification. The role of crystalloids versus colloids and the use of α-2 agonists to decrease intraocular pressure during prone spine surgery will also be discussed as a potential preventative strategy.

Key words: Perioperative visual loss; Ischemic optic neuropathy; Central retinal artery occlusion; Cortical blindness; Posterior reversible encephalopathy; Spine surgery; Prone positioning

Core tip: Perioperative visual loss (POVL) is an uncommon, but devastating complication that remains primarily associated with spine and cardiac surgery. The incidence and mechanisms of visual loss after surgery remain difficult to determine. Ischemic optic neuropathy accounts for the vast majority of these cases, with retinal ischemia, cortical blindness, and posterior reversible encephalopathy observed with low incidence. Recently identified risk factors include obesity, male sex, Wilson frame use, longer anesthetic duration, greater estimated blood loss, and decreased percent colloid administration. POVL is often permanent and untreatable, so prevention is key to limiting its impact.

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INTRODUCTION

Perioperative visual loss (POVL) associated with spine surgery is a rare and disastrous complication that is generally irreversible and without definitive etiology.

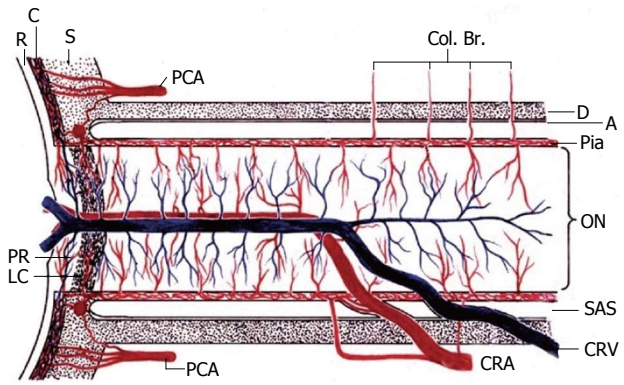

Figure 1 Schematic representation of blood supply of the optic nerve. Reproduced from Hayreh *et al*[20]. A: Arachnoid; C: Choroid; CRA: Central retinal artery; Col. Br.: Collateral branches; CRV: Central retinal vein; D: Dura; LC: Lamina cribrosa; ON: Optic nerve; P: Pia; PCA: Posterior ciliary artery; PR: Prelaminar region; R: Retina, S: Sclera; SAS: Subarachnoid space.

First described by Hollenhorst *et al*[1] in 1954, there have been numerous reports since establishing a clear link between spine surgery in the prone position and vision loss. Unfortunately, however, the research on this topic is limited due to its rare occurrence and consists largely of individual case reports and series[2-5]. This article reviews the different types of postoperative visual loss complications after spine surgery. The theoretical pathogenesis, risk factors, and prevention strategies including the use of colloids versus crystalloids and α-agonists to decrease intraocular pressure (IOP) are also discussed.

EPIDEMIOLOGY

Vision loss occurring with spine surgery may result from: anterior ischemic optic neuropathy (AION) or posterior ischemic optic neuropathy (PION); central retinal artery occlusion (CRAO); cortical blindness; and posterior reversible encephalopathy (PRES). Two large retrospective studies determined that the incidence of POVL is approximately 1/60000 to 1/125000 of all general anesthetics[6,7]. However, the risk of POVL is believed to be significantly greater following cardiac and spine surgeries. A recent review by Shen and colleagues of 5.6 million patients from the National Inpatient Sample (NIS) found that the incidence of POVL to be 3.09/10000 (0.03%) after spinal fusion and 8.64/10000 (0.09%) after cardiac surgery[5]. Other large-scale series suggest that the rate of POVL may be even higher after spine surgery, with incidence rates ranging from 0.094%[4] to 0.2%[8]. Visual loss was more common after spinal fusion for scoliosis and posterior lumbar fusion than anterior lumbar fusion or cervical fusion[4]. It was also noted to be significantly increased in hip and femur operations (1.86/10000, or 0.19%)[5]. These procedures share several features including large blood loss, hemodynamic perturbations, high embolic loads, and significant inflammation.

According to the American Society of Anesthesiologists (ASA) Postoperative Visual Loss Registry, the most common causes of POVL in spine procedures are the two different forms of ischemic optic neuropathy (ION): AION and PION, accounting for 89% of the cases[9]. PION was diagnosed in 60% of these cases[9]. In this database, CRAO only accounted for 11% of the cases.

According to the most recent NIS review, gender plays an important role with men displaying a higher risk of POVL after spinal fusion relative to women (OR = 1.75), which is consistent with the ASA POVL Registry[9], previous case series[10], and a recent multicenter case-control study[11]. Age appears to be a factor as well with those aged 50-64 years displaying an increased risk (OR = 1.75). Also notable and unexplained was the finding that children < 18 years old had the highest overall risk for POVL (OR = 6.91), which was primarily attributed to cortical blindness rather than AION/PION and may represent a different etiology[5].

ANATOMY

Blood supply to the optic nerve

In order to understand POVL, especially ION, it is important to have a basic understanding of the blood supply to the optic nerve (Figure 1). For an exhaustive review, please see Hayreh[12], 2001. The ophthalmic artery, originating from the internal carotid artery, and its various branches is the principal blood supply to the retina, globe, and optic nerve. The central retinal artery, a branch of the ophthalmic artery, supplies the inner retina.

The anterior portion of the optic nerve (optic nerve head) has a rich arterial supply principally from the posterior ciliary artery (PCA) circulation, except for the surface nerve fiber layer, which is supplied by the retinal circulation. The blood supply in the optic nerve head has a sectorial distribution, which may explain the segmental vision loss seen in ischemic disorders[13].

The posterior portion of the optic nerve is supplied by the pial vascular plexus, which is supplied by multiple pial branches originating from the peripapillary choroid, circle of Haller and Zinn, central retinal artery, ophthalmic artery, and other orbital arteries[13].

In contrast to the densely supplied anterior and posterior portions of the nerve, the central portion within the optic canal is supplied only by the pial vascular plexus derived from arterial extensions of the anterior and posterior blood supplies and intraneural branches of the central retinal artery. This comparatively sparse vascular supply to the mid portion of the optic nerve renders it more susceptible to ischemia and it is this portion of the nerve that is though to be related to PION[14]. However, it is important to note that there is significant interindividual variability in the complex blood supply to the optic nerve, especially in terms of the location and pattern of watershed zones[12].

Venous drainage occurs mostly via the central retinal vein that is drained by the internal jugular vein. In the pre-laminar region of the eye, there are retinociliary collaterals to the peripapillary choroidal veins and drainage through these collaterals can become significant in case

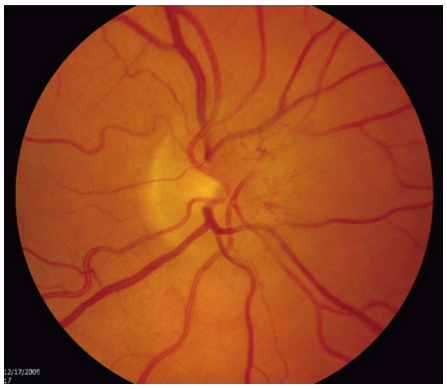

Figure 2 Fundoscopic exam of acute anterior ischemic optic neuropathy demonstrating blurring of the optic disk margin from edema.

of central retinal vein thrombosis[14].

VISION LOSS AFTER SPINE SURGERY

Ischemic optic neuropathy

Postoperative ION is a devastating complication that can occur after a variety of surgical procedures, most often following cardiothoracic surgery[15], instrumented spinal fusion[16,17], and head and neck surgery[18]. ION can be categorized as either anterior or posterior, depending on whether the insult occurs in the anterior or posterior portion of the optic nerve. The type of ION observed varies depending on the type of surgery performed, with AION occurring most frequently after cardiac surgery and PION occurring most frequently after spine surgery in the prone position or radical neck dissection[9].

Anterior ischemic optic neuropathy

AION is likely caused by occlusion or hypoperfusion of the anterior optic nerve head by the PCAs and typically presents with sudden onset painless vision loss and a visual field defect. It is distinguished on fundoscopy by diffuse or segmental disc edema with ensuing atrophy and sometimes splinter hemorrhages around the optic disc (Figure 2)[19,20]. AION can be further classified as either arteritic or nonarteritic. Arteritic AION is rarely found perioperatively. It is caused by temporal arteritis and often presents in the elderly with an elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), markers that are entirely non-specific in the postoperative period[21].

Nonarteritic AION occurs both spontaneously in the community and in the perioperative setting, often in patients with pre-existing vascular disease[22]. Additional risk factors include diabetes mellitus, arterial hypotension, arterial hypertension, blood loss, prone positioning during surgery, prolonged surgery, atherosclerosis, sleep apnea, and migraine[13]; however, it can occur in patients that are otherwise healthy. The pathology is likely a combination of these factors, perhaps together with abnormal autoregulation and other patient specific characteristics that predispose to ischemic injury[23]. Perioperative nonarteritic AION is most often associated with cardiac surgery, especially CABG, and generally presents immediately upon awakening from surgery. On rare occasion, AION may occur abruptly after a "delay" or period of normal vision lasting hours to days[24].

Posterior ischemic optic neuropathy

Posterior ION results from infarction of the optic nerve posterior to the lamina cribrosa and also manifests as sudden onset painless visual loss and visual field deficiencies. In contrast to AION, the fundoscopic examination initially reveals a completely normal appearing fundus, with optic nerve pallor and atrophy occurring only after approximately 4-6 wk[24]. It tends to cause significant bilateral visual loss or complete blindness and is usually discovered on waking from the surgical procedure[13]. In the ASA Registry of spine-related ION, 46% of the patients reported had no light perception[9], which is usually permanent. Like AION, PION may also be classified as either arteritic or nonarteritic. The arteritic form is attributable to temporal arteritis and the nonarteritic form is seen most commonly following spine surgery.

A host of hemodynamic derangements could contribute to the development of postoperative PION including: hypotension, anemia, increased venous pressure, prone positioning during surgery, increased cerebrospinal fluid, and direct ocular compression[25]. Anemia and hypotension are almost always observed in patients that develop postoperative PION[26]. The pial vessels that supply the posterior optic nerve lack an autoregulatory mechanism, rendering them susceptible to ischemia during periods of hypotension and when the blood oxygen carrying capacity is decreased[27]. However, studies comparing patients with POVL after spine surgery with those of controls demonstrated no difference in perioperative hematocrit and blood pressure, suggesting a multifactorial cause[10,28].

The prone position, a key element to spine surgery, is also the setting in which the majority of postoperative PION is observed. Prone positioning, especially when in the Trendelenburg position, leads to increased orbital venous pressure through an increase in abdominal venous pressure, thus increasing resistance to local blood flow[29]. Direct orbital pressure, often seen with face pillows/cushions or other positioning devices, has also been implicated in the pathogenesis of PION. However, with the resultant decreased perfusion pressure to the optic nerve head and central retinal artery, AION or CRAO would be more likely observed[26]. Avoidance of the prone position and direct ocular pressure is insufficient, however, to prevent postoperative PION, as cases have been documented following surgery in the supine position and with the use of head pins[3,9,30].

Risk factors associated with ischemic optic neuropathy and spine surgery

Recently in 2012, the Postoperative Visual Loss Study Group published a multicenter case-control study that explored the risk factors for ION after spinal fusion sur-

gery in the prone position[11]. Prior studies of ION after spine surgery were limited by small numbers without appropriately matched controls or by lack of associated intraoperative data (estimated blood loss, fluids administered, type of surgical frame, case duration, *etc.*)[4,5,10]. This study comparing 80 cases from the ASA Postoperative Visual Loss Registry to 315 controls from 17 institutions throughout the United States addressed these shortcomings. Obesity, male sex, Wilson frame use, longer anesthetic duration, greater estimated blood loss, and decreased percent colloid administration were significantly and independently associated with ION after spinal fusion surgery[11].

Theoretical mechanisms for ischemic optic neuropathy after prone spine surgery

The most popular pathophysiologic explanations used today for ischemic optic neuropathy during prone position are the elevation of venous pressure and development of interstitial edema[11]. Theoretically, these two processes can cause damage to the optic nerve by compression of the vessels that feed the optic nerve, venous infarction or direct mechanical compression. A rise in central venous pressure can occur in obese patients when their abdomen is compressed during prone position. Venous pressure can also elevate when the head position is lower than the heart, a given when patients are placed in the Wilson frame. Lower oncotic pressure leading to a growing interstitial edema can occur when there is significant inflammation and capillary leak such as in situations of major blood loss and/or prolonged cases. The same can occur when less colloid is used overall. Thus far, these explanations are simply theories that require further investigation. Why the male sex appears to be a risk factor for ischemic optic neuropathy during prone position is still a puzzle, but it has been suggested that estrogen may serve a protective role[31].

Retinal ischemia: Branch and central retinal artery occlusion

Central retinal artery occlusion (CRAO) decreases blood supply to the entire retina, whereas occlusion of a retinal branch (BRAO) affects only a portion of the retina. Both are ophthalmic emergencies and analogous to an acute stroke of the eye. Retinal ischemia has been documented in both adults and children following ocular trauma[32], and also embolic[33] and vasospastic episodes[34].

With respect to spine surgery, these conditions are mostly commonly seen during the perioperative period from improper patient positioning and external compression on the eye[35]. Of the 93 cases submitted to the ASA Visual Loss Registry, there were 10 cases of CRAO[9], representing a much smaller percentage than ION. Perioperative trauma was noted in 70% of the cases, as evidenced by corneal abrasion, ipsilateral decreased supraorbital sensation, ophthalmoplegia, ptosis, or unilateral erythema[9].

Theoretical mechanisms that have been used to explain CRAO include thromboembolism, direct pressure to the globe, and increased intraocular pressure. Decreased oxygen carrying capacity and blood flow to optic nerve such as from hypovolemia, anemia, large blood loss, and peripheral vascular disease, have also been suggested etiologic factors for CRAO. The use of horseshoe-shaped headrest has been associated with this complication. Hollenhurst *et al*[1] described CRAO in eight patients after prone spine surgery on horseshoe headrest. In fact CRAO in spine surgery was subsequently referred to as "headrest syndrome[22]". Increased risk is also observed in patients with altered facial anatomy, osteogenesis imperfecta, and exophthalmos, all of which can increase effects of external compression[36].

CRAO is often unilateral in presentation with severe visual loss in the affected eye. Patients are found to have a cherry-red spot on the macula, a white ground-glass appearance of the retina, attenuated arterioles, and an afferent pupillary defect[37]. Visual loss from CRAO is almost always irreversible and there are no established effective treatment options.

Cortical blindness

Cortical blindness is the result of decreased perfusion to the occipital cortex by the posterior cerebral artery. The cause is either hypoperfusion or embolic phenomenon. Patients with cortical blindness have normal light reflex and fundoscopic examination as the optic tracts and radiations are unaffected. When one side is affected, the patient presents with contralateral homonymous hemianopsia. If both sides suffer ischemic insult, the patient may have peripheral vision loss or complete blindness. Cortical blindness may improve initially after the infarct, but total recovery is rare.

PRES

PRES is a neurologic syndrome that presents as a combination of seizures, visual changes, vomiting, headache, and decreased level of consciousness. It is associated with acute medical illnesses such hypertensive episodes, autoimmune disease, malignancy, chemotherapy, immunosuppressant therapy, infection, renal disease, vasculitis, eclampsia, and preeclampsia[38]. Although more closely identified with obstetric patients, PRES has also been reported after lumbar fusion[39], hysterectomy[40] and video-assisted-thoracoscopic wedge resection[41]. PRES has characteristic MRI findings. There are two leading theoretical explanation for PRES. One is acute increase in blood pressure above the brain's autoregulatory limit thereby causing brain edema. The other pathophysiologic explanation is cytotoxic drugs or diseases causing endothelial injury and edema formation. Management is appropriate use of anti-seizure and anti-hypertensive agents and treatment of causative factor(s). Unlike ION and CRAO, PRES has a favorable recovery pattern.

TREATMENT AND PREVENTION OF POVL

When a patient reports any visual symptoms following surgery, an urgent ophthalmologic consultation should be obtained to determine its cause. If an apparent ocular

Table 1 American Society of Anesthesiologists perioperative visual loss practice advisory consensus conclusions

There is a subset of patients who undergo spine procedures while they are positioned prone and receiving general anesthesia that has an increased risk for the development of POVL. This "high-risk" subset includes patients who are anticipated preoperatively to undergo procedures that are prolonged, have substantial blood loss, or both
Consider continuous blood pressure and central venous pressure monitoring in high-risk patients
Consider informing high-risk patients that there is a small, unpredictable risk of POVL
The use of deliberate hypotensive techniques during spine surgery has not been shown to be associated with the development of POVL
Colloids should be used along with crystalloids to maintain intravascular volume in patients who have substantial blood loss
At this time, there is no apparent transfusion threshold that would eliminate the risk of POVL related to anemia
High-risk patients should be positioned so that their heads are level with or higher than the heart, when possible. In addition, their heads should be maintained in a neutral forward position (without significant neck flexion, extension, lateral flexion, or rotation) when possible
Consideration should be given to the use of staged spine procedures in high-risk patients

POVL: Perioperative visual loss.

injury or central retinal artery occlusion is not obvious, neuroimaging should be obtained, preferably MRI with gadolinium to assess for intracranial pathologies, including occipital stroke or pituitary apoplexy[42]. If imaging is negative, the most likely etiology is ION. Treatment has often involved high dose steroids, mannitol or other agents to decrease intraocular pressure, and anti-platelet agents; however, none of these approaches have been shown to be effective[13,24,43].

Our group recently examined the effect of crystalloid versus colloid and the use of the α-agonist Brimonidine on IOP during prone spine surgery[44]. Of note, the mean rate of IOP rise in the prone position and mean IOP at the end of surgery was significantly greater in patients receiving crystalloid than those receiving colloid. Topical Brimonidine also led to a significant reduction in IOP, both intraoperative and postoperative. Ocular perfusion pressure, however, did not vary significantly between the groups as hypotension was aggressively treated, suggesting that maintenance of blood pressure may be a more important factor in determining perfusion pressure. Much larger studies are needed to determine whether maintaining appropriate ocular perfusion pressure reduces the risk of POVL after spine surgery.

Given the poor prognosis and lack of validated treatment options, it is essential to take prophylactic measures during surgery to prevent the development of POVL. The ASA Task Force on Perioperative Blindness, consisting of anesthesiologists, neuro-ophthalmologists, and spine surgeons was formed in 2005 to evaluate the literature and develop a practice advisory to help deal with this issue. In 2006, a "practice advisory" was published and the consensus conclusions are listed in Table 1[42]. Other guidelines found in this advisory as well as the update published in 2012[43], suggest periodically checking hemoglobin and hematocrit values, and avoidance of direct pressure on the globe to avoid CRAO injuries. A variety of commercially available devices are available to help limit mechanical ocular compression during prone surgery, but these still require vigilance on the part of the surgeon and anesthesiologist as patient movement and shifting of the device may occur. If POVL is suspected, additional efforts directed towards optimizing hemoglobin/hematocrit values, hemodynamic status, and systemic oxygenation may be appropriate[43].

PERIOPERATIVE VISUAL LOSS IN OTHER SURGERIES

Perioperative visual loss has also been associated with robotic and laparoscopic surgeries. Cases of visual impairment have been reported to occur in minimally invasive proctocolectomy, laparoscopic nephrectomy and robotic prostatectomy[45-48]. During robotic prostatectomy, increased intraocular pressure occurs due to prolonged duration in steep Trendelenburg position combined with CO_2 insufflation of the abdomen. The central venous pressure within the thorax increases with Trendelenburg position, which may reduce drainage of blood flow from the head, thereby leading to elevation in IOP. During CO_2 insufflation, the increase in intra-abdominal pressure will further augment the increase in intrathoracic pressure. Furthermore, insufflation of CO_2 increases the carbon dioxide in the blood, which can lead to cerebral vasodilatation and increased cerebral blood volume. The end result is elevation in venous pressure. It is unknown whether the same risk factors for POVL in spine surgery can be applied to laparoscopic and robotic surgeries, but it appears venous congestion and interstitial edema are commonalities among these surgeries. As robotic surgeries gain popularity, studies to find population at risk are underway. Conservative management, however, with attempts to decrease venous congestion and interstitial edema would seem appropriate.

CONCLUSION

In summary, POVL in spine surgery is extremely rare, but it remains a dreaded complication despite significant efforts to identify risk factors and a pathophysiological mechanism. Potential causes of POVL after spine surgery include anterior ischemic optic neuropathy, posterior ischemic optic neuropathy, cortical blindness, retinal ischemia, and posterior reversible encephalopathy syndrome. The vast majority of cases are related to ischemic optic

neuropathy. Many reports have attempted to link hypotension, anemia, and blood loss to the development of this disease; however, no single mechanism can entirely explain the varied circumstances in which it occurs. This suggests a multifactorial etiology and perhaps individual susceptibility related to varied optic nerve blood supply and anatomy.

In the largest and most comprehensive study to date, the Postoperative Visual Loss Group, using data from the ASA Post Operative Visual Loss Registry, identified obesity, male sex, Wilson frame use, longer anesthetic duration, greater estimated blood loss, and decreased percent colloid administration as significant independent risk factors for the development of ION. These risk factors, with the possible exception of male sex, are thought to promote a rise in venous pressure and interstitial edema limiting optic nerve perfusion. Further studies will hopefully elucidate whether the use of colloid and/or topical a-agonists to limit the rise in IOP during complex prone spine surgeries is important in maintaining ocular perfusion and reducing the incidence of POVL.

Given the complete lack of effective treatment modalities, prevention is crucial for limiting the incidence and destruction of POVL. Practitioners are encouraged to follow the ASA guidelines listed in Table 1, especially for patients identified as high risk undergoing procedures that are known to result in visual loss.

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Techniques and accuracy of thoracolumbar pedicle screw placement

Varun Puvanesarajah, Jason A Liauw, Sheng-fu Lo, Ioan A Lina, Timothy F Witham

Varun Puvanesarajah, Jason A Liauw, Sheng-fu Lo, Ioan A Lina, Timothy F Witham, Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, MD 21287, United States
Author contributions: Puvanesarajah V, Liauw JA, Lo SF, Lina IA and Witham TF contributed to research and writing of this manuscript.
Supported by Gordon and Marilyn Macklin Foundation
Correspondence to: Timothy F Witham, MD, Department of Neurosurgery, Johns Hopkins Hospital, 600 North Wolfe Street, Meyer 7-109, Baltimore, MD 21287, United States. twitham2@jhmi.edu
Telephone: +1-410-5022383 Fax: + 1-410-5023399
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Abstract

Pedicle screw instrumentation has been used to stabilize the thoracolumbar spine for several decades. Although pedicle screws were originally placed *via* a free-hand technique, there has been a movement in favor of pedicle screw placement with the aid of imaging. Such assistive techniques include fluoroscopy guidance and stereotactic navigation. Imaging has the benefit of increased visualization of a pedicle's trajectory, but can result in increased morbidity associated with radiation exposure, increased time expenditure, and possible workflow interruption. Many institutions have reported high accuracies with each of these three core techniques. However, due to differing definitions of accuracy and varying radiographic analyses, it is extremely difficult to compare studies side-by-side to determine which techniques are superior. From the literature, it can be concluded that pedicles of vertebrae within the mid-thoracic spine and vertebrae that have altered morphology due to scoliosis or other deformities are the most difficult to cannulate. Thus, spine surgeons would benefit the most from using assistive technologies in these circumstances. All other pedicles in the thoracolumbar spine should theoretically be cannulated with ease via a free-hand technique, given appropriate training and experience. Despite these global recommendations, appropriate techniques must be chosen at the surgeon's discretion. Such determinations should be based on the surgeon's experience and the specific pathology that will be treated.

Key words: Thoracic vertebrae; Lumbar vertebrae; Pedicle screw; Fluoroscopy; Computed tomography

Core tip: Pedicle screws are currently placed in the thoracolumbar spine via three main techniques: free-hand, fluoroscopy guidance, and stereotactic navigation. Various studies have reported success with each of these techniques. However, it is clear that there is some difficulty in comparing such studies due to differing definitions of accuracy and methods of evaluation. Regardless, it is evident that image-assisted techniques provide some benefit when cannulating mid-thoracic vertebral levels and vertebrae that have altered morphology due to deformation from complex pathologies. However, a surgeon's ultimate decision must be based on individual experience and comfort with a given technique.

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INTRODUCTION

Since it was first described by Boucher[1] in the 1950s, used more extensively by Roy-Camille *et al*[2] later in the

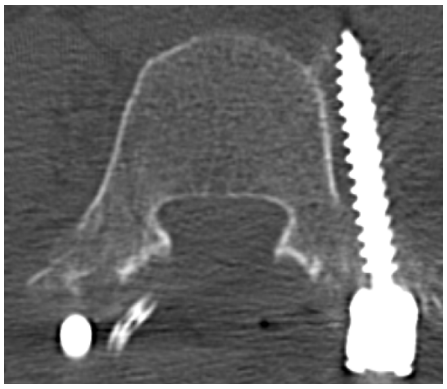

Figure 1 Axial computed tomography image depicting lateral breach of a pedicle screw intended for the L4 vertebrae.

1960s and 1970s, and then downclassified from an FDA Class Ⅲ to Class Ⅱ device in 1998, pedicle screw instrumentation has been steadily gaining popularity. This technology is now almost exclusively used when securing fusion constructs in the thoracolumbar spine, due to the purported improved fusion rates and rigidity afforded by these constructs[3-9]. Furthermore, studies have found that pedicle screws are biomechanically advantageous when compared to predecessors, including previous rod and hook systems[10-12]. Furthermore, pedicle screws are generally considered to be safer than other constructs, including sublaminar wiring, which often necessitate placement of instrumentation within the spinal canal with resultant neurological risk[13].

Initially, pedicle screws were used more frequently in the lumbar spine, where pedicles are thicker and thus easier to cannulate and generally have trajectories that do not skirt important neural or vascular structures. In particular, these lower spinal levels are less susceptible to serious neural damage from medially directed screws, as components of the cauda equina are much less prone to damage[14]. However, the inherent biomechanical advantages of pedicle screws led to their adoption in the thoracic spine. In the thoracic spine, there is admittedly a much lower margin of error, as errant screws are capable of injuring the spinal cord and other structures intimately related to the vertebrae, including the thoracic pleura, esophagus and intercostal and segmental vessels. Other structures within the thoracic cavity at risk include the thoracic duct, azygous vein, inferior vena cava, and aorta[15].

Placement of thoracic pedicle screws can be even more challenging as the thoracic vertebrae tend to be more anatomically varied than lumbar vertebrae when considering pedicle angles and attachment to the vertebral body[16]. This is particularly observed at the middle thoracic levels (T3-T9), which have the narrowest pedicles and have decreased space between the medial border of the pedicle and spinal cord[17-19]. Studies have estimated that screws placed in this region have a 1 mm translational margin of error and a maximal permissible rotational error of 5° off the pedicular axis, due to anatomically small pedicle diameters[17]. Apart from complexity associated with normal anatomy, pedicles can be difficult to instrument due to presenting pathologies. In patients with significant scoliosis, rotation and asymmetric compression of vertebrae can significantly alter pedicle anatomy and complicate pedicle screw placement[20]. Surgeons must be cognizant of such asymmetries intraoperatively as there is little margin for error in optimal screw placement in the thoracic spine. In reality, there are three general technique classes currently used by surgeons for placement of pedicle screws. Techniques can be classified as either free-hand (*i.e.*, without the aid of any imaging) or assisted with either fluoroscopy or stereotactic navigation technology. Free-hand technique relies on appreciation of normal and abnormal spinal anatomy, as the surgeon is entirely reliant on pre-operative imaging and intra-operative anatomical landmarks. Assistive fluoroscopy and navigation are helpful in that they guide pedicle screw placement more or less in real time, but are limited by time costs and in the case of fluoroscopy, significant radiation exposure.

Assistive techniques were designed to decrease the breach rate and improve pedicle screw placement accuracy. However, it is unclear whether assistive technologies actually decrease cortical breach and improve outcomes when compared to free-hand techniques. There have been many studies both illustrating institutional practices and pedicle screw placement accuracy, but due to differing definitions of breach and the lack of explicit control groups, many of these studies are difficult to interpret. In this review, we first define different methods of assessing cortical breach of pedicle screws and summarize the literature to date concerning pedicle screw placement accuracy by these various techniques. From this analysis, we hope to make conclusions regarding the necessity of assistive technology when placing pedicle screws in the thoracolumbar spine.

BREACH CLASSIFICATION

As mentioned previously, incorrect placement of pedicle screws (Figure 1) is a potential source of great patient morbidity. As such, there has been a large volume of data concerning how best to interpret pedicle screw cortical breaches. Several metrics have been applied to characterize cortical breach. These metrics vary slightly when applied in studies from different institutions, which adds an extra level of difficulty when comparing study results. However, they often all require the use of postoperative CT scans, which are generally accepted as being the most beneficial imaging study when judging pedicle screw accuracy[21-25].

In essence, variations of two grading scales are currently used to describe pedicle screw placement. In the first, which is often referred to as the Gertzbein scale, cortical breaches are described by the extent of extracortical screw violation. In this system, Grade 0 screws are those that are fully contained within a pedicle with no evidence of cortical breach, while higher grades are assigned

Table 1 Gertzbein classification[5]

Grade	Breach distance
0	0 mm (no breach)
1	< 2 mm
2	2-4 mm
3	> 4 mm

in breach distances of multiples of 2 mm, where distance is measured from the medial border of the pedicle (Table 1)[5]. This scale was first applied when assessing screws placed from T8 to S1. During this initial application, the scale was intended to only assess the degree of spinal canal encroachment, as lateral screws were excluded from graded classification. A later study by Youkilis *et al*[14] slightly altered this classification to specify three different grades: Grade 1 screws did not show evidence of pedicle breach, Grade 2 screws breached 2 mm or less, and Grade 3 screws were those that breached more than 2 mm. However, recent studies have expanded on the original Gertzbein scale by applying it in every direction of possible cortical breach. One more recent study pioneered the use of this graded classification in each of six possible directions of cortical breach: anterior, lateral, medial, inferomedial, inferolateral, and superior. As such, each screw was given six different grades ranging from 0-3[25].

In practice, multiple studies have used variations of the Gertzbein classification and initial assertions from his pioneering study have been used to define pedicle screw accuracy. Gertzbein and Robbins noted that at the levels investigated by the authors, cortical breaches of greater than 4 mm were associated with neurologic deficits, leading them to conclude that this 4 mm range may constitute a "safe zone" for screws placed from T10 to L4[5]. Other studies have similarly termed breaches ranging from 2 mm medially and 4 mm laterally as a "safe zone"[26]. However, these safe zone definitions reflect opinions that have not necessarily been substantiated by specific data or facts.

A study conducted by Heary *et al*[22] noted that such grading of inaccurate screw placement may not be representative of clinical repercussions of cortical breaches. In particular, the thoracic spine is characterized by pedicle-rib complexes, where laterally penetrating pedicle screws can often be contained within the posterior rib. In fact, the study's authors considered lateral breach at mid-thoracic and lower thoracic regions to be sometimes optimal, as additional bony rib purchase could theoretically increase pullout strength. As such, at these levels, they advocated for the use of larger screws at these levels with the intention of lateral pedicle breach. At T1 or T2, where nerve root injury was a greater concern due to their role in upper extremity function, smaller screws were purposefully used to more easily keep screws within the pedicles. The Heary classification is summarized in Table 2. In essence, this classification scheme serves to stress that some screws require immediate removal due to proximity to critical structures (Grade 5), while other screws that breach laterally but are still contained within the rib may be acceptable (Grade 2). Additionally, this scheme was novel in that it was the first classification that graded anterior breaches, *i.e.*, those through the vertebral body (Grade 3). This scale is limited in that it doesn't consider the metric extent of breach in any direction, although this is somewhat rectified by the Grade 5 classification, which is ultimately most clinically relevant[22].

Table 2 Heary classification[22]

Grade	Breach
1	None
2	Lateral, but screw tip is within VB
3	Anterior or lateral breach of screw tip
4	Medial or inferior breach
5	Breach that requires immediate revision (due to proximity to sensitive structures)

Other classification schemes include methods that grade screws as either "in" or "out" by using a cortical breach threshold defined by the amount of the screw's diameter that exists outside of the pedicle. The most notable example of this technique was illustrated in a study that defined breached screws as those where 25% of the screw diameter was located outside of the pedicle. In this study, it was theorized that CT-related metal artifact, which was estimated to distort perceived screw location by 25% of the diameter of the screw, could skew perception of cortical breach[27]. Importantly, this particular breach classification appropriately adjusts for screws that increase in size at lower vertebral levels. However, this classification is not often used due to the frequent usage of the Gertzbein classification scheme.

PEDICLE SCREW PLACEMENT TECHNIQUES

In the following section, we briefly review each of the three major classes of techniques: free-hand, fluoroscopy-guided, and stereotactic navigation. In these sections, we describe each technique and discuss some of the salient pros and cons associated with each technique. Furthermore, studies reporting isolated use of each technique are provided in a tabular format to demonstrate institutional success with a given technique and associated concerns. Comparison studies are also provided when available. For each study, accuracies and revision rates are listed. Some studies reported multiple accuracy measurements. For these studies, accuracies that were defined by the lowest margin of error were tabulated.

FREE-HAND TECHNIQUE

Free-hand pedicle screw placement relies on an intricate appreciation of the relationship of various anatomical landmarks at each level of the thoracolumbar spine.

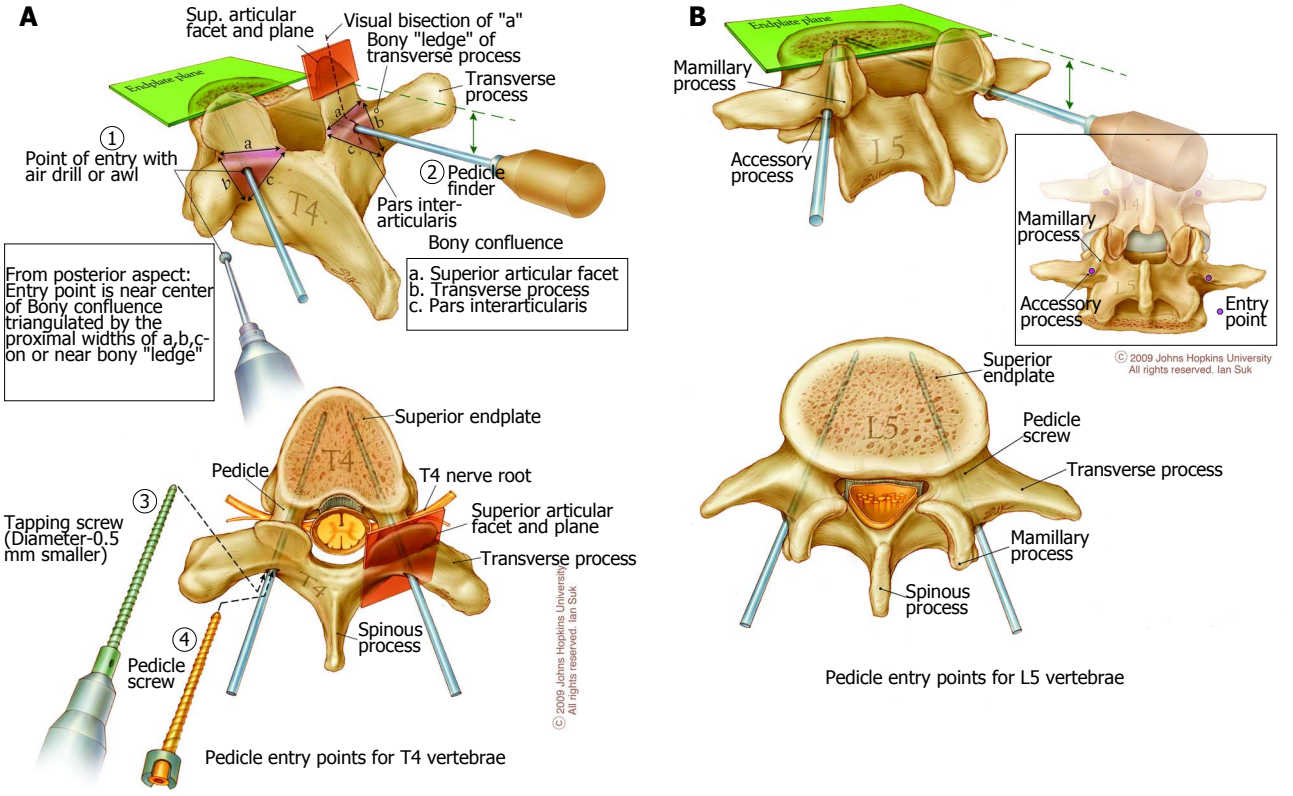

Figure 2 Artist depiction of the entry site used in the T4 (A) and L5 (B) vertebrae. Image has been reproduced (WITH PERMISSION) from manuscript published by Parker *et al*[27].

Analogous entry sites guided by differential anatomy are utilized for both the thoracic and lumbar spine. These anatomical sites are specified in such a way that allows direct trajectory along the pedicle axis, providing maximal screw stability. Before targeting an initial entry site, an intraoperative localizing radiograph is often performed to assess spinal alignment.

In the thoracic spine, the lower border of the superior articular facet, the medial border of the transverse process, and the pars interarticularis form a triangle, the center of which should be targeted for initial entry (Figure 2A)[27]. This has been variably reported as "the base of the superior articular process at the junction of the lateral one-third and medial two-thirds[28]." Within the thoracic spine, entry sites tend to be more medial and cephalad when progressing from T12 to T7. Above T7, entry sites tend to be more lateral and caudad[29]. In the thoracic spine, the "in-out-in" technique, where screws are intentionally placed more laterally to decrease the risk of medial breach and potentially increase bony rib purchase, is often also utilized. The "in-out-in" technique can also be used in situations where patients have congenitally small thoracic pedicles.

In the lumbar spine, the entry site is located at the intersection of the bony confluences of the pars interarticularis, the transverse process, and the mammillary process of the vertebrae that will be instrumented (Figure 2B)[27]. In patients with degenerative joint disease that precludes adequate pedicle screw stability at this location, an appropriate entry site would be one that is further medial, at the inferior border of the superior articular process[27].

After using a drill or awl to create a hole at the thoracic pedicle entry site, a trajectory that parallels the superior endplate is often used due to biomechanical superiority over more anatomical trajectories[30]. A curved gear shaft pedicle probe should first be directed laterally to avoid medial breach for approximately 15-20 mm. This distance represents a distance just past the widest portion of the spinal canal. At this point, the risk of medial breach is decreased significantly and the probe or drill can be directed more medially to prevent lateral breach. After assessing the integrity of the tract with a feeler, it is optional to first use a "tap" to determine if the screw tract is correct and appropriately directed, before using the final, larger screw.

There have been several studies that have investigated the accuracy of free-hand techniques for pedicle screw placement. Selected studies from the last ten years that reported case series where screw placement was only performed *via* the free-hand method are reported in Table 3. In these studies, accuracy rates ranged from 71.9% to 98.3%[5,9,23,26,27,31-33]. Of note, the lowest accuracies were associated with the mid-thoracic spine. In particular, Parker *et al*[27] found that screws inserted into T4 and T6 were most likely to breach, while Modi *et al*[26] found that screws inserted into the pedicles of T5-T8 had a greater incidence of breaches, particularly those that breached beyond a 6-mm wide safe zone. Furthermore, as expected, free-hand techniques have been noted to have a

Table 3 Summary of studies that have evaluated free-hand pedicle screw placement

	Most common pathology	Screw location	Number of patients	Number of screws	Accuracy (%)	Revision rate (%)
Gertzbein *et al*[5], 1990	Trauma	T8-S1	40	167	71.9	N/A
Liljenqvist *et al*[9], 1997	Scoliosis	T4-T12	32	120	75.0	N/A
Kim *et al*[23], 2004	Scoliosis	T1-T12	Unclear	577	93.8	0
Karapinar *et al*[31], 2007	Trauma	T10-L3	98	640	94.2	0
Schizas *et al*[32], 2007	Trauma	T1-T6	13	60	88.3	0
Kotil *et al*[33], 200	Trauma	T1-L5	Unclear	368	93.5	1.5
Modi *et al*[26], 2009	Scoliosis	T1-T12	43	854	93.0	N/A
Parker *et al*[27], 2011	Degenerative/Deformity	T1-S1	964	6816	98.3	0.8

N/A: Not applicable.

significant learning curve. In one particular study, accuracy rates were observed to increase when comparing the accuracy rate of the entire study (71.9%) to that of only the last 25% of placed screws (84.0%)[5].

The greatest benefit from usage of a free-hand technique lies in decreased radiation exposure and decreased procedure time. Both increased radiation exposure and operative time will be discussed at length in later sections that review both fluoroscopy and navigation techniques.

FLUOROSCOPY-GUIDED

Free-hand pedicle screw placement is essentially a blind technique that relies on correct identification of anatomical landmarks, surgeon experience, and reproducible technique to ensure adequate screw placement. As such, early on, the learning curve associated with usage of this technique became apparent, leading to increased surgeon-usage of image-assisted techniques. One such assistive technology is intraoperative fluoroscopy. Intraoperative fluoroscopy relies on serial X-rays to allow surgeons to view a screw's trajectory in real time. Fluoroscopy is used so often during pedicle screw placement that it has been referred to as the "conventional" method, perhaps reflecting its almost expected usage when attempting to employ free-hand techniques[34,35].

Fluoroscopy often utilizes a C-arm to take AP and lateral images parallel to the superior endplate. After an entry site hole is created using anatomic landmarks as described above, it is subsequently marked and the C-arm is utilized in either a lateral plane, anterior-posterior plane, or a combination of both at the level to be instrumented. Subsequent serial images guide surgeon screw placement.

Fluoroscopy has a much lower associated learning curve when compared to free-hand pedicle screw placement. In theory, the breach rate should be lower as fluoroscopy can give surgeons a chance to correct errors while the surgical field is still open. However, this added safety mechanism comes at a cost. The use of intraoperative fluoroscopy is associated with increased operating times and increased radiation exposure. Increased operating times are mostly due to the time it takes to request a technician and subsequently set-up a C-arm, including sterile draping and positioning of the device at the correct location. Additionally, each use of the C-arm requires movement of the equipment into the surgeon's working field, disrupting the workflow and thus increasing operating time. Apart from trivial decreases in efficiency, increased operating times are associated with very real clinical consequences for patients. Increased operating times have been associated with increased incidences of surgical site infection[36].

The radiation risk associated with fluoroscopy during pedicle screw placement has been well-studied in the literature. This risk exists for both the patient and the surgeon, the latter of whom arguably has a greater chance for later development of adverse side effects. Three studies have used anthropomorphic phantoms to approximate radiation exposure in patients treated with pedicle screws guided via intraoperative fluoroscopy[37-39]. In the most recent study, the study's authors first acquired radiation exposure data (including total duration of radiation exposure, parameters associated both AP and lateral images, and the cumulative dose-area product) from 20 patients undergoing procedures requiring pedicle screw instrumentation. Using this data, the authors subsequently treated anthropomorphic phantoms with embedded dosimeters with radiation beams to represent clinical operative exposure. From this experimentation, they were able to approximate the radiation dosage experienced by various organ systems. The study found that on average 4.8 pedicle screws were placed, with the average pedicle screw placement requiring 1.2 and 2.1 min of AP and lateral radiation exposure. When the applicable dose was applied to the anthropomorphic phantom, radiation doses were centered over L4, which the study found to be the most common location of screw placement. This resulted in a mean dose of 1.5 mSv[37], which is comparable to radiation doses postulated by other studies that have noted mean effective doses of 6.8 mSv[38] and 1.0 mSv[39], which as expected are somewhat dependent on the number of pedicle screws used and the time it takes to seat a pedicle screw, the latter of which can be directly attributable to surgeon experience. Perisinakis *et al*[37] estimated that the adjusted risk of fatal cancer in patients receiving an average of 4.8 pedicle screws at the L4 level was about 110 per million, which when compared to a spontaneous cancer risk of 200000 per million is fairly insignificant.

This data suggests that radiation exposure during fluoroscopy is not a relevant consideration when evaluating

Table 4 Summary of studies evaluating fluoroscopy-aided pedicle screw placement

	Most common pathology	Screw location	Number of patients	Number of screws	Accuracy (%)	Revision rate (%)
Halm *et al*[44], 2000	Scoliosis	T10-L4	12	104	81.7	8.3
Belmont *et al*[7], 2001	Scoliosis	T1-T12	40	279	57.0	5.0
Carbone *et al*[45], 2003	Trauma	T1-T12	22	126	86.5	N/A
Kuntz *et al*[46], 2004	Trauma	T1-T12	28	199	27.6	N/A
Vougioukas *et al*[47], 2005	Degenerative	T1-T12	41	328	78.0	0.0
Amato *et al*[48], 2010	Degenerative	L1-S1	102	424	92.2	8.8

N/A: Not applicable.

the merits of this assistive modality during pedicle screw placement. However, it must be noted that these cancer risks are heightened in pediatric populations and patients who have much larger numbers of pedicle screws placed. As such, patients with adolescent idiopathic scoliosis and other significant deformities should be considered at increased risk, although likely still significantly less risk than that incurred from daily living[37].

Although patient radiation exposure is a significant consideration, it is arguable that cumulative surgeon radiation exposure from years of instrumentation procedures is a much more pressing concern. In one study that placed a dosimeter both inside and outside of the thyroid shield to approximate whole-body and thyroid radiation doses, respectively, it was determined that within ten years, a thirty-year old surgeon would supersede the maximum allowable whole body radiation dosage[40]. However, this study did not take into account the dose reduction that occurs through wearing a lead apron, which is estimated to be around 94%[41]. The study further found that thyroid doses were significantly lower than the threshold suggested by the same organization. Hands, on the other hand, are subjected to radiation doses without any real lead protection and undoubtedly receive a significant radiation dose[42].

In recognition of this potential safety issue, studies have postulated that minimizing fluoroscopic time and moving away from beam sources may be indicated to decrease surgeon radiation exposure[43]. Hand doses can be reduced with lead impregnated gloves, which reduce radiation exposure by 33%[42]. Though most studies have focused on surgeon radiation exposure, it is also important to note that other individuals on a surgical team are at similar risk for heightened radiation doses[43].

Studies have generally shown that accuracy rates of screws placed with this technique have ranged from as low as 27.6% to above 90%. These results are summarized in Table 4, which lists a series of publications that reported institutional experience with only fluoroscopic guided pedicle screw technique[7,44-48]. The accuracy range observed here is extended by a study by Kuntz *et al*[46], which reported absence of cortical breach in only 27.6% of studied screws. This rate is substantially lower than that reported in other studies that used intraoperative fluoroscopy to guide thoracic screws, owing to the fact that a majority of the screws included in this study were placed in the mid-thoracic region (T3-T9), a region with proven screw placement difficulty, and that many of the screws were purposefully chosen such that their diameters were larger than corresponding pedicle widths (for purported increased pullout strength).

Interestingly enough, the combination of narrow pedicles and difficult pedicle trajectories in the mid-thoracic spine again resulted in the greatest number of misplaced pedicle screws. The same Kuntz study noted that "high-risk medial wall perforation" was observed much more frequently when trying to place screws into the pedicles of T3-T9[46].

In addition to its use with open techniques, fluoroscopy is often also used with percutaneous pedicle screw placement. Percutaneous screws placed under fluoroscopic guidance have been shown to be as least as accurate as screws placed with open techniques, if not more accurate[49-52].

IMAGE-GUIDED OR STEREOTACTIC PEDICLE SCREW PLACEMENT

Stereotactic neurosurgical techniques were first applied during cranial procedures before being applied in the spinal axis, an inherently complex structure due to numerous degrees of freedom. Stereotactic guidance requires initial image registration for eventual computer model generation. This computer-generated structure must then be matched to the actual operating room volume space by way of fiducial markers placed on prominent bony landmarks, a spinal reference marker, and subsequent matching of these points to analogous points on the generated image. This process was originally accomplished with a pre-operative CT and then surgeon matching of points on the computer-generated image to anatomical points on the patient[53]. From the reference marker, "virtual" fiducial markers, and strategically placed cameras in the operating room, a surgeon's instruments can be triangulated and displayed relative to a 3D reconstruction displayed on a screen within the operating room. This allows the surgeon to plan screw entry site and adjust the trajectory of screws in real-time.

However, with increased use of fluoroscopy and more recently intraoperative CT scans, both the reference marker and fiducials are now often placed on bony landmarks prior to image acquisition within the operating room. This prevents any inaccuracy that might result

from re-positioning of the patient that undoubtedly occurs between pre-operative CT scans and transition to the operating table[54]. Fluoroscopy, as it was first pioneered, only captures images in the lateral and AP planes. As such, appreciation of pedicular structure is typically limited to only two planes. The development of intraoperative 3D imaging techniques has given surgeons the ability to navigate in a truly three-dimensional fashion, without the inaccuracy of images generated by preoperative scans. Recently, intraoperative CT scanners and O-arms have been used more frequently for pedicle screw navigation purposes.

In its infancy, navigated pedicle screw placement was limited by poor image registration due to re-positioning after pre-operative CTs and computing power. However, currently, these limitations are relatively non-existent with the development of sophisticated intraoperative CT and O-arm technology. Regardless, there are still some clear limitations associated with the technique. For example, image-guided techniques have been associated with decreasing accuracy with increasing distance from the spinal reference marker[54-55]. Furthermore, it is reasonable to believe that the process of tapping vertebrae and placing screws can cause motion of vertebral segments relative to one another and can also result in advertant movement of the reference arc. To circumvent any errors caused by such motion, more frequent auto registration verification steps must be taken, which can add time to procedures. Scheufler *et al*[55] further noted that certain inaccuracies pertaining to CT image registration exist with respiration, which moves the entire vertebral column. This was most notable at the mid-thoracic levels. Theoretically, ventilation could be halted during image acquisition, although this carries its own risks.

One of the more prominent criticisms of image-guided techniques centers on associated workflow interruption and additional time costs when compared to free-hand techniques. Much time is spent on vertebral registration and assessing image quality, which can vary from patient to patient. However, some studies have noted that surgical navigation systems used by well-trained operating room staff can decrease surgical time when compared to usage of intraoperative fluoroscopy[56]. Another possible criticism is the exorbitant cost associated with purchase and installation of an image-guided surgical suite.

As mentioned earlier, fluoroscopy-guided pedicle screw placement has been associated with increased radiation exposure to both the operating room staff and the patient. Since image registration occurs fairly infrequently, as compared to fluoroscopy shots, there is very little radiation exposure to operating room staff and the surgeon. In particular, there is theoretically much less radiation exposure to the surgeon's hands, which are probably the most exposed area during fluoroscopic-guided techniques. During image registration via intraoperative imaging, both the surgeon and operating staff can move safely away from the radiation source. However, these techniques, which often rely on CT-based image registration, still result in increased radiation exposure to the patient. Recent technological developments, such as helical CT, can potentially limit this radiation risk to the patient[57].

Studies evaluating the individual use of image-guided techniques have reported accuracy rates ranging from 91.5%-97.7% (Table 5)[14,53-55,58-62]. These rates are subjectively much higher on average than the rates observed for both free-hand and fluoroscopy-guided screw placement. Again, perforation rates were higher in the mid-thoracic spine[14].

Navigation techniques have also benefited from direct comparisons with other techniques in both retrospective and prospective institutional studies with multiple treatment groups (Table 6)[34,35,56,63-66]. These studies have almost unilaterally shown that image-guided techniques have improved accuracy when compared to fluoroscopy-based[34,35,56,64-66] and free-hand techniques[63]. Of interest, one study by Waschke *et al*[66] directly calculated the improvements in accuracy that were observed with CT-navigated pedicle screw placement in both the thoracic and lumbar spine. In the lumbar spine, accuracy improvements were marginal, with a reported accuracy of 96.4% with CT-navigation, as compared to 93.9% with fluoroscopy. However, in the thoracic spine, CT-navigation was associated with a breach rate of 4.5%, while fluoroscopy resulted in breached screws 21.0% of the time, suggesting that image-guided techniques have much higher benefit when applied in the thoracic spine. CT-navigation may similarly be advantageous over fluoroscopy in the context of minimally invasive screws[67].

DISCUSSION

Regardless of technique, pedicle screw-based instrumentation remains one of the strongest posterior fixation techniques for the thoracolumbar spine. In essence, it is only limited by the risk of patient morbidity due to errant screw placement. As such, techniques such as fluoroscopy and stereotactic screw placement have come in vogue to improve on free-hand technique. In combination, all three techniques have resulted in impressive pedicle screw accuracies. A recent meta-analysis investigating studies published between 1990 and 2009 demonstrated that 89.2% of 7533 pedicle screws were placed accurately[68].

For the most part, pedicle screw placement technique as it is practiced today anecdotally appears to be based more or less on institutional practices and surgeon preference. Understandably, there has been a recent push across the field for usage of more guided techniques, to instill confidence and assure the best patient outcome. In keeping with this message, published data has generally reported improved pedicle screw accuracy with such techniques. However, it must be noted that accuracy data from studies must be interpreted. As mentioned before, studies invariably have different metrics for assessing screw accuracy and thus may present improved institu-

Table 5 Summary of studies evaluating navigation-aided pedicle screw placement

	Most common pathology	Screw location	Number of patients	Number of screws	Accuracy (%)	Revision rate (%)
Idler *et al*[53], 1996	Postlaminectomy instability and spinal stenosis	L1-S1	30	139	95.7	N/A
Youkilis *et al*[14], 2000	Assorted	T1-T12	52	224	91.5	N/A
Bledsoe *et al*[58], 2009	Cervical deformity	T1-T3	34	150	93.3	0
Nottmeier *et al*[59], 2009	Unclear	T1-S1	184	951	92.5	N/A
Oertel *et al*[60], 2011	Degenerative Disease	T8-S1	50	278	96.8	0
Scheufler *et al*[55], 2011	Idiopathic and Degenerative Deformity	T2-S1	46	Ta-243 LSb-542	T-96.5 LS-94.4	4.3
Dinesh *et al*[54], 2012	Metastasis	T1-T12	43	261	97.3	1.5 (intraop) 1.2 (postop)
Lee *et al*[61], 2013	Degenerative Spondylolisthesis	T1-S1	178	932	96.8	1.4
Ling *et al*[62], 2013	Degenerative Disease	T5-S1	92	467	95.3	1.3 (intraop)

T: Thoracic spine; LS: Lumbosacral spine; N/A: Not applicable.

Table 6 Studies comparing navigation methods to either free-hand or fluoroscopic methods

	Most common pathology	Screw location	Method	Patients (*n*)	Screws (*n*)	Revision rate (%)	Accuracy (%)	Method	Patients (*n*)	Screws (*n*)	Revision rate (%)	Accuracy (%)	Study design
Amiot *et al*[34], 2000	Degenerative disease	T2-S1	CT-navigation	50	294	0	95	Fluoroscopy	100	544	2	85.0	R, P
Laine *et al*[63], 2000	Spinal stenosis	T8-S1	CT-navigation	41	219	4 (intraop)	95.4	Free-hand	50	277	0 (intraop)	86.8	P
Rajasekaran *et al*[56], 2006	Deformity	T1-T12	Fluoroscopy-navigation	17	242	N/A	98	Fluoroscopy	16	236	N/A	77.0	P
Merloz *et al*[35], 2007	Trauma and degenerative disease	T8-L5	Fluoroscopy-navigation	26	140	N/A	95	Fluoroscopy	26	138	N/A	87.0	R
Tormenti *et al*[64], 2010	Deformity	T1-S1	CT-navigation	12	164	0	98.8	Fluoroscopy	14	211	7.1	94.8	R
Shin *et al*[65], 2013	Degenerative disease	T9-S1	O-arm navigation	20	124	5 (intraop)	91.9	Fluoroscopy	20	138	5 (postop)	87.7	P
Waschke *et al*[66], 2013	Trauma and degenerative disease	T1-S1	CT-navigation	505	2422	1.2	L-96.4 T-95.5	Fluoroscopy	501	2002	4.4	L-93.9 T-79.0	R

R: Retrospective; P: Prospective; N/A: Not applicable.

tional accuracies with certain techniques solely due to differing interpretations of misplacement or breach. A clear example of this is the usage of accuracy to variably represent everything from placement of the entire screw within the pedicle to placement of the screw within a six millimeter wide "safe zone" (four mm laterally and two mm medially)[26]. The concept of a "safe zone" has been based on previous assertions by Gertzbein *et al*[5] that there is a total of 4 mm of allowable medial pedicle screw encroachment within the lower thoracic spine and lumbar spine consisting of 2 mm of epidural space and 2 mm of subarachnoid space. In the thoracic spine, this "safe zone" has been generally decreased to 2 mm to reflect both reduced margin of error[17] and to adjust for cortical expansion and benign pedicle fracture[7]. Regardless of previous literature examinations of this notion of a "safe zone", it is important to point out that the "safe zone" is fairly arbitrary and warrants discussion of the true necessity of its existence as a conceptual entity. A more realistic measure would be revision rates or patient morbidity, which are direct clinical entities that are not reflected in reported accuracy rates. Both morbidity and revision rates are much lower than reported accuracy rates, suggesting that perhaps ever increasing accuracy rates might be associated with diminishing returns in terms of patient outcomes. One last consideration that provides added difficulty in comparing and interpreting reported accuracies is that accuracy rates have a large dependence on the relative proportions of various instrumented levels. A preponderance of lumbar screws, for example, invariably inflates accuracy as these vertebrae tend to have much larger pedicles that are easier to instrument when compared to those in thoracic vertebrae. Due to these reasons, systematic reviews are not completely effective at painting a complete picture when comparing pedicle screw placement, although several have been published[69,70].

As alluded to earlier, the study of pedicle screw placement techniques and their relative accuracies is important in terms of revision of faulty screws. In the literature, screw revision rates are low and generally occur less than once out of every forty pedicle screws placed[55,64,71-73].

However, screw revision can be difficult and time-consuming, as the faulty screw track often hinders effective screw repositioning[61]. When considering screw revision time and possible decreases in biomechanical stability, it is reasonable to use image-guided techniques when there is a high chance of failure.

Considering this information, we have fairly specific recommendations concerning pedicle screw placement and choice of technique. It is the authors' opinion that free-hand pedicle screw placement still has a definite role in modern day posterior instrumentation. It is difficult to argue against this technique when used in either the lumbar spine and/or in patients with no significant deformity. Anecdotally, these patients would derive less benefit from image-based techniques that require more radiation exposure and operating room time. Placement of lumbar screws have a much larger margin of error when compared to thoracic screws, due to pedicle size and the transition of the spinal cord into the cauda equina[17]. However the free-hand technique has demonstrated reasonable results with regards to accuracy in thoracic pedicle screw placement in the hands of surgeons well versed with the free-hand technique. It is particularly important to mention that accuracy with the free-hand technique increases with experience[5], as noted earlier, although a recent study demonstrated a 15% breach rate of thoracic pedicle screws when placed by neurosurgery residents, a rate that is comparable to reported accuracies and suggests that less experienced surgeons may be able to place pedicle screws with high accuracy[74]. Regardless, the free-hand technique may be limited in patients with complicated pathology that can make it difficult to accurately place screws.

In patients with significant deformity or a requirement of mid-thoracic instrumentation, image-guided techniques are recommended. In the literature, high accuracies have in fact been demonstrated in patients with severe scoliosis when using the free-hand technique. However, this can be extremely challenging as even with the aid of pre-operative imaging as curve correction can alter the expected trajectory of non-anatomic pedicles. Thoracic screws similarly pose challenges due to inherent anatomical characteristics. This is particularly evident in the mid-thoracic spine, which is characterized by narrow pedicles[17-19]. As expected, this region is characterized by the lowest accuracy rates[14,26,27,46]. This has real clinical consequences, as the mid-thoracic region is also associated with a smaller "safe zone" in terms of injury to sensitive structures. Usage of pedicle screws at the T4-T9 vertebral levels has an increased risk of injury to both the cord and the aorta[75].

Regardless of technique, there are a number of methods by which pedicle screw placement accuracy can be improved. Such methods include saline irrigation of drilled pedicles to detect breaches[76], endoscopic visualization[77], and electromyographic monitoring[78]. Additionally, with the advent of O-arm and intraoperative CT technology, surgeons can now radiographically assess pedicle screw placement before full closure of the patient, albeit at increased radiation risk to the patient.

Usage of image-guided techniques has clear benefits due to improved pedicle visualization. However, it may not be needed and might ultimately result in an added hindrance that can be avoided with free-hand pedicle screw placement without endangering the patient. The benefits and disadvantages of each technique must be appropriately weighed on a patient-by-patient basis in order to establish the best possible treatment strategy that both limits morbidity and ensures positive patient outcomes. Ultimately, it is the surgeon's experience with a particular screw technique that determines his or her ability to accurately place pedicle screws.

CONCLUSION

There are many published studies evaluating the use of free-hand technique, fluoroscopy-guidance, and stereotactic navigation in placing thoracolumbar pedicle screws. Between studies, assessment of screw accuracy varies significantly, which adds difficulty when interpreting and comparing them. When considering time expense and radiation exposure, it is our recommendation to utilize free-hand techniques when instrumenting regions outside of the mid-thoracic spine in pathologies without significant deformity. Screws placed in the mid-thoracic spine and/or in spines with significant deformity should be guided stereotactically to ensure accuracy. However, these are general recommendations and ultimately appropriate screw placement techniques should be determined on a case-by-case basis, taking into account a surgeon's experience.

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Surgical advances in the treatment of neuromuscular scoliosis

Federico Canavese, Marie Rousset, Benoit Le Gledic, Antoine Samba, Alain Dimeglio

Federico Canavese, Marie Rousset, Benoit Le Gledic, Antoine Samba, Pediatric Surgery Department, University Hospital Estaing, 63003 Clermont-Ferrand, France
Alain Dimeglio, Faculté de Médecine, Université de Montpellier, 34000 Montpellier, France
Author contributions: Canavese F, Rousset M, Le Gledic B and Dimeglio A contributed equally to this work, designed the aim of the editorial content, generated the figures and wrote the manuscript; Samba A revised the manuscript and granted final approval to the version to be published.
Correspondence to: Federico Canavese, MD, PhD, Professor of Pediatric Surgery, Pediatric Surgery Department, University Hospital Estaing, 1 Place Lucie et Raymond Aubrac, 63003 Clermont-Ferrand, France. canavese_federico@yahoo.fr
Telephone: +33-4-73750293 Fax: +33-4-73750291
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Abstract

Neuromuscular disorders are a group of diseases affecting the neuro-musculo-skeletal system. Children with neuromuscular disorders frequently develop progressive spinal deformities with cardio-respiratory compromise in the most severe cases. The incidence of neuromuscular scoliosis is variable, inversely correlated with ambulatory abilities and with a reported risk ranging from 80% to 100% in non-ambulatory patients. As surgical and peri-operative techniques have improved, more severely affected children with complex neuromuscular deformities and considerable co-morbidities are now believed to be candidates for extensive surgery for spinal deformity. This article aimed to provide a comprehensive review of how neuromuscular spinal deformities can affect normal spine balance and how these deformities can be treated with segmental instrumentation and sub-laminar devices. Older concepts have been integrated with newer scientific data to provide the reader with a basis for better understanding of how treatment of neuromuscular scoliosis has evolved over the past few decades. Recent advances, as well as challenges that remain to be overcome, in the surgical treatment of neuromuscular curves with sub-laminar devices and in the management of post-operative infections are outlined.

Key words: Neuromuscular scoliosis; Surgery; Sub-laminar bands; Luque rod; Unit rod

Core tip: In patients with neuromuscular disease, the likelihood and severity of the scoliosis increase with the degree of neuromuscular involvement. There is little doubt that segmental instrumentation techniques have revolutionized the care of patients with neuromuscular scoliosis by providing lasting correction and significant relief of pain and by restoring quality of life and sitting position. The state of knowledge regarding neuromuscular scoliosis is a dynamic process, and a current literature review is mandatory. The somewhat large bibliography for this subject reflects the many opinions and findings currently available.

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INTRODUCTION

Scoliosis is a three-dimensional deformity of the spine with lateral, antero-posterior and rotational components. In most cases, the disease is idiopathic. Non-idiopathic cases are often secondary to neuromuscular diseases affecting the neuro-musculo-skeletal system.

Children with neuromuscular disorders frequently

Table 1 Incidence

Diagnosis	Incidence of scoliosis
Cerebral palsy	25% (GMFCS Ⅰ and Ⅱ) to 100% (GMFCS Ⅳ and Ⅴ)
Charcot-Marie-Tooth disease	30%
Myelodysplasia	60% (lumbar level) to 100% (thoracic level)
Spinal muscular atrophy	70%
Friedreich ataxia	80%
Duchenne muscular dystrophy	90%[1]
Paralysis from spinal cord injury	100%

The incidence of neuromuscular scoliosis is variable. Among patients with neuromuscular disorders, the probability of developing scoliosis is inversely correlated with ambulatory ability, with a reported risk ranging from 80% to 100% in non-ambulatory patients. [1]Corticoids have lowered this percentage[47].

develop progressive spinal deformities, with cardio-respiratory compromise in the most severe cases. Among patients with neuromuscular disorders, the probability of developing scoliosis is inversely correlated with ambulatory ability, with a reported risk ranging from 80% to 100% in non-ambulatory patients (Table 1). Patients with neuromuscular disorders have many similarities in curve patterns, despite different etiologies of the main disease; therefore similar strategies are implemented for treatment.

Neuromuscular scoliosis is characterized by a long collapsing spine, pelvic obliquity and changes in sagittal plane alignment that can affect sitting balance and cardio-respiratory function. Long C-shaped thoraco-lumbar and lumbar curves are very often diagnosed in patients with underlying neuromuscular pathologies. Associated negative predictors include osteopenia and concomitant congenital malformations, which are responsible for rapid progression (collapsing spine)[1-3].

Patients with neuromuscular disorders tend to develop scoliosis at younger ages than patients with idiopathic scoliosis, and a large proportion of neuromuscular curves are progressive and often non-responsive to orthotic management. Unlike idiopathic scoliosis, neuromuscular spine deformities can progress beyond skeletal maturity, particularly in wheelchair-bound patients[1,3-6].

Surgical treatment is more complex in neuromuscular scoliosis than in idiopathic scoliosis. Complex reconstruction can be necessary to obtain satisfactory results. However, a bone stock of poor quality, longer fusions, the frequent need for fusion to the pelvis and increased bleeding can significantly affect operative time and make such surgery difficult.

As surgical and peri-operative techniques have improved, more severely affected children with complex neuromuscular deformities and considerable co-morbidities are now believed to be candidates for extensive surgery for spinal deformity[1,4-6].

Pulmonary, neurologic, genitourinary, nutritional and gastroenterological comorbidities are common in patients with neuromuscular scoliosis and must be managed (pre- and post-operatively) by a multidisciplinary team of care providers. A multidisciplinary approach is the key to a successful outcome. Comorbidities often make corrective operations high-risk procedures. Orthopedic surgeons experienced in undertaking major spine reconstruction, anesthesiologists, pulmonologists, cardiologists, nutritionists and pediatricians must work together to evaluate and handle these complex surgical patients to obtain the best possible outcomes[1,3,7-9].

Furthermore, the post-operative complication rate is much higher (approximately 30%) in patients with neuromuscular deformities, compared to patients with idiopathic scoliosis. Therefore, the risk-to-benefit ratio is an important parameter that must be considered before surgery as the results can be gratifying if patients are properly selected[2,6,10].

Luque rods, or variations on the Luque technique, often remain the preferred instrumentation for neuromuscular curves. The success of treatment depends on the maintenance of a balanced spine on the coronal and sagittal planes over a level pelvis[11-13].

This article aims to provide a comprehensive review of how neuromuscular spinal deformities can affect normal spine balance and how such deformities can be treated with segmental instrumentation and sub-laminar devices.

Older concepts have been integrated with newer scientific data to provide the reader with a basis for better understanding of how treatment of neuromuscular scoliosis has evolved over the past few decades. Recent advances, as well as challenges that remain to be overcome, are outlined in the surgical treatment of neuromuscular curves with sub-laminar devices and in the management of post-operative infections.

HISTORY AND PRINCIPLES OF SURGICAL TREATMENT

Surgical management of scoliotic curves in patients with neuromuscular conditions has evolved over the past five decades. Segmental fixation, sub-laminar wires, L-rods, unit-rods and sub-laminar bands have been progressively developed for the treatment of neuromuscular curves and they now form part of the armamentarium of the spinal surgeon in addressing such deformities. The surgical treatment must be adapted to the severity of the deformity and the neuromuscular disease. The treating surgeon should not be a prisoner of a single strategy; rather, the strategy should depend on the health of the patient (Table 2).

Segmental fixation (early 1960s)

The concept of segmental fixation was pioneered in 1963 by Resina and Alves from Portugal, by fixation with segmental wiring for the treatment of scoliotic curves[11].

Stainless steel wires are passed through a hole at the base of the spinous processes (one wire per vertebra) and are twisted around to two straight rods placed on either

Table 2 Surgical risk

Surgical risk	Walking abilities	Weight	Cardiac Function	Respiratory function (VC)	Sleep	Comorbidities
Average	Ambulatory	> 40 kg	Normal	Normal	Normal	No
Increased	Ambulates with aid	20-40 kg	Reduced	Reduced, but > 50%	Hypersomnia	
High	Non ambulatory	< 20 kg or obese	Significantly impaired	< 50%	Nocturnal hypercapnic Hypoventilation, Obstructive sleep apnea	Yes

In addition to neuromuscular pathology, factors such as walking abilities, nutritional status, cardiopulmonary function and the presence of other comorbidities, must be considered prior to surgery to minimize surgical risk. Morbidity is higher in non-ambulatory patients, with reduced weight and impaired cardiopulmonary function.

Table 3 Decade 1980-1989

Decade-Year of publication	Authors	Patients (*n*)	Neuromuscular condition	Instrumentation	Complications (number of patients)
1980-1989					
1982	Allen *et al*[13]	10	Cerebral palsy	L-rod	
1986	Sponseller *et al*[14]	34	Cerebral palsy	Interspinous process instrumentation	
1988	Gersoff *et al*[16]	33	Cerebral palsy	L-rod	5 deep wound infections *Complications rate:* 15%
1989	Broom *et al*[18]	74	Various	L-rod	1 death; 3 deep wound infections; 2 pressure sores; 6 sets of broken rods; 1 distal rotation and migration of the rod *Complications rate:* 18%
1989	Boachie-Adjei *et al*[17]	46	Various	L-rod	3 cases of pseudarthrosis; 3 deaths *Complications rate:* 13%

Most significant works published between 1980 and 1989.

side of the spine.

This technique allows for translation of the spine and correction of the deformity (mostly on the frontal plane) using an even distribution of corrective forces.

Sub-laminar wires and L-rods (late 1970s)

Eduardo Luque from Mexico popularized sub-laminar wires to attach to L-shaped rods during the late 1970s (Table 3)[12].

In Luque's system, two L-shaped rods are placed on either side of the spine, and they are wired to each of the vertebrae. The L-rods are contoured or bent to conform to the curve and to provide proper sagittal alignment. The wires are threaded through the spinal canal at each vertebral level and are then twisted around the rods on each side of the spine. The wires are usually doubled (to reduce the risk of fracturing the lamina), with one end joined by a bead and the other by a loop. The beaded end is contoured by creating a small bend at the tip that will emerge on the cephalad side of the lamina. A flatter contour minimizes intrusion into the canal. However, it is important to bear in mind that once metal wires are passed under the lamina, great care must be taken to ensure that none of the operating team inadvertently pushes one of the wires into the canal. To minimize this danger, each wire should be temporarily bent over the lamina.

Segmental instrumentation with sub-laminar wires results in even distribution of corrective forces with two lateral fixation points on each segment, which provide good rotatory control. The rods apply pressure on the spine to correct the deformity[12-16].

The L-rods and wire constructs aim at translation and coronal and sagittal balancing, rather than derotation, as their principle, so the extent of derotation is not the purpose that is intended to be achieved with this technique. Because there are multiple points of fixation with the Luque technique, the patient does not have to wear a brace after surgery. Therefore, segmental instrumentation with sub-laminar wires has been widely adopted in the treatment of neuromuscular curves because it provides rigid fixation and allows for early mobilization without external support[12,16-18].

Overall, the technique has proved to be safe and relatively easy to perform with a relatively low complications rate, providing rigid fixation and predictable correction with minimal post-operative external support required, and it is applicable for a wide variety of spinal deformities, offers a high rate of fusion with a low incidence of failure of the instrumentation and provides sagittal plane correction comparable to more recent implants.

Table 4 Decade 1990-1999

Decade-Year of publication	Authors	Patients (*n*)	Neuromuscular condition	Instrumentation	Complications (number of patients)	Outcome/Conclusions
1990-1999						
1991	Gau *et al*[34]	68	Various	Luque-Galveston instrumentation	14 hardware problems; 7 cases of pseudarthrosis; 3 neurologic deficits *Complications rate:* 35%	
1992	Hopf *et al*[35]	44	Various			
1992	Neustadt *et al*[36]	18	Various	CDI of the pelvis	1 hardware failure; 1 deep wound infection *Complications rate:* 11%	Posterior spinal fusion with CDI of the pelvis is an effective treatment for patients with neuromuscular scoliosis.
1992	Onimus *et al*[37]	32	Cerebral palsy		3 deaths; 10 other *Complications rate:* 41%	Pain disappeared in 2/3 of cases; sitting position was acquired in all the cases at follow-up; motor possibilities improved in 25% of cases; associated medical pathologies were reduced in 67% of cases.
1996	Sussman *et al*[38]	25	Cerebral palsy	L-rod		Posterior fusion and instrumentation from the upper thoracic spine to L5 without anterior fusion provides adequate correction and control of spinal deformity for many patients with cerebral palsy
1997	Frischhut *et al*[39]	41	Various	29 L-rod, Luque-Galveston, CDI and ISOLA; 12 Harrington instrumentation	3 deep wound infections *Complications rate:* 7%	
1997	Marchesi *et al*[40]	25	Duchenne muscular dystrophy	L-rod with sacral screws		In every patient, a good sitting balance could be restored after surgery

Most significant works published between 1990 and 1999. CDI: Cotrel-Dubousset instrumentation.

Unit-rod for segmental spinal fixation (late 1980s)

The unit-rod (U-rod) technique was developed in the late 1980s by Bell, Moseley and Koreska from Canada[19].

This technique uses a U-shaped, double, prebent rod, and it is a modification of Luque's segmental instrumentation technique, which, in contrast, must link together two single L-shaped rods[20-22].

The distal portion of the U-rod is inserted into both iliac wings, while the middle and proximal portions are wired to sub-laminar wires threaded through the spinal canal at each vertebral level, from the upper thoracic (T1-T2) to the lower lumbar (L4-L5) spine. Sub-laminar wires are progressively twisted around the U-rod from caudal to cephalad to provide gradual deformity correction.

U-rod instrumentation has become a common, standard technique and the primary instrumentation system for the treatment of pediatric patients with neuromuscular spine deformities and pelvic obliquity (Tables 4 and 5). The technique is simple to apply, it is less expensive than most other systems, and it can achieve good deformity correction and a low reoperation rate[19].

Sub-laminar band technique (late 2000s)

The sub-laminar band devices and technique were first described in 2009 by Mazda *et al*[23] from France. The technique is also known as the universal clamp technique (Table 5).

The technique of placing sub-laminar bands is similar to Luque's wire technique. However, while Luque's wires are made of steel or titanium alloy, the bands with this technique are made of acrylic or polyester material. The bands are supple and, once inserted, cannot be inadvertently pushed into the canal.

The sub-laminar system is composed of a connector, a band-locking set screw, a polyester or acrylic band and, depending on the manufacturer, a rod-locking set screw.

Compared to Luque's metal wires, the technique described by Mazda *et al*[23] allows the surgeon to perform progressive tensioning and deformity correction because of the simplicity of the implant and the tensioning of the strips[24].

Sub-laminar bands have the same stress resistance as steel or titanium alloy sub-laminar wires. Moreover, the increased contact area between the bands and bone improves corrective forces and reduces laminar fracture risk[24].

Today, band-only and hybrid constructs, with lumbar transpedicular screws, thoracic sub-laminar bands and pedicle-transverse hooks at the upper end of the curve, have become widely used and have been shown to provide good correction of spinal deformities, as well as reduced operating time, radiation exposure, and blood loss, compared to all-screw constructs.

SURGICAL TECHNIQUE OF SUB-LAMINAR BANDS PLACEMENT

Basic principles

Patients can be treated either with band-only or hybrid

Table 5 Decade 2000-2011

Decade-Year of publication	Authors	Patients (*n*)	Neuromuscular condition	Instrumentation	Complications (number of patients)	Outcome/Complications
2000-2011						
2000	Yazici *et al*[25]	47	Various	ISOLA-Galveston	2 deep wound infections; 2 hardware removals; 4 cases of pseudarthrosis; 1 pseudarthrosis repair *Complications rate:* 19%	ISOLA-Galveston instrumentation is as safe and effective as other types of instrumentation
2009	Modi *et al*[20]	52	Cerebral palsy	U-rod and pedicle screws	2 deaths; 1 neurologic deficit; 17 respiratory complications (atelectasia, pneumonia, hemothorax) *Complications rate:* 38%	U-rod with pedicle screws provides good frontal and sagittal plane correction, as well as pelvic obliquity improvement (56% correction)
2010	Nectoux *et al*[21]	28	Cerebral palsy	Luque-Galveston, U-rod	1 case of blindness; 1 death; 16 respiratory complications (atelectasia, pneumonia, pneumothorax) *Complications rate:* 64%	
2010	Modi *et al*[22]	27	Spinal muscular atrophy and Duchenne muscular dystrophy	U-rod and pedicle screws	1 death; 4 respiratory failure; 2 neurological deficits; 1 ileus; 2 cases of atelectasia; 3 UTIs; 7 cases of coccydynia; 1 rod dislodgement *Complications rate:* 77%	Although flaccid neuromuscular scoliosis can be corrected well with U-rod and posterior-only pedicle screws, there is a high rate of associated complications
2011	La Rosa *et al*[24]	84	Cerebral palsy	Universal clamps, hooks and L-rod	5 respiratory complications *Complications rate:* 6%	

Most significant works published between 2000 and 2011.

instrumentation.

Band-only instrumentation (Figure 1) is a construct characterized by two bilateral claws at the upper instrumented vertebra (one per side) and sub-laminar bands as thoracic and lumbar anchorages. Band-only instrumentation should be preferred in non-ambulatory patients.

The hybrid construct (Figure 2) consists of two bilateral claws at the upper instrumented vertebra (one per side), multiple transpedicular screws as distal anchorages and sub-laminar bands between the upper claws and distal screws. Hybrid instrumentation can be used in both ambulatory and non-ambulatory patients.

In cases of severe pelvic obliquity, iliac screws can be added to both constructs. Moreover, Ponte's posterior osteotomies can be performed at and around the apex for rigid curves (less than 30% reduction on bending films).

Screws and claws

Instrumentation is performed with the PASS® LP side connection segmental system (MEDICREA, Neyron, France), using 5.5 mm titanium (Ti) or cobalt-chrome (Co-Cr) rods, pedicle screws, auto-stable claws, cross-links and various rod-anchorage connectors locked by nuts.

Transpedicular screws can be inserted with the free-hand technique, and they are mostly placed at the lumbar level.

Auto-stable claws consist of a main pedicular hook and a counter-hook, which can be placed under the lamina or above the transverse process of the upper instrumented vertebra (thoracic region). Upper claws and lumbar screws should be placed before band insertion.

Sub-laminar band insertion

Sub-laminar fixation is performed with the LigaPASS® system (MEDICREA, Neyron, France), which consists of a titanium alloy connector, a rod-locking set screw, a polyester band and a band-locking set screw.

A portion of the ligamentum flavum must be removed from each intervertebral space. Once the canal is opened, the bands can be placed from caudal to cephalad.

Each band ends with malleable Ti leads. The malleable Ti end is contoured by creating a small bend at the tip that will emerge on the cephalad side of the lamina. Contouring the malleable Ti leads helps to slide the band under the lamina from caudal to cephalad, with a very low risk of damaging the thecal sac.

If two bands must be slid under the same lamina, the second band placement can be facilitated using the first band as a guide. The second band should be inserted between the first band and the lamina. By doing so, the thecal sac is protected throughout the whole insertion maneuver of the second band. Moreover, insertion is easier

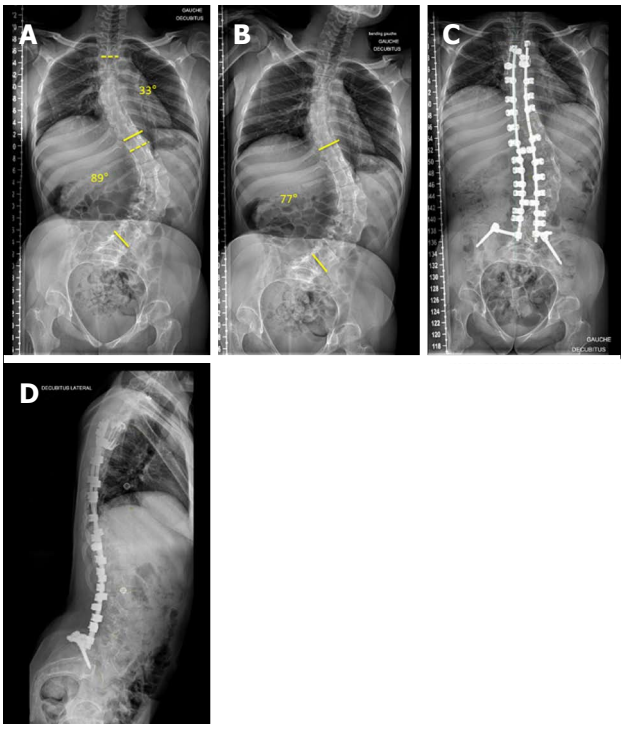

Figure 1 A 16-year-old girls with cerebral palsy (GMFCS IV). This non-ambulatory patient was operated on with band-only instrumentation. A: Pre-operative supine anteroposterior X-rays; B: Pre-operative supine left bending X-rays (reducibility of 13%). C: Post-operative supine anteroposterior X-rays; D: Post-operative supine lateral X-rays.

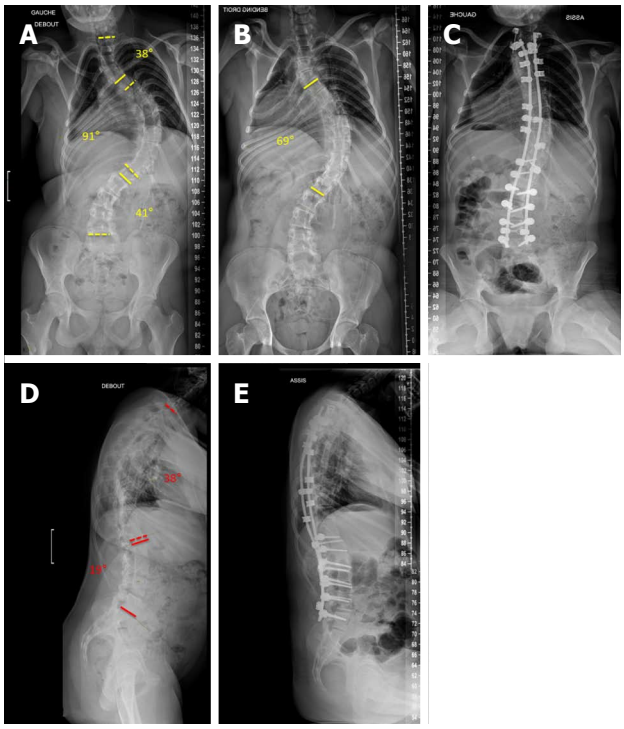

Figure 2 A 15-year-old boy with a genetic syndrome. This ambulatory patient was operated on with a hybrid construct. A: Pre-operative standing anteroposterior x-rays; B: Pre-operative supine left bending X-rays (reducibility of 24%); C: Post-operative seated anteroposterior X-rays; D: Pre-operative standing lateral X-rays; E: Post-operative seated lateral X-rays.

as the first band can be glided from caudal to cephalad, thus bringing the second band into its movement.

The polyester band can be simply passed under the lamina or inserted in a figure-8 belt (under the lamina and around the transverse process). In any case, attention should be paid to ensuring that the band is not twisted during the passing maneuver.

Reduction maneuver

Once band placement is completed, all the connectors can be slid on the previously contoured rod. Subsequently, the two extremities of each band are introduced into the opening situated below the band-locking set screw, ensuring that each end of the band is paired correctly and inserted through the corresponding connector.

The rods are then placed and properly oriented on both the sagittal and coronal planes without any attempt to reduce the deformity. In hybrid constructs, rods can be locked to the lowest lumbar transpedicular screws and pelvic screws. If band-only constructs are used, the rods are locked to pelvic screws. Locking of the rods stabilizes the construct and avoids undesired rotation during band tensioning. The rods should not be locked to the upper claws to allow for rod movements during band tensioning and subsequent deformity correction.

The LigaPASS connectors must be locked perpendicularly to the rod on the coronal plane by setting the rod-locking set screw. This procedure prevents the connector from rotating around the rod and creates a platform for self-stable band tensioning.

The reduction is performed sequentially by progressively tensioning all the bands with the tension pulleys. This process gradually translates the spine toward the rods and reduces the deformity by sharing forces among all the implants. The tension applied to each band can be assessed by observing the strain gauge on the pulley.

Maximum reduction is achieved when the band connector is seated on the vertebra. Once the desired reduction is achieved, the band is locked within the connector by tightening the band-locking set screw. At this point, the remaining screws and upper claws can also be locked.

WHEN TO OPERATE ON A PATIENT WITH NEUROMUSCULAR SCOLIOSIS

Indications for and goals of surgical treatment

In neuromuscular scoliosis, bracing is usually not effective, and surgery becomes the primary treatment option[8].

The type of spinal stabilization is influenced by the age of the patient, the severity of the deformity, the ambulatory status, and the underlying neuromuscular condition.

Posterior instrumentation for neuromuscular deformity treatment should be segmental and low-profile, with sound pelvic purchase if needed[5,11,18,25]. In all cases, fitness for surgery and psychological status should be assessed prior to surgery, as the results can be gratifying if

patients are properly selected.

Surgical treatment is indicated in large curves (> 50°) and in curves progressing beyond skeletal maturity. However, puberty can begin earlier or, more frequently, later in patients with neuromuscular disease (than the puberty of children with idiopathic curves)[1]. Depending on the neuromuscular disease, the rate of progression of the scoliotic deformity during pubertal growth spurt can increase by 2° to 4° per month, especially in patients who are wheelchair-bound. Scoliosis continues to progress beyond skeletal maturity at a rate of approximately 1° to 4° per year if the curvature is greater than 50° at the end of growth, compared to approximately 0.5° to 1° per year for curves of less than 50°[1,8,26].

In addition, neuromuscular curves are responsible overall for a greater decrease in lung volumes compared to idiopathic curves, which, in contrast, are characterized by normal muscle function[27-29].

Sleep-disordered breathing, with or without nocturnal hypercapnic hypoventilation, is a common complication of respiratory muscle weakness in children and adolescents with neuromuscular disorders (Table 2). Nocturnal hypercapnic hypoventilation is a sign of respiratory muscle fatigue and a poor prognosis. It is recommended to perform a polysomnographic evaluation, searching for sleep-disordered breathing in patients with neuromuscular compromise and spinal deformities. Children with neuromuscular scoliosis are at risk for sleep-disordered breathing when the inspiratory vital capacity is less than 60% during daytime hours. Moreover, they are at risk for hypercapnic hypoventilation during the nighttime if their inspiratory vital capacity is less than 40%, and $PaCO_2$ is greater than 40 mmHg[30].

Overall, the indications for surgery are: (1) A significant curve resulting in functional disturbance and/or cardio-respiratory compromise; (2) A progressive spinal deformity not controllable with orthosis; (3) A small curve with inevitable progression; and (4) Painful deformities.

The goals of surgical treatment are: (1) To prevent curve progression; (2) To maintain the spine balanced on the coronal and sagittal planes, with a level and upright trunk position; (3) To provide a balanced and comfortable sitting position to reduce repositioning; (4) To reduce pain; (5) To reduce the discomfort caused by the impingement of the ribs against the iliac crest on the concave side of the curve; (6) To maximize patients' health and function; and (7) To maintain walking ability in ambulatory patients.

Although spinal surgery can restore proper spinal alignment, it has some potential disadvantages. In particular, spinal fusion and instrumentation can adversely affect those patients with neuromuscular disorders who have developed functional compensation techniques requiring a short and mobile trunk. Moreover, surgery stops any further growth over the fused segments, and it can accentuate hip deformity[1,2,6,31].

Hip dislocation, pelvic obliquity and the extent of instrumented fusion

A large number of patients with neuromuscular scoliosis have involvement of the sacrum and subsequent pelvic obliquity. However, patients with neuromuscular scoliosis can develop pelvic obliquity from other sources, such as hip joint and other lower extremity contractures, which will eventually affect the lumbar spine. Furthermore, deformity progression can interfere with trunk stability[32,33].

It is important to assess hip motion and contracture carefully in any patient with neuromuscular spinal deformity. Hip contracture and dislocation can secondarily deform the spine dynamically when the patient attempts to accommodate the hip deformity while sitting.

In cases of unilateral dislocation, pelvic obliquity increases spine deformities and can cause ischiatic pressure sores and loss of sitting position. In such situations, hip surgery is recommended. The choice of surgical procedure depends on the morphology of the femoral head and the presence of necrosis and degenerative cartilage changes. The current recommendations are to reconstruct the hip whenever it is possible. Otherwise, a total hip prosthesis or a femoral head resection can be considered. For patients who present with scoliosis and hip dislocation, hip surgery is usually performed before spinal fusion unless pelvic obliquity is caused by the spine deformity. The goal of orthopedic surgery in non-ambulatory patients is to achieve a sitting position with a level pelvis and an upright trunk position[19,22,24,32].

Instrumentation and fusion should be extended to the pelvis in non-ambulatory patients with pelvic obliquity. In contrast, instrumented fusion can stop at L5 or above when the patient is still ambulatory and shows minimal or no signs of pelvic obliquity. Small amounts of pelvic obliquity (less than 10° to 15°) are compatible with comfortable sitting. in contrast, larger fixed obliquities are not compatible with comfortable sitting and must be corrected surgically or, if not fixed, with wheelchair modifications[34-36].

COMPLICATIONS OF SURGERY

Surgical treatment of neuromuscular spine deformities is more complex than the treatment of idiopathic scoliosis[37-40]. Complex reconstruction can be necessary to obtain satisfactory outcomes. However, the post-surgical complication rate is higher in neuromuscular scoliosis patients, compared to patients with idiopathic scoliosis. The Scoliosis Research Society Morbidity and Mortality Committee reported an infection rate of 5.5% for neuromuscular cases compared to 1.4% in idiopathic patients and a new neurological deficit rate of 1.03% *vs* 0.73%, respectively[41,42]. These rates are often due to the presence of multiple comorbidities. Chronic cardiovascular disease as a consequence of a severe scoliotic deformity can lead to complications such as hypoxemia, hypercapnia, cor pulmonale, and pulmonary hypertension. A preoperative forced vital capacity less than 30% is strongly predictive

of pulmonary complications, and a significant association between restrictive lung disease and increased pulmonary complications has been reported[16-18,22,39].

The nutritional status of patients with neuromuscular disorders is extremely important, as nutritional depletion has been associated with increased complication rates[7,34,36,37].

Complications can be divided into early and late. Early complications are those diagnosed immediately after or within 4 to 6 wk from the index surgery. In contrast, late complications are diagnosed more than 6 wk after the index surgery.

Early post-operative complications include infections, cardio-respiratory, neurologic and nutritional issues, prolonged ileus, constipation, fluid overload, skin breakdown, bleeding and death. Late post-operative complications include chronic infections, non-union, coccigodinia, crankshaft phenomena, implant-related issues, loss of correction and inadequate correction[20,21,25,36,37].

MANAGEMENT OF EARLY SPINE INFECTIONS IN PATIENTS WITH NEUROMUSCULAR SCOLIOSIS

Deep infections after instrumented fusion for the management of scoliosis are uncommon. However, when they do occur, they can result in considerable morbidity, costs and compromise of correction. As surgical and peri-operative techniques have improved, more severely affected children with complex neuromuscular deformities and considerable co-morbidities are now believed to be candidates for extensive surgery for spinal deformity. In the literature, the rate of spinal infections has been reported to increase with the complexity of the procedure, ranging between 1.9% and 20.0%[5,7,21,33,43].

In acute deep spinal infection, the goals are to eradicate the infection by proper debridement of infected and devitalized tissues and to maintain the hardware to avoid losing correction. Most common organisms are *Staphylococcus aureus* and Enterococcus spp. However, rises in methicillin-resistant *S. aureus* (MRSA) and *S. aureus* has been observed.

Various treatment protocols for debridement, soft-tissue management and antibiotic therapy have been recommended with mixed results. The use of the wound vacuum-assisted closure (VAC) system (KCI Inc., San Antonio, Texas, USA) has gained increasing popularity in the management of acute, sub-acute and chronic wounds. Vacuum-assisted closure is a relatively new technique for promoting the healing of infected wounds that are resistant to treatment by established methods[33,43].

The controlled application of sub-atmospheric pressure facilitates the formation of granulation tissue, assists debridement of necrotic tissue and acts as a sterile barrier. Increasing use of the VAC system for complex soft-tissue injuries has generally resulted in accelerated wound healing, compared with traditional methods.

Application of the VAC system

The VAC system consists of a polyurethane ether foam sponge with open pores, 400 μm to 600 μm in size, a connecting tube and a plastic sealant. After thorough lavage and removal of all macroscopic contamination, devitalized tissue and loose bone grafts, the VAC sponge is cut and fitted into the wound. The plastic sealant is used to cover the sponge and is applied several centimeters beyond the margins of the wound to create an airtight seal. A cruciate incision is made in the plastic sealant covering the sponge, through which a suction tube is inserted and fixed. The tubing is connected to a negative pressure device. The sponge is compressed at sub-atmospheric pressure (-125 mmHg), continuously or intermittently. "Controlled negative pressure" is used to evacuate edema from the wound, increase blood flow, decrease bacterial load and increase the formation of granulation tissue. The system also assists the debridement of necrotic tissue and acts as a sterile barrier[33,43].

Intra-operative debridement should involve thorough lavage and removal of all macroscopic contamination, devitalized tissue and loose bone grafts. No attempt should be made to remove grafts that are partially or fully fused. Intra-operative specimens for bacteriological culture must be obtained before application of the VAC system[33,43].

Canavese *et al*[43] treated 14 patients with early post-operative infections in which removal of the implant was undesirable because fusion had not been achieved. These authors had no patients who required removal of hardware and no loss of correction at an average of 44 mo of follow-up.

DISCUSSION/CONCLUSION

In patients with neuromuscular disease, the likelihood and severity of scoliosis increase with the degree of neuromuscular involvement. There is little doubt that segmental instrumentation techniques have revolutionized the care of patients with neuromuscular scoliosis by providing lasting correction, significant relief of pain, and restoration of quality of life and sitting positions. Moreover, continuous evolution in segmental instrumentation has increased the percentage of successful surgical corrections.

However, it must be stressed that although neuromuscular scoliosis can be well corrected with different constructs (hooks, screws, sub-laminar bands, U-rods, L-rods), there is a high rate of associated complications[5,33,44,45]. The complication rates have increased with time, and an increasing number of complications have been reported in the recent literature. This can be explained by the improvement in complication recording but also that more severe patients are now operated. The evidence of such complications should never be underestimated by the treating surgeon, and the rate of such complications is particularly high in patients with flaccid neuromuscular scoliosis, *i.e.*, spinal muscular atrophy and Duchenne muscular dystrophy[22].

The literature regarding the surgical management of spinal deformities in neuromuscular disorders has suggested that bilateral instrumentation and fusion to either L5 or the sacrum are the most effective, and multiple fixation points, such as sub-laminar wires or bands, are preferred[23,24,36,38,45]. In our opinion, instrumentation of the pelvis is indicated in non-ambulatory patients with pelvic obliquity. Fixation of the pelvis can be obtained with iliac screws, while hybrid instrumentation (screws, hooks, sublaminar bands) or band-only instrumentation can be used for deformity correction. Fusion to the sacrum should be avoided in patients with residual walking ability.

In contrast, ambulatory patients should be fused to L5 at most with hybrid constructs (screws as distal anchorages, hooks and sub-laminar bands as proximal anchorages).

Restoring the sagittal balance of the spine is one of the most challenging goals in scoliosis surgery. Sublaminar bands have been demonstrated to provide good deformity correction on both the coronal and sagittal planes[46]. Moreover, the operative time, bleeding and radiation exposure are reduced, with a low rate of early or late surgical complications.

The state of knowledge regarding neuromuscular scoliosis is a dynamic process, so a current literature review was mandatory. The somewhat large bibliography for this subject reflects the many opinions and findings presented here[1,10,43,46,47].

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Pathophysiology, diagnosis and treatment of intermittent claudication in patients with lumbar canal stenosis

Shigeru Kobayashi

Shigeru Kobayashi, Department of Orthopaedics and Rehabilitation Medicine, Faculty of Medical Sciences, and the Research and Education Program for Life Science, the University of Fukui, Fukui 910-1193, Japan
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Supported by Grant-in Aid from the Ministry of Education, Science and Culture of Japan, No, 25460719
Correspondence to: Shigeru Kobayashi, MD, PhD, Department of Orthopaedics and Rehabilitation Medicine, Faculty of Medical Sciences, and the Research and Education Program for Life Science, the University of Fukui, Shimoaizuki 23, Fukui 910-1193, Japan. kshigeru@u-fukui.ac.jp
Telephone: +81-776-618383 Fax: +81-776-618125
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Abstract

Spinal nerve roots have a peculiar structure, different from the arrangements in the peripheral nerve. The nerve roots are devoid of lymphatic vessels but are immersed in the cerebrospinal fluid (CSF) within the subarachnoid space. The blood supply of nerve roots depends on the blood flow from both peripheral direction (ascending) and the spinal cord direction (descending). There is no hypovascular region in the nerve root, although there exists a so-called water-shed of the bloodstream in the radicular artery itself. Increased mechanical compression promotes the disturbance of CSF flow, circulatory disturbance starting from the venous congestion and intraradicular edema formation resulting from the breakdown of the blood-nerve barrier. Although this edema may diffuse into CSF when the subarachnoid space is preserved, the endoneurial fluid pressure may increase when the area is closed by increased compression. On the other hand, the nerve root tissue has already degenerated under the compression and the numerous macrophages releasing various chemical mediators, aggravating radicular symptoms that appear in the area of Wallerian degeneration. Prostaglandin E_1 (PGE_1) is a potent vasodilator as well as an inhibitor of platelet aggregation and has therefore attracted interest as a therapeutic drug for lumbar canal stenosis. However, investigations in the clinical setting have shown that PGE_1 is effective in some patients but not in others, although the reason for this is unclear.

Key words: Lumbar canal stenosis; Cauda equine; Nerve root; Prostaglandin E1; Blood flow

Core tip: The radicular symptoms associated with degenerative disease of the lumbar spine are reported to be attributable to a combination of mechanical nerve root compression and resultant circulatory disturbance. Disturbance of blood flow in the cauda equina and nerve roots is reported to play an important role in the mechanism of intermittent claudication in patients with lumbar canal stenosis. Prostaglandin E_1 (PGE_1) is a potent vasodilator as well as an inhibitor of platelet aggregation and has therefore attracted interest as a therapeutic drug for lumbar canal stenosis with intermittent claudication. However, investigations in the clinical setting have shown that lipo-PGE_1 is effective in some patients but not in others, although the reason for this is unclear.

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INTRODUCTION

Lumbar canal stenosis (LCS) is increasingly a common disease in the elderly. The number of patients with LCS

Table 1 International classification of lumbar canal stenosis

Congenital/developmental
Acquired
Degenerative (spondylosis)
Central
peripheral
Degenerative spondylolisthesis
Combined
Congenital/developmental + Degenerative
Congenital/developmental + Hernia
Degenerative IIernia
Congenital/developmental + Degenerative + Hernia
Spondylolisthetic/spondylolytic
Iatrogenic
Post-tranmatic
Miscellaneous

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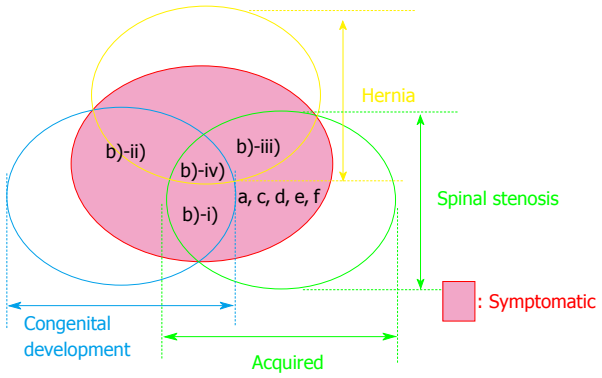

Figure 1 Schematic drawing illustrating the international classification of lumbar canal stenosis.

complaining of low back pain, lower extremity pain and/or numbness, and neurogenic intermittent claudication (NIC) has increased yearly[1,2]. Compression of the cauda equina and nerve roots by LCS is a major clinical problem associated with NIC[3-5]. The development of NIC in LCS has been reported to involve circulatory disturbance due to circumferential compression of cauda equina by the surrounding tissues. When lumbar lordosis increases in the standing position, the severity of stenosis increases and the cauda equina are constricted more strongly, while the constriction decreases in the sitting position or when the trunk is flexed. As a result, NIC is often noted as a characteristic feature. The main symptoms of NIC include deep muscular pain, weakness and loss of sensation in the lower limbs. Such symptoms do not develop immediately after the start of walking, but eventually become severe enough to disturb walking. The patient can only walk from 40-50 m to 400-500 m without resting and the symptoms resolve after resting for several to 10 min. Thus, it is generally agreed that the primary cause of NIC is chronic compression of the cauda equina. In this article, we have reviewed the pathophysiology, diagnosis, and treatment of LCS associated with NIC.

DEFINITION AND CLASSIFICATION OF LCS

In 1910, Sumida gave the first description of LCS due to fetal chondrodystrophy[6]. Sarpyener reported such stenosis due to congenital partial skeletal dysplasia in 1945[7]. Thus, both of them reported congenital conditions. The concept of LCS has been known widely since Verbiest reported on idiopathic developmental stenosis in French in 1949[8], in Dutch in 1950[9], and in English in 1954[10] and 1955[11]. In 1976, Arnoldi *et al*[12] proposed the international definition and classification of lumbar spinal canal stenosis that is still used widely. However, confusion has arisen with regard to interpretation, because it covers both central stenosis (spinal canal stenosis) and lateral stenosis (nerve root canal and intervertebral foramen stenosis), and also covers acquired stenosis due to various degenerative diseases as well as congenital and developmental stenosis. Here, the international classification (Table 1) is interpreted and the problems with it are clarified. The word 'stenosis' implies narrowing of a hollow tubular structure. On this basis, LCS may be defined as any type of narrowing of the spinal canal, nerve root canals (or tunnels) or intervertebral foramina. It may be local, segmental or generalized. It may be caused by bone or by soft tissue and the narrowing may involve the bony canal alone or the dural sac or both. Herniations of the nucleus pulposus have in the past been considered as a distinct and separate entity. They are included in this classification when they occur together with other types of stenosis, which is frequently the case. Space occupying lesions due to the products of inflammation or neoplasm are in the strictest sense types of "stenosis" but are excluded. According to this definition, the symptoms caused by LCS are non-specific and very varied.

Figure 1 is designed to make this classification easier to understand. Among the acquired types of stenosis, spondylosis and degenerative spondylolisthesis are classified as degenerative stenosis accompanied with LCS (a, c, d, e, f in Figure 1). The condition is classified as combined stenosis (b-i) if congenital or developmental factors are also present. Disc herniation is not covered by the concept of spinal stenosis when it exists alone. However, it is classified as spinal stenosis (combined stenosis) when congenital or developmental (b-iii, iv) or degenerative (b-iii, iv) factors are also present. The success of surgical treatment for disc herniation is dependent on the presence of factors causing spinal stenosis. However, it is not always easy to determine whether there are such factors in patients with herniation and whether the stenosis is developmental or acquired. As a result, herniation accompanied by spinal canal or nerve root canal stenosis (b-ii, iii, iv) is often treated after misdiagnosis as simple herniation. On the other hand, patients with central or lateral stenosis who are treated under the diagnosis of spinal stenosis due to spondylosis or degenerative spondylolisthesis may also sometimes have combined devel-

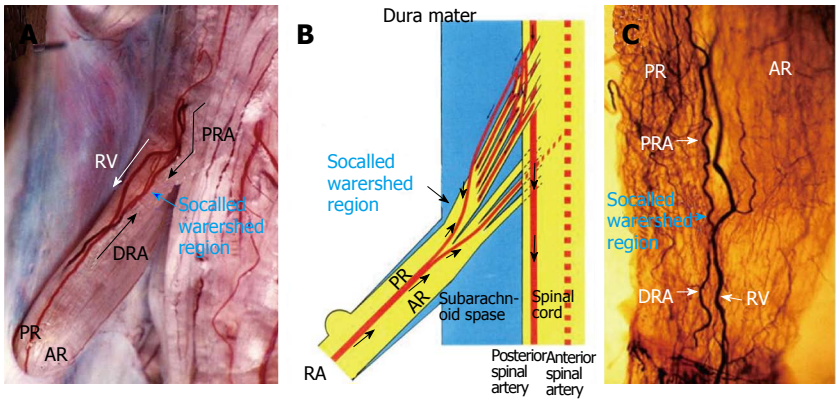

Figure 2 Circulatory dynamics of the radicular artery for the lumbar nerve root in a dog. A: After 3 mL of India ink was injected quickly through a catheter fixed in the aortic arch, seriograhy was performed using a motor-driven camera and repeating flash to observe the flow of India ink into vessels supplying the nerve root. After injection of India ink, at first the proximal radicular arteries (PRA) running along each root filament filled with India ink in a downward direction (↓). Next, the distal radicular arteries (DRA) filled with India ink in an upward direction (↑). A watershed region of blood flow was observed in a radicular vessel (blue arrow). At last, the radicular vein (RV) filled with India ink in the downward direction (white arrows); B: A watershed region was noted in the radicular artery, and in this region the velocity of both blood streams showed a decrease; C: A clear specimen of the nerve root from the same subject as shown in A. An abundant vascular network was noted in the root near the watershed area of the radicular artery observed by seriography. AR: Anterior root. Reproduced with permission from Kobayashi *et al*[28].

opmental stenosis (b-i).

BLOOD SUPPLY OF CAUDA EQUINA NERVE ROOT

Anatomical studies of the vasculature of the nerve roots have developed in association with studies on the vasculature of the spinal cord. In the 19th century, Adamkiewicz[13,14] and Kadyi[15,16] clarified the particularly important role of radicular arteries in the blood supply of the spinal cord. After that, much work was devoted to the vasculature of the spinal cord[17-24], but no research placed emphasis on the supply to the nerve roots until the mid-twentieth century. Corbin described anatomic details of radicular arteries and classified them into three groups: artères radiculo-grères, artères radiculo-piemeriennes, and artères radiculo-medullares[25]. The first two arteries were named as distal and proximal radicular arteries by Parke *et al*[26] and were thought to be nutrient arteries of the nerve roots. They described that each lumbosacral spinal nerve root receives its intrinsic blood supply from both distal and proximal radicular arteries, through which the blood flows toward a mutual anastomosis in the proximal one third of the root. They postulated that the region of relative hypovascularity formed below the conus by the combined areas of anastomoses in the cauda equina may provide an anatomic rationale for the suspected neuroischemic manifestations concurrent with degenerative changes in the lumbar spine. Crock *et al*[27] based on their studies, hold a different view: that there is no area of hypovascularity in the region of the middle third of the cauda equina. Kobayashi *et al*[28] also examined the vasculature of the cauda equina nerve root in dogs with the aid of high-speed serial photography after injecting India ink in the Aorta. Consequently, the blood flow direction of the extradural nerve root and descending in the cauda equina nerve root, and there existed a so-called watershed of the blood-stream in the radicular artery itself near the root of the dural sleeve (Figure 2A, B). When the stream of the ascending radicular artery was intercepted by compression, however, the blood flow direction changed quickly and the blood supply was compensated by the descending radicular artery. Also abundant fine intrinsic arteries form networks in every part of the nerve root, including the area of so-called watershed of the radicular artery (Figure 2B). These observations indicate that there is no relatively hypovascular region in the nerve root, which is vulnerable in the course of degenerative changes of the lumbosacral spine. Although there exists a so-called watershed of the bloodstream in the radicular artery itself, the site of which is, however, changeable due to circumstances. Microangiograms showed an abundant vascular network with repeating T-shaped branching throughout the length of the nerve root (Figure 3). This was also present near the watershed region in the radicular artery, and there was no hypovascular region as suggested by Parke *et al*[26]. Thus, the intraradicular vessels controlled segmentally by radicular arteries have no fixed direction of flow and there appears to be no particular clinical significance in the watershed region of arteries maintaining a high intravascular pressure. Regarding the onset of compression-induced disturbance of nerve root circulation as observed in disk herniation and spinal canal stenosis, it is improbable that obstruction of the arterial system, which has thick walls and a high pressure, precedes obstruction of the venous system[29,30].

EFFECT OF ARTERIAL ISCHEMIA AND VENOUS CONGESTION ON NERVE ROOT FUNCTION

Whether mechanical deformation or a circulatory disturbance plays the more prominent role in the pathogenesis

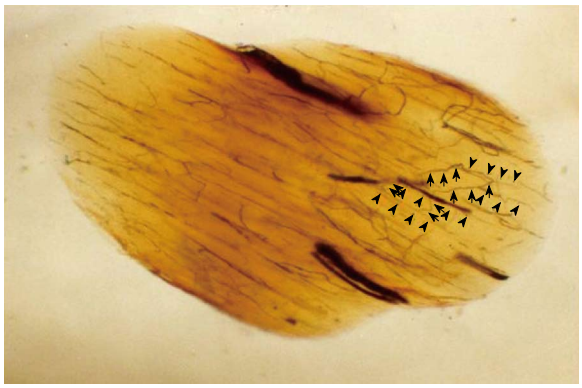

Figure 3 Oblique cleared section of the lumbar nerve root in a dog. There are many longitudinal (arrow head) and transverse (arrow) microvessels in the nerve root. Intraradicular vessels are abundant throughout the nerve root, and their flow is in various directions. Intraradicular vessels arising from the radicular artery as T-shaped branches rarely were affected by the direction of blood flow in the nerve root, suggesting the presence of a mechanism that maintains the blood supply to the intrinsic vessels.

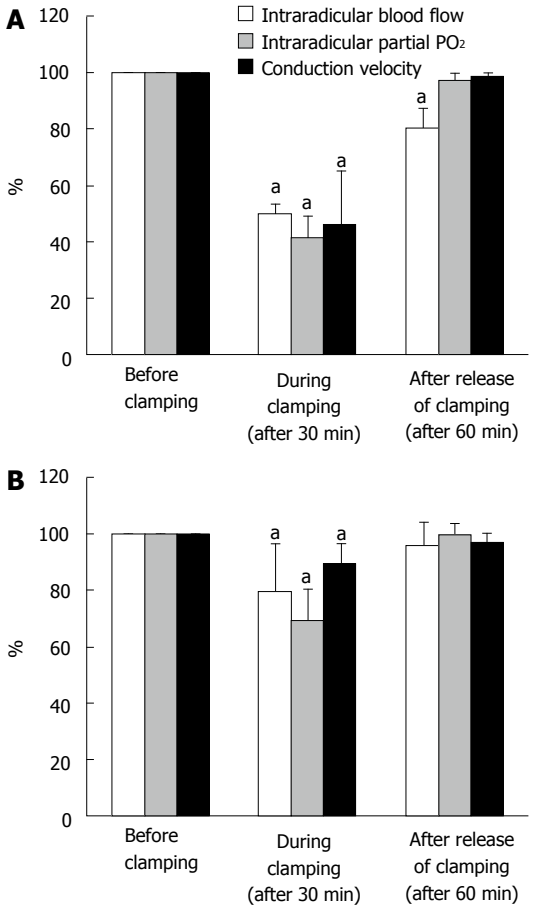

Figure 4 Changes of intraradicular blood flow, partial oxygen pressure and conduction velocity after Aorta (A) or inferior vena cava (B) clamp. Immediately after Aorta clamping, blood pressure in the femoral artery dropped to 26-40 mmHg and meantime, central venous pressure was slightly elevated. When the vena cava was clamped, central venous pressure increased to about 4 times of the pressure before clamping and blood pressure in the femoral artery was reduced by half. The blood flow in the seventh posterior nerve root due to Aorta and vena cava clamping fall to 50% to 60% of the blood flow before clamping in the ischemic model ($^aP < 0.05$) and to about 20% in the congestion model ($^aP < 0.05$). The changes of partial oxygen pressure (PO_2) in the nerve root indicated a similar tendency to blood flow, 50% to 60% drop in the ischemic model ($^aP < 0.05$) and 20% to 40% drop in the congestion model. Conduction velocity of the nerve root diminished by 40% to 50% in the ischemia model ($^aP < 0.05$) and 10% to 20% in the congestion model. After release of clamping, both arterial and venous pressures quickly returned to the pressure before clamping. The intraradicular blood flow in the congestion model was restored within 1 h. The intraradicular blood flow in the ischemic model, however, did not recover and stayed at the reduced level ($^aP < 0.05$). Intraradicular PO_2 recovered completely in both models. The drop of conduction velocity returned almost completely within one hour after release of clamping. Reproduced with permission from Kobayashi *et al*[42].

of NIC with LCS has been a subject of speculation for 5 decades. Blau and Logue postulated that NIC might be evoked with ischemic neuritis of the cauda equina[31]. Evans advocated exercise-induced ischemia as the cause of NIC, which is the characteristic syndrome of this disease[32]. They supposed that reduced blood flow in the spinal nerve roots has been demonstrated during exercise, and this might contribute to the pathogenesis of NIC. Ehni *et al*[33] stressed the postural changes in the spinal canal on standing. He demonstrated a myelographic block in the lordotic position, but flexion permitted the contrast medium to pass. Yamada *et al*[34] reported the importance of intermittent constriction of the cauda equina associated with postural change. They thought that the ligamentous fulvum had a significant role in dynamic narrowing of the canal. Kavanaugh *et al*[35] reported that the increase of cerebrospinal fluid pressure below the blocked area might obstruct venous return and be the cause of anoxia of the cauda equina. Verbiest thought that this theory deserved further consideration, because he commonly found enlargement of the epidural venous plexus during decompression of spinal canal stenosis[36]. Although pathophysiology of the cauda equina induced by arterial ischemia or venous congestion has been an object of study for a long time, there is little agreement over which is more essential for NIC, ischemia or congestion.

Ischemic nerve root injury is a ubiquitous insult that can lead to a wide range of neuropathologic consequences, depending on the severity and duration of the ischemic event. Ischemic injury to nerve roots predominantly causes demyelination, although prolonged ischemia can also interfere with axonal transport, leading to axonal damage and Wallerian degeneration of the nerve fiber[37-40]. Vascular damage and fibrosis are common findings within the spinal canal and intervertebral foramina, and such vascular damage is significantly related to the severity of degenerative disc disease. Disc protrusion may lead to compression of epidural veins and dilation of non-compressed veins. Cooper *et al*[41] noted a significant relationship between evidence of venous obstruction, intraneural and perineurial fibrosis, and neural atrophy. Fibrosis may further impede nutrient transfer to endoneurial fibers, as well as predisposing to nerve stretch injury. Kobayashi *et al*[42,43] assessed the influence of arterial ischemia and venous congestion resulting from obstruction of blood flow without nerve root compression on intraradicular blood flow and radicular function (Figure 4). As a result, it was confirmed that nerve root ischemia had a

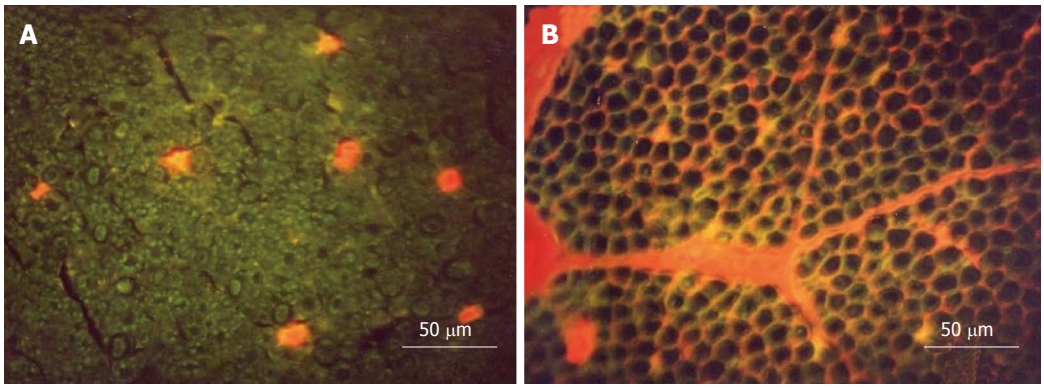

Figure 5 Transverse sections of the nerve root seen under a fluorescence microscope. A: Ischemia model. Evans blue albumin (EBA) emits a bright red fluorescence in clear contrast to the green fluorescence of the nerve tissue. After intravenous injection of EBA, EBA was limited inside the blood vessels, and the blood-nerve barrier was maintained; B: Congestion model. EBA emits a bright red fluorescence, which leaked outside the blood vessels, and intraradicular edema was seen under a fluorescent microscope. Reproduced with permission from Kobayashi *et al*[42].

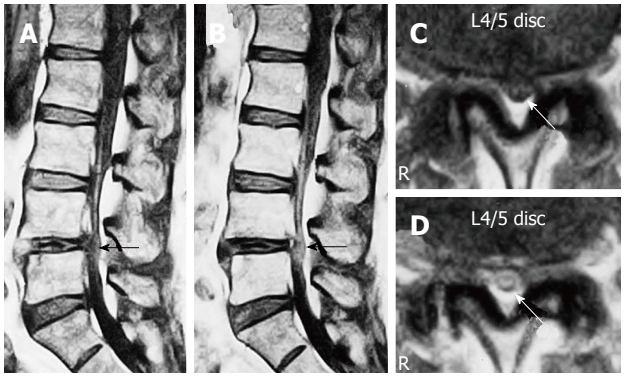

Figure 6 Gadolinium-enhanced magnetic resonance imaging of the cauda equina edema in lumbar canal stenosis. A 73-year-old man complained of weakness and numbness of the lower extremities after walking about 300 m, but no obvious sensory loss and muscle weakness was noted. Precontrast T1-weighted (500/35) sagittal (A) and axial (C) conventional spin echo MR image indicated a diagnosis of LCS at L4/5 disc level (arrows). T1-weighted (500/35) sagittal (B) and axial (D) Magnetic resonance image acquired at L4/5 disc level obtained after 0.1 mmol/kg intravenous Gd-DTPA administration showing the generalized central canal stenosis as well as punctuate areas of intrathecal enhancement (arrows) indicating a breakdown in the blood-nerve barrier. Reproduced with permission from Kobayashi *et al*[46].

more serious influence on blood flow, PO_2, and conduction velocity than nerve root congestion. After 30 min of nerve root ischemia, recovery occurred with reperfusion, but longer ischemic periods will cause a permanent effect on radicular function due to oxygen deficiency. When changes of the femoral arterial and central venous pressures were monitored after obstruction of blood flow, both the arterial and venous pressures decreased after aortic blockade and the arterial pressure increased slightly after obstruction of the inferior vena cava. However, the central venous pressure showed an approximately 4-fold increase immediately after obstruction of the inferior vena cava, and this sudden increase in venous pressure could have a marked influence on the capillary pressure in the nerve roots. Usubiaga *et al*[44] demonstrated that clamping of the vena cava can be used experimentally to increase the systemic venous pressure. The same maneuver also produces congestion of the epidural veins and increases the epidural pressure[45]. But they did not describe the changes in nerve root circulation.

The arachnoid membrane acts as a diffusion barrier for the nerve root and the blood-nerve barrier is also created by the vascular endothelial cells of the endoneurial microvessels. These nerve root barriers protect and maintain the nerve fibers in a constant environment. The capillary vessels of the nerve roots are lined by endothelial cells that contain only a few pinocytotic vesicles and are bound by tight junctions to form the blood-nerve barrier. Protein tracers that are injected intravenously do not normally leak out of the vessels due to this barrier[29,46]. When arterial ischemia was induced, protein tracers remained in the blood vessels, indicating maintenance of the integrity of the blood-nerve barrier (Figure 5A). On the other hand, venous congestion disrupted the blood-nerve barrier and there was extravasation and edema in the nerve roots (Figure 5B). Thus, the blood-nerve barrier that regulates vascular permeability in the nerve root seems to be susceptible to congestion which raises the intra vascular pressure rather than to ischemia which decreases the pressure.

PATHOMECHANISM OF INTERMITTENT CLAUDICATION

MR imaging is useful because it can noninvasively reveal the severity of LCS. It is known that sites of nerve root compression by spinal canal stenosis frequently show gadolinium enhancement on MR images, suggesting that there is breakdown of the blood-nerve barrier and edema of the nerve root (Figure 6)[29,47-50]. In LCS associated with NIC, Kobayashi *et al*[46] and Jinkins *et al*[47-49] first reported gadolinium enhancement of the cauda equina above the level of stenosis. When the nerve roots in the cauda equina are compressed in association with LCS, the pressure is distributed in a circumferential manner

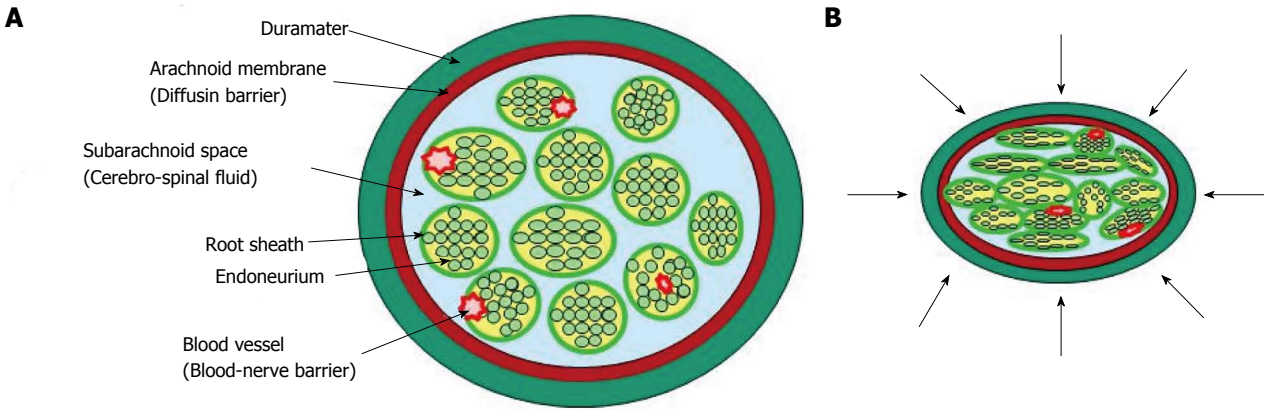

Figure 7 Diagram that illustrates possible mechanical effects on cauda equine. A: Normal state; B: Lumbar canal stenosis. The pressure is applied to the cauda equina with many nerve roots in a circumferential manner.

around the nerve root (Figure 7). Kobayashi *et al*[29] described that the blood-nerve barrier of the nerve root is disrupted and intraradicular edema is produced by acute compression with a microsurgical clip at more than 15 g of force for one hour or by chronic compression due to wrapping the nerve root for at least one month with a silastic tube slightly larger than the nerve root diameter[50]. They also demonstrated that the histological studies in circumferential constriction model of cauda equina revealed congestion and dilation of the intraradicular veins and Wallerian degeneration at site of constriction (Figure 8)[46]. These changes were considered to be attributed to intraradicular edema and were thought to explain the enhancement effect at the site of canal stenosis on gadolinium-enhanced MR images in LCS patients. These results suggest that NIC in LCS is caused by the following mechanism. Stenosis of the lumbar canal is aggravated by posterior flexion during walking, and circumferential mechanical compression of the cauda equina occurs repeatedly and increases in severity (Figure 7). As a result, the subarachnoid space is occluded, and congestion as well as degeneration of nerve fibers occurs in the cauda equina. Elevation of the capillary pressure induced by venous stasis is thought to cause intraradicular edema and the inflammatory response produced by compression, as well as mechanical damage to the blood-nerve barrier, because venous blood flow is stopped by compression at a very low pressure. An experiment performed by Olmarker demonstrated that the capillaries and venules of the nerve root could be occluded by mild compression of around 30-40 mmHg[30]. Takahashi *et al*[51] found that the epidural pressure is only 15 to 18 mmHg during lumbar flexion in LCS patients, but reaches 80 to 100 mmHg during lumbar extension. The epidural pressure increases with walking and the patient then stops walking because of leg pain and/or NIC. The pressure decreases immediately after walking is stopped and leg pain then subsides. There is a repeated pattern of increasing and decreasing pressure during walking. Although, these pressure changes are not great enough to disturb arterial blood flow, the epidural venous system may become congested if the pressure is higher than 10 to 30 mmHg. Ikawa *et al*[52] demonstrated that ectopic firing was elicited by venous stasis in a rat model of lumbar canal stenosis. As a result, the subarachnoid space is occluded, and congestion as well as nerve fiber degeneration occurs in the cauda equina. Efflux of excess fluid into the subarachnoid space becomes impaired by the breakdown of the blood-nerve barrier, leading to an increase in endoneurial pressure[53,54]. Although such a pressure rise is reversible, a compartment syndrome may occur in the cauda equina at the site of stenosis, blood flow[55,56] and axonal flow disturbance[38,39], provoking ectopic discharge or conduction disturbance[57,58] that is essentially responsible for NIC in nerve fibers which have been chronically damaged. Thus, venous congestion may be an essential factor precipitating circulatory disturbance in compressed nerve roots and inducing neurogenic intermittent claudication (Figure 9).

EFFECT OF PROSTAGLANDIN-E1 TO NORMAL NERVE ROOT AND COMPRESSED NERVE ROOT

Prostaglandin E_1 (PGE_1), a potent vasodilator and platelet aggregation inhibitor, is well known as a useful drug for peripheral arterial disease, such as Raynaud's and Burerger's diseases[59], and diabetic neuropathy[60]. PGE_1 has been reported to relax the contraction of vascular smooth muscle cells[61] and increase blood flow in peripheral arteries[62], followed by improvement of endothelial function[63]. Since PGE_1 is rapidly inactivated in the lungs, PGE_1 must be administered into the obstructed artery or a large amount of it has to be given intravenously. The distribution of PGE_1 *in-vivo* induces the systemic effects of diarrhea, hypotension, fever and hepatic dysfunction. PGE_1 also causes irritation in blood vessels near the site of injection. To avoid these problems, PGE_1 was mixed with microparticles 0.2 μm in diameter made of soybean oil. Because PGE_1 is incorporated into the lipid particles in this preparation, it is less susceptible to inactivation in the lung[64]. In addition, this preparation characteristically becomes concentrated and acts selectively in lesions be-

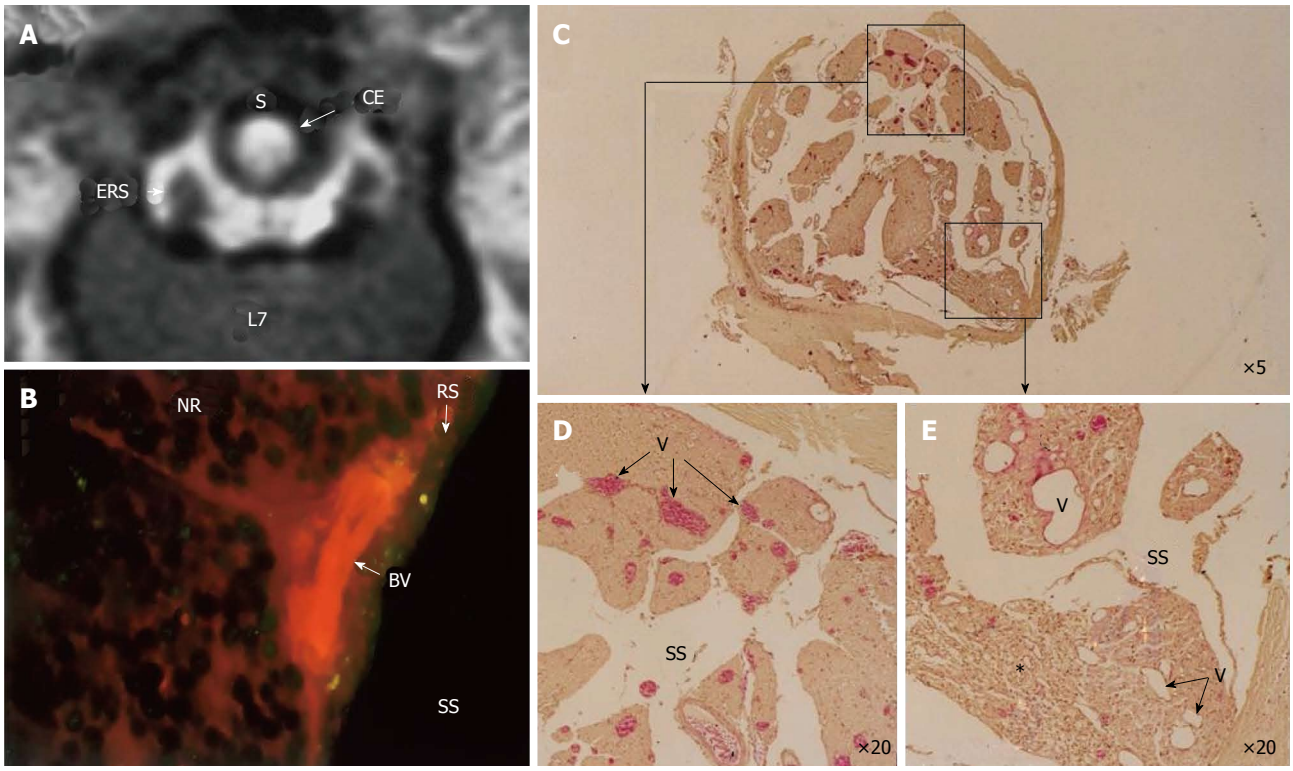

Figure 8 Circumferential compression of the dog cauda equine. The cauda equina was constricted outside the dura mater using a silicone tube (S), which caused 30% constriction of the diameter of the dura mater using a silicone tube at L6/7 disc level. After 3 wk constriction, clear enhancement was seen inside the cauda equina constricted by a silicon tube (S) as seen on gadolinium-enhanced magnetic resonance (MR) image [T1-weighted spin-echo (SE) image, 600/25 (TR/TE)] (A). No enhancement of epidural root sleeves (ERS) was found on this image. In the cauda equina, where enhancement was found on MR imaging, Evans blue albumin emits a bright red fluorescence which leaked outside the blood vessels, and intraradicular edema was seen under a fluorescent microscope (B). Light microscopy revealed congestion and dilation of the radicular veins (C-E) inside the cauda equina, inflammatory cells infiltration, and Wallerian degeneration (E, asterisk) was observed in the entrapped region. This situation was reflected as breakdown of blood–nerve barrier on fluorescent microscopy and high intensity on gadolinium- enhanced MR imaging. BV: Blood vessel; CE: Cauda equina; ENS: Epidural root sleeves; NR: Nerve root; RS: Root sheath; S: Silicon tube; SS: Subarachnoid space.

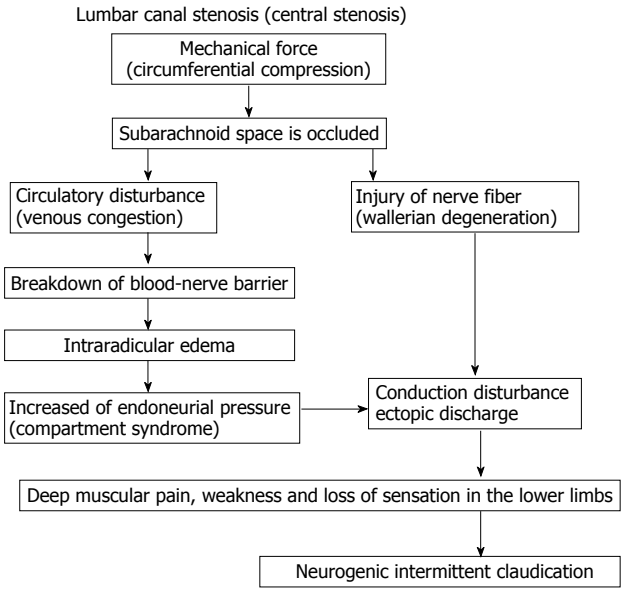

Figure 9 Pathogenesis of neurogenic intermittent claudication in lumbar canal stenosis.

cause the lipid particles adhere to the endothelial cells of injured blood vessels[65]. Lipid microspheres incorporating prostaglandin E1 (lipo-PGE1) has therefore attracted interest as a therapeutic drug for LCS. However, investigations in the clinical setting have shown that lipo-PGE1 is effective in some patients but not in others[66-75], although the reason for this is unclear.

So far, some experimental studies of the effect of lipo-PGE1 on blood flow in normal[68,70] and compressed[76-80] nerve roots have reported an increase in flow, but none have examined the effect of lipo-PGE1 on compressed sections with apparently Wallerian degeneration after nerve root compression. After investigating the changes of nerve root blood flow caused by bolus intravenous injection of Lipo-PGE1, Toribatake *et al*[68] reported a 59% increase of blood flow at a dose of 0.1 μg/kg, while Murakami *et al*[70] reported a 37.8% increase at a dose of 0.15 μg/kg. These experimental studies of the effect of lipo-PGE1 on blood flow in normal nerve roots revealed an increase in flow, but did not examine the effect of lipo-PGE1 on compressed nerve roots. Subsequently, the effect of PGE1 on intraradicular blood flow was assessed in a rat cauda equina compression model, and PGE1 was reported to increase blood flow. However, the extent of compression applied to the nerve root and its duration were both insufficient, and the response was not compared with tissue changes of the nerve root after compression[76-80]. Kobayashi *et al*[81] firstly demonstrated that intravenous injection of lipo-PGE1 significantly

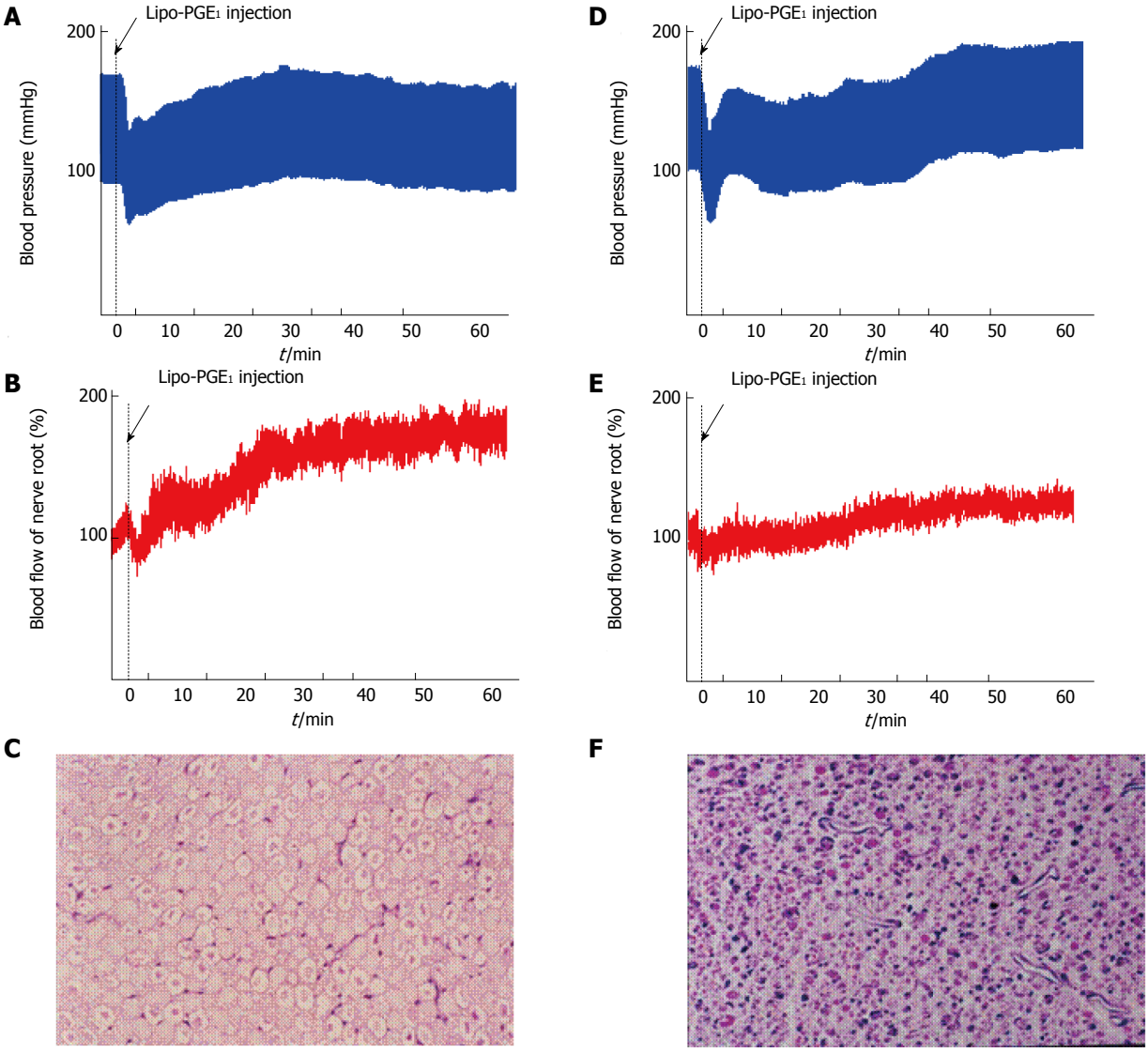

Figure 10 Effect of prostaglandin E1 on normal (A-C) and compressed nerve root (D-F). The seventh lumbar nerve root was clamped with a clip for 3 wk using dogs. After release of clipping, the intraradicular blood flow was measured before and after intravenous injection of lipo-prostaglandin E1 (PGE1) (D-F). As the control group, animals were evaluated at 3 wk after laminectomy. The nerve root was only exposed and wasn't clamped with a clip (A-C). In the control (A) group, the mean blood pressure fell immediately after intravenous injection of lipo-PGE1 due to the peripheral vasodilation, but then gradually increased and recovered after 20 min. The changes of blood pressure in the nerve root compression group were the same as those seen in the control group (D). Intravenous injection of lipo-PGE1 also resulted in marked increase of blood flow in the normal nerve roots (B), but caused minimal enhancement of blood flow at the sites of nerve root compression exhibiting Wallerian degeneration (E). Histological examination revealed no degeneration of the nerve fibers in the control group (C). However, marked Wallerian degeneration was seen in the nerve root compression group (D). The relative number of small diameter axons increased in the compression group at 3 wk after operation compared with the control group (HE stain, original magnification X 50).

increased intraradicular blood flow in the normal nerve root without compression, but the increase of blood flow observed in the compressed region of the nerve root exhibiting Wallerian degeneration was transient and not sustained (Figures 10 and 11). It is therefore concluded that lipo-PGE1 has less effect on severely damaged nerve roots than it does on normal nerve roots.

EFFECT OF PGE1 ON PATIENTS WITH NIC

PGE1 has been used in the field of orthopedic surgery for the treatment of cervical and lumbar diseases. The results of numerous studies have also suggested that PGE1 is likely to be useful for LCS, but its position has not been firmly established among the treatments available[66-75]. It was reported that PGE1 was effective for 57%-87% of patients with LCS accompanied by NIC (Table 2), but was ineffective in many patients with severe neurological deficits such as muscle weakness. Since it can be assumed that the impaired intraradicular blood flow is improved by the drug in patients whose NIC responds to administration of PGE1, this agent can be used for screening and staging of the disease. Yone *et al*[82] have reported that when lipo-PGE1 was injected intravenously in 11 LCS patients during surgery, symptoms were alleviated in 6 patients with dilation of vessels running along the cauda equina, but not in 5 patients with no change of their vessels. Dezawa *et al*[83] observed the movement of red blood

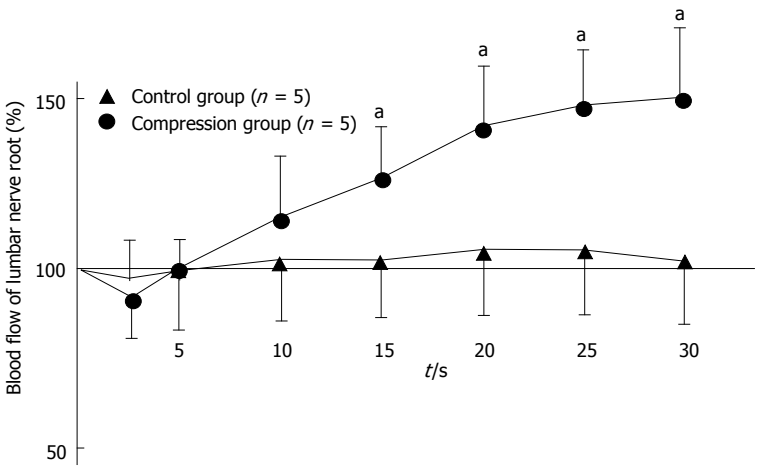

Figure 11 Changes in intraradicular blood flow after intravenous injection of lipo-prostaglandin E$_1$. In normal (control) nerve roots (n = 5), intraradicular blood flow fell immediately after intravenous injection of lipo-Prostaglandin E$_1$ (PGE$_1$), but gradually increased ($^aP < 0.05$). After 30 min, the mean blood flow was 49% higher than before lipo-PGE$_1$ injection. However, the changes of intraradicular blood flow in the nerve root compression group (n = 5) were not as marked as in the control group, with the mean value after 30 min being only 5% higher than pretreatment value. Reproduced with permission from Kobayashi *et al*[81].

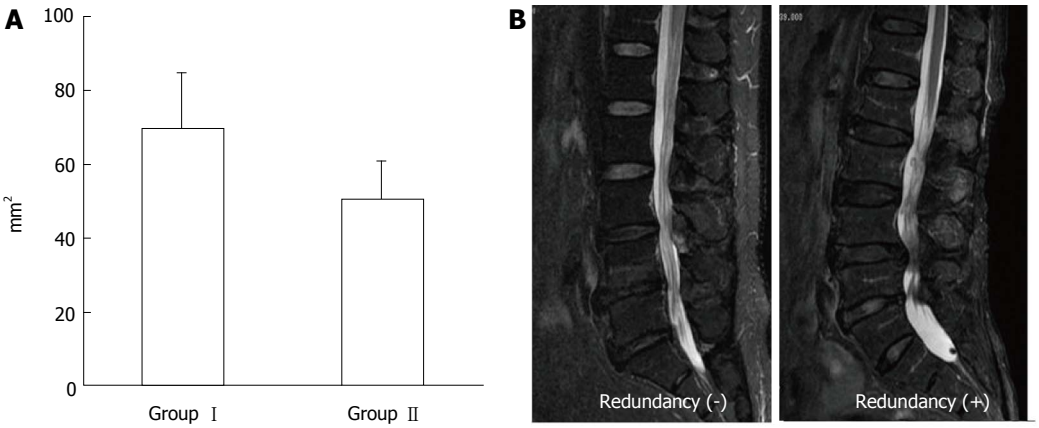

Figure 12 Magnetic resonance imaging of lumbar canal stenosis patients with neurogenic intermittent claudication. A: Cross-sectional area of dural sac (T1-w) at the site of maximal canal stenosis; B: Magnetic resonance imaging of redundunt nerve root (T2-w).

Table 2 Effect of lipo-prostaglandin E$_1$ on patients with neurogenic intermittent claudication in lumbar canal stenosis

Author	Year	Drag	Dose	Period	Effective rate to NIC
Takakura[66]	1986	PGE$_1$	40-60 μg/d	14-28 consecutive days	79.5% (39/49 cases)
Miura *et al*[67]	1992	Lipo-PGE$_1$	10 μg/d	10 d	57.1% (8/14 cases)
Toribatake *et al*[68]	1993	Lipo-PGE$_1$	10 μg/d	10 consecutive days	75.0% (12/16 cases)
Kurihara *et al*[69]	1996	Limaprost	3 μg/d	42 consecutive days	27.3% (21/77 cases)
			15 μg/d		47.8% (33/69 cases)
Murakami *et al*[70]	1997	Lipo-PGE$_1$	10 μg/d	10 consecutive days	77.5% (31/40 cases)
			5 μg/d		87.0% (40/46 cases)
Ono *et al*[71]	1997	Lipo-PGE$_1$	10 μg/d	14 consecutive days	71.1% (27/38 cases)
			20 μg/d		76.5% (26/34 cases)
Miura *et al*[72]	1997	PGE$_1$	120 μg/d	14 consecutive days	33.0% (5/12 cases)
Uratuji *et al*[73]	2003	Limaprost	15 μg/d	42 consecutive days	59.3% (54/91 cases)
Harrison *et al*[74]	2007	Limaprost	15 μg/d	42 consecutive days	50.7% (74/146 cases)
Nakanishi *et al*[75]	2008	PGE$_1$	60 μg/d	14 consecutive days	71.4% (45/63 cases)

Reproduced with permission from Kobayashi *et al*[81]. NIC: Neurogenic intermittent claudication; PGE$_1$: Prostaglandin E$_1$.

cells in blood vessels running along the cauda equina by myelofiber scope in 8 LCS patients with NIC under local anesthesia, and reported that blood flow increased in 3 patients, stopped in 1, became retrograde in 2, and was unchanged in 2. In LCS patients, myelography and MRI often reveal a redundant nerve root. Suzuki *et al*[84] pathologically investigated the cauda equina at autopsy and reported that the cause of nerve root redundancy was Wallerian degeneration.

We treated LCS patients with PGE$_1$ and compared their response with the magnetic resonance (MR) imaging. The subjects were 50 LCS patients with NIC (walking distance ⩽ 300 m) and MR imaging evidence of central canal stenosis. They comprised 38 men and 12 women

aged 75-95 years (mean: 81 years). Each patient received PGE_1 intravenously at a dose of 10 μg/d for 14 d. After completing treatment, the MRI findings of 25 patients achieving relief from NIC (group Ⅰ) and 25 patients without relief (group Ⅱ) were retrospectively compared. In all patients, T_1- and T_2-weighted images were obtained. On T_1-weighted images, the transverse area of the dural tube at the site of maximal canal stenosis was measured using a digitizer. The presence or absence of redundant nerve roots was also identified on T_2-weighted images.

The transverse area of the dural tube at the site of maximal canal stenosis on MR images was 50.8-88.6 mm^2 (mean: 69.8 ± 15.2 mm^2) in group Ⅰ and 35.8-59.8 mm^2 (mean: 50.6 ± 10.3 mm^2) in group Ⅱ (Figure 12A). Redundant nerve roots were observed in 14 (56%) of the 25 patients from group Ⅱ, being located proximal to the site of maximal stenosis, but were not seen in group Ⅰ (Figure 12B). Intraradicular edema was observed in 21 (84%) of the 25 patients from group Ⅱ, being located proximal to the site of maximal stenosis, but was only seen in 2 (8%) patients from group Ⅰ (Figure 6). These results indicate that patients who have a transverse dural area ≤ 60 mm^2 and redundant nerve roots (suggesting Wallerian degeneration) may achieve little relief of NIC with PGE_1 therapy. From the findings of these clinical studies, it has been postulated that the severity of nerve degeneration is an important determinant of the response to PGE_1. It is considered that LCS patients who are unresponsive to PGE_1 have nerve root degeneration that progresses to the irreversible stage, so that decompression by laminectomy or other methods cannot be expected to provide immediate marked improvement of neurological deficits such as sensory disorders and muscle weakness. In other words, it seems that the outcome of decompression surgery may be predicted from the response to PGE_1, but further studies are required to confirm this possibility.

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Scoring system for prediction of metastatic spine tumor prognosis

Yasuaki Tokuhashi, Hiroshi Uei, Masashi Oshima, Yasumitsu Ajiro

Yasuaki Tokuhashi, Hiroshi Uei, Masashi Oshima, Department of Orthopaedic Surgery, Nihon University School of Medicine, Itabashi-ku, Tokyo 173-8610, Japan
Yasumitsu Ajiro, Department of Orthopaedic Surgery, Surugadai Nihon University Hospital, Chiyoda-ku, Tokyo 101-8309, Japan
Author contributions: Tokuhashi Y performed the literature review, drafted the article; Uei H and Oshima M helped in the literature review, revised the article critically for important intellectual content; Ajiro Y helped in the literature review, making tables, checked references; all finally approved for print.
Correspondence to: Yasuaki Tokuhashi, MD, Professor, Department of Orthopaedic Surgery, Nihon University School of Medicine, 30-1 Oyaguchi-kamicho, Itabashi-ku, Tokyo 173-8610, Japan. tokuhashi.yasuaki@nihon-u.ac.jp
Telephone: +81-33972-8111 Fax: +81-33972-8201
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Abstract

Assessing the prognosis before treatment for metastatic spine tumor is extremely important in therapy selection. Therefore, we review some prognostic scoring systems and their outcomes. Articles with combinations of two keywords among "metastatic spine tumor" and "prognosis", "score", "scoring system", "predicting", or "life expectancy" were searched for in PubMed. As a result, 236 articles were extracted. Those referring to representative scoring systems about predicting the survival of patients with metastatic spine tumors were used. The significance and limits of these scoring systems, and the future perspectives were described. Tokuhashi score, Tomita score, Baur score, Linden score, Rades score, and Katagiri score were introduced. They are all scoring systems prepared by combining factors that affect prognosis. The primary site of cancer and visceral metastasis were common factors in all of these scoring systems. Other factors selected to influence the prognosis varied. They were useful to roughly predict the survival period, such as, "more than one year or not" or "more than six months or not". In particular, they were utilized for decision-making about operative indications and avoidance of excessive medical treatment. Because the function depended on the survival period in the patients with metastatic spine tumor, it was also utilized in assessing functional prognosis. However, no scoring system had more than 90% consistency between the predicted and actual survival periods. Future perspectives should adopt more oncological viewpoints with adjustment of the process of treatment for metastatic spine tumor.

Key words: Metastatic spine tumor; Prognosis evaluation system; Surgical indication; Treatment modality; Decision-making

Core tip: Some representative scoring systems for the prediction of metastatic spine tumor outcome were reviewed. Tokuhashi score, Tomita score, and others were introduced. They were useful to roughly predict the survival period, and were utilized for the purpose of decision-making about operative indications and the avoidance of excessive medical treatment. While the function in the patients was associated with the survival period, it was also useful to assess functional prognosis. However, no scoring system had more than 90% consistency between the predicted and actual survival periods. They also need a stronger oncological perspective with adjustment of the process of treatment.

Original sources: Tokuhashi Y, Uei H, Oshima M, Ajiro Y. Scoring system for prediction of metastatic spine tumor prognosis. *World J Orthop* 2014; 5(3): 262-271 Available from: URL: http://www.wjgnet.com/2218-5836/full/v5/i3/262.htm DOI: http://dx.doi.org/10.5312/wjo.v5.i3.262

Table 1 Tokuhashi score original (1990)[1-3]

Predictive factor	Score (points)
General condition (KPS)	
Poor (KPS 10%-40%)	0
Moderate (KPS 50%-70%)	1
Good (KPS 80%-100%)	2
Number of extraspinal bone metastases foci	
⩾ 3	0
1-2	1
0	2
Number of metastases in the vertebral body	
⩾ 3	0
2	1
1	2
Metastases to the major internal organs	
Unremovable	0
Removable	1
No metastases	2
Primary site of the cancer	
Lung, stomach	0
Kidney, liver, uterus, others, unidentified	1
Thyroid, prostate, breast, rectum	2
Spinal cord palsy	
Complete (Frankel A, B)	0
Incomplete (Frankel C, D)	1
None (Frankel E)	2
Total points	Mean survival periods
0-5	⩽ 3 mo
6-8	< 12 mo
9-12	⩾ 12 mo

KPS: Karnofsky's performance status.

INTRODUCTION

The objectives of treatment for metastatic spinal tumors are to mitigate pain and paralysis and maximize the activities of daily living (ADL) and quality of life (QOL) during the rest of life. The most important point regarding the therapeutic strategy is to predict the survival period accurately before treatment.

In the classification of the stage of cancers, the malignant tumours (TNM) classification is used for primary lesions, and approximate prediction of the survival period after detection and treatment of the primary lesion has been considered possible in most cancers. However, prediction of the survival period after the appearance of symptoms of spinal metastasis has not been satisfactory, unlike that after the detection and treatment of primary cancer.

Prediction of the survival period before treatment for spinal metastasis is extremely important for the selection of treatment. Naturally, the opinion of physicians of the department treating the primary lesion should be given priority, but their estimation of the survival period is not necessarily accurate, and the treatment should be determined by taking into consideration the estimations of orthopedists and radiologists, who are also directly involved in the treatment. For this purpose, some prognosis evaluation methods have also been developed by spine surgeons and radiologists, and scoring systems by which factors that affect the survival period are scored in an additive manner have been reported to be useful for assessing the prognosis.

Therefore, to evaluate the clinical significance and limitations in the prognostic scoring systems for metastatic spine tumors, we reviewed them and their validation studies that have been reported to date. Furthermore, it was verified which scoring system was the best. The review was conducted as follows; the literature was searched in PubMed using two-word combinations of "metastatic spine tumor" with "prognosis", "score", "scoring system", "predicting", and "life expectancy" as index terms. As a result, 236 papers were extracted. We checked their contents and describe representative scoring systems that correspond to "scoring systems for the prognosis of patients with metastatic spinal tumors" with comments on their significance and limitations. The representative prognostic scoring systems which we introduced were cited on PubMed more than at least five times. Also, as a result, it was considered the future of the prognostic scoring systems.

REPRESENTATIVE PROGNOSTIC SCORING SYSTEMS

Tokuhashi score

This system was reported by Tokuhashi *et al*[1-3] in 1989 as a "scoring system for the preoperative evaluation of a patient's prognosis with a metastatic spinal tumor". These papers have become landmark articles concerning prognostic scoring systems for patients with metastatic spinal tumors. A revised version was published in 2005[4], and the results of a prospective study in which the treatment was selected using this revised version were reported in 2009[5].

This scoring system consists of 6 items considered to affect the outcome (general condition[6], number of bone metastases other than spinal metastases, number of spinal metastases, type of the primary lesion, presence or absence of metastases to major organs, and state of paralysis). The survival periods were predicted from the total score using prognostic criteria (Tables 1 and 2). According to the original version, the estimated survival period was ⩽ 3 mo when the total score was 0-5, < 12 mo when the total score was ⩽ 8, and ⩾ 12 mo when the total score was ⩾ 9. In the revised version, the staging of the primary lesion was changed from 3 (0-2) to 6 (0-5) levels, and the survival period was predicted to be ⩽ 6 mo when the total score was 0-8, ⩾ 6 mo when the total score was 9-11, and ⩾ 1 year when the total score was ⩾ 12.

In the original version, each item was scored as 0-2, but the hazard ratio was not evaluated for the weighting of the factors. Statistically, the survival period was retrospectively shown to be correlated with the total score in 47 surgical cases[1,2]. With both the original and the revised versions, relatively broad prognostic criteria were prepared, and their clinical application was proposed.

While this scoring system was insufficient on statisti-

Table 2 Revised Tokuhashi score (2005)[4]

Predictive factor	Score (points)
General condition (KPS)	
Poor (KPS 10%-40%)	0
Moderate (KPS 50%-70%)	1
Good (KPS 80%-100%)	2
Number of extraspinal bone metastases foci	
≥ 3	0
1-2	1
0	2
Number of metastases in the vertebral body	
≥ 3	0
2	1
1	2
Metastases to the major internal organs	
Unremovable	0
Removable	1
No metastases	2
Primary site of the cancer	
Lung, osteosarcoma, stomach, bladder, esophagus, pancreas	0
Liver, gallbladder, unidentified	1
Others	2
Kidney, uterus	3
Rectum	4
Thyroid, prostate, breast, carcinoid tumor	5
Spinal cord palsy	
Complete (Frankel A, B)	0
Incomplete (Frankel C, D)	1
None (Frankel E)	2
Total points	Mean survival periods
0-8	< 6 mo
9-11	≥ 6 mo
12-15	≥ 12 mo

KPS: Karnofsky's performance status.

cal evaluation, the factors selected as affecting the survival period were relatively simple and easy to examine. In addition, it contained no factor concerning therapeutic intervention and was flexible on application. For this reason, it was applied for validation in various countries, and relatively favorable results have been reported[7-9].

Chen *et al*[10] reported that the revised Tokuhashi score was the most practical and provided the most accurate prognosis in 41 patients with spinal metastasis of hepatocellular carcinoma among 4 scoring systems: the revised score, Tomita score, Bauer score, and revised van der Linden score. Moreover, they suggested that the serum albumin and lactate dehydrogenase (LDH) levels are useful as prognostic factors.

Tokuhashi *et al*[5] also prospectively evaluated 183 patients treated according to the revised version, and reported that the prediction was in agreement with the actual survival period in 87.9% of the patients. In the revised version, the survival period was classified into 3 levels with 6 mo and 1 year, which are clinically important points, as benchmarks. According to these broad criteria, the prognoses for the moderate and favorable prognosis groups partially overlapped, but a score of 9-11 was erroneously converted to a survival period of 6 mo to 1 year in some papers[11-14], in which the agreement rate between the prognosis and actual survival period was low.

In addition, the rate of agreement between the predicted and actual survival periods differs depending on the type of primary lesion, and the usefulness of the criteria has been suggested to vary. Yamashita *et al*[15] (2011) reported that the predicted and actual survival periods agreed in 67 (79%) of 85 patients followed-up for 1 year or longer. In addition, they reported that the Tokuhashi score was useful regardless of the selected treatment. However, they observed that low scores were closely correlated with poor outcomes but that the outcome was more often poorer than predicted based on the score concerning the kidney, and suggested that the score allocation to the kidney was disproportionately heavy. On the other hand, Hessler *et al*[16] (2011) evaluated 76 patients who underwent surgery for spinal metastasis of lung cancer, and argued that the agreement rate between the survival period predicted according to the revised Tokuhashi score and the actual survival period was 67.1% and that the criteria did not reflect recent improvements in treatments for spinal metastases of cancer. They reported that some patients even with spinal metastasis of lung cancer survived for 1 year or longer and that the outcome was relatively favorable in those aged 50 years or less, those with metastasis in the lumbar spine, and those with no paralysis. Tokuhashi *et al*[5] basically agreed with Hessler *et al*[16], admitting that treatments had improved during the 13 years since the revised scoring system had been prepared and that some patients with spinal metastasis of lung cancer had survived for 2 years or longer. However, they maintained that the prognosis of patients with spinal metastasis of lung cancer is basically poor and that the precision of the score should be evaluated by including patients who tolerated only conservative treatments as well as those who underwent surgery[17].

Some papers focused on the accuracy of differentiation of good-prognosis, poor-prognosis, and intermediate groups. Quraishi *et al*[18] (2013) reported that 201 surgical cases could be differentiated into poor-, moderate-, and good-prognosis groups, that the agreement rate with the actual survival period was 64% or higher in each group and 66% in all patients, and that the usefulness of the score was moderate. However, in the 142 surgical cases reported by Pointillart *et al*[19] (2011), the agreement rate between the predicted and actual survival rates was 60% or lower with either the original or the revised version.

There have also been studies comparing the original and revised versions. Wang *et al*[20] (2012) considered that the revised version was particularly useful for the prognosis of patients with metastases of prostate and breast cancers and that the original version was excellent for the prognosis of patients with metastases of colon cancer. In addition, their usefulness was insufficient concerning metastases of lung or kidney cancers, and the overall accuracy was higher for the revised than the original version. However, Liang *et al*[21] (2013) reported that the original version was more useful than the revised version or Tomita score.

Kostuik[22] (1997) added 3 items: the radiographic appearance of the metastatic lesion, degree of kyphosis

Table 3 Tomita score (2001)[23,24]

Prognostic factors	Points
Primary tumor	
Slow growth (breast, thyroid, *etc.*)	1
Moderate growth (Kidney, uterus, *etc.*)	2
Rapid growth (Lung, stomach, *etc.*)	4
Visceral metastases	
Treatable	2
Untreatable	4
Bone metastases	
Solitary or isolated	1
Multiple	2
Total points	Predicted prognosis
2-4	> 2 yr
4-6	1-2 yr
6-8	6-12 mo
8-10	< 3 mo

of the secondary lesion, and rate of canal compromise secondary to the metastatic lesion, to the original version and reported the usefulness of this partially modified scoring system with a full mark of 18.

Tomita score

Tomita *et al*[23] and Kawahara *et al*[24] retrospectively evaluated 67 patients including those treated conservatively and developed a new scoring system in 2001 (Table 3).

Since the score of each item of the original Tokuhashi scoring system lacked weighting, each factor of each item was weighted by Cox hazard analysis in the new scoring system. Paralysis, which was considered not to affect the survival period, was excluded, and the new scoring system was simplified compared with Tokuhashi' s. In addition, the expected survival period and indicated treatment were 2 years or longer and en bloc excision, respectively, when the total score was 2-4, 1-2 years and debulking when it was 4-6, 6-12 mo and palliative decompression when it was 6-8, and 3 mo or less and terminal care when it was 8-10.

This scoring system is patient-centered and is often used along with Tokuhashi's system for evaluation of the surgical indication, and its usefulness has been evaluated in many reports[25-32].

Bauer[33] (2002) reported that this scoring system successfully differentiated poor- and good-prognosis groups but pointed out that it downplayed pain and paralysis, lacked specificity for impending paralysis, and disregarded indications for many conservative treatments and palliative surgery due to an excessive emphasis on aggressive surgical treatments.

Baur scoring system

In 1995, Bauer *et al*[34] developed a simple scoring system by studying 153 cases of limb bone metastases and 88 cases of spinal metastases by combining 3 influential items selected by univariate analysis and Cox regression analysis of prognostic factors: the site of the primary tumor, metastatic load, and pathologic fracture (Table 4).

Table 4 Baur score original

Positive prognostic factors	Score (Points)
No visceral metastases	1
Absence of pathologic fracture	1
solitary skeletal metastasis	1
No lung cancer	1
Primary tumor = breast, kidney, lymphoma, multiple myeloma	1
Total score (points)	1-yr survival rate (%)
0-1	0% (< 6 mo survival)
2-3	25%
4-5	50%

Table 5 Modified Baur score

Positive prognostic factors	Points
No visceral metastases	1
No lung cancer	1
Primary tumor = breast, kidney, lymphoma, multiple myeloma	1
One solitary skeletal metastasis	1
Total points	Median overall survival
0-1	4.8 mo
2	18.2 mo
3-4	28.4 mo

As a result, the 1-year survival rate was predicted to be 0% when the score was 0-1 (all patients die within 6 mo), 25% when it was 2-3, and 50% when it was 4-5.

Disadvantages of this scoring system are that the judgment of pathologic fracture is difficult in the spine and that it was developed based on a multi-center collaborative study restricted to surgical cases with large variations in the surgical indications and procedures among the facilities.

However, Leithner *et al*[35] (2008) and Wibmer *et al*[36] (2011) considered that, of the 7 scoring systems including the Tokuhashi, Tomita, and Linden scoring systems, those other than the Bauer scoring system were also useful until 4 years after treatment. However, they reported that the Bauer score and modified Bauer score (Table 5), in which the item concerning the presence or absence of pathologic fracture was excluded, were superior for the prognosis after 4 or more years and differentiation between the good- and moderate-prognosis groups[35,36]. According to the modified Bauer score, the median OS and indications for treatment are 4.8 mo and no surgical indication, respectively, when the score is 0-1, 18.3 mo and palliative surgery from a posterior approach when the score is 2, and 28.4 mo and control by a combination of anterior and posterior approaches when the score is 3-4.

Van der Linden scoring system

In 2005, van der Linden *et al*[37] devised a scoring system consisting of 3 items: Karnofsky's performance status, type of primary lesion (lung cancer, breast cancer, prostate cancer, others), and the presence or absence of visceral metastasis, by studying 342 cases of spinal metas-

Table 6 Linden score

Prognostic factors	Points
Karnofsky performance status	
80-100	2
50-70	1
20-40	0
Primary tumor	
Breast	3
Prostate	2
Lung	1
Other	0
Visceral metastases	
No	1
Yes	0
Total points	Mean overall survival
0-3 (n = 116)	4.8 mo
4-5 (n = 164)	13.1 mo
6 (n = 62)	18.3 mo

Table 7 Rades score

Prognostic factor	Score (points)
Type of primary tumor	
Breast cancer	8
Prostate cancer	7
Myeloma/lymphoma	9
Lung cancer	3
Other tumors	4
Other bone metastases at the time of RT	
Yes	5
No	7
Visceral metastases at the time of RT	
Yes	2
No	8
Interval from tumor diagnosis to MSCC	
≤ 15 mo	4
> 15 mo	7
Ambulatory status before RT	
Ambulatory	7
Nonambulatory	3
Time of developing motor deficits before RT	
1-7 d	3
8-14 d	6
> 14 d	8
Total score	6-mo survival (%)
20-30 (n = 237)	16
31-35 (n = 162)	48
36-46 (n = 253)	81

RT: Radiotherapy; MSCC: Metastatic spinal cord compression.

tasis (Table 6), and reported that it was effective in 73% of the patients[37].

Rades score

Rades *et al*[38] prepared a few scoring systems on the basis of data obtained from patients who underwent radiation therapy for spinal cord compression by metastatic tumors, all by Cox proportional-hazards survival analysis. The first and largest of them was derived from 1852 cases (2008, Table 7)[38], followed by one derived from a prospective study of 439 cases (2010, Table 7)[39] and a scoring system based on the type of cancer. There is also a scoring system for metastases of prostate cancer (2012, Table 8)[40], one for metastases of breast cancer (2013, Table 9)[41], and one for unknown primary lesions by Douglas *et al*[42] (2012, Table 10).

All are for the evaluation of conditions that are indications of radiation therapy for spinal cord compression by metastatic tumors at an advanced stage and consist of other bone metastases at the time of RT, visceral metastases at the time of RT, the interval from tumor diagnosis

Table 8 Rades score for prostate cancer metastases

Prognostic factor	Score (points)
ECOG performance status	
1-2	9
3-4	4
Ambulatory status prior to RT	
Not ambulatory	4
Ambulatory before RT	8
Other bone metastases	
No	7
Yes	5
Visceral metastases	
No	8
Yes	2
Interval from cancer diagnosis to RT	
≤ 15 mo	5
> 15 mo	7
Score group	Survival at 6 mo (%)
20-24 (n = 58)	6.5-7.4
25-34 (n = 189)	44.6-45.4
35-39 (n = 189)	94.7-95.8

ECOG: Eastern Cooperative Oncology Group. RT: Radiotherapy.

Table 9 Rades score for breast cancer metastases

Prognostic factor	Score (points)
ECOG performance status	
1-2	9
3-4	5
Ambulatory status prior to RT	
Not ambulatory	4
Ambulatory before RT	8
Other bone metastases	
No	8
Yes	7
Visceral metastases	
No	9
Yes	4
Interval from tumor diagnosis to radiotherapy of MSCC	
≤ 15 mo	6
> 15 mo	8
Time of developing motor deficits	
1-7 d	4
> 7 d	8
Total score	Survival at 6 mo (%)
30-35	12-14
36-40	41-46
41-45	74-77
46-50	98-99

ECOG: Eastern Cooperative Oncology Group. RT: Radiotherapy; MSCC: Metastatic spinal cord compression.

Table 10 Douglas score for unknown primary metastases

Prognostic factor	Score (points)
ECOG performance status	
1-2	6
3-4	2
Ambulatory status prior to RT	
Not ambulatory	2
Ambulatory before RT	4
Visceral metastases	
No	5
Yes	0
Time of developing motor deficits	
1-7 d	1
> 7 d	5
Score group	Survival at 6 mo (%)
< 14 (n = 112)	5-7
14-16 (n = 26)	38-41
> 16 (n = 24)	91-92

ECOG: Eastern Cooperative Oncology Group. RT: Radiotherapy.

Table 11 Katagiri score

Prognostic factor	Score
Primary lesion	
Rapid growth(Hepatocellular carcinoma, gastric carcinoma, lung carcinoma)	3
Slow growth(Breast carcinoma, prostate carcinoma, multiple myeloma, malignant lymphoma, thyroid carcinoma)	0
Moderate growth(Other carcinoma and sarcoma)	2
Visceral or cerebral metastases	2
Performance status (ECOG) 3 or 4	1
Previous chemotherapy	1
Multiple skeletal metastases	1
Total score (n = 350)	6 and 12 mo survival rate (%)
0-2	97.9; 89.1
3-5	70.6; 48.8
6-8	31.3; 10.9

ECOG: Eastern Cooperative Oncology Group.

to metastatic spinal cord compression (MSCC), ambulatory status before RT, and time of developing motor deficits before RT, but they vary in their combination and allocation of scores depending on the cancer type. Important points regarding this scoring system are that its application is restricted to an advanced stage of spine metastases of cancer with impending paralysis, and that the prediction of the outcome for patients with some cancer types is impossible with a single pattern. In addition, the therapeutic options are restricted to radiation therapy, and the scoring systems cannot be applied to the selection of diversified treatments for spinal metastases of cancer.

Katagiri score

Katagiri score is a scoring system prepared retrospectively by Cox proportional-hazards analysis of 350 cases of skeletal metastases (2005, Table 11)[43]. Its unique characteristics not observed in other scoring systems are that the history of chemotherapy before the crises of metastases is incorporated and bone metastases are captured as metastases of the entire skeleton rather than of the spine alone. For this reason, only 37 patients (10.6%) underwent surgery due to spinal metastases.

The greatest demerit of this scoring system is that it includes the history of chemotherapy, a therapeutic intervention, and that the evaluation of the degree of intervention and sensitivity for each cancer is unclear. It is likely to be affected by individual variation in attending physicians and has major problems with versatility and objectivity.

SIGNIFICANCE OF, AND PROBLEMS WITH, SCORING SYSTEMS

All scoring systems for the prognosis of patients with metastatic spinal tumors are composed of combinations of factors that affect the survival periods. Among these prognostic factors, the type of primary lesion and visceral metastases are included in all scoring systems, and other factors are arbitrarily selected. Rades *et al*[38-41] and Douglas *et al*[42] attached importance to functional factors and reported a scoring system incorporating the ambulatory ability before treatment and speed of progression of paralysis, but many scoring systems, including one by Tomita *et al*[23], Bauer *et al*[34], van der Linden *et al*[37] and Katagiri *et al*[43], totally disregarded paralysis. This wide variation is considered to have been due to differences in the patients evaluated for the preparation of the scoring systems. The patients studied by Rades *et al*[38] consisted entirely of those who had progressive spinal cord paralysis and underwent radiation therapy, and included a high percentage of those with a poor prognosis in whom the surgical indication could not be evaluated from the beginning. Therefore, the prognosis of patients with progressive paralysis based on this system is considerably poorer than that by other scoring systems. As suggested by Kawai *et al*[44] (2013), reevaluation of prognostic factors is considered necessary based on the historical background that asymptomatic metastases detected in an early stage began to be treated as new metastases.

At any rate, it is certain that such additive scoring systems combining factors considered to affect the outcome are useful for rough estimation of the survival period in terms of "6 mo or longer or less than 6 mo" and "1 year or longer or less than 1 year". At least, they are much more reliable than the prognosis based on a single prognostic factor.

However, which of the scoring systems is the best remains unclear. There have been few validation studies concerning the prognostic accuracy of scoring systems other than Tokuhashi's system and Tomita's system, which succeeded it. At least, all scoring systems have limitations, and there is no system by which the agreement rate between the predicted and actual survival periods is 90% or higher.

Table 12 Rades risk score for death within 2 mo after radiotherapy

Characteristic	Score(points)
ECOG performance status	
2	0
3-4	4
Tumor type	
Breast cancer	1
Prostate cancer	2
Myeloma/lymphoma	1
Lung cancer	3
Other	3
Further bone metastases	
No	1
Yes	3
Visceral metastases	
No	1
Yes	4
Interval from cancer diagnosis to MSCC	
≤ 15 mo	3
> 15 mo	1
Ambulatory status prior to RT	
Not ambulatory	4
Ambulatory before RT	1
Time of developing motor deficits	
1-7 d	4
> 7 d	1

ECOG: Eastern Cooperative Oncology Group; MSCC: Metastatic spinal cord compression; RT: Radiotherapy.

Scoring systems are practically used most frequently for the evaluation of surgical indications[25-32,45-53]. Some scoring systems were prepared to avoid selecting excessive treatments for patients with a poor prognosis[54-56]. Rades *et al*[56] (2013) examined risk factors for dying within two months after radiotherapy. As a result, for those with 24 points or more, 96.0% died within two months after radiotherapy, and the specificity was 99.8% (Table 12)[56]. Scoring systems are often important for preventing the unnecessary widening of surgical indications in particular. As cost-effectiveness has recently begun to be demanded in medical care, evaluation in this regard has also become necessary.

Moreover, because of the nature of the disease, the functional prognosis depends on the survival period. Therefore, scoring systems have also begun to be used for assessing the functional prognosis. Tang *et al*[57] (2007) used the Tokuhashi score to determine the indications of rehabilitation by admission on the basis of its correlation with the functional independence measure (FIM). In addition, Yamashita *et al*[58] (2008) and Putz *et al*[59] (2008) reported that the Tokuhashi score can also be used for the prediction of functional recovery due to its correlation with neurological recovery. Rades *et al*[60,61] also reported that the ambulatory ability after treatment can be predicted using factors related to the survival period of prognostic scoring systems.

Under these circumstances, scoring systems have begun to be applied clinically as outcome measures[62,63], but no scoring system is satisfactory regarding the validity, reliability, or responsiveness.

On the other hand, there is criticism against limiting treatment alternatives based on simple numerical indices of such scoring systems[64-66]. Gasbarrini *et al*[64,65] attached importance to the evaluation of individual patients in consideration of the sensitivity, particularly to adjuvant therapies, and proposed a treatment algorithm emphasizing the multidisciplinary selection of treatments including scoring systems. Paton *et al*[67] also proposed a therapeutic strategy taking the location level (L), mechanical instability (M), neurology (N), oncology (O), patient fitness, prognosis, and prior therapy (P) into consideration.

FUTURE SCORING SYSTEMS

Scoring systems for the prognosis of patients with metastatic spinal tumors have been prepared by frontline orthopedists and radiologists from clinical viewpoints. Many of these scoring systems were proposed when sufficient systematic treatments were not performed for metastatic spinal tumors and have been used as simple and excellent tools[68]. However, as metastatic tumors have also begun to be treated aggressively, the scoring systems have become unfit for the actual situation with the diversification of treatments. Therefore, challenges for future scoring systems need some discussion.

First, oncological viewpoints, which conventional scoring systems lacked, should be incorporated with progress in cancer treatments. They include: (1) consideration of the stage and level of the disease; (2) evaluation according to the nature of the primary cancer; (3) introduction of serum levels of prognostic markers; and (4) multidisciplinary approaches, among others.

Regarding the disease stage, metastatic spinal tumors varying from those in the asymptomatic period, those in the period of progression of spinal paralysis, to those in the terminal period must be handled due to the improvement in the metastasis-detection power, but they cannot be evaluated uniformly with a single scoring system. At least, the disease stage should be specified, and scoring systems should be prepared and used accordingly. In addition, little attention has been paid to the level of involvement, and the lack of an appropriate scoring system for the cervical spine, which is infrequently affected, has been suggested as a problem to be addressed in the future[69].

Concerning evaluation according to the nature of the primary cancer, Chen *et al*[10] and Morgen *et al*[51] (2013) reported that, in some cancer types, the prognosis of patients with spinal metastases was significantly improved during a period of 5 years due to rapid improvements in the treatment, and stressed that the improvements in the prognosis should be reflected in scoring systems. The necessity of scoring systems for different types of cancer has been discussed for some time[70-72], and the development of those for different cancer types is expected to be promoted by the accumulation of cases and systematization of treatments. In this process, it is possible to incor-

Table 13 Crnalic score for prostate cancer metastases

Prognostic factor	Score (points)
Hormone status	
Hormone native	2
Hormone refractory	0
KPS (%)	
80-100	2
≤ 70	0
Visceral metastasis	
Absent	1
Present	0
PSA (ng/mL)	
Hormone native	1
Hormone refractory	
< 200	1
≥ 200	0
Total points	Median overall survival
0-1	3 mo
2-4	16 mo
5-6	61.7 mo

KPS: Karnofsky performance score; PSA: prostate-specific antigen.

porate specific markers of particular types of cancer as prognostic factors. Crnalic *et al*[73] reported a specialized scoring system for prostate cancer metastases including prostate-specific antigen (Table 13).

Finally, attention to multidisciplinary approaches is necessary instead of preparing scoring systems on the basis of the results of, or for the selection of, a single treatment. Gregory *et al*[74] proposed that prognostic scoring systems should be changed by introducing anti-vascular endothelial growth factor. The introducti ion of such new treatments may exert favorable effects on other conventional treatments[75]. Therefore, the importance of considering multidisciplinary treatments must be stressed.

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Positioning patients for spine surgery: Avoiding uncommon position-related complications

Ihab Kamel, Rodger Barnette

Ihab Kamel, Rodger Barnette, Temple University School of Medicine, Philadelphia, PA 19140, United States
Author contributions: Kamel I and Barnette R solely contributed to this paper.
Correspondence to: Ihab Kamel, MD, Associate Professor of Anesthesiology, Temple University School of Medicine, 3401 N. Broad Street, 3rd floor outpatient building (Zone-B), Philadelphia, PA 19140, United States. ihab.kamel@tuhs.temple.edu
Telephone: +1-215-7073326 Fax: +1-215-7078028
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Abstract

Positioning patients for spine surgery is pivotal for optimal operating conditions and operative-site exposure. During spine surgery, patients are placed in positions that are not physiologic and may lead to complications. Perioperative peripheral nerve injury (PPNI) and postoperative visual loss (POVL) are rare complications related to patient positioning during spine surgery that result in significant patient disability and functional loss. PPNI is usually due to stretch or compression of the peripheral nerve. PPNI may present as a brachial plexus injury or as an isolated injury of single nerve, most commonly the ulnar nerve. Understanding the etiology, mechanism and pattern of injury with each type of nerve injury is important for the prevention of PPNI. Intraoperative neuromonitoring has been used to detect peripheral nerve conduction abnormalities indicating peripheral nerve stress under general anesthesia and to guide modification of the upper extremity position to prevent PPNI. POVL usually results in permanent visual loss. Most cases are associated with prolonged spine procedures in the prone position under general anesthesia. The most common causes of POVL after spine surgery are ischemic optic neuropathy and central retinal artery occlusion. Posterior ischemic optic neuropathy is the most common cause of POVL after spine surgery. It is important for spine surgeons to be aware of POVL and to participate in safe, collaborative perioperative care of spine patients. Proper education of perioperative staff, combined with clear communication and collaboration while positioning patients in the operating room is the best and safest approach. The prevention of uncommon complications of spine surgery depends primarily on identifying high-risk patients, proper positioning and optimal intraoperative management of physiological parameters. Modification of risk factors extrinsic to the patient may help reduce the incidence of PPNI and POVL.

Key words: Spine surgery; Complication; Position; Nerve injury; Visual loss

Core tip: Perioperative peripheral nerve injury (PPNI) and postoperative visual loss (POVL) are rare complications related to patient positioning during spine surgery. It is important for spine surgeons to be aware of PPNI and POVL to participate in safe, collaborative perioperative care of spine patients. Proper education of perioperative staff, combined with clear communication and collaboration while positioning patients in the operating room is the best and safest approach. The prevention of uncommon complications of spine surgery depends primarily on identifying high-risk patients, proper positioning and optimal intraoperative management of physiological parameters.

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INTRODUCTION

Surgical procedures involving the spine are one of the commonly performed procedures worldwide. The number of spine fusion surgeries performed in the United States has increased steadily over the past two decades[1-4]. Positioning patients for spine surgery is pivotal for optimal operating conditions and operative-site exposure. During spine surgery, patients are placed in positions that are not physiologic, would not be tolerated for prolonged periods by the patient in the awake state, and may lead to complications. Although the incidence of complications associated with positioning patients for spine surgery is relatively low, position-related complications can be devastating and life changing to patients and their families. Understanding these uncommon complications and their etiology is pivotal to prevention, and necessary if one is to obtain a truly informed consent from the patient. In this review article we discuss two of the uncommon, less recognized complications related to patient positioning during spine surgery; perioperative peripheral nerve injury and postoperative visual loss (POVL).

PERIOPERATIVE NERVE INJURY

Perioperative peripheral nerve injury (PPNI) is a rare but important perioperative complication resulting in significant patient disability, functional loss and the potential for litigation[5,6]. The reported incidence of PPNI is 0.03%-0.1%[7,8]. The mechanism of perioperative peripheral nerve injury is not well understood[9]. In the American society of anesthesiologists (ASA) closed claims study, there is no apparent mechanism of injury in the majority of the nerve injury claims[6]. Neurosurgical and orthopedic surgical procedures have a significant association with perioperative peripheral nerve injury[7].

The normal reaction to increased loading of the peripheral nervous system (PNS) elements is progressively increasing muscle activity; this acts as a nociceptive mediated reflex to prevent further harmful elongation. But the use of muscle relaxants and inhaled anesthetics during general anesthesia may suppress this protective mechanism subjecting the PNS to greater elongation than would be tolerated in the normal awake state[10].

In an attempt to raise awareness and reduce the occurrence of PPNI, ASA formed a task force on the prevention of perioperative peripheral neuropathies. The task force published a practice advisory for the prevention of perioperative neuropathies in 2000 and 2011[11].

Anatomy and physiology of peripheral nerves

The PNS carries information to and from the central nervous system (CNS). The functional unit of the peripheral nerve system is the neuron. The neuron consists of a cell body, dendrites and a long axon. The cell body contains the cytoplasm and the nucleus. Dendrites are attached to the cell body and carry impulses to the cell. Axons are attached to the cell body and carry impulses away from the cell. Conduction of an impulse along a neuron progresses from the dendrite to the cell body to the axon. The axon of one neuron and the dendrite of the next neuron are connected through the synapse. The synapse is a gap where the dendrites of one neuron and the axon of the next neuron communicate *via* chemical transmitters. Portions of the cell body and the axon are covered by Schwan cells, which form myelin segments. Myelin is an insulating layer around the axons allowing quicker and more efficient impulse transmission.

The interior of all nerve cells is negatively charged with respect to the exterior of the cell. Once the action potential of the nerve cell reaches the threshold voltage, sodium channels in the region of the action potential open, allowing sodium to flow into the nerve cell and leading to complete depolarization of the membrane. The depolarization caused by sodium influx opens adjacent voltage-gated sodium channels in the membrane leading to depolarization. The repetition of this depolarization process creates a wave of depolarization along the nerve fiber known as the action potential.

The peripheral nerve is composed of multiple nerve fibers (axons) bundled together. The bundles of nerve fibers are bound together by connective tissue sheaths and form fascicles. The endoneurium is a connective tissue sheath containing blood capillaries (vasa nervorum) that supply nutrients and oxygen to the nerve tissues. The endoneurium secretes the endoneurial fluid which surrounds the axons. The fascicles are wrapped in a fibrous tissue, the perineurium. Epineurium is the fibrous sheath that covers the entire nerve (Figure 1). The extrinsic plexus of blood vessels present in the epineurium penetrate the perineurium to anastomose with the intrinsic circulation in the endoneurium.

Tissue perfusion in the peripheral nerve is dependent on perfusion pressure. Perfusion pressure is defined as the difference between the mean arterial blood pressure and the internal pressure within nerve. In experimental animal models, high blood flow in the sciatic nerve was observed between mean blood pressures of 80-110 mmHg[12]. Acute hypotension was associated with a decrease in blood flow in the peripheral nerve[13]. Peripheral nerves lack vascular autoregulation[12-14]. Autoregulation is the intrinsic ability of an organ to maintain a constant blood flow despite changes in perfusion pressure. At mean blood pressures below 85 mmHg, there was marked decrease in the peripheral nerve blood flow[12]. A significant reduction in the blood flow to the nerve is required to affect the conduction of impulse in the nerve because blood flow to the peripheral nerve exceeds the metabolic requirements of the peripheral nerve by a significant margin[15]. Acute nerve ischemia leads to focal and generalized impairment of impulse conduction across the nerve that can be detected within 10 min of ischemia[16].

Mechanism of perioperative nerve injury

Direct trauma causing disruption and destruction of nerve fibers can lead to peripheral nerve dysfunction. Although direct trauma to peripheral nerves can be the

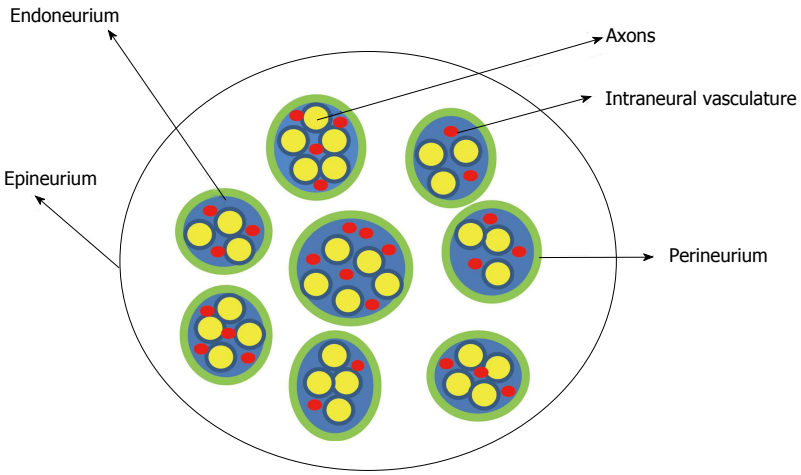

Figure 1 Schematic representation of the cross section of the peripheral nerve.

cause of PPNI, it is not the cause in the majority of cases.

One of the main and crucial mechanisms of PPNI is ischemia of nerve fibers[17,18]. Slowing of nerve conduction due to ischemia of the nerve fibers is the hallmark of peripheral nerve injury. Focal demyelination may occur if local ischemia is prolonged, leading to sustained axonal damage[19-21]. Peripheral nerve studies in experimental animal model demonstrated that reperfusion injury after prolonged ischemia (3-7 h) results in endoneurial edema, conduction block, blood-nerve barrier disruption, intramyelinic edema and demyelination[22-24]. Ischemia leads to demyelination in rat sciatic nerve[25]. Focal nerve ischemia is an important pathologic mechanism in hyperesthesia, Wallerian degeneration and axonal injury in animal models[17]. Persistence of ischemia can lead to permanent peripheral nerve injury. Ischemia may be the final pathway of perioperative neuropathy[26-30]. The interdependence between ischemic and mechanical factors (stretch and compression) as a cause to nerve injury is well established, although incompletely understood.

Stretch of the peripheral nerve is one of the main mechanisms of peripheral nerve injury in perioperative patients[31]. During spine surgery, under general anesthesia, patients are frequently placed in positions that may stretch nerve fibers beyond their resting length. Overstretch of the nerve can lead to direct nerve damage *via* disruption of axons and vasa nervosum. Peripheral nerve injury occurs if nerves are stretched beyond 5%-15% of their resting length[32-34]. Stretch of the peripheral nerve leads to an increase in the intraneural pressure and compression of the intraneural capillaries and venules leading to a reduction in the perfusion pressure of the nerve fibers and ischemia[34,35]. Stretch may lead to reduction in the intraneural blood flow, leading to ischemia and endoneurial edema[34,36,37]. Stretch of the peripheral nerves has been shown to suppress axonal transport leading to changes in conduction characteristics[32,33,38,39].

Peripheral nerve compression is another related mechanism of PPNI[31]. Compression of peripheral nerve leads to damage of nerve fibers. Compression may lead to an increase in intraneural and extraneural pressures leading to a reduction in perfusion pressure; a reduction in the perfusion pressure leads to ischemia and slowing of conduction in the nerve fibers. Many operative positions during spine surgery subject peripheral nerves to compression.

Recent evidence suggests an inflammatory mechanism leading to perioperative ulnar nerve injury. Patients with persistent postoperative neuropathy had evidence of inflammatory reaction in peripheral nerves. Nerve biopsy of these patients revealed diffuse generalized microneuritis. Immunotherapy treatment with high-dose steroids resulted in significant improvement of ulnar neuropathy in these patients[40].

Risk factors for nerve injury

Certain drugs and chemicals may predispose patients to peripheral neuropathies[41]. Many conditions and medical diseases may render peripheral nerves more vulnerable to injury during the perioperative period[41]. Diseases affecting microvasculature, and anatomical differences, may contribute to nerve injury or render patients more susceptible to nerve injury. Hypertension, tobacco use, diabetes mellitus, general anesthesia, neurosurgical procedures and orthopedic surgery have been significantly associated with PPNI[7]. Advanced age has been linked to peripheral neuropathy after median sternotomy[42]. Hypovolemia, dehydration, hypotension, hypoxia, electrolyte disturbance and induced hypothermia have been associated with nerve injury[43]. The etiology of PPNI is multifactorial and involves patient predisposition, precipitating mechanical and physiologic factors.

Ulnar neuropathy

Ulnar neuropathy is the most common site of PPNI[8]. Ulnar nerve injuries comprised 28% of all anesthesia-related nerve injury malpractice claims[6]. Perioperative ulnar neuropathy occurred in 0.5% of surgical patients; primarily men between 50-75 years of age[44]. Ulnar neuropathy can lead to significant morbidity and loss of function. Ulnar nerve injury results in the inability to oppose or abduct the fifth finger and loss of sensation of the fourth and fifth fingers. Permanent injury will lead to a claw-like hand deformity due to atrophy of the intrinsic muscle of the hands. In one study, 3 out of 7 patients

who developed perioperative ulnar neuropathy had permanent neuropathy with residual symptoms beyond 2 years[44]. Perioperative ulnar nerve injury has a delayed onset, most cases manifest within 2-7 d post-operatively (median 3 d)[5,19,44-49].

In a large retrospective review of ulnar neuropathy in anesthetized patients, the major complaints among patients with persistent ulnar neuropathy were their inability to grip tools and equipment due to loss of grip strength, discomfort and numbness. Perioperative ulnar neuropathy presented as sensory deficit in 47% of the cases while 53% of the deficits were mixed sensory and motor. Bilateral symptoms of ulnar neuropathy developed in 9% of the cases. Initial symptoms of were usually noted more than 24 h after the procedure, and appeared within 7 d in 90% of patients. Fewer than 10% of ulnar neuropathies were noted in the postoperative recovery unit. Fifty-three percent of patients with perioperative ulnar neuropathy who survived the first postoperative year regained complete sensory and motor functions and were asymptomatic. Six percent regained complete sensory and motor function but still complained of pain. At 1 year, 41% of patients had persistent deficits. Patients with sensory deficits had a better chance of complete recovery (80%) compared to patients with mixed motor and sensory deficits (35%)[19].

Patient related risk factors for perioperative ulnar nerve injury include male gender, older population, very thin and very obese patients, and prolonged postoperative immobilization[19]. The ulnar nerve may be susceptible to injury due to a pre-existing subclinical neuropathy. Pre-existing asymptomatic abnormal conduction in the contralateral ulnar nerve has been observed in patients who developed postoperative ulnar neuropathies[46]. Pre-existing subclinical neuropathy may manifest clinically in the perioperative period when patients are subject to certain predisposing factors[19,48,50]. Induced and prolonged hypotension has been associated with perioperative ulnar nerve injury[26,51,52]. Positioning during anesthesia has been related to ulnar neuropathy[52].

As stated above ulnar neuropathy occurs predominantly in men[5,19,47,53,54] with 70% of perioperative ulnar nerve injury cases occurring in males[19]. Anatomical differences may be responsible for this higher incidence of ulnar nerve injury. Studies of human male and female cadavers, showed that females have a significantly higher fat content (2-19 times) on the medial aspect of the elbow while men have a significantly larger tubercle of the coronoid process (1.5 times)[55]. Men have a thickened and more developed flexor retinaculum[8]. Men are more susceptible to direct pressure on unmyelinated ulnar nerve fibers than women[49].

The ulnar nerve has a superficial path along the medial epicondyle of the humerus[52]. The ulnar collateral artery and vein run in close proximity to the ulnar nerve and may be affected by external pressure leading to reduced perfusion, ischemia and nerve injury[30]. Compression of the ulnar nerve and its blood supply (the posterior ulnar collateral artery) at the area of the tubercle of the coronoid may lead to ischemia[55]. The ulnar nerve is relatively more sensitive to ischemia compared to median and radial nerves[27]. Experimental animal models demonstrated that the effects of compression on the ulnar nerve are potentiated by previous ischemia, even if the ischemia is of short duration[56]. The forearm position is a significant factor in determining pressure over the ulnar nerve at the elbow. Prielipp *et al*[30] investigated the relationship between forearm position and direct pressure on the elbow in awake normal volunteers, using a computerized pressure sensing mat. The study provided clear evidence that forearm supination significantly minimizes pressure over the ulnar nerve at the elbow (2 mmHg) compared with the neutral (69 mmHg) and prone (95 mmHg) forearm positions. Neutral forearm position resulted in significantly less pressure compared to the prone forearm position but more pressure compared to the supine forearm position. In the supine forearm position, the pressure over the ulnar nerve was low regardless of the degree of abduction of the arm at the shoulder. In the neutral forearm position, pressure over the ulnar nerve decreased as the arm was abducted between 30° and 90°. Pronation of the forearm produced the largest pressure over the ulnar nerve regardless of the abduction of the arm between 30° and 90°[30]. Extraneural pressures recorded along the path of the ulnar nerve in fresh cadaveric arms were significantly increased with elbow flexion beyond 90°. Concomitant shoulder abduction caused further increase in the pressure recorded at the post-condylar groove and the carpal tunnel[57].

Gelberman *et al*[58] investigated the relationship between the ulnar nerve and the cubital tunnel during flexion of the elbow in normal human cadavers. They observed a significant decrease in the cross-sectional area of the cubital tunnel coupled with an increase in the pressure within the cubital tunnel and ulnar nerve. Intraneural pressure of the ulnar increased significantly with the elbow flexed 70° or more. Extraneural pressure increased significantly when the elbow was flexed to 100° or more. The intraneural pressure was significantly increased at lesser degrees of flexion compared to the extraneural pressure. The authors conclude that the increase in the intraneural pressure of the ulnar nerve is not entirely due to extraneural compression. Dynamic changes in the cubital tunnel and the cross-section of the ulnar nerve contribute to the increased intraneural pressure with flexion. Compared with full extension, the mean area of the cubital tunnel in the subaponeurotic region decreased by 18% and 39% and the ulnar nerve mean area decreased by 24% and 50% with elbow flexed 90 and 135 degrees respectively. Intraneural and extraneural pressures within the cubital tunnel are lowest at approximately 45° of flexion[58]. Flexion of the elbow to 135° resulted in an 18% elongation of the ulnar nerve[59]. Elongation of peripheral nerve beyond 5%-15% of resting length can cause ischemia and nerve injury[32-34]. Stretch of the ulnar nerve by elevation of the shoulder, flexion of the elbow and dorsiflexion of the wrist caused a marked increase in the intraneural pressure[60].

Patel *et al*[61] assessed the morphologic changes in the ulnar nerve and cubital tunnel with elbow motion in fresh

human cadavers using magnetic resonance imaging. During full extension the ulnar nerve appeared round in serial cross-sectional images and was surrounded by fat except at the inferior aspect of the medial epicondyle where the nerve was directly adjacent to bone. On flexion the nerve displaced the fat posteriorly and was relocated to a more anterior position in the cubital tunnel. On flexion the cross-section of the nerve progressively flattened from a round to an elliptical shape. With progressive flexion the course of the nerve changed from tortuous to more direct. With progressive elbow flexion the proximal cubital tunnel takes a wider and flatter appearance with the largest diameter changing from anteroposterior to mediolateral. The diameter of cubital tunnel in the subaponeurotic region decreased with progressive elbow flexion[61].

Although the proportion of nerve damage claims has not changed between the 2 ASA closed claims studies performed almost a decade apart, the pattern of nerve injury has changed. Compared to the ASA closed claims report published in 1990, the report published in 1999 showed a relative decrease in the incidence of ulnar nerve injury claims as a proportion of total nerve injury claims and a relative increase in spinal cord injury claims. However, the actual incidence and trend of nerve injury cannot be determined based on the closed claims data since it lacks a denominator. The closed claims project examines anesthesia-related malpractice claims; it does not present the nerve injury in population. In the ASA closed claims study, the mechanism of ulnar neuropathy was explicitly stated in only 9% of the claims[6].

Perioperative ulnar neuropathy is not confined to surgical patients. A prospective study of ulnar neuropathy in patients admitted to internal medicine services for nonsurgical conditions revealed that 0.2% of the patients developed new onset ulnar neuropathy while in hospital. Patients commonly rest in a supine position, flexing their elbows and resting their arms on their chest and abdomen. Elbow flexion may increase pressure on the ulnar nerve in the postcondyler groove of the humerus due to stretching of the cubital tunnel retinaculum. Forearm pronation may lead to external compression of the ulnar nerve[45]. It is therefore prudent to instruct patients to avoid prolonged flexion of the upper extremity on the abdomen and chest in the supine position.

Brachial plexus injury

Brachial plexus is the second most common site of PPNI accounting for 20% of all anesthesia-related nerve injury malpractice claims[6]. The reported incidence of brachial plexus injury in non-cardiac surgery is 0.02%[62]. The main mechanisms of brachial plexus injury are compression and stretch. The brachial plexus has a long course between the vertebra and the axillary fascia. Brachial plexus injury usually involves the upper nerve roots. Lower brachial nerve injuries are commonly associated with median sternotomy[43].

In the ASA closed claims project, patient positioning was responsible for 10% of brachial plexus malpractice claims. The use of shoulder braces and head-down position, arm malpositioning and prolonged neck extension were commonly identified mechanisms for brachial plexus injury[6]. The use of shoulder braces in Trendelenburg position may lead to compression of the brachial plexus between the clavicle and the first rib[8,63].

Brachial plexus injury is commonly due to overstretch of the brachial plexus[43]. Shoulder abduction greater than 90°, external rotation of the arm and posterior shoulder displacement can stretch the brachial plexus[43,64]. Downward tilting of the head and hyperabduction of the independent arm in the lateral position may stretch the brachial plexus and lead to brachial plexus injury[65]. Extension and lateral flexion of the head in the supine position may contribute to stretch of the brachial plexus on the contralateral side[43].

In the supine position, submaximal joint positions may stretch the brachial plexus to the extent it may affect physiologic processes in the peripheral nerve. Contralateral flexion of the cervical spine, lateral rotation of the shoulder combined with shoulder abduction and wrist extension may stress the brachial plexus. Elbow extension can cause substantial stress to the PNS. Simultaneous application of the different aforementioned components has a cumulative stressful impact on the brachial plexus. Individuals react differently to elongation of the peripheral nerve and individual variability increases as more components leading to stretch of the brachial plexus are added[10].

Median neuropathy

Median nerve injury is relatively rare and responsible for only 4% of all anesthesia-related nerve injury malpractice claims[6]. The median nerve may be injured during the insertion of an intravenous catheter in the antecubital fossa. However, stretch is the main mechanism of median nerve injury due to operative positioning.

Median neuropathy usually presents as a motor neuropathy with loss of the ability to oppose the first and fifth digits and decreased sensation over the palmar surface of the lateral three and half fingers. Median neuropathies do not resolve easily with most patient having sustained symptoms of motor dysfunction. Extension of the elbow may overstretch the median nerve leading to injury[11]. Muscular patients and patients with limited elbow extension range may be at risk for median nerve injury if the arm is fully extended under general anesthesia. The reduced range of extension in these patients may lead to similar contraction of median nerve making it more prone to overstretch[66]. Overextension of the elbow in the supine position to a point that is uncomfortable to the patient in the awake state should be avoided[11]. Wrist hyperextension for arterial line placement may lead to transient but significant impairment of the median nerve function. Prolonged hyperextension of the wrist may lead to slowing of nerve conduction and median nerve injury[67].

Radial neuropathy

Radial nerve injury is rare and accounts for just 3% of

all anesthesia-related nerve injury malpractice claims[6]. The most common mechanism of radial nerve injury is direct compression at the spiral grove of the humerus. It may occur in the lateral position with abduction of the independent arm beyond 90° and suspension of the arm from a vertical screen support[68]. Direct compression by the overhead arm board at the mid-humerus may occur in the lateral position. Injury to the radial nerve results in wrist drop, inability to extend the metacarpophalangeal joint and inability to abduct the thumb with loss of sensation from the lateral and posterior arm, posterior forearm and a portion of the dorsal hand.

Intraoperative neuromonitoring

Intraoperative neuromonitoring is available in most institutions in the United States and is frequently used during spine surgery[69]. Commonly used intraoperative neuromonitoring modalities are somatosensory evoked potential (SSEP) and motor evoked potential. Neuromonitoring is primarily used to monitor the integrity of the spinal cord during spine surgery. However, SSEP monitoring has been used to detect peripheral nerve conduction abnormalities indicating peripheral nerve stress and impending injury during surgery under general anesthesia in variable intraoperative positions[70-86]. Conduction changes detected by SSEP may indicate position-related impending peripheral nerve injury. In a retrospective study of 1000 consecutive spine cases, position modification of the upper extremity lead to resolution of 92% of upper extremity SSEP changes[86]. Position modification strategies used in the review included correcting extreme elbow flexion and extension, decreasing shoulder abduction, releasing shoulder traction on tucked arms (caused by taping down the shoulder) and moving the upper extremity into the original position if the position had been modified. After position modification of the upper extremity and resolution of SSEP change, patients experienced no post-operative upper extremity peripheral nerve injury[86]. Significant SSEP change indicating impending upper extremity nerve injury is usually defined as reduction in amplitude of 50% or more and/or increase in latency of 10% or more[73,86]. Usually changes in both amplitude and latency are monitored and evaluated. Compared to latency, amplitude changes may be a more sensitive and valid measure of changes in nerve conduction[87,88]. Most SSEP components are mediated by large myelinated fibers. Some secondary peaks may be transmitted by smaller fibers. Potentials recorded from Erb's point may be the most sensitive to ischemia[28].

Significant SSEP changes indicate abnormal conduction and impending nerve injury. If the changes persist for a prolonged period of time, permanent nerve injury may occur[30]. The use of SSEP to monitor extremity nerve function and guide position modification of the upper extremity into a more favorable position for the peripheral nerve may protect peripheral nerves from injury under general anesthesia. The incidence of position related significant upper extremity SSEP changes during spine surgery ranges from 1.8% to 15% depending on the operative position, patient group and type of spine surgery[79,83,86].

POSTOPERATIVE VISUAL LOSS

POVL is a rare but traumatic and devastating complication of spine surgery and general anesthesia. The reported prevalence rate of POVL after spine surgery is 0.0028%-0.2%[89-92]. The incidence of POVL associated with spine surgery in the prone position under general anesthesia has increased over the past several decades[93]. POVL usually results in permanent unilateral or bilateral visual loss. Most cases are associated with prolonged spine procedures in the prone position under general anesthesia. Posterior lumbar fusion and surgery for correction of scoliosis were associated with the highest rate of POVL[92]. POVL has been associated with instrumented spine surgery in the prone position[94]. The most common causes of POVL after spine surgery are ischemic optic neuropathy (ION) and central retinal artery (CRA) occlusion. ION is further classified into anterior ION (AION) and posterior ION (PION). PION is the most common cause of POVL after spine surgery. In 1999, the ASA committee on professional liability established the ASA POVL registry to identify predisposing factors and intraoperative risk factors. It is important for spine surgeons to be aware of POVL and to participate in safe, collaborative perioperative care of spine patients positioned in the prone position.

Anatomy and physiology of the optic nerve

The eye is a sphere that gathers and converts light information into neuronal signals. The wall of the globe has 3 layers; the outermost sclera (white of the eye), the middle uveal tract (contains the choroid) and the innermost layer (the retina). There are no blood vessels in the retina; the choroid layer, located posterior to the retina contains blood vessels and provides the retina with oxygen and nutrients. Retinal ganglion cells (RGC) in the retina are highly specialized neurons that produce neural signals when stimulated by light. Neural signals are transmitted to the brain along axons of RGC in the optic nerve (cranial nerve Ⅱ).

The optic nerve is composed of about 1.2 million individual RGC axons and support cells. Axons of the RGC travel across the retina and converge near the center forming the optic nerve. This convergence of the RGC axons creates the blind spot of the eye, an area where no photoreceptors exist, only nerve fibers.

The optic nerve has a structure similar to the CNS tracts and is considered part of the CNS. In contrast to the ability of the mammalian PNS to regenerate axons after injury, mammalian CNS structural and functional regeneration after injury is minimal. Injury to the RGC usually results in lifelong visual loss due to the limited ability of RGC to regenerate their axons after optic nerve injury[95].

The blood supply of the eye comes from the ophthalmic artery, a branch of internal carotid artery. The CRA

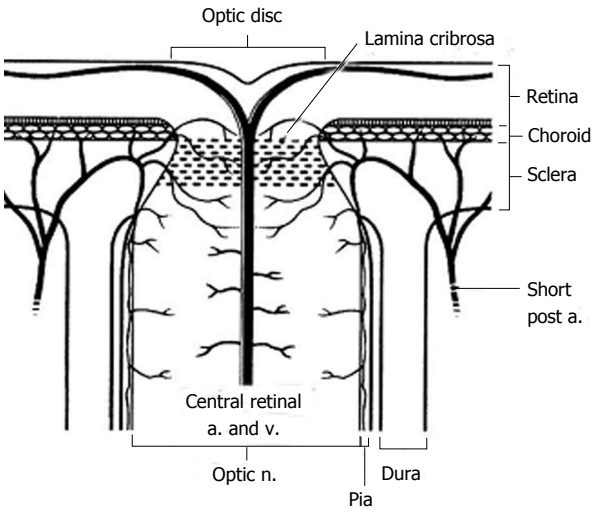

Figure 2 Diagram of the anterior optic nerve showing the arterial and small vessel supply to the choroid and optic nerve as it passes through the lamina cribrosa. Short post a: Short posterior ciliary artery; a: Artery; v: Vein; n: Nerve (Reprinted from Williams *et al*[140] with permission).

is a branch of the ophthalmic artery. The CRA penetrates the optic nerve superiorly and continues its course in the optic nerve to supply the retina. The ophthalmic artery gives rise to 1-5 posterior ciliary arteries. The posterior ciliary arteries give rise to short and long posterior ciliary arteries. The posterior ciliary arteries are end-arteries that provide blood supply to the head of the optic nerve and the retina.

The optic nerve can be divided into anterior and posterior portions based on differences in anatomy and blood supply[96]. The anterior portion (intraocular) of the optic nerve is that part of the optic nerve that lies anterior to the lamina cribrosa. The posterior (retrolaminar or intraorbital) portion of the optic nerve is the part of the optic nerve posterior to the lamina cribrosa. Lamina cribrosa is an elastic multilayered network of collagen fibers that insert into the scleral canal wall. The nerve fibers forming the optic nerve exit the eye posteriorly through the lamina cribrosa. The CRA and the central retinal vein pass through the lamina cribrosa to enter the optic disc.

The predominant cells in the anterior optic nerve are astrocytes, while microglial cells and oligodendrites are relatively more common in the posterior optic nerve. Unlike peripheral nerves, the posterior (retrolaminar) optic nerve is covered by all three meningeal layers; dura, arachnoid and pia matter.

The blood supply of the anterior optic nerve is derived from retinal arterioles, centripetal branches from the peripapillary choroid and short posterior ciliary arteries (Figure 2). The anterior optic nerve may receive blood from the intrascleral circle of Zinn and Haller when present.

The blood supply of the posterior (retrolaminar) optic nerve is derived from two vascular systems; the centripetal (peripheral) system and centrifugal system (axial). The centripetal vasculature is the main and most consistent system supplying the posterior optic nerve. It is formed primarily of recurrent branches of the peripapillary choroid, and the circle of Zinn and Haller, with additional pial branches from the CRA and other orbital arteries. The centrifugal blood vascular system consists of a few branches of the CRA The centrifugal system is not always present and the number of branches is inconstant. To summarize, the main blood supply of the anterior optic nerve is derived from the short posterior ciliary arteries and the peripapillary choroid. The main blood supply to the posterior optic nerve is derived from recurrent branches of the peripapillary choroid and pial branches of the CRA.

It is important to realize there is not one universal pattern of blood supply for the optic nerve. There are many anatomic variations in vascular supply, which can lead to variable patterns of ischemia among individuals[97-100]. In most individuals, there are 2 to 3 posterior ciliary arteries; however in some the number may range from 1 to 5. It is also important to note that posterior ciliary arteries are end-arteries, and thus watershed zones exist between them[100]. Watershed areas, by definition, are areas that are at risk for decreased blood supply. Blood flow to the posterior optic nerve may be particularly vulnerable to ischemia because most of the arteries supplying the posterior optic nerve are end-arteries[98].

Blood flow to the optic nerve

The blood flow to the optic nerve head is dependent on perfusion pressure. Ocular perfusion pressure is the difference between mean arterial blood pressure and intraocular pressure (IOP) or venous pressure (whichever is higher)[101]. It is important to note that the mean arterial pressure determining optic nerve blood flow refers to that of the optic nerve vasculature and not the pressure in the brachial or radial arteries. Local arteriolar vasoconstriction may reduce perfusion to the optic nerve leading to ischemia despite a normal brachial blood pressure measurement. Thus three main factors determine optic nerve perfusion; vascular tone, arterial blood pressure and IOP.

Autoregulation

There is evidence that the optic nerve head autoregulates blood flow[102-105]. Autoregulation is achieved through alterations in resistance of the terminal arterioles. There are limitations to the degree to which arteriolar resistance can be altered to maintain perfusion. Autoregulation works within a range of mean arterial pressure, below or above which the local perfusion is dependent entirely on the difference between mean arterial blood pressure and intraocular or venous pressure. Factors leading to the breakdown of autoregulation of blood flow to the optic nerve include age, hypertension, uncontrolled blood pressure, diabetes mellitus, atherosclerosis, hypercholesterolemia, and vascular endothelial disorders[106-109]. A study of the blood flow to the optic nerve head using laser Doppler flowmetry in healthy volunteers demonstrated that blood flow was constant between ocular perfusion pressures of 56 to 80 mmHg. Not all patients have autoregu-

lation of the blood flow to the optic nerve[105]. A study of autoregulation of the optic nerve in humans showed that 2 out 10 healthy young volunteers did not demonstrate autoregulation[104].

Arterial blood pressure

Arterial blood pressure is one of the main determinants of blood flow to the anterior and posterior optic nerve. There is a progressive fall in the blood pressure from the internal carotid artery, to the ophthalmic artery, to the posterior ciliary artery and then to the small branches supplying the optic nerve. The blood pressure in optic nerve may be half or less than that measured in the brachial artery[109]. Vascular changes such as atherosclerosis, vasospasm and vasculitis may lead to further decreases in blood flow to optic nerve. Critical drops in blood pressure below the lower limit of autoregulation will lead to a reduction in optic nerve blood flow. Hypotension resulting from antihypertensive medications or shock may lead to ischemia of the optic nerve and anterior ischemic optic neuropathy[110-113]. Nocturnal hypotension has been associated with glaucomatous visual loss[110,113,114]. Nocturnal arterial hypotension may be a key factor in the development of non-arteritic AION as more than 75% of these patients discover visual loss upon awakening in the morning[115]. Arterial hypertension can decrease blood flow to the optic nerve if it is outside the upper limit of autoregulation or there is an absence of autoregulation. In this setting a decrease in the blood flow is due to arteriolar vasoconstriction[109].

IOP

IOP is defined as the pressure exerted by the contents of the eye on its containing wall. Intraocular components like blood and aqueous humor can undergo significant volume changes that significantly alter IOP. External pressure on the eye globe can increase IOP by direct and indirect effects through volume changes of intraocular components. The normal IOP ranges from 10-20 mmHg with a diurnal variation of 2-3 mmHg. IOP decreases at night. IOP is a key determinant of blood flow to the optic nerve head. The blood flow to the optic nerve head is inversely proportionate to the IOP outside the range of autoregulation or if autoregulation is absent or defective. This effect may be intensified when coupled with hypotension or local vasospasm[116]. IOP may affect the blood flow to the anterior (intraocular) optic nerve. The effect IOP has on blood flow to the posterior (retrobulbar) optic nerve is unclear and probably of lesser significance.

Changes in arterial PCO_2 tension can affect intraocular blood volume and IOP independent of hemodynamic changes[117-121]. The vascular resistance of the choroidal vessels varies directly with inhaled CO_2[122]. High levels of PCO_2 lead to intraocular vasodilation increasing intraocular blood volume and IOP.

The choroid is a vascular structure that contains the majority of the intraocular blood volume. Congestion of the choroid leads to an increase in the intraocular blood volume and IOP. The choroid is characterized by very high blood flow[123]. Most of the blood volume of the choroid is in the venules of the choroid. Venular filling of choroid depends on the pressure in the orbital veins[117]. Pressure in the orbital veins can be affected by body position[117,124,125]. Increases in orbital venous pressure may lead to an increase in IOP though choroid congestion. Trendelenburg position increases central venous pressure and may lead to an increase in IOP through congestion of the choroid. The choice of the operating room table and frame (Jackson table or Wilson frame) has no significant role in IOP increase caused by the prone position[126].

The majority of the aqueous humor outflow is passively drained into the episcleral veins[127,128]. This passive outflow process depends on the gradient between IOP and episcleral vein pressure (EVP). High IOP may reduce aqueous humor drainage while having minimal effect on production leading to an increase of the total aqueous humor volume[126]. The episcleral veins are valveless veins connected to the central venous circulation. Cephalad shift of blood and increase in central venous pressure (CVP) will increase the EVP[124,129]. A positive correlation exists between episcleral venous pressure and IOP.

Elevation in central venous pressure may reduce venous return from the eye leading to an increase in IOP. There is close correlation between CVP and IOP[117,118,130]. A parallel and instantaneous decrease in CVP and IOP was noticed with a change from Head-down (Trendelendburg) position to head-up (reverse Trendelenburg) position[117]. Factors that cause significant increase in CVP may lead to an increase in IOP. These include increased intrathoracic pressure, extreme neck flexion, dependent position of head relative to the heart and abdominal compression. The venous pressure may increase beyond IOP, and in such cases it becomes a key determinant of ocular perfusion pressure and blood flow to the optic nerve.

Effects of general anesthesia and surgical position

General anesthesia decreases IOP in the supine position[116,130,131]. IOP pressure has been shown to increase in anesthetized patients in the supine head-down (Trendelenburg) position[130,132]. Peak airway pressure, mean arterial blood pressure, duration of surgery and end-tidal CO_2 are significant predictors of IOP in the anesthetized patient placed in the supine head-down position[132]. The prone position has been shown to increase IOP under general anesthesia in adult and pediatric patients[131,133]. IOP has been shown to increase in awake vertically inverted volunteers[134]. IOP has been shown to increase with elevated arterial carbon dioxide tension in anesthetized patients without eye disease[117]. Hyperventilation caused a rapid fall of IOP. IOP changes due to arterial carbon dioxide tension in anesthetized patients are presumably vascular in nature and are related to changes in the choroidal blood volume[117]. Intraoperative fluid balance may affect IOP. Acute oral water loading has been shown to significantly, though transiently, elevate IOP[135] while dehydration has been associated with significant

reduction in IOP[136]. In the prone position, general anesthesia may lead to an increase in the intraocular blood volume by impairing autoregulation in the choroid circulation[137]. The IOP may become a critical factor in the perfusion of the anterior optic nerve in the presence of decreased hematocrit and mean arterial blood pressure[126]. Ozcan *et al*[126], showed that an increase in the IOP caused by the prone position in awake volunteers was ameliorated but not normalized by a 10° head-up (reverse Trendelenburg) position[126].

ION

ION is the most common reported cause of POVL after spine surgery[138-140]. Perioperative ischemic neuropathy is a multifactorial disease that is not well understood. ION presents as acute loss of vision or visual field defect. More than 50% of the cases present in ASA POVL registry had bilateral ION[141]. ION is divided into AION and PION. AION involves ischemia and infarction of the anterior optic nerve, while PION involves ischemia and infarction of the posterior optic nerve. It is uncommon for AION and PION to be present simultaneously. Usually ION presents as selective AION or PION, presumably due to different predisposing factors and differences in the blood supply to those portions of the nerve[141]. Hypertension, diabetes, obesity, hypotension, anemia, prone position, smoking, vascular disease, increased blood viscosity and abnormal anatomy have been associated with ION and perioperative visual loss[139,140,142-147]. Anemia, hypotension, peripheral vascular disease and blood transfusion were associated with ION after spine surgery[90,92]. ION has been associated with adverse effects of hypertensive medications and with sildenafil[110,148]. ION is more common in males[139,149]. The protective effect of estrogen in experimental animal models of cerebral ischemia has been established and may contribute to the lower incidence of ION in females[150]. Obesity, the use of the Wilson spinal frame, longer anesthetic duration and lower colloid use during intraoperative fluid administration have been associated with ION and POVL[149]. Most cases of ION occurred in relatively healthy individuals, further confirming the role interindividual anatomic and physiologic variations may play in the development of ION.

The association between hypotension, anemia and ION is unclear. Anemia and hypotension has been associated with ION[90,92]. However ION has been diagnosed in patients with a hematocrit nadir of 40% during spine surgery. In a retrospective case-control study by Myers *et al*[94], there was no difference in the lowest blood pressure between patients who developed POVL and those who did not. ION may occur in the absence of hypotension[139]. Although deliberate hypotension for spine cases has not been associated with POVL in previous studies, the studies lack power to detect a complication with a significantly low incidence like POVL[151,152]. ION may be due to a "compartment syndrome of the optic nerve", a hypothesis related to increased venous pressure and interstitial fluid accumulation within the lamina cribrosa of the optic nerve (semi-rigid) or the bony optic canal[139].

Awake volunteers positioned in the prone position demonstrated a significant increase (20 mmHg) in the IOP after 8 min compared to the supine position (14.1 mmHg)[153]. Cheng *et al*[131] investigated the effect of prone positioning on IOP in 20 anesthetized patients having spine surgery. Patients with preexisting eye disease or previous eye surgery were not included. Patients were positioned in the prone position with their heads in pinned head-holder in a neutral position with neck flexion limited to less than 15° from horizontal. Mean arterial pressure was kept within 20% of awake values and end–tidal carbon dioxide level was maintained at 30-35 mmHg. IOP was measured at baseline and 5 times throughout the procedure. Two measurements of the IOP were made in the prone position; before incision and after the conclusion of the surgery. The IOP in the prone position before incision was significantly higher (27 mmHg) than both supine anesthetized and awake (baseline). The IOP was significantly higher (40 mmHg) in the prone position after the conclusion of surgery compared to all previous measurements. The mean duration in the prone position before the second measurement was 320 min. The authors concluded that IOP increased significantly in the anesthetized patient in the prone position and the magnitude of this increase is related to the amount of time spent in that position. Increases in IOPmay lead to reductions in ocular perfusion pressure despite normal systemic blood pressure[131].

Lee *et al*[139] analyzed 93 spine cases with POVL from the ASA POVL registry. Ischemic optic neuropathy was the cause of visual loss in 89% of cases. PION was the most common cause of optic neuropathy occurring in 56 of 83 ION cases. Nineteen patients were diagnosed with AION and 8 patients had unspecified ION. Compared to cases of CRAO, ION cases occurred more often in males (72%) undergoing elective surgery (96%). Most patients were relatively healthy with no preoperative history of glaucoma. Most cases of ION occurred with spine fusion and instrumentation involving more than one vertebral level in the thoracic, lumbar or sacral spine. All but 2 patients were positioned prone. The mean anesthetic duration was 9.8 h with 84% of cases lasting 6 h or longer. The mean prone duration was 7.7 h. Eighty-two percent of cases had an EBL of 1 liter or more. Only one patient in 83 showed signs of periocular trauma. Bilateral ION was documented in 66% of ION cases with a median onset time for reporting symptoms of 15 h. ION can occur without compression of the globe as 16 patients who developed ION were placed in Mayfield pins. Key findings of the review were the higher incidence of ION in males, the association of ION with an EBL of 1000 mL or greater, and a duration of surgery of 6 h or longer. The authors recommend discussing the risk of POVL with patients undergoing lengthy spine surgery in the prone position[139].

Shen *et al*[89] investigated the prevalence of POVL in the United States over a 10-year period from 1996 to 2005 using The Nationwide Inpatient Sample. The preva-

lence rate for POVL was 0.03% after spinal fusion and 0.0086% after laminectomy without fusion. Age, male gender, anemia, and posterior approach for surgery were associated with significantly higher odds of developing POVL. Patients younger than 18 years had the highest prevalence rate (0.35%). The prevalence rate of POVL was 0.05% in the posterior approach compared to 0.006% in the anterior approach. Men had 1.3 time higher odds ratio of visual loss, and twice the odds ratio for developing ION compared to women. Contrary to POVL after cardiac surgery, existing co-morbidities were not associated with greater odds for developing POVL and ION with spine fusion surgery[89].

Holy *et al*[138] performed a retrospective matched case-control study to determine the incidence and risk factors of ION in a single institution. The reported incidence of documented ION after spine surgery was 0.36%. The majority of cases (75%) of ION patients after spine surgery had PION. The majority (94%) of the patients with ION in all surgical procedures (including spine surgery) were men. The authors found no difference in hematocrit levels or blood pressure values or the use vasopressor between cases and controls[138].

Grant *et al*[147] investigated the effect of prolonged prone positioning on ocular parameters in 10 volunteers. The authors demonstrated a progressive increase in the IOP, choroid layer thickness and retrobulbar diameter of the optic nerve in the prone position compared to supine position over 5 h. The peak increase for most parameters was at 5 h in the prone position. Compared to the prone horizontal position, a 4° reverse Trendelendburg prone position had minimal effect on these changes. With elevation of the head of the stretcher 30° in the supine position, all parameters retuned to baseline after 30 min. In the prone position, the optic nerve diameter showed a significant increase in diameter without significant difference between horizontal and 4° Trendelenburg. Choroid layer thickness showed mild improvement (reduction) with 4° Trendelenburg position. The authors related the increase in the prone diameter of retrobulbar optic nerve to a dependent increase in subarachnoid fluid or venous congestion rather than intrinsic swelling[147].

AION

AION is associated with spine surgery and is the most common cause of ION associated with open heart surgery[138]. AION results from ischemia of the anterior (intraocular) optic nerve presumably due to occlusion of the posterior ciliary circulation[154]. AION is painless and usually irreversible[141]. High cholesterol, smoking, high fibrinogen levels[154], diabetes[155], nocturnal arterial hypotension[110] and lack of autoregulation[104] have been associated with occurrence of non-arteritic spontaneous AION. Interindividual variation in the blood supply to the anterior optic nerve may predispose patients to ischemia in watershed zones leading to AION[99]. Variability in the severity of the visual loss associated with AION may be due to variation in the blood supply resulting in various ischemic effects[140,156]. An increase in IOP may play a role in reduced perfusion to the anterior (intraocular) optic nerve. AION has been associated with increased blood viscosity. An increase in blood viscosity may reduce perfusion pressure leading to ischemia of the anterior portion of the optic nerve. Sickle cell disease and polycythemia may be associated with AION presumably due to increased blood viscosity and decreased perfusion of the optic nerve in certain individuals[141,157]. AION may occur due to reduced oxygen carrying capacity and transport, as in the case anemia and hemorrhage[158,159]. Patients with a small optic disc are at higher risk of developing AION[160,161].

In AION the optic disc is initially swollen. Early swelling of the optic disc is a key differentiating point from PION. Over months the swelling gradually evolves into optic atrophy[138,141,156,162-164]. Splinter hemorrhages around the optic disc may be present[165]. Visual defects most commonly occur in the inferior half of the visual field[145,166,167].

PION

PION is the most common type of ION after spine surgery and is the most common cause of POVL associated with spine surgery[139,141,162]. PION occurs due to ischemia of the retrobulbar (intraorbital) optic nerve. Reported risk factors associated with PION include; prone position, prolonged spine surgery, systemic hypertension, intraoperative hypotension, anemia, diabetes, smoking and coronary artery disease[142].

In contrast to anterior ION, optic nerve swelling is absent on ophthalmoscopic examination. Later in the course of PION, the atrophy of the posterior optic nerve fibers will involve the anterior optic nerve head resulting in a pale and atrophic optic disc. The etiology of PION is multifactorial[140,141]. Severe anemia and hypotension in predisposed individuals placed in the prone position for prolonged periods of time are reported to be more likely causes of PION rather than occlusive vascular disease[141]. Interindividual variability and inconsistency in the blood supply to the posterior (retrobulbar) optic nerve plays a role in the development of postoperative PION[140,168]. PION have been associated with surgery, trauma and gastrointestinal bleeding in which severe anemia and hypotension occurred[91,94,140,169,170]. Prognosis is usually poorer with PION compared to AION[171].

Arterial infarction of the retrobulbar optic nerve due to ischemia is primarily due to decreased oxygen delivery. Decreased oxygen delivery may be due to a decrease in arterial perfusion pressure, increased resistance to blood flow or a reduction in oxygen carrying capacity[147]. The prone position may contribute to increased orbital venous pressure or venous congestion which may contribute to a decrease in arterial perfusion pressure and venous infarct respectively. One of the postulated mechanisms for PION is venous infarct. Venous infarct is a venoarteriolar response caused by secondary constriction in small arterioles in response to venous congestion[172,173].

Gill *et al*[141] reviewed 7 studies representing 102 cases of POVL associated with spine surgery. PION was the

most common cause of POVL. Patients who developed POVL after spine surgery had an age range of 46 to 53 years and at least one co-morbidity. Median operative time ranged from 385 to 410 min while the average blood loss ranged from 3.5 to 4.3 L. There was no visual improvement in the majority of cases. The authors concluded that an acute anemic state may have additive or synergistic effects in predisposed patient with certain comorbidities leading to the visual loss associated with spine surgery[141].

Enlargement of the superior ophthalmic veins with bilateral PION after prolonged spine surgery has been reported in a 55 years old male. Magnetic resonance imaging revealed significant enlargement of the superior ophthalmic veins 19 h after the surgery that resolved 5 mo after the surgery. Enlargement of the superior ophthalmic veins indicate the role of orbital venous pressure in the development of PION associated with surgery in the prone position[174]. Prolonged prone positioning has been shown to increase the diameter of the retrobulbar optic nerve possibly due venous congestion[147].

Central retinal artery occlusion

Central retinal artery occlusion (CRAO) may be caused by direct pressure on the globe, emboli or low retinal perfusion pressure[141]. Pressure on the eye globe increases IOP and has been associated with POVL [91,175,176]. The use of a horseshoe headrest for spine surgery in the prone position has been associated with CRAO and POVL[176,177]. Analysis of the spine cases with POVL showed that CRAO was present in 10 of the 93 cases[139]. The mean age for patients with CRAO was 46 years. Horseshoe headrests were used in 3 cases. Mayfield pins were not used in any of the cases with CRAO. Median estimated blood loss and mean anesthetic duration were significantly less in CRAO cases compared to patients with ION. All cases of CRAO were unilateral. Periocular trauma was documented in 7 of the 10 cases of CRAO. Risk factors for CRAO differ considerably from those of ION. Cases of CRAO after spine surgery have not been associated with degree of blood loss, anemia, bilateral loss of vision, or duration of the prone position, indicating a different etiology than ION[139]. Ophthalmologic examination shows pale, edematous retina, fibrin or cholesterol emboli and cherry-red spot on the fovea. Optic atrophy occurs in half the patient with CRAO[140].

POSITIONING PATIENTS FOR SPINE SURGERY

Awareness of the potential rare complications of patient positioning during spine surgery is essential for improved care and reducing the likelihood of occurrence of such complications. Complete prevention of PPNI and POVL is unrealistic because of the multifactorial etiology of the complications and lack of clear, definitive knowledge regarding etiology. Proper education of perioperative staff, combined with clear communication and collaboration while positioning patients in the operating room is the best and safest approach. The prevention of uncommon complications of spine surgery depends primarily on identifying high-risk patients, proper positioning and optimal intraoperative management of physiological parameters. Modification of risk factors extrinsic to the patient may help reduce the incidence of perioperative peripheral nerve injury and POVL.

Identifying high risk patients

High-risk patients for PPNI are usually middle aged males, with extreme body habitus. Prolonged hospitalization is a risk factor for the development of perioperative ulnar neuropathy. Certain operative positions used during spine surgery may create risks for loss of nerve function of the upper extremity. The prone position has been linked to claims of nerve injury[5]. Patients placed in the prone surrender (superman) position and lateral decubitus position had a significantly higher incidence of position-related impending upper extremity nerve injury compared to patients positioned in the supine arms tucked, supine arms out, and prone arms tucked positions[86]. Patients with a previous history of upper extremity peripheral nerve injury should be considered at increased risk of developing PPNI.

High-risk patients for POVL are those expected to undergo prolonged procedures on multiple vertebral levels in the prone position with a significant anticipated blood loss. The ASA task force for the prevention of POVL considers a surgery prolonged when it exceeds 6.5 h and significant blood loss when the patient's blood loss exceeds 44.7% of estimated blood volume[178]. It is advisable to discuss POVL with these patients when obtaining informed consent. It is also important to inform patients about the multifactorial etiology of POVL, the lack of clear understanding of the etiology, anatomical differences between individuals and the very low incidence of this rare, but devastating complication. Consideration should be given to staging surgery in high-risk patients, as this may reduce the risk of POVL[178]. However, the decision to stage spine surgery for high-risk patient should be individualized and weighed against other perioperative risks.

Proper positioning

The prone surrender position: In the prone surrender (superman) position, injury can occur along the entire length of the brachial plexus. Patients placed in the prone surrender(superman) position had a significantly higher incidence of position-related impending upper extremity nerve injury detected by SSEP compared to patients positioned in the supine arms tucked, supine arms out and prone arms tucked positions[86]. Stretch is the main mechanism of injury. If the head is directed away from the arm this can stretch the brachial plexus, therefore lateral neck rotation should be avoided. Although patients may comfortably tolerate arm abduction greater than 90° in the prone surrender position[11], it is advisable to limit the shoulder abducted to less than 90° to avoid overstretch

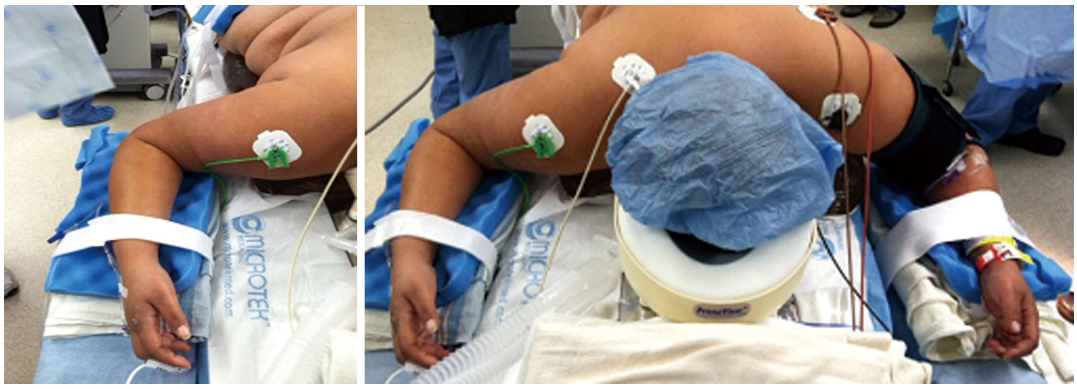

Figure 3 Positioning patient in the prone surrender (superman) position. The head should be in neutral position on foam supporting head frame (*e.g.*, proneview®) to avoid any direct pressure to the eye. The shoulders should be abducted less than 90°, lateral rotation of the upper arm and extreme elbow flexion should be avoided. The forearm should be positioned in the neutral position to minimize direct pressure on the ulnar nerve in the elbow. Soft foam padding should be placed under the elbows and between the inner upper around the gel rolls (or supporting frame) supporting the body. The level of the forearm should be at or below the mattress surface.

of the brachial plexus. Depression of the shoulder girdle should be avoided. The longitudinal axis of the forearm should be parallel to the longitudinal axis of patient to avoid outward rotation of the arm. Extreme elbow flexion should be avoided. However, in the prone position the range of motion for the elbow extension and flexion is limited. The forearm should be placed in a neutral position to minimize the direct pressure on the ulnar nerve at the elbow (Figure 3). The forearm should be at or below the table mattress surface. The elbow and the inner aspect of the upper arm should be padded with foam to avoid direct pressure on the nerves. Prolonged overextension of wrist over the wrist board placed for arterial lines should be avoided as it may stretch the median nerve. The head of the humerus may compress the neurovascular bundle in the axilla leading to nerve damage[179]. In a steep, prone Trendelenburg position the brachial plexus may be compressed between the clavicle and the first rib especially with use of shoulder braces. Vigilance and frequent checking of patient positioning is important. The use of SSEP helps to detect impending upper extremity peripheral nerve injury and guide position modification of the upper extremity.

The prone position is a known risk factor for POVL[139]. When patients are placed in the prone position, direct pressure on the eye must be avoided as it may cause CRAO[178]. The horseshoe head rest has been associated with CVAO and POVL in the prone position and therefore should be avoided if possible. Head positioning in Mayfield pins avoids direct pressure on the eye globe (Figure 4). Another choice is using foam positioning devices for the head, like the proneview®. The proneview® consists of a foam cushion in a plastic frame that supports the face without applying pressure on the eyes, nose or mouth and a mirror that allows frequent examination of the eye and facial structures (Figure 5). The use of the Wilson spinal frame has been associated with ION and POVL[149]. High-risk patients should be positioned with the head above the heart when possible. This will help reduce venous congestion in the eye and orbit and hopefully avoid an increase in the IOP and intraorbital pressure. The head should be in a neutral forward position when possible avoiding significant neck flexion, extension, lateral flexion or rotation[178].

The lateral decubitus position: The lateral decubitus position is used less frequently than the prone position for spine surgery. Patients placed in the lateral decubitus position had a significantly higher incidence of position-related impending upper extremity nerve injury detected by SSEP compared to patients positioned in the supine arms tucked, supine arms out and prone arms tucked positions[86]. In the lateral decubitus position compression is the main mechanism of peripheral nerve injury of the dependent brachial plexus. The brachial plexus may be compressed between the thorax and the humeral head[43]. The use of chest roll (also known as axillary roll) may help reduce the brachial plexus injury at this compression point. It is important to apply the chest roll under the chest and not in the axilla (Figure 6). Placing the roll in the axilla will increase the pressure on the brachial plexus in the axilla predisposing the patient to nerve injury. In the lateral decubitus position, there is increased pressure under the dependent shoulder. The average pressure under the dependent shoulder in the lateral position is 66 mmHg (and can exceed 100 mmHg). The pressure under the dependent shoulder decreased to 20 mmHg when the chest wall was elevated using an inflatable chest roll. The pressure further decreased to 12 mmHg when the head was supported by a second inflatable pillow to allow straightening of the cervical spine avoiding lateral angulation of the cervical spine. Patients placed in the lateral decubitus position had an average lateral angulation of neck of 14 degrees. After applying an inflatable chest roll, the average lateral angulation of the neck significantly increased to 20°. When the neck was brought into alignment by inflating a second pillow under the head, the lateral neck angulation decreased significantly to 4°. Using inflatable pillows beneath the dependent chest was associated with significantly less pressure beneath the

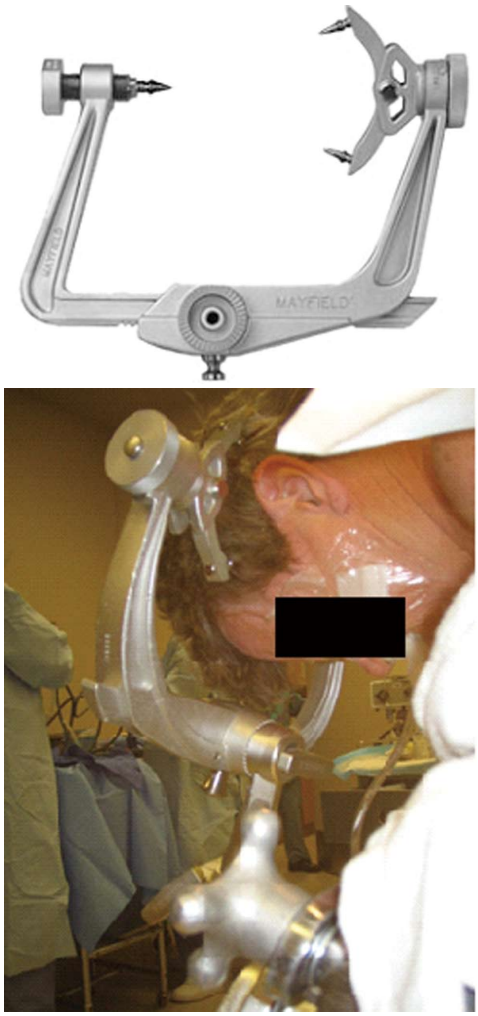

Figure 4 Mayfield (pinned) head holder.

Figure 5 The proneview® allows prone positioning without any pressure on the facial structures. The mirror provided allows frequent checking of facial structures in the prone position.

dependent shoulder and chest compared to a 1000 mL intravenous fluid bag or gel-pads. Prolonged lateralization of the cervical spine can stretch the brachial plexus on the nondependent side[180]. Pronation of the forearm, shoulder abduction more than 90°, extreme elbow flexion and extension should be avoided in the nondependent arm. The nondependent arm rest should be positioned in a way that maintain the arm horizontal and at the same level of shoulder joint (Figure 7). Excessive elevation of the nondependent arm at a level higher than the shoulder joint can overstretch the brachial plexus and predispose the patient to radial nerve injury in the nondependent arm.

POVL has been associated with spine surgery in the lateral decubitus position[139]. Asymmetric bilateral PION with significant involvement of the dependent eye has been reported after spine surgery in the lateral decubitus position[181]. Compression of the dependent eye should be avoided. Neutral forward position of the neck should be maintained to optimize venous drainage from the eye and the orbit. High-risk patients should be positioned with the head above the heart when possible[178].

Supine and prone arms tucked positions: Patients are placed in the supine arms tucked and prone arms tucked position for anterior and posterior cervical spine fusion surgeries respectively. The incidence of impending position-related upper extremity nerve injury detected by SSEP changes are 1.8% and 2.1% for the supine arms tucked and prone arms tucked positions respectively[86]. In both positions, it is important to position the forearm in a neutral position while padding the elbow with foam pad. The neck should be maintained in the neutral forward position whenever possible. In the prone arms tucked position, the use of a horseshoe head rest should be avoided. The use of the Mayfield pinned head holder is preferable to avoid direct external pressure on the eye. High-risk patients should be positioned with the head above the heart when possible[178].

Intraoperative management of physiological parameters

Ischemic times and thresholds that may lead to clinical perioperative injury of the peripheral nerve and the optic nerve are not documented in humans. With the lack of

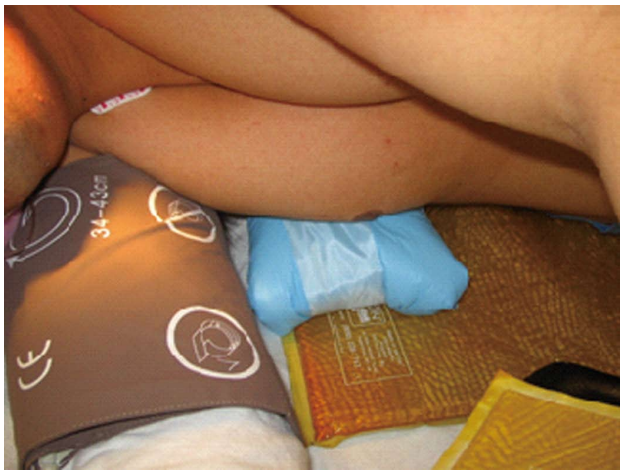

Figure 6 Proper placement of chest roll under the dependent chest in the lateral decubitus position. The chest roll should not be placed under the dependent axilla.

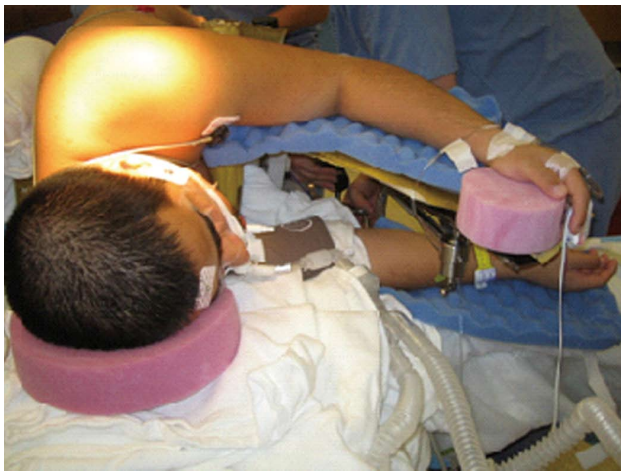

Figure 7 Positioning the upper extremity in the lateral decubitus position. The shoulder abduction more than 90°, extreme elbow flexion and forearm pronation should be avoided in the nondependent arm. The nondependent and dependent elbows should be padded with foam. Placing foam or blankets under the dependent hand and foreram to avoid full extension may reduce the likelihood of median nerve injury. Head and neck should be in neutral forward position avoiding neck flexion extension, lateral rotation and lateral flexion.

this knowledge, it is advisable to optimize physiologic parameters by maintaining them close to patient's baseline values, especially in high-risk cases. Physiologic parameters determining oxygen delivery to the peripheral nerve and the optic nerve may have additive or synergistic effect in predisposed patients placed in challenging operative positions for prolonged periods. Maintaining physiologic mean arterial blood pressure parameters, avoiding severe anemia and venous congestion are important aspects of intraoperative management that may improve oxygen delivery to areas at risk.

Although patient predisposition and intraoperative positioning are usually the risk factors associated with peripheral nerve injury, hypotension and anemia can affect oxygen delivery to the peripheral nerve especially in the presence of stretch or compression. Mean arterial blood pressure has been identified as an independent predictor of upper extremity neurapraxia detected by SSEP in the prone surrender position[182]. The extent and duration of hypotension, and anemia that may cause PPNI in predisposed individuals is not documented.

The ASA task force on the prevention of POVL believes that the use of deliberate hypotension during spine surgery has not been shown to be associated with the development of perioperative visual loss; however, it is advisable to avoid deliberate hypotension in high-risk patients (*e.g.*, with preoperative chronic hypertension). If deliberate hypotension will be used in patients without preoperative hypertension, the blood pressure should be maintained on average within 24% of baseline MAP or with a minimum systolic BP of 84 mmHg. Central venous pressure monitoring should be considered in high-risk cases. Colloids should be used with crystalloids in patients with substantial blood loss. Hemoglobin should be monitored periodically in high-risk cases with significant blood loss. There is no documented lower level of hemoglobin that would eliminate the risk of POVL[178].

Until we have a better understanding of the effects of hypotension and anemia on PPNI and POVL it is advisable to maintain intraoperative mean arterial blood pressure and hemoglobin levels close to preoperative levels in patients at high-risk for PPNI and POVL.

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Management of proximal humerus fractures in adults

Leonidas Vachtsevanos, Lydia Hayden, Aravind S Desai, Asterios Dramis

Leonidas Vachtsevanos, Lydia Hayden, Department of Trauma and Orthopaedics, Abertawe Bro Morgannwg University Health Board, Swansea SA6 6NL, United Kingdom
Aravind S Desai, Department of Trauma and Orthopaedics, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle-upon-Tyne, NE7 7DN, United Kingdom
Asterios Dramis, Department of Trauma and Orthopaedics, University Hospital of Wales, Cardiff CF14 4XW, United Kingdom
Author contributions: Vachtsevanos L, Hayden L, Desai AS, Dramis A contributed to conception and design of the study, analysis and interpretation of data; Vachtsevanos L, Hayden L performed the literature review; Vachtsevanos L drafted the article; Dramis A, Desai AS revised the article; all the authors read and approved the final manuscript.
Correspondence to: Asterios Dramis, BM, MSc, MRCS, FEBOT, FRCS (Orth), Senior Trauma Fellow, Department of Trauma and Orthopaedics, University Hospital of Wales, Heath Park, Cardiff CF14 4XW,
United Kingdom. ad199@doctors.org.uk
Telephone: +44-12-14403044 Fax: +44-29-20716310
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Abstract

The majority of proximal humerus fractures are low-energy osteoporotic injuries in the elderly and their incidence is increasing in the light of an ageing population. The diversity of fracture patterns encountered renders objective classification of prognostic value challenging. Non-operative management has been associated with good functional outcomes in stable, minimally displaced and certain types of displaced fractures. Absolute indications for surgery are infrequent and comprise compound, pathological, multi-fragmentary head-splitting fractures and fracture dislocations, as well as those associated with neurovascular injury. A constantly expanding range of reconstructive and replacement options however has been extending the indications for surgical management of complex proximal humerus fractures. As a result, management decisions are becoming increasingly complicated, in an attempt to provide the best possible treatment for each individual patient, that will successfully address their specific fracture configuration, comorbidities and functional expectations. Our aim was to review the management options available for the full range of proximal humerus fractures in adults, along with their specific advantages, disadvantages and outcomes.

Key words: Proximal humerus fracture; Reconstruction; Non-operative management; Hemiarthroplasty; Reverse polarity total shoulder arthroplasty

Core tip: Non-operative management is associated with good outcomes in the majority of proximal humerus fractures in adults. There is currently insufficient evidence to suggest superiority of one treatment option over the others. Any surgical intervention should have clear aims and indications and the appropriate technique should be selected for each individual patient. Decision-making should involve detailed fracture evaluation, careful patient selection with thorough consideration of individual patient characteristics, comorbidities and functional expectations and profound understanding of the benefits and limitations of each management option.

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INTRODUCTION

Epidemiology

Fractures of the proximal humerus are relatively common injuries in adults, representing 4%-5% of all fractures presenting to the accident and emergency de-

partment[1] and approximately 5% of fractures of the appendicular skeleton[2,3]. The vast majority are low-energy osteoporotic fractures resulting from simple falls from standing height[4] with a 2-3 to 1 female to male preponderance[2,3,5].

Classification

Proximal humerus fractures may either occur in isolation or be associated with concurrent dislocation of the glenohumeral joint. Additional injuries to the shoulder girdle may also be present, such as co-existing scapular fractures giving rise to the "floating shoulder" variety. As such, a wide range of fracture patterns has been described[6-10], rendering accurate and reproducible classification of prognostic value complex and difficult. Neer's classification[10] remains the most commonly used system[11], although additional classification systems have been described more recently[12-14].

Neer's classification system is based on six groups and four main fracture segments (parts) comprising the head, greater tuberosity, lesser tuberosity and shaft[10]. Displacement is defined as more than 1cm of translation or 45 degrees of angulation of the respective fracture part. Group I includes all fracture configurations with *minimum displacement*. Group II includes two-part fractures of the anatomical neck with *articular-segment displacement*. Group III comprises three types of displaced two-part surgical neck fractures (*i.e.,* angulated, separated and comminuted surgical neck fractures) with *shaft displacement*. Group IV consists of two- or three-part fractures with *greater tuberosity displacement*. Group V includes two- or three-part fractures with *lesser tuberosity displacement*. Groups IV and V merge in the four-part fracture where both tuberosities are displaced in addition to the head and shaft. Group VI comprises true *fracture-dislocation* of two-, three- or four-part fractures with ligamentous injury and is subdivided into anterior and posterior dislocations of the glenohumeral joint and partial dislocations of the humeral head with articular surface fractures (*i.e.*, impression fracture and head-splitting fracture).

The AO/OTA classification employs a combination of letters and numbers to describe different levels and patterns of proximal humerus fractures. Proximal humerus fractures are described as 11 fractures with further subdivision into unifocal extra-articular denoted as 11-A, bifocal extra-articular denoted as 11-B and articular fractures denoted as 11-C. Further numbers are assigned according to fracture configuration with 3 representing more complex configurations than 1 and 2, giving rise to a total of twenty-seven subtypes[14].

Nevertheless, both interobserver reliability and intraobserver reproducibility of proximal humerus fracture classification systems have been shown to be poor[15], even when 3-D CT reconstructions are utilised[16,17].

Radiological assessment

Plain radiographs are the main baseline investigation for the diagnosis, classification and management planning of proximal humerus fractures. The proximal humerus should be imaged in a minimum of two planes. Routine assessment includes true anteroposterior and either transcapular "Y" or axillary lateral views, if tolerated by the patient. Additional investigations are then performed as necessary, on the basis of clinical and plain radiographic findings.

Doppler ultrasound examination may be used for the evaluation of associated vascular injuries, as well as of concomitant rotator cuff tears.

Computerised tomography (CT) is employed in the evaluation of complex fracture patterns, whilst it also allows quantification of available bone stock and assessment of the extent and position of fracture union.

CT angiography may accurately diagnose and guide interventional management of co-existing arterial injuries.

Magnetic resonance arthrography and angiography are additional high-quality imaging tools for the assessment of periarticular soft tissue and vascular injuries respectively.

Aim of study

The challenges of proximal humerus fracture classification, alongside individual patient characteristics and functional expectations, surgeon expertise, implant characteristics and availability of rehabilitation services render management decisions complicated and difficult. Our aim was therefore to perform a concise review of the available literature on the current management options of these complex injuries, with a particular focus on their respective advantages, disadvantages and outcomes.

LITERATURE REVIEW

A thorough literature search of the Embase, Ovid Medline(R), Ovid Medline(R) In-Process and Other Non-Indexed Citations, Ovid Journals and the Cochrane Library databases was conducted by two investigators. The search terms used included the title terms proximal AND humerus AND fractur* and the limits were set to adult (> 19 years of age) human trials, English language and published in the last 5 years. This search yielded 368 hits.

PubMed was also searched using the following MeSH term search strategy: ("Shoulder Fractures/analysis"[Majr] OR "Shoulder Fractures/anatomy and histology"[Majr] OR "Shoulder Fractures/classification"[Majr] OR "Shoulder Fractures/complications"[Majr] OR "Shoulder Fractures/diagnosis"[Majr] OR "Shoulder Fractures/epidemiology"[Majr] OR "Shoulder Fractures/etiology"[Majr] OR "Shoulder Fractures/history"[Majr] OR "Shoulder Fractures/mortality"[Majr] OR "Shoulder Fractures/physiopathology"[Majr] OR "Shoulder Fractures/prevention and control"[Majr] OR "Shoulder Fractures/radiography"[Majr] OR "Shoulder Fractures/rehabilitation"[Majr] OR "Shoulder Fractures/surgery"[Majr] OR "Shoulder Fractures/therapy"[Majr]), which yielded an additional 1738 hits. Limiting these to Clinical Trials, Controlled Clinical Trials and Reviews in Humans published within the last 5 years resulted in 112 hits.

The 480 studies obtained were searched manually for exclusion of duplicate hits and irrelevant publications. Case reports, studies focusing on pain management and biology of fracture healing were excluded. Additional relevant studies were identified through scrutinising the reference lists of the studies included.

DISCUSSION

The management of proximal humerus fractures in adults encompasses a constantly expanding range of non-operative, reconstructive and prosthetic replacement options. Good outcomes are highly dependent upon appropriate management decisions, which should be based on a thorough, combined evaluation of fracture-, patient- and treatment centre-related factors.

Non-operative management

Conservative treatment generally consists of analgesia and a period of immobilisation in a sling, with various rehabilitation and physiotherapy regimes. Early physiotherapy commencing within two weeks from injury has been associated with better functional results than prolonged immobilisation[18-20]. Hanging casts are perceived to be less useful than simple collar and cuff slings, as they do not seem to improve reduction and may in fact contribute to fracture distraction and non-union[21,22]. Hospital admission may be required in up to 43% of patients, as the majority of these injuries tend to be osteoporotic fractures in elderly patients culminating in loss of independence and inability to cope[5].

Complications encountered with closed treatment include malunion, subacromial impingement, avascular necrosis, shoulder pain and stiffness secondary to osteoarthritis and rotator cuff deficiency[22]. Most conservatively treated fractures will progress to full union with an estimated risk of non-union between 1.1% and 10%[23].

A number of studies have revealed very good functional results in conservatively managed minimally displaced, stable fractures of the proximal humerus[10,18,24]. Such fractures were classified by Neer as group I fractures, and were estimated to comprise over 85% of all proximal humerus fractures[10]. More recent studies have reported lower rates of minimally displaced fractures, ranging between 42% and 49%[4,5]. Despite higher rates of displaced fractures however, the majority of patients are still being treated non-operatively, in view of their advanced age at presentation, lower functional demands and significant comorbidities[5].

Non-operative management has also been successful in certain types of displaced fractures. These include translated two-part fractures of the proximal humerus with minimal alteration of the neck-shaft angle[24], valgus and varus impacted fractures of the proximal humerus[7,8]. Increasing degrees of displacement and instability, as seen in conservatively managed Neer three- and four-part fracture configurations, are associated with less optimal results than one- or two-part fractures[21]. Certain types of fixation of however, have been shown to confer no benefit to non-operative management in unstable displaced Neer three- and four-part fractures[25].

Operative management

Operative interventions for the management of proximal humerus fractures are constantly evolving and may be broadly classified into reconstructive and prosthetic replacement options.

Reconstruction

A wide range of joint preserving reconstructive techniques have been employed in the management of proximal humerus fractures. These aim to reduce complications and optimize function by restoring anatomy and conferring stability for early rehabilitation and promotion of fracture union. Reduction may be achieved closed, through a minimally invasive approach (mini-open) or open, while fixation may be performed percutaneously (pins, wires, screws) or internally (intramedullary nails, trans-osseous sutures, tension-band constructs or plates and screws).

Closed or mini-open reduction and percutaneous fixation

This technique utilizes image intensifier-guided closed manipulation or mini-open fracture reduction by means of 'joystick' pins, followed by fixation with a constellation of threaded pins to confer stability[26]. Its main advantages include soft-tissue preservation, cosmesis, reduced blood loss and postoperative pain. Disadvantages include possibility of axillary nerve injury during percutaneous pin insertion[27,28], fixation failure[29], intra-articular pin migration during fracture collapse leading to re-operation and need for elective removal of metalwork[30].

Stable fixation to allow early range of motion has been demonstrated in patients with two- and three-part fractures fixed percutaneously with 2.5 mm threaded Schantz or Dynamic Hip Screw guide pins, alongside good functional results and a union rate of 94% at an average of 2.6 mo[29]. This type of fixation however is not suitable for patients with four-part fractures, due to a high risk of avascular necrosis and fixation failure. Herscovici *et al*[29] have also demonstrated a 100% failure rate with smooth Kirschner wires and recommend the use of threaded pins. Brunner *et al*[30] have shown successful maintenance of reduction in 91% of 58 displaced proximal humerus fractures treated with the "humerus block". They have reported no intraoperative complications, but had a 40% unplanned re-operation rate, secondary to wire migration and associated fracture displacement[30].

Closed or open reduction and intramedullary nailing

Closed or open reduction and internal fixation by means of a statically locked intramedullary nail is a further joint preserving reconstructive option. Nails are usually inserted anterogradely through a small proximal incision and locked percutaneously. As such, they allow preservation

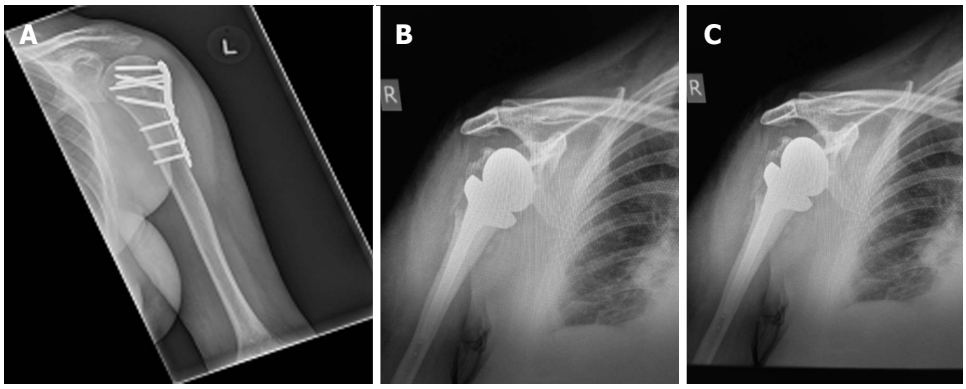

Figure 1 Plain radiograph. A: Showing internal fixation of a left proximal humerus fracture with a locking plate; B: Showing a cemented right shoulder hemiarthroplasty; C: Showing a reverse polarity right total shoulder arthroplasty.

of the periosteal blood supply and surrounding soft tissue envelope, whilst their intramedullary position confers greater stability than other minimally invasive fixation techniques. The benefits of soft tissue preservation and enhanced biomechanical stability render long nails ideal for internal stabilisation of severely osteoporotic and pathological fractures and for prophylactic fixation of impending pathological fractures. In this context, long nails provide protection from additional periprosthetic and skip lesion fractures and allow adjuvant radiotherapy to proceed as necessary with minimal wound healing concerns.

A number of studies using a range of intramedullary nails have produced good results with union rates between 96% and 100%[31-34] in patients with two- and three-part fractures. In a prospective randomised trial comparing locking intramedullary nails to locking plates in the treatment of two-part surgical neck fractures, the authors reported less complications in the nail cohort with equivalent functional scores between the two groups at three years[35].

Complications reported include avascular necrosis and pain especially in four-part fractures[36], proximal screw migration[31,34], loss of proximal fixation[37,38], infection, non-union, impingement[31] and rotator cuff pain and dysfunction[39]. Entry point proximity to the rotator cuff tendons may lead to long-term rotator cuff dysfunction-related morbidity, though new designs of straight instead of curvilinear nails have shown reduced rates of rotator cuff-related symptoms and re-operations[39].

Open reduction and internal fixation

Open reduction can be achieved through various approaches to the proximal humerus. The extended deltopectoral approach remains the most commonly utilised exposure, despite its limited access to the lateral and posterior aspects of the proximal humerus[40]. An alternative extended deltoid-splitting approach has been described, with a view to improve access to the posterior aspect of the shoulder[41] through direct lateral[40] or anterolateral acromial incisions[42]. A recent study by Buecking *et al*[43] has demonstrated no difference in complications, re-operations, fluoroscopy use, function and pain scores between the extended deltoid-splitting and the anterior deltopectoral approach.

Internal fixation has historically been achieved through various implants and techniques ranging from trans-osseous suture fixation[44] and tension-band wiring of fracture fragments[25] to application of semi-tubular[45], buttress and cloverleaf plates. These have currently been superseded by the use of pre-contoured mono- or poly-axial locking proximal humerus plates[22,46], which have been shown to significantly increase fixation stability in osteoporotic bone[38,47,48] (Figure 1A).

Proximal humerus locking plates may provide reliable fixation in two-, three- and four-part fractures, as well as in some pathological fractures of the proximal humerus[49], particularly when used in conjunction with cement augmentation[50]. Application of the plate may facilitate indirect reduction of the distal diaphyseal fragment to the proximal parts, upon insertion of the working screw[49]. Through a combination of meticulous plate application and appropriately placed rotator cuff tendon fibre-wire suture loops, near anatomical indirect reduction of the tuberosities to the head and shaft fragments becomes possible, without additional soft tissue stripping and compromise to the blood supply[49]. Locking plates may also be used in conjunction with bone autograft, allograft[51-53], as well as devices such as the "Da Vinci System"[54], in cases of comminuted fractures with substantial metaphyseal bone voids and loss of the medial column. As such, unstable three- and four-part fractures may be adequately reconstructed.

Anatomical reduction and restoration of the neck-shaft angle are of paramount importance in reducing the risk of locking plate fixation failure[55,56], while several clinical and cadaveric studies have demonstrated the benefit of medial support screws in maintaining reduction of unstable three- and four-part fractures[57-59]. Good results with union rates of 97%-98% have been reported[60,61] and minimally invasive techniques have been developed to minimise soft tissue dissection[62].

Complications include intra-articular screw penetration, subacromial impingement, varus collapse of fracture and osteonecrosis. These may lead to unplanned re-operations in 13%[60] to 19%[63] of patients, with a

predilection for those older than 60 years of age with unstable three- and four-part fractures[56,60]. In some patient series with high rates of three- and four-part fractures, revision surgery to arthroplasty was required in more than 50% of the patients, whilst screw penetration-mediated glenoid erosion, significantly limited revision options and adversely affected long-term outcomes[64]. Displaced four-part fractures and fracture-dislocations with a high risk of osteonecrosis may therefore qualify for primary replacement surgery, particularly in the elderly, low-demand patient.

In high-demand, younger patients however, it is the authors' opinion that reconstruction followed by close monitoring should be attempted first. In the event of failure, early conversion to hemiarthroplasty remains an option, whilst satisfactory tuberosity reduction at reconstruction, may improve function following revision to hemiarthroplasty. Non-reconstructible fractures may still be converted to hemiarthroplasty intraoperatively and adequate preoperative planning should allow for this.

Replacement

Despite significant advances in surgical technique and a constantly expanding armamentarium of reconstructive options, adequate fixation of metalwork in osteoporotic bone remains a problem[61,64]. Joint replacement options for proximal humerus fractures include shoulder hemiarthroplasty, stemmed total shoulder and reverse polarity total shoulder replacements. These may be used either primarily in elderly patients with displaced four-part fractures, fracture dislocations and head-splitting fractures with a high risk of avascular necrosis, or as salvage procedures following failed reconstruction. Primary replacement surgery, however, is less attractive in young active patients, given the expected longevity of the prosthesis and potential need for several revision operations[65].

Hemiarthroplasty

Hemiarthroplasty is the most commonly used replacement option[66] (Figure 1B). It is indicated in non-reconstructible four-part fractures, fracture-dislocations and head-splitting fractures and for the revision of failed reconstructions, provided the tuberosities remain intact. A number of investigators have emphasised the importance of anatomical tuberosity re-attachment and proper implant positioning in terms of component version, height and offset in restoring rotator cuff function and optimising outcome following hemiarthroplasty[46,67-69]. The upper border of the pectoralis major tendon insertion provides a reliable landmark for estimation of prosthesis height and version[70] and its use has been associated with good clinical and radiological results[71]. Modular implant design improvements enable fine adjustments in the height, offset and version of the prosthesis following stem insertion and along with meticulous surgical technique and rehabilitation have been associated with better outcomes[67,72]. The overall implant survival for shoulder hemiarthroplasty has been reported to be 96.9% at one year, 95.3% at five and 93.9% at ten years[69].

In the event of revision surgery, certain modular implants allow conversion of hemiarthroplasty to total shoulder reverse polarity arthroplasty, without the need for stem removal and lead to shorter operative times and good mid-term outcomes[73].

Complications reported with hemiarthroplasty include infection, dislocation, loosening, reflex sympathetic dystrophy, subacromial impingement, intraoperative or periprosthetic fractures, rotator cuff dysfunction secondary to tuberosity displacement and resorption and heterotopic ossification[22,74]. Poor results have been associated with advanced patient age, implant malpositioning resulting in head-glenoid mismatch, increasing degree of tuberosity displacement, persistent neurological deficit, postoperative complications requiring early re-operation and use of hemiarthroplasty for salvage of previous failed conservative management or operative reconstruction[67,69,72]. In the long-term, hemiarthroplasty has been shown to achieve satisfactory pain relief, but overall functional outcome remains less predictable[69,74,75].

Reverse polarity total shoulder arthroplasty

Reverse polarity total shoulder arthroplasty was originally designed to treat glenohumeral arthritis with rotator cuff arthropathy[76,77]. It is currently also employed in the management of proximal humerus fractures (Figure 1C), in which re-attachment of the tuberosities to a hemiarthroplasty is impossible[78-80]. Reverse polarity total shoulder arthroplasty may be inserted primarily or as a salvage of failed hemiarthroplasty secondary to glenoid arthritis or tuberosity resorption-induced shoulder pseudoparesis[81,82].

Cuff *et al*[81] have compared primary hemiarthroplasty to primary reverse polarity total shoulder arthroplasty and noted improved forward elevation following reverse polarity total shoulder arthroplasty with similar complication rates between the two groups. In a further comparison by Boyle *at al*[83] reverse polarity total shoulder arthroplasty was associated with better 5-year functional outcomes compared to hemiarthroplasty, with similar revision and 1-year mortality rates. Previous studies have failed to demonstrate statistically significant differences between functional outcomes of hemiarthroplasty and reverse polarity total shoulder arthroplasty[84]. Forward elevation however, appears to be consistently slightly better in patients treated primarily with reverse polarity total shoulder arthroplasty[81,83-85], albeit at the expense of increased treatment cost in a group of patients with potentially limited life expectancy[85].

A high rate of complications with reverse polarity total shoulder arthroplasty has been reported by Brorson *et al*[66] in a recent systematic review of the literature. These included dislocation, infection, haematoma, instability, neurological injury, intraoperative and periprosthetic fracture, baseplate failure, reflex sympathetic dystrophy and scapular notching[66], which in the long-term has been associated with component loosening and glenoid bone

loss[80]. Nevertheless, reverse polarity total shoulder arthroplasty remains a good option for independent elderly patients with non-reconstructible fractures and associated cuff deficiency, as well as a valuable salvage solution for failed first-line reconstructive or prosthetic replacement management.

CONCLUSION

The management of proximal humerus fractures in adults is a challenging and demanding task. Good outcomes depend on detailed fracture evaluation, careful patient selection with thorough consideration of individual patient characteristics, comorbidities and functional expectations and advanced surgical expertise across a wide range of reconstructive and joint replacement options. A multi-disciplinary team approach should be utilised with experienced musculoskeletal radiologists, geriatricians and specialised physiotherapists for optimal rehabilitation.

Treatment of these complex injuries requires careful planning and should therefore be provided in centres, with appropriate resources and expertise in their management and rehabilitation. There is at present not enough evidence to suggest superiority of one treatment option over the others[11]. The ProFHER trial is an ongoing UK-based multi-centre randomised controlled trial that aims to compare the effectiveness and cost-effectiveness of surgical versus non-operative management for displaced fractures of the proximal humerus in adults[86]. Currently available evidence however suggests that treatment should be individualised and tailored to specific fracture-, patient- and treatment centre-related factors[46].

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Arthroscopic treatment options for irreparable rotator cuff tears of the shoulder

Cameron M Anley, Samuel KL Chan, Martyn Snow

Cameron M Anley, Samuel KL Chan, Martyn Snow, Arthroscopy Division, The Royal Orthopaedic Hospital, Birmingham B31 2AP, United Kingdom

Author contributions: Anley CM designed and contributed to all the subsections and responsible for revisions and submission; Chan SKL contributed to the design all the subsections of the paper and reviewed the paper prior to submission; Snow M (senior author) contributed to the overall design and each section, final editing prior to submission.

Correspondence to: Cameron M Anley, MBChB, FCS (Ortho) SA, Arthroscopy Division, The Royal Orthopaedic Hospital, Bristol Road South, Birmingham B31 2AP, United Kingdom. cam_anley@yahoo.com

Telephone: +44-121-6854000 Fax: +44-121-6854213

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Abstract

The management of patients with irreparable rotator cuff tears remains a challenge for orthopaedic surgeons with the final treatment option in many algorithms being either a reverse shoulder arthroplasty or a tendon transfer. The long term results of these procedures are however still widely debated, especially in younger patients. A variety of arthroscopic treatment options have been proposed for patients with an irreparable rotator cuff tear without the presence of arthritis of the glenohumeral joint. These include a simple debridement with or without a biceps tenotomy, partial rotator cuff repair with or without an interval slide, tuberplasty, graft interposition of the rotator cuff, suprascapular nerve ablation, superior capsule reconstruction and insertion of a biodegradable spacer (Inspace) to depress the humeral head. These options should be considered as part of the treatment algorithm in patients with an irreparable rotator cuff and could be used as either as an interim procedure, delaying the need for more invasive surgery in the physiologically young and active, or as potential definitive procedures in the medically unfit. The aim of this review is to highlight and summarise arthroscopic procedures and the results thereof currently utilised in the management of these challenging patients.

Key words: Irreparable; Arthroscopy; Rotator cuff; Repair; Massive

Core tip: This paper reviews the current literature and available techniques to arthroscopically address irreparable rotate cuff tears. It includes all historic and recent innovative methods to address this difficult and challenging clinical problem. Readers of this article will be in a position to make an informed decision as to the most appropriate treatment for their patients based on the most up to date literature.

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INTRODUCTION

The management of patients with irreparable rotator cuff tears (IRCT) without the presence of arthritis remains a challenge for orthopaedic surgeons. Currently, the reverse shoulder arthroplasty is advocated for patients with[1-3] and more recently without[4,5] glenohumeral arthritis in the presence of an IRCT. Although early to midterm results are promising, the long term results are still questioned[1] as highlighted by a recent paper reviewing the satisfaction in patients under 60 years of age[2]. In addition the complication rate varies from 4.3% to 50 %[3,6] with a revision rate of 10%[6]. The subsequent treat-

ment options in a failed reverse shoulder arthroplasty are complex and limited. An alternative in younger patients with an IRCT without arthritis is a tendon transfer[7]. Although Gerber *et al*[8] have recently presented promising long term results (> 10 years) the overall outcome is still variable with unpredictable results[7].

It is important to differentiate between massive and irreparable rotator cuff tears, as not all massive tears are irreparable[7]. By definition, massive tears have been described as > 5 cm[7,9] and tears involving two or more tendons[10]. An IRCT, as the name suggests, is any RCT which cannot be repaired back to the rotator cuff footprint on the greater tuberosity of the humerus or as Gerber *et al*[1] suggested, any repair that is successful but will almost certainly be associated with structural failure[1]. Reparability is influenced by a variety of factors and the exact incidence of IRCT is unknown[7]. Warner suggested that it may be as high as 30% in a dedicated shoulder practice[11], while other studies have quoted an incidence of 6.5%-22.4%[12-14].

Although the final decision on reparability of the rotator cuff is made intraoperatively, various symptoms, signs and radiology findings may suggests irreparability prior to surgery allowing for appropriate preoperative planning. Classically patients will present with pain and disability, these symptoms however do not correlate directly with the size or reparability of the tear. Clinical signs which suggest that a repair is unlikely to be successful include static anterosuperior subluxation and associated pseudoparalysis on anterior elevation[1]. Tears associated with dynamic anterosuperior subluxation of the humerus upon resisted abduction[1], a lag sign and a positive Hornblowers sign[15,16] are also poor prognostic signs.

Superior migration of the humerus, with an acromiohumeral interval of < 7 mm on a standard anterior-posterior shoulder radiograph, is highly suggestive that a repair may fail[1,17]. Superior migration can be accentuated by taking the radiograph with the arm in slight abduction due to pull of the deltoid muscle overriding the deficient force coupling of the incompetent rotator cuff[7]. The amount of tendon retraction and fatty infiltration can be assessed on ultrasound[7,18], Computed tomography (CT)[1,7] and/or magnetic resonance imaging (MRI)[1,7]. Grade 3 and 4 fatty infiltration according to the Goutallier is commonly considered irreparable[1,19], although Burkhart has disputed this is a recent study[20].

Once a rotator cuff is deemed irreparable, a variety of arthroscopic treatment options have been proposed to reduce pain and improve function in patients with IRCT. These options should be considered as part of the treatment algorithm and include simple debridement with or without a tenotomy, partial rotator cuff repair with or without interval slide, tuberplasty, graft interposition of the rotator cuff, suprascapular nerve ablation, superior capsule reconstruction and insertion of a biodegradable spacer (Inspace). Although these procedures vary in terms of outcome and operating time, they are generally considered less invasive with a lower complication rate compared to tendon transfers and reverse arthroplasty.

This paper reviews the current literature and available techniques to arthroscopically address irreparable rotate cuff tears. It includes all historic and recent innovative methods to address this difficult and challenging clinical problem.

DEBRIDEMENT WITH OR WITHOUT BICEPS TENOTOMY

A debridement of the rotator cuff and subacromial decompression was first proposed by Rockwood *et al*[21] in 1995 as a treatment option for patients with an irreparable rotator cuff tear. In this study, 50 patients (53 shoulders) where followed up at an average of 6.5 years, with 83% of patients having a satisfactory outcome with a significant decrease in pain. The average active elevation improved from an average of 105° to 140°[21]. Further to this study, Kempf *et al*[22] showed a significant improvement in pain following a biceps tenotomy in a trial involving 210 patients. Although a variety of studies have shown that this remains a viable option in the elderly and low demand patient, it does not slow the progression of osteoarthritis[1].

PARTIAL ROTATOR CUFF REPAIR

In 1993, Burkhart *et al*[23] first introduced the biomechanical concept of the "suspension bridge" in the rotator cuff. This theory evolved into the functional rotator cuff and provided a rationale for partial repair of the rotator cuff. This involves the restoration of the cables involved in force transmission as well as force couples around the shoulder. The rotator cables have been defined anatomically at the level of the biceps tendon above supraspinatus anteriorly and the lower border of infraspinatus posteriorly. Most irreparable tears have a degree of extension anteriorly or posteriorly, which also affect the transverse couples. The importance of addressing the imbalance between the transverse couples (consisting of subscapularis and infraspinatus-teres minor complex) has been stressed. Repair must include all of subscapularis as well as the inferior half of infraspinatus as a minimum. This restores the transverse force couples and allows a stable fulcrum for normal shoulder kinematics. Burkhart *et al*[24] also warned against subscapularis tendon transposition to cover the residual defect as it alters the centroid (line of action) so that it lies above the centre of rotation and destroys the coronal plane force couple between subscapularis and deltoid, thus contributing to superior migration of the humeral head. In the context of the irreparable rotator cuff tear, it was felt that these tears could be partially repaired to fulfil the above criteria and hence, improve function[25].

Suitable patients include those who clinically have an imbalance in subscapularis and infraspinatus function and have difficulty with overhead function. Burkhart identified this cohort using lift-off and resisted external rotation tests. There have been several studies assessing

the outcomes of partial repair although initial studies were performed as open procedures. Burkhart's original paper showed an improvement in various parameters including active elevation (improved from 59.6° to 150.4°), strength (0-5 scale) (improved from 2.1 to 4.4) and UCLA score (improved from 9.8 to 27.6). In his cohort of 14 patients, one patient had a poor result. Duralde *et al*[26] reported similar outcomes to Burkhart in their retrospective study with statistically significant improvements in American Shoulder and Elbow (ASES) index, pain and active elevation.

Berth *et al*[27] have since described arthroscopic partial repair of large and massive rotator cuff tears. In their series, partial repair was compared to debridement[27]. Both treatment arms showed similar improvements although several studies suggest that the partial repair provides a longer lasting improvement when compared to debridement alone[28]. It was noted that 52% had structurally failed when imaged using ultrasound at 24 mo, although this rate of failure is similar to the current literature for cuff repairs[29]. Therefore, partial repair represents a reasonable option in this challenging subset of patients by providing pain relief and restoring function[25].

INTERVAL SLIDE

Tauro[30] popularised the arthroscopic technique of the interval slide after it was originally described by Bigliani as an open procedure[31]. This involves release of the supraspinatus tendon from the rotator interval to improve mobility. Burkhart redefined this as the anterior interval slide and described a second interval slide between the supraspinatus and the infraspinatus tendon as the posterior interval slide[32]. These techniques allowed isolated mobilisation of the supraspinatus tendon laterally to its bony footprint and subsequent repair.

Lo *et al*[32] showed statistically significant improvements in mean pain scores (from 2.1 to 8.7), forward elevation (108.9 to 146.1), mean strength (2.2 to 3.6) and UCLA score (10.0 to 28.3). Numerous studies have corroborated the results of arthroscopic interval slide repairs[33-35]. The advantages of this technique are thought to be a more anatomical and reliable repair. However, studies comparing the results of partial repair with interval slide and found no significant difference in outcomes[34,35].

Concerns regarding this technique include devascularisation of the supraspinatus tendon and defunctioning of an already impaired muscle tendon unit from the interval slide[34]. Despite these concerns, Iagulli only had one re-tear secondary to trauma. This underwent revision repair with a fair result[34]. Although, Kim *et al*[35] found that 91% of complete repairs had re-tears, this did not clinically correlate with outcomes in terms of pain or function.

TUBEROPLASTY

The concept of tuberoplasty is to create an acromiohumeral articulation; it was first introduced by Fenlin *et al*[36] as an open procedure in 2002. The goal is to contour and reshape the greater tuberosity to create a smooth and congruent articulation between the greater tuberosity of the humerus and the under surface of the acromion. The initial study[36] in 2002 included 20 patients at an average age of 63 years (44-82 years), with a mean follow-up of 27 mo (7-58 mos). Overall the average UCLA scores improved from 9.3 to 27.7, with 95% satisfactory results (12 excellent, 6 good and 1 fair) and only one poor result.

Inevitably, an arthroscopic approach to this procedure was presented by Scheibel *et al*[37] in 2004, who described the reversed arthroscopic subacromial decompression. This study presented the results in 23 patients with an average age of 69 years (range 60-81) at a mean follow-up of 40 mo (range 20-58). One patient who underwent revision surgery at 6 mo was excluded. The mean weighted Constant score improved significantly ($P < 0.001$) from 65.9% to 90.6%, with significant improvements in pain, range of motion and activities of daily living. Although there was progression of osteoarthritis by 1 grade in the majority of patients, this was not reflected in the eventual outcome with 14 excellent, 5 good, 2 satisfactory and 1 poor results according to the Constant score.

Subsequently, two studies have been published confirming the benefits of an arthroscopic tuberoplasty with[38] and without acromioplasty[39] as a treatment option in patients with irreparable rotator cuff tears. Verhelst *et al*[38] followed up 34 shoulders (33 patients) with an average age of 69.6 years at 38 mo (21-52), while Lee *et al*[39] reported on 32 patients with an average age of 62.5 at 40 mo (24-63). Both studies showed a significant improvement in range of motion and decrease in pain following surgery with 84.4% and 81% patients reporting excellent or good results. While there was no significance difference in the improvement related to gender, age and preoperatively range of motion, poor outcomes where attributed to increased preoperative pain, patients with pseudoparalysis[38] and a disruption of the inferior scapulohumeral line[39].

The importance of maintaining the coracoacromial arch as a passive stabiliser to anterior and superior subluxation of the proximal humerus was highlighted in all 4 studies. These studies concluded that this remains an excellent treatment option in patients with an irreparable rotor cuff tear.

GRAFT INTERPOSITION

The first reported use of a graft interposition in IRCT is by Neviaser *et al*[40] in 1978, who used freeze-dried rotator cuff allograft to restore the continuity between the retracted irreparable rotator cuff tendon and the greater tuberosity in 16 patients. Although a standardised scoring system was not used, 13 of the 16 patients reported good to excellent results with all having pain relief at an average age of 20 mo follow-up. These results where however contradicted a decade later by Nasca[41] in his report on 7 patients with a similar technique. Only 2 had reasonable function although 5 had pain relief following the surgery and the authors concluded that freeze dried allografts do not appear to be of significant value in patients with

chronic massive rotator cuff tears[41].

A variety of biological and synthetic interposition grafts have been suggested. Biological grafts used include allografts such as freeze dried rotator cuff[41,42], quadriceps tendon[12], patellar tendon[12] achilles tendon[12], dermal matrix (Graftjacket)[12,42-46], tensor fascia lata[47] and autografts such as the biceps tendon[48,49] and tensor fascia lata[50]. Xenografts have also been used for interposition and include porcine dermal collagen[51,52] and porcine small intestinal submucosa[53]. A variety of synthetic grafts have been researched including Polyester ligament (Dacron)[54], Gore-Tex soft tissue patch[13], Mersilene mesh[55], Teflon felt[14] and Carbon fibre patches[56].

In 2008, the Snyder group were the first to present results of an arthroscopic interposition technique using Human dermal allograft (Graftjacket)[42]. Graftjacket is currently only registered for augmentation of rotator cuff repairs and not interposition grafting to bridge gaps[44,57]. Despite this many of the studies on interposition have used Graftjacket as a graft. The choice of graft is influenced by a variety of factors including mechanical properties, host response and potential for ingrowth.

The mechanical properties of biological allografts have been shown to be inferior to both autografts and synthetic grafts[57]. With regards to host response, xenografts appear to induce the most significant hypersensitivity, thought to be related to the galactose-a (1,3)-galactose (a-Gal) terminal disaccharide[57]. Although it appears to be low, more work is required to assess the host response to synthetic grafts. An important factor in the longevity and strength of a graft is the amount of ingrowth. This is thought to be influenced by the surface topography and porosity of the graft and been shown to be favourable in biological grafts, due to type 1 collagen, when compared to synthetic grafts.

The majority of the studies published on interposition grafting were performed via an open or mini open approach, a study[49] which included patients with both open and arthroscopic surgery showed there was no difference in outcome between the two approaches. Although Moore *et al*[12] questioned the use of allograft interposition based on a high failure rate on MRI and results equivocal to a simple debridement, the majority of studies reporting the use of graft interposition as a treatment option for IRCT support their use with a statistically significant decrease in pain, improvement in subjective scores and improvement in Range of Motion (Tables 1-4).

Only one randomised prospective study[50] has compared interposition (done with autograft tensor fascia lata) and partial repair in irreparable rotator cuff tears. This randomised trial included 48 patients in two groups of similar demographics and tear patterns. Although there was a significant improvement in clinical outcomes in both groups, there were significantly less retears of the infraspinatus muscles in the patchgraft group (8.3% *vs* 41.7%)[50] . In addition, shoulders with retears of the ISP had significantly inferior clinical outcomes when compared to those without retears ($P < 0.001$).

SUPRASCAPULAR NERVE ABLATION

The suprascapular nerve is derived from the upper trunk of the brachial plexus and is a mixed motor and sensory nerve. It provides the main sensory innervation to the posterior shoulder joint capsule, acromioclavicular joint, subacromial bursa, coracoclavicular and coracohumeral ligament[58]. Blockade of the suprascapular nerve has been shown to improve chronic pain in numerous studies[59].

In the irreparable rotator cuff, suprascapular nerve ablation is a salvage procedure. The main indication is in poor surgical candidates with significant medical co-morbidities and/or poor glenoid bone stock and end-stage rotator cuff arthropathy. Patients are often considered for nerve ablation after conservative therapies have been exhausted[60]. Different techniques have been described including percutaneous SSN pulsed radiofrequency and arthroscopic SSN neurectomy[61].

Pulsed radiofrequency techniques were originally described in the treatment of chronic back pain[62]. It is thought to be a non-destructive modality and works by delivering an electrical field to neural tissue rather than thermal coagulation[63]. The theoretical advantage is that it affects the smaller, pain fibres more than the larger motor fibres, thus preserving any residual motor function. Since its inception, pulsed radiofrequency has been applied to a wider range of clinical conditions including its use on the suprascapular nerve as a percutaneous technique[64].

Shah *et al*[65] first described this technique in a case report of a polytrauma patient with post-traumatic osteoarthritis, who had gained temporary pain relief after a suprascapular nerve block. The patient subsequently underwent four cycles of pulsed radiofrequency to the suprascapular nerve over 16 mo, with an improvement in numerical rating scale (NRS-11) score from 7-8 to 2-3. The duration of pain relief varied from 12-18 wk[65].

Kane *et al*[60] showed that pulsed radiofrequency to the suprascapular nerve in a cohort of twelve patients with painful cuff tear arthropathy resulted in a significant improvement in Constant, Oxford and Visual Analogue scores at three months. However, it was felt that efficacy of the treatment was wearing off by the six month end point in up to 50% of the patients[60].

Nizlan *et al*[66] described an arthroscopic SSN neurectomy technique in patients who were poor surgical candidates for shoulder arthroplasty with significant chronic pain. 75% of patients reported good to excellent pain relief and 80% noted an improvement in quality of life in this cohort. However, no assessment or comment was made with regard to outcomes due to loss of residual infraspinatus function[66].

ARTHROSCOPIC SUPERIOR CAPSULE RECONSTRUCTION

The superior capsule of the glenohumeral joint lies on the inferior surface of the supraspinatus and infraspinatus tendons and in conjunction with the rotator cuff plays a role in providing superior stability to the joint[67]. Rotator

Table 1 Results of allograft interposition

Study and graft	Number	Ave age (yr)	F/U (mo)	Outcome score Pre/post/*P* value	ROM Pre/post/*P* value	Conclusion
Neviaser *et al*[40] Freeze dried rotator cuff	16	58	20	13/16 excellent results Criteria used: Nocturnal pain Degree of abduction	> 160:6 120-160:3 90-120:5 < 90:2 Average: 122.5	In our patients there has been no sign that the grafts were rejected and the goals of the procedure to improve motion and to relieve pain usually were attained
Nasca *et al*[41] Freeze dried rotator cuff	7	62	42	Good 2, fair 2, poor 3	FF: 78/90 Abd: 69.2/84	Freeze dried rotator cuff allografts do not appear to be of significant value in the surgical management of chronic massive rotator cuff tears
Venouziou *et al*[43] HDA	14	54.6	30.2	ASES: 23.8/72.3/*P* = 0.001	FF: 73.6/129.3/*P* = 0.002 ABD: 67.5/117.9/*P* = 0.002 ER: 7.9/ 43.2/*P* = 0.001	The ROM and the functional outcome were all improved in the patients with less than 2 cm tendon gap. In the case of larger tendon defects the outcome is unpredictable
Moore *et al*[12] 26 Patellar 5 Achilles 1 Quadriceps	32	59.1	31.3	UCLA: 12.1/26.1/*P* < 0.001 Excellent 3, good 12, fair 8, poor 5	Active FF UCLA: 3/3.8/*P* < 0.17 Resisted FF UCLA: 2.9/3.7/*P* < 0.002	15/15 showed failure on MRI. Allograft reconstruction for massive, irreparable rotator cuff tears is not recommended
Bond *et al*[42] HDA	16	54.4	28.8	UCLA: 18.4/30.4/*P* = 0.0001 Excellent 4, good 9, Fair 3, Poor 0 53.8/84/*P* = 0.0001	FF: 106/142/*P* = 0.0001 ER: 43/47.2/NR	Our study supports the hypothesis that GJA is a viable treatment option for surgical salvage in select cases of symptomatic massive, irreparable rotator cuff pathology
Gupta *et al*[44] HDA	24	63	36	ASES: 66.6/88.7/*P* = 0.003 SF-12: 48.8/56.8/*P* = 0.03	FF: 111.7/157.3/*P* = 0.0002 ABD: 105/151.7/*P* = 0.0001 ER: 46.2/65.1/*P* = 0.001	Human dermal interposition repair of massive rotator cuff tears through a mini-open approach is a reproducible technique that leads to significant improvement in pain, ROM, strength and subjective scores
Wong *et al*[45] HDA (Extreme)	45	53.6	24 min	UCLA: 18.4/27.5/*P* < 0.001 ASES: 84.1 (post)		Arthroscopic rotator cuff reconstruction with GraftJacket (Human dermal allograft) is safe and is associated with high patient satisfaction, without the morbidity of tendon transfer or arthroplasty
Ito *et al*[47] Allograft fascia lata	9	62.8	35	JOA: 47.9/91.7/*P* = 0.0059	FF: 84.4/159.6/*P* < 0.005 ADB: 62.2/163.3/*P* < 0.005 ER: 43.9/41.7/NR	Patch Grafts are considered to have the advantages of achieving anatomical repair with minimal restriction of range of motion and minimal occurrence of re-tearing
Modi *el al*[46] HDA	61	62.6	42	OSS: 26/42/*P* = 0.001	FF: 97/160/*P* = 0.001 ABD: 90/155/*P* = 0.001 ER: 42/60/0.04	GraftJacket allograft regenerative tissue matrix provides a very good option for bridging irreparable rotator cuff tears in the short to medium term

HDA: Human Dermal allograft; FF: Forward flexion; Abd: Abduction; ER: External rotation; UCLA: University of California-Los Angeles; ASES: American Shoulder and Elbow Surgeon evaluation form; JOA: Japanese Orthopaedic Association; OSS: Oxford shoulder score.

cuff tears are therefore associated with a defect of the superior capsule. Mihata *et al*[67,68] recently described an arthroscopic technique to reconstruct the superior capsule in patients with an irreparable rotator cuff tear in order to prevent superior migration of the humeral head with associated impingement.

Although this procedure is presented as an arthroscopic technique, it can be performed via open surgery if preferred by the surgeon. After an acromioplasty to avoid abrasion of the graft, a partial repair of infraspinatus and a repair of the subscapularis should be undertaken. The reconstruction of the capsule is undertaken with a tensor fascia lata autograft, with thick (doubled or tripled to size of 6-8 mm) and large grafts being better. The graft is attached laterally to the greater tuberosity by using a double row anchor technique and medially to superior aspect of the glenoid. The graft is then sutured to the residual infraspinatus posteriorly and if required to the subscapularis or subscaularis tendon anteriorly with side to side sutures. This is thought to restore the force coupling of the joint. Attention should be paid to the correct tension of the anterior sutures to prevent contractures. If the medial, lateral and posterior is satisfactory, the anterior suture is not necessary. Postoperative rehabilitation is required for 6-12 mo[68].

In order to assess the superior stability provided by the Arthroscopic Superior Capsule Reconstruction the authors undertook a cadaver study[67] which concluded that superior capsular reconstruction completely restored superior stability and thus prevented impingement, while interposition patch grafting to the torn tendon only partially restored stability allowing impingement of the interposition[67].

A clinical trial published by the same authors[68], a to-

Table 2 Results of autograft interposition

Study and graft	Number	Ave age (yr)	F/U (mo)	Outcome Score Pre/post/*P* value	ROM Pre/post/*P* value	Conclusion
Mori *et al*[50] Tensor fascia	24	65.9	35.5	ASES: 40.8/94.1/$P < 0.001$ Constant: 37.4/81.1/$P < 0.001$	FF: 114/160.8 ER: 27.9/46	The patch graft procedure showed an 8.3% retear rate for the repaired ISP with improved clinical scores and recovery of muscle strength
Sano *et al*[48] Biceps	14	64	28	JOA: 13.1/22.9/$P = 0.0019$	Active elevation 69/149/$P = 0.0010$	LHB tendon patch grafting provided significant improvement in both the active elevation angle and for the JOA score. The LHB tendon patch grafting seems to be one of the useful options for surgical treatment of irreparable massive rotator cuff tears
Rhee *et al*[49] Biceps 15 open 16 arthro	31	61	32	Constant 48.4/81.8/$P < 0.001$ UCLA 12.5/31.1/$P < 0.001$	FF: 124/162/$P < 0.001$ ABD: 134/168/$P < 0.001$ ER: 38/47/$P = 0.46$	An augmentation technique using the tenotomised biceps as a potential graft for rotator cuff tears is particularly useful in bridging the gap in immobile massive rotator cuff tears with posterior defects and retraction. Differences in postoperative clinical results between the open and arthroscopic groups were not statistically significant

FF: Forward flexion; Abd: Abduction; ER: External rotation; UCLA: UCLA: University of California-Los Angeles; ASES: American shoulder and elbow surgeon evaluation form; JOA: Japanese orthopaedic association.

Table 3 Results of Xenograft interposition

Study	Number	Ave age (yr)	F/U (mo)	Outcome score Pre/post/*P* value	ROM Pre/post/*P* value	Conclusion
Badhe *et al*[51] PDC (Permacol)	10	65.7	54	Constant: 42/62/$P = 0.0004$	Post-operative: Active abd: 89 Passive abd: 98	Porcine dermal collagen is effective as an augmentation graft in the treatment of chronic extensive rotator cuff tears, providing excellent pain relief with a moderate improvement in active ranges of motion and strength
Soler *et al*[52] PDC (Permacol)	4	76		Reduced range and strength, increased pain	Mean active ER: 50 Not recorded	While the use of porcine dermal collagen (Permacol) has many obvious advantages, we do not advocate using it to bridge irreparable defects

PDC: Porcine dermal collagen; FF: Forward flexion; Abd: Abduction; ER: External rotation.

tal of 23 patients (24 shoulders) with irreparable rotator cuff repair where reviewed between 24 and 51 mo (average 34.1) following an arthroscopic superior capsular repair. The average age of the patients was 65.1 years. Patients demonstrated a significant improvement in clinical scores, ASES 23.5 to 92.1 ($P < 0.0001$) and range of motion, elevation 84° to 148° ($P < 0.001$) and external rotation 26° to 40° ($P < 0.01$). Radiographically the acromiohumeral distance increased significantly from 4.6 mm to 8.7 mm ($P < 0.0001$) postoperatively, with no progression of osteoarthritis of the glenohumeral joint. A postoperative MRI scan confirmed that 20 patients (83.3%) had an intact graft, with no progression of muscle atrophy. The authors surmised that the reconstruction of the superior capsule restored the force coupling due to suturing the graft to the infraspinatus posteriorly and the residual supraspinatus or subscapularis anteriorly (Figure 1).

BIODEGRADABLE SPACER

The most recent treatment modality proposed for an irreparable rotator cuff tear is the InSpace system[69]. This device is a biodegradable spacer (balloon shape) which is implanted between the acromion and the humeral head in an attempt to restore the shoulder biomechanics by reducing subacromial friction through lowering the humeral head during abduction[69]. The spacer is made of a copolymer poly-L-lactide-co-ε-capro-lactone which biodegrades over 12 mo, during which stage the force coupling should return and allow for long term improvement in the glenohumeral joint movement.

The insertion method is reported to be simple, safe and reproducible[69]. After a standard arthroscopy including debridement and bursectomy, the rotator cuff is assessed for reparability. Once deemed irreparable, the correct size is selected by the measuring between the lateral border of the acromion and superior rim of the glenoid rim. The rolled up spacer is inserted through a lateral portal and inflated with saline to fill the subacromion space. The shoulder is then taken though a full range of motion to ensure stability. The InSpace system can be used in patients with tears of SST, IS although it is preferable for Subscapularis to be intact or repaired. Contraindications include arthritis, allergies to the device materials and active infections. Potential complications include foreign body response, local irritation or inflammation, tissue necrosis and device displacement.

Senekovic *et al*[70] published their early results of 20

Table 4 Results of Synthetic interposition

Study	Number	Ave age (yr)	Follow-up (mo)	Outcome Score Pre/post/*P* value	ROM Pre/post/*P* value	Conclusion
Nada *el al*[54] Polyester ligament (Dacron)	21	66.5	36	Constant: 46.6/84.5/$P < 0.001$ Excellent 17, good 2, fair 1, poor 1	FF: 65/120/$P < 0.001$ Abd: 60/120/$P < 0.001$ ER: 39/57/$P = 0.01$	Polyester (Dacron) ligament augmentation can result in a pain free successful return of function in active symptomatic patients with massive chronic tears of the rotator cuff
Hirooka *et al*[13] Gore-Tex soft tissue patch	26	62	44	JOA: 57.8/86/NR		Good clinical results, especially pain relief, could be achieved with this procedure in both the small- and the large-patch groups, but good abduction strength was obtained only in the small-patch group
Audenaert *et al*[55] Mersilene mesh	41	67	43	Constant: 25.7/72.1/$P < 0.001$	FF: 69.2/136/$P < 0.001$ Abd: 68.4:133.7/$P <$ 0.001	A polyester patch for the closure of massive rotator cuff tears is a satisfying procedure in this complex and technically challenging group of patients
Ozaki *et al*[14] Teflon felt	25	67.3	42	23: No pain, 2: Some pain	ER: 32.4/38.2/$P < 0.05$ 16: Normal, 7: > 120 2: < 30	Of 25 patients with massive rotator cuff tears, 23 had satisfactory functional results
Visuri *et al*[56] Carbon fibre patch	10	53.9	50.4	Excellent 7, good 2, poor 1	Abd: 73/166/NR	A carbon fiber tow application combined with Neer's anterior acromioplasty seems useful in the reconstruction of large tears of the rotator cuff

FF: Forward flexion; Abd: Abduction; ER: External rotation; JOA: Japanese Orthopaedic Association.

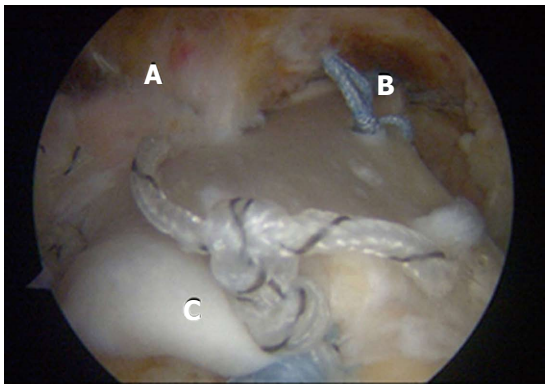

Figure 1 Arthroscopic view of a superior capsular repair with (A) the irreparable rotator cuff, (B) attachment of the Graftjacket to the superior glenoid and (C) Attachment of the Graftjacket to the rotator cuff footprint.

Figure 2 Inspace balloon insertion system.

patients treated with the InSpace system. The average age in this cohort was 70.5 years (range 54-85 years) and the follow up period was 34.7 mo (range 4-95 mo). The average total Constant score increased from 33.4 to 65.4 points, with a statistically significant improvement in all aspects of the constant score. Although improvement in power became evident at 18 mo the improvement in shoulder function was sustained at 3 years. Once again, prospective randomised trials and longer follow up is required in order to confirm promising early results (Figures 2 and 3).

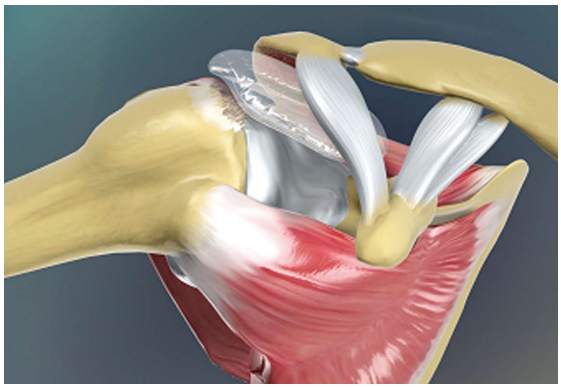

Figure 3 An illustration of the Inspace balloon between the acromion and the humeral head.

CONCLUSION

The management of patients with an irreparable rotator cuff tear remains a challenge. A variety of less invasive arthroscopic techniques have been presented in the literature, the majority of which have reported satisfactory results. These treatments can be considered as a potential therapy with a decision as to which one based on a thorough clinical assessment, an individual's requirements and co-morbidities.

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Eccentric training as a new approach for rotator cuff tendinopathy: Review and perspectives

Paula R Camargo, Francisco Alburquerque-Sendín, Tania F Salvini

Paula R Camargo, Department of Physical Therapy, Federal University of São Carlos, São Carlos, SP 13565-905, Brazil
Francisco Alburquerque-Sendín, Department of Physical Therapy, University of Salamanca, 37008 Salamanca, Spain
Tania F Salvini, Department of Physical Therapy, Federal University of São Carlos, São Carlos, SP 13565-905, Brazil
Author contributions: All authors contributed to this work.
Correspondence to: Paula R Camargo, PT, PhD, Department of Physical Therapy, Federal University of São Carlos, Rodovia Washington Luis, km 235, São Carlos, SP 13565-905, Brazil. prcamargo@ufscar.br
Telephone: +55-16-33066696 Fax: +55-16-33512081
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Abstract

Excessive mechanical loading is considered the major cause of rotator cuff tendinopathy. Although tendon problems are very common, they are not always easy to treat. Eccentric training has been proposed as an effective conservative treatment for the Achilles and patellar tendinopathies, but less evidence exists about its effectiveness for the rotator cuff tendinopathy. The mechanotransduction process associated with an adequate dose of mechanical load might explain the beneficial results of applying the eccentric training to the tendons. An adequate load increases healing and an inadequate (over or underuse) load can deteriorate the tendon structure. Different eccentric training protocols have been used in the few studies conducted for people with rotator cuff tendinopathy. Further, the effects of the eccentric training for rotator cuff tendinopathy were only evaluated on pain, function and strength. Future studies should assess the effects of the eccentric training also on shoulder kinematics and muscle activity. Individualization of the exercise prescription, comprehension and motivation of the patients, and the establishment of specific goals, practice and efforts should all be considered when prescribing the eccentric training. In conclusion, eccentric training should be used aiming improvement of the tendon degeneration, but more evidence is necessary to establish the adequate dose-response and to determine long-term follow-up effects.

Key words: Cellular; Mechanotransduction; Rehabilitation; Shoulder Impingement; Supraspinatus; Tendon injuries

Core tip: Eccentric training can be considered a new and ambitious treatment approach for several tendinopathies. The paper establishes the basic principles for explaining the effects on the tendon of an intense mechanical load, as the eccentric training. Further, the authors bring other possible explanations of the success of this training for tendinopathies, as the individualization of the exercise programs and the motivation of the patients who reach specific goals. Negative and side effects are also identified. Finally, the main evidence afforded by original articles is commented and future research purposes are defined.

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INTRODUCTION

Tendon injuries in the shoulder account for overuse injuries in sports as well as in jobs that require repetitive activity[1-4]. Excessive mechanical loading is considered the major causation factor. Although tendon problems are very frequent, they are not always easy to manage.

Rehabilitation of shoulder tendinopathy can take several months and conservative treatment is usually used as it can help the healing of the tendon by changing its metabolism and their structural and mechanical properties[5]. The use of eccentric exercise in rehabilitation has increasingly gained attention in the literature as a specific training modality. The eccentric exercise is an overall lengthening of a muscle as it develops tension and contracts to control motion. This kind of training differs from conventional training regimen because the tension in muscle fibers when lengthening is considerably greater than when muscle fibers are shortening[6]. There is some evidence that eccentric training may be effective in the management of tendinopathy of the Achilles and patellar tendons[7-9]. Histological changes in the supraspinatus tendinosis have been found to have similarities with those of the Achilles and patellar tendinosis[10,11]. Collagenous changes, extracellular matrix changes, increased cellularity and increased vascularity are among the histological and molecular changes observed in rotator cuff tendinosis[12]. As such, few studies were done evaluating the effectiveness of eccentric training in subjects with this condition[13-16].

The purpose of this paper is to review the studies that used eccentric training program in the treatment of rotator cuff tendinopathy as well as the tendon structure, the healing process and the possible mechanisms for why eccentric exercises can be effective in treating tendinopathy.

TENDON STRUCTURE

Tendons are mechanically responsible for transmitting muscle forces to bone as they connect bone to muscle belly at their ends. Consequently, motion is allowed and joint stability is enhanced.

As a type of connective tissue, tendon properties are determined primarily by the amount, type and arrangement of an abundant extracellular matrix[17]. Thus, the tendon has a multi-unit hierarchical structure composed of collagen molecules, fibrils, fiber bundles, fascicles and tendon units that run parallel to the tendon's long axis[5,18]. The fibril is the smallest tendon structural unit consisted of collagen molecules[5], which slide performing up to 50% of the longitudinal deformation of a tendon[19]. Fibers form the next level of tendon structure and are composed of collagen fibrils and are bound by endotenons, a thin layer of connective tissue[20,21]. They are responsible for the ability of the fascicles (fiber bundles) to slide independently against each other, transmitting tension despite the changing angles of a joint as it moves, and allowing tendons to change shape as their muscles contract[22]. Bundles of fascicles are enclosed by the epitenon, which is a fine, loose connective-tissue sheath[5]. More superficially, a third layer of connective tissue called the paratenon surrounds the tendon. Together, the epitenon and paratenon can also be called as the peritendon, which reduce friction with the adjacent tissue[23]. Vascular and nerve supply derive from all layers of the tendon and also from the myotendinous and osteotendinous junctions[24]. In general, tendons have a less vascular supply than that of the muscles with which they are associated[25].

The rotator cuff is composed of four tendons (supraspinatus, infraspinatus, teres minor and subscapularis) that blend into a single structure. First, the supraspinatus and infraspinatus bind 1.5 cm before insertion. Second, the infraspinatus and teres minor merge near its myotendinous union. Finally, the supraspinatus and subscapularis tendons also intertwine to form a sheath around the tendon of the biceps[26]. This sheath and the superior glenohumeral ligament and the coracohumeral ligament form the biceps pulley[27]. The supraspinatus, infraspinatus, subscapularis and the adjacent structures are strongly associated and form a capsule-cuff complex. The tendon proper acts with the capsule to transmit tensional force from the muscle to the bone[26].

Specifically, the supraspinatus consists morphologically of two different sub-regions. Anterior muscle fiber bundles were found to be bipennate, while posterior fiber bundles demonstrated a more parallel disposition[28]. Further, the anterior sub-region tendon is thick and tubular while the posterior tendon is thin and strap-like. These sub-regions have shown different mechanical properties[29]. In fact, anterior tendon stress is significantly greater than posterior tendon stress[28]. Each of the two sub-regions could also be divided into superficial, middle, and deep parts. This division has been associated to the initiation and progression of supraspinatus tendon tears[30].

Other authors have described four functional structurally independent parts in the supraspinatus tendon. The first part, also called the proper tendon, is extended from the musculotendinous junction to approximately 2.0 cm medial to the humerus insertion and it is composed of parallel collagen fascicles oriented along the tensional axis and separated by a prominent endotenon region. The second part is the attachment fibrocartilage that extends from the first part of the tendon to the greater tuberosity and it consists of a complex basket-weave of collagen fibers. The densely packed unidirectional collagen fibers of the rotator cable extend from the coracohumeral ligament posteriorly to the infraspinatus to form the third part, coursing both superficial and deep to the first part. Finally, the capsule is composed of thin uniform collagen sheets each, whose alignment differs slightly between sheets. This structure allows the tendon to adapt to tensional load dispersion and resistance to compression[22].

The upper fibers of the subscapularis tendon interdigitate with the anterior fibers of the supraspinatus tendon and the other structures of the rotator cuff, such as the coracohumeral ligament and the superior glenohumeral ligament[29].

The vascular anatomy of the healthy rotator cuff tendon has been controversial, with authors who have described a reduction in the number of capillaries[31], while others support the absence of hypovascularity. However, the changes in blood supply could be a secondary phenomenon, instead of an etiologic phenomenon, in the

rotator cuff lesions[26].

TENDON COMPOSITION

Tendons are consisted of collagens, proteoglycans, glycoproteins, glycosaminoglycans, water and cells[5]. The predominant elements of the tendon are the fibrillar collagen molecules. Type I collagen (more rigid) constitutes about 95% of the total collagen and the remaining 5% consists of types Ⅲ and V collagens[5,32]. Type Ⅲ forms smaller and less organized fibrils, which may result in decreased mechanical strength. This type of collagen was found in highly stressed tendons such as the supraspinatus[33]. The principal role of the collagen fibers is to resist tension, although they still allow for a certain degree of compliance (*i.e.*, reversible longitudinal deformation). Such apparently conflicting demands are probably resolved because of the hierarchical architecture of tendons[25]. Proteoglycans, as highly hydrophilic molecules, are primarily responsible for the viscoelastic behavior of tendons, but do not make any major contribution to their tensile strength[34]. Aging can cause a decrease in mean collagen fibril diameter, which is possibly regulated by type V collagen. The size shift may be related to the reduced mechanical strength of older tendons[35].

Fibroblasts are the dominant cell type in the tendon[5]. Tendon fibroblasts are responsible for the secretion of the extracellular matrix (*i.e.*, collagen orientation, assembly and turnover)[25], being considered a key player in tendon maintenance, adaptation to changes in homeostasis and remodeling in case of minor or more severe disturbances to tendon tissues. These cells are aligned in rows between collagen fibers bundles. Fibroblasts surrounded by biglycan and fibromodulin within the tendon ("niched" fibroblasts) exhibit stem-cell-like properties[36]. They are scarce in tendon tissue and decrease with age, but their prolongations create a large net in healthy status[10]. Tenocytes, the tendon fibroblasts, are increasingly recognized as a defined cell population that is functionally and phenotypically distinct from other fibroblast-like cells[25].

The supraspinatus tendon is a highly specialized inhomogeneous structure that is subjected to tension and compression[12]. The extracellular matrix composition of the insertion anatomy of the supraspinatus tendon has been categorized in four transition zones[37]. The first one is made up of largely type I collagen and small amounts of decorin, and could be considered as proper tendon. The second zone consists of largely types II and III collagen, with small amounts of types I , IX and X collagen forming a fibrocartilage. A mineralized fibrocartilage defines the third zone composed of type II and type X collagen and aggrecan. Finally, the fourth zone is bone with mineralised type I collagen. The mineral content and collagen fiber orientation define the effective bone-tendon attachment and are important in the appearance of rotator cuff tears[12].

Histological analysis of the rotator cuff tendon shows layers of loosely organized glycosaminoglycans between the longitudinal collagen fiber fascicles, which are usually undetectable in other tendons. These molecules, incorporated into collagen fibrils during the early, lateral assembly of fibrils[38], may be necessary to allow transmission of inhomogeneous strains during glenohumeral stabilization. Further, the increased amount of glycosaminoglycans in the supraspinatus may serve to resist compression and to separate and lubricate collagen bundles as they move relative to each other (shear) during normal shoulder motion[39]. In fact, the kinematics of the shoulder joint and shape of the supraspinatus tendon dictate that different regions of the supraspinatus tendon move independently in relation to each other, providing a mechanism of compensation[22]. It should also be stated that the total collagen content of the normal supraspinatus tendon does not change significantly with age and was similar to other shoulder tendons as the biceps tendon[40], for example.

ETIOLOGY AND PATHOLOGIC PROCESSES OF TENDINOPATHIES

The supraspinatus tendon is the most common injured tendon of the shoulder due to its location just under the coracoacromial ligament[41]. Shoulder impingement is one of the most common causes of shoulder tendinopathy[42,43] and refers to the compression of the subacromial structures against the coracoacromial ligament during elevation of the arm[44]. Apoptosis[45], vascular changes[26,31], tears[46] and calcifications[47] of the supraspinatus tendon have already been described in subjects who were treated with subacromial decompression.

Tendinopathy is a term usually used to cover all pain conditions both in and around the tendon. Although the knowledge of the causes of the tendinopathies continues to evolve[48], different intrinsic (anatomical variants and alterations, muscle tightness/imbalance/weakness, nutrition, age, joint laxity, systemic disease, vascular perfusion, overweight and all conditions linked to apoptosis[49]) and extrinsic factors (occupation, physical load and overuse, technical errors, inadequate equipment and environmental conditions) contributing to the pathologic processes have been identified. It is now recognized that most tendinopathies are rarely associated with any single factor, and the degenerative process that precedes tendon rupture may result from a variety of different pathways and etiology factors[50].

Classically, pain in tendinopathy has been attributed to inflammatory processes and the patient would be diagnosed as having "tendinitis"[18]. However, there are evidences that tendinopathy could be considered a non-inflammatory injury of the tendon at the cellular level[51,52], with absence of inflammatory precursors and cells in the tendon[48]. This condition is labeled as "tendinosis" and is defined from histopathologic findings involving widening of the tendon, disturbed collagen distribution, neovascularization and increased cellularity[53]. In fact, tendinopathies represent several degenerative processes mixed and, sometimes, overlapped. Tendinosis can lead to rupture of the tendon for vascular and/or mechanic reasons[50].

Among the most common sites of tendinopathy are the Achilles tendon, the patellar tendon, the wrist extensors tendon and the supraspinatus tendon[7,13,54,55]. The degenerative changes found in these tendons are associated with old age and with the high physical demands (strain, compression or shear forces) at the neighboring joints[6,56] with high rates of matrix turnover[50].

TENOCYTES BIOLOGY: MECHANOTRANSDUCTION IN EXERCISE

Tendons are metabolically active[57], but the mechanisms in transmitting/absorbing tensional forces within the tendon, and how tension affects the tendon, are not completely understood[58]. Nevertheless, tendons as a whole exhibit distinct structure-function relationships geared to the changing mechanical stresses to which they are subject[25].

The activity and microscopy architecture of the tenocytes could be modified by mechanical factors[5,59]. Further, the local stimulation of the tenocytes, which depends on the load, is the main fact associated to the tendinosis apparition[50], instead of apoptosis, that appears in more advanced stages[60]. In other words, the mechanical stress changes the cellular activity, and these changes alter the tendon structure[50] with a final negative balance of collagen[57]. However, different stress patterns provoke different cellular reactions depending on the amount and duration of the tensional stress applied[25].

The tenocytes are also responsible for producing an organized collagen and remodeling it during tendon healing[5]. Tenocyte strain regulates the collagen protein synthesis response. The increase in collagen formation peaks around 24 h after exercise and remains elevated for about 3 d, which produces a positive balance of collagen formation[57].

Kjaer *et al*[61] have suggested that gender difference exists in collagen formation where females respond less than males with regard to an increase in collagen formation after exercise. Also, the adaptation time to chronic loading is longer in tendon when compared to contractile elements of skeletal muscle, and only very prolonged loading can change the gross dimensions of the tendon[61].

In conclusion, the role of the tenocytes is relevant in both degeneration and healing processes of the tendon depending on the mechanical load applied[62]. The response of tendon cells to load is both frequency and amplitude dependent, and tendon cells appear to be "programmed" to sense a certain level of stress[62]. An adequate dose of mechanical load could improve the repairing, but an insufficient of inadequate stimulation could inhibit or prevent it.

TENDON LESION AND HEALING PROCESSES

The tendon is submitted to a constant process of synthesis and proteolysis (matrix turnover). The main actions of this cycle activity occur in the tendon matrix. Proteoglycan and glycoprotein activities are involved in the organization of the collagen fibers, and all their activities are mediated by the tenocytes. The changes in cellular activity in the extracellular matrix have been identified as a precursor of tendon lesion[61]. These changes include loss of matrix organization, high number of mechanoreceptors and fatty infiltration[12].

Lesions of the rotator cuff typically start where the loads are presumably the greatest: at the deep surface of the anterior insertion of the supraspinatus[63]. In absence of a total tear, when the repetitive load exceeds the healing capacity of the tenocyte (overuse), the tendinopathy appears[60]. Although the precise mechanism of injury that leads to tendinopathy remains unknown, the proposed mechanisms imply that there are one or more "weak link" in the tendon structure that result in the pathological response of the tenocyte[57].

Poor blood supply has also been implicated as a factor contributing to tendon injuries because it could delay the regeneration process, but tendon vascularization appears ample both around and inside the tendon in patients with tendinopathy[23,64]. Thus, tendinopathy itself is often associated with neovascularization and elevated intratendinous blood flow that seems to normalize during the course of exercise-based conservative treatment[65].

Although other degenerative features are associated with tendinopathy, including glycosaminoglycan accumulation, calcification and lipid accumulation, many of these features are found in normal tendons and are not necessarily pathological[66,67].

The role of each of the anatomical structures (*i.e.*, the supraspinatus tendon, the subacromial bursa and the glenohumeral joint capsule) are not completely known[12], but the progressive histological changes in rotator cuff disease include a characteristic pattern, which includes thinning of the collagen fibres, a loss of collagen structure, myxoid degeneration, hyaline degeneration, chrondroid metaplasia and fatty infiltration[68]. Total collagen content decreases, with a significant increase in the proportion of type Ⅱ and Ⅲ collagen relative to type Ⅰ collagen, decreasing the mechanical tendon properties. As previously commented, the tendon matrix also changes, and its attempt to heal, leads to a mechanical weak scar tissue as part of this failing remodelling process[12]. The histopathology shows that severity of tendon matrix degeneration increased with age and that more severe degeneration is associated with the development of tendinopathy[67].

For the supraspinatus tendon, extracellular matrix shows an increase of the concentrations of hyaluronan, chondroitin, and dermatan sulfate in chronic rotator cuff ruptures, that could represent an adaptation to an alteration in the types of loading (tension *vs* compression *vs* shear)[40]. Other pathologic factors such as low oxygen tension or the autocrine and paracrine influence of growth factors may also be important in the altered matrix following rupture[62]. In conclusion, higher rates of turnover in the nonruptured supraspinatus may be

part of an adaptive response to the mechanical demands on the tendon and to an imbalance in matrix synthesis and degradation. An increase in type Ⅲ collagen in some "normal" cadaver supraspinatus tendons is evidence that changes in collagen synthesis and turnover may precede tendon rupture[40].

The most common form of tendon healing is by scarring, which is inferior to healing by regeneration[6]. The contraction of tenocytes and the processes associated to its transformation in myofibroblasts seem to facilitate wound closure while minimizing scar tissue formation, playing an important role in tissue scarring[5].

Tendon healing can be divided into 3 overlapping phases: the inflammatory, repairing and remodeling phases[69]. The inflammatory phase lasts from 1 to 7 d with the phagocytosis as the main activity in this phase[70]. The repairing phase starts a few days after the injury and may last a few weeks[5]. The tenocytes starts the synthesis of large amounts of collagen after the 5th day until 5th week at least[70]. Type Ⅲ collagen is synthesized and then is gradually replaced by collagen type I with increase in tensile strength[71]. After about 6 wk the remodeling phase starts. This phase is characterized by decreased cellularity and decreased collagen. During this phase, the tissue becomes more fibrous and the fibrils become aligned in the direction of mechanical stress[72]. The final maturation stage occurs after 10 wk when there is an increase in crosslinking of the collagen fibrils, which causes the tissue to become stiffer. Gradually, over a time period of about one year, the tissue will turn from fibrous to scar-like[5].

Although the injured tendon tends to heal, there is evidence that the healing tendon does not reach the biochemical and mechanical properties of the tendon prior to injury[6]. In fact, collagen fibrils can be reduced as a result of injury[73]. A specific treatment approach, which takes into account each healing phase, has been recommended for improving these results[74].

The ability of the rotator cuff tendon to regenerate instead of repair is controversial, although the tendon heals better when good conditions are preserved. The functions of the subacromial bursa in healing include the gliding between two layers of tissue, the blood supply to the cuff tendons and the contribution of cells and vessels after surgical repair[12]. The changes in collagen composition in rotator cuff tendinopathy are consistent with new matrix synthesis, tissue remodelling and wound healing, attempting to repair the tendon defect even though when there is no visible evidence of a tendon fiber rupture. These changes may be the result of repeated minor injury and microscopic fiber damage or factors such as reduced vascular perfusion, tissue hypoxia, altered mechanical forces and the influence of cytokines, that could lead to tendon rupture[40].

Sometimes, in the last period of the remodeling and maturation of the healing, calcium apatite crystals are deposited in the damaged tissues. The location of this is close to the greater tubercule of the humerus where is the supraspinatus insertion[75].

When surgical treatment is necessary, the aim is to provide a better mechanical environment for tendon healing. Despite a normal response healing, the resultant tendon healing does not regenerate the tendon-bone architecture initially formed during prenatal development. Instead, a mechanically weaker, fibrovascular scar is formed, leading to suboptimal healing rates[76].

CLINICAL ASSESSMENT OF SHOULDER TENDINOPATHY

To diagnose tendinopathy, the anamnesis should include questions that allow the clinician to recognize if there is increase in inactivity and to identify which are the aggravating activities and also the relieving factors. The use of self-report questionnaires focused on the shoulder and upper extremity can be useful to quantify the patient's level of function in the shoulder, contributing for clinical decision-making process. Some of the commonly used questionnaires are the Disabilities of the Arm, Shoulder and Hand Questionnaire[77], the Western Ontario Rotator Cuff Index[78], the Shoulder Pain and Disability Index[79] and the Penn Shoulder Score[80]. Careful palpation helps in the search of points of tenderness that reproduce the pain of the patient. The clinician should use provocation tests that load the tendon to reproduce pain during the physical examination and other loading tests that load alternative structures[18]. The literature recommends that a combination of 3 positive of 5 tests (Neer, Hawkins-Kennedy, painful arc, empty can, and external rotation resistance tests)[81] can confirm the diagnosis of rotator cuff tendinopathy. Tendon pain itself usually does not radiate[18], although referred pain can contribute to the development of a secondary muscle problem as occurs with myofascial pain[82,83]. Imaging assessment (ultrasound and magnetic resonance imaging) improves the diagnosis of tendinopathy as it provides morphological information[84] about the tendon leading to a better clinician's make-decision. The ultrasound may provide an appropriate quantitative measure of the thickness of supraspinatus tendon that is important for determining improvement or deterioration in muscle function[85]. Fatty infiltration and tear can be better analyzed in magnetic resonance imaging. The presence and severity of fatty infiltration have been associated with increasing age, tear size, degree of tendon retraction, number of tendons involved and traumatic tears[86].

CONSERVATIVE TREATMENT OF SHOULDER TENDINOPATHY

Treatment of any organic medical condition must be based on understanding of pathophysiology. In fact, the knowledge of connective tissue properties, mechanotransduction, types of lesions, and tissue healing are important aspects for the correct and safe development of an exercise program[87]. However, this guide has not always been attended, and nowadays more questions than

answers remain around tendon injury treatment[10]. For example, although there are no established rules about the magnitude of the tear and the treatment options, the presence and the size of the rotator cuff tears could limit the therapeutic capacity of the exercises that underline the necessity of a correct diagnostic[9,88]. Massive chronic rotator cuff tears are often associated to restricted or loss of active shoulder range of motion[89]. Further, size of the tears could be related to joint inflammation and tissue remodeling, both of which are important for the advancement of rotator cuff treatment[90], but more research is necessary.

The common modalities used to treat a painful tendon include the use of anti-inflammatory drugs, rest and stretching and strengthening exercises[10]. It is important to highlight that the rest and anti-inflammatory are mainly used for the symptomatic relief with no direct effect in the tendinopathy as chronic tendon disorders are predominantly degenerative. Further, both non steroidal anti-inflammatory drugs[91] and corticosteroid drugs[92,93] could have deleterious effects on long-term tendon healing.

Another interesting point associated to rehabilitation process is the deterioration of the tendon after immobilization. A decrease of protein synthesis[94] and an increase of collagenase activity in damaged and not damaged fascicles[95] degenerate the immobilized tendon. Curiously, these deleterious processes have been stopped through cyclic stretching in *in vitro* studies[96,97].

As such, stretching techniques must be applied in the correct dose because its capacity of turnover the collagen synthesis[10]. Stretching techniques can consist of 3 repetitions of 30 s with a 30-s rest between the repetitions[1,98], 2 to 3 times per week[99].

Ultrasound, laser and electrical stimulation improve biomechanical and biochemical factors of the tendons and could help to reverse the tendinosis by stimulating fibrosis and repair[10]. However, there is lack of randomized trials that confirm the efficacy of these therapeutic approaches.

An effective treatment strategy that stimulates a healing response of the injured tendon need to be developed. So, exercises with mechanical loading should be started as soon as the pain "allows". The mechanical loading stimulates the healing response of the tendon as it accelerates tenocytes metabolism and may speed repair[5,71,100].

ECCENTRIC TRAINING

The eccentric training consists of the contraction of a muscle for controlling or decelerating a load while the muscle and the tendon are stretching or remain stretched. This technique has been advocated as a treatment of tendinopathy, such as chronic Achilles, patellar, lateral humeral epicondylalgia and rotator cuff tendinopathies[18]. Good clinical results were already demonstrated[7,13,55,101], although some controversies of this success also appears in the literature[102]. More evidence is necessary to support those results[103]. Currently, the eccentric training is included in algorithms of treatment[104] and has been considered a guiding principal of the rehabilitation[87,105].

The high forces produced eccentrically seem to induce remodeling response when applied chronically and progressively[100]. However, the specific mechanisms as to why eccentric training seems to optimize the rehabilitation of painful tendons are not totally known.

Three basic principles in an eccentric loading regime have been proposed, but the use of them still requires confirmation[70]: (1) length of tendon: the tendon length increases when the tendon is pre-stretched, and less strain will happen on that tendon during movement; (2) load: the strength of the tendon should increase by progressively increasing the load exerted on the tendon; and (3) speed: by increasing the speed of contraction, a greater force will be developed.

It has been suggested that eccentric exercises expose the tendon to a greater load than concentric exercises[106]. So, the prescription of an eccentric exercise program could be the best mechanism for strengthening the tendon[107]. Nevertheless, Rees *et al*[8] reported that peak tendon forces in eccentric loading are of the same magnitude as those seen in concentric loading suggesting that the tendon force magnitude alone cannot be responsible for the therapeutic benefit seen in eccentric loading. Thus, another possible mechanism that might explain the efficacy of eccentric loading is the high-frequency oscillations in tendon force produced by eccentric contractions. It was proposed that these fluctuations in force may provide an important stimulus for the remodeling of the tendon[8].

Other possible mechanisms may be related to the increase in fibroblast activity, acceleration of collagen formation, increase in type I collagen, collagen organization/alignment (remodeling of the tendon)[107,108] by muscular lengthening (stretching)[99,109] and increase in the number of sarcomeres in series[110]. Ohberg *et al*[84] have showed a localized decrease in tendon thickness and a normalized tendon structure in patients with chronic Achilles tendinosis after treatment with eccentric training. All these beneficial adaptations could allow proposing the eccentric training as a "tendon-strengthening" program[9].

Finally, another explanation of the eccentric training effectiveness is the traction and consequent disappearance of neovessels[65] that could lead to a lack of perfusion produced by the tendinosis. Although the decreased capillary tendon blood associated with increasing age might imply a consecutive bad perfusion and leads to tendinopathy and finally to tendon rupture, it was found that neovascularization is associated with a significantly increased capillary blood flow at the point of pain in symptomatic tendinopathy.

In fact, it has been hypothesized that the resolution of the tendinosis neovascularization by eccentric training, closely associated with new nerve endings, will be disturbed or even destroyed due to a lack of perfusion by their nutrient neovessels[53]. These studies speculate that some of the good clinical effects of the eccentric training may be mediated through decreasing pathological increased capillary tendon flow without deterioration of

local tendon microcirculation, but more evidence is necessary.

Another mechanism of the well tolerated reactions of the patients under eccentric training treatment includes neuromuscular benefits through central adaptations[8] and pain habituation, but there are not high quality trials to support this[103].

One of the most important aspects for the success of an exercise program is the individualization of the prescription. The exercise program should be as similar as possible to the usual mechanical stressors identified in each patient[87]. The comprehension and motivation of the patients, and the establishment of specific goals, practice and efforts could make easy the motor learning[111]. The more exhaustive process of the information (explanations, knowledge, motivation, attention), the deeper learning[112]. All these aspects, clearly linked to the eccentric training, could partially explain the effectiveness of this treatment approach.

It is well documented that the first bout of eccentric training could result in damage, including muscle pain, inflammation, cellular and subcellular alterations, force loss, blood markers of muscle damage[113]. The damage of eccentric contractions is related to a "mechanical insult", because as muscle lengthens, the ability to generate tension increases and a higher load is distributed among the same number of fibers, resulting in a higher load per fiber ratio and, curiously, a lower muscle activity[114]. However, this fact is still controversial[115].

Hypoxia has been described as a mechanism of tenocyte changes and death[76]. As previously commented, this is another controversial point because the intermittent capillary flow interruptions associated to eccentric training have been proposed as a benefic effect, but it could also produce tissue hypoxia and damage in capillaries[116].

Nevertheless, these adverse effects are mainly associated to the first bout of eccentric exercise. In fact, the following bouts of eccentric exercises do not produce the same muscle soreness or alteration in blood markers, and the recovery of the strength is faster when compared to the first bout[113].

In summary, eccentric training effects could be compared with the mechanical effects in tenocyte biology, where an adequate load increases healing and an inadequate (over or underuse) load can deteriorate the tendon structure.

Rotator cuff tendons attach the humerus very close to the glenohumeral joint, blending imperceptibly with the joint capsule. This increases the speed with which they can move the joint, producing a most effective moment arm[117]. The tendons "compete" with the glenohumeral capsule for bony anchorage, multiplying their functions. The conflict may be resolved by the fusion of the two structures[25].

Although the literature supports the use of strengthening and stretching exercises to reduce pain and functional loss in subjects with shoulder impingement[1,118], few studies have evaluated the effects of the eccentric training in subjects with this condition. Further, the literature supporting the beneficial effects of eccentric training in Achilles and patellar tendinopathy is abundant, but these effects are less known in rotator cuff tendon disorders[9].

Jonsson *et al*[13] have shown good clinical results of eccentric training for the supraspinatus and deltoid muscles in chronic painful subjects. The authors completed the study in 9 subjects that were on the waiting list for surgery. All subjects had to perform painful eccentric training for the supraspinatus and deltoid muscles for 12 wk, 7 d a week, 3 sets of 15 repetitions, twice a day. After this period of training and at 52-wk follow-up, 5 out of 9 subjects were satisfied with the result of the treatment and withdrew from the waiting list for surgical treatment.

Bernhardsson *et al*[14] have evaluated the effects of an exercise focusing on specific eccentric training for the rotator cuff on pain intensity and function in subjects with shoulder impingement. The training programme comprised 5 exercises, of which 2 were warm-up and scapular control (shoulder shrug and scapular retraction) exercises and stretching for the upper trapezius. The 2 main exercises were eccentric strengthening exercises for the supraspinatus and infraspinatus performed in a side-lying position and using dumbbells. The frequency of the protocol was the same as proposed by Jonsson *et al*[11]. The training was effective to decrease pain and increase function.

Camargo *et al*[15] had their patients with shoulder impingement to perform eccentric isokinetic training at 60°/s for shoulder abductors during 6 wk (3 sets of 10 reps, 2 d a week). Subjects improved pain and function, but isokinetic variables were only moderately changed after the intervention. This type of training may be difficult to be incorporated in a clinical setting, as it requires an isokinetic device.

The main limitation of the previous studies is that none of them included a control group. They all had one group performing the same exercises. The lack of control group does not allow us to completely rule out that the natural maturation of the condition may have influenced the results.

Based on this, Maenhout *et al*[16] investigated if adding heavy load eccentric training to rehabilitation of patients with shoulder impingement would result in better outcome. One group of patients performed the traditional rotator cuff training and the other group performed the same exercises combined with heavy load of eccentric training. The protocol consisted of 3 sets of ten reps, daily, for 12 wk. The eccentric exercises were performed twice a day. Adding heavy load of eccentric training resulted in higher gain in isometric strength, but was not superior for decreasing pain and improving shoulder function.

It is important to highlight that different doses of eccentric training were used in the previous studies. The lack of understanding about the basic pathophysiology of tendinopathy makes determining the optimal dosage of intervention difficult. Because the studies in this area have not used an underlying rationale to determine load-

ing parameters, progressions and frequency of treatment, further research needs to be undertaken before an optimal dosage can be determined.

Other studies have also incorporated the use of eccentric exercises along with other exercises in the rehabilitation protocol for subjects with shoulder impingement[119-121], but they didn't intend to evaluate the effects of the eccentric training. The cited studies on eccentric training[13-16] only evaluated the effects of the eccentric training on shoulder pain, function and strength. None of the studies assessed the effects on the shoulder kinematics and muscle activity.

It is known that subjects with shoulder impingement present increased retraction and elevation of the clavicle, increased internal rotation and decreased upward rotation and posterior tilting of the scapula[122], and increased anterior and superior translations of the humerus during elevation of the arm as compared to healthy subjects[123]. The literature also brings that these alterations are commonly associated with increased activity of the upper trapezius, decreased activity of the lower trapezius, serratus anterior and rotator cuff muscles[124]. Based on the alterations above, many protocols are proposed in an attempt to restore kinematics and muscle activity in these individuals. Most of the protocols include stretching exercises for the anterior and posterior shoulder, strengthening exercises for the lower trapezius, serratus anterior and rotator cuff muscles, relaxation for the upper trapezius and techniques of manual therapy[1,118,125-127]. Good clinical results were observed in these investigations.

Further clinical trials should be done to evaluate the effects of eccentric training programs on scapular and humeral kinematics and shoulder muscles activity[104]. Future investigations should include long-term follow-up of large groups, and the comparison of different eccentric training protocols. Imaging evaluation before and after the period of treatment is also necessary to check on possible improvements of the injured tendon.

Finally, there is still lack of evidence of the really benefits that the eccentric exercises may bring to subjects with shoulder tendinopathy. In the treatment of shoulder impingement, the approach should not only focus on decreasing the impingement, but should additionally address the tendon degeneration. As such, eccentric training should be used aiming improvement of the tendon degeneration, and usual stretching and strengthening exercises associated with manual therapy techniques to restore kinematics and muscle activity.

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Reverse polarity shoulder replacement: Current concepts and review of literature

Ling Hong Lee, Aravind Desai

Ling Hong Lee, Aravind Desai, Specialist Registrar, Trauma and Orthopaedics, Northern Deanery, Newcastle Upon Tyne, NE12 8RF, United Kingdom
Author contributions: Lee LH and Desai A contributed equally to this work.
Correspondence to: Aravind Desai, MS (Orth), MRCS, MSc, MCh (Orth), FRCS (Tr&Orth), Specialist Registrar, Trauma and Orthopaedics, Northern Deanery, 17 Maybury Villas, Newcastle Upon Tyne, NE12 8RF, United Kingdom. desaiaravind@yahoo.co.uk
Telephone: +44-78-85994545 Fax: +44-78-85994545
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Abstract

Shoulder replacement in cuff tear arthropathy (CTA) is an unsolved challenge. CTA poses a soft tissue deficiency in an arthritic glenohumeral joint which the anatomical total shoulder replacement and hemiarthroplasty cannot reliably provide stability, range of movement, function or satisfactory long term outcome. In the past two decades since the introduction of the reverse shoulder replacement, the prosthesis has evolved and has shown promising results. It is a partially constraint joint by virtue of its design features. The reversal of the concavity and convexity of the joint to the proximal humerus and the glenoid, respectively, also shifts and improves its center of rotation onto the osseous surface of the glenoid with less exposure to shear stress. It is a successful pain relieving procedure, offering good outcome in patients with irreparable massive rotator cuff tear with or without osteoarthritis. Consequently, this has led to wider use and expansion of its indication to include more complex elective and trauma cases. Whereas originally used in the more elderly patients, there is increasingly more demand in the younger patients. It is important to have good quality long term data to support these increasing indications. Therefore, we review the literature on the concepts of reverse shoulder replacement and the contemporary evidence.

Key words: Reverse shoulder replacement; Biomechanic; Cuff tear arthropathy; Shoulder arthritis; Proximal humerus fracture; Review

Core tip: Cuff tear arthropathy is a challenging condition to manage. Hemiarthroplasty and total shoulder replacement have been tried but reported to have poor outcome. Reverse polarity shoulder has evolved since last two decades and its outcome is promising in this pathology. It is a complex procedure associated with significant risks. It is important to understand the bio-mechanics, principles of surgery, extended indications, pitfalls associated with it and the available literature. This review summarises the concept of this procedure. We also review the most recent available biomechanical and clinical evidence to aid clinicians' practice.

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INTRODUCTION

Shoulder replacement can give excellent pain relief and restore shoulder motion in primary osteoarthritis, inflammatory arthropathy or post-traumatic osteoarthritis[1]. Shoulder replacement in cuff tear arthropathy (CTA) presents a challenge as there is lack of soft tissue constraint to allow a satisfactory shoulder function. Unconstrained shoulder replacement such as hemiarthroplasty was a standard surgical option in the treatment for CTA

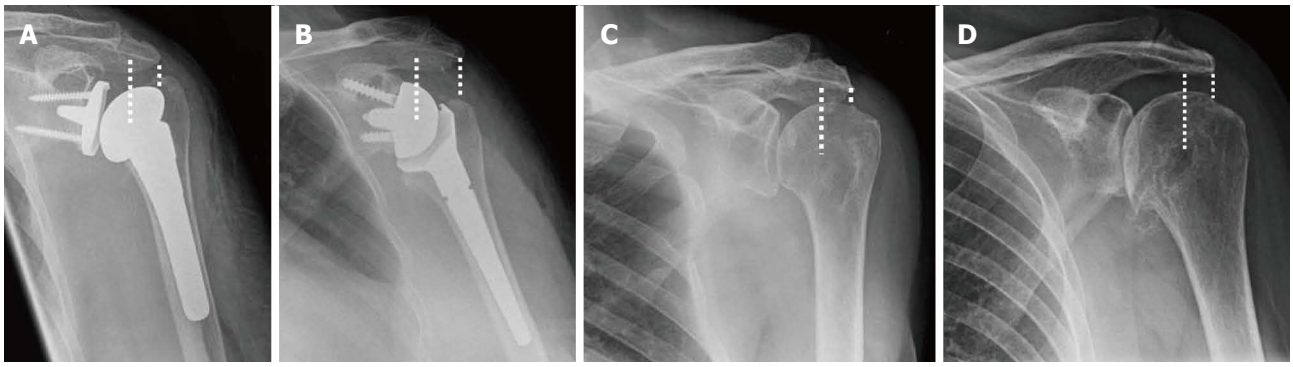

Figure 1 Shoulder replacement, shoulder with native glenohumeral joint and osteoarthritis. A: Following total shoulder replacement; B: Following reverse shoulder replacement. The interval between the two plumb lines is wider than in Figures 1A, C and D, indicating medialisation of the center of shoulder rotation. The longer distance between the acromion and humerus allows restoration of the deltoid length and tension; C: Native glenohumeral joint. A short plumb line showing the distance between the lateral edge of acromion and humerus head. A long plumb line is drawn from the inferior surface of acromion to the center of shoulder rotation. The interval between the short and long plumb lines is smaller than the interval in Figure 1B; D: Shoulder with osteoarthritis.

but the results were unpredictable and confined to patients who were expected to have limited rehabilitation potential[2-4]. Total shoulder replacement is not suitable in CTA due to early failure[5] (Figure 1A). Reverse shoulder replacement addresses most of the limitations of hemiarthroplasty or total shoulder replacement in the presence of rotator cuff deficiency[6,7] (Figure 1B). Since its initial success, the indications for reverse shoulder replacement are increasing. This article reviews the current evidence of reverse shoulder replacement mainly in managing CTA, acute proximal humerus fracture and its use in young patients.

BIOMECHANICS OF REVERSE SHOULDER REPLACEMENT

Anatomical total shoulder replacement can restore the full articular surface of the humeral head and the glenoid contour in cases of osteoarthritis. Deficiency of the rotator cuff and capsule can be repaired to provide soft tissue stability for the anatomical shoulder replacement. Massive irreparable rotator cuff tear and a deficient coracoacromial arch result in deficit of concavity compression to allow anterosuperior escape and pseudoparalysis. In such cases, anatomical total shoulder replacement cannot restore shoulder stability[7].

The design features of the reverse shoulder replacement provide stability not inherent in a total anatomical shoulder replacement. The reverse shoulder replacement is partially constrained by a spherical convex glenoid component and a deep and large diameter humeral cup (Figure 1B) in contrast to the shallow concave glenoid and spherical humeral head in a normal glenohumeral joint (Figure 1C). The Grammont *et al*[6] glenoid component in reverse shoulder replacement does not have a polyethylene component and is fixed with screws onto a base plate which in return is fixed onto the glenoid with divergent screws forming a triangular device. This geometry changes the center of rotation of the reverse shoulder replacement medial and distal onto a more stable point on the osseous surface of the glenoid thus avoiding shear stress of the humeral head on the glenoid component[6,8]. The full surface contact throughout the movement of articulation prevents glenohumeral translation thus removing the rocking horse mechanism by eliminating rim loading[7,9]. The more distal and medial center of rotation restores the deltoid tension, increases its lever arm and indirectly improves its power (Figures 1). The reversal of deltoid action to a centripetal action in reverse shoulder replacement in addition to the structural stability of the design provides a stable semi-constrained joint[6,7].

The current available reverse shoulder replacement systems in the market are based on the successful concept and principles introduced by Professor Grammont *et al*[6], a prosthesis that is stable, mobilises solely by deltoid and without risk of glenoid support loosening. Common features are the glenoid component (half a sphere in the Grammont design), the humeral cup (a third of a sphere) and the humeral neck with less vertical inclination (155° in the Grammont design). The large ball allows a greater arc of motion and more stability. The short neck of glenoid component medialises the center of rotation to reduce shear force which can loosen the component. The inclination of the humeral cup lowers and medialises the humerus to allow tension of deltoid by increasing the lever arm and recruiting more deltoid bulk[7,9].

INDICATIONS

Following successful reports of reverse shoulder replacement for CTA[6,9,10], its role has expanded with time. It is particularly useful in cases with deficient rotator cuff, such as painful irreparable massive cuff tear without osteoarthritis[11,12], inflammatory arthritis with cuff deficiency[13,14], acute complex proximal humerus fractures[15-17] and proximal humerus bone tumour surgery[18]. Rotator cuff deficiency is a common feature in all and is the best indication for a reverse shoulder replacement. Caution remains in the young population as there is still lack of long term knowledge about the longevity of reverse

shoulder replacement but this is anticipated to be clearer in the next few years[8,17]. Non-functioning deltoid muscle is a contraindication for reverse shoulder replacement.

Irreparable massive rotator cuff tear (with and without osteoarthritis)

A large comparative study between age, sex and ASA-score matched patients undergoing hemiarthroplasty and reverse shoulder replacement for CTA using the New Zealand joint registry showed better Oxford Shoulder Score (OSS) in the reverse shoulder group at 6 mo after surgery[19]. Although 102 patients were identified in each group, only 64 hemiarthroplasty and 74 reverse shoulder replacement were available for final analysis. In a small subgroup of patients with 5 year follow up (18 hemiarthroplasty and 14 reverse shoulder), the improvement in OSS was still observed to be greater in the reverse shoulder group[19].

Naveed *et al*[8] presented a prospective series of the use of a single type of reverse shoulder replacement in 50 shoulders (43 patients) with CTA performed by a single surgeon. Functional outcome scores improved significantly at 8 to 81 mo postoperative follow up. The mean OSS improved by more than a third of the overall score and was a successful pain relieving pain procedure in 84% of the patients.

Wall *et al*[11] reviewed 191 mixed cases including 59 CTA and 34 massive rotator cuff tear without arthritis up to almost twelve years. These two groups of cases reported the best outcomes in function and subjective scorings following reverse shoulder replacement compared to patients with primary osteoarthritis, posttraumatic arthritis and revision arthroplasty. Movements were also improved but less in external rotation compared to elevation.

Similar observation was reported by Ek *et al*[20]. In a case series of 40 reverse shoulder replacement in patients younger than 65 years old performed for heterogenous cases, the functional outcome after a mean of 93 mo were similar between patients who did not have glenohumeral arthritis preoperatively and those who did.

Acute complex proximal humerus fracture

Reverse shoulder replacement in acute complex proximal humerus fracture not amenable to surgical fixation can be a good pain relief and functional restoration operation[16,17]. Although hemiarthroplasty is widely performed for complex proximal humeral fracture, there is concern regarding tuberosity union[15,17], integrity of rotator cuff especially in the elderly[21] and potential glenoid wear[22,23].

A prospective series of non-randomised comparison between patients over the age of seventy undergoing hemiarthroplasty and reverse shoulder replacement for complex proximal humerus fracture reported favourable clinical outcomes in the reverse replacement group[17]. Cuff *et al*[17] reported significantly better shoulder specific outcome scores in the reverse replacement group although the criticisms of the study were the small sample (26 hemiarthroplasty *vs* 27 reverse shoulder replacement) and the follow-up for reverse shoulder was shorter compared to the group of patients undergoing hemiarthroplasties due to the non-randomised design of the study. Functional results were dependent on the healing of tuberosities as worse outcome was seen in patient undergoing hemiarthroplasty with tuberosities resoption compared to hemiarthroplasty with healed tuberosities. Regardless of the healing of the tuberosities, patients with reverse replacement reported superior functional outcome compared to hemiarthroplasty but healed tuberosities conferred better range of external rotation[17].

A systematic review of 14 studies with 2-4 years of follow up using statistical pooling of outcomes and standard deviation reported 4 times greater odds of developing postoperative complications after reverse shoulder replacement compared to hemiarthroplasty using fracture-specific stem following proximal humerus fracture[16]. Most of the complications in the reverse replacement group were attributed to neurologic complications, reflex sympathetic dystrophy and dislocation[15,24]. The reoperation rates were, however, not different although the exact reason for this is debatable. The authors argued that there could be higher revision surgery in the reverse shoulder group if there was a good alternative salvage procedure. In the hemiarthroplasty group, the follow up period may have been too short to adequately report number of revision surgery. In addition, patients in the reverse shoulder replacement group were significantly older and suffered more fracture dislocations and were followed-up longer compared to patients in reverse shoulder replacement[16].

Chalmers *et al*[25] retrospectively compared 9 reverse shoulder *vs* 9 hemiarthroplasty *vs* 9 open reduction internal fixation for severe proximal humerus fracture and reported better active forward elevation, external rotation, cheaper and faster rehabilitation and total costs in the reverse group but similar outcome scores in all three. This study has its own limitation being a short follow up (minimum 1 year) especially in the reverse shoulder replacement group. In contrast, Gallinet *et al*[26] reported better abduction, forward flexion and Constant score in the reverse shoulder replacement but worse rotation compared to hemiarthroplasty.

Reverse shoulder replacement can provide good pain relief and allow satisfactory range of motion following complex proximal humerus fracture. In relation to internal fixation or hemiarthroplasty, the shorter and less restrictive postoperative rehabilitation after a reverse shoulder replacement may be an attractive factor for patient and in cost[25]. Similar to other areas of orthopaedic surgery, strong evidence for the use of reverse shoulder replacement in acute complex proximal humerus fracture is still not reported. Studies with a robust methodology and appropriate assessments will better inform the indication of reverse shoulder replacement in acute complex fractures.

Reverse shoulder replacement in the younger population

There is an acceptance that reverse shoulder replacement

should be performed cautiously in the younger population[8,9,19]. This is due to the relatively new concept of the modern reverse prosthesis therefore there is at present limited amount of long term outcome on this technology. There is also a lack of salvage options for failed reverse shoulder replacement. Acceptable medium term result from using a stemless reverse shoulder prosthesis in a single surgeon case series represents a step towards preservation of bone stock but still does not solve glenoid complications[27].

Reverse shoulder replacement in the younger population was reported to be a good operation to improve range of motion, function and pain compared to the older population[28,29]. However, subjective reporting was weaker as 20% of the patients were not satisfied (either very dissatisfied, dissatisfied or not satisfied) after an average 36.5 mo following the surgery[29]. In these studies, the patients were younger than 60 years old with mixed cohort of pathologies including rotator cuff deficiency with or without osteoarthritis, revision arthroplasty, rheumatoid arthritis and posttraumatic arthritis which may negatively skewed the results.

Performing a reverse shoulder replacement in the younger population (65 years or younger) with rotator cuff arthropathy did not produce a better functional outcome compared to hemiarthroplasty at 6 mo review[19]. While longer data is required to inform practice surgeons should be reminded that delaying reverse shoulder replacement by performing other procedures could be detrimental to the final outcome[29] as demonstrated that patients with multiple operations before the reverse replacement surgery reported less improvement in functional scores.

Complication rates after reverse shoulder replacement were also high. Muh *et al*[29] reported 5 revisions and 2 resection arthroplasties in 67 reverse replacements, with survival rate of 89.5% within 6 years in patients age 60 years or younger. Sershon *et al*[28] reported 14% complication rate including 3 revisions within 4 years after reverse shoulder replacement in 36 shoulders, with total survival rate of 91% in patients with mean age of 54 years. Ek *et al*[20] reported 37.5% complications in 40 reverse shoulder replacements performed in patients younger than 65 years old. 6 (15%) required removal of prosthesis or conversion to hemiarthroplasty. Their survival rates were reported to be 76% (if any reoperation was taken as endpoint) and 88% (implant survival as endpoint) at 10 years postop. A positive finding from this study showed that the functional outcomes and range of active forward flexion were similar throughout the 10 years of follow up[20].

PITFALLS IN REVERSE SHOULDER REPLACEMENT

Approach

Adequate exposure is required for proper implantation of the reverse shoulder prosthesis especially of the glenoid. The deltopectoral (with or without extension) and deltoid split are the two most commonly used approaches. Naveed *et al*[8] experienced difficulty exposing the inferior glenoid adequately using deltoid split therefore changed their practice to extended deltopectoral which also allowed them to identify and protect the axillary nerve better. Deltopectoral approach disturbs the integrity of the subscapularis. A disadvantage of deltopectoral approach is a reported higher risk of dislocation in patients with irreparable subscapularis tendon in a prospective series by one surgeon[30]. In contrast, a retrospective study incorporating practices of three surgeons showed similar dislocation rates in patients undergoing reverse shoulder replacement using the deltopectoral approach with or without subscapularis repair[31].

Dislocations

Dislocation is usually due to insufficient soft tissue tension, especially the deltoid or due to worn polyethylene bearing. This could be managed by closed reduction alone or lengthening of the humeral liner[8,9,18,32]. Martinez *et al*[33] reported two patients with dislocation after reverse shoulder replacement for proximal humerus non-union treated with exchanging to a larger diameter glenosphere. Other causes of dislocation included CAM effect of the tubercle remnants, anteversion of humeral stem and obesity[24,25].

Notching

Notching prevalence increases with the longevity of prosthesis, reported from 40% at year 1 to 87% at 10 year follow up[9,24,29,32]. It is suggested as a cause of glenoid loosening and therefore a clinical concern and negatively affected functional outcomes[20,24] but some reported no effect on Constant score or reoperation rate[9,34]. Notching is not strongly proven to be associated with glenoid component loosening.

A reverse shoulder replacement with notching which extended beyond the inferior fixation screws when examined at post mortem did not show evidence of loosening of the glenoid base plate[35]. Although the true effect of scapular notching is still being investigated and debated, it is best to avoid loss of osseous tissue around prosthesis[9,20,24,34].

Scapular notching is likely related to mechanical impingement by the medial-inferior rim of the humeral cup against the posterior-inferior scapular neck in adduction[9,32,35]. Retrieval of the prosthesis/humeral cup revealed polyethylene wear due to this collision erosive effect[9,35]. The rim rubbed on denuded screw during flexion, extension and rotational movements in adduction[35]. Further to this, there may be detrimental effect of foreign-body reaction as a result of the wear particle to tissue surrounding the joint[35]. Radiolucencies were also seen at the lateral and medial proximal metaphyseal zone of the proximal humerus[24,32].

Identification of the inferior glenoid is also critical to allow inferior placement of the glenoid component.

Inferior placement, inferior eccentricity or even overhang of the glenoid component was associated with less common occurrence of scapular notching[9,32,36-38]. The recommended overhang of 5.7 mm in female was predicted to decrease notching rate to 0.9% from 13% and 5.6 mm in male to 8.7% from 13%[39]. Notching seemed to be less common when a lateralised humeral cup was used that resulted in higher tension therefore restricting movement of the humeral component[32]. Notching was seen in 60% of 6 mm lateralised cup compared to 78% using standard cup (Levigne 2008). A larger and lateralised glenosphere allows more degree of adduction and abduction without inferior impingement[37]. Lesser notching was seen when using glenosphere of size 42 mm *vs* 38 mm and none in 46 mm[39]. Other factors such as less horizontal humeral neck and lesser prosthesis-scapular-neck-angle also contributed towards lesser chance of notching[39]. Lateralised centre of rotation resulted in early failure of the glenoid component therefore it should be used with caution[40]. A prospective randomised study comparing fixation of 36 mm glenosphere in neutral or in an inferiorly tilted position with 3 mm of overhang did not revealed difference in incidence of scapular notching or clinical outcome[41].

Range of movement

Abduction and anterior flexion of the shoulder with reverse replacement is provided mainly by the deltoid muscle. The amount of motion is affected by several factors. In a cadaveric study, Berhouet *et al*[37] shows that the shortest abduction were achieved using a 36 mm glenosphere. When a larger diameter glenosphere of 42 mm was used and lateralised 10 mm, it allowed the largest range of abduction (97° *vs* 87°).

External rotation is seen to be better in reverse shoulder replacement with an intact teres minor[6,9] and a less medialised glenoid component[34]. Lateralising the glenoid component alters the center of rotation to the component itself and may cause glenoid loosening without erosion[9,40]. Increasing the humeral retroversion improves the external rotation but at the cost of internal rotation.

Latissimus dorsi transfer can improve external rotation and subsequently function[42-44]. Ortmaier *et al*[43] reported harvesting the tendon together with a small piece of bone. The effect of latissimus dorsi transfer during reverse shoulder replacement for pseudoparesis on outcome scores and movement was reported to be preserved at 5 year review in 17 patients[44].

Internal rotation was reported to be less satisfactory or not improved after reverse shoulder replacement[9,45]. This is most likely due to insufficient internal rotator not compensated by the anterior deltoid fibers. The design of the prosthesis in lowering the humerus may also weaken the subscapularis by changing the vector of muscle contraction. The best rotationally balanced reverse shoulder replacement in a cadaveric study was native 17.5 degree retroversion[37].

Perioperative fractures

Complication decreases with learning curve[46]. Acromial fracture weakens the deltoid therefore rendering the reverse shoulder replacement non functional and clinically relevant. Fracture at the base of the acromion resulted in the worst outcome[47]. Pain along the acromion or scapular spine should alert the physician to such complication. CT scan may be required to help aid diagnosis where the plain radiographs are not diagnostic[47]. The decision of management needs to be tailored to the individual patient[47,48]. Humeral fracture is less common but perforation or propagation of cracks can occur during cementation or implantation of prosthesis. Fracture of the glenoid at the rim, glenoid surface or glenoid neck can occur during glenoid reaming or tightening of screws[7].

CONCLUSION

CTA presents a challenging scenario. Reverse shoulder replacement is a reliable pain relieving procedure. The resultant fixed and medialised center of rotation minimises the torque on glenoid and improves the power of deltoid to provide a functioning shoulder. Good quality long term data are needed to support its expanding indications especially as there are still unsolved issues about this shoulder replacement.

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Superior labrum anterior to posterior lesions of the shoulder: Diagnosis and arthroscopic management

Nuri Aydin, Evrim Sirin, Alp Arya

Nuri Aydin, Alp Arya, Department of Orthopedics and Traumatology, Cerrahpasa Medical School, University of Istanbul, 34116 Istanbul, Turkey
Evrim Sirin, FSM Research and Teaching Hospital, Turkish Ministy of Health, 34400 Istanbul, Turkey
Author contributions: Aydin N contributed to writing the treatment section, total revision of the written manuscript; Sirin E contributed to writing the introduction and anatomy section of the manuscript; Arya A contributed to writing imaging and revising the manuscript.
Correspondence to: Nuri Aydin, MD, Associate Professor, Department of Orthopedics and Traumatology, Cerrahpasa Medical School, University of Istanbul, I.U. Cerrahpasa Tip Fakultesi, Ortopedi ve Travmatoloji AD, K.M.P, 34116 Istanbul, Turkey. nuri.aydin@istanbul.edu.tr
Telephone: +90-532-5986232
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Abstract

After the improvement in arthroscopic shoulder surgery, superior labrum anterior to posterior (SLAP) tears are increasingly recognized and treated in persons with excessive overhead activities like throwers. Several potential mechanisms for the pathophysiology of superior labral tears have been proposed. The diagnosis of this condition can be possible by history, physical examination and magnetic resonance imaging combination. The treatment of type 1 SLAP tears in many cases especially in older patients is non-operative but some cases need arthroscopic intervention. The arthroscopic management of type 2 lesions in older patients can be biceps tenodesis, but young and active patients like throwers will need an arthroscopic repair. The results of arthroscopic repair in older patients are not encouraging. The purpose of this study is to perform an overview of the diagnosis of the SLAP tears and to help decision making for the surgical management.

Key words: Superior labrum anterior to posterior tear; Glenoid labrum; Arthroscopy; Repair; Shoulder

Core tip: The arthroscopic management of type 2 lesions in older patients can be biceps tenodesis, but young and active patients like throwers will need and arthroscopic repair.

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INTRODUCTION

The long head of the biceps tendon and superior labrum help to stabilize the humeral head usually in the abducted and externally rotated arm. Injuries to the glenoid labrum represent a significant cause of shoulder pain especially among athletes involved in repetitive overhead activities[1]. After the development of shoulder arthroscopic interventions superior labrum anterior to posterior (SLAP) tears are well recognized in recent times[2]. The name "SLAP" was used by Snyder *et al*[3] for the first time in the literature. These lesions occur either an isolated or in a conjunction with other shoulder problems like rotator cuff tears, instability or other biceps tendon pathologies[4,5]. There are different types of treatment modalities in different type of SLAP lesions. The treatment plan changes not only about the type of the lesion but also the age and functional level of the patient. Different treatment modalities were discussed in the literature. Our primary objective for this study was to help surgeons to better understand the pathology and make a decision for surgical management of SLAP tears according to type of the tear and patient's characteristics.

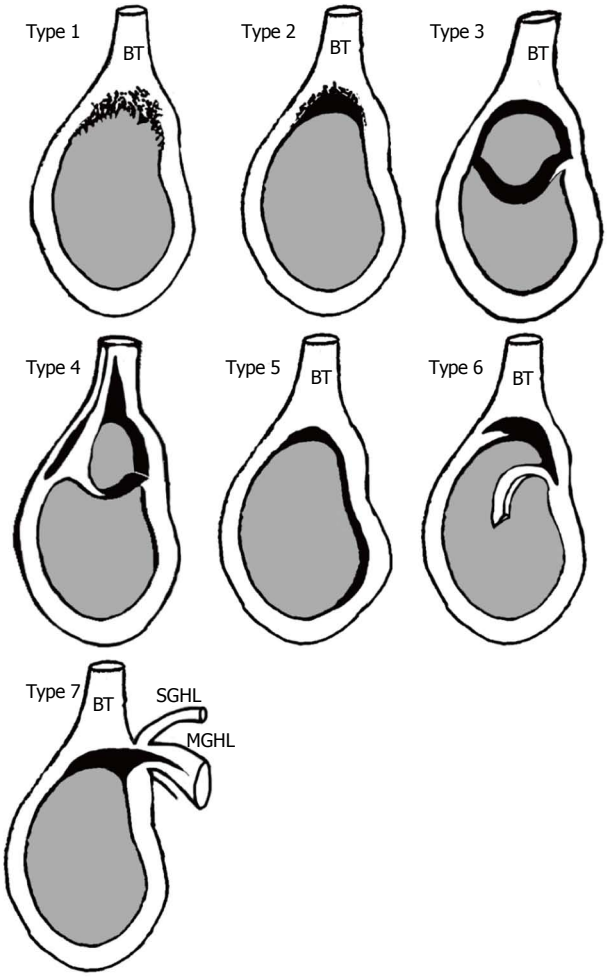

Figure 1 Superior labrum anterior to posterior tear classification. Type 1: Degenerative fraying of the superior labrum, biceps anchor is intact; Type 2: Superior labrum and biceps tendon detachment from glenoid rim; Type 3: Bucket-handle tear of labrum with intact biceps anchor; Type 4: Bucket-handle tear of labrum extended into the biceps tendon; Type 5: Superior labrum anterior to posterior (SLAP) with anterior inferior extension; Type 6: Anterior or posterior flap tear with the bucket handle component tear; and Type 7: SLAP with extension to the middle glenohumeral ligament.

ANATOMY

In order to understand the mechanism of this event it is best to understand the anatomic features around the glenoid. The glenohumeral joint is surrounded by a fibrocartilage tissue called labrum[6,7]. It increases the depth of glenoid fossa limiting the translation of humeral head and stabilizes the long head of biceps tendon improving glenohumeral joint stability[1]. Glenohumeral joint is stabilized by static and dynamic restraints. Static restraints include capsuloligamentous structures, labrum and negative intraarticular pressure. Dynamic restraints include rotator cuff muscles, periscapular muscles and biceps muscle[8]. The vascular supply of labrum is provided by suprascapular, circumflex scapular and posterior humeral arteries[6]. The anterosuperior margin of the glenoid rim has limited vascularity making it more vulnerable to injuries and having impaired healing potential[6]. The relationship between superior labrum and long head of biceps tendon is a special concern because of the considerable anatomic variability between this structures[8]. There are some anatomic variants for glenoid labrum and biceps tendon; the most common normal variation is a labrum attached to the glenoid rim and there is a broad middle glenohumeral ligament. One kind of anatomic variation is the sublabral recess, which represents a gap located inferior to the biceps anchor and the anterosuperior portion of the labrum. It is usually seen in 12-o'clock position of the glenoid in arthroscopic surgery[1]. Another variant is the sublabral foramen, which is a groove between the normal anterosuperior labrum and the anterior cartilaginous border of the glenoid rim. Another variation is the Buford complex which is characterized by the absence of the anterosuperior labral tissue with the presence of a thick cord-like middle glenohumeral ligament[1,8].

HISTORY AND CLASSIFICATION

Since the mid-1980s SLAP lesions were recognized as a cause of shoulder pain[9]. Kim *et al*[10] were the first authors who described that superior glenoid labrum tears are related to the long head of the biceps. After that Snyder et al. made the first classification system and established the current understanding of the pathologic anatomy of SLAP lesions[9]. They emphasized the concept that some of these lesions require repair rather than debridement[11]. Knesek *et al*[1] classified these tears into 4 distinct types (Figure 1).

Type 1 lesions are characterized by fraying and degeneration of the free edge of the superior labrum with intact biceps anchor; there is no any other concomitant shoulder pathology[12]. In type 2 lesions the labral degeneration is similar to type 1 lesions however there is detachment of the biceps anchor from the superior glenoid tubercle which leads to displacement of the biceps-superior labrum complex into the glenohumeral joint. Type 2 lesions are the most common subtype involving 41% of those shoulders identified in Snyder et al.'s original series[1]. The finding in type 3 lesions is the bucket handle tear of the superior labrum like meniscus in the knee joint. The biceps anchor in type 3 lesions is intact. Type 4 lesions involve the same bucket handle tear of the superior labrum but this tear extends into the biceps tendon root[13].

This classification system later required some modifications. According to Maffet *et al*[5] only 62% of their shoulder series was fitting to the Snyder's classification schema. So they composed a new classification system. As a result they described 6 new subtypes; Type 5 lesions are characterized by a Bankart lesion that extends to the superior labrum and biceps anchor. In type 6 lesions there is an unstable labral flap with biceps tendon separation. If this separation of the biceps tendon-labral complex extends to the middle glenohumeral ligament, the lesion is called type 7[5]. Type 8 tears are same as type 2 tears with a posterior labral extension to the 6 o'clock position[14]. Type 9 lesions are more severe labral tears with circumferential involvement whereas type 10 lesions

involve superior labral tear combined with a posteroinferior labral tear (reverse Bankart lesion)[14].

PATHOPHYSIOLOGY

SLAP tears have been recognized as a common cause of shoulder pain and dysfunction in a specialized patient population namely athletes taking part in overhead activities and heavy duty workers[15,16]. Several potential mechanisms for the pathophysiology of superior labral tears in overhead athletes have been proposed[17]. With the hyperabduction and external rotation during throwing, there is an increase of shear and compressive forces on the glenohumeral joint and strain on the rotator cuff and capsulolabral structures[18]. Kinematic chain is a concept that refers to a combination of successively arranged rigid parts connected by joints. An example is the simple chain. When a force applies to the proximal part of the chain it will transfer to distal part through the joints. In a thrower, large forces and high amounts of energy are transfered from the legs, back and trunk to the arm and hand. The shoulder acts as a funnel and force regulator; and the arm acts as the force delivery mechanism. Uncontrolled throwing with relative imbalance of shoulder muscles, especially during the late cocking phase, may contribute to anterior glenohumeral instability and play a role in the development of SLAP tears[19,20]. Today it is known that glenohumeral external rotation increases by time, but this change might be accompanied by a loss of internal rotation capacity[16]. This internal rotation deficit is caused by contracture of the posteroinferior capsule that initiates the cascade of events ultimately resulting in tendinous and labral lesions[16]. This tight posteroinferior capsule shifts the glenohumeral contact point posterosuperiorly especially during overhead-throwing activitiy. This creates an internal impingement of the articular side of the rotator cuff tendons and posterosuperior labrum between the humerus and the glenoid rim, precipitating a SLAP lesion[1]. This internal impingement was first described by Walch *et al*[21] as an intraarticular impingement of the rotator cuff in the abducted and externally rotated shoulder. With 90 degrees of both abduction and external rotation, the articular surface of the posterosuperior rotator cuff becomes pinched between the labrum and the greater tuberosity.

There is also another causative factor for the superior labral tear called "peel-back" mechanism[13]. The twisting at the base of the biceps transmits torsional forces to the posterosuperior labrum, resulting in peel-back of the labrum[1]. This mechanism usually happens in a position of abduction and maximal external rotation, the rotation produces a twist at the base of the biceps tendon insertion which transmits torsional force to the area[13]. In a throwing shoulder, repeated initiation of this mechanism can lead to failure of the labrum over time with avulsion from the bone[22]. This happens usually during the deceleration phase of the arm[23].

The result of these events is a SLAP tear and possible rotator cuff tear. It should be kept in mind that scapula plays an important role in shoulder kinematics and altered scapular mechanics might also contribute to patient's pain and shoulder dysfunction[19]. When the scapula does not perform its action properly, its malposition decreases normal shoulder function a condition called "scapulothoracic dyskinesis". This condition causes visible alterations in scapular position and motion patterns. It is believed that it occurs as a result of changes in activation of the scapular stabilizing muscles; damage to the long thoracic,dorsal scapular or spinal accessory nerves or possibly reduced pectoralis minor muscle length may be the reason of this condition[24]. Visual findings of this dyskinesis are winging or asymmetry. It is observed during coupled scapulohumeral motions. This pathology should always be kept in mind for most of the shoulder disorders.Treatment of scapular dyskinesis is directed as managing underlying causes and restoring normal scapular muscle activation patterns by kinetic chain-based rehabilitation protocols[25].

PHYSICAL EXAMINATION

The clinical diagnosis of a SLAP lesion is an extremely challenging procedure because there are no unique clinical findings associated with this type of pathology. Also the condition is frequently associated with other shoulder problems such as impingement, rotator cuff tears, degenerative joint disease and other soft tissue-related injuries[14]. Before the physical examination, a proper patient history should be documented. There are often mechanical symptoms like clicking or popping especially during the cocking phase of throwing[1,6]. Concomitant lesions such as impingement, cuff tears or biceps tendinopathy might cause complaints like night pain, weakness and instability[1,5]. Physical examination starts with careful assessment of glenohumeral and scapulothoracic range of motion[1]. As previously mentioned, the external rotation capacity of the shoulder might even increase whereas the internal rotation capacity decreases as seen in overhead throwing athletes. This condition called glenohumeral internal rotation deficit (GIRD), should be measured if present with the patient lying supine on examination table and the shoulder is positioned at 90 degrees abduction with the elbow flexion respectively while the scapula is stabilized to eliminate any scapulothoracic motion. Any side-to-side difference in glenohumeral motion is then assessed by internally and externally rotating the arm[1].

There are numerous physical examination tests described to detect a SLAP injury. They are usually sensitive but not specific[1]. These include Active Compression / O'Briens's Test (Figure 2A), Biceps Load Test Ⅱ (Figure 2B), O'Driscoll's Dynamic Labral Shear Test (Figure 2C), Speed's Test (Figure 2D) and Labral Tension Test[14]. Of these tests, only Biceps Load Test Ⅱ shows utility in identifying patients with a SLAP-only lesion with no other concomitant pathology[26,27], however there are no convincing data either of these clinical tests is superior for accurate detection of a SLAP lesion (Table 1)[1,27,28].

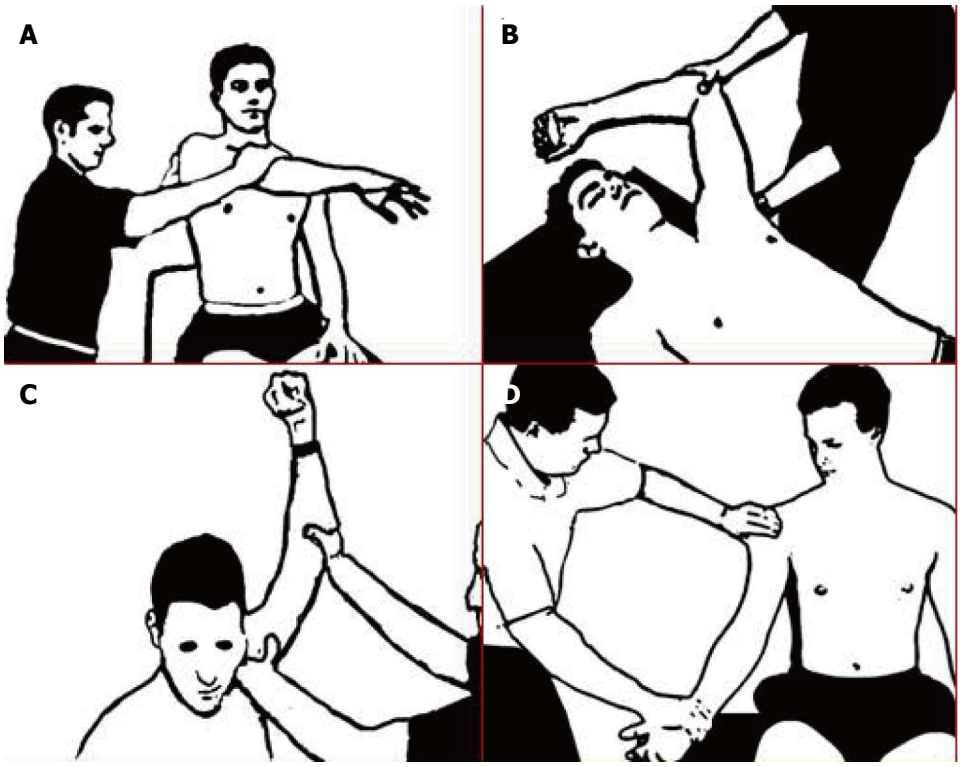

Figure 2 Physical examination tests described to detect a superior labrum anterior to posterior injury. A: O'Briens's test. When the patient sitting with 90° of shoulder flexion and 10° of horizontal adduction, completely internally rotates the shoulder and pronates at the elbow. The physician applies downward force at the wrist or elbow and the patient resist the force. Pain on top of or inside the shoulder is considered a positive test; B: Biceps Load test. The patient supinates the arm, abduct the shoulder to 120 degrees, flex elbow to 90 degrees, externally rotate arm until the patient becomes apprehensive and provide resistance against elbow flexion, pain considered a positive test; C: O'Driscoll's Dynamic Labral Shear test. When the the patient is standing with the arm laterally rotated at 120 degrees abduction, the examiner applies anterior shear force. A positive test is indicated by pain; D: Speed's test. The patient's elbow is extended, forearm supinated and the arm elevated to 90°. The examiner resists shoulder forward flexion. Pain in the bicipital groove is considered a positive test.

Bennett reported a specifity of 14%, sensitivity of 90%, positive predictive value of 83% based on correlations of a positive Speed's test with arthroscopic findings of biceps pathology[28,29].

Another important part of the physical examination is evaluation of scapular kinematics. There might be scapular dyskinesis which is described as altered scapular position and motion relative to the thoracic cage[1,23]. If a periscapular muscle atrophy or scapular winging is noted an associating cervical spine pathology should always be kept in mind[1].

IMAGING

Like any other musculoskeletal disease the painful shoulder evaluation begins with plain radiographs. This includes anteroposterior, outlet and axillary views. SLAP lesions have no specific findings in routine radiographs but coexisting pathologies such as outlet impingement, subluxation of glenohumeral joint and acromioclavicular abnormalities may be detected[1]. Currently MRI, particularly MR artrography (MRA) is the gold standard imaging method to detect SLAP tears[30,31]. Some physicians prefer computed tomography arthrography (CTA) to MRA as it is a cost effective method of imaging for labral pathologies[32]. In some studies the sensitivity and specificity were comparable in both MRA and CTA for labral lesions[32], but many studies showed that the sensitivity and specificity of CTA is lower than of the MRA, so in our opinion choosing CTA rather than MRA is a matter of physicians preference and availability of the imaging technique. As the indications and operative procedures varies in different types of SLAP lesions, pre-operative MR imaging is essential to detect detailed description of lesions. While sensitivity of MRI to detect SLAP tears is about 50%, in several studies sensitivity of MR arthrography is reported near 90%[1,30,31]. MR arthrography is the superior imaging technic and this superiority is because of the fact that the intra-articular injected contrast medium distends the joint capsule, outlines intra-articular structures and leaks into tears[30,31]. It means more clear delineation of the anatomic structures and SLAP lesions from anatomic variations like sublabral recess or sublabral foramen[1]. Sublabral recess or superior sulcus is a normal variant that is present in more than 70% of individuals. In this variation the base of superior labrum is not attached to the superior glenoid and in some cases this recess can be up to 1.4 centimeters deep[28]. MR artrography can also detect spinoglenoid cysts. These cysts may cause entrapment of suprascapular nerve causing shoulder pain, weakness in external rotation and infraspinatus muscle atrophy. Though MRA sensitivity is high, in several studies high

Table 1 Diagnostic accuracy of physical examination tests

Test	Sensitivity	Specificity	PPV/NPV
Biceps load test	55	53	67/41
O'Brien's test	91	14	66/44
Speed's test	48	55	65/38
O'Driscoll's test	89	30	69/60
Labral tension test	28	76	67/39

NPV: Negative predictive value; PPV: Positive predictive value.

incidence of false positive are reported[30,33,34]. SLAP tears are best seen on coronal oblique sequences in the ABER position as the contrast medium fills the gap between glenoid and superior labrum[33]. As mentioned before MR arthrography is the best imaging technic to evaluate the SLAP lesions but because of high incidence of false positive cases a detailed correlation with clinical history and physical examination is the key to diagnosis.

TREATMENT

The first step for the treatment of a suspected superior labral lesion should be a period of conservative treatment[35]. This includes rest, physical therapy and nonsteroidal anti-inflammatory drugs. Physical therapy seems only successful in few patients, mainly in type I SLAP lesions, it is only implemented in patients with this type of lesion or patients who do not wish to undergo surgery. Exercises to improve strength and endurance are not initiated until the pain is resolved[1]. Edwards *et al*[36] showed that successful non-operative treatment of superior labral tears results in pain relief and functional improvement compared with pre-treatment assessments. They found that return to sports was successful but return to overhead throwing sports at the same level was not possible. The goals of rehabilitation should include regaining the scapula and rotator cuff muscles strength and normal range of motion. Proprioception and neuromuscular control should be improved[1]. Besides the rehabilitation, nonsteroidal anti-inflammatory drugs and massage therapy can be used[37]. In case of conservative treatment failure, surgical procedures can be planned according to clinical history, examination and radiological findings for the patients doing sports, particularly overhead throwing athletes[38,39]. Repair, tenodesis, debridement, tenotomy, and observation have been recommended depending on the characteristics of the disease. Zhang et al. searched the database in United States between 2004 to 2009 with 25574 arthroscopic SLAP repairs. They found that there is a significant increase in repair number by time. The highest incidence of repair is in the 20-29 years and 40-49 years of age groups. Also there is a significant gender difference with men having three times higher incidence of repair[40].

Type 1 lesions which represents degenerative fraying without compromise of the labral attachment to the glenoid are treated with debridement only and rarely considered a source of clinical symptoms[12]. Simply arthroscopic shaving without damaging biceps anchor is enough for the surgical treatment of these type of lesions. Among various types of SLAP lesions, type 2 lesions are the most common form seen in clinical practice with visible detachment of the biceps anchor from the supraglenoid tubercle[2,41,42]. With the advancement of arthroscopic techniques, surgical treatment has evolved from isolated arthroscopic debridement to surgical repair of the lesion. These types of lesions can be treated with arthroscopic fixation of the superior labrum to establish biceps anchor stability. The initial studies suggested an extremely high level of success in arthroscopic repairs[35,43]. Morgan *et al*[13] published a retrospective review of 102 patients who underwent arthroscopic repair of type II SLAP tears. They reported 97% good or excellent results. However, the clinical results of elite throwing athletes has shown that this is not, in fact, always the case[44]. In a prospective analysis of type 2 SLAP repairs in 179 patients, Provencher *et al*[3] found clinical and functional improvement in shoulder outcomes. However, a reliable return to the previous activity level is limited with 37% failure rate with a 28% revision rate. The patients older than 36 years were associated with high chance of failure[3]. Because of unsatisfactory results in older patients[3], Boileau *et al*[45] suggested biceps tenodesis in these patients. They found that tenodesis is superior to the repair of type 2 SLAP tears in older population. However in another study by Alpert *et al*[46], it is shown that type 2 SLAP repairs using suture anchors can yield good to excellent results in patients older and younger than age 40. Their findings show no difference between two age groups[46]. So there is a conflict at the literature about the repairs of the older patients.

Type 3 lesions are characterised by bucket-handle tears of superior labrum with intact biceps anchor. Usually, the symptoms are because of the mobile labral fragment. This fragment can easily be debrided by an arthroscopic shaver. There is no need to repair this type of injury[47]. After the resection of the free fragment, a pain free shoulder can be established. There are limited information in the literature about the types other than type 2 lesions.

There are different surgical repair options for SLAP tears. These are nonabsorbable, absorbable and knotless anchors. Metallic anchors have been used over time. However, some complications like articular surface damage, migration, artifact production in postoperative MRI were reported. Then bioabsorbable tacks and anchors were used[48]. Also tacks are used in different types. There are some bad results with persistent pain and disability following the use of polyglycolide lactic (PLLA) tacks[49]. Foreign body reaction, synovitis and chondral damage were also reported[50,51]. The newer versions of absorbable anchors are proven to have equal pull-out strength as metallic anchors, with reported lower complication rates[52,53]. Although there are low complication rates, a recent study by McCarty *et al*[54] reported high complication rates. In revision cases, they found papillary synovitis, chondral damage and giant cell reactions in most of the patients[54].

But, it should be kept in mind that this study was performed on the revision cases. Knotless anchors are another option with shorter operation time and no knot at the joint which may be a cause for irritation. There are good results with knotless anchors that are equal to results of using standard anchors[55]. Biomechanically, knotless anchors' initial fixation strength was found similar to that of simple suture repairs and the repairs restore the anatomy without over constraining the shoulder[56].

Diagnosis of the SLAP tears is based on clinical history, a detailed physical examination and MRI. MR arthrography is the best imaging technic for evaluating SLAP lesions. Arthroscopic SLAP repairs remain the gold standard with increased complication rates[57]. The clinicians should carefully choose the surgical treatment options for older patients and overhead athletes. In the older patients and revision cases, the biceps tenodesis or tenotomy should be kept as another option for treatment. Overhead throwers and young active people with type 2 SLAP tears can benefit from an arthroscopic repair. To date repair with knotless anchor systems seems to be as strong as simple sutures with less irritation in the joint.

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Functional outcomes assessment in shoulder surgery

James D Wylie, James T Beckmann, Erin Granger, Robert Z Tashjian

James D Wylie, James T Beckmann, Erin Granger, Robert Z Tashjian, Department of Orthopaedic Surgery, University of Utah, Salt Lake City, UT 84108, United States
Author contributions: Wylie JD, Beckmann JT, Granger E and Tashjian RZ solely contributed to the concept, writing and editing of this paper.
Correspondence to: Robert Z Tashjian, MD, Department of Orthopaedic Surgery University of Utah, 590 Wakara Way, Salt Lake City, UT 84108,
United States. robert.tashijan@hsc.utah.edu
Telephone: +1-801-5875457 Fax: +1-801-5875411
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Abstract

The effective evaluation and management of orthopaedic conditions including shoulder disorders relies upon understanding the level of disability created by the disease process. Validated outcome measures are critical to the evaluation process. Traditionally, outcome measures have been physician derived objective evaluations including range of motion and radiologic evaluations. However, these measures can marginalize a patient's perception of their disability or outcome. As a result of these limitations, patient self-reported outcomes measures have become popular over the last quarter century and are currently primary tools to evaluate outcomes of treatment. Patient reported outcomes measures can be general health related quality of life measures, health utility measures, region specific health related quality of life measures or condition specific measures. Several patients self-reported outcomes measures have been developed and validated for evaluating patients with shoulder disorders. Computer adaptive testing will likely play an important role in the arsenal of measures used to evaluate shoulder patients in the future. The purpose of this article is to review the general health related quality-of-life measures as well as the joint-specific and condition specific measures utilized in evaluating patients with shoulder conditions. Advances in computer adaptive testing as it relates to assessing dysfunction in shoulder conditions will also be reviewed.

Key words: Shoulder; Functional outcome; Quality-of-life; Health utility measure; Patient reported outcome

Core tip: Health related quality of life evaluation includes general health measures, health utility measures, general shoulder measures and condition specific shoulder measures. A combination of a general/health utility measure with a shoulder measure or condition specific measure is needed to fully capture outcomes in the treatment of shoulder conditions.

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INTRODUCTION

Measuring outcome of orthopedic procedures has changed remarkably over the last twenty to thirty years. Objective physician measurements in large part have given way to subjective patient reported outcome measures[1]. The driving force for this was the inherent bias in the clinician assessment along with how this assessment method marginalized the patient's perception of their outcome[2-4]. Quality of life is the main outcome measure in orthopedics due to the simple fact that most orthopaedic interventions do not increase a patient's life span, so survival is not a realistic outcome measure. A growing body of literature has evolved over the past 30 years regarding measurement of health related quality of life in orthopedic patients, and more specifically patients with

shoulder disorders, both at baseline and after operative or non-operative intervention.

Patient reported health related quality of life (HRQoL) can be measured in multiple ways. Activity level measures reflect the effect of a disease or intervention on a patient' s ability to recreate; these are more commonly used in the evaluation of lower extremity disease because the lower extremity has a more profound effect upon patient activity[5]. However, a shoulder activity level questionnaire has been published but so far used sparingly in the literature[6,7]. General HRQoL measures evaluate the effect of a condition on the patients overall health. These measures may be less responsive to shoulder diseases and their treatment because they are designed to evaluate patients general well being[8]. Health utility measures allow calculation of quality adjusted life years (QALY) and are used to economically evaluate treatments[9]. Shoulder HRQoL measures are designed to either be general shoulder measures or condition specific measures that are validated only for certain diagnoses[10,11]. The more specific the measure, the more change the can be elucidated in treatment of a given shoulder condition, however the more general the measure the better it judges the patient's change in overall health. This article will review the various patient reported measures used to evaluate patients with shoulder disorders and the outcome of their treatment.

GENERAL HRQOL AND HEALTH UTILITY MEASURES

General HRQoL measures are commonly used across medical specialties. This fact underscores their importance in the evaluation of patient outcomes from orthopedic conditions. Including general health measures in the evaluation of shoulder treatment allows the comparison of quality of life improvements from orthopedic intervention to those across other organ systems, and can be used to compare the effect of treatment of shoulder conditions to those of the lower extremities. In the current era of healthcare reform, using general HRQoL and health utility measures to evaluate the effect of shoulder treatment compared to that of other conditions across the body will be important to justify health care dollars for the treatment of shoulder disease[12]. This section will review the most commonly used general HRQoL and health utility measures in orthopaedics.

The medical outcomes study short form-36 (SF-36) was originally described in 1992 and is the most commonly used tool to assess general health-related quality of life[13,14]. The Sickness Impact Profile and the Nottingham Health Profile are other general health related quality of life measures that are less commonly used in the orthopaedic literature but their properties and usefulness in musculoskeletal conditions have been recently reviewed[15]. The SF-36 measures eight dimensions of general health [physical functioning (PF), Role Physical, Bodily Pain, General Health, Vitality, Social Functioning (SF), Role Emotional, and Mental Health] and has two summary scores [physical component score (PCS) and mental -component score (MCS)]. The scales are scored based on general United States population norms with a mean of 50 and a standard deviation of 10, with a score of 50 for each scale representing "average" health. The Short-Form-12 (SF-12) was described shortly thereafter and is a validated brief subset of the SF-36 that provides good approximation of the SF-36 summary scores (PCS and MCS) and only moderate approximation of the eight SF-36 domains[16].

The Short Forms are the most commonly used general health related quality of life measure in orthopedics and medical research at large[8,17]. It has been extensively validated and is responsive to treatment of many disease states. For detailed explanation, extensive references, and information on use of the Short Forms please visit www.sf-36.org. The SF-36 has been used to evaluate patients after a variety of shoulder surgical procedures including rotator cuff repair, anatomic shoulder arthroplasty and reverse total shoulder arthroplasty[18,19]. In general the PCS component of the SF-36 score improves after surgical treatment while the MCS component has little change[19,20]. Rotator cuff tears, glenohumeral arthritis, anterior glenohumeral instability, adhesive capsulitis and impingement have been determined to rank in severity with hypertension, congestive heart failure, acute myocardial infarction, diabetes mellitus and clinical depression as evaluated by the SF-36[21]. Boorman *et al*[22] has found that while anatomic total shoulder arthroplasty does not restore general health status to age adjusted controls it does provide improvement to the same level as seen after coronary artery bypass surgery. Finally, most shoulder outcome instruments do not adequately reflect general health-related quality of life[23,24]. Consequently, inclusion of general health-related quality of life measures in the evaluation of shoulder conditions is recommended not only because shoulder outcome instruments do not adequately capture general health status but also as a tool to compare the outcomes and utility of shoulder diseases and their treatments to other disease processes.

Health utility measures are another option for the measurement of general HRQoL. These measures were developed for use in health economics studies. They judge the patients health status on a scale that includes 1.0 as perfect health and 0.0 as death, however there are conditions that can be negative, as they are considered worse than death from a quality of life standpoint[12,25]. The reason that these are scaled from 0.0 to 1.0 is that this makes calculations for QALY easy for economic analyses and allows comparisons of cost per QALY between different conditions and treatments, for example justifying the cost of rotator cuff repair. Vitale *et al*[26] showed that the cost per improvement in quality of life from rotator cuff repair was the equivalent of total hip arthroplasty, coronary artery bypass, and more cost efficient than the medical treatment of hypertension. Commonly used health utility measures are the EuroQol 5-domain (EQ-5D) and the Short Form 6D (SF-6D), among others, whose properties are beyond the scope of this review but have been

recently reviewed[15]. Of note, the SF-6D can be calculated if either the SF-36 or the SF-12 is administered as a general HRQoL measure. Health utility measures are an important evaluation tool to include in the functional assessment of shoulder problems if the plan is to understand the financial implications of treatment.

SHOULDER HRQOL MEASURES

While general HRQoL measures are an important part of evaluating patients with shoulder disease, they are not responsive enough to evaluate a patient's overall level of dysfunction in isolation[8]. Some patients with improvement in shoulder function show a decrease in their SF-36 scales after treatment, likely due to the deterioration of other conditions affecting their general health at the same time as their improvement in shoulder pain/function[27]. Because of this, tools evaluating the shoulder or specific disease affecting the shoulder need to be used to complement general HRQoL measures. There have been over thirty shoulder questionnaires described in the literature for evaluation of shoulder pathology[5]. These can be broken down into general shoulder measures and condition (disease) specific shoulder measures.

General shoulder measures are recommended for practice-based evaluation of a heterogeneous group of patients undergoing treatment for shoulder conditions. Condition or disease specific shoulder measures are designed to evaluate homogenous groups of patients with a specific diagnosis and are highly recommended for controlled trials evaluating a specific shoulder disorder. In general, condition specific shoulder measures are less commonly utilized in comparison to the general shoulder measures. The shoulder disorder requiring a condition specific measure the greatest is shoulder instability since many patients with symptomatic shoulder instability have a ceiling effect with general shoulder measures[28]. This section will outline the most commonly utilized general shoulder measures (Table 1) as well as condition specific measures for glenohumeral instability and rotator cuff disease (Table 2).

GENERAL SHOULDER MEASURES

The Constant-Murley score

The Constant-Murley score (CMS) was developed in 1986 and published in 1987 to better estimate the overall functional state of normal and diseased shoulders[29]. A higher score indicates better shoulder function. The CMS continues to be the most commonly reported outcome scale in Europe[11]. The scale combines two fundamentally different metrics: physical examination findings of motion and strength (65 points), and patient-reported subjective evaluation of shoulder function (35 points). In the original description of the CMS, there was no rationale reported for the development and selection of items, or the relative weighting of each component: 15% pain, 20% patient-reported function with activities of daily living, 40% range of motion, and 25% strength testing.

Combining performance-based measures with patient-reported outcomes could be considered an advantage of the CMS; however, it is likely that the reliability of the Constant-Murley score is reduced because patient assessment does not necessarily correlate with objective measurements of shoulder function[30-32]. Still, several studies evaluating the surgical treatment of rotator cuff tears and proximal humerus fractures have found satisfactory correlation between the Constant score and other patient-reported measures[33,34].

The reliability of the Constant score has been questioned with a reported variation between observers as high as 10 units (out of a possible 100)[35]. Conboy *et al*[36] found a low interobserver reliability with 3 different observers evaluating 25 patients using the CMS. On average, these observers differed significantly with regards to total score; the 95% confidence interval that a single measurement represented the true score was 17.7 points. These large, unsatisfactory standard errors contrast the high reliability found in the original publication, where only a 3% interobserver error was reported between 3 observers in 100 abnormal shoulders[29]. Measurement error is most likely attributable to wide variations in strength testing methodology, which was inadequately explained in the original description. Constant *et al*[37] published modifications and guidelines for use of the CMS in 2008 to address these concerns.

Potential advantages of the CMS include its widespread use and prolonged existence, allowing for comparisons across procedure and time. Accordingly, population normative values of the CMS have been established, which aid in score interpretation[38]. Recently, minimum clinically important differences (MCIDs) for the CMS have been reported improving the ability to interpret the clinical relevance of the score as well as design studies using the CMS as the primary outcome tool[39]. The heavy weighting on range of motion and strength may be of benefit when assessing rotator cuff repairs and shoulder arthritis, but has been demonstrated to have problematic ceiling affects in instability patients[36,40]. Reliability, validity, and responsiveness of the CMS are detailed in Table 1.

The University of California Los Angeles shoulder score

The University of California Los Angeles (UCLA) shoulder score was developed in 1981 before modern psychometric development was routinely used[41]. Consequently, the methods utilized in its development are not explained, including question development and weighting. The score is a combination of physical exam findings (active forward elevation and strength) and subjective patient-reported measures (pain, satisfaction, and function). Pain and function are preferentially weighted (20 out of 35 possible points). A higher score indicates better function. The UCLA score has been used to assess a variety of shoulder conditions including total shoulder arthroplasty, rotator cuff repair, and subacromial decompression[42,43].

Limitations of the UCLA are inherent in its design. Many of the questions are double-barreled, meaning that multiple inquiries are combined within a single question.

Table 1 General shoulder measures

Measure	Description	Validity	Reliability	Responsiveness	MCID
The constant score[36,39,74,75]	10 items: Physical Examination (4 motion, 1 strength) Subjective evaluation (1 pain, 4 ADL) Score: 0-100 (Higher = better) 65 points for physical examination 35 points for subjective evaluation	Criterion validity with WORC, Penn, SST, Oxford, and others. Weaker correlation with DASH, ASES, SF-36 Content validity - concern over methods for strength testing Construct validity high except for shoulder instability; scores and strength decrease with age for both sexes	Very good ICC for shoulder dysfunction 0.8-0.87 SEM 8.9	Excellent except for Shoulder instability Effect size: Arthroplasty: 2.23- 3.02 Rotator cuff repair: 1.92 Shoulder instability: 0.20	10.4
UCLA shoulder score[27,65,76-78]	5 items Likert pain scale (1) Function (1) Active forward elevation (1) Forward elevation strength (1) Patient satisfaction (yes/no) Score 0-35 10 pts for pain/function, 5 pts each for active foreward elevation, strength, and satisfaction Can be converted to 0-100 pts for comparison	Criterion validity: Correlated sternly with Constant, ASES, and SF-36; fair to good correlation with SST; fair correlation with constant score; very good correlation with WOSI Construct validity: Demonstrated improvement after subacromial decompression; UCLA score had poor and fair correlation to forward motion and the abduction ratio respectively	Not evaluated	Limited Evaluation Effect size: Subacromial decompression 2.73 at 6 mo Proximal humerus fractures-moderate responsiveness	Not established
DASH[75,79]	30 items Physical activities in arm, shoulder, hand (21) symptoms of pain, tingling, weakness (5) Impact on social activities (4) Score: 0-100 (Lower = Better) Must answer 27 questions to be scored 4 optional sport/music/work items	Criterion validity: Correlated with other scores over different regions of the upper extremity and general outcome measures including the SF-36 Construct validity Difference between: working/not able to work; disease and health state; ability to do what they want versus not able	Excellent ICC: 0.77-0.98 SEM: 2.8-5.2	Excellent Effect size (all studies): 0.4-1.4	10 for shoulder complaints 17 for elbow, wrist and hand
SST[49,68,75]	12 yes/no items	Criterion validity: Strong correlation with ASES, moderately correlated with physical function portion of SF-12 Content validity Differences between: Age groups; shoulder instability versus rotator cuff injury; workers compensation status	Excellent ICC: 0.97-0.99 SEM: N/E	Limited Evaluation Effect size 0.8 in shoulder instability and rotator cuff injuries	2 for rotator cuff disease
ASES evaluation form[55,56,75,80]	11 items Pain VAS (1) Function (10) Score: 0-100 (Higher is better) 50 pts pain/50 pts function Physician assessment is not scored	Criterion validity: Strong correlation with constant-Murley, UCLA, and SST; strong correlation with multiple rotator cuff specific scores; and highly correlated with the SF-12 functional domains, but not the emotional, mental health, and social portions. Content validity Differences found between: Gotten much better and slightly better; minimally, moderately, and maximally functionally limited	Excellent ICC: 0.84-0.96 SEM: 6.7	Excellent Effect size (all studies) 0.9-3.5	6.4 for various shoulder pathologies 12-17 for rotator cuff disease
PENN shoulder score[56,58,81-83]	24 items Pain VAS scales with rest, ADLs, strenuous activities (3) Patient satisfaction VAS (1) Functional assessment section (20) Score 0-100 (Higher = Better) Pain 30 pts Satisfaction 10 pts Function 60 pts	Criterion validity: Excellent correlation with constant; excellent to very good correlation with ASES; Content validity: PSS is negatively affected by chest related, but not other medical comorbidities; pain subscale was not responsive to surgical and nonsurgical treatments	Excellent ICC: 0.94 SEM: 8.5	Not rigorously evaluated Effect size of pain subscale 1.84 for all comers	11.4 for patients with shoulder problems undergoing physical therapy 21 for patients with impingement

UCLA: University of California Los Angeles; ASES: American shoulder and elbow surgeons; DASH: Disabilities of the arm, shoulder and hand; SST: Simple shoulder test; PENN: Pennsylvania; MCID: Minimum clinically important difference: SF-36: Short Form 36; SEM: Standard error of measurement; ICC: Intraclass correlation coefficient; VAS: Visual analog scale; ADL: Activity of daily living.

Table 2 Condition specific shoulder measures

Instability	Description	Validity	Reliability	Responsiveness	MCID
WOSI[62,65,84]	21 items: Physical symptoms (10) Sport/recreation/work function (4) Lifestyle function (4) Emotional function (3) Score: 0-2100 (Lower = Better) (can be converted into 0%-100% scale)	Content validity: Items established by experts and patients Criterion validity: Excellent Correlate: VAS Function and DASH, good with CMS and Rowe	Excellent ICC: 0.87-0.98	Excellent Effect size: 1.67 for stabilization	220/2100
OSIS[28,62]	12 Items: Score: 12-60 (Lower = Better)	Criterion validity: Correlated with rowe and constant scores	Excellent PCC: 0.97	Very good Effect size: 0.8	Not reported
MIIS[62,66]	22 items: Pain (4) Instability (5) Function (8) Occupation and sports (5) Score: 0-100 (lower = better)	Criterion validity: Low to moderate correlation with shoulder rating questionnaire. Otherwise untested	Excellent ICC: 0.98	Not reported	Not reported
Rowe score[63,64]	3 items: Stability (50 points) Motion (20 points) Function (30 points) Score: 0-100 (both subjective and examination dependant)	Content Validity: poorly described development and methodology Criterion Validity: Correlated with WOSI and CMS	Fair ICC 0.7	Very good Effect size 1.2	Not reported
Rotator cuff					
WORC[69]	21 items: Physical symptoms (10 items) Sport/recreation/work function (4 items) Lifestyle function (4 items) Emotional function (3 items) Score: 0-2100 (Lower = Better) (can be converted into 0%-100% scale)	Content validity: Items established by experts and patients Criterion validity: Correlated with ASES, DASH and UCLA	Excellent ICC: 0.96	Excellent Effect size: 0.96	245/2100
RCQoL[85]	34 items: Symptoms and physical complaints (16 items) Sport/recreation (4 items) Work related concerns (4 items) Lifestyle issues (5 items) -Social and Emotional Issues (5 items) Score: 0-3400 (Lower = Worse) (can be converted into 0-100 scale)	Content validity: Items established by experts and patients Criterion validity: Correlated with ASES. Construct validity: able to differentiate large and massive tears	Poor ICC: Not reported Reported as average difference of final score = 5%	Excellent Effect size: Not reported SRM: 1.43	Not reported

WOSI: The Western Ontario Shoulder Instability Index; OSIS: The Oxford Shoulder Instability Score; MIIS: The Melbourne Instability Shoulder Scale; WORC: The Western Ontario rotator cuff index; RCQoL: Rotator cuff quality-of-life measure; MCID: Minimum clinically important difference; ICC: Intra-class correlation coefficient; VAS: Visual analog scale; SRM: Standardized response mean.

For example, the pain scale responses address both frequency of pain along with analgesia type. Respondents might have difficulty picking an appropriate response to the question when they endorse only a portion of one selection, but not the entire response. Furthermore, the satisfaction portion of the instrument only allows for the UCLA score to be logically used post-intervention, making responsiveness impossible to determine. Like the Constant score, including both physical exam and patient self-assessment makes the UCLA multi-dimensional, meaning that it combines multiple domains into a single score. The reliability, validity, and responsiveness are poorly established compared to other outcome measures (Table 1).

Disabilities of the arm, shoulder and hand

The disabilities of the arm, shoulder and hand (DASH) was constructed in 1996 *via* a collaborative effort by the Council of musculoskeletal specialty societies, the American Academy of Orthopaedic Surgeons (AAOS), and the Institute for Work and Health[44]. Sophisticated psychometric techniques were used for item generation to help establish face validity. Lower scores are associated with improved function. The 30-question scale assesses multiple domains including physical function, symptoms, and social/psychological function.

The DASH is intended to measure shoulder, elbow, wrist, and hand function in one combined metric. By design, it does not discriminate between the affected and non-affected extremity. These two properties make the scale more generalizable, but could also be considered an inherent weakness. For example, functional items may not reflect a response to treatment if they mostly involve the dominant arm, especially when the non-dominant are was treated. Despite the possible limitation of a more generalized score, Beaton *et al*[45] found good correlation and responsiveness comparing the DASH and joint-specific measures in a combined population of shoulder, wrist, and hand patients; however, some studies have found only fair responsiveness with the DASH, especially regarding hand conditions[46].

The DASH has been widely studied and offers several advantages. It has been validated in over 15 languages, and normative data has been established for American and Norwegian populations[5,47]. These normative values were 5 for both males and females between the ages of 20 and 29. They increased to 22 and 13 in females and males aged 70 to 79, respectively[47]. The MCID has been reported for both shoulder (MCID = 10) as well as elbow, wrist, and hand patients (MCID = 17)[48]. It is also freely distributed through the AAOS website and has been shown to be valid and reliable for many upper extremity conditions (Table 1). Even though the DASH has been rigorously correlated with shoulder-specific measures and has been shown to have sound psychometric properties, it has not been reported frequently in many shoulder-focused studies. Despite its psychometric properties, shoulder surgeons tend to favor more familiar scales such as the CMS, the American shoulder and Elbow surgeons (ASES), and the simple shoulder test (SST) allowing comparisons of outcomes with prior studies.

The SST

SST was developed in 1992 to reduce responder burden and simplify the process of acquiring outcome information. Questions were developed from: (1) neer's evaluation; (2) ASES evaluation; and (3) Patient complaints and inputs. All twelve questions require yes/no responses. Although this basic format simplifies the survey, the limited range of total points could limit the potential of the SST to detect small but clinically significant changes. The MCID for the SST has been found to be 2 points[49].

The SST has overall sound psychometric properties. Known-group validity tests have shown that the SST can detect differences expected to be observed across different age groups, associated with different shoulder pathologies including instability and rotator cuff tears, and between worker's compensation patients and non-worker's compensation patients[50]. The test is responsive; patients with healed rotator cuff repairs score similarly to normal healthy controls with proven intact rotator cuff tendons by ultrasound[51]. The SST has also been able to distinguish between healthy patients and those with shoulder conditions including osteoarthritis, rheumatoid arthritis, rotator cuff tears, adhesive capsulitis, and instability. The validity, reliability, and responsiveness of the SST are not as well developed as other measures, but it appears to be psychometrically sound based on available data (Table 1).

The ASES

The ASES score was created by the Society of the American Shoulder and Elbow Surgeons to facilitate standardization of outcome measures and to promote multicenter trials in shoulder and elbow surgery[52]. The ASES score contains a physician-rated and patient-rated section; however, only the pain visual analog scale (VAS) and 10 functional questions are typically used to tabulate the reported ASES score. The total score - 100 maximum points - is weighted 50% for pain and 50% for function. Calculation of the ASES score is somewhat more arduous that other shoulder outcome measures[53]. The final pain score (maximum 50 points) is calculated by subtracting the VAS from 10 and multiplying by five. For the functional portion, each of 10 separate questions is scored on an ordinal scale from 0-3 for a maximal raw functional score of 30 points. The raw score is multiplied by 5/3 to make the maximal functional score out of 50 possible points. The pain and functional portions are then summed to obtain the final ASES score.

Psychometric properties of the ASES have been well established. The validity, reliability, and responsiveness have been assessed in a variety of shoulder problems including: rotator cuff disease, glenohumeral arthritis, shoulder instability, and shoulder arthroplasty[54,55]. The ASES score has also been shown to be valid, reliable, and responsive to non-operative treatments[56]. Minimal clinically important difference for the ASES ranges from 6.4 for various shoulder disorders to 12-17 points - depending on confidence level - in rotator cuff problems[49,56]. The ASES score has been translated into German and validated, but is not available in as many languages as the DASH. Correlation with other shoulder and upper extremity measures is high for the ASES score (Table 1).

Although the ASES score has been rigorously evaluated, some inherent limitations are noteworthy. Weighting of the ASES score favors the domains of pain and patient-reported function. Unlike the Constant-Murley score, physician assessment is not included in the final score. This could be considered both a strength and weakness of the ASES, but it should be noted in interpreting results. The shoulder instability VAS of the ASES has been removed in some versions, although the scale has still been responsive to instability treatments without this portion of the survey[55]. A final limitation is that higher functioning patients may experience ceiling effects due to the response structure[57].

Pennsylvania shoulder score

The pennsylvania shoulder score (PSS) is a 100-point shoulder specific scale comprised of pain (30%), satisfaction (10%), and function (60%). There are three pain VAS scores: one each for pain at rest, pain with everyday activities, and pain with strenuous activities. Patient satisfaction is determined from 0-10 on numeric rating scale.

The remaining functional portion of the scale is comprised of 20 questions with maximal ordinal responses that are assigned a maximal value of 3 points each.

The psychometric properties of the PSS appear favorable, but this scale has not been rigorously tested in multiple investigations. Leggin *et al*[58] performed the most thorough assessment of the PSS finding overall good reliability, internal consistency, and correlation with the ASES and CMS. The PSS was found to be responsive, and had an MCID of 11.4 in patients that underwent non-operative treatment of various shoulder problems.

The PSS has been used less frequently in the literature compared to other outcome scales discussed in this article. It seems that this outcome measure has been embraced regionally in the United States, with the majority of studies using the Penn shoulder scale originating out of only a handful of institutions. The PSS was used in one study that recommended against augmentation of large and massive rotator cuff tears with porcine xenografts[59]. Proximal humerus fractures, latissimus tendon transfers for irreparable rotator cuff, and non-operative therapies have all been evaluated with the PSS[58,60,61].

CONDITION SPECIFIC SHOULDER MEASURES

Instability

Instability is the most common diagnosis in which condition specific measures are used. The presentation of patients with symptomatic instability is different from other shoulder pathology. After reduction of the acute dislocation, patients with symptomatic instability requiring treatment commonly present with recurrent instability or apprehension, not pain and decreased function as is more common with other shoulder diagnoses. This leads to poor responsiveness and significant ceiling effects when general shoulder measures are used for patients with instability[28]. Because of this, specific instability scores have been developed to study shoulder instability that are more responsive to treatment effects[62]. The most common validated patient reported outcome measures for shoulder instability are the Western Ontario Shoulder Instability Index (WOSI), the Oxford Shoulder Instability Score (OSIS), and the Melbourne Instability Shoulder Scale (MISS). However, the most commonly used evaluation is the Rowe score, which was also the first shoulder score described in 1978. The Rowe score, similar to the UCLA shoulder score, was first described before modern psychometric development was implemented limiting it's psychometric properties[63,64]. The WOSI, MISS and OSIS have been developed with recent psychometric evaluations[28,65,66]. The properties of these scores are described in Table 2. The WOSI is more responsive to treatment of instability than the Rowe score in patients both non-operatively and operatively treated for traumatic instability[65,67]. Overall, the WOSI has the strongest psychometric properties and has undergone the most rigorous testing despite the fact that the Rowe is the most commonly reported instability measure. Based upon the strength of its psychometric properties, the WOSI is the recommended condition specific instrument for shoulder instability.

Rotator cuff

There had also been evaluation tools designed specifically for the evaluation of patients with rotator cuff disease. The two most common rotator cuff specific tools are the Western ontario rotator cuff Index (WORC) and the rotator cuff quality-of-life measure (RCQoL). General shoulder measures are commonly used for patients with rotator cuff disease as well and these have been shown to be valid and responsive in this patient population[55,68]. Because of the utility of other general shoulder instruments the need for specific rotator cuff instruments is called into question. Overall, generalized shoulder instruments do not show the same kind of ceiling effect with rotator cuff disease that they do with instability. Again, the WORC has the strongest psychometric properties and has undergone the most rigorous testing[69]. This makes it the instrument of choice if a condition specific measure for rotator cuff disease is desired. The properties of these two scores are presented in Table 2.

COMPUTER ADAPTIVE TESTING

The National Institutes of Health Roadmap Initiative has recently launched the Patient-Reported Outcomes Measurement Information System (PROMIS) that is available for clinical use for a variety of health domains, including physical function[70]. This novel instrument was developed to: (1) obtain precise estimations of specific health-related domains; (2) eliminate floor and ceiling effects by validating a large "bank" of questions; and (3) reduce patient respondent burden by minimizing the number of questions (typically only 3-5)[71]. PROMIS is made possible using computerized adaptive testing (CAT), which takes each individual's previous answer into account when asking subsequent questions. By asking "intelligent" questions - *i.e.*, it is unnecessary to ask if a patient can comb their hair if they can throw a baseball - precise results can be achieved with only a few questions selected from a large item bank[72]. Therefore, different sets of questions will be administered to different individuals with the results reported on a common scale. This approach differs from classical test theory, where all (or nearly all) questions included in the static survey must be answered to use the metric[44].

The PROMIS Physical Function CAT (PF-CAT) is designed to measure a single domain. This contrasts with commonly used shoulder scales such as the ASES, CMS, DASH, and UCLA that lump multiple domains (pain, physical function, and objective tests) into a single scale. This can be considered both an advantage and disadvantage; however, if desired, CAT tests that measure pain, anxiety, and depression are also available for administration. One concern regarding the PF-CAT is that it includes questions on both the upper and lower extremi-

ties that could limit the responsiveness of the metric. To address this concern, an upper extremity CAT (UE CAT) has been developed and has been shown to correlate strongly with the DASH in non-shoulder upper extremity patients[73]. An upper extremity specific CAT could eliminate small ceiling effects that were found when assessing the PF CAT in some upper extremity patients[72].

In general, the psychometric properties of the PF and UE CAT have not yet been rigorously evaluated. The potential benefits of CAT testing include: reduced time to completion and decreased patient responder-burden; reducing or eliminating floor and ceiling effects; unidimensionality that could clarify interpretation of results; and the ability to add or subtract questions from the item bank without the need to recreate and validate an entirely new scale. It is likely that PROMIS PROs will be reported in studies evaluating shoulder outcomes going forward, and therefore the reader should become aware of this methodology.

CONCLUSION

A variety of outcome assessment tools can be utilized to evaluate patients with shoulder disorders including general HRQoL measures, health utility measures, general shoulder HRQoL measures and, in the setting of instability, condition specific shoulder measures. The SF-36 and SF-12 are the most validated and commonly used general HRQoL measures in the orthopaedic literature. Utilizing one of these also allows for calculation of the SF-5D as a health utility measure for economic analysis. There are multiple general shoulder measures that are acceptable for use as a general shoulder measure including the ASES score, SST and CMS, however in the setting of instability it is recommended to use a condition specific measure due to the ceiling effects of general shoulder measures. The WOSI is the most rigorously tested and validated of the instability measures. Finally, computer adaptive testing and the PROMIS database is emerging as a unique and powerful tool in evaluating both general and joint specific HRQoL that may allow for more efficient evaluation of patient outcomes in the near future.

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Management of femoral neck fractures in the young patient: A critical analysis review

Thierry Pauyo, Justin Drager, Anthony Albers, Edward J Harvey

Thierry Pauyo, Justin Drager, Anthony Albers, Edward J Harvey, Montreal General Hospital, McGill University Health Center, Department of Orthopaedics, Montreal Quebec H3G 1A4, Canada
Author contributions: Pauyo T, Drager J and Albers A designed manuscript, acquired and analyzed literature and drafted manuscript; Pauyo T and Harvey EJ finalized manuscript; Harvey EJ provided substantial input concerning the conception and design and critically revised the manuscript; all authors provided final approval of the article to be published.
Correspondence to: Edward J Harvey, MD, MSc, FRCSC, McGill University Health Center, Department of Orthopaedics, 1650 Cedar Avenue-Room B5.159.5, Montreal Quebec H3G 1A4, Canada. harvey.ej@gmail.com
Telephone: +1-514-9341934 Fax: +1-514-9348283
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Abstract

Femoral neck fractures account for nearly half of all hip fractures with the vast majority occurring in elderly patients after simple falls. Currently there may be sufficient evidence to support the routine use of hip replacement surgery for low demand elderly patients in all but non-displaced and valgus impacted femoral neck fractures. However, for the physiologically young patients, preservation of the natural hip anatomy and mechanics is a priority in management because of their high functional demands. The biomechanical challenges of femoral neck fixation and the vulnerability of the femoral head blood supply lead to a high incidence of non-union and osteonecrosis of the femoral head after internal fixation of displaced femoral neck fractures. Anatomic reduction and stable internal fixation are essentials in achieving the goals of treatment in this young patient population. Furthermore, other management variables such as surgical timing, the role of capsulotomy and the choice of implant for fixation remain controversial. This review will focus both on the demographics and injury profile of the young patient with femoral neck fractures and the current evidence behind the surgical management of these injuries as well as their major secondary complications.

Key words: Osteonecrosis; Femoral neck fracture; Young patient; Capsulotomy; Surgical timing

Core tip: This critical analysis review provides an overview of the pathophysiology of femoral neck fractures in the young adults. Additionally, it offers recommendations to guide the orthopedic surgeon in the management of femoral neck fractures and its most common surgical complications. Few studies have reviewed this controversial subject and provided treatment guidelines.

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INTRODUCTION

Femoral neck fractures account for nearly half of all hip fractures with the vast majority occurring in elderly patients after simple falls[1]. Currently there may be sufficient evidence to support the routine use of hip replacement surgery for low demand elderly patients in all but non-displaced and valgus impacted femoral neck fractures. This is based on a multitude of randomized controlled trials documenting improved short and long-term hip function and lower re-operation rates with hip

arthroplasty as compared to internal fixation in elderly adults[2-5]. Furthermore, early weight bearing protocols post-arthroplasty minimizes complications of prolonged inactivity[6].

For the non-elderly patient with good bone quality, preservation of the natural hip anatomy and mechanics is a priority as their high functional demands and young age preclude their candidacy for replacement procedures[7]. While only 3%-10% of these fractures occur in younger adults, the major differences in physiology, injury characteristics and activity level necessitate a dedicated treatment pathway[8,9]. However, the biomechanical challenges of femoral neck fixation and the vulnerability of the femoral head blood supply lead to a high incidence of non-union and osteonecrosis of the femoral head (ONFH) after internal fixation of displaced femoral neck fractures[10-15]. These complications are highly symptomatic in active patients leading to salvage procedures with significant failure rates.

Undisputedly, anatomic reduction and stable internal fixation are essentials for achieving the goals of treatment in this young population allowing preservation of the femoral head while minimizing rates of non-union and osteonecrosis[16]. Other management variables such as surgical timing, the role of capsulotomy and the choice of implant remain controversial. This review will focus both on the demographics and injury profile of young patients with a femoral neck fractures and the current evidence behind the management of these injuries and their secondary complications.

Consideration of physiological age

The age range describing a young patient is most often between skeletal maturity and the age of fifty[8,9,12-15,17]. More recently, patients up to 65 years have been considered within this definition[6,18,19]. The majority of surgeons prefer to treat young patients (< 60 years) and elderly patients with non-displaced fractures with internal fixation and favor arthroplasty for displaced fractures in patients above 80 years[20]. However, for patients outside these categories, the treatment approach is variable. For the "young-elderly" population, chronologic age becomes less important and establishing a patient's physiologic age becomes the first step in management[21]. Several variables have been used to characterize the physiologic age of a patient; pre-injury activity level, medical co-morbidities and bone quality. In addition to chronological age these variables dictate the goals of management for these two populations and have an impact on the outcomes of surgical treatments. Bone quality influences the success of internal fixation of femoral neck fractures. Cadaveric studies of femoral neck fixation have shown a positive correlation between bone density and achieved fixation stability[22,23]. In a review of over one thousand patients with femoral neck fractures, Parker et al. found the incidence of non-union to be age dependent with a rate of 5.9% in patients younger than 40 years compared to 24.9% for patients in their 70s. In addition to non-union, failure of osteoporotic bone around multiple screw fixation leads to increased screw sliding and shortening of the femoral neck. Femoral neck shortening of more than 5 mm has been correlated with decreased functional outcomes and an increased incidence of requiring walking assistance[24].

Overall, secondary surgical procedures are significantly more common in elderly patients treated with internal fixation compared to those treated with arthroplasty[25]. Although risks of non-union and osteonecrosis are significant in the younger patient, arthroplasty is avoided as first line treatment. Highly active patients have increased failure rates of hip prosthetics and less favorable functional outcomes compared to their elderly counterparts[7,26]. Robinson *et al*[19] developed a scoring system used to categorize patients between the ages of 65-85 years within the two physiological age categories. Five variables were quantified: mobility, patient living conditions, bone quality, cognitive status and medical condition. Patients with a high "physiologic status score" underwent internal fixation and patients with a lower score underwent arthroplasty. Forty two percent of patients had scores in the arthroplasty range. Observed revision rates at 21 mo were 5% for internal fixation group and 2% for the arthroplasty group. Although follow-up observation time was short these rates were significantly lower than those previously published. This work imparts the necessity of appropriate patient selection based on physiological age.

Demographics of the young femoral neck fracture patient

The literature suggests that femoral neck fractures in young adults are most often a result of high-energy trauma such as motor vehicle collisions[14,27]. Patients often present with poly-traumatic injuries such as other fractures or head, chest and abdominal trauma[28]. While this is true for patients with dense bone, more recent work demonstrates femoral neck fractures in chronologically young patients occur from low energy trauma with a higher than expected frequency[13,29,30]. A study conducted by Robinson *et al*[8] examined ninety-five patients with both intra and extra-capsular hip fractures under the age of 50 over a five-year period. They identified two demographics within this population; a male predominant group between the ages of 20 and 40 years who sustained high-energy injuries, and a larger group between the ages of 40 and 50 years who sustained fractures after falls. The majority of patients within the latter group had long standing medical conditions and a high prevalence of alcoholism. This demonstrates that there are two main reasons for femoral neck fractures in chronologically young adults, significant trauma in healthy patients or comparatively low energy trauma in patients with predisposing diseases, alcoholism or early age related bone fragility. A low threshold for referral to specialist services for analysis of bone marrow density and/or treatment of osteoporosis should be observed in young patients with

femoral neck fractures.

Anatomy

Femoral head vascularity is at risk after femoral neck fractures because the vascular supply is intra-capsular. The most common hypotheses of causes for femoral head ischemia after femoral neck fracture are direct disruption or distortion of the intra-capsular arteries during the initial femoral neck fracture, compression secondary to elevated intra-capsular pressure due to fracture hematoma, pre-operative traction and quality of the surgical reduction and its ability to restore blood flow[31-41].

Blood supply to the femoral head comes from three main sources, the medial femoral circumflex artery (MFCA), the lateral femoral circumflex artery (LFCA) and the obturator artery. The majority of the blood supply to the femoral head, more specifically to the vital superior-lateral weight-bearing portion, comes from the lateral epiphyseal artery, a branch of the MFCA. This artery courses up the posterior-superior aspect of the femoral neck where it is prone to damage during femoral neck fracture fragment displacement. The second largest contributor to femoral head blood supply is the LFCA whose ascending branch gives rise to the inferior metaphyseal artery supplying the anterior-inferior aspect of the femoral head. Finally, the smallest and most variable contributor to blood supply in the adult femoral head is *via* the obturator artery which enters the head via the ligamentum teres[42-46].

INITIAL EVALUATION

The mechanism of injury is important. As previously discussed, a large majority of young patients with femoral neck fractures present after high-energy trauma. If a young patient with femoral neck fracture presents after a low-energy trauma or no clear history of trauma, a more in depth history should be carried out. Low-energy fracture can be due to underlying osteoporosis[29,47], stress fracture or pathologic bone. One should inquire specifically about risk factors for osteoporosis, previous pain about the hip both at rest or with activity and constitutional symptoms including fever, weight loss and night sweats.

In a poly-trauma presentation, Advance Trauma Life Support (ATLS) protocol is promptly initiated; fixation of the femoral neck fracture is dealt with following the appropriate treatment algorithm based on priority of the injuries. Nevertheless, in isolated or in poly-trauma situations, the patient needs to be medically optimized prior to surgery and evaluated by an anesthesiologist.

Physical examination findings in patients of all ages with femoral neck fractures are similar. Classically, the affected limb is painful, especially with movement, shortened, flexed and externally rotated. However, the diagnosis of femoral neck fracture in young patients can be more elusive. With a significant proportion of patients presenting after high-energy injuries and often in poly-traumatized patients, these fractures can easily be overlooked[28]. In the presence of a femoral shaft fracture, an ipsilateral femoral neck fracture will occur up to 9% of the time[48]. In this clinical setting, the diagnosis is missed approximately 30% of the time[49,50]. Most of these fractures (between 25% and 60%) are non-displaced at initial presentation[51]. Because of the morbidity associated with osteonecrosis, a high index of suspicion should be entertained when evaluating the poly-traumatized patient. Prompt recognition of femoral neck injuries cannot be underemphasized as timing to surgical intervention may affect outcomes[6].

IMAGING AND CLASSIFICATION

Regardless of the mechanism of injury, antero-posterior (AP) pelvis, AP and lateral plain radiographs of the affected hip and entire femur should be obtained. In addition, traction-internal rotation radiographs may allow for a better interpretation of fracture pattern[52]. Up to 2%-10% of femoral neck fractures may not be clearly visible on standard radiographs and computed tomography (CT) can aid in the diagnosis[53]. In cases of significant trauma where an abdomino-pelvic CT scan is required, it is recommended to extend imaging to the level of the lesser trochanter in order to fully evaluate the femoral neck. This enables identification of occult injuries, especially in the obtunded patient where a reliable physical examination is difficult. Recent studies have found CT scan to be as effective as MRI in detecting these fractures and reducing the chance of a missed injury[54].

Several characteristics identified on imaging have been shown to influence the biomechanical stability of the fracture. First, the verticality of the fracture line in the coronal plane should be assessed. Pauwels first recognized the significance of high angle fractures in the 1930s. He established a descriptive classification scheme that helps determine fracture stability based on the "Pauwels angle". A femoral neck fracture line < 30 degrees from the horizontal plane is Pauwels Type Ⅰ, fractures with an angle between 30 and 50 degrees is Pauwels Type Ⅱ, and an angle of > 50 degrees categorizes a Pauwels Type Ⅲ fracture. Increased verticality of the fracture decreases the load shared through the fracture fragments resulting in a biomechanically unstable pattern, susceptible to the development of mal-unions, non-unions and osteonecrosis[6,52,55-57].

Another well-known and widely used classification system is that of Garden, originally published in 1961[58] (Figure 1). Low inter and intra-rater reliability has led to it being mostly used for femoral neck fractures in the elderly population where the classification can be simplified to non-displaced (Garden Ⅰ or Ⅱ) *vs* displaced (Garden Ⅲ or Ⅳ) in order to dictate appropriate management[59-61]. Secondly, special consideration should also be given to fractures with posterior neck comminution. Several studies have indicated this to be a poor prognostic factor after internal fixation and correlate the comminution with

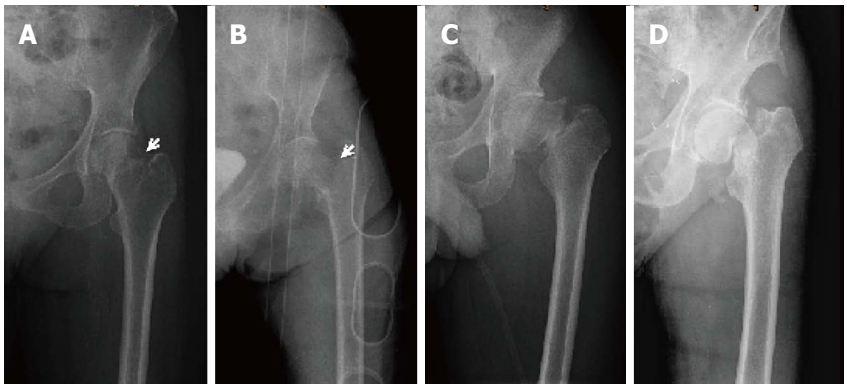

Figure 1 Garden classification. A: Incomplete fracture of the femoral neck with valgus impacon. Note the radiopaque overlap of the femoral neck and head; B: Displaced complete fracture of the femoral neck; C: Less than 50% displacement of a complete fracture of the femoral neck; D: Complete fracture of the femoral neck with complete displacement.

fracture severity and instability[62-64].

PRINCIPLES OF MANAGEMENT

Non-operative treatment of femoral neck fractures in younger patients has a very limited role and is only reserved for the sickest of patients whose surgical risks negate any benefit of fixation. Moreover, operative management is recommended for non-displaced impacted fractures. In a prospective study of three hundred and twelve patients with impacted femoral neck fractures (Garden Ⅰ-Ⅱ), Raaymakers *et al*[65] found that 5% of healthy patient below age 70 had secondary displacement and only 87% of patients in this age group achieved union. Considering the pre-injury activity level of most young patients, surgical management is recommended, as union rates are higher with operative treatment[17,62,66]. Goals of the surgical management of femoral neck fractures in young adult patients are three-fold: (1) Return to pre-injury level of function; (2) Achieve an anatomic reduction of the fracture to preserve the blood supply and effectively prevent ONFH; and (3) Provide a stable fixation while preserving bone stock to achieve union.

PRE-OPERATIVE CONSIDERATIONS

Surgical timing of displaced and non-displaced fracture

The consensus for time to surgery following femoral neck fracture in the young patient is still a matter of debate. Minimally or non-displaced fractures are classically treated on an urgent basis and displaced fractures are managed on an emergent basis with the aim to regain and preserve blood flow to the femoral head. The difficulty with basing this decision on an X-ray finding is that the single time radiographs may not represent ongoing instability or displacement. Studies have shown that early fixation decreases osteonecrosis and increases functional outcome[14,67]. In a retrospective study, Jain *et al*[68] looked at thirty-six young patients with femoral neck fractures. Patients treated within twelve hours of injury had a decreased rate of osteonecrosis as compared to the delayed fixation group. However, there was no difference in functional outcome between the early and delayed fixation group. In contrast, other studies have found no difference in osteonecrosis rates between early and delayed time to fixation[17,69]. Razik *et al*[70] retrospectively analyzed ninety-two patients with femoral neck fractures and found no difference in rates of osteonecrosis when comparing treatment within 6 h post-injury, and delayed treatment 48 h post-injury. They found that the rate of osteonecrosis was related to the type of fixation, which may be indicative of surgeon treatment bias. The conflicting results in the literature are indicative of the wide amount of variance in the studies, which did not uniformly control for cofounding variables such as the quality or the type of reduction and fixation[71]. Given the controversial evidence and considering the impetus to prevent osteonecrosis and improve functional outcome, we recommend treating displaced femoral neck fractures on an urgent basis.

Anesthesia consideration

There is little debate regarding the benefits of intra operative regional anesthesia compared to general anesthesia in young healthy adults; however special circumstances including extreme hypovolemia or coagulopathy associated with poly-trauma, or patient specific factors including respiratory or cardiovascular comorbidities might warrant a particular anesthetic approach. A meta-analysis of randomized controlled trials of hip fractures in all aged group showed a decrease in incidence of deep vein thrombosis and reduction in fatal pulmonary embolism with regional anesthesia[72]. General anesthesia was associated with a reduction in the length of the operation. A lumbar plexus block may be the post-operative modality of choice for analgesia of the hip as it reliably blocks the lateral femoral cutaneous, femoral and obturator nerves[73].

SURGICAL MANAGEMENT

Open vs closed reduction

The decision between attempting an open or closed

approach for fracture reduction is the first step when attempting primary fixation. Most authors agree on performing a closed reduction and internal fixation for management of non-displaced femoral neck fractures (Garden Ⅰ-Ⅱ) given low rates of ONFH and non-union[17,74]. However there is considerable debate between the two strategies for reduction of displaced fractures (Garden Ⅲ-Ⅳ). Obtaining an anatomic reduction is paramount in the young patient as a poorly reduced fracture is a major risk factor for non-union and ONFH[62,75,76]. Some authors argue that closed reduction can achieve anatomic reduction with intra-operative fluoroscopy; they suggest that this approach decreases cost, is less invasive and saves operating time[77]. Care should be taken while performing the close reduction, as multiples attempts are associated with an increased risk of ONFH[34,78]. Others support the need for an open reduction to facilitate direct visualization for anatomic reduction, and with the same token, provide relief of a possible intra-capsular tamponade[66]. Traditionally, there are two different surgical approaches for the internal fixation of femoral neck fractures; the Watson-Jones (antero-lateral) and the Modified Smith-Peterson (anterior)[77,79]. There is no gold standard as to proceed with closed or open reduction for displaced femoral neck fractures in young adults as long as anatomic reduction is achieved.

Closed reduction can be attempted by adequate sedation and relaxation of muscle tone. Leadbetter first described in 1939 the maneuver to reduce of femoral neck fractures[80]. The affected leg is flexed to 45° with slight abduction and then extended with internal rotation while longitudinal traction is applied. The reduction is verified with fluoroscopy in the AP and lateral view of the hip to verify the anatomic reduction. The quality of reduction can be ascertained using Garden's alignment index, which evaluates the angle of the compressive trabeculae as compared to the femoral shaft on both AP and lateral hip radiographs. Anatomic reduction is achieved with an angle of 160° on the AP, and 180° on the lateral view. Varus angulation of less than 160° on the AP view and posterior angulation of more than 5° on the lateral view indicate an unsatisfactory reduction[62,77].

Hematoma decompression

Another topic of controversy in treating femoral neck fractures in young patients is the role of capsulotomy for hematoma decompression. The theoretical goal of capsulotomy is to relieve the tamponading effect of the developed intra-capsular hematoma and subsequently increase blood flow to the femoral head. There is good evidence in the literature correlating hemarthrosis following femoral neck fracture and increased intra-articular joint pressure[36].

In an interventional study, Beck *et al*[81] injected saline into intact intra-capsular space of eleven patients before having surgical dislocations and subsequently measured blood flow to the femoral head with laser Doppler flowmetry. The measurable blood flow to the femoral head disappeared with increased pressure (average 58 mmHg) and the blood flow returned once the saline was re-aspirated. In contrast, in a prospective study involving thirty-four patients with femoral neck fractures, Maruenda *et al*[35] found no correlation between increased intra-capsular pressure and femoral head perfusion. Interestingly they also showed no difference in intra-capsular pressure between non-displaced and displaced fractures. Others have suggested higher pressures are found in non-displaced fractures[34]. Disruption of the hip capsule during facture fragment displacement is thought to be responsible for the decreasing intra-capsular pressures.

Numerous clinical studies have shown a reduction in intra-capsular pressure with capsulotomy and a resulting improvement in femoral head blood flow[33,38-40]. However there are no clinical data documenting improved outcomes with capsulotomy. In their retrospective study of ninety two young patients with femoral fractures, Upadhyay *et al*[62] found no difference in the rate of osteonecrosis with patients treated with open (capsulotomy) or closed reduction (no capsulotomy) and internal fixation. In the above-mentioned study by Maruenda *et al*[35] five out of the six patients that developed osteonecrosis had pre-operative intra-capsular pressures below diastolic pressure. They concluded what many presently think: high-energy trauma and the initial fracture displacement probably play a more significant role than intra-capsular tamponade in the development of osteonecrosis.

Some surgeons perform capsulotomy while proceeding with their open procedures while others opt for fluoroscopic guided hip capsulotomy; this latter technique has been previously found to be safe and effective at decreasing intra-articular pressure[82]. Nevertheless, given the current evidence, we do not recommend the routine use of capsulotomy for femoral neck fractures.

Choice of construct

There are several biomechanical constructs available for the fixation of femoral neck fractures and knowing when and how to position the implant is paramount to attain a stable fixation. Compression screws (CS) and fixed-angle dynamic implants, or a combination of both, promote union during weight bearing by allowing the fracture fragments to slide along the implant while being axially loaded[71]. Fixed-angle and length stable implants, such as blade plates, maintain intraoperative reduction by providing a rigid construct[71]. Currently, hemiarthroplasty or total hip arthroplasty are not used as the primary surgery in young patients. Total hip arthroplasty and valgus osteotomy are used as salvage operations in case of failure of fixation. There is still a debate on the optimal method of fixation for promoting union and preventing ONFH in young patients[70]. This is mainly because most opinions on fixation in this population are extrapolated from studies in elderly osteoporotic patients.

Multiples compressive screws: The use of the multiple compressive screws has been advocated for Garden type

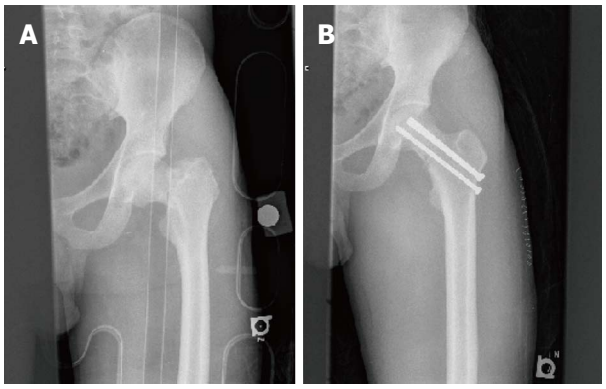

Figure 2 Cannulated screw fixation. A: Anterior posterior view; B: Anterior posterior view with cannulated screw.

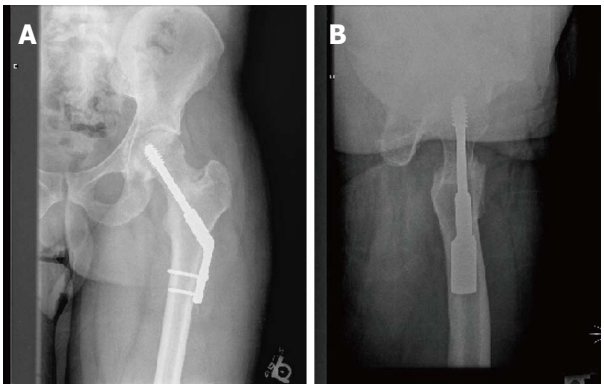

Figure 3 Dynamic hip screw fixation. A: Anterior posterior view with 2 holes 135° dynamic hip screw; B: Lateral view of 2 holes 135° dynamic hip screw.

Ⅰ-Ⅱ in attaining union[83]. In a prospective randomized controlled trial of patients allocated to CS or dynamic hip screw (DHS) with non-displaced or minimally displaced femoral neck fracture, Watson *et al*[84] found no difference in union rate, ONFH or functional outcome between the groups. Numerous studies have looked at biomechanical variations of this construct including the number and placement of the screws or variability in the proprieties of the screws themselves such as the length of the threads[85]. For instance, parallel screws have been shown to be superior construct than convergent screws in maintaining stability reduction[86]. Some authors advocate the use of a fourth screw in cases of fractures with posterior comminution[6]. However, optimal stiffness can be achieved with a three-screw configuration[16]. Three parallel screws placed perpendicular to the fracture line in a inverted triangle with the most inferior screw placed on the medial aspect of the distal femoral neck provides the ideal stability and compression at the fracture site[6] (Figure 2).

Fixed angle implants: The dynamic compressive screw has been advocated as a more stable construct than compressive screws for high shear angle neck fractures (Pauwels type Ⅲ)[86] (Figure 3). Addition of a derotational screw placed in the cranial part of the femoral neck superior to the dynamic hip screw can improve the rotational stability of the construct (Figure 4). In a biomechanical study comparing four commonly used constructs for Pauwels type Ⅲ fractures, Bonnaire *et al*[86] found the DHS with derotational screw to be more load stable than compressive screws, a fixed-angle plate or a simple DHS construct. However, for more stable fracture patterns this screw may be of little benefit. Recently Makki *et al*[87] showed no benefit in union rate or development of ONFH in patients with Garden Ⅰ-Ⅱ femoral neck fractures treated with a DHS alone or with a DHS with a derotational screw[87]. Furthermore, in their retrospective study of ninety-two young patients with femoral neck fractures, Razik *et al*[70] found that DHS alone or DHS supplemented with a derotational screw had significantly less osteonecrosis for Garden Ⅲ-Ⅳ fractures.

In a cadaveric study, Aminian *et al*[88] compared the stability of DHS, CS, dynamic condylar screw and a proximal femoral locking plate (PFLP) for Pauwels type Ⅲ femoral neck fractures. PFLP was the most stable for this fracture pattern, followed by the dynamic condylar screw, the DHS and CS. Currently, no clinical studies directly compare proximal femoral locking plate with DHS and/or DHS with derotational screw. We recommend the treatment of Garden Ⅰ-Ⅱ fracture with CS and Garden Ⅲ-Ⅳ with a DHS and the addition of a derotational screw for Pauwels type Ⅲ fractures.

Replacement arthroplasty: Replacement arthroplasty is not considered a first line treatment in young patients as bone stock should be preserved and the potential complications of replacement arthroplasty avoided. The major early complications are dislocations for total hip arthroplasty and acetabular erosion for hemiarthroplasty[89]. In the elderly patients, short-term follow up has shown better functional outcome for total hip arthroplasty over hemiarthroplasty[90,91]. Studies have shown that internal fixation has higher re-operation rates and that both hemiarthroplasty and internal fixation have comparable functional outcomes[92]. To this date, there are no level- Ⅰ studies comparing arthroplasty to internal fixation in the young adult.

SUBACUTE PRESENTATION AND MANAGEMENT

The term "neglected" femoral neck fracture has been described as a subacute presentation of at least 30 d delay after initial injury[93]. This pathology is more prevalent in developing countries where urgent orthopedic care is not readily available[93]. There is no consensus on the treatment of this pathology and different surgical managements have been described in treating non-union of femoral neck fractures in young adults[94]. Operations such as internal fixation with valgus intertrochanteric osteotomy and internal fixation with vascularized muscle pedicle bone grafting or non-vascularized bone grafting

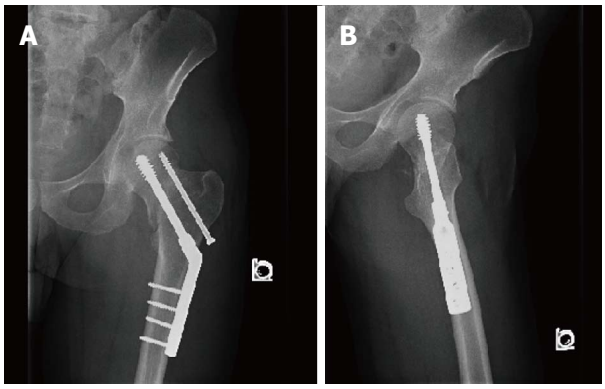

Figure 4 Dynamic hip screw with derotation screw. A: Anterior posterior view pre-operative of 4 holes 145° dynamic hip screw; B: Lateral view pre-operative of 4 holes 145° dynamic hip screw.

are frequently used to achieve union[95]. Valgus osteotomy and free fibular bone graft has had better reported outcomes with osteonecrosis rates ranging from 0-17% and non-union from 0%-15%[93].

POST-OPERATIVE CONSIDERATIONS

The postoperative recommendations are geared to lower the incidence of wound infection, deep vein thrombosis (DVT), and pulmonary embolism as well as to encourage mobilization. An antibiotic regimen with a first generation cephalosporin is indicated for 24 h[96]. The patients should be placed on DVT prophylaxis for thirty days with a pharmacologic agent such as low molecular weight heparin[97]. Physiotherapy should not be delayed and patients should be encouraged to mobilize with no restriction on range of motion of the hip. The patients are usually subject to toe-touch weight bearing with a walker or crutches for 12 wk until the fracture is healed. They are then progressed to full weight bearing as tolerated. The patient should follow-up in 10-14 d post-operatively to assess the wound for infection and to assess the stability of the fixation construct. Follow up visits are indicated at six weeks and three months to assess for clinical and radiologic signs of non-union, osteonecrosis and hardware failure.

COMPLICATIONS

Femoral neck fractures in the young are not known to be associated with a high mortality rate as they are in the elderly population[28]. However, young patients suffer great morbidity from the injury due to high rates of osteonecrosis and tolerable yet significant delays in union. In this section we present a brief overview of these two complications with an emphasis on their management.

Osteonecrosis of the femoral head

Osteonecrosis of the femoral head, previously referred to as avascular necrosis, remains one of the greatest concerns in the young patient with a femoral neck fracture. Despite our increasing understanding of the pathophysiology surrounding post-traumatic osteonecrosis, the incidence has been documented to be as high as 86% in young adults post femoral neck fracture[6]. The development of osteonecrosis has been correlated with multiple factors including age at time of injury (older patients develop less osteonecrosis), the degree of displacement, presence of posterior comminution, verticality of the fracture line, quality of reduction, and implant removal[25,55-58,98]. Osteonecrosis of the femoral head can present anywhere between 6 mo and many years after the initial injury, however, most cases will present within 2 years[99,100]. For this reason, patients should be followed at least for two years post-operatively looking for signs of osteonecrosis, both clinically and radiologically.

Patients will characteristically present complaining of pain localized in the groin, sometimes radiating to the anterior-medial thigh and/or ipsilateral knee. The pain is usually described as deep, throbbing and is exacerbated by weight-bearing activities or at night. There exist many different imaging modalities for diagnosing ONFH however plain radiographs and MRI remain the most useful[101-104]. To date, there is no universally accepted classification. Ficat and Arlet, one of sixteen different systems existing in the literature, is the most commonly quoted[105,106].

Surgical management of osteonecrosis of the femoral head: Treatment of post-traumatic osteonecrosis depends on multiple factors including patient age, stage of disease, level of activity and symptoms. In the majority of cases, once osteonecrosis develops and particularly if it is symptomatic, it will eventually progress to subchondral collapse and secondary osteoarthritis[107]. Once this occurs, the only definitive option remaining is total hip arthroplasty. However, questions remain surrounding the young patient with pre-collapse and early post-collapse ONFH. Multiple joint salvaging techniques have been proposed for patients in whom revision arthroplasty within the patient's lifetime is a foreseeable concern.

Core decompression has been almost exclusively studied in the treatment of idiopathic ONFH. It is the most common method of treatment for pre-collapsed stages of ONFH[108]. It is theorized to work by reducing elevated intra-osseous pressure, improving venous outflow and thereby restoring vascular inflow. Despite early studies showing improvement for all stages of disease, a recent review of four prospective studies with validated outcome scores and a minimum two year follow up showed only minimally improved outcomes[109]. In all four studies, better results were found in pre-collapse and smaller femoral head lesions[110]. Overall, core decompression is a cost-effective choice over observation and its use is recommended as a first line treatment for pre-collapse disease[100].

Various methods of non-vascularized bone grafting have also been used in the treatment of ONFH. Bone grafting has been recommended when there is less than 2 mm of subchondral bone depression, when under 30% of the femoral head is involved and when core decom-

pression fails[111]. It has also been used in conjunction with other methods, such as core decompression. Post-traumatic osteonecrosis tends to create large lesions and decompression alone is thought to be insufficient to completely prevent collapse[100,112-118]. Without good reproducible evidence, evaluation of these techniques in long-term prospective studies is necessary before they can be recommended for routine use.

Vascularized bone grafting using either a local muscle pedicle iliac crest graft or a free vascularized fibular graft have been described for young patients with femoral neck non-union or ONFH. Commonly cited indications from studies of non-traumatic ONFH include no evidence of bony collapse or articular collapse of less than 3-mm in lesions involving less than 50% of the femoral head[119]. The main pitfalls of vascular grafting are donor site morbidity and advanced microvascular surgical techniques[120]. Although less predictable for larger lesions typical of post-traumatic ONFH, when following indications, vascularized bone grafting can be effective if used early and should be considered for improving hip function and delaying disease progression[119-125].

For patients with more advanced ONFH, usually with post-collapse disease, proximal femoral osteotomies have been proposed with the premise of moving the lesion away from the weight bearing zone. There is currently no general consensus on indications for proximal femoral osteotomies with some authors obtaining good results while others observed high failure rates[126-134]. Other concerns surrounding these procedures are poorer outcomes with more challenging subsequent total hip arthroplasty, with increased rates of blood loss, operative time, femoral shaft fracture and component loosening[135,136]. We believe that in the right hands osteotomies can lead to reproducible results however without generalizable results one should proceed cautiously when considering proximal femoral osteotomies for treatment of ONFH.

Non-union

The incidence of non-union after femoral neck fixation has been reported to be between 10% to 33%[137]. Initial fracture displacement, quality of reduction and increasing patient age correlate with a higher risk of non-union[16,138-140]. A recent study evaluating the survivorship of the hip in patients younger than 50 years after femoral neck fractures, reported that 8% of patients were diagnosed with non-union and 23% with evidence of osteonecrosis[17]. Moreover in this series, patients with anatomic reductions had only a 4% rate of aseptic nonunion.

In comparison to osteonecrosis of the femoral head, patients with non-unions present with symptoms earlier, often several months after internal fixation. Most commonly patients describe a history of persistent pain, typically localized to the groin and over the anterolateral aspect of the injured leg, aggravated by weight-bearing[141]. Three to six months should have elapsed before a nonunion may be diagnosed but evidence of failure of fixation can allow the diagnosis to be made sooner[141]. Plain radiographs may demonstrate a lucent fracture zone, osteopenia or bone loss, or signs of instability of the implant such as changes in screw position or backing out of the screws. When plain radiography is equivocal, computed tomography can help determine whether bony union has occurred[140].

Once non-union has been diagnosed, several factors will decide whether salvage of the femoral head is a viable revision option, including the patient's physiological age, femoral head viability, the amount of femoral neck resorption, and the duration of the nonunion[140]. Four options are available for treatment: fixation with new hardware, angulation osteotomy, prosthetic replacement and arthrodesis. In the physiologically young patient, salvage of the femoral head and preservation of the hip joint is preferable. This can be achieved by either improving the mechanical environment to favor healing with valgus-producing osteotomies or by improving the biologic milieu at the non-union site with bone graft[140].

In young patients femoral neck non-union is thought to be more often a result of mechanical factors over biological ones. Varus displacement of the femoral head leads impaired blood supply to the fracture and femoral head resulting in non-union and avascular necrosis[142]. Two features commonly seen in young patients have been identified as predicting higher incidences of fixation failure and non-union; posterior wall comminution and high shear angled fractures (Pauwels Type Ⅲ)[62,143-147]. With a vertical fracture line, the calcar does not offer enough support to prevent the femoral head from shearing and displacing into varus[74]. It is unclear whether posterior comminution indicates a more extensive soft tissue and vascular injury or whether this pattern compromises stability after fixation[141].

Valgus osteotomy reorients the fracture so that its plane is nearly perpendicular to the force across the hip joint. This converts the shearing forces parallel to the nonunion to compressive forces to stabilize the non-union and promote healing. This procedure also restores femoral length improving the abductor mechanics by restoring the abductor moment arm[140]. As much as 2 cm of length can be gained in some instances[148]. Rotational and angular deformities can also be corrected at the same time. The disadvantage of this osteotomy as a salvage procedure is that the valgus orientation of the proximal femur increases contact pressures on the femoral head potentially leading to degenerative disease or progression of osteonecrosis. Although there are no concrete contraindications for this procedure, Varghese *et al*[149] have demonstrated that a decreased preoperative femoral neck bone stock was a risk factor for non-union after valgus osteotomy.

Several published series reporting on the outcomes of valgus-producing proximal femoral osteotomies for the treatment of femoral non-union have demonstrated positive results. Marti *et al*[150] reported a union rate of 86% after osteotomy in 50 patients with femoral neck non-unions with a average time to union of 4 mo. Mean

postoperative Harris Hip Score was 91 points in reviewed patients. Although 22 patients had radiographic evidence of osteonecrosis at the time of osteotomy only three of these patients showed progressive collapse of the femoral head that eventually required hip replacement surgery. Four other patients required replacement surgery for persistent non-union or hardware failure. Ballmer *et al*[151] reported on a series of 17 patients treated with valgus osteotomies with a total union rate of 88%. Three patients required revision fixation but eventually healed. Three patients had progressive osteonecrosis and required hip arthroplasty. Excellent functional results were reported in 11 of the 17 patients. Some authors have recently advocated sliding hip screws for the same purpose based on favorable outcomes and technical ease associated with this implant[152,153]. We recommend the use of valgus intertrochanteric osteotomy for the treatment of aseptic non-union after femoral neck fracture fixation.

Autogenous bone grafting is used in an attempt to improve the biologic milieu at the nonunion site. This can be done using non-vascularized, free vascularized or muscle pedicle-type grafts[154-157]. Rarely are bone grafting procedures undertaken for isolated femoral non-unions, but are indicated more so when concomitant ONFH is present. There are no clear indications for the use of grafting techniques for femoral neck non-union, however these procedures should be considered when there is considerable loss of bone stock or non-unions are present in well-aligned fractures with low shear angles.

RECOMMENDATIONS

The role of conservative management in young patients with femoral neck fracture is limited to patients who are medically unfit; we recommend treating displaced femoral neck fracture on an urgent basis; we do not recommend the routine use of capsulotomy for femoral neck fractures given the lack of evidence to support the development of osteonecrosis from intracapsular hematoma; we recommend the treatment of Garden Ⅰ-Ⅱ fracture with compressive screws and Garden Ⅲ-Ⅳ with a dynamic hip screw and the addition of a derotational screw for Pauwels type Ⅲ; we recommend core decompression for pre-collapse osteonecrosis of the femoral head; we recommend the use of valgus intertrochanteric osteotomy with or without bone grafting for the treatment of aseptic non-union after femoral neck fracture fixation.

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Dual mobility cups in total hip arthroplasty

Ivan De Martino, Georgios Konstantinos Triantafyllopoulos, Peter Keyes Sculco, Thomas Peter Sculco

Ivan De Martino, Georgios Konstantinos Triantafyllopoulos, Peter Keyes Sculco, Thomas Peter Sculco, Department of Orthopaedic Surgery, Division of Adult Reconstruction and Joint Replacement, Hospital for Special Surgery, New York, NY 10021, United States

Author contributions: De Martino I, Triantafyllopoulos GK and Sculco PK performed the literature review and drafted the article; Sculco TP revised the article critically for important intellectual content; De Martino I, Triantafyllopoulos GK, Sculco PK and Sculco TP finally approved for print.

Correspondence to: Thomas Peter Sculco, MD, Department of Orthopedic Surgery, Division of Adult Reconstruction and Joint Replacement, Hospital for Special Surgery, 535 East 70th Street, New York, NY 10021, United States. sculcot@hss.edu
Telephone: +1-212-6061475 Fax: +1-212-7349572
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Abstract

Total hip arthroplasty (THA) is considered one of the most successful surgical procedures in orthopaedics. With the increase in the number of THAs performed in the world in the next decades, reducing or preventing medical and mechanical complications such as post-operative THA instability will be of paramount importance, particularly in an emerging health care environment based on quality control and patient outcome. Dual mobility acetabular component (also known as unconstrained tripolar implant) was introduced in France at the end of the 1970s as an alternative to standard sockets, to reduce the risk of THA dislocation in patients undergoing primary THA in France. Dual mobility cups have recently gained wider attention in the United States as an alternative option in the prevention and treatment of instability in both primary and revision THA and offer the benefit of increased stability without compromising clinical outcomes and implant longevity. In this article, we review the use of dual mobility cup in total hip arthroplasty in terms of its history, biomechanics, outcomes and complications based on more than 20 years of medical literature.

Key words: Dual mobility; Total hip arthroplasty; Dislocation; Revision total hip arthroplasty; Instability

Core tip: Instability remains a significant issue after both primary and revision total hip arthroplasty. Dual mobility or tripolar unconstrained acetabular components can provide a viable alternative in preventing and treating instability. Reported outcomes of several European studies using dual mobility cups with mid- to long-term follow up support their effectiveness. Concerns such as intra-prosthetic dislocation and accelerated wear have been emphasized, although they seem to be less significant in older, low-demand patients. The use of dual mobility cups in younger patients should be viewed with caution based on a lack of current data concerning this high demand patient population.

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INTRODUCTION

Total hip arthroplasty (THA) is considered one of the most successful surgical procedures providing pain relief and improvement of function in patients with end-stage hip arthritis that is non-responsive to non-operative treatments[1,2]. As health care continues to improve and life expectancy increases, the demand for total joint replacement will grow to reflect this more active, aging population. The number of THAs performed in the United States is projected to reach 572000 by 2030, an increase of 174% compared to 2005[3].

Reducing or preventing medical and mechanical complications such as post-operative THA instability will be of paramount importance, particularly in an emerging health care environment based on quality control and patient outcome. The incidence of instability after THA in the primary and revision setting has been reported as high as 7% and 25% respectively[4]. Risk factors for instability after THA are multifactorial and may be patient-specific (gender, age, abductor deficiency) or related to operative variables (surgical approach, component malposition, femoral head diameter)[5]. Instability after THA remains one of the major causes of readmission and revision surgery accounting for 32.4% of THA readmissions and 22.5% of all THA revisions in the United States[6,7]. Readmission and revision surgery carry considerable economic cost as the surgical treatment of a dislocating THA can raise cost 148%[8]. Modifications in surgical technique (*e.g.*, anterior surgical approach, repair of posterior soft-tissues, increased offset and restoration of abductor tension) and the incorporation of larger femoral heads with greater inherent stability decrease the risk of instability after THA. Conversion to a bipolar arthroplasty and a constrained liner are salvage procedures for recurrent instability that provide stability but reduce functional outcome and implant longevity. Dual mobility acetabular components (also known as unconstrained tripolar implants) have recently gained wider attention in the United States as an alternative option in the prevention and treatment of instability in both primary and revision THA and offer the benefit of increased stability without compromising clinical outcomes and implant longevity.

HISTORY OF AND EVOLUTION OF DUAL MOBILITY CUPS

The dual articulation cup was developed by Professor Gilles Bousquet and André Rambert (engineer) in 1974 and combined the "low friction" principle of THA popularized by Charnley[9] with the McKee-Farrar concept of using a larger diameter femoral head to enhance implant stability[10]. The goal of the dual articulation was to achieve the greatest possible range of motion in a stable environment in addition to reducing wear. The original design (Novae-1®, Serf, Décines, France) incorporated a 22.2 mm metallic head articulating with a polyethylene liner, which in turn articulated with the acetabular shell. The shell was manufactured from stainless steel, coated with a porous plasma sprayed alumina (AL_2O_3) and had a cylindrical/spherical configuration. A three-point fixation system consisted of two Morse taper pegs, for impaction into the ischiopubic ramus and the ischium, and a bicortical iliac screw designed to enhance press-fit cup fixation. The liner was made from ultra-high molecular weight polyethylene (UHMWPE), gamma sterilized in air.

Modifications and improvements were made to the mechanics, metallurgy, and materials of the original design: titanium and hydroxyapatite replaced alumina coating[11], flanges and modular shells were added for screw fixation[12], highly cross-linked UHMWPE enriched with vitamin-E improved wear[13], larger femoral heads added stability[14], and anatomic designs decreased anterior overhang[15]. Advances in polyethylene manufacturing and sterilization decreased risk of catastrophic volumetric wear and allowed for the use of larger femoral heads and the use of a 10/12 Morse taper and a highly polished neck reduced liner impingement[16]. While the dual mobility was intended for primary and revision THA with minimal bone loss, cemented designs with concomitant impaction grafting were introduced for cases with more significant bone loss[17].

Dual mobility cups have been in clinical use for many years in Europe, but did not receive U.S. Food and Drug Administration approval until 2009. The designs currently available include the POLARCUP® (Smith and Nephew Orthopaedics AG, Rotkreuz, Switzerland), Anatomic Dual Mobility (ADM®) (Stryker, Mahwah, NJ), Active Articulation E1® (Biomet, Warsaw, IN) (Stick/K-Arm) and uncemented variations (SunFit TH, Coptos TH, Evolution TH) of the original Novae® cup (Serf, Décines, France). The POLARCUP® offers both cemented and press-fit options with the use of pegs and screws. The shell consists of a plasma sprayed titanium fixation surface and a stainless steel bearing surface. The Anatomic Dual Mobility (ADM®) (Stryker, Mahwah, NJ) also includes a titanium plasma sprayed fixation surface, but has a cobalt-chrome bearing surface and features an anatomic design with a recess in the shell to accommodate the iliopsoas tendon and reduce impingement symptoms. The Active Articulation E1® (Biomet, Warsaw, IN) integrates a vitamin-E impregnated polyethylene with a cobalt-chrome bearing surface. Again, fixation is promoted through osseointegration with a plasma sprayed titanium surface. The Modular Dual Mobility X3® (MDM®) (Stryker, Mahwah, NJ) uses a shell with screw holes for additional fixation and a modular highly polished cobalt-chrome liner which articulates with polyethylene. The MDM offers the advantage of screw fixation and the use of a standard shell which is available in hospital inventories and can be implanted with familiar instrumentation. The MDM acetabular shell can be converted to a dual mobility component by placing the metallic insert[18].

BIOMECHANICS

The dual mobility component increases hip range of motion (ROM) until impingement occurs through its two articulations design. In the first articulation the head is "engaged" but mobile within the polyethylene (PE) liner and follows the typical mechanical behavior of a hard-on-soft bearing in a standard THA. However, if the femoral neck and the rim of the PE liner come into contact, a second articulation begins to function and consists of the back of the PE liner and the metallic acetabular shell. As the PE liner articulates, effective ROM is increased until impingement of the femoral neck against the rim of the shell ultimately occurs (Figure 1). In this way, the head-

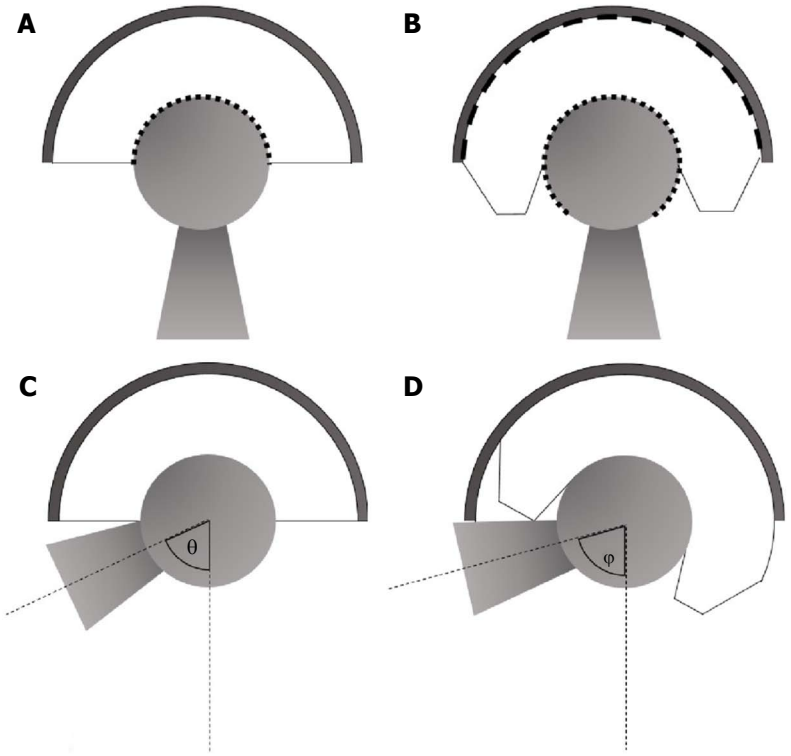

Figure 1 Standard cup *vs* dual mobility cup. Standard metal-on-polyethylene implants (A) include one articulation between the femoral head and the acetabular liner (dashed line). A dual mobility cup (B) consists of two distinct articulations, one between the femoral head and the liner, and another one between the liner and the shell. This configuration allows for greater range of motion before impingement of the femoral neck occurs (C and D, angle φ > angle θ).

liner complex theoretically functions as a large femoral head, increasing the head-neck ratio and subsequently the jump distance before dislocation. In an experimental setting, dual mobility cups with 22.2 mm and 28 mm femoral heads demonstrated significantly greater ROM compared to conventional implants with similar head sizes[19]. While there was no statistically significant difference between the two dual mobility head sizes and ROM, a larger head increases the range of motion before impingement of the neck against the PE liner, theoretically reducing the risk of intraprosthetic dislocation (IPD)[16].

OUTCOMES

Dual mobility in primary THA

Several studies on DM cups in primary THA have reported a low rate of postoperative implant instability[19-22]. Farizon[23], Philippot[12], Lautridou[24], Vielpau[21] and Boyer[25] reported their experience on the use of first generation Bousquet cups (Novae®, Serf, Décines, France) with a 22.2 mm metal head and conventional PE. At 15 years follow-up, survivorship ranged from 81.4% to 96.3% with a dislocation rate (with large articulation) between 0% and 1%. However, these authors did not include the dislocation rate of the femoral head and the mobile PE bearing (the small articulation) that ranged from 0% to 5.2%. Causes of cup failure included aseptic loosening (1.8%-3.4%), excessive PE wear (1%-2%) and acetabular screw fracture (1%). Guyen[19], Leclercq[20] and Vielpeau[21] published series of 167, 200, and 231 primary THA patients using current DM designs with a follow-up time period of 3 to 6 years and reported a 0% dislocation rate.

Dual mobility in revision THA

Dislocation rate after revision THA ranges from 5% to 30%[26-29]. Many factors have been implicated in postoperative instability including muscular insufficiency, aggressive capsulectomy, bone loss and implant positioning problems[30]. Leiber-Wackenheim[14], Hamadouche[31], Langlais[17] and Guyen[16] reported their results on the use of DM cups in patients revised for instability after primary THA. Survivorship of the cups at a mean follow-up period of 5 years was between 94.5% and 98% with a dislocation rate of 1.1% to 5.5%. These studies suggest DM cups are a reliable treatment option for patients revised for instability after primary THA.

Dual mobility in femoral neck fractures

Femoral neck fractures (FNF) treated with osteosynthesis have an increased risk of reoperation when compared to hip arthroplasty[32]. Although THA showed better functional results than osteosynthesis in FNF treatments[33], prosthetic dislocation remains a serious problem. In a recent meta-analysis by Iorio *et al*[34] the mean dislocation rate was 10.7% in patients with FNF treated with THA, five times higher than THA for osteoarthritis. Adam *et al*[35] reported 3 dislocations (1.4%) at 9 mo follow-up in a series of 214 patients with FNF treated with DM implants. Tarasevicius *et al*[36] compared dislocation rates of DM cups with that of conventional cups in patients with FNF treated with THA through a posterior approach. At 1 year follow-up, there were 8 dislocations (14.3%) in the conventional THA group and no dislocations in DM group. DM cups may also be considered as an option to prevent postoperative dislocation when treating FNFs in

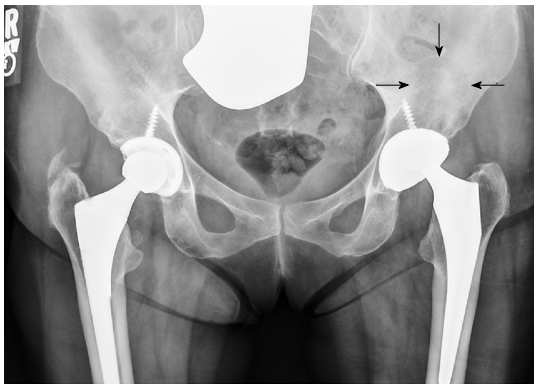

Figure 2 Bubble sign. AP pelvis radiograph of a patient with acute onset of left hip pain and limp. On the left, eccentric position of the femoral head within the dual mobility cup can be noted. Careful scrutiny reveals a circular radiolucent area superior to the acetabular component (arrows), which represents the dislocated polyethylene liner ("bubble sign").

elderly patients who are candidates for THA.

Dual mobility in tumor resection

THA after tumor resection has also been associated with a high risk of dislocation due to bone loss and soft tissue compromise. Philippeau *et al*[37] retrospectively analysed 71 patients with bony lesions of the hip treated with a THA and DM cups. They reported 7 postoperative dislocations (9.8%). Dislocation rate was lower when abductors were preserved (3.5%) and higher when abductors were sectioned/reattached (9.5%) and when the gluteus medius muscle or nerve were resected (18%). They also reported acetabular loosening in 4 cases (5.6%).

Dual mobility in spastic disorders

Several studies on THAs in patients with cerebral palsy (CP) showed good results on pain relief and function outcome; however the dislocation rate in this challenging patient group is reported to be as high as 14%[38-43]. Sanders *et al*[44] reported on 10 hips (8 patients) with CP treated[41-43,45] with THA and a DM cup and had no dislocations after a mean follow-up of 39 mo.

Indications and contraindications

The original goal of the DM cup, introduced at the end of the 1970s as an alternative to standard sockets, was to reduce the risk of THA dislocation in patients undergoing primary THA. Currently, DM cups are a well-accepted treatment option for any patient at an elevated risk for instability after primary or revision THA and in the treatment of recurrent dislocation[12,14,16,17,20,23-25,30,31,46-48]. Patients at higher risk of dislocation include patients with neuromuscular diseases, cognitive dysfunction, an American Society of Anesthesiologists score of 3 or more, and all patients older than 75 years with a history of prior hip surgery[28,49-53]. In addition, the use of DM cups is indicated in revision THA for any cause[17,30], primary THA after femoral neck fracture[35,36], and primary THA after tumor resection[37]. While several studies demonstrate a reduction in the dislocation rate in patients over 60 years, limited data is currently available on active patients younger than 50 years old and care should be taken when using DM cups in a population more prone to develop wear and osteolysis[20,21,24,48,54].

Special considerations and complications

Dual mobility acetabular components are associated with some specific complications secondary to its dual articulating design. For example, intra-prosthetic dislocation or retentive failure is a complication observed exclusively with this type of implant and involves failure of the articulation between the femoral head and the PE liner. The proposed mechanism for dissociation is a result of wear of the PE liner's retentive chamfer[25]. After dissociation, the head articulates directly with the metallic bearing surface of the acetabular shell, producing acute limb shortening and limp. Furthermore, as the shell is not designed for a metal-on-metal articulation, friction between its bearing surface and the femoral head results in rapid wear, metal ion release and surrounding soft-tissue metallosis[55]. In plain X-rays, the asymmetric position of the femoral head within the cup can be visualized which may be mistakenly attributed to "polyethylene wear". However, the characteristic "bubble sign" which corresponds to the dislocated liner is pathognomonic of retentive failure (Figure 2). Management is dependent on the time interval from dislocation to diagnosis. If IPD is diagnosed early, before significant wear of the femoral head and acetabular shell occurs, it can be treated with simple liner exchange. In cases of late diagnosis, revision of the acetabular component, as well as femoral head exchange may be necessary due to femoral head and acetabular shell damage. Boyer *et al*[25] in a series of 240 hips followed for 9 years and 11 months reported a 4.1% incidence of IPD. A similar incidence (4%) was reported by Philippot *et al*[15] among 1960 primary THAs with a mean follow-up of 14 years. The authors recognized three distinct types of IPD: type 1, which was typically due to liner wear; type 2, which was related with arthrofibrosis blocking the liner; and type 3, which was associated with cup loosening. When comparing the two stems with different neck diameters and incidence of retentive failure, no statistically significant difference was observed. The authors note that the narrower neck was unpolished titanium (which is rougher than stainless steel used in the larger neck diameter stem) and could have counteracted the positive effects of the smaller neck size. In their series of 231 primary THAs where a second generation dual mobility cup was used, Vielpeau *et al*[21] reported 0% retentive failure rate at 5.2 years. In 437 hips using the original Bousquet implant design, intra-prosthetic dislocation after a mean of 16.2 years was observed in 3 hips. The authors attributed the low incidence of intra-prosthetic dislocation to the smooth, polished, and narrow femoral neck. In other studies with mid- to long-term follow-up, the incidence of retentive failure ranges from 0% to 5.2%[12,14,19,20,47,48,56]. Table 1 summarizes reported retentive failure rates in the literature.

The configuration of the dual mobility cup with its

Table 1 Main published results of dual mobility cups in total hip arthroplasty

Ref.	N. of hips	Indication	Mean FU	Implant design (cup)	Head size (mm)	Intraprosthetic dislocation (%)	Dislocation rate (%)
Boyer *et al*[25], 2012	240	Primary THA	22 yr	Novae®[1]	22.2	4.1	0
Farizon *et al*[23], 1998	135	Primary THA	12 yr	Novae®[1]	22.2	2	0
Lautridou *et al*[24], 2008	437	Primary THA	16.5 yr	Novae-1®[1]	22.2	0.7	1.1
Philippot *et al*[47], 2006	106	Primary THA	10 yr	Novae-1®[1]	22.2	1.9	0
Philippot *et al*[12], 2009	384	Primary THA	15.3 yr	Novae-1®[1]	22.2	3.6	0
Philippot *et al*[48], 2008	438	Primary THA	17 yr	Novae-1®[1]	22.2	5.2	0
Guyen *et al*[19], 2007	167	Primary THA	3 yr	Saturne®[2]	n/a	0	0
Leclercq *et al*[20], 2008	200	Primary THA	6 yr	Evora®[3]	22.2 (n = 175) 26 (n = 18) 28 (n = 7)	0	0
Hamadouche *et al*[56], 2012	168	Primary THA	6 yr	Tregor®[4]	22.2	2.4	0
Vielpeau *et al*[21], 2011	437 (Group A) 231 (Group B)	Primary THA	16.5 yr 5.2 yr	Original Bousquet Novae-E®[1]	22.2	0.7 0	0 0
Bouchet *et al*[54], 2011	105	Primary THA	2.3 yr	Novae®[1], Statfit®[5], Avantage®[6], Gyros®[7]	28	n/a	0
Bauchu *et al*[60], 2008	150	Primary THA	6.2 yr	Polarcup®[8] 3rd gen	n/a	0	0
Combes *et al*[22], 2013	2480	Primary THA	7 yr	Novae®[1], Avantage®[6], Collegia®[9], EOL®[10], Gyros®[7], Tregor®[4], Polarcup®[8], Saturne®[2], Evora®[3]	28 (n = 1484) 22 (n = 956)	0.1 0.6	0.7 0.5
Tarasevicius *et al*[36], 2010	42	Neck Fractures	1 yr	Avantage®[6]	28	n/a	0
Adam *et al*[35], 2012	214	Neck Fractures	3-9 mo	Saturne®[2]	28 (n = 182) 22.2 (n = 32)	0	1.4
Sanders *et al*[44], 2013	10	Spastic disorders	3.2 yr	Avantage®[6]	n/a	0	0
Philippeau *et al*[37], 2010	71	Tumor resection	3.3 yr	Avantage®[6], Saturn®[2], Novae®[1], other	n/a	n/a	9.8
Langlais *et al*[17], 2008	85	Revision THA	3.2 yr	Tregor®[4]	22	n/a	1.1
Leiber-Wackenheim *et al*[14], 2011	59	Revision THA	8 yr	Novae-1®[1] Novae-E®[1]	28	0	1.7
Hamadouche *et al*[31], 2010	51	Revision THA	4.3 yr	Tregor®[4]	22.2	2	2
Guyen *et al*[16], 2009	54	Revision THA	3.9 yr	Saturne®[2]	n/a	3.7	1.8
Hailer *et al*[61], 2012	228	Revision THA	2 yr	Avantage®[6]	n/a	n/a	2
Philippot *et al*[30], 2009	163	Revision THA	5 yr	Novae®[1]	22.2	0	3.7

[1]Serf, Décines, France; [2]Amplitude, Valence, France; [3]Science et Médecine, Créteil, France; [4]Aston, St Etienne, France; [5]Zimmer, Etupes, France; [6]Biomet, Valence, France; [7]DePuy, St Priest, France; [8]Smith and Nephew Orthopaedics AG, Rotkreuz, Switzerland; [9]Cremascoli-Wright, Paris, France; [10]Norton-Ceramconcept, Paris, France. n/a: Not available.

two articulations and thinner liner has raised concern for accelerated PE wear and associated osteolysis. In a retrieval study of liners removed after revision surgery for infection or aseptic loosening, no difference in total volumetric polyethylene wear was noted between tripolar unconstrained cups and conventional cups with 22.2 mm heads[57]. However, greater wear was noted at the convex bearing surface of the liner. Failure rate due to accelerated polyethylene wear was 2% in a series of patients with first generation PE[25]. In the same series, age < 50 years was associated with significantly greater wear rates, apparently due to the higher activity level of these patients. Similarly, in a series of Philippot *et al*[48] revision rate due to PE wear was 1.6%. Combes *et al*[22] reported a 7% rate of osteolysis (with first-generation PE), especially in patients of younger age and those treated for sequelae of childhood hip disease.

Radiographic evaluation of PE wear can be difficult in the setting of a dual mobility component, because of the deep position of the head within the cup and the cylindrical-spherical shape of the shell itself. An eccentric femoral head implies concomitant wear of both the concave and the convex bearing surface of the liner[58]. Highly cross-linked UHMWPE and vitamin-E impregnated polyethylene has reduced volumetric wear in standard implants[13,59] and have been integrated into dual mobility implants in an effort to deal with accelerated wear issues. Bauchu *et al*[60] in a retrospective series of primary THAs with the POLARCUP® component (Smith and Nephew Orthopaedics AG, Rotkreuz, Switzerland), which incorporates a highly cross-linked UHMWPE liner, reported no incidents of wear-related osteolysis. However, there are currently no independent studies of tripolar cups further supporting these findings. For all these reasons, the use of dual mobility cups should be used with caution in younger patients with high demands and increased risk of wear-related osteolysis.

Another issue with the DM cup is aseptic loosening. Loss of fixation of the original design was attributed to delamination of the plasma sprayed alumina layer[23]

which led to design modifications. Some authors propose that fixation of tripolar cups, particularly second-generation implants, should always be supplemented with screws[11]. Nonetheless, as noted earlier, current shell options include monoblock cups, which take advantage of modern porous coated surfaces for enhanced osseointegration. A potential drawback of these monoblock cups is the difficulty assessing proper seating of the cup within the acetabulum which may contribute to the reported rates of aseptic loosening ranging from 0% to 8.3%[12,14,19-22,47,48,56] (Table 1).

CONCLUSION

Instability remains a significant issue after both primary and revision THA. Dual mobility or tripolar unconstrained acetabular components can provide a viable alternative in preventing and treating instability. Reported outcomes of studies using DM cups with mid- to long-term follow up support their effectiveness. Concerns such as intra-prosthetic dislocation and accelerated wear have been emphasized, although they seem to be less significant in older, low-demand patients. The use of dual mobility cups in younger patients should be viewed with caution based on a lack of current data concerning this high demand patient population.

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New oral pharmacotherapeutic agents for venous thromboprophylaxis after total hip arthroplasty

Garrett B Aikens, Jacob R Osmundson, Michael P Rivey

Garrett B Aikens, Department of Pharmacy, Central Alabama Veterans Health Care System, Montgomery, AL 36109, United States
Garrett B Aikens, Department of Pharmacy Practice, Auburn University Harrison School of Pharmacy, Auburn University, Auburn, AL 36849, United States
Jacob R Osmundson, Michael P Rivey, Department of Pharmacy Practice, University of Montana Skaggs School of Pharmacy, Missoula, MT 59812, United States
Jacob R Osmundson, Michael P Rivey, Department of Pharmacy, Community Medical Center, Missoula, MT 59804, United States
Author contributions: Aikens GB, Osmundson JR and Rivey MP were all involved in the conception and writing of the manuscript.
Correspondence to: Garrett B Aikens, PhD, BCACP, Department of Pharmacy, Central Alabama Veterans Health Care System, Montgomery, Columbus CBOC, 1310 13th Avenue, Columbus, AL 36109, United States. garrett.aikens@va.gov
Telephone: +1-706-2577200 Fax: +1-706-6536645
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Abstract

Patients undergoing total hip arthroplasty (THA) are at high risk for developing venous thromboembolism and, therefore, require short term prophylaxis with antithrombotic agents. Recently, target specific oral anticoagulants (TSOA) including the direct thrombin inhibitor, dabigatran, and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban have been approved for THA thrombopropylaxis in various countries. The TSOAs provide a rapid acting, oral alternative to parenteral agents including low-molecular weight heparins (LMWH) and fondaparinux; and compared to warfarin, they do not require routine laboratory monitoring and possess much fewer drug-drug interactions. Based on phase Ⅲ clinical studies, TSOAs have established themselves as an effective and safe option for thromboprophylaxis after THA compared to LMWH, particularly enoxaparin, but require additional evaluation in specific populations such as the renally impaired or elderly. The ability to monitor and reverse these TSOAs in the case of bleeding complications or suspected sub- or supra-therapeutic anticoagulation is of importance, but remains investigational. This review will focus on the drug-specific characteristics, efficacy, safety, and economic impact of the TSOAs for thromboprophylaxis following THA, as well as the aspects of therapeutic monitoring and anticoagulation reversal in the event of bleeding complications or a need for urgent reversal.

Key words: Oral; Thromboprophylaxis; Venous thromboembolism; Hip; Arthroplasty

Core tip: This review focuses on the drug-specific characteristics, efficacy, safety, and economic impact of the target specific oral anticoagulants including dabigatran, rivaroxaban, apixaban, and edoxaban for thromboprophylaxis following total hip arthroplasty, as well as the aspects of therapeutic monitoring and anticoagulation reversal in the event of bleeding complications or a need for urgent reversal.

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INTRODUCTION

Patients undergoing major orthopedic surgery including

total hip arthroplasty (THA) are at increased risk for developing venous thromboembolism (VTE) that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Methods of mechanical and/or pharmacologic thromboprophylaxis have greatly reduced the VTE risk. The historical risk of symptomatic VTE following orthopedic surgery without thromboprophylaxis ranged from 15%-30% but more recent analysis suggest a cumulative VTE rate of 4.3% in the 35 d following major orthopedic surgery including THA, hip fracture repair, and total knee arthroplasty (TKA)[1]. In contrast, the rate of symptomatic VTE in the presence of thromboprophylaxis prior to hospital discharge has recently been determined to be as low as 0.53% following orthopedic surgery[2]. The rate of VTE is increased when followed up to 35 d post-surgery with a 1%-3% incidence of symptomatic DVT and 0.2%-1.1% incidence of PE after orthopedic surgery[1]. The 90-d symptomatic VTE rate after THA using thromboprophylaxis for the indicated duration ranges from 2.4%-2.8%[1]. Also, pharmacologic thromboprophylaxis was significantly associated with a decrease in 90-d mortality in a recent analysis of over 400000 THA patients from the National Joint Registry for England and Wales[3].

THROMBOPROPHYLAXIS FOR THA

The value of pharmacologic thromboprophylaxis in THA has been recognized in evidenced-based treatment guidelines by several groups including the American College of Chest Physicians (ACCP)[1], the American Academy of Orthopedic Surgeons (AAOS)[4], and the National Institute for Health and Clinical Excellence (NICE)[5,6]. Low-molecular weight heparins (LMWHs), fondaparinux, warfarin, and acetylsalicylic acid (aspirin) are recommended as options for routine thromboprophylaxis, with a LMWH currently the most widely used agent worldwide[7]. However, disadvantages that may lead to patient nonadherence and consequently an increased risk of thrombotic events are associated with these agents. LMWHs and fondaparinux are parenteral agents that require daily injections by the patient and are costly. Warfarin takes several days to weeks to achieve stable therapeutic effects, thereby requiring a patient to comply with frequent laboratory monitoring. Moreover, whether the efficacy of a simple oral aspirin regimen is comparable to that of the other agents remains controversial[8-11].

The benefit of pharmacologic thromboprophylaxis must be weighed against an increased risk of major bleeding estimated to be as high as 5.4% compared to 1.5% without thromboprophylaxis in orthopedic surgery patients[1,12,13]. Bleeding at the surgical site and neuraxial hematoma are of particular concern[12]. The incidence of surgical site bleeding has been found to be 1%-2% in patients receiving anticoagulation following orthopedic surgery, an event that increases pain, inflammation, the risk of infection, and readmission[14]. Although rare, the risk of neuraxial hematomas is increased with the use of anticoagulants and can lead to severe neurological complications and/or death[15].

Thromboprophylaxis is recommended to be continued up to 35 d following THA, making both outpatient medication compliance and the risk of anticoagulant adverse effects areas of concern[1]. The need for an improved agent for thromboprophylaxis for THA as well as other thrombotic disorders has driven the development of rapid acting, effective and safe oral anticoagulants with predictable pharmacokinetics and pharmacodynamics that alleviate the need for frequent laboratory monitoring. New oral anticoagulant agents (NOACs) include agents that target the inhibition of one of two critical elements of the clotting cascade, factor Ⅱ (thrombin) and factor Xa (FXa). Since the agents have now been available for a period of time, they are also termed target-specific oral anticoagulants (TSOAs). Regardless, the class of new oral anticoagulant agents presently includes the direct thrombin inhibitor dabigatran and the FXa inhibitors rivaroxaban, apixaban, and edoxaban; each agent has been approved in various countries for primary prevention of VTE following THA.

This review will focus on the drug-specific characteristics, efficacy, safety, and economic impact of the TSOAs for thromboprophylaxis following THA. Also, aspects related to therapeutic monitoring of suspected sub- or supra-therapeutic anticoagulation and the issue of anticoagulation reversal in the event of bleeding complications or a need for urgent reversal will be discussed.

OVERVIEW OF TSOAS

Each of the TSOAs has, or is being studied for therapeutic indications beyond thromboprophylaxis for THA. Dabigatran was originally approved in the United States by the Food and Drug Administration (FDA) in 2010 for the prevention of stroke in patients with non-valvular atrial fibrillation and again in 2014 for the treatment and secondary prevention of VTE[16]. It currently is approved in Europe and Canada, and used off-label in the United States for thromboprophylaxis of orthopedic surgery including THA[17]. Rivaroxaban is approved in the United States for thromboprophylaxis in orthopedic surgery, as well as treatment of VTE and for stroke prevention in patients with non-valvular atrial fibrillation[18,19]. Apixaban is indicated for thromboprophylaxis after orthopedic surgery by the European Medicine Agency (EMA) and more recently the FDA in 2014, and for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation by the FDA and EMA[20,21]. Edoxaban is approved in Japan for VTE thromboprophylaxis in major orthopedic surgery, and is under current investigation for other indications in several countries[22-25]. Betrixaban is a fourth FXa inhibitor that is currently under investigation for orthopedic thromboprophylaxis[26]. It is important to note that the recommended dosage for each of the drugs varies according to the treatment indication and that the recommended dosage for orthopedic thromboprophylaxis is lower than that used for VTE treatment or stroke prophylaxis in patients with atrial fibrillation.

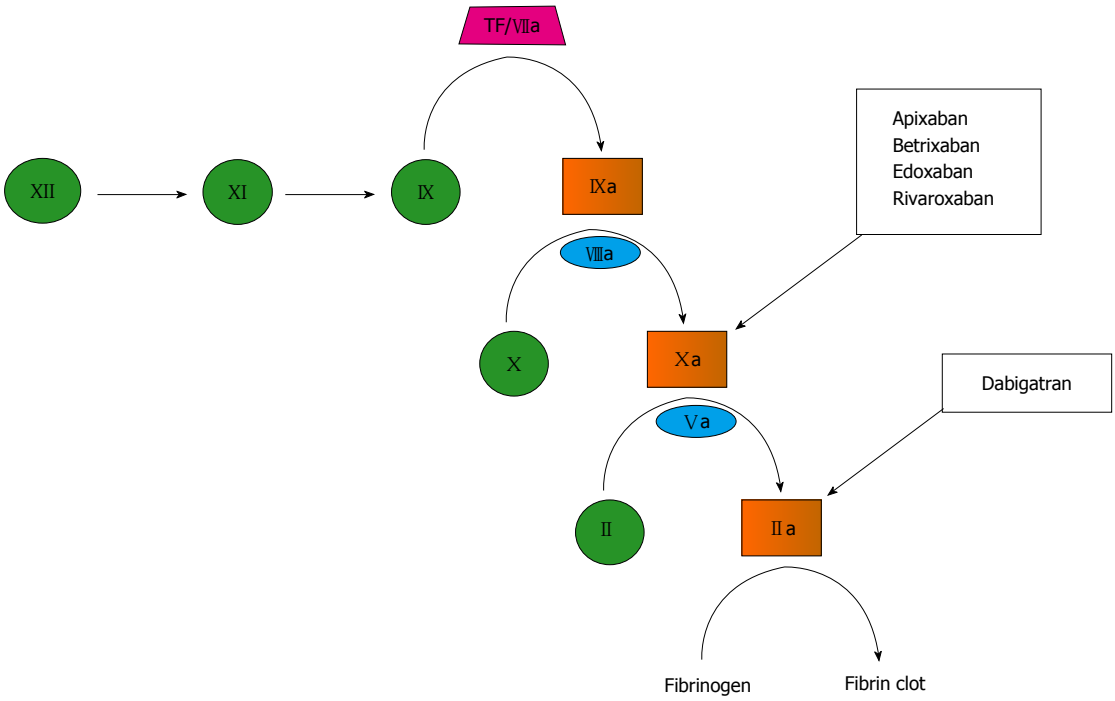

Figure 1 Coagulation cascade and site of target specific oral anticoagulants action.

Dabigatran directly binds to the active catalytic site and reversibly inhibits both free and clot-bound thrombin. Inhibition of thrombin disables conversion of fibrinogen to fibrin, inhibits activation of factors Ⅴ, Ⅷ, Ⅺ (factors that further promote thrombin generation), and inhibits factor Ⅻ that promotes clot stabilization[26-28]. Rivaroxaban, apixaban, and edoxaban directly inhibit both free and clot-bound FXa, as well as prothrombinase activity. Inhibition of FXa in turn prevents the formation of thrombin. Platelet aggregation is directly inhibited by dabigatran and indirectly inhibited by the FXa inhibitors due to their effects to reduce thrombin production[29-31] (Figure 1).

Pharmacokinetics and pharmacodynamics of the TSOAs

Because dabigatran is poorly absorbed after oral administration, the drug product is formulated as a pro-drug dabigatran etexilate that is rapidly hydrolyzed to its active form[16]. Dabigatran undergoes hepatic glucouronidation to form 4 active acyl glucuronides, each accounting for < 10% of total dabigatran in plasma. Peak plasma concentration is seen in 1 h in a fasting state but prolonged up to 3 h if administered with a meal high in fat. Once absorbed, dabigatran is only 35% plasma protein bound. Dabigatran primarily undergoes renal elimination and approximately 80% is excreted as unchanged active drug. As with all TSOAs, dabigatran's half-life of 12-17 h in healthy adults is much shorter than that seen with warfarin[32-35] (Table 1).

As would be expected, the half-life of dabigatran is prolonged to approximately 27-28 h in the presence of significant renal impairment, defined as a creatinine clearance (CrCl) of < 30 mL/min[36]. A dose reduction from 220 to 150 mg daily has been recommended for patients with moderate renal impairment (CrCl 30-50 mL/min) based on a post hoc analysis of phase Ⅲ clinical studies in orthopedic patients[37]. It has also been recommended to avoid use of dabigatran following THA in the case of severe renal impairment (CrCl < 30 mL/min), although a reduced dose of 150 mg daily in two divided doses down to a CrCl of 15 mL/min has been approved for other therapeutic indications based on pharmacokinetic analysis[38]. Additionally, due to its lack of CYP450 involvement, no dosing adjustment is necessary in the case of hepatic dysfunction[16].

The pharmacokinetics of rivaroxaban have been described for the THA thromboprophylaxis dosage of 10 mg once daily[18,19,39,40]. The drug is rapidly and nearly completely absorbed (80%-100%) without regard to food, with a peak concentration seen in 2-4 h. Unlike dabigatran, the drug is almost entirely protein bound (92%-95%). Approximately one-third of a rivaroxaban dose is eliminated unchanged through the kidneys while the remaining parent drug is metabolized to inactive metabolites by cytochrome P-450 (CYP450) isoenzymes CYP3A4/5, and CYP2J2. A half-life of 5-9 h in healthy young adults (age 25-45 years) is prolonged to approximately 11-13 h in the elderly population[18,19,27].

As noted, rivaroxaban concentrations may be increased in patients with moderate to severe renal impairment. Based on outcomes from phase Ⅲ studies, no dosing adjustment is required in patients with moderate renal impairment (CrCl 30-50 mL/min). In the case of severe renal impairment, rivaroxaban has been considered contraindicated in the United States at a CrCl < 30, and in Europe at a CrCl < 15[18,19]. Rivaroxaban dose

Table 1 Target specific oral anticoagulant pharmacokinetics

	Dabigatran etexilate[17,32-36]	Rivaroxaban[19,27,39,40]	Apixaban[21,27,41,42]	Edoxaban[43-45]
Half Life ($t_{1/2}$)	(1) Healthy subjects: 12-15 h (2) Mild renal impairment (50–80 mL/min): 15 h (3) Moderate renal impairment (30-50 mL/min): 18 h (4) Severe renal impairment (15-30 mL/min): 27 h	(1) Healthy subjects: – 5-9 h (2) Elderly: 11-19 h (3) Mild to moderate hepatic impairment: 10.1-10.4 h (4) Mild renal impairment (50–79 mL/min): 8.7 h (5) Moderate renal impairment (30-49 mL/min): 9 h (6) Severe renal impairment (15-29 mL/min): 9.5 h	(1) 2.5 mg: 6.8 h (2) 5 mg: 15.2 h (3) 10 mg: 11.1 h	8.75-10.4 h
Distribution	Vd: 50-70 L	Vd: 50 L	Vd: 21 L	Vd: > 300 L
Protein binding	35%	92%-95%	87%	40%-59%
Metabolism	(1) Hepatic: dabigatran etexilate is hydrolyzed to dabigatran (active form). (2) Dabigatran undergoes hepatic glucouronidation to 4 active acyl glucuronides, each accounting for < 10% of total dabigatran in plasma.	Hepatic: oxidative metabolism *via* CYP3A4/5 and CYP2J2	Hepatic: mainly *via* CYP3A4/5 with minor contribution from CYP1A2, CYP2C8/9/19, and CYP2J2	Hepatic: minimal hepatic contribution from CYP3A4
Bioavailability	3%-7%	Dose dependent (absolute bioavailability) (1) 10 mg 80%-100% in fasted state (2) 20 mg approximately 66% in fasted state	50%	62%
Onset (T_{Cmax})	1-6 h (1) Healthy subjects in fasted state–1 h (2) Healthy subjects following high fat meal–3 h (3) Subjects undergoing elective hip surgery–6 h	2-4 h	2.5 mg: 1.5 h 5 mg: 3.3 h 10 mg: 3-4 h	1-2 h
Excretion	80% renal clearance	(1) 66% renal clearance (36% unchanged and 30% as inactive metabolite); (2) 28% fecal excretion (7% unchanged and 21% as inactive metabolite)	(1) 27% renal clearance unchanged (2) 25% fecal excretion unchanged	49% renal clearance

reduction is approved for use in patients with atrial fibrillation and who have a CrCl 15-50 mL/min; the drug is not recommended for any indication if the CrCl < 15 mL/min[18,19,39]. Additionally, rivaroxaban use is not recommended for use in the presence of moderate to severe hepatic dysfunction or hepatic disease that is associated with coagulopathy[40].

While it might be expected that apixaban pharmacokinetics are similar to those of rivaroxaban, such is not entirely the case. The drug is rapidly absorbed with a peak effect in 3-4 h; however, only 50% of a dose reaches circulation while the remainder is excreted unchanged in the feces. The drug is approximately 87% protein bound and like rivaroxaban, is eliminated by both hepatic and renal mechanisms. Apixaban is primarily metabolized *via* CYP3A4 with minor contribution by other CYP enzymes and there are no active circulating metabolites.

Because only 25% of a dose is eliminated unchanged through the kidneys, renal impairment does not significantly prolong the average half-life of 8-15 h[27,41,42]. However, due to limited clinical evidence, apixaban should be used with caution in patients with severe renal impairment (CrCl 15-30 mL/min) and is not recommended in those with a CrCl < 15 mL/min or undergoing dialysis. No apixaban dosing adjustments are required for patients with moderate hepatic impairment although the drug is not recommended for patients with severe hepatic dysfunction[21].

Edoxaban is rapidly absorbed with 60% bioavailability, and reaches peak plasma concentrations in 1-2 h[43,44]. Most of an edoxaban dose is excreted unchanged in either the urine or feces. Edoxaban appears to be eliminated through a multitude of pathways with negligible contribution from CYP450 isoenzymes[44]. Roughly half of edoxaban present in plasma is eliminated by the kidneys, causing prolonged drug exposure in those with renal dysfunction. In healthy individuals, repeated doses of edoxaban demonstrate a half-life of 9-10 h and would likely be prolonged with renal impairment, although to what extent has not been fully delineated[44,45].

Drug interactions with TSOAs

Drug interactions with TSOAs can occur when another drug alters the pharmacokinetics of the anticoagulant or as a result of additive pharmacodynamic effects on coagulation. Either type of drug interaction can affect the predictable effects on coagulation of the newer agent. Pharmacokinetic-based interactions may lead to decreased or increased exposure of the TSOA, resulting in greater risk of thrombosis or bleeding, respectively. Pharmacodynamic-based interactions are of concern because of an enhanced bleeding risk. Because of the lower dosage and shorter duration of therapy of the TSOA used for THA thromboprophylaxis, drug interactions contributing to an increased bleeding risk may be less important compared to other patient populations. On the other hand, drug interactions resulting in a diminished TSOA effect almost certainly represent a clinically significant concern.

The permeability glycoprotein (P-gp) is an efflux

Table 2 Effects on target specific oral anticoagulants plasma concentrations from drug-drug interactions and dosing recommendations

	Drug interaction *via*	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Verapamil	P-gp inhibition and weak CYP3A4 inhibition	+ 12%-180% (take simultaneously and reduce dose)	Minor effect (use caution with CrCl 15-50 mL/min	No data yet	+ 53% (SR verapamil) (reduce dose by 50%)
Diltiazem	P-gp inhibition	No effect	Minor effect (use caution with CrCl 15-50 mL/min	+ 40%	No data yet
Quinidine	P-gp inhibition	+ 50%	+ 50%	No data yet	+ 80% (reduce dose by 50%)
Amiodarone	P-gp inhibition	+ 12%-60%	Minor effect (use caution with CrCl 15-50 mL/min	No data yet	No effect
Dronedarone	P-gp and CYP3A4 inhibition	+ 70%-100% (75 mg BID)	No data yet	No data yet	+ 85% (reduce dose by 50%)
Azole antifungals (1) Voriconazole (2) Ketoconazole (3) Itraconazole (4) Posaconazole	Strong P-gp and CYP3A4 inhibition	+ 140%-150% (75 mg BID)	Up to + 160%	+ 100%	No data yet
Fluconazole	Moderate CYP3A4 inhibition	No data yet	+ 42%	No data yet	No data yet
Clarithromycin Erythromycin	Strong P-gp and CYP3A4 inhibition	-0.05	+ 30%-54%	No data yet	No data yet
HIV Protease Inhibitors	Strong P-gp and CYP3A4 inhibition	No data yet	Up to + 153%	Strong increase	No data yet
Rifampin St. John's Wort Carbamazepine Phenytoin Phenobarbital	Strong P-gp and CYP3A4 induction	- 66%	Up to - 50%	- 54%	- 35%

Table adapted from EHRA Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation[46]. Grey boxes indicate drug contraindicated or not recommended. AUC: Area under the curve; TSOA: Target specific oral anticoagulant; P-gp: Permeability glycoprotein; BID: Twice daily.

transporter protein that is primarily expressed in the small intestines, hepatocytes, and the renal proximal tubules of the kidneys. P-gp mediates the transportation of many medications and endogenous compounds across the cell membranes. Drugs can either induce or inhibit the action of the P-gp transporter, resulting in drug-drug interactions. Regarding some TSOAs, inducing P-gp can lead to reduced plasma drug concentrations and a greater risk of thrombosis, while inhibiting P-gp will elevate serum drug concentration and increase the risk of bleeding. Alteration of one or more of the CYP450 isoenzymes is another common source of drug-drug interaction, since many medications have the potential for either inducing or inhibiting CYP450 isoenzymes, thus affecting the metabolism of certain other drugs[42].

Dabigatran is a substrate for the P-gp efflux transporter that is responsible for most of its clinically significant drug interactions; the drug is not a substrate for any CYP450 isoenzymes. Only moderate (*e.g.*, amiodarone, quinidine, and verapamil) and strong (*e.g.*, cyclosporine, dronedarone, itraconazole, systemic ketoconazole, and tacrolimus) P-gp inhibitors impact the serum concentration of dabigatran and potentiate its effects. Dabigatran use should be avoided in patients requiring the use of strong P-gp inhibitors. Renal dysfunction, in addition to concomitant use of a P-gp inhibitor, can greatly increase the exposure to dabigatran. Consequently, a reduced dose of dabigatran has been recommended if co-administered with moderate P-gp inhibitors such as amiodarone or quinidine (each reduced to 150 mg daily), or verapamil (reduced to 75 mg daily) in a patient with a CrCl 30-50 mL/min. Concomitant use of dabigatran and moderate or strong P-gp inhibitors should be avoided in patients with severe renal dysfunction (CrCl < 30 mL/min). Similarly, dabigatran co-administration with all moderate to strong inducers of P-gp should be avoided, as they can decrease serum dabigatran concentrations and potentially decrease efficacy[17,42,46,47] (Table 2).

Both rivaroxaban and apixaban are metabolized via CYP450 isoenzymes and also are substrates of the P-gp efflux transporter leading to several significant drug-drug interactions, particularly with agents that are strong inhibitors or inducers of both CYP3A4 and P-gp[42,46]. Strong "combined" inhibitors of both CYP3A4 and P-gp (*e.g.*, ketoconazole, itraconazole, ritonavir, and conivaptan) can significantly increase rivaroxaban or apixaban concentrations. In contrast, strong inducers of both CYP3A4 and P-gp (*e.g.*, carbamazepine, phenytoin, rifampin, and St. John's wort) may decrease the serum concentration of rivaroxaban or apixaban. Therefore, co-administration of either of rivaroxaban or apixaban with strong combined CYP3A4 plus P-gp inhibitors or inducers should be avoided[18]. It has been determined however, that inhibition of P-gp alone will cause only modest changes to the pharmacokinetic properties of rivaroxaban or apixaban[42].

As is the case with other TSOAs, edoxaban is a substrate of P-gp. Both inducers and inhibitors of the P-gp

will influence the serum concentrations of edoxaban. Increased edoxaban exposure has been demonstrated with the co-administration of P-gp inhibitors verapamil, quinidine, and dronedarone. However, unlike other FX a inhibitors, there is minimal CYP enzyme involvement and drugs influencing CYP enzymes theoretically pose little risk of interacting with edoxaban[1,2,42,48].

Regarding pharmacodynamic interactions resulting in an increased bleeding risk, there is a clear theoretical additive risk when a TSOA is concomitantly used with an antiplatelet agent, a nonsteroidal anti-inflammatory drug (NSAID), or another anticoagulant. While it is preferred to avoid or limit simultaneous use of a TSOA with any of these agents, many THA patients are taking antiplatelet agents for cardiovascular disease and approximately 50%-70% of orthopedic surgery patients received concurrent NSAID or aspirin therapy during the major clinical trials[49-51].

Friedman *et al*[50] conducted a post-hoc analysis of major bleeding rates from pooled data of three major orthopedic thromboprophylaxis trials of dabigatran compared to enoxaparin; 42% of the 8135 patients studied had undergone THA. The investigators separately analyzed the bleeding rates for concomitant anticoagulant plus either aspirin (4.7%) or a NSAID (54.1%). Results demonstrated no significant difference in major bleeding risk when either dabigatran or enoxaparin was combined with either aspirin or a NSAID. A similar analysis by Eriksson *et al*[51] used rivaroxaban versus enoxaparin pooled data from phase Ⅲ studies; 57% of the 12220 patients studied had undergone THA. Co-administration of the anticoagulant with a either a NSAID or an antiplatelet agent occurred in 72.3% and 8.9%of patients, respectively. Rate ratios (RRs) for any bleeding event and for major bleeding were not significantly increased in patients with concomitant anticoagulant plus NSAID or antiplatelet drug use, and there was no difference between RRs for rivaroxaban compared to enoxaparin. Nevertheless, it is prudent to evaluate the signs and symptoms of blood loss frequently when concomitant use of a TSOA and an antiplatelet or NSAID is warranted[1,16,18,20].

CLINICAL STUDIES OF TSOAS IN THA PATIENTS

Dabigatran in THA

Dabigatran was first evaluated in THA patients in the phase Ⅱ studies *B*oehringer *I*ngelheim *S*tudy in Th*RO*mbosis (BISTRO) Ⅰ and BISTRO Ⅱ. Results of the dose-ranging BISTRO Ⅰ study[52] demonstrated that an acceptable safety profile would be seen with dabigatran dosages of 12.5 to 300 mg daily after THA or TKA, but the study was not powered to determine efficacy. Investigators in the larger BISTRO Ⅱ study[53] determined that a dose dependent relationship existed for both dabigatran efficacy and safety, with significantly fewer VTE events at higher doses compared to enoxaparin 40 mg after THA or TKA, and a strong trend towards an increased rate of major bleeding with the highest dabigatran dose (300 mg daily) *vs* enoxaparin (P = 0.051). Collectively, data from the BISTRO studies established dabigatran 150 mg and 220 mg daily as the two most effective thrombopropylaxis dosages, while maintaining a comparable safety profile to enoxaparin.

The extended thromboembolism prevention after hip surgery (RE-NOVATE)[54] and RE-NOVATE Ⅱ[47] studies were randomized, double-blind, non-inferiority Phase Ⅲ studies of 3494 and 2055 patients, respectively, designed to evaluate the efficacy and safety of dabigatran compared to enoxaparin for VTE prophylaxis after THA (Table 3). RE-NOVATE randomized patients to either dabigatran 150 mg or 220 mg given orally once daily, or enoxaparin 40 mg subcutaneously once daily. RE-NOVATE Ⅱ focused solely on dabigatran 220 mg daily compared to enoxaparin. In each study, dabigatran was started 1-4 h after surgery at a half-dose then continued at its full dose daily beginning post-operative day 1. Enoxaparin was started the evening before surgery, and then continued once daily following surgery, although the investigators did allow for enoxaparin to be initiated post-operatively if consistent with local practice. Thromboprophylaxis was continued for either agent for 28-35 d. A primacy efficacy outcome of any VTE or all-cause mortality and a primary safety outcome of major bleeding during the treatment period were established. Both studies evaluated major VTE as defined by proximal DVT, non-fatal PE, or VTE-related death as a secondary outcome[47,54].

The RE-NOVATE investigators found the incidence of primary efficacy outcome occurred in 8.6% (75/874) of dabigatran 150 mg, 6.0% (53/880) of dabigatran 220 mg, and 6.7% (60/897) of enoxaparin 40 mg patients, respectively. Both doses of dabigatran achieved non-inferiority (P < 0.0001) with no differences in the rates of major VTE for either dabigatran group compared to enoxaparin. Major and minor bleeding rates were also similar between all groups[54].

RE-NOVATE Ⅱ was focused solely on dabigatran 220 mg orally once daily compared to enoxaparin 40 mg subcutaneously daily. Results showed any VTE or death occurred in 7.7% (61/792) of dabigatran compared to 8.8% (69/785) of enoxaparin patients (P = 0.43), establishing non-inferiority with dabigatran. There was, however, a significant difference in the rate of major VTE between dabigatran and enoxaparin (2.2% *vs* 4.2%, P = 0.03)[47].

Results of both RE-NOVATE and RE-NOVATE Ⅱ studies demonstrated similar rates of major and minor bleeding between dabigatran and enoxaparin[47,54]. A pooled analysis of phase Ⅲ studies of orthopedic thromboprophylaxis (excluding RE-NOVATE Ⅱ) found no differences in surgical site bleeding or wound infection although smaller independent investigations have since suggested a possible increased risk of post-operative wound complications with dabigatran compared to LMWH[55,56]. No incidence of spinal hematoma was ob-

Table 3 Phase Ⅲ clinical trials of target specific oral anticoagulants (target specific oral anticoagulants)

Clinical trial	TSOA regimen (duration)	Enoxaparin regimen (duration)	Composite of total venous thromboembolism and death		*P*-value, non-inferiority (superiority)	Major bleeding		*P*-value
			TSOA % (*n*/*N*)	Enoxaparin % (*n*/*N*)		TSOA % (*n*/*N*)	Enoxaparin % (*n*/*N*)	
RE-NOVATE[54] (*N* = 3494)	Dabigatran 220 mg daily (28-35 d)	40 mg daily (28-35 d)	220 mg; 3.1% (28/909)	6.0% (53/880)	< 0.0001 (n/a)	220 mg; 2.0% (23/1146)	1.6% (18/1154)	0.44
	Dabigatran 150 mg daily (28-35 d)		150 mg; 8.6% (75/874)		< 0.0001 (n/a)	150 mg; 1.3% (15/1163)		0.6
RE-NOVATE II[47] (*N* = 2055)	Dabigatran 220 mg daily (28-35 d)	40 mg daily (28-35 d)	7.7% (61/792)	8.8% (69/785)	< 0.0001 0.43	1.4% (14/1010)	0.9% (9/1003)	0.4
RECORD 1[62] (*N* = 4541)	Rivaroxaban 10 mg daily (31-39 d)	40 mg daily (31-39 d)	1.1% (18/1595)	3.7% (58/1558)	n/a (< 0.001)	0.3% (6/2209)	0.1% (2/2224)	0.18
RECORD 2[63] (*N* = 2509)	Rivaroxaban 10 mg daily (31-39 d)	40 mg daily (10-14 d)	2.0% (17/864)	9.3% (81/869)	n/a (< 0.0001)	0.08% (1/1228)	0.08% (1/1229)	n/a
ADVANCE 3[73] (*N* = 5407)	Apixaban 2.5 mg BID (32-38 d)	40 mg daily (32-38 d)	1.4% (27/1949)	3.9% (74/1917)	< 0.001 (< 0.001)	0.8% (22/2673)	0.7% (18/2659)	0.54
STARS J-5[75] (*N* = 610)	Edoxaban 30 mg daily (11-14 d)	20 mg BID (11-14 d)	2.4% (6/255)[1]	6.9% (17/248)[1]	< 0.001 0.016	2.6% (8/303)[2]	3.7% (11/301)[2]	0.48

[1]All events were asymptomatic DVT. [2]Rate of major and clinically relevant non-major bleeding. TSOA: Target specific oral anticoagulant; RE-NOVATE: The extended thromboembolism prevention after hip surgery; RECORD: Regulation of Coagulation in Orthopedic Surgery to Prevent DVT and PE; STARS: Studying thrombosis after replacement surgery.

served in patients receiving both dabigatran and neuraxial anesthesia during three of four phase Ⅲ studies (excluded RE-NOVATE Ⅱ)[57]. As previously noted, the risk of bleeding in Phase Ⅲ studies of dabigatran in orthopedic surgery patients was not increased by concurrent NSAID or antiplatelet drug use[50].

Rivaroxaban in THA

Rivaroxaban was initially evaluated in the THA population in three phase Ⅱ studies. A dose-ranging study[58] determined an acceptable safety profile for rivaroxaban when orally dosed between 2.5 to 30 mg twice daily or 30 mg once daily after THA. A phase Ⅱb study[59] evaluated rivaroxaban 2.5 to 30 mg twice daily versus enoxaparin 40 mg subcutaneously once daily after THA and found that only rivaroxaban 2.5 to 10 mg twice daily compared favorably to enoxaparin. A second phase Ⅱb study[60] evaluated rivaroxaban 5 to 40 mg once daily versus enoxaparin 40 mg daily. No dose-dependent response was seen with rivaroxaban and the rate of VTE; however, the incidence of bleeding did correlate with rivaroxaban in a dose-dependent manner. Based on these results, investigators recommended that rivaroxaban given as 10 mg once daily be evaluated in phase Ⅲ studies. The recommendation was corroborated by a pharmacokinetic and pharmacodynamics analysis conducted by Mueck *et al*[61] in THA patients.

The four Regulation of Coagulation in Orthopedic Surgery to Prevent DVT and PE (RECORD) studies provided the basis for rivaroxaban's approval for VTE prophylaxis following orthopedic surgery. RECORD 1[62] (n = 4541) and RECORD 2[63] (n = 2509) evaluated the efficacy and safety of rivaroxaban following THA (Table 3). Both studies were randomized and double-blinded in comparing oral rivaroxaban 10 mg once daily started 6-8 h after surgery to enoxaparin 40 mg subcutaneously started the evening prior to surgery then continued once daily following surgery. The study protocol for RECORD 1 provided for continuation of each treatment for 31-39 d while in the RECORD 2 study, rivaroxaban was given for 31-39 d compared to a shorter course of enoxaparin given for 10-14 d. Both studies used a primary efficacy outcome measure of total VTE, including asymptomatic VTE detected with venography, plus all-cause mortality, and a primary safety outcome measure of major bleeding. A secondary efficacy outcome of major VTE including proximal DVT, non-fatal PE, and VTE-related death also was pre-defined in both studies[62,63].

In RECORD 1 that compared rivaroxaban and enoxaparin for the same extended duration of treatment, total VTE or death occurred in 1.1% (18/1595) and 3.7% (58/1558) of patients receiving rivaroxaban and enoxaparin, respectively ($P < 0.001$). Furthermore, major VTE was observed in 0.2% (4/1686) and 2% (33/1678) in the rivaroxaban versus enoxaparin groups ($P < 0.001$). Rivaroxaban efficacy was determined to be superior to enoxaparin in both the intention-to-treat and per protocol analyses with similar rates of major and minor bleeding[62].

Comparing extended duration rivaroxaban versus short-term enoxaparin, RECORD 2 observed a rate in any VTE or death of 2% (17/864) and 9.3% (81/869) with rivaroxaban and enoxaparin, respectively ($P < 0.0001$). Major VTE was observed in 0.6% (6/961) patients receiving rivaroxaban and 5.1% receiving enoxaparin ($P < 0.0001$). Rivaroxaban superiority was again determined. Moreover, the results of the RECORD-2 study added further evidence supporting the use of extended thromboprophylaxis beyond 10-14 d after THA[63].

An additional prospective non-interventional study has been conducted to validate the findings of the RECORD program. The *Xa*relto® in the Prophylaxis of

Post-surgical VTE after Elective *M*ajor *O*rthopedic *S*urgery of Hip or Knee (XAMOS) investigation by Turpie *et al*[64] included 17413 patients undergoing orthopedic surgery including both THA and TKA who received either rivaroxaban 10 mg once daily or conventional thromboprophylaxis, the majority of which included LMWH (81.7%). A focused comparison was made between those receiving rivaroxaban and those receiving LMWH. The investigators determined a rate of symptomatic VTE in 0.9% of patients receiving rivaroxaban and 1.5% of patients receiving LMWH. This correlated with a statistically significant hazard ratio of 0.57 (95%CI: 0.41-0.81).

Major and minor bleeding rates were similar between rivaroxaban and enoxaparin in each of the RECORD studies as well as the non-interventional XAMOS study[62-64]. Wound complications including excessive wound hematoma, surgical site bleeding, and post-surgical wound infection were similar between rivaroxaban and enoxaparin in a pooled analysis of RECORD 1 and 2[65]. However, the potential for an increased risk of wound complications associated with rivaroxaban has been brought into question by several recent institutional studies[66-70]. In a multicenter analysis of 13123 major orthopedic surgery patients (including 5974 THA), Jameson *et al*[69] found an increased rate of wound complications including hematoma, superficial wound infection, and deep infection requiring return to surgery, with rivaroxaban compared to enoxaparin use (3.85% *vs* 2.81%, P = 0.005). Additionally, no incidence of spinal hematoma was observed with the use of rivaroxaban and neuraxial anesthesia in the RECORD program (n = 4086)[71].

Apixaban in THA

Apixaban was not studied for use after THA in the phase Ⅱ format; however, the results of the phase Ⅱ study *A*pixaban prophylaxis in patients undergoing total knee replacement surgery (APROPROS)[72] concluded that apixaban 2.5 mg twice daily had a similar efficacy and safety profile compared to enoxaparin for this indication and should be investigated in phase Ⅲ clinical studies for use after orthopedic surgery. The *A*pixaban dosed orally *vs* *An*ti*x*oagulation with injectable *e*noxaparin to prevent VTE (ADVANCE-3) study[73] was a phase Ⅲ double-blinded study that randomly assigned 5407 patients to either oral apixaban 2.5 mg twice daily or subcutaneous enoxaparin 40 mg once daily following an elective THA or a revision of a previously inserted hip prosthesis (Table 3). For those randomized to apixaban, therapy was initiated 12-24 h following the closure of the surgical site, where as enoxaparin therapy was initiated 12 h prior to surgery. Similar to other TSOA studies, the primary efficacy outcome included the occurrence of any VTE or death by any cause, and the primary safety outcome was a bleeding event categorized into major, clinically relevant non-major, and minor bleeding. A secondary efficacy outcome measured the occurrence of major VTE.

ADVANCE-3 demonstrated apixaban therapy to be more effective compared to enoxaparin in preventing DVT, nonfatal PE, or death from any cause in patients after an average treatment duration of 34 d. Superiority analysis was conducted regarding apixaban *vs* enoxaparin after non-inferiority was established. Among the patients that were evaluated (n = 3866), the composite primary endpoint of adjudicated asymptomatic or symptomatic DVT, nonfatal PE, or death from any cause during the treatment period occurred in 1.4% (27/1949) apixaban compared to 3.9% (74/1917) enoxaparin patients, respectively. Results demonstrated that apixaban was non-inferior (P < 0.0001) as well as superior (P < 0.001) to enoxaparin. Apixaban also was found to be superior to enoxaparin in preventing major VTE defined as proximal DVT, non-fatal PE, or VTE-related death (0.5% *vs* 1.1% P = 0.01). There was no significant difference in major and nonmajor clinically relevant bleeding between apixaban and enoxaparin groups[73].

Edoxaban in THA

Edoxaban like apixaban, has been modestly studied for VTE thromboprophylaxis in THA patients. Two phase II and one phase Ⅲ THA studies provided data that were combined with additional data in TKA patients to substantiate the drug approval in Japan. Each of the studies evaluated the same primary efficacy endpoint of total VTE during the treatment period, composed of asymptomatic DVT determined by venography at the end of the treatment period and any symptomatic VTE determined by objective means. The primary safety endpoint was major or clinically relevant but non-major bleeding events[23].

Raskob *et al*[74] conducted a multicenter phase Ⅱ dose-ranging study of 903 THA patients. Patients were randomized to receive oral edoxaban in dosages of either 15, 30, 60, or 90 mg given once daily or dalteparin 2500 IU subcutaneously initially, followed by 5000 IU once daily. Either drug therapy was started within 6-8 h postoperatively and continued for only 7-10 d. Edoxaban was associated with a significant (P < 0.001) dose-response effect, with VTE occurring in 28.2%, 21.2%, 21.2%, and 15.2% for the 15, 30, 60, and 90 mg daily doses, respectively. Each dose of edoxaban was associated with a significantly (P < 0.005) lower incidence of VTE, compared to dalteparin (43.8%). The incidence of bleeding was similar for all groups.

A smaller phase Ⅱb trial entitled studying thrombosis after replacement surgery (STARS) J-2[75] was a similar study in 264 THA patients but compared only oral edoxaban 15 or 30 mg once daily to enoxaparin 20 mg subcutaneously twice daily (standard orthopedic prophylaxis dosage in Japan) for 11-14 d. The first dose of edoxaban was given within 6-8 h while enoxaparin was started 24-36 h postoperatively. Interestingly, all VTE events in this study were asymptomatic distal DVT. Results of the study demonstrated low VTE incidences in all groups that were not significantly different (P > 0.05), occurring in 3.8%, 2.8%, and 4.1% in the edoxaban 15mg, edoxaban 30 mg, and enoxaparin groups, respectively. Bleeding

events also did not differ between groups, with only one major bleeding event (edoxaban 30 mg group) occurring in the study[23,75].

The STARS J-5 trial[76] was a phase Ⅲ study of oral edoxaban 30 mg once daily compared to enoxaparin 20mg subcutaneously twice daily for 11-14 d (Table 3). Results of the study in 610 THA patients demonstrated a significantly lower incidence of VTE of 2.4%in the edoxaban compared to 6.9% in the enoxaparin groups ($P < 0.001$ for noninferiority and $P = 0.0157$ for superiority). However, like STARS J-2, all VTE detected in the study were asymptomatic and primarily distal DVT, possibly due to a relatively small sample size. No difference was observed between the groups for major and clinically significant bleeding, occurring in 2.4% of edoxaban and 3.7% of enoxaparin patients, respectively ($P = 0.475$)[23,76].

Comparison of TSOAs in THA

It is important to note that there have been no direct comparisons between TSOAs for thromboprophylaxis in THA. However, several investigators have published systematic analyses that attempt to give perspective regarding the comparable efficacy and/or bleeding risk of individual new agents[77-80]. At least two meta-analyses have provided results that indirectly compared the efficacy and safety of the TSOAs, while one other meta-analysis focused solely on the safety[77-81].

Dabigatran, rivaroxaban, and apixaban were indirectly compared by Gómez-Outes *et al*[78] based on study results that compared the given TSOA to enoxaparin. Eight of 16 included studies were in THA patients but results of the indirect comparisons were not separated by orthopedic surgery type. In this analysis, rivaroxaban tended to be associated with a lower relative risk (RR) for symptomatic VTE but also a greater RR for clinically relevant and major bleeding, although no differences were statistically significant. A random effects meta-analysis performed by Loke *et al*[79] included nine studies three of which were conducted in elective THA patients. They found that in THA patients, rivaroxaban 10mg daily compared to dabigatran 150 or 220 mg daily was more effective in preventing VTE (RR 0.46) but caused more bleeding (RR = 1.14)[79]. In a similar indirect comparison, Alves *et al*[80] reported no differences between rivaroxaban and apixaban for total or major bleeding safety in the subgroup of patients undergoing THA.

A recent meta-synthesis by Adam *et al*[81] analyzed six previous systematic reviews that compared the TSOAs to other thromboprophylaxis agents, primarily LMWHs. As would be expected, their findings mirror previous conclusions regarding the individual TSOAs. However, they also noted that the strength of evidence was greater for FXa inhibitors than for dabigatran comparisons to LMWH.

PHARMACOECONOMIC CONSIDERATIONS OF TSOA USE IN THA

The economic burden associated with VTE has been well established and the use of thromboprophylaxis has lessened this burden following major orthopedic surgery[82-84]. LMWH was determined to be a cost-effective alternative to warfarin largely due to a significant comparative reduction in VTE with LMWH and the avoidance of monitoring costs associated with warfarin[85]. With the approval of TSOAs, newer pharmacoeconomic analyses comparing TSOAs to LMWH have been performed to assess their potential economic impact.

Despite a similar incidence of VTE and bleeding in the RE-NOVATE study, Wolowacz *et al*[86] determined that dabigatran was less costly than enoxaparin, largely due to comparative medication costs associated with each agent in the British Health Service, providing a potential advantage for dabigatran use over LMWH after THA. McCullagh *et al*[87] sought to determine the cost-effectiveness of both dabigatran and rivaroxaban compared to enoxaparin in the Irish Healthcare System. The results of the RE-NOVATE and RECORD 2 studies were used to estimate the expected efficacy and safety outcomes after THA associated with the use of each TSOA, respectively. A base-case analysis showed that the 35 d use of rivaroxaban was more cost-effective than either 35 d of dabigatran or 10-14 d of enoxaparin. The results were not significantly affected by sensitivity analyses.

In a pharmacoeconomic model utilizing the pooled results from the RECORD 1 and RECORD 2 studies, Duran *et al*[88] determined that rivaroxaban significantly reduced the cost associated with THA by 511.93 US dollars per patient compared to enoxaparin. The finding was attributed to a 0.0145 reduction in symptomatic VTE per patient over a one year time period. The cost effectiveness of rivaroxaban was maintained throughout the a sensitivity analysis that included different potential drug costs, the range of event rates observed in clinical studies, along with other variables that could impact healthcare cost following a THA. Supporting these results, Kwong *et al*[89] has more recently observed a similar cost savings with rivaroxaban compared to enoxaparin when also including the all-cause mortality results provided in the RECORD studies as part of the economic analysis.

Mahmoudi *et al*[90] pooled results of phase Ⅱ and Ⅲ orthopedic studies evaluating both rivaroxaban and apixaban to assess the impact of the FXa inhibitors as a class. Including multiple doses of each FXa inhibitor and assuming a 10-14 d duration of thromboprophylaxis, the investigators found a 135 US dollar reduction per patient associated with FXa inhibitor compared to LMWH (enoxaparin or dalteparin) use following THA in the 180 d post-surgery period. The cost effectiveness associated with the FXa class was maintained throughout all sensitivity analysis of cost variables.

The potential cost savings associated with the TSOAs, particularly rivaroxaban, are based on reductions in the expected incidence of symptomatic VTE events, as well as a reduction in administration and monitoring costs, while taking into account the potential for, and cost of major bleeding complications.

ANTICOAGULATION MONITORING AND REVERSAL OF TSOAS

The most challenging aspect regarding use of one of the TSOAs centers on the issue of reversing the anticoagulant effect. Limited clinical data especially in humans are available to address the issue of reversal and two factors complicate the matter. First, there are no well accepted and widely available laboratory methods for monitoring the new agents, meaning the routine assessment of anticoagulation intensity during reversal is impaired. Second, there are no direct acting antidotes for either dabigatran or any of the FXa inhibitors. Nevertheless, recommendations have been made in treatment guidelines regarding how to manage anticoagulation reversal of the new agents, and several recent reviews on the topic have been published[91-93]. Moreover, some groups have offered consensus expert opinions by the authors regarding optimal approaches for anticoagulation reversal of the new agents[93,94].

As previously noted, the risk of bleeding with the new agents is similar to that seen with other anticoagulants. Minor or major bleeding may be encountered in patients or reversal may be needed for an urgent invasive procedure. As such, the approach to management of anticoagulant reversal must be individualized as is the case with older established anticoagulants. Patient assessment for bleeding risk also is similar and increased risk is associated with anticoagulation intensity, a history of bleeding, advanced age, comorbid conditions, and other drug therapy such as concomitant antiplatelet drugs[91]. Attention, particularly for dabigatran, should be given to renal status which correlates with the half-life and therefore the anticoagulation intensity for the new agents[16,18,21]. Factors associated with increased bleeding risk are more common in the elderly population who represent a majority of THA patients.

Anticoagulation monitoring of TSOAs

Because of the more predictable anticoagulant response of the TSOAs, routine laboratory monitoring was not performed in major clinical studies of the new oral anticoagulants. However, identification of a laboratory monitoring test to assess the anticoagulant intensity of a given agent could greatly assist during reversal. Moreover, laboratory testing could have value to determine if bleeding risk is correlated with certain patient factors such as renal impairment or age and thereby identify patients at greater risk, to detect nonadherence or overdose, and to assess the impact of drug interactions[95]. Several laboratory assays have been evaluated as monitoring tests to assist in reversal decisions with the TSOAs.

The common anticoagulation tests prothrombin time (PT) and activated partial thromboplastin time (aPTT) are readily available but react differently to the TSOAs. The PT test is of limited utility since its value varies according to the thromboplastin reagent used, and conversion to the International Normalized Ratio (INR) further increases variability. If a reagent sensitive to rivaroxaban is used, the PT can be used to detect and roughly quantify an anticoagulant effect from that agent; it is unreliable to detect dabigatran or apixaban. In contrast, the aPTT test has been used to monitor dabigatran and a normal test value suggests a minimal or absent anticoagulant effect from the drug[96,97]. The aPTT test result elevation was correlated with the dosage and serum concentrations of dabigatran in THA patients in the BISTRO I trial, but the correlation was nonlinear[91,52]. The aPTT test result is also prolonged with the FXa inhibitors but effects are weaker than those on the PT test[91].

Samama *et al*[98] recently determined the effects of dabigatran and rivaroxaban on the various coagulation tests in 106 patients receiving the drugs for major orthopedic surgery, including 36 who underwent THA. As would be expected, they found that the aPTT was sensitive to dabigatran and the PT was sensitive to rivaroxaban. Perhaps more importantly however, results also showed significant inter-individual variability in the peak serum concentration for each drug, indicating considerable variation in drug response and suggesting the value of laboratory monitoring.

Since the TSOAs "target" individual coagulation factors for their anticoagulant effect, laboratory tests more specific to those targets should have utility. The thrombin time (TT) test is affected by dabigatran but is very sensitive to the drug effects, rendering it a qualitative measure at typical drug concentrations. However, it can be used to exclude a dabigatran drug effect[92,95,96]. Liew *et al*[96] suggested a normal aPTT result combined with a prolonged TT indicated low anticoagulation intensity with dabigatran, whereas prolonged results for both tests would indicate full anticoagulation. The Hemoclot test is a dilute TT already used for direct thrombin inhibitors hirudin and argatroban. The test has been shown to best correlate with dabigatran serum concentrations in a linear manner[99]. Presently, the Hemoclot test is available in Canada and Europe, with approval pending in the United States[96]. Finally, the ecarin clotting time (ECT) is sensitive to dabigatran serum concentrations across the usual therapeutic range but the test is costly, not widely available, and used primarily in research settings[93,96].

Anti-factor Xa assays are widely available in practice settings for monitoring the effects of LMWH, and are logical for use to monitor rivaroxaban, apixaban, and edoxaban. However, the assay must be modified with calibrators specific to the given FXa inhibitor. Calibrators for the new drugs are becoming available and the test will likely emerge as the preferred measure of anticoagulation intensity associated with the FXa inhibitors[92,93,95,96].

Anticoagulation reversal of TSOAs

Reversal of the anticoagulant effect of a TSOA follows the same principles utilized for older anticoagulant agents, particularly warfarin. If reversal is nonemergent or occurring in the patient suffering only mild bleeding, withholding the anticoagulant, monitoring hematologic

and coagulation tests as discussed above, and providing supportive care such as maintaining good urinary output will suffice. If the TSOA was taken within the past 2 h (or overdose is suspected), activated charcoal can be considered to reduce drug absorption. Because the drug half-lives of the new agents are shorter at approximately 8-16 h even in the elderly, the drug serum concentration will significantly decline in a 24 h period. One caveat that must be remembered is the effect of renal insufficiency to slow elimination, particularly with dabigatran[91]. Several investigators have offered suggestions for timing of the discontinuation of the new oral anticoagulants before an elective or nonemergent surgery[92,93,100].

Anticoagulation reversal of a TSOA in the patient with moderate to severe bleeding or in need of urgent surgery is more challenging. No specific antidote exists for any of the new oral agents, although work is ongoing by van Ryn *et al*[101] to evaluate a promising humanized antibody fragment against dabigatran Lu *et al*[102] has developed a modified and inactive form of factor Xa that may function as a universal antidote to all factor Xa inhibitors.

For removal of a TSOA from the body, the pharmacokinetic differences between dabigatran and the factor Xa inhibitors have relevance and affect recommended modalities. Since dabigatran has low protein binding, hemodialysis can effectively remove the drug. Stangier *et al*[36] determined that over 60% of a single 50 mg dose of dabigatran was removed by hemodialysis after 2 h in a small study of patients with end-stage renal failure. The combination of high-dose recombinant factor Ⅶa and hemodialysis has been used to successfully treat a massive postoperative bleed in a patient who underwent cardiac surgery[103]. Charcoal hemoperfusion may also represent an effective way to remove dabigatran[94]. Both of the modalities appear as recommendations for dabigatran removal by consensus groups[93,94,104]. However, while these methods are effective to remove dabigatran and presumably reverse its anticoagulant effect, both have limited application since availability is low, vascular access is required, and the time to implement is often prolonged[92-94,96]. In contrast, high protein binding characterizes rivaroxaban (92%-95%) and apixaban (84%-87%), meaning a significant amount of either drug is unlikely to be removed by hemodialysis or hemoperfusion[93,94].

Since no specific antidote exists and methods to remove drug from the system are limited, reversal of a TSOA's anticoagulant effect has been focused on the use of hemostatic agents and coagulation factor replacement. Traditional approaches used with warfarin have no or very little benefit in patients who are anticoagulated with the new agents. Specifically, vitamin K has no effect to reverse anticoagulation and fresh frozen plasma (FFP) requires long preparation time and large volumes, and has not been shown to have value for bleeding due to a TSOA[94,96]. The use of FFP has given way to use of prothrombin complex concentrates (PCC) even for warfarin reversal[105].

Recently, interest in the use of hemostatic agents for reversal of anticoagulation with the TSOAs has focused on use of PCC products that contain concentrated amounts of vitamin K dependent clotting factors and are available in several forms. PCCs include products that contain three (factors Ⅱ, Ⅸ, and Ⅹ) or four (Ⅱ, Ⅶ, Ⅸ, and Ⅹ) virally inactivated clotting factors, and an activated product (also known as factor eight inhibitor bypassing activity or FEIBA) that contains an activated factor Ⅶ with inactivated factors Ⅱ, Ⅸ, and Ⅹ. Factor Ⅶ alone is also available as a recombinant product that is in activated form and can be added to the three-factor PCC to essentially make the four- factor PCC that has only recently become available in the United States[92,93]

Despite the extensive interest in the use of PCCs to reverse anticoagulant effects of the TSOAs, there is a paucity of data especially in humans. The majority of data regarding the use of PCCs comes from preclinical animal and phase Ⅰ *in vitro* and *ex vivo* studies[92,93]. An extensive review of those data is beyond the scope of this article; an excellent review was recently published by Dickneite *et al*[106].

In their recent review, Thigpen and Limdi[92] described 5 case reports of severe bleeding due to dabigatran that were treated with factor replacement, including only 2 patients who received a PCC product. Eerenberg *et al*[107] conducted a randomized, double-blind, crossover study of a four-factor PCC (Cofact®) effect on dabigatran and rivaroxaban's effect on coagulation assays in 12 healthy men. The PCC reversed coagulation changes induced by rivaroxaban but had no effect on coagulation changes associated with dabigatran. In contrast, a recent retrospective, observational study of five emergency room patients who received a four-factor PCC (Octaplex®) for urgent reversal of dabigatran-associated bleeding showed that PCC product administration was associated with normalization of the aPTT ratio in the single patient with an elevated ratio at admission[108]. Understandably, a recent clinical practice guideline states the hemostatic factor products "should be considered" for use in "ongoing, life-threatening bleeding, " a statement that reflects the lack of human clinical data addressing this issue[109]. Nevertheless, Alikhan *et al*[110] has recently published algorithms for the management of dabigatran in the settings of bleeding, a need for emergency surgery, and overdose that give recommendations for the use of factor replacements. Nutescu *et al*[93] have similarly given recommendations for anticoagulation reversal of dabigatran, rivaroxaban, and apixaban based on the level of urgency.

Finally, several aspects likely affect interpretation of available data surrounding the use of factor replacements. Animal-derived data while useful may not accurately reflect the coagulation process in humans. Some three-factor PCCs may have a short duration of benefit if factor Ⅶ is a key factor to sustain reversal action. While activated PCCs such as FEIBA present a known increased risk for thrombosis, they may be required to reverse anticoagulation for some or all of the TSOAs. Variation in the reversal of anticoagulation by various

PCCs may be related to the product composition, some which contain antithrombotic proteins C and S; it is unknown which factor(s) in a PCC product is/are critical to achieve reversal. And finally, it must be remembered that a correlation of what appears to be favorable effects on various laboratory tests with a decreased bleeding risk or intensity has not been established in humans[92-94,106].

CONCLUSION

TSOAs offer several clear advantages to traditional antithrombotic agents including rapid onset of action, short half-life, predictable pharmacokinetics and pharmacodynamics, and minimal drug-drug interactions. Dabigatran, rivaroxaban, and apixaban have been approved for thromboprophylaxis after THA in many countries, while rivaroxaban and apixaban are currently the only agents approved by the FDA in the United States, and a fourth additional agent, edoxaban, has been approved only in Japan for this indication. TSOAs have provided safe and effective options for thromboprophylaxis after THA and represent a cost-effective alternative to the most widely used LMWH class of anticoagulants. Although long-term clinical experience is lacking, and the ability to reliably monitor or reverse the anticoagulant effect of the agents is still under development, TSOAs have established a new approach to thromboprophylaxis after THA.

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WJO 5th Anniversary Special Issues (4): Hip

Can periprosthetic hip joint infections be successfully managed by debridement and prosthesis retention?

Konstantinos Anagnostakos, Cornelia Schmitt

Konstantinos Anagnostakos, Cornelia Schmitt, Klinik für Orthopädie und orthopädische Chirurgie, Universitätsklinikum des Saarlandes, D-66421 Homburg/Saar, Germany
Author contributions: All authors contributed to this work.
Correspondence to: Konstantinos Anagnostakos, PD, Klinik für Orthopädie und orthopädische Chirurgie, Universitätsklinikum des Saarlandes, Kirrbergerstr. 1, D-66421 Homburg/Saar, Germany. k.anagnostakos@web.de
Telephone: +49-6841-1624520 Fax: +49-6841-1624516
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Abstract

To evaluate the current literature about how successfully periprosthetic hip joint infections can be managed by debridement and prosthesis retention. A literature search was performed through PubMed until September 2013. Search terms were "DAIR (debridement, antibiotics, irrigation, and retention)" alone and in combination with "hip" as well as "hip infection + prosthesis retention". A total of 11 studies reporting on 292 cases could be identified. Five different treatment modalities have been described with varying success rates (debridement-21% infection eradication rate; debridement + lavage-75% infection eradication rate; debridement, lavage, with change of modular prosthesis components-70.4% infection eradication rate; debridement, lavage, change of modular prosthesis components + vacuum-assisted closure-92.8% infection eradication rate; acetabular cup removal + spacer head onto retained stem-89.6% infection eradication rate). With regard to the postoperative antibiotic therapy, no general consensus could be drawn from the available data. Debridement, antibiotic therapy, irrigation, and prosthesis retention is an acceptable solution in the management of early and acute hematogenous periprosthetic hip joint infections. The current literature does not allow for generalization of conclusions with regard to the best treatment modality. A large, multi-center study is required for identification of the optimal treatment of these infections.

Key words: Hip joint infection; Prosthesis retention; Debridement; Hip revision; Antibiotic therapy; Irrigation

Core tip: Infections after total hip arthroplasty are a hazardous complication. Prosthesis retention is though to be possible in case of early infections, whereas several treatment modalities might be applied. The ideal treatment procedure is still unknown. The present work reviews the current literature about how successfully periprosthetic hip joint can be managed by debridement and prosthesis retentiond and treid to shed some light onto this difficult topic.

Original sources: Anagnostakos K, Schmitt C. Can periprosthetic hip joint infections be successfully managed by debridement and prosthesis retention? *World J Orthop* 2014; 5(3): 218-224 Available from: URL: http://www.wjgnet.com/2218-5836/full/v5/i3/218.htm DOI: http://dx.doi.org/10.5312/wjo.v5.i3.218

INTRODUCTION

Despite numerous prophylactic measures infections still occur in 1%-2% after total hip arthroplasty (THA), whereas this rate may increase after revision surgery[1]. In the future, the overall infection rate is likely to increase as the life expectancy of the implants is increased and patients are followed up longer. Depending on the time of infection manifestation, duration of symptoms, virulence and antibiotic resistance profile of the pathogen organism, and the general medical condition of the patient, several treatment options are available including both one- and two-stage procedures[1].

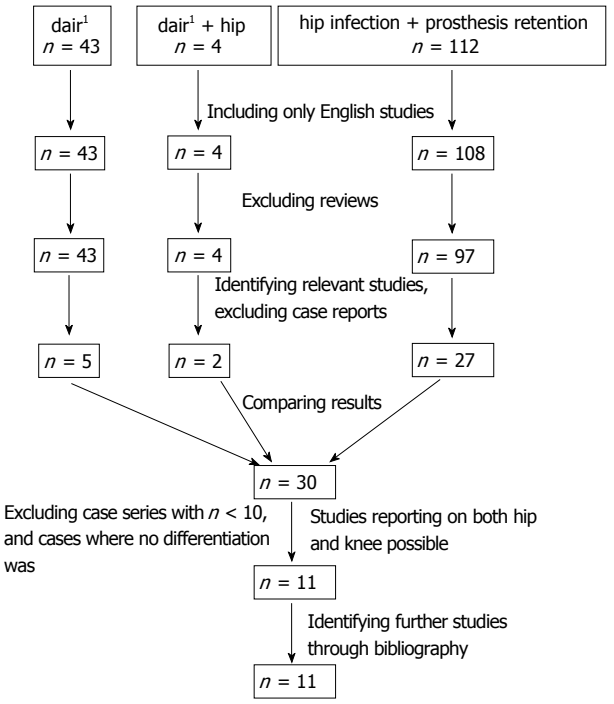

Figure 1 Flow chart diagram showing the single steps of literature search for identification of relevant studies. [1]dair: Debridement, antibiotics, irrigation, and retention.

Hip joint infections are actually categorized into early, delayed, and late infections[1]. Although these terms are widely accepted, a discrepancy regarding the precise differentiation of the time periods still exists. Some authors define early infections as those occurring within the first four[2,3] or six[1] postoperative weeks, whereas others propose the first three months to be the limit[4]. Similar to that, the definition of late infections vary from the period beyond the first four postoperative weeks[2,3] to beyond the first 24 postoperative months[4].

The correct definition of the joint infection with regard to the time of infection manifestation is important for making the correct decision about the ideal treatment procedure. Generally, it is accepted that early infections are likely to be successfully managed by debridement, lavage, and prosthesis retention, whereas late infections require prosthesis removal and one- or two-stage-reimplantation in order to achieve infection eradication[5]. However, the literature data about this topic cannot be always evaluated and compared to each other to a sufficient and reliable way due to inhomogenities in the treatment procedure, patients' collective, antibiotic therapy or length of follow-up.

Hence, the aim of the present study was to evaluate the current literature about how successfully periprosthetic hip joint infections can be managed by debridement and prosthesis retention.

LITERATURE SEARCH

A literature search was performed through PubMed from the begin of PubMed until September 2013 (Figure 1). Search terms were "DAIR (debridement, antibiotics, irrigation, and retention)" alone and in combination with "hip" as well as "hip infection + prosthesis retention". Only English studies were included. Reviews, case reports and case series with a number of patients < 10 were excluded from the study. Studies reporting about both hip and knee cases but not allowing for differentiation between the particular outcome were also excluded. From the identified studies, a search was carried through the bibliography of each article in order to identify further studies. All studies were analysed with regard to publication date, number of patients treated, type of infection, surgical treatment modalities, surgical complications, type and length of antibiotic therapy, follow-up, and level of evidence. Studies reporting only partly on these parameters were also excluded.

RESEARCH

A total of 11 studies reporting on 292 cases could be identified (Figure 1)[2-3,6-14]. Two studies were published before and nine after 2000. Two studies had a level of evidence Ⅲ and nine level of evidence Ⅳ (Table 1).

Of the 292 cases, there were 216 early and 57 late infections (with a variable definition of early vs. late infection). The remaining 19 cases were acute hematogenous according to the criteria by Tsukayama *et al*[2] (Table 1).

Regarding the treatment procedures, five different modalities have been described (Figure 2). One study[10] reported on debridement and another on debridement and irrigation[12]. Six studies performed debridement, lavage and change of modular prosthesis components (polyethylene (PE) liner, femoral stem head)[2,3,6,7,9,14], whereas in one of these studies the PE liner was not changed in all patients[9]. One study combined this procedure along with the use of the vacuum-assisted closure therapy[11]. Two studies reported on partial prosthesis retention[8,13]. In both studies, the infected acetabular cup was removed and an antibiotic-loaded spacer head was placed onto the retained femoral stem. Although it is difficult to evaluate the cumulative infection eradication rate for each procedure separately, literature data indicate a higher success rate for the two latter procedures (Figure 2).

Complications beside persistence of infection or emergence of new infection included mostly prosthesis dislocations and aseptic prosthesis loosening (Table 2).

With regard to the postoperative antibiotic therapy, no general consensus could be drawn from the available data (Table 3). Some studies gave only intravenous antibiotics, whereas others combined intravenous and oral antibiotics. Similar discrepancies could be observed regarding the length of antibiotic therapy, which varied from four weeks to one year (Table 3).

All studies provided a mean follow-up of at least 24 mo (Table 2). Depending on the salvage procedure used in each study, the infection eradication rate ranged from 21% to beyond 90% (Table 2).

DISCUSSION

The aim of the present study was to evaluate the cur-

Table 1 Overview of 11 studies reporting about prosthesis retention at the site of periprosthetic hip joint infections with regard to publication year, number of patients treated, type of infection, and level of evidence

Ref.	Publication year	Number of patients	Type of infection	Level of evidence
Aboltins *et al*[6]	2007	13	7 early[1] 6 late	IV
Aboltins *et al*[7]	2013	19	All early[1]	III
Anagnostakos *et al*[8]	2010	12	All late[2]	IV
Choi *et al*[9]	2012	28	All early[3]	III
Crockarell *et al*[10]	1998	42	19 early[3] 19 late 4 acute hematogenous	IV
Kelm *et al*[11]	2009	28	All early[2]	IV
Klouche *et al*[12]	2011	12	All early[3]	IV
Lee *et al*[13]	2013	19	10 late[3] 9 acute hematogenous	IV
Tsukayama *et al*[2]	1996	41	35 early[3] 6 acute hematogenous	IV
Waagsbø *et al*[3]	2009	40	30 early[4] 10 late	IV
Westberg *et al*[14]	2013	38	Early[3]	IV

[1]Early < 3 mo after surgery; late > 3 mo after surgery; [2]Early < 6 wk after surgery; late > 6 wk after surgery; [3]Early < 4 wk after surgery; late > 4 wk after surgery; Acute hematogenous > 4 wk after surgery due to bacteremia; [4]Early < 4 wk after surgery; late > 4 wk after surgery.

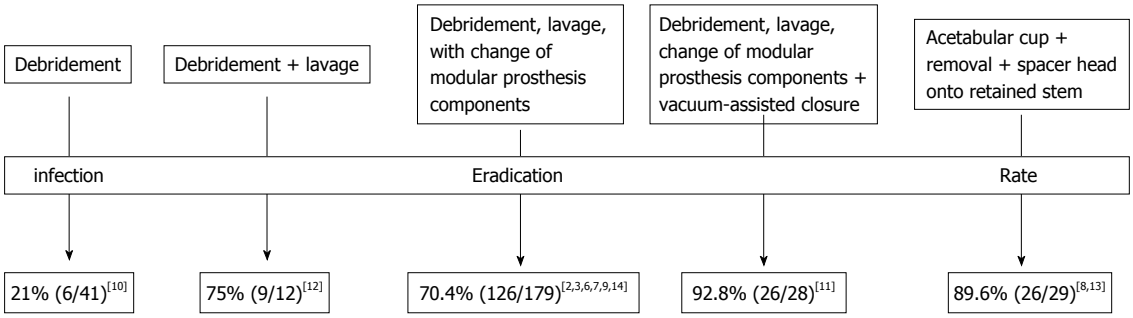

Figure 2 Overview of treatment procedures for management of periprosthetic hip joint infections.

rent literature about how successfully periprosthetic hip joint infections can be managed by debridement and prosthesis retention. There was a low level of evidence among the 11 identified studies. Most infections were early infections, whereas a variable definition of the type of infection was evident through the studies. Five different modalities have been described with an infection eradication rate ranging from 21% to beyond 90%. With regard to the postoperative antibiotic therapy, no general consensus could be drawn from the available data about the ideal type or length of the therapy.

Periprosthetic joint infections (PJI) still remain a hazardous complication after primary and revision THA. A regimen of debridement, irrigation, prosthesis retention, and antibiotic therapy is generally accepted for acute infections without complicating factors such as significant comorbidity, not intact soft tissues surrounding the prosthesis or loosening of the prosthesis[15]. The aim of the present review was to investigate whether it is possible to treat these infections by prosthesis retention.

To the best of our knowledge, our literature search revealed 11 relevant studies. One possible cause for that might be the literature review only through PubMed and not also through other libraries. Moreover, our strict inclusion criteria led to the exclusion of numerous studies which might have provided more information and allowed for a more reliable interpretation of the data. On the other hand, more heterogenous data may not allow for meaningful conclusions. However, the purpose of the present study was to evaluate only studies reporting on hip joint infections. Several well-designed studies with a higher level of evidence report about DAIR including both THA and total knee arthroplasty (TKA) cases, whereas a differentiation of the results between both primary surgeries is not possible[15-28]. Similar to that, other studies present data only about small case series[29-31]. We represent the opinion that the proper identification of relevant studies is crucial when a systematic literature review is performed.

The findings of the present review indicate that the infection eradication rates with regard to prosthesis retention are lower compared to those reported after one- or two-stage revision surgery[5]. Although single studies demonstrated high success rate exceeding 90%, the relative small number of patients treated as well as the low level of evidence does not allow for generalization of

Table 2 Overview of 11 studies reporting about prosthesis retention at the site of periprosthetic hip joint infections with regard to surgical treatment modalities, -complications, infection eradication rate and length of follow-up

Ref.	Surgical treatment procedure	Surgical complications	Infection eradication rate
Aboltins *et al*[6]	Debridement, lavage, Change of PE-liner [Median = 1 (1-4)]	1/13 aseptic prosthesis loosening	92.30%
Aboltins *et al*[7]	Debridement, lavage, Change of PE-liner [Median = 3 (3-6)]	N.c.d.	89.50%
Anagnostakos *et al*[8]	Acetabular cup removal + Spacer head onto retained stem Mean implantation period 88 (35-270) d	2/12 draining sinus After spacer head implantation; 1/12 spacer dislocation; 3/12 prosthesis dislocation	91.60%
Choi *et al*[9]	19/28 debridement, irrigation, Change of PE-liner 9/28 debridement, irrigation, No change of PE-liner	5/28 staged revision, 6/28 repeated debridement, 4/28 resection arthroplasty	50%
Crockarell *et al*[10]	Debridement	1/42 prosthesis dislocation, 1/42 periprosthetic femoral fracture, 1/42 exitus due to sepsis	21%[1]
Kelm *et al*[11]	Debridement, pulsatile lavage, Change of PE-liner, Vacuum-assisted closure	None	92.80%
Klouche *et al*[12]	Debridement, irrigation Change of PE-liner and femoral head	n.r.	75%
Lee *et al*[13]	Acetabular cup removal + Spacer head onto retained stem	n.r.	89.50%
Tsukayama *et al*[2]	Debridement, change of PE-liner	1/35 acetabular component loosening 2/6 acetabular component loosening	71% (early) 50% (acute hematogenous)
Waagsbø *et al*[3]	Debridement + prosthesis retention	n.r.	67.50%
Westberg *et al*[14]	Debridement, pulsatile lavage, Change of modular prosthesis components	8/38 prosthesis dislocation	71%

PE: Polyethylene; N.c.d.: Not clearly described; n.r.: Not reported; [1]4/19 early successful, 2/4 acute hematogenous, 0/19 late.

conclusions. Two possible causes might be responsible for this lower infection eradication rate: the low power of the included patients of the identified studies, and the patients' collectives themselves, which are different compared with those treated by one- or two-stage revision arthroplasty.

The present review identified five different treatment modalities for management of THA-PJIs with varying success rates. Especially older studies showed lower success rates compared to younger ones. This discrepancy might be possibly explained by advances in surgical and debridement techniques, introduction of the vacuum-assisted therapy, use of pulsatile lavage or even antiseptic solutions as well as application of new and more potent antimicrobial drugs. Moreover, some studies present some partly surprising results. Choi *et al*[9] retrospectively compared 28 cases having prosthesis retention with 65 cases having been treated by staged revision and identified risk factors for infection persistence, whereas different surgical indications were present for acute *vs* late infections. Infection of revision THA, acute phase treatment (less than four weeks), and polybacterial infection were identified as independent predictors for failure of infection control after initial surgery. The only risk factor associated with failure of infection control at the latest follow-up was the S. aureus microorganism. Additional subgroup analysis to identify other possible contributing factors identified no difference between methicillin-sensitive and methicillin-resistant staphylococcus or head/liner exchange and no exchange[9]. These findings are contradictory to the general acceptance that prosthesis retention is feasible at the site of early infection with a short duration of symptoms. Similar accounts for the non-significant difference between head/liner exchange and no exchange. Theoretically, the change of modular prosthesis components should reduce the bacterial load in the wound, and hence lead to better infection eradication rates. However, Choi *et al*[9] concluded that retention treatment can be considered an initial treatment option in selected cases of primary THA with a single organism, non-S. aureus infection with 50% chance of infection control and no disadvantages in terms of additional procedure, hospital stay, and treatment duration.

The decision with regard to the ideal treatment procedure for management of PJIs of the hip joint is made based on several factors such as time of infection manifestation, duration of symptoms, local soft-tissue situation, number of prior surgeries, identification of pathogen organism, its virulence and antibiotic resistance profile as well as patient's comorbidities. Various risk factors have been described that are associated with occurrence of PJI, such as rheumatoid arthritis, diabetes mellitus, malignancy, obesity, and use of immunosuppressive drugs[15,20,32-34]. Revision surgery also increases the

Table 3 Overview of 11 studies reporting about prosthesis retention at the site of periprosthetic hip joint infections with regard to the systemic antibiotic therapy

Study	Systemic antibiotic therapy
Aboltins *et al*[6]	All intravenous glycopeptide or beta-lactam for median 10 (3-29) d All oral rifampicin+fusidic acid for median 17 (6-33) mo
Aboltins *et al*[7]	All intravenous glycopeptide + beta-lactam for median 15 (12-34) d All oral rifampicin + fucidic acid or ciprofloxacin for median 356 (230-395) d
Anagnostakos *et al*[8]	All intravenous for 4 wk + oral for 2 wk
Choi *et al*[9]	All intravenous for 6 wk
Crockarell *et al*[10]	41/42 intravenous for 29 (2-72) d 26/42 oral after iv For 70 (5-376) d; 3/42 chronic suppression
Kelm *et al*[11]	Intravenous for 2 wk followed by oral for 2 wk
Klouche *et al*[12]	Intravenous for 6 wk followed by oral for 6 wk
Lee *et al*[13]	Intravenous for 4-6 wk
Tsukayama *et al*[2]	Early: intravenous for 4 wk; acute hematogenous: intravenous for 6 wk
Waagsbø *et al*[3]	Overall duration of antibiotic therapy 0.1 (8.2-14.2) wk, of which intravenous 4.4 (4.2-6.1) wk
Westberg *et al*[14]	Overall duration of antibiotic therapy 7 (3-39) wk

risk of PJI[17,33,34]. Factors that have been associated with a worse outcome of PJI treatment including both THA and TKA involve infections caused by *Staphylococcus* species[15], and more specifically by *Staphylococcus aureus* and methicillin-resistant Staphylococcus aureus (MRSA)[17,35-37], polymicrobial PJI[20], intra-articular purulence[15], retention of exchangeable components[20], and longer time between initial arthroplasty and PJI diagnosis[16,20,36,38].

Despite the aforementioned known risk factors the ideal treatment procedure is difficult to choose due to the definition of the infection itself. Although several classification systems have been proposed[1-4], the exact definition of an early vs. late periprosthetic infection still remains controversial. This distinguishment is essential since it is widely accepted that only early infections can be successfully treated by prosthesis retention. With regard to early as well as late infections the discrepancy between the several classification systems means that symptoms that are present for several weeks to months might not be ideally treated. The only point that all these systems agree for is the cause for the emergence of each infection[1]. Early infections are attributed to an intraoperative contamination[1]. Delayed or low-grade infections are also attributed to an intraoperative contamination, however an infection manifestation has not evolved due to a small bacteria number, low virulence of the causative organism or adverse local conditions for bacteria growth[1]. Late infections are hematogenously acquired, whereas in 20%-40% of the cases the primary infection source remains unidentified[1]. Acute hematogenous infections take a special place among periprosthetic infections. These infections occur like late infections months after the surgery, are characterized by a sudden onset of symptoms and caused by bacteremia. Practically, all these definitions are an attempt to separate surgically from nonsurgically acquired infections, and the problem is where to draw the line. Clearly, not every early infection is surgically acquired and not all late infections are from other sources[1].

Moreover, an unanswered question regards the insertion of antibiotic-loaded device (cement beads or collagen sponges) when DAIR is performed. To the best of our knowledge, the effect of antibiotic-impregnated beads at the site of DAIR has not been studied. A possible disadvantage of the insertion of beads regards the removal of the beads in an additional surgery. The use of gentamicin-loaded collagen sponges has been described in a few studies in the treatment of PJI[39-41].

The optimal antibiotic treatment (the choice and duration) of PJIs is still unknown. Some authors recommend a duration of antibiotic treatment for 6 mo for TKA-PJIs and 3 mo for THA-PJIs when treated with DAIR[4]. In some recent studies, it has been reported that a shorter course of antibiotics might be also an alternative in DAIR treatment[21,23,28,37]. This confusion regarding the optimal duration of antibiotic therapy is also evident in the present literature review. Antibiotics were administered over different periods varying from four weeks to one year. Due to the relative small power of the included cases and inhomogenities in the treatment procedures and collectives themselves it cannot be stated which antibiotic treatment is the optimal.

In conclusion, the present literature review shows that debridement, irrigation, antibiotic therapy, change of modular prosthesis components and prosthesis retention is an acceptable solution in the management of early and acute hematogenous periprosthetic hip joint infections. Factors that have been associated with a worse outcome of PJI treatment involve infections caused by *Staphylococcus* species, and more specifically by *Staphylococcus aureus* and MRSA, polymicrobial PJI, intra-articular purulence, retention of exchangeable components, and longer time between initial arthroplasty and PJI diagnosis. The current literature does not allow for generalization of conclusion with regard to the best treatment modality. A large, multi-center study is required for identification of the optimal treatment of these infections.

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Perioperative outcomes and type of anesthesia in hip surgical patients: An evidence based review

Mathias Opperer, Thomas Danninger, Ottokar Stundner, Stavros G Memtsoudis

Mathias Opperer, Ottokar Stundner, Department of Anesthesiology, Perioperative Medicine and Intensive Care Medicine, Paracelsus Medical University, Salzburg 5020, Austria
Thomas Danninger, Stavros G Memtsoudis, Department of Anesthesiology, Hospital for Special Surgery, New York, NY 10021, United States
Author contributions: Opperer M, Danninger T, Stundner O and Memtsoudis SG contributed equally to this work.
Correspondence to: Stavros G Memtsoudis, MD, PhD, FCCP, Department of Anesthesiology, Hospital for Special Surgery, Weill Medical College of Cornell University, 535 East 70th Street, New York, NY 10021, United States. memtsoudiss@hss.edu
Telephone: +1-212-6061206 Fax: +1-212-5174481
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Abstract

Over the last decades the demand for hip surgery, be it elective or in a traumatic setting, has greatly increased and is projected to expand even further. Concurrent with demographic changes the affected population is burdened by an increase in average comorbidity and serious complications. It has been suggested that the choice of anesthesia not only affects the surgery setting but also the perioperative outcome as a whole. Therefore different approaches and anesthetic techniques have been developed to offer individual anesthetic and analgesic care to hip surgery patients. Recent studies on comparative effectiveness utilizing population based data have given us a novel insight on anesthetic practice and outcome, showing favorable results in the usage of regional *vs* general anesthesia. In this review we aim to give an overview of anesthetic techniques in use for hip surgery and their impact on perioperative outcome. While there still remains a scarcity of data investigating perioperative outcomes and anesthesia, most studies concur on a positive outcome in overall mortality, thromboembolic events, blood loss and transfusion requirements when comparing regional to general anesthesia. Much of the currently available evidence suggests that a comprehensive medical approach with emphasis on regional anesthesia can prove beneficial to patients and the health care system.

Key words: Perioperative outcome; Regional anesthesia; Neuraxial anesthesia; Hip arthroplasty; Hip fracture

Core tip: Recent studies on comparative effectiveness utilizing population based data have given us a novel insight on anesthetic practice and outcome, showing favorable results in the usage of regional vs. general anesthesia. In this review we aim to give an overview of anesthetic techniques in use for hip surgery and their impact on perioperative outcome. While there still remains a scarcity of data investigating perioperative outcomes and anesthesia, most studies concur on a positive outcome in overall mortality, thromboembolic events, blood loss and transfusion requirements when comparing regional to general anesthesia.

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INTRODUCTION

The increasing demand for hip arthroplasties over the last decades has sparked the creation of new and innovative anesthetic techniques and analgesic pathways with the goal to support best possible outcomes among this frequently elderly patient population. As a result, today different perioperative treatment pathways are available

to physicians and their patients. In this context, the focus has shifted to techniques based on regional anesthetic and analgesic techniques. This trajectory has been fueled by a number of advantages including effective, long-lasting and focused pain control, decreased need for systemic analgesics and earlier mobilization[1]. While traditional views of anesthetic interventions have seen them in a more supportive role, allowing for surgery to take place and to alleviate pain postoperatively, an increasing body of literature has highlighted numerous beneficial effects of the use of regional anesthesia beyond the outcome of analgesia. Following this context, the use of regional compared to general anesthesia has been associated with beneficial results such as a lower incidence of mortality, reduced blood loss, thromboembolic events, cardiopulmonary complications, infections and favorable economic outcomes. However, evidence remains rare and there exists a paucity of publications focusing on comparatively reviewing perioperative outcomes among different types of anesthesia in hip surgical patients.

In this manuscript we will focus on the discussion of available types of anesthesia in the hip surgical patients and discuss their epidemiologic distribution. We aim to present and discuss common perioperative complications and evaluate the literature with respect to different anesthetic and analgesic techniques and their impact on these outcomes, including medical and economic factors.

EPIDEMIOLOGY OF HIP SURGERY AND ANESTHESIA TYPES

Surgeries involving the hip joint have dramatically increased over time and are expected to continue to rise in incidence within the coming decades. Fueling these trends, among other factors, are their high success rate both in elective as well as in traumatic settings and the fact that the target population, including the elderly is rapidly expanding.

It is estimated that by 2030 the demand for primary total hip arthroplasties in the United States will grow by 174% to 572000. Equally, the need for total hip revisions is projected to more than double to 137% in the same time frame[2]. Based on demographic changes and trends in the decades to come, the annual rate of hip fractures has been projected to increase worldwide from 1.66 million in 1990 to 6.26 million in the year 2050[3]. This is of special concern as of all osteoporotic fractures, hip fractures have been identified as the most expensive fracture type as measured by hospitalization costs[4]. In addition, compounding the associated burden on the health care system exerted by the sheer volume alone, recent trend data are suggesting an increase in the average comorbidity burden and incidence of many serious complications among hip surgical patients[5]. Therefore, any intervention that may impact on perioperative outcomes is bound to profoundly affect the public health of entire countries.

Epidemiologic information on the utilization of various types of anesthesia in hip surgical patients is more difficult to come by, as such information is not easily retrievable from data collection constructs. However, newer and more detailed databases have afforded researchers a rare glimpse of current anesthetic practice on a national level. A recent analysis of population based data, which included 382236 patient records undergoing primary hip or knee arthroplasty in the United States, showed that approximately 11% were performed solely under neuraxial, 14.2% under combined neuraxial-general and 74.8% under general anesthesia[6]. This shows that even today, despite a trend to regional anesthesia, the majority of operations in the United States are carried out using solely general anesthesia. These percentages differ greatly between hospitals and likely among countries. While reasons for these findings have to remain speculative at this time, the choice of anesthesia might be based in part on historic developments and local or personal preferences. Similar disparities have been reported for the anesthetic care of hip fracture patients[7]. Information on the use of peripheral nerve blocks in hip arthroplasty patients is even scarcer, but it is likely that the proportion of patients receiving such interventions remains low.

ANESTHETIC AND ANALGESIC TECHNIQUES FOR HIP SURGERY-BENEFITS AND PITFALLS

Despite some conflicting reports, a growing number of studies indicate that neuraxial anesthesia may prove beneficial to patients undergoing major joint replacement[8-13]. However, and as mentioned previously, neuraxial anesthetic techniques remain widely underutilized on a national level. Reasons for this underutilization remain speculative but include a number of practical and perception based variables. As with all medical interventions, risks and benefits have to be taken into account when applying anesthetic and analgesic techniques in the context of ones practice. Below follows a brief discussion of commonly utilized approaches.

Surveys conducted with orthopedic surgeons noted primarily the perceived delay to achieve surgical readiness and lack of reliability as hindering to the wider acceptance of regional anesthesia. Still most surgeons queried stated to understand the benefits and they are supportive of the use of these methods[14]. One of the factors why many patients and physicians might be reluctant to use neuraxial anesthesia is the fear of urinary retention and bladder catheterization. Contrary to prior belief it has been shown that patients undergoing hip arthroplasty have a low risk of urinary retention after neuraxial anesthesia and there has been no significant difference compared to general anesthesia[15].

The risk of epidural/spinal hematoma formation is also frequently quoted as a concern, although this event is arguably rare. In a series of over 100000 patients undergoing orthopedic surgery with neuraxial anesthesia only 8 patients out of 97 patients reporting neurologic

deficits were found to have epidural blood or gas collection. Of these affected individuals, all patients were using at least one potentially coagulation-impairing medication, but only one took an antiplatelet drug. In this series no patient sustained lasting nerve damage. This data suggests a slightly higher risk of complication then in an obstetric surgery setting, where patients are younger and healthier[16]. Furthermore, it has been shown that peripheral nerve blocks are safe to use even in patients requiring thromboprophylaxis after joint arthroplasty. In approximately 7000 procedures among patients receiving warfarin, aspirin, fondaparinux, dalteparin and enoxaparin no perineural hematomas have been recorded in continuous lumbar plexus, femoral and continuous or single sciatic blocks[17]. The general neurological complication risk of a central nerve blockade has been reported to lie below 0.04% and the rate of neuropathy after peripheral nerve block below 3%, with even less leading to permanent nerve damage. In fact, only one such case was reported in a review of 16 studies after peripheral nerve block with sample sizes ranging from 20 to 10309 blocks[18].

A number of specific regional anesthetic procedures have been described, all with advantages and pitfalls. The psoas compartment block has been described as analgesically potent as an epidural technique during hip surgery, but reports caution regarding the possibility of severe complications, with the main risk being intrathecal or intravasal application of cardiotoxic doses of local anesthetics. With the advanced use of ultrasound however, these deep blocks may become even safer and their role in an intraoperative setting during hip surgery will have to be further evaluated[19]. Due to the perceived risk involved in epidural, spinal or lumbar plexus blocks under anticoagulants, the femoral block has been developed as a possible alternative and has shown promising results considering postoperative analgesia, but has been criticized as an impediment to early postoperative ambulation[20]. Some data suggest that a 4-d continuous lumbar plexus block may be compatible with successful postoperative ambulation. Recent studies did not have enough power though, to show statistical significant superiority compared to overnight use[21]. Further, it has to be noted that under peripheral nerve block, for example a continuous lumbar plexus block, the risk of postoperative falls seems to be increased compared to non-continuous or no block used in patients with major lower extremity orthopedic surgery. However, the attributable risk of 1.7% seems to be within expectable range after major orthopedic surgery[22].

In keeping with the trend of delivering anesthetic potency as close to the source of pain as possible, investigators have studied if pain could be reduced in minimally invasive hip arthroplasty patients receiving spinal anesthesia and an epicapsular catheter delivering ropivacaine to the wound. This approach showed a statistically significant reduction in postoperative morphine intake compared to administration of a placebo agent[23]. To date, only few trials have shown corresponding results either by one-time local injection or continuous application, highlighting the fact that near-wound infiltration techniques warrant further studies for optimization. Due to the early stage of these techniques, no standard approaches or guidelines have been defined to date[24]. But many different approaches to regional anesthesia have shown promising results in postoperative pain reduction[25].

In trying to provide guidance on best practices for hip surgical patients, the PROSPECT workgroup, focusing on procedure specific postoperative pain management, has recommended the use of peripheral nerve blocks as the primary choice for postoperative pain management in patients undergoing total hip arthroplasty, followed by spinal or epidural anesthesia depending on risk factors and comorbidities. The newer local infiltration techniques still warranted a grade A recommendation, if applicable for postoperative pain management. Even though the need to identify the proper intraoperative anesthetic method is focused on the consideration of the comorbidities of an individual patient and postoperative analgesia is therefore considered to be a secondary concern[26].

ANESTHESIA TYPE AND PERIOPERATIVE OUTCOMES

While traditionally viewed as a means to provide surgical conditions, increasing evidence suggests that the choice of anesthesia significantly impacts on perioperative outcomes and thus may be viewed as a major component in an attempt to optimize patient care. Below follows a brief summary of the available evidence in respect to a number of important endpoints.

In-hospital mortality and 30-d mortality

Utilizing data from the UK collected between the years 2003 and 2011, a retrospective analysis of 90-d mortality in total hip replacements for osteoarthritis identified 4 major modifiable clinical factors for an improved outcome: A posterior surgical approach, mechanical and chemical thromboembolic prophylaxis and spinal anesthesia. Positive changes in management of the procedures could be shown as a steady decrease in 90-d mortality from 0.56% in 2003 to 0.29% in 2011[27]. On the contrary, preexisting factors such as advanced age, male gender and a history of cardiorespiratory disease were associated with an increased risk of mortality within thirty days after elective hip arthroplasty[28,29]. Interestingly, a new study evaluating the impact of the type of anesthesia on joint arthroplasty patients in the US, identified beneficial effects on major complications including 30-d mortality among all age groups of patients irrespective of comorbidity status, thus supporting the use of neuraxial anesthesia in all patient groups. Arguably though, the positive effect size was larger among older, sicker patients with cardiopulmonary diseases compared with younger, healthier patients[30].

Further, a population based comparative effectiveness

study has shown a trend of reduction in 30-d mortality in hip arthroplasty with neuraxial compared to general anesthesia alone, with respective mortality rates of 0.2% and 0.3%[6]. This mentioned positive effect of neuraxial anesthesia could also be shown in patients after hip fracture, a procedure typically affecting an elderly population[7]. Meta-analyses have shown that spinal anesthesia is associated with significantly reduced early mortality, fewer incidents of deep vein thrombosis, less acute postoperative confusion, a tendency to fewer myocardial infarctions, fewer cases of pneumonia, fatal pulmonary embolism and postoperative hypoxia. In this population general anesthesia and respiratory diseases were identified as significant predictor of morbidity[31].

Partially due to the fact that patients after traumatic injury are struggling with a number of contributing complications, this patient population suffers from a significantly higher mortality risk. In recent studies 30-d mortality has been reported as high as 13.3% and 3-6 mo mortality at around 15.8% in geriatric patients after hip fracture surgery. Indicators for this included advanced age, male gender, nursing home or facility residence, poor preoperative walking capacity, poor activities of daily living, higher ASA grading, poor mental state, multiple comorbidities, dementia or cognitive impairment, diabetes, cancer and cardiac disease. This extensive comorbidity burden helps to explain an overall mortality within 2 years of up to 34.5%[32].

In hip fracture patients, trials noted a beneficial outcome in patients receiving regional anesthesia, with the main benefit lying in reduced 1-mo mortality and incidence of deep vein thrombosis[13]. A recent comparative effectiveness trial of general versus regional anesthesia in hip fracture patients documented an in-hospital mortality rate of 2.4%. There were lower adjusted odds of mortality and pulmonary complications in patients receiving regional anesthesia. The rate of patients operated on with regional anesthesia was however noted to be at only 29%. In the subgroup analysis, regional anesthesia, *i.e.*, neuraxial, proved to be especially beneficial in patients with intertrochanteric fractures but no significant benefit in patients with femoral neck fractures could be shown[7].

Of interest may be that among elderly patients undergoing hip or knee surgery neither general nor regional anesthesia does seem to contribute to impairment of cognitive and functional competence[33].

Blood loss and transfusion need

For many years it has been repeatedly noted, that the type of anesthesia significantly impacts on intra and perioperative blood loss. These effects have primarily been attributed to hemodynamic differences, with lower and more stable blood pressures achieved through regional anesthesia resulting in less blood loss[34]. Others have suggested a negative effect of general anesthesia utilizing nitrous oxide in the anesthetic gas mix to hinder erythropoiesis during endogenous recovery of red blood cells as a contributing factor[35]. Studies showed favorable results pairing spinal anesthesia to general anesthesia, noting a reduction of blood loss and transfusion requirement, as well as higher postoperative hemoglobin levels on days 1 and 2[36]. Since these differences have been reported to occur even in similar systemic blood pressure anesthesia, some authors have suggested differences in the distribution of blood flow caused by spontaneous versus positive pressure ventilation[37]. Especially in patients undergoing total hip replacement the use of neuraxial anesthesia has shown a reduction in blood loss as well as transfusion rates[38]. The posterior lumbar plexus block has also been shown to be associated with reduced perioperative blood loss, perhaps in part due to its hemodynamic stability evoking pain control benefits and related decrease in sympathetic discharge[39].

Researchers have speculated that hypothermia in patients might contribute to coagulopathies and might have an impact on perioperative blood loss. While some studies seem to affirm these effects, others have failed to show significant differences in normothermic to hypothermic patients. Until further studies have been conducted it seems safe to strive for normothermic surgical patients[40]. Anesthesia generally affects body temperature, though neuraxial anesthesia seems to impair thermoregulatory control less than general anesthesia[41].

All in all, the reduction in blood loss and transfusion requirement associated with neuraxial anesthesia is one of the best established concepts. A previously discussed comparative effectiveness analyses showed a significant difference in blood product transfusion with a 14% reduction in neuraxial versus general anesthesia. Also neuraxial anesthesia, even in combination with general anesthesia, showed beneficial outcomes with an increased risk for transfusions (odds ratio 1.4) after total hip arthroplasties for general anesthesia alone when compared to combined neuraxial/general anesthesia[6].

Thromboembolic events

A number of pre-existing risk factors that have been shown to be associated with the development of thromboembolic events after hip surgery include a history of prior venous thromboembolism, obesity, delayed ambulation and female sex. Factors associated with lower risk could be identified in Asian/Pacific Islander ethnicity, the use of pneumatic compression among non-obese patients after surgery and extended thromboprophylaxis after hospital discharge. With these predisposing factors in mind some chemical markers have helped to identify high-risk patients, including elevated plasma D-Dimer and hyperlipidemia[42,43].

Many studies have shown differences in thromboembolic risks comparing the use of general versus neuraxial anesthesia[44]. Some authors suggest that the systemic effect of local anesthetics, as is seen during epidural anesthesia, might also lower surgery induced hypercoagulation in patients, leading to the aforementioned favorable difference in thromboembolic events. In patients undergoing epidural anesthesia after major orthopedic surgery

coagulation parameters were reported as not significantly altered from baseline[45]. Observational studies have failed to this day to show differences in homeostatic markers undergoing general or neuraxial anesthesia, leaving the reasons for the observed clinical differences to be discussed and studied[46].

Cardiopulmonary complications

The most frequent causes of death in modern joint replacement surgery are related to cardiopulmonary complications, even when excluding pulmonary embolism[47].

From a cardiovascular perspective, it has been shown that the use of general anesthesia in combination with an epidural block increased the probability of patients experiencing clinical significant hypotension during anesthetic induction as compared to patients receiving either anesthesia alone. Still, no differences in heart rate or frequency of bradycardia have been observed[35]. Recent population based data have failed to show differences in the risk for myocardial infarction in patients receiving general or neuraxial anesthesia. However, a 13% reduction in risk for non-ischemic cardiac events such as arrhythmias was noted[6].

From a pulmonary perspective, regional anesthesia has been shown to be the preferable type of anesthesia in hip fracture patients with COPD and seems to be also associated with less pulmonary complications in all hip fracture patients[7,48]. In patients undergoing total hip arthroplasty the use of general anesthesia *vs* neuraxial anesthesia showed a favorable outcome in respect to pulmonary complication risk with an adjusted odds ratio of 3.34. Since this significant beneficial effect could not be shown when a combination of neuraxial and general anesthesia was used, the reduced need for airway instrumentation and mechanical ventilation leading to less risk for aspiration, pneumonia or atelectasis might be possible underlying factors. Additionally, the reduction in postoperative opioid use might be a further reason for reduced pulmonary compromise and reduced utilization of critical care services[6,49].

Infections

Surgical site infections are feared complications associated with significant morbidity and mortality[50]. After adjustment for influencing factors, the odds of surgery site infections have been reported 2.21 times higher in patients receiving general anesthesia when compared to epidural or spinal anesthesia[51]. The overall rate of infections (including surgical site and systemic) in elective hip surgery has been shown to be significantly increased with an adjusted odds ratio of 1.45 when comparing general anesthesia with neuraxial anesthesia alone[6].

Some explanation for the aforementioned effects may be, that in-vitro and in-vivo experiments showed local anesthetics to modulate inflammatory response. Since epidural administration of local anesthetics leads to blood levels close to intravenous application, a systemic effect of these local anesthetics has to be considered. There have been beneficial reports of systemic use of local anesthetics in sterile inflammation. However, it has been hypothesized, that with bacterial contamination this might lead to an increased risk of infection[52].

Therefore it has been questioned whether neuraxial anesthesia is safe in patients with pre-existing infections such as infected prosthesis. Studies showed, that in these settings there was only a minimal risk of central nervous infections based on clinical criteria[53]. Furthermore there has been no difference noted in cell-mediated or humoral immune response comparing spinal or general anesthesia[54].

Economic outcomes

The international trend to reduce length of stay in surgical patients also applies to hip surgery. With multi-modal anesthesia, minimal invasive-surgery and home rehabilitation it has been shown that up to 44.4% of patients following total hip arthroplasty can be discharged within 24 h. Many patients can be discharged with indwelling peripheral nerve catheters and up to three-quarters of these patients do not require outpatient or home nursing care. Negative predictive factors for early discharge seem to be female gender, increasing age, increasing estimated blood loss and ASA III or IV[55].

Concerns that complicated procedures may raise operating costs can be addressed by strategy and structural changes in the perioperative process, as has been shown in using an induction room in which pre-operative neuraxial anesthesia is being performed adjacent to the operating room[56]. In contrast to perceived delays total hip replacement surgery operating times were significantly reduced in patients receiving regional anesthesia[12]. Some studies argue that spinal anesthesia is associated with a benefit reflected in significant cost-reduction both in anesthesia times and recovery compared to general anesthesia in total hip or knee replacement operations[57]. When studying population data, results suggest a lower incidence of increased cost in neuraxial patients combined with a lower risk for prolonged length of stay[6]. In addition to lower complication rates and decreased resource utilization associated with the latter (as expressed in lower intensive care unit utilization and need for mechanical ventilation), economic benefits achieved with neuraxial anesthesia seem to make a sound economic argument[49].

CONCLUSION

Randomized controlled trials on the differential impact of the type of anesthesia on outcomes are rare, underpowered and often present single-institutional data from specialized institutions. Meta-analyses and population based comparative effectiveness studies however, have shown that regional anesthesia seemingly improves perioperative outcomes in hip surgical patients. Most studies concur on positive outcome in overall mortality, thromboembolic events, blood loss and transfusion requirements. Despite some criticisms of the retrospective

nature of such analyses and those associated with methodological limitations, the evidence suggest that regional anesthesia is widely underused but could be a major factor in reducing medical and economic adverse outcomes.

While the reasons for these findings have to remain speculative to a certain extent, future investigations into the mechanisms of benefits observed with regional over general anesthesia may convince more clinicians of the benefits that could be gained by employing low cost and safe interventions in the form of regional techniques. Certainly, given the fact that only a small minority of patients currently receive regional anesthesia in some form, an increase in utilization could have profound effects on the health care system as a whole. Concluding, much of the currently available evidence suggests that a comprehensive medical approach with emphasis on regional anesthesia can prove beneficial to patients and the health care system.

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Survival outcomes of cemented compared to uncemented stems in primary total hip replacement

Michael Wyatt, Gary Hooper, Christopher Frampton, Alastair Rothwell

Michael Wyatt, Gary Hooper, Christopher Frampton, Alastair Rothwell, Department of Orthopaedic Surgery and Musculoskeletal Medicine, University of Otago, Christchurch, Canterbury 8011, New Zealand
Author contributions: Wyatt M, Hooper G and Rothwell A wrote article; Frampton C contributed to statistical analysis.
Correspondence to: Michael Wyatt, BSc(Hons), MBChB, MRCS(Ed), Department of Orthopaedic Surgery and Musculoskeletal Medicine, University of Otago, 2 Riccarton Avenue, Christchurch 4710, Canterbury 8011,
New Zealand. mcwyatt@xtra.co.nz
Telephone: +64-3-3640640 Fax: +64-3-3640806
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Core tip: There has been a worldwide trend towards uncemented fixation in total hip replacement yet paradoxically cemented fixation has the highest survival rate when failure has been defined as a revision of the primary implant for aseptic loosening. However closer analysis of registry data shows that revision for aseptic loosening is low with uncemented total hip replacement, and in particular revision of uncemented stems is the lowest in young patients under 65 years, who would be expected to have higher physical demands with higher failure rates secondary to loosening.

Original sources: Wyatt M, Hooper G, Frampton C, Rothwell A. Survival outcomes of cemented compared to uncemented stems in primary total hip replacement. *World J Orthop* 2014; 5(5): 591-596 Available from: URL: http://www.wjgnet.com/2218-5836/full/v5/i5/591.htm DOI: http://dx.doi.org/10.5312/wjo.v5.i5.591

Abstract

Total hip replacement (THR) is a successful and reliable operation for both relieving pain and improving function in patients who are disabled with end stage arthritis. The ageing population is predicted to significantly increase the requirement for THR in patients who have a higher functional demand than those of the past. Uncemented THR was introduced to improve the long term results and in particular the results in younger, higher functioning patients. There has been controversy about the value of uncemented compared to cemented THR although there has been a world-wide trend towards uncemented fixation. Uncemented acetabular fixation has gained wide acceptance, as seen in the increasing number of hybrid THR in joint registries, but there remains debate about the best mode of femoral fixation. In this article we review the history and current world-wide registry data, with an in-depth analysis of the New Zealand Joint Registry, to determine the results of uncemented femoral fixation in an attempt to provide an evidence-based answer as to the value of this form of fixation.

INTRODUCTION

The best mode of implant fixation in primary total hip replacement (THR) has been a source of debate. Cemented implants achieve stability from cement-bone mechanical interlock, once the polymethylmethacrylate has cured, whereas cementless fixation relies on primary press fit stability with long term stability occurring secondary to endosteal microfractures at the time of preparation and subsequent bone ongrowth or ingrowth. The optimum fixation choice should be guided by patient based outcomes, in particular the implant survivorship as measured by revision for aseptic loosening, as this was

a major reason for the introduction of uncemented implants.

Advocates of cemented implants cite the excellent and reliable long-term reported survivorship[1-3] whereas proponents of cementless fixation contend that this method is equally reliable[4-7] and in fact superior in younger, high-demand patients[8,9]. Furthermore, cementless implants provide a broader range of options especially for the acetabulum where liner exchange may be required for postoperative instability; the commonest cause for early re-operation in all primary THR[10]. Modular cups also offer the option for changing the femoral head diameter which may improve the functional outcome especially in the younger or more active patient. A hybrid THR, where the stem is cemented and the cup uncemented, has been suggested to provide the benefits of both fixation methods[11,12] although the reported results have been mixed[13-15]. Worldwide there has been an observed trend towards uncemented fixation with confirmatory joint registry results in Australia, New Zealand, England, Wales and Sweden. Both Canada and the United States have continued to have a predominant use of uncemented THR[14-18].

One of the traditional arguments against uncemented THR has been the increased cost with implants often being 3-4 times more expensive than the cemented variety. In the immediate future, the burden of an ageing population with the projected increase in demand for THR will put considerable strain on health funding agencies requiring balanced economic arguments for the use of THR implants. There is also likely to be an increase in the absolute number of revision procedures which are approximately 4 times more expensive than primary procedures, especially when both the femoral and acetabular components are revised. This has implications if one form of fixation is inferior to the other. Those that advocate uncemented implants suggest that following successful bonding of both the femoral and acetabular components to bone then future revision procedures may only involve exchange of articulating surfaces, which is likely to be a procedure whereby patients recover rapidly with a lower overall health cost[19].

Uncemented acetabular implants are widely used in all age groups with registry results showing satisfactory early and mid-term results[4,14-18]. However, uncemented femoral implants have been less widely accepted with several countries continuing to favour the cemented option as seen in the increasing number of hybrid THR performed in registries across the world[15,18]. We have reviewed the recent evidence supporting femoral implant fixation, in particular joint registry outcomes, in an attempt to provide sound recommendations for future practise.

HISTORY OF FIXATION IN PRIMARY TOTAL HIP REPLACEMENT

The British Orthopaedic Association meeting in London, September 1964 was a turning point for the treatment of patients with crippling osteoarthritis of the hip. McKee (Norwich) presented the results of the cemented metal-on-metal McKee-Farrar arthroplasty and Charnley (Wrightington) demonstrated the results of his cemented metal-on-polyethylene THR by having one of his patients walk normally across the stage. Widespread high rates of aseptic loosening of cemented THR during the 1960's and 1970's tempered enthusiasm and "Cement disease" was widely held as the cause of this loosening. Many surgeons began to favour the use of cementless fixation as recommended by Ring with his metal-on-metal replacement[2]. However excellent results with cemented fixation were maintained with the Charnley prosthesis. The Exeter group, who believed that poor cementing technique and not cement *per se* was the issue, developed their collarless, taper-slip cemented prosthesis specifically designed to subside into the cement mantle while providing even load. The early metal-on-metal design soon fell from favour with high failure rates, possibly related to poor manufacturing tolerances of the implant, and the improving results of cemented metal-on-polyethylene replacements.

The high rates of early loosening and failures observed in younger, active patients coupled with concerns regarding "cement disease" continued to drive a renewed interest in uncemented fixation[20-22]. Early failures of cemented implants in these younger patients were often associated with a varus positioning of the femoral stem whereas the acetabular component often failed after 12 years with polyethylene wear and loosening. The use of cementless components in this patient cohort initially established the wider use of these implants throughout the world in the hope that they would improve survivorship. Once it had been established that aseptic loosening was in fact due to the polyethylene debris and not 'cement disease' uncemented THR had become firmly established as a recognised and viable option for surgeons.

MODERN PRIMARY FEMORAL STEM

Over the last 20 years significant attention has been paid to improving the cementing technique which has emphasised both the preparation of the femoral canal and the pressurisation of the cement on insertion. These changes have improved the cement-bone interface with more stable inter-locking and as a result the intermediate survival rates of cemented stems have improved. Current joint registries record between 92% at 11 years and 86% at 22 years survival for these implants[14,15,18]. These improved survival statistics have been interpreted as a cemented THR is likely to be a "life long" implant for patients aged sixty-two or older, whereas for a fifty-eight-year-old patient there is a 50:50 chance of undergoing a revision within their life time[23].

There are currently two philosophies of cemented femoral fixation: composite beam and polished, tapered wedge. The former is predominant in North America whereas the latter is more widely used in Europe. A composite beam relies on rigid bonding to the cement and is

Table 1 Thirteen year New Zealand Joint Registry results for revision rates *vs* fixation method

Fixation	Component years	Events	Rate/100 cy	95%CI
Cemented	149098	870	0.58	0.55-0.62
Hybrid	168604	117	0.66	0.62-0.70
Reverse hybrid	3124	19	0.61	0.37-0.95
Uncemented	148214	1313	0.89	0.84-0.94

not intended to subside. This is in contrast to the loaded taper wedge which converts radial compression into hoop stresses within the cement mantle, and is expected to subside. The addition of cement around an implant provides an additional buffer that the surgeon can manipulate to control correcting leg length and version during insertion. Cement use has sporadically been reported as producing potentially fatal associated cardiovascular and embolic phenomena at implantation, especially in the elderly compromised patient[24].

Cementless stems rely on bone on-growth or in-growth to provide stability. A roughened titanium stem has been shown to attract bone and provide early stability[25] and most uncemented stems today have this type of surface. The addition of hydroxyapatite to this surface has been show to also stimulate bony fixation[26] without the initial early concern of producing ceramic particles in the joint that could cause third body wear.

There are two major uncemented stem designs: proximal (metaphyseal) loading or fully coated. Proximal loading has been advocated to avoid the stress shielding that was observed with early "distal fitting" implants[27]. Often these implants are bulky in the proximal metaphyseal region, which is responsible for the early resistance to subsidence and rotation, and smooth distally to prevent bone apposition. They are inserted following minimal reaming and are rarely associated with femoral fracture. On the other hand, fully coated stems rely on a graduated loading of the proximal femur, allow bone apposition throughout their length and provide stability by their wide, flat nature. Initial stability is achieved by reaming the femur to accept a maximally sized implant that undergoes three-point fixation in the proximal femur. These implants require exact sizing and significant reaming and are associated with a higher incidence of femoral fracture[28].

EUROPEAN JOINT REGISTRY OUTCOMES AND TRENDS IN FEMORAL FIXATION

The Swedish hip registry reports a gradual trend for the increased use of uncemented fixation although cemented THR's were used in 64% of all patients in 2011 regardless of age[14]. Overall cementless stem fixation was more common in the younger, active patient with good bone quality whereas cemented fixation was favoured for patients over seventy years of age. Cemented THR had a 90% 16-year survivorship and was 30%-80% less likely to be revised compared to uncemented and hybrid THRs

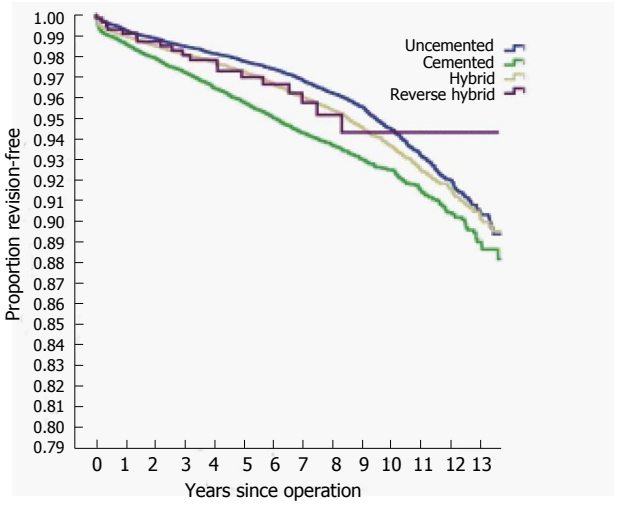

Figure 1 Thirteen New Zealand Joint Registry Kaplan-Meier survival curve of total hip replacement by fixation type.

during the first 8 years, suggesting that early revision was more likely to be related to acetabular problems. After 8 years the survivorship of the uncemented group tended towards that of the cemented group. Up to age 70 years the uncemented hips had fewer revisions attributed to loosening. The hybrid combinations did not convey a clear advantage over either group.

The Norwegian Hip Registry also reported an overall trend towards less cemented fixation but in Norway this was largely due to an increase in hybrid THR[15]. Overall cemented THR's had a twenty-year survival rate of 85% compared to 50% for uncemented total hips. Hybrids had no clear advantage over either cemented or uncemented THR's in terms of implant survival during the same time period. Uncemented or hybrid fixation were preferred in patients under the age of 60 years whilst cemented fixation was used in the great majority > 60 years old.

In the National Joint Registry of England and Wales cemented THR represented only 33% of all primary THR's yet was used the majority of times for patients over eighty years of age[19]. Total cementless fixation was used in 43% of patients and was the major type of fixation for patients less than seventy years old. Hybrid THRs accounted for 20% of primary THR's. The cumulative percentage of revision (with 95%CI) at 9 years was 2.71% (2.57-2.87) for cemented, 6.71% (6.40-7.05) for uncemented and 3.42% (3.10-3.76) for hybrid THR.

RESULTS FROM THE NEW ZEALAND JOINT REGISTRY

The data from the world-wide joint registries portray a similar pattern for the survival of cemented THR compared to uncemented THR, and these results are supported by those of the New Zealand Joint Registry (NZJR, Table 1 and Figure 1). On this basis it would be easy to dismiss the uncemented variety as inferior, but revision

Table 2 Thirteen year New Zealand Joint Registry reasons for revision for loosening within 90 d *n* (%)

Fixation/*n*	Loose cup	Loose stem	Unstable	Deep infection	Pain	Femoral fracture
Cemented/77	6 (7.8)	3 (3.9)	58 (75.3)	9 (11.7)	9 (2.6)	3 (3.9)
Hybrid/189	31 (16.4)	7 (3.7)	113 (59.8)	26 (13.8)	5 (2.6)	9 (4.8)
Reverse hybrid/2	0	1 (50)	0	0	0	1 (50)
Uncemented/270	23 (8.5)	23 (8.5)	108 (40)	26 (9.6)	5 (1.9)	81 (30)

Table 3 Thirteen year New Zealand Joint Registry reasons for revision for loosening by fixation method *n* (%)

Fixation/*n*	Loose cup	Loose stem	Unstable	Deep infection	Pain	Femoral fracture
Cemented/870	415 (48)	148 (17)	200 (23)	105 (12)	86 (10)	74 (8.5)
Hybrid/1117	160 (14)	235 (21)	384 (34)	157 (14)	136 (12)	141 (11)
Reverse Hybrid/19	4 (21)	1 (5)	5 (26)	4 (21)	2 (11)	3 (16)
Uncemented/1313	198 (15)	192 (15)	307 (24)	124 (9)	222 (17)	141 (11)
P value	< 0.001	< 0.001	< 0.001	0.003	< 0.001	0.208

as an end point is a "blunt tool" and needs to be interpreted in conjunction with several other factors. We have reviewed the results of the New Zealand joint Registry in detail to elucidate this and to look at cofounding variables that may contribute to these revision rates.

One of the primary reasons for the introduction of the uncemented stem was to improve the outcome in younger, more active patients, particularly males. The New Zealand joint registry has shown a revision rate of 0.89/100 component years (cy) for uncemented THRs in patients under 55 years compared to 1.73/100 cy for cemented THR and 0.90/100 cy compared to 0.98/100 cy for those between 55-65 years ($P < 0.001$)[16]. Over 65 years this was reversed with the cemented THR surviving longer than the uncemented variety ($P < 0.001$). The overall revision rate was significantly higher ($P < 0.001$) in patients under 65 years (1.00-0.83/100 cy) compared to those over 65 years (0.65-0.45/100 cy) and an argument could be made that because of this the uncemented stem was more robust in a high demand patient. Hybrid fixation also showed poorer survival in the under 55 year group compared to uncemented THR (1.03/100 cy compared to 0.93/100 cy, $P < 0.002$) suggesting that it may be the uncemented stem in this age group which has helped improve the survival statistics.

Early revision (within 90 d) was far more common ($P < 0.001$) in the uncemented THR (0.899%) compared to cemented THR (0.353%) which continued across all age groups but only reached significance in those over 65 years ($P < 0.001$).When the reason for revision was analysed the major cause for early revision in uncemented implants was either due to femoral fracture (30%) or dislocation (40%) whereas 75% of early revisions in the cemented group were secondary to dislocation (Table 2). Femoral fracture with uncemented stems has been identified as an early cause for failure by others[14]. Femoral fracture was shown to be age dependent, with older patients and presumably those with poorer bone density having a much higher incidence of this complication (Figure 2). This complication may be due to surgical inexperience and/or attempting to "over ream" the femur to insert the largest implant to avoid early subsidence or failure of bonding to the prosthesis. The early rate of femoral fracture did not continue beyond 90 d as the overall 13 year results showed there was no significant difference in revision for femoral fracture between the fixation methods ($P = 0.208$) (Table 3). This contradicts the Swedish registry results which show that uncemented stems are revised twice as frequently as cemented stems during the first five years and that cemented stems were ten times less likely to require revision for periprosthetic fracture. The reason for this discrepancy is not immediately apparent.

The rate of femoral loosening within 90 d was significantly higher in uncemented stems ($P < 0.009$) but decreased over the 13-year period to become essentially the same as cemented stems (0.62% *vs* 0.66%). This early "loosening" of uncemented stems is likely to be associated with surgical technique and under sizing of the component, whereas the longer results are more likely to reflect the true aseptic loosening rate. Removing the early failures due to loosening makes the performance of the uncemented stem much more impressive and suggests that long term aseptic loosening may not affect it to the same extent as cemented THR. Figure 3 shows the increasing failure rate of cemented stem due to aseptic loosening compared to uncemented stems, suggesting that in the future this failure mode may remain static in uncemented stems but increase in the cemented variety. The fact that failure of hybrid fixation secondary to femoral loosening was 0.77% ($P < 0.001$) adds evidence to the suggestion that the cemented femoral stem may be more likely to fail by this mechanism. These results are supported by the Swedish registry which showed that from eight to sixteen years cemented stems had a higher rate of revision over cementless stems and 80% of these were for loosening.

In the past there has been controversy over the use of antibiotic loaded cement and whether this would decrease revision for prosthetic infection. Most have accepted that it was unlikely to do any harm, however the results from the NZJR are interesting when you consider that the great majority (> 90%) of cemented implants are performed with antibiotic cement. The combined revision rate for infection for both cemented and hybrid THR was 0.50% compared to 0.40% for uncemented THR which suggests that antibiotic cement may not have the protective effect against infection that has been assumed. This result is similar to the Swedish registry which demonstrated that cemented stems were 1.4 times more likely

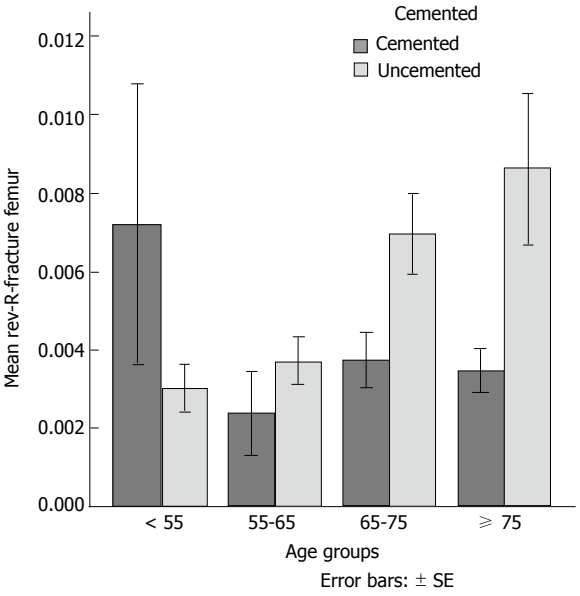

Figure 2 The New Zealand Joint Registry results showing the comparison of the incidence of femoral fracture and age with cemented and uncemented stems (65-75 yr, *P* = 0.008; > 75 yr, *P* = 0.001).

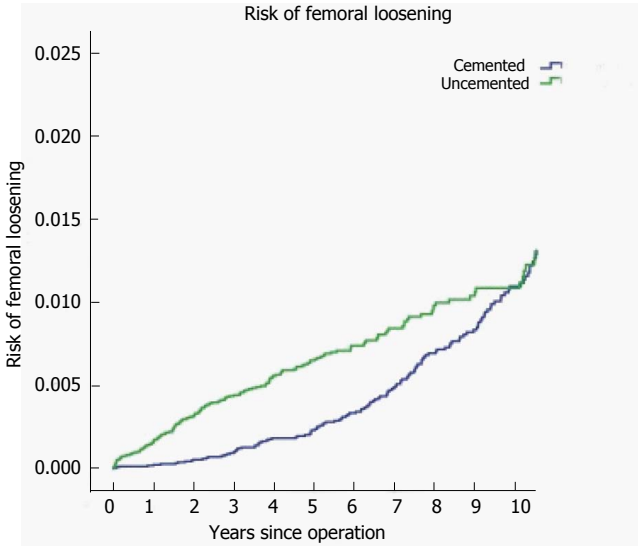

Figure 3 The New Zealand Joint Registry results showing the comparison between cemented and uncemented stems and the incidence of revision for aseptic loosening.

to be revised for infection.

In the past unexplained pain has been a feature of the uncemented femoral stem but with a move away from distal fixation the incidence of revision for this complication was low at 90 d, however by 13 years pain became the second commonest cause for revision surgery behind dislocation in this group of implants. Pain as a cause for revision was not specified and so may not have been due to femoral pain. Regardless it is encouraging to find that pain was now a low cause for early revision of uncemented stems.

Another complicating variable which is unique to uncemented THR has been the ability to use different bearing surfaces in an attempt to improve the wear associated with a polyethylene articulation. Both metal on metal and ceramic on ceramic surfaces however have been associated with early failures due to reasons not associated with cemented THR. However most of these complications have arisen from the articulating surface itself, with ceramic fracture and excessive metal ion debris two of the primary reasons for early failure. These problems have not necessarily resulted in failure of the uncemented stem secondary to loosening and as a result have almost certainly skewed the overall revision rates in favour of cemented THR. The problem can be illustrated in the 14-year NZJR report where the revision rate for metal on metal articulations with femoral head size > 36 mm was 3.08/100 cy. The use of larger femoral head sizes is almost solely used in uncemented implants and those with a head size > 36 mm had a combined revision rate of 2.75/100 cy, irrespective of the articulating surface. This offers a potential explanation for the different revision rates between the two forms of femoral fixation.

IMPLANT COST

Although uncemented implants are more costly than cemented there have been studies suggesting that the overall cost differential between the two types of fixation is not dramatically different[29,30]. With the increasing use of hybrid fixation the cost difference between a cemented and uncemented stem is even smaller and likely to be less relevant in the overall economic assessment. Determining the exact cost of a femoral stem can be difficult as the list price may be significantly different from the purchase price after discounting for bulk purchases and other company driven incentives. We cannot make a comment about pricing in other countries but are aware that companies in our country are required to price their implants in reasonable price bands to remain commercially viable and competitive.

CONCLUSION

Controversy continues to exist regarding the best form of fixation to use in THR. Often opinions are polarised by such factors as training, tradition, and personal preference with proponents of cemented fixation often citing the overall poorer revision rates for uncemented THR reported in the various national joint registries. This review has attempted to clarify the differences between cemented and uncemented THR, with the emphasis on femoral fixation, by analysing the reported joint registry data. There has been a world-wide trend towards uncemented THR over the last 10 years, and even countries who in the past have been the major proponents of cemented fixation have not been excluded from this trend.

Uncemented THR was introduced to address the poorer results observed with cemented THR in younger patients with higher functional requirements and to this end the registry results would confirm that inpatients < 65 years have a lower revision rate with uncemented fixation. In particular the uncemented stem has performed better in this age group with a lower rate of aseptic loos-

ening compared to the cemented variety. Femoral fracture remains a significant reason for early revision with uncemenetd stems which is more likely to be related to surgical technique and potentially could be improved by increased exposure to this technique in surgical training.

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Management bone loss of the proximal femur in revision hip arthroplasty: Update on reconstructive options

Vasileios I Sakellariou, George C Babis

Vasileios I Sakellariou, First Department of Orthopaedics, Medical School, University of Athens, ATTIKON University General Hospital, Chaidari 12462, Greece
George C Babis, Second Department of Orthopaedics, Medical School, University of Athens, Nea Ionia General Hospital, Athens 14233, Greece
Author contributions: Sakellariou VI and Babis GC solely contributed to this paper.
Correspondence to: George C Babis, MD, PhD, Professor and Chairman of Orthopaedics, Second Department of Orthopaedics, Medical School, University of Athens, Nea Ionia General Hospital, 3-5 Ag. Olgas Street, Athens 14233, Greece. george.babis@gmail.com
Telephone: +30-213-2057956 Fax: +30-213-2057783
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Abstract

The number of revision total hip arthroplasties is expected to rise as the indications for arthroplasty will expand due to the aging population. The prevalence of extensive proximal femoral bone loss is expected to increase subsequently. The etiology of bone loss from the proximal femur after total hip arthroplasty is multifactorial. Stress shielding, massive osteolysis, extensive loosening and history of multiple surgeries consist the most common etiologies. Reconstruction of extensive bone loss of the proximal femur during a revision hip arthroplasty is a major challenge for even the most experienced orthopaedic surgeon. The amount of femoral bone loss and the bone quality of the remaining metaphyseal and diaphyseal bone dictate the selection of appropriate reconstructive option. These include the use of impaction allografting, distal press-fit fixation, allograft-prosthesis composites and tumor megaprostheses. This review article is a concise review of the current literature and provides an algorithmic approach for reconstruction of different types of proximal femoral bone defects.

Key words: Arthroplasty; Proximal; Femur; Reconstruction; Bone loss

Core tip: Massive osteolysis, stress-shielding, periprosthetic infections or multiple revisions can consist the most common etiologies for extensive loss of bone stock of the proximal femur. The amount of femoral bone loss and the bone quality of the remaining metaphyseal and diaphyseal bone dictate the selection of appropriate reconstructive option. These include the use of impaction allografting, distal press-fit fixation, allograft-prosthesis composites and tumor megaprostheses. The present study is a concise review of the current literature presenting an algorithmic approach for reconstruction of different types of proximal femoral bone defects.

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INTRODUCTION

Approximately 250000 primary and over 50000 revision total hip arthroplasty procedures are performed in the United States each year[1]. The number of revision total hip arthroplasties is expected to rise as the indications for arthroplasty will expand due to the aging population and the continuous advances in technology and surgical techniques[1,2]. Massive osteolysis, stress-shielding, peripros-

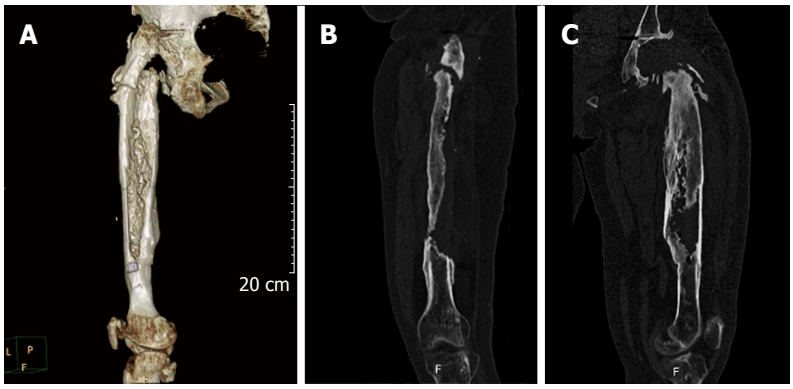

Figure 1 Computed tomography scan images with metallic artifact subtraction and three-dimensional reconstruction consist a useful tool for precise assessment of the amount of bone loss and the specific variations of the femoral anatomy preoperatively. A: Computed tomography scan image of the left femur (posterior projection) with metallic artifact subtraction and three-dimensional reconstruction showing precisely the amount of bone loss of the proximal part of the femur; B: Coronal; C: Sagittal view of the same case.

thetic infections or multiple revisions can eventually lead to extensive loss of bone stock in the proximal femur[2,3]. Additionally, osteolysis due to loosening and wear and pre-existing osteoporosis may result to deficient femoral bone stock. Femoral bone loss as a result of failed total hip arthroplasty is a problem that continues to challenge orthopaedic surgeons. The aim of the present study is to provide an algorithmic approach for reconstruction of different types of proximal femoral bone defects through a concise review of the current literature.

CLASSIFICATION

Multiple systems have been used to classify the severity of bone loss of the proximal femur. Most of these classification systems are descriptive of the amount and the area of bone loss. Using a standardized approach the investigators try to accurately define the structural integrity of the metaphyseal and diaphyseal bone, suggesting the available options of implant fixation to the remaining host bone.

The classifications proposed by (1) the AAOS Committee on the Hip[4]; and (2) Della Valle and Paprosky[5] are most commonly used to describe the amount of femoral bone loss and propose guidelines for treatment of each type of proximal femoral bone deficiency.

The AAOS classification divides the femoral bone defects into segmental and cavitary[4]. Segmental defects include loss of supporting cortical bone, whereas the cavitary defects are defined as any bony loss of the cancellous medullary bone. Malalignment refers to any compromise of the femoral architecture and natural geometry resulting into angular or rotational deformities. Stenosis is the partial or complete occlusion of the femoral canal as a result of a previous trauma or hypertrophic bone reaction. Discontinuity is defined as the loss of cortical continuity due to pre-existing fracture or established non-union.

The Paprosky classification[5] of proximal femoral defects is used to assess the amount of bone loss and define the morphology of remaining proximal femoral bone stock; it also provides guidelines for treatment. Paprosky type I defects are characterized by minimal metaphyseal cancellous bone loss with intact diaphysis. Type II defects have more extensive cancellous bone loss including the whole metaphysis down to the level of the lesser trochanter. In type ⅢA defects, there is an extensive bone deficit of the proximal femur; the metaphyseal bone is non-supportive; however, there is adequate diaphyseal bone (intact circumferential bone more than 4 cm in length) for distal fixation of a cementless stem. In Type ⅢB defects the available diaphyseal bone is less than 4 cm in length. Type Ⅳ femora have a widened diaphysis that provides no support for cementless fixation.

PREOPERATIVE PLANNING

Meticulous preoperative planning is of paramount importance before proceeding to a complex revision surgery that includes exchange of the femoral component. Preoperative planning is helpful in assessing the type of proximal femur defficiency, evaluating the radiographic leg length discrepancy and selecting the proper implant in terms of size, length and offset. Calibrated X-rays of the pelvis and the affected hip in 2 projections (anteroposterior and lateral) are required in order to better evaluate the amount of bone loss, classify the bony defect and select the optimal reconstructive option[6].

However, plain radiographs are not always sufficient to assess with accuracy the amount of bone loss and the quality of remaining bone. Computed tomography (CT) scans provide superior image quality and may be processed and reconstructed into 3 dimensional projections that are extremely valuable for preoperative planning and implant selection. However, metallic artifacts may limit the clarity of imaging especially in the presence of metal implants in the under-study area. In complex cases, CT scan images with metallic artifact subtraction and three-dimensional reconstruction consist a useful tool for precise assessment of the amount of bone loss and the specific variations of the femoral anatomy preoperatively (Figure 1).

Magnetic resonance imaging (MRI) has gained popularity in assessing the integrity of soft tissue and especially of the abductor musculature in a painful THA. Especially, in the presence of metal-on-metal articulation identification of potential adverse reaction to metal debris is of significant importance. Metal artifact reduction MRI appears to be the most useful tool for diagnosing, staging and monitoring these types of adverse reactions

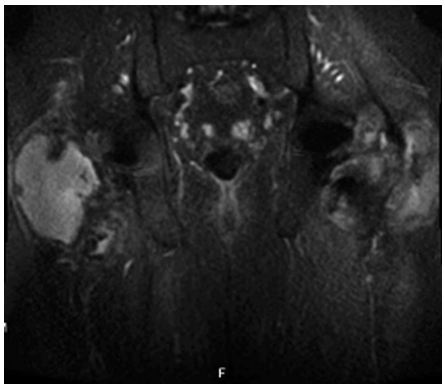

Figure 2 Metal artifact reduction magnetic resonance imaging (coronal view) showing the adverse reactions to metal debris and formation of pseudocapsules in both hips following bilateral total hip arthroplasties with modular necks.

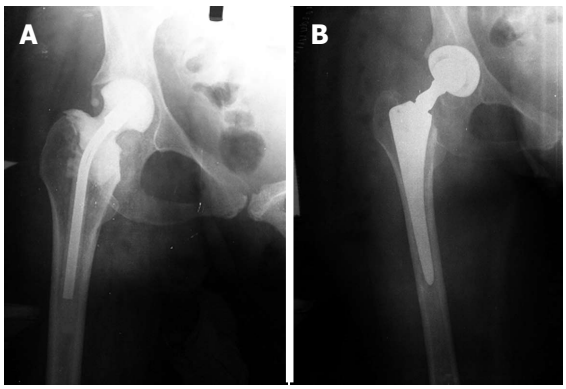

Figure 3 Anteroposterior radiograph of bone loss. A: Anteroposterior (AP) radiograph of the right hip showing minimal bone loss of the proximal metaphyseal bone secondary to periprosthetic hip infection. A antibiotic cement spacer was implanted after irrigation and debridement during the first stage of a two-stage exchange arthroplasty; B: AP radiograph of the same hip after the second stage. The metaphyseal bone loss was minimal and a cementless primary stems with common length and geometry was used.

to metal debris[7] (Figure 2).

RECONSTRUCTIVE OPTIONS

Revision of the femoral component and reconstruction of a femur with severe bone loss is a complex procedure. Improvements in prosthetic designs and implant materials have been associated with superior clinical outcomes and better implant survivorship.

The main objectives of femoral reconstruction during revision hip surgery are to preserve the remaining bone of the femur, as much as possible, and to provide a stable implant fixation. Restoration of hip function, joint stability and leg length equality are important goals of reconstructive procedure[3,5].

An algorithmic approach to restore the bone defect of the proximal femur based on previously published classification systems is presented in Table 1[4,5].

According to Paprosky classification[5], type I proximal femoral defects that are characterized by minimal metaphyseal cancellous bone loss with intact diaphysis may be easily reconstructed using cementless or cemented primary stems with common length and geometry (Figure 3). No additional mode of fixation (fully porous coating or distal fixation implants) is usually required.

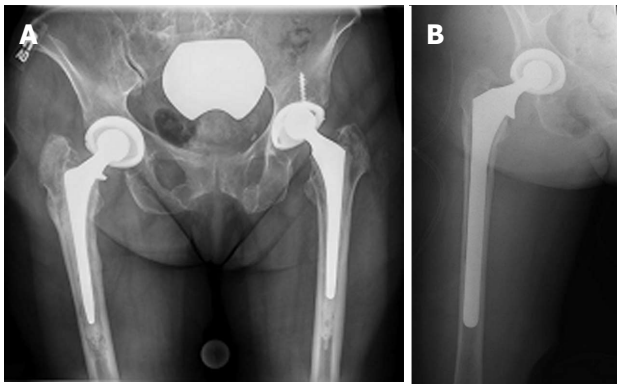

Figure 4 Extensively porous coated stems. A: Anteroposterior (AP) radiograph of the pelvis demonstrating bilateral total hip arthroplasties. In right hip there is evident loosening of the femoral stem and extensive metaphyseal cancellous bone loss with some diaphyseal bone loss, which is limited to less than 4 cm of diaphyseal bone; B: AP radiograph of the same hip post revision using an extensively porous coated stem.

In type Ⅱ defects, with extensive metaphyseal bone loss and intact diaphysis, the reconstructive options are associated with the quality of metaphyseal bone. Modular stems with proximal fixation are preferred[8]. This permits load transfer through the proximal metaphyseal bone more physiologically. However, when the medial cortex of the femoral neck is compromised a calcar replacement stem may be used in order to provide a more secure proximal fixation and accurately restore leg length. In a recent study, Emerson *et al*[9] showed that calcar replacement stems with 40% porous-coating have excellent clinical outcome with a very low incidence of mechanical failure (3%). Ninety-four percent of these stems remain in-situ 11.5 years after implantation, which is a superior outcome comparing to most cemented femoral revision series[9].

In type ⅢA defects, the cancellous bone of the proximal femoral metaphysis is defective; However, the femoral diaphysis is still intact and more than 4 cm of cortical bone is available for distal fixation. This type of femoral defects requires the use of cementless stems with distal (diaphyseal) fixation[10-12]. Extensively porous coated stems (Figure 4) or modular stems (Figure 5), which are fluted distally and porous coated proximally, may be used to achieve adequate diaphyseal fixation[13,14]. Under-sizing of the femoral component is the most frequently referred cause of failure that leads to implant subsidence and loss of mechanical support[13,14]. Meticulous preparation of the femoral canal is of paramount importance in order to achieve optimal fit and fill of the stem to the femoral canal and secure fixation of the flutes into the cortical bone[13,14].

In the type ⅢB femoral defects, less than 4 cm of

Table 1 Algorithmic approach of proximal femur reconstruction according to Paprosky classification

Type	Description	Treatment option
I	Minimal metaphyseal cancellous bone loss Intact diaphysis	Cementless or cemented primary stems with common length and geometry
II	More extensive cancellous bone loss including the whole metaphysis down to the level of the lesser trochanter	Proximally fixed stem (usually modular) Calcar replacement stem if medial cortex of the femoral neck is compromised
IIIA	Extensive metaphyseal and diaphyseal bone loss of the femur; More than 4 cm of diaphyseal bone are available for distal fixation of cementless stem	Cementless stems with distal (diaphyseal) Extensively porous coated stems Modular stems fluted distally and porous coated proximally
IIIB	Available diaphyseal bone is less than 4 cm in length	Extensively porous-coated stems Impaction grafting + cemented stem Modular cementless tapered fluted stem
IV	Widened diaphysis that provides no support for cementless fixation	Impaction grafting + cemented stem Allograft prosthetic composite Tumor megaprosthesis

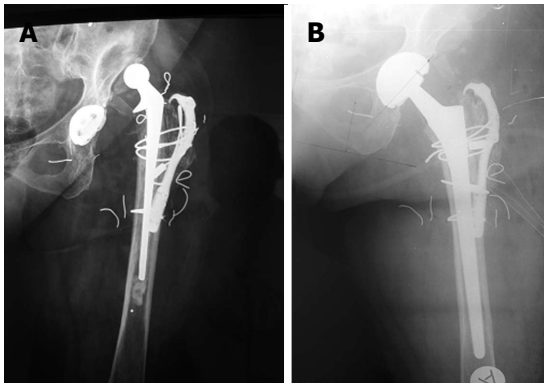

Figure 5 Modular stems. A: Preoperative anteroposterior (AP) radiograph of a dislocated left hip with a paprosky type IIIA defect; B: Postoperative AP radiograph of the revised hip with a modular stem.

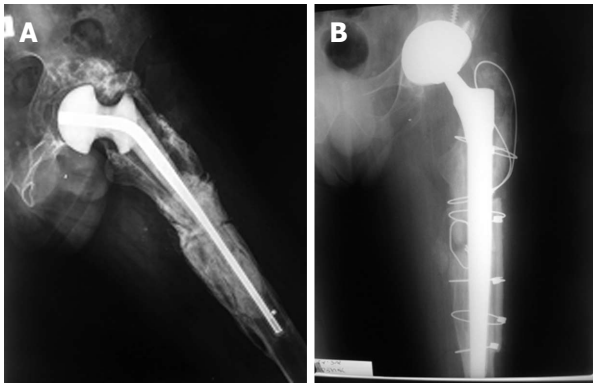

Figure 6 Newer stem designs with modular configuration have been associated with lower rates of subsidence and improved restoration of limb length and femoral offset. A: Anteroposterior (AP) radiograph of the left hip showing extensive bone loss of the proximal metaphyseal bone with significant diaphyseal bone loss (Paparosky type IIIB) secondary to periprosthetic hip infection. A antibiotic cement spacer was implanted after irrigation and debridement during the first stage of a two-stage exchange arthroplasty; B: AP radiograph of the same hip after the second stage using a distal fixation taper fluted stem.

intact diaphysis is available for distal fixation. The use of extensively porous-coated stems have been associated with poor survivorship and therefore they are not recommended. The current literature includes a number of studies presenting cementless femoral revisions using extensively porous-coated stems. Lawrence *et al*[15] showed that 5.7% of these stems failed and needed revision of the femoral implant 7.4 years post operatively. In another study, Weeden and Paprosky found that extensively porous-coated revision stems are associated with an incidence of aseptic loosening and mechanical failure of 4.1% after a 14.2 years postoperatively[14].

Impaction grafting of the defective femur and reconstruction using a cemented stem would be a favorable option for this setting[16-20]. In a study of Lamberton at al., the technique of impaction allografting and use of cemented revision stem was presented[18]. The authors included a cohort 540 revision arthroplasties and showed that the survival rate of impaction grafting is approximately when considering the aseptic loosening and revision for any reason as the endpoints is 98% and 84% respectively after a mean 10 years of follow-up. Dislocation (4.1%) and femoral fracture (5.4%) were shown to be the most common complications of this procedure. In another study, incorporating the data from the Sweedish registry, that included 1305 revisions of the femoral component and reconstruction using the impaction grafting technique found that the survival rate at 15 years postoperatively was very high approaching 94%[21]. The effect of surface finish of the femoral components still remains debatable. Polished stems without collar and roughened stems with a collar have been both used. Studies from the current literature have failed to reveal any statistically significant difference on the clinical outcome and the survivorship of these arthroplasties[21]. However, the technique of impaction grafting is challenging and time consuming. Specialized instrumentation and a large volume of cancellous bone allografts are required[21]. Therefore, reconstruction with a modular cementless tapered fluted stem would be a viable alternative option.

Tapered fluted stems have been historically susceptible to subsidence and associated with high dislocation rates[22-25]. Newer stem designs with modular configuration, which allow independent size selection of the proxi-

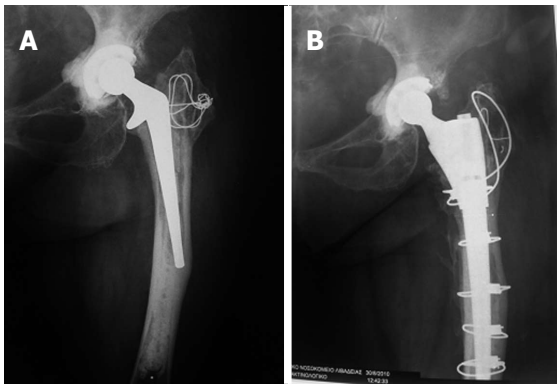

Figure 7 Multiple osteotomies allow for restoration of the anatomical axis of the femur, an easier access of the distal segment of the modular stem, thus reducing the risk of femoral fracture or perforation of the cortex. A: Anteroposterior (AP) radiograph of the left hip showing a cemented femoral component that is failed in varus, resulting in a slight angular malalignment of femur; B: AP radiograph of the same hip after revision of the femoral component using a modular stem, which combines both proximal metaphyseal and distal fixation due to the taper design and the distal flutes. A healed corrective osteotomy at the level of the mid-diaphysis facilitated the insertion of the stem and correction of the angular deformity to its neutral axis.

mal and distal segments, have been associated with lower rates of subsidence and improved restoration of limb length and femoral offset (Figure 6). Mechanical failure of the modular taper due to fretting corrosion has been reported[26]. For this reason, several authors recommend the use of some kind of additional structural support to the proximal body of the prosthesis by using allografts or by wrapping the remaining host bone around the proximal segment of the modular stem[27]. A recent retrospective multicenter study that included a series of 143 hips reconstructed with the same modular fluted tapered stem, found that the mean survivorship of these stems reaches 97% at an average 40 mo follow-up while the mean subsidence was 2.1-mm[10]. These components may be combined with various types of single or multiple femoral osteotomies (*i.e.*, sish-kebab technique); multiple osteotomies allow for restoration of the anatomical axis of the femur, an easier access of the distal segment of the modular stem, thus reducing the risk of femoral fracture or perforation of the cortex[28] (Figure 7) .

Type Ⅳ femoral defects are the most challenging subtype because there is no intact isthmus to provide adequate distal fixation of the component. For this reason, the treatment options include reconstruction of the femoral canal with impaction grafting and insertion of a cemented stem or using a tumor megaprosthesis to replace the defective proximal femur[3,29-33].

The use of allograft prosthetic composite (*i.e.*, combination of a cemented long stem and a bulk allograft of the proximal femur) that is attached to the host bone distally is another reconstructive option[3,29-33]. This technique has attracted interest because it may potentially preserve the existing bone stock and establish a good bony foundation for future revisions, especially in younger patients. The allograft offers mechanical properties similar to the patient's own bone and allows reconstruction of sizeable deficits. This may be considered as a biologic reconstructive option; except for the preservation of bone stock, the use of a structural allograft may allow for reattachment of the hip abductors in an effort to preserve hip function and gait[3,29-33].

The technique of reconstruction of large defects of the proximal femur using an allograft-prosthesis composite is very demanding. An appropriately sized allograft is osteotomized at the desired subtrochanteric level in order to match the bony defect of the proximal femur. Next, the allograft is reamed and broached and a long stem is cemented at the back table (Figure 8). Then, the allograft-prosthesis composite is implanted to the native femur with the use of cement or not, depending on the selected type of implant and the quality of host bone (Figure 9). Although the issue of proximal cementing of the stem into the proximal femoral allograft is well documented by Haddad *et al*[34,35] and Gross *et al*[36] showing that there is a high failure rate in cases of cementless fixation, there is no such a reconciliation regarding distal fixation into the host bone. In a recently published study, we have found that there is no statistically significant difference between cemented and cementless fixation regarding implant survivorship. Gross *et al*[36] however have shown cementing the allograft-prosthesis composite distally into the host bone should probably be avoided because it might compromise the distal femur during future revision.

Size matching of the allograft to the host bone may be problematic, and has been addressed by the use of additional cortical struts and circumferential cables or wires. Intussusception of the allograft bone into the host bone has also been reported in cases of significant allograft-host canal mismatch[3,31]. When rigidly fixed, strut grafts may also provide an extensive surface area of contact with the host bone for supplemental union and incorporation[37]. Several techniques have been utilized in order to improve the rotational stability of the whole construct, including different types of osteotomies (oblique, step-cut, lateral sleeve) or stabilization with the use of additional hardware (plates and screws, plates and cables, strut grafts and cables).

While the published results of APC technique have been encouraging, they have generally involved relatively short-term follow-up. However, interpretation of many clinical studies is problematic because they use different (or no) classifications for proximal bone loss and utilize different surgical techniques of allograft fixation. The reported survival rates of APC reconstruction vary in the current literature, ranging from 72 to 90 percent at five years and 64 to 86 percent at ten years[35,38-41]. We have recently published a study with probably the longest clinical follow-up showing a survival rate that reaches 92.7 percent at two years 78.2 percent at five years, and 69 percent at ten years[3].

Allograft resorption has been reported as the major concern, which has been occasionally associated with early failures and could be a significantly greater problem at

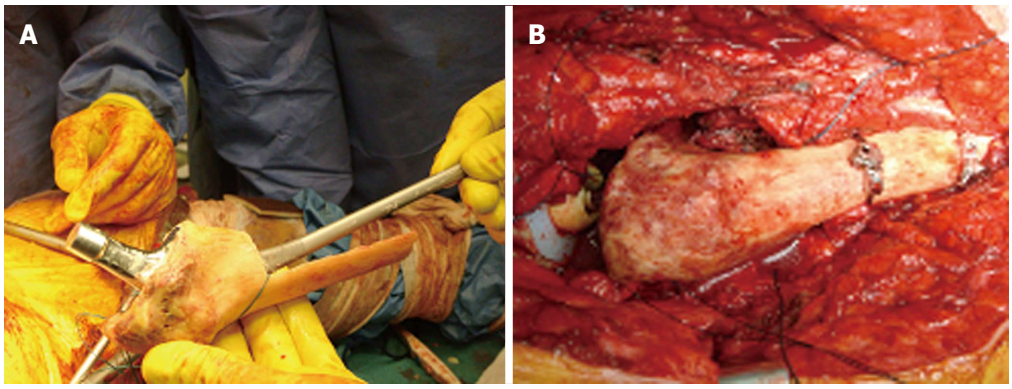

Figure 8 The allograft is reamed and broached and a long stem is cemented at the back table. A: Intraoperative picture demonstrating the allograft-prosthesis composite preparation. An allograft of appropriate size is osteotomized at the desired subtrochanteric level in order to match the bony defect of the proximal femur. The allograft is reamed and broached and a long stem is cemented at the back table; B: Intraoperative picture showing the allograft-prosthesis composite with a lateral sleeve that offers a wide area of bone contact with the distal host femur. Circlage cables are used to secure the allograft-host bone fixation.

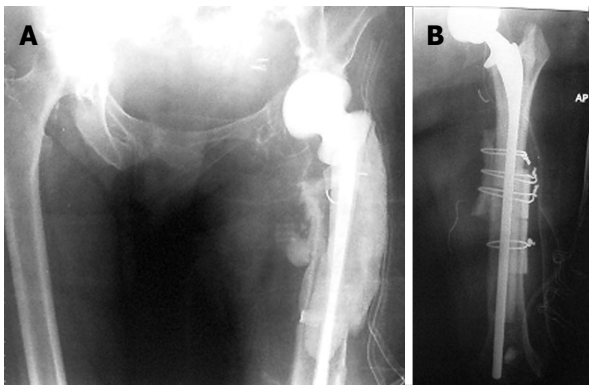

Figure 9 The allograft-prosthesis composite is implanted to the native femur with the use of cement or not, depending on the selected type of implant and the quality of host bone. A: Anteroposterior (AP) radiograph of the pelvis demonstrating a Paprosky type Ⅳ femoral defect of the left hip as a result of a periprosthetic infection. The femoral canal is widened and there is no sufficient diaphyseal support for future cementless fixation; B: Postoperative AP radiograph of the left hip showing reconstruction of the proximal femoral defect with the use of an allograft-prosthesis composite. Remnants of the host bone are wrapped-around the femur at the level of the allograft-host bone junction in order to improve incorporation of the allograft to the host femur.

a longer follow-up[41,42]. Immunological matching between allograft and host femora, condition of the soft tissues attachments and vascularity of the host bed are other parameters that may affect incorporation of the allograft and could be related to the survivorship of the APC reconstructions[33,41,42].

Resorption of the allograft is a potential complication. Resorption is usually found at the periosteal surface of the allograft[38,43,44]. A possible explanation is that the cement on the endosteal surface inhibits access by host granulation tissue[38,43,44]. Contrarily, on the periosteal surface there is access to host tissue and, therefore, neo-vascularization may lead to bone resorption[38,43,44]. By using strong cortical allograft bone, this process is expected to be evident at a later stage, and therefore composite graft-cement-implant reconstructions should last for an adequate period of time. Gross *et al*[45] reviewed 168 proximal femoral allografts reporting only one significant and six minor resorptions at an average follow up of 4.8 years. In another study, Masri *et al*[46] found four mild and ten severe resorptions in thirty-nine cases at mean 5.1 years postoperatively. Haddad *et al*[41] used cementing technique to both proximal and distal femur in forty femoral revisions and found nine cases with mild resorption, four with moderate, and seven with severe resorption, which resulted in an overall 50 percent resorption rate at 8.8 years. Blackley *et al*[38] opted to wrap the remnants of the proximal femur around the allograft; the authors found twelve mild to moderate and only one severe resorption in forty-eight allograft-prosthesis composites eleven years post revision surgery. Safir *et al*[47] conducted a study with a minimum 15 year-follow-up, and showed that minor resorption was radiographically evident in 93 hips resulting in an overall resorption rate of 58%.

The literature shows a large variety of complications and a wide range of complication rates associated with proximal femur reconstructions using APCs. Hip dislocations, allograft-host bone junction non-unions, postoperative infections, periprosthetic fractures and aseptic loosening of the femoral components are the most significant complications. The incidence of these complications is quite variable: Hip dislocation is seen in 3.1% to 54% of cases, nonunion of the allograft host bone junction in 4.7% to 20%, trochanteric non union in 25%to 27%, postoperative infection in 3.3% to 8%, periprosthetic fracture in 2% to 5%, and aseptic loosening in 1 to 12 percent[3,29,30,32,33,35,36,38,41,45,48].

Proximal femur replacement using the so-called "mega-prostheses" is an alternative option in cases of severe proximal femoral bone loss[49,50] (Figure 10). These implants are primarily designed for reconstruction of large bony defects after tumour resection, but they have also been utilized to replace the deficient proximal femur during hip revision surgery. In general, our philosophy is to use proximal femoral replacement implants in older, less active patients. The Mayo experience with proximal femoral replacement prostheses[50] showed survivorship

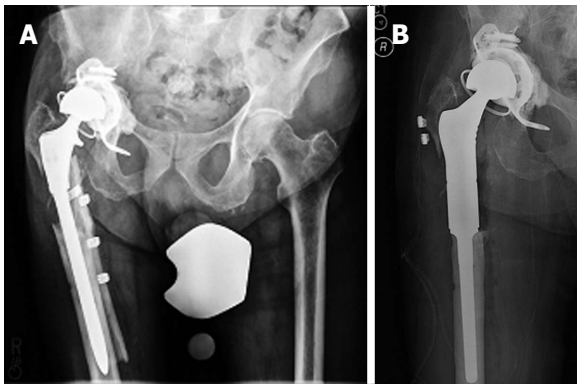

Figure 10 Proximal femur replacement using the so-called "mega-prostheses" is an alternative option in cases of severe proximal femoral bone loss. A: Anteroposterior (AP) radiograph of the pelvis showing a left revision total hip arthroplasty in a 82-year-old male patient with an extensive structural defect of the lateral femoral cortex resulting in a painful and mechanically loose construct of a periprosthetic hip fracture; B: Postoperative AP radiograph of the right hip showing the replacement of the proximal femoral with a megaprosthesis.

of the femoral component, with revision as the endpoint, of 81 per cent at eleven years. However, the improvement in function was not statistically significant. Deficiency of the abductor mechanism or inability to secure the abductor mechanism to the metal surface of the implant is a major concern associated with the use of megaprostheses[37]. New prosthetic designs offer several options for re-attachment of the abductors. However, insufficiency of their function is associated with high dislocation rates, which still remains the major drawback of this type of reconstruction. Nonetheless, current proximal femur replacement may be best suited for the elderly and inactive patients for whom resection arthroplasty would probably be the only alternative[49,50].

CONCLUSION

Reconstruction of the proximal femur during revision surgery is a challenging procedure. The remaining supportive bone of the metaphyseal and diaphyseal segments of the femur is the main contributing factors to determine the selection of the appropriate reconstructive option during revision surgery. Planning ahead is always essential to assure that multiple reconstructive techniques will be available at the time of surgery.

With regards to reconstruction of massive proximal femoral bone defects allograft-implant composites consist a more biologic reconstructive technique. This is a very demanding and challenging procedure that requires meticulous preoperative planning; it is time-consuming and potential intraoperative modifications may be needed. Ten-year survival rates reach 70%. Considering the complexity of these cases, the reported clinical and radiographic outcome of APCs is satisfactory. A stable allograft-host junction is essential for success. Allograft-host femoral canal mismatch can be managed with the intussusception technique, which is a good alternative over standard step-cut osteotomies. Distal fixation can be achieved using either cemented or cementless stems without compromising total survivorship. Proximal femur replacement consists a viable alternative that is best suited for elderly and inactive patients.

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Metallic debris from metal-on-metal total hip arthroplasty regulates periprosthetic tissues

Christoph H Lohmann, Gurpal Singh, Hans-Georg Willert, Gottfried H Buchhorn

Christoph H Lohmann, Gurpal Singh, Department of Orthopaedic Surgery, Otto-von-Guericke University, 39120 Magdeburg, Germany
Gurpal Singh, University Orthopaedics, Hand and Reconstructive Microsurgery Cluster, National University Health System, Singapore 119228, Singapore
Hans-Georg Willert, Gottfried H Buchhorn, Department of Orthopaedics, University Hospital Goettingen, 37075 Göttingen, Germany
Author contributions: Lohmann CH, Singh G Willert HG and Buchhorn GH contributed to the study design, literature review, preparation and editing of this manuscript.
Correspondence to: Christoph H Lohmann, MD, Department of Orthopaedic Surgery, Otto-von-Guericke University, LeipzigerStrasse 44, 39120 Magdeburg, Germany. christoph.lohmann@med.ovgu.de
Telephone: +49-391-6714000 Fax: +49-391-6713840
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Abstract

The era of metal-on-metal (MoM) total hip arthroplasty has left the orthopaedic community with valuable insights and lessons on periprosthetic tissue reactions to metallic debris. Various terms have been used to describe the tissue reactions. Sometimes the nomenclature can be confusing. We present a review of the concepts introduced by Willert and Semlitsch in 1977, along with further developments made in the understanding of periprosthetic tissue reactions to metallic debris. We propose that periprosthetic tissue reactions be thought of as (1) gross (metallosis, necrosis, cyst formation and pseudotumour); (2) histological (macrophage-dominated, lymphocyte-dominated or mixed); and (3) molecular (expression of inflammatory mediators and cytokines such as interleukin-6 and tumor necrosis factor-alpha). Taper corrosion and modularity are discussed, along with future research directions to elucidate the antigen-presenting pathways and material-specific biomarkers which may allow early detection and intervention in a patient with adverse periprosthetic tissue reactions to metal wear debris.

Key words: Periprosthetic tissue response; Metal-on-Metal; Total hip arthroplasty; Metal debris; Lymphocyte-dominated; Macrophage-dominated; Taper corrosion; Modularity

Core tip: Valuable lessons have been learnt from the era of metal-on-metal total hip arthroplasty. We present a review of the concepts introduced by Willert and Semlitsch in 1977, along with further developments made in the understanding of periprosthetic tissue reactions to metallic debris. We propose that periprosthetic tissue reactions be thought of as (1) gross (metallosis, necrosis, cyst formation and pseudotumour); (2) histological (macrophage-dominated, lymphocyte-dominated or mixed); and (3) molecular (expression of inflammatory mediators and cytokines such as interleukin-6 and tumor necrosis factor-alpha). Taper corrosion and modularity is discussed, along with future research directions in this area.

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INTRODUCTION

Retrieval studies on failed metal-on-metal (MoM) total hip arthroplasties (THAs) have contributed significantly to the understanding of adverse local tissue reactions to metallic debris. The McKee Farrar and Ring implants

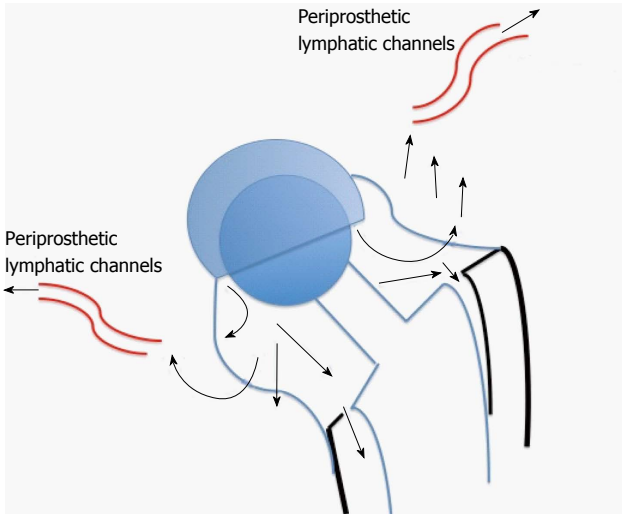

Figure 1 The Willert-Semlitsch concept of clearance of wear debris by periprosthetic lymph channels. If production of wear debris exceeds the ability of the lymph channels to clear it, the debris then "spills" over into the effective joint space and initiates osteolytic pathways.

used in the 1960s had MoM bearing surfaces[1-3]. Weber introduced the first second-generation MoM THA (cobalt-chrome alloy with a high carbon content)in 1988[4] .The success of large-diameter hip surface replacement further popularized MoM hip replacements[5-8]. Large-diameter MoM heads (36 mm diameter or larger), started being used in revision hip surgery and were later used in primary THAs. Registry data suggest that MoM devices have been implanted into over 60000 patients in England and Wales since 2003 and the figure is closer to a million in the United States[9,10].

Metal wear products in periprosthetic tissue may exist as particulate wear debris, metal ions in solution, metallo-protein complexes and byproducts of synergistic corrosion and wear processes (especially when modular interfaces are involved)[11,12]. Proteins present in body fluids and tissue can associate with metal particulate debris especially those in the nanoscale range. These complexes can form haptens and there may exist interindividual variability in immunological threshold and response to these antigens[13,14]. Corrosion and wear at modular interfaces *i.e.*, head-neck and neck-stem junction can contribute to the overall particle load[15-21].

Taper corrosion has also been recognized in metal-on-polyethylene THAs[19,21,22]. Kurtz and colleagues has studied a hundred femoral head-stem pairs. They have reported that by using a ceramic femoral head, cobalt and chrome fretting and corrosion from the modular head-neck taper can be decreased partially but it is difficult to eliminate it completely[23]. Metal particulate debris tends to be in the nanometre size range and MOM articulations generate approximately 10^{12}-10^{14} particles per year[24]. Difficulties associated in isolating and characterizing these small nanometric particles suggest that the actual number of particles produced *in vivo* may be higher, taking into account also that intracellular corrosion of phagocytosed nanometric metal particles may occur[25,26].

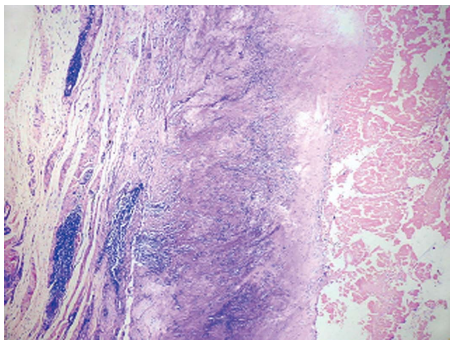

Figure 2 Plain radiograph showing early, progressive osteolysis in response to metallic wear debris.

TISSUE REACTIONS TO WEAR PRODUCTS

Willert *et al*[27] in 1977, described the tissue reactions of the articular capsule to wear products of artificial joint prostheses. In their landmark article, they reported the development of a foreign-body reaction (consisting of macrophages and foreign-body giant cells) to wear debris. This foreign-body reaction takes place in the neocapsule and, depending on its magnitude, may lead to the formation of granulation tissue, which may subsequently cause scarring and decrease joint mobility. They went on to discuss the concept of an "equilibrium state", which is achieved when the periprosthetic lymph vessels are effectively clearing the wear debris at the rate of debris production (Figure 1). If the periprosthetic lymph channels are overwhelmed, excess wear debris then spills over via the surrounding tissue into the implant-bone interface, mainly trabecular bone and marrow. Additionally, effusions into the joint space become enriched with wear products. The increase of intracapsular pressure due to muscular activity and compression not only increases local bone resorption[28] but also introduces dissociation of the interface membranes and implant surfaces. We now know this as the "effective joint space" as described by Schmalzried and colleagues in 1992[29]. Joint fluid helps to transport wear particles to new sites, resulting in activation of osteoclasts and inhibition of osteoblasts *via* molecular signaling pathways involving a host of inflammatory mediators. This phenomenon has also been called "particle disease"[30,31]. The "threshold" of the periprosthetic lymphatics to effectively clear wear debris is subject to interindividual variability as well as on the volume of wear (*e.g.*, high rates of UHMWPE wear). This phenomenon may partially explain why some people develop adverse tissue reactions and early osteolysis (Figure 2) in response to metal debris whilst others seem to have a mild or no reaction, assuming all other factors being equal. Since then, research efforts have focused on the types of tissue reactions, immunological and molecular pathways

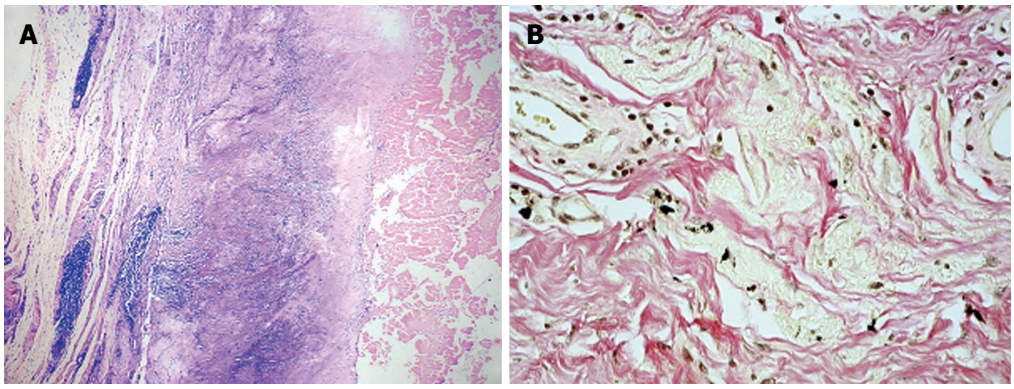

Figure 3 Pathologic figure. A: Diffuse and perivascular lymphocytic infiltration (lymphocyte-dominated tissue response) seen in retrieved periprosthetic tissues from small-diameter metal-on-metal (MoM) total hip arthroplasties (THAs). Haematoxylin-eosin, magnification, × 10; B: Intracellular metal particles seen in retrieval tissues from large-diameter MoM THA. These particles may undergo intracellular corrosion. Haematoxylin-eosin, magnification, × 40.

involved. These pathways are still not well-understood, though some light has been shed on the types of tissue reactions to particulate wear debris.

ADVERSE TISSUE REACTIONS IN MOM THAS

Adverse tissue reactions may be systemic or local. Higher serum and solid organ metal ion levels may theoretically have carcinogenic and teratogenic potential. Various terms have been coined to describe the adverse local tissue reactions seen in MoM THA and the nomenclature is debatable. Essentially, adverse local tissue reaction (ALTR) encompasses all types of adverse local tissue reactions to debris, whereas adverse reaction to metallic debris (ARMD) and aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) represent more specific descriptions. For clarity of thought, it may be useful to think about local periprosthetic tissue reactions at the gross, histological and molecular levels.

GROSS TISSUE REACTIONS

Gross intraoperative findings in revision operations for failed aseptic metal-metal hip replacements range from metallosis, large joint effusions, necrosis and pseudotumours[32-46]. "Metallosis" comprises local damage and changes in tissue characteristics provoked by a metallic foreign body in the host with (1) direct (by pressure, destruction or displacement of tissues); (2) collateral (by chemical reactions with body fluids, electrolytic processes with direct galvanic impairment of cellular activity and impregnation of host tissue with ionizing metallic particulate matter; and (3) the resulting biologic reactions of the adjacent tissues"[47]. A pseudotumour is defined as a granulomatous lesion or a destructive cystic lesion, neither infective nor neoplastic, that is at least 5 cm in size, has developed in the vicinity of the total joint replacement (with or without communication with the joint), and resembles a tumour[48].

HISTOLOGY: MACROPHAGE-DOMINATED AND LYMPHOCYTE-DOMINATED REACTIONS

Histologically, to avoid confusion associated with the nomenclature, we differentiate the predominant cellular responses into a macrophage-dominated type and a lymphocyte-dominated type. Other features which may be seen are fibrin exudation and necrosis. The lymphocyte based tissue response differs from macrophage dominated tissue response as the former is adaptive and displays "memory". The lymphocyte dominated tissue response may resemble a type IV delayed hypersensitivity reaction. This type of tissue reaction can lead to development of early aseptic loosening and progressive osteolysis in patients with MoM total hip arthroplasty. This phenomenon may also be seen in the context of corrosion and wear at modular interfaces in non-MoM THA[49-54]. The two responses may co-exist and research efforts are being channeled into identifying the factors which are responsible for the predominant type of tissue response.

We analyzed tissue response, serum and periprosthetic tissue metal content among a cohort of 28 small-diameter MoM THAs and found that the overall metal content in the periprosthetic tissues correlated with type of tissue response. Serum metal content did not predict type of tissue response (Table 1)[54].

Twenty-seven patients (28 hips) who were revised from second-generation small-diameter MoM bearing couples (Sikomet®, 0.08% carbon content) to ceramic-on-ultra high molecular weight polyethylene (UHMWPE) (8 hips), metal-on-UHMWPE- (19 hips), or ceramic-on-ceramic (1 hip). The duration of implantation was 54 to 86 mo with a mean of 66 mo. The Cobalt, Chromium, and Nickel content of the periprosthetic tissue was in the range of 1.4 to 4604.0 μg/g. The tissues with a dominant lymphocytic response had a higher mean metal content as compared to macrophage dominant response *i.e.*, 222.2 ± 52.9 μg/g and 3.0 ± 0.9 μg/g respectively ($P = 0.001$). The content of nickel in the tissue was similar in both groups but the

Table 1 Tissue metal content, but not serum metal content has a positive correlation with type of periprosthetic tissue response in a series of 28 small diameter metal-on-metal total hip arthroplasties

	Cobalt, mg/L	Chrome, mg/L	Nickel, mg/L
Tissue metal content			
Macrophage-dominated	17.25	21	22.5
Lymphocyte-dominated	13.41	21.92	8.41
Serum metal content			
Macrophage-dominated	0.3	2	0.6
Lymphocyte-dominated	45.2	163.6	1.6

amount of cobalt was approximately hundred and fifty times higher in the lymphocyte-dominant group. Figure 3 illustrates the typical lymphocyte-dominated tissue response seen in a small-diameter MoM THA and phagocytosed intracellular metal particles from retrieved tissues in large diameter MoM THA.

Head size may be another factor which drives the predominant type of tissue response in one direction or another. Bosker *et al*[55] has described that the MoM hip replacements with large heads had higher rates of pseudotumour development. The incidence of pseudotumour formation was 38.5% in this study at a mean follow-up of 3.6 years. In their cohort, patients with higher serum metal levels quadrupled their risk of forming pseudotumors. Langton *et al*[56] described an ALVAL type of tissue reactionin failed ASR hips. Kawakita *et al*[57] has described a case of histologically proven pseudotumour following a large diameter MoM hip arthroplasty. The patient developed unilateral leg edema secondary to a pelvic mass (pseudotumour) 14 mo after hip replacement surgery. Corrosion at the head-neck interface in large diameter MoM THA[17,18] may be contributory to their failure and possibly lead to different profile of wear debris in the periprosthetic tissues. This is presented in more detail in the subsequent section on modularity and taper corrosion.

MOLECULAR PATHWAYS

Molecular pathways leading to early aseptic loosening among MoM implants are not well understood either. A variety of inflammatory mediators such as interleukin-6 (IL-6), prostaglandin E2 (PGE2) and tumor necrosis factor-alpha (TNF-α) have been shown to be expressed by monocytic cells in periprosthetic tissue of failed joint arthroplasties[58,59]. Caicedo and colleagues suggested that soluble ions more than particulate cobalt-alloy implant debris induce monocyte co-stimulatory molecule expression and release of proinflammatory cytokines which contribute to metal-induced lymphocyte reactivity[60]. Tuan *et al*[61] observed that many pro-osteoclastic inflammatory cytokines not only promote osteoclastogenesis but also interfere with osteogenesis led by osteoprogenitor cells. Lin *et al*[62] investigated the suppression of chronic inflammation by inhibiting NF-κB activity as a strategy to combat wear particle induced periprosthetic osteolysis. Ren and colleagues from the University of Kansas group previously reported that VEGF inhibitor treatment prevented UHMWPE particle-induced inflammatory osteolysis[63]. Most of these inflammatory chemokines are upregulated in MoM implant failures, periprosthetic tissue affected by osteolysis due to polyethylene wear debris as well as other disease states involving chronic inflammation and even malignancy (*e.g.*, multiple myeloma) and are not specific to the inciting agent or material[64]. The common end-point for each of these pathways is osteoclast activation and bone resorption[65,66], leading to implant loosening and revision surgery. Future research efforts should be channeled towards identifying a molecular marker which is material-specific *i.e.*, is upregulated by the presence of metallic wear debris but not affected by polymeric wear debris and infection.

TAPER CORROSION AND MODULARITY

Modular interfaces in joint replacement surgery perhaps represent a double-edged sword. Modularity has, beyond doubt, made the technical complexity of surgical operations (particularly revisions) much easier but has also introduced a new set of problems for the revision surgeon - problems associated with the release of corrosion and wear debris from these interfaces. The cone-taper (head-neck) interface and neck-stem interface (when modular necks are used) in THA surgery represent two potential interfaces for a crevice environment and mechanically assisted corrosion leading to instability.

Collier *et al*[67,68] were one of the pioneer groups who studied the head-neck or cone-taper interface. They reported corrosion at the head-neck junction in a cohort of THAs which had dissimilar metal alloys in the head and neck but not in endoprosthetic components made from similar metals. This has since been shown to not be the case, with many cases of marked corrosion reported at the head-neck of same alloy systems. Willert *et al*[53] observed that a protective passivation layer of an alloy may prevent corrosion until micromotion sets in and abrades this layer. The current understanding of this process is termed mechanically-assisted crevice corrosion.

Gill *et al*[19] reported corrosion at the neck-stem junction as an important source of debris leading to pseudotumour formation. Higgs *et al*[16] studied 134 heads and 60 stems (41 modular necks) of 8 different bearing designs (5 manufacturers) and concluded that dissimilar alloy pairing, larger head sizes, increased medio-lateral offsets and longer neck moment arms were all associated with increased taper damage at the modular interfaces. Cook *et al*[22] have reported pseudotumour formation due to tribocorrosion at the taper interface of large diameter metal-on-polyethylene modular total hip replacements. Cooper's group reported the occurrence of adverse local tissue reactions (ALTR) similar to those seen in MoM THAs and corrosion at the head-neck junction in ten patients with a metal-on-polyethylene total hip prostheses, from three different manufacturers[21].

We have reported the occurrence of corrosion and

instability at the cone-taper interface, tissue metal content and element analysis of periprosthetic wear debris and type of tissue response (macrophage-dominated *vs* lymphocyte dominated) among 2 cohorts of failed MoM total hip arthroplasties (THA's)[17,18,54]. The first cohort consisted of 27 patients (28 hips) with small-diameter MoM bearing couples (Sikomet®, 0.08% carbon content) as described above. The second cohort consisted of 110 patients who had 114 revisions of large-diameter head MoM THAs (LDH® head (Zimmer Inc, Warsaw, IN, United States) and a DUROM® hip cup (Zimmer Inc, Warsaw, IN, United States).The head size ranged from 46-58 mm. The duration of implantation was 26 to 68 mo with a mean of 46 mo. All implants were revised to ceramic-on-polyethylene articulating couples. Among the first cohort of small diameter MoM THA's, there was no evidence of corrosion or instability at the cone-taper interface of the retrieved implants intraoperatively. In contrast, we have reported corrosion at the cone-taper interface as being a significant mode of failure in large-diameter MoM hip arthroplasties[18]. Out of 114 revisions of large-diameter MoM THA's, 107 (94%) had evidence of corrosion and instability at the head-neck interface. One hundred six (93%) of the 114 hips had joint effusions and tissues with a grayish necrotic appearance were found around the implants, respectively. Intraoperatively, in 94% (n = 107), the cones and the tapers were unstable and showed a black color suggestive of corrosion. Interestingly, only 9 cases in this series had a lymphocyte-dominated tissue response and all other cases had a foreign-body type, macrophage-dominated tissue response. Element analysis with Inductive-Coupled Plasma Mass Spectrometry (ICPMS) showed a very different profile of wear debris with titanium or iron predominating, suggestive of abrasive wear from the neck taper.

Goldberg *et al*[69] reported that the combination of dissimilar alloys, metallurgical condition of the alloys, implantation time, and flexural rigidity of the femoral neck were predictors of corrosion of the neck and head. Implantation time, lateral offset, femoral stem modularity, and dissimilar alloys have been implicated as predictors of taper corrosion in a recent multicenter retrieval study[16]. The emergence of this phenomenon in non-MoM THAs certainly brings to light the reality of the problem and we recommend that modularity should be used with a hint of caution.

CONCLUSION

MoM total hip arthroplasties and their failures have given the orthopedic community valuable insights into periprosthetic adverse tissue reactions. Further research needs to be directed towards the immunological mechanisms, antigen-presenting and molecular pathways responsible for these adverse tissue reactions. Identification of material-specific biomarkers will potentially allow early diagnosis of adverse tissue reactions and facilitate early intervention in these patients.

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Dr med. Hans-Georg Willert, Professor, to whom this work is dedicated, passed away on September 25th, 2006.

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Triple pelvic osteotomy: Report of our mid-term results and review of literature

Tomohiro Mimura, Kanji Mori, Taku Kawasaki, Shinji Imai, Yoshitaka Matsusue

Tomohiro Mimura, Kanji Mori, Taku Kawasaki, Shinji Imai, Yoshitaka Matsusue, Department of Orthopaedic Surgery, Shiga University of Medical Science,Tsukinowa-cho, Shiga 520-2192, Japan

Author contributions: Mimura T conceptulized and drafted this manuscript; Kawasaki T performed the surgeries; Mori K, Imai S and Matsusue Y equally analyzed this work.

Correspondence to: Kanji Mori, MD, Department of Orthopaedic Surgery, Shiga University of Medical Science, Tsukinowa-cho, Seta, Otsu, Shiga 520-2192, Japan. kanchi@belle.shiga-med.ac.jp
Telephone: +81-77-5482252 Fax: +81-77-5482254
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Abstract

A wide variety of pelvic osteotomies have been developed for the treatment of developmental dysplasia of the hip (DDH). In the present paper, we present a detailed review of previous studies of triple osteotomy as an alternative treatment for DDH. We also report our experience treating 6 adult cases of DDH by triple osteotomy in order to highlight the various aspects of this procedure.The mean age of our patients was 31.2 years with a mean follow-up period of 6 years. We assessed range of motion, center-edge angle, acetabular index angle, Sharp angle, acetabulum head index, head lateralization index, Japanese Orthopedic Association score, Harris hip score, patient satisfaction, and the difference between lower limb lengths before and after the procedure. At final follow-up, clinical scores were significantly improved and radiographic parameters also showed good correction of acetabulum.

Key words: Pelvic osteotomy; Triple osteotomy; Developmental dysplasia of the hip

Core tip: Various pelvic osteotomies have been developed for treating developmental dysplasia of the hip (DDH). In the present paper, we review previous studies on triple osteotomy as an alternative treatment for DDH and also report our experience with 6 DDH cases treated by triple osteotomy in order to highlight the various aspects of this procedure. In our cases, clinical scores as well as radiographic parameters were significantly improved. We found that the clinical results of triple osteotomy were satisfactory and it should be considered as an alternative pelvic osteotomy procedure in adults with DDH.

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INTRODUCTION

Developmental dysplasia of the hip (DDH) is well known as a cause of secondary osteoarthritis of the hip. In Japan, approximately 80%-90% of hip osteoarthritis cases occur secondary to DDH.

An acetabular osteotomyto treat DDH is a clinically important therapeutic modality especially in young adults with low-grade osteoarthritis, pre-osteoarthritis. Restoration of the anatomical and biomechanical relationship in cases of DDH may delay or prevent development of coxarthrosis[1]. To date, a variety of acetabular osteotomies of the adult pelvis have been reported, including the Bernese periacetabular osteotomy[2], rotational acetabular osteotomy (RAO)[3], and triple osteotomy procedure[4]. The aims of these osteotomies have been to achieve acquire good containment of the femoral head and stability

Table 1 Pre-operative angle values and scores of all cases

	Age, yr	CE angle	Acetabular index	Sharp angle	AHI	HLI	JOAS	HHS
Case 1	19	-9	31	48	44.2	0.63	63	70
Case 2	20	13	20	46	65.8	0.54	73	80
Case 3	27	5	20	45	57.8	0.71	52	59
Case 4	29	9	19	45	60.0	0.69	52	59
Case 5	43	16	14	47	70.5	0.65	80	93
Case 6	43	0	26	54	52.2	0.56	54	73

CE angle: Center-edge angle; AHI: Acetabular head index; HLI: Head lateralization index; JOAS: Japanese Orthopedic Association score; HHS: Harris hip score.

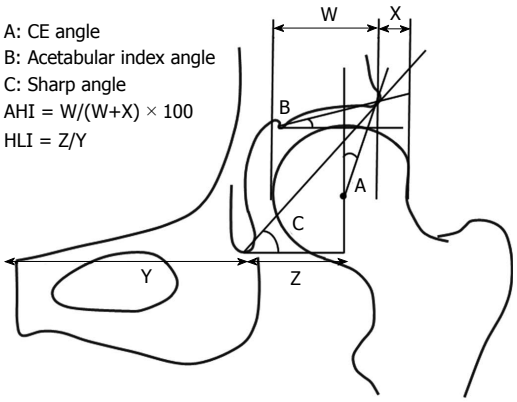

Figure 1 The center-edge angle, acetabular index angle, Sharp angle, acetabular head index, and head lateralization index were evaluated in anteroposterior X-ray images. CE: Center-edge; AHI: Acetabular head index; HLI: Head lateralization index.

of the hip joint.

A triple osteotomy is widely employed for treating DDH in adolescents and young adults, especially in those in whom the triradiate cartilage remains unfused[5-9].

The limited number of existing reviews of triple osteotomy prompted us to write an up-to-date review. In addition, few studies of triple osteotomy in older patients (age > 30 years) have been reported. In the present study, we also report a case series of triple osteotomyin relatively older patients (> 30 years of age).

OUR CASES

We performed 6 triple osteotomies in 4 adult patients with DDH, with bilateral osteotomies performed in 2 patients. The average age of the patients was 31.2 years (19-49 years) and all were female in the pre-osteoarthritis stage. The mean follow-up was 6 years. The center-edge (CE) angle[10], acetabular index angle[11], Sharp angle[12], acetabular head index (AHI)[13], and head lateralization index (HLI)[3], were evaluated on anteroposterior (AP) X-ray images (Figure 1). Range of motion (ROM), Japanese Orthopedic Association score (JOAS), Harris hip score (HHS), patient satisfaction (well satisfied, satisfied, and dissatisfied), and difference in lower limb lengths before and after the procedure were also assessed. JOAS consists of the items pain (0-40), ROM (0-20), walking ability (0-20), and activities of daily living (ADL; 0-20), with a total of 100 indicating the best hip function. Student's *t*-test was used to determine significant differences between groups, with a P value of < 0.05 considered significant.

Table 2 Post-operative angle values and scores of all cases

	CE angle	Acetabular index	Sharp angle	AHI	HLI	JOAS	HHS
Case 1	25	9	26	80.0	0.52	95	100
Case 2	53	-12	12	97.7	0.63	95	100
Case 3	10	15	36	66.7	0.70	91	100
Case 4	21	15	37	73.9	0.70	91	100
Case 5	26	2	35	80.0	0.70	88	96
Case 6	18	9	35	72.3	0.65	78	96

CE angle: Center-edge angle; AHI: Acetabular head index; HLI: Head lateralization index; JOAS: Japanese Orthopedic Association score; HHS: Harris hip score.

OPERATIVE TECHNIQUES

Arthroscopy was performed in all cases to evaluate the condition of cartilage and acetabular labrum, as well as the degree of osteoarthritis before the osteotomy procedure. All cases were in the pre-osteoarthritis stage and there were no acetabular labral tear. The triple osteotomy sites were nearly the same as those reported by Tönnis[14-16]. First, an ischial osteotomy was performed in a side-up position with 90° hip flexion. Next the position was changed to a supine position, and pubic and iliac osteotomies were performed through two independent skin incisions. The iliac osteotomy was performed using a Gigli saw, using a technique similar to that of Salter osteotomy. For the acetabular osteotomy, the acetabulum was initially rotated laterally. Then an iliac wedge graft was obtained and grafted between the acetabulum and the ilium. Three 3.0 mm K-wires were used for fixation of the acetabulum. Hip spicas were not required for postoperative immobilization.

RESEARCH

Pre-operative ROM was full in all patients. At the final follow up examination, mean flexion was 108.3° (100°-120°), abduction was 33.3° (30°-40°), external rotation was 58.3° (50°-60°), and internal rotation was 35° (20°-50°). Details follow-up findings are presented in Tables 1 and 2. With regard to acetabular coverage, HHS and JOAS were both improved. The average pre-

Table 3 The mean values of pre-operative and post-operative angles and scores

	Pre-op (mean ± SD)	Post-op (mean ± SD)	*P* value
CE angle	5.67 ± 8.26	25.5 ± 13.4	0.0184[1]
Acetabular index	21.7 ± 5.44	6.33 ± 9.0	0.0098[1]
Sharp angle	47.5 ± 3.09	30.2 ± 9.0	< 0.0001[1]
AHI	58.4 ± 8.60	78.4 ± 9.8	0.0063[1]
HLI	0.63 ± 0.06	0.65 ± 0.1	0.6286
JOAS	62.3 ± 10.9	89.7 ± 6.5	0.0006[1]
HHS	72.3 ± 11.9	98.7 ± 1.9	0.0006[1]

CE angle: Center-edge angle; AHI: Acetabular head index; HLI: Head lateralization index; JOAS: Japanese Orthopedic Association score; HHS: Harris hip score. [1]$P < 0.05$ based on a Student's *t*-test.

operative CE angle, acetabular index angle, Sharp angle, AHI, and HLI value were 5.67, 21.7, 47.5, 58.4, and 0.63, respectively, with the corresponding postoperative values being 25.5, 6.33, 30.2, 78.4, and 0.65, respectively (Table 3). HLI showed no improvement, suggesting that medialization of the femoral head was not achieved, whereas HHS, JOAS, CE angle, acetabular index angle, Sharp angle, and AHI were all significantly improved ($P < 0.05$). JOAS was improved from 62.3 to 89.7 and HHS from 72.3 to 98.7. The average operative time was 5 h and 25 min, including arthroscopy and changing of position. All patients chose "well satisfied" for the satisfaction score. The average lower limb elongation was 12 mm. Two complications were encountered in 1 patient (case 6), temporary lateral femoral cutaneous nerve (LFCN) dysfunction and delayed union of the ischium. No patients had infection, non-union, other nerve injuries, vascular injury, or osteonecrosis of the acetabulum.

REPRESENTATIVE CASES

Cases 1 and 2

Patient at age at the time of surgery was 19 years old. The same patients underwent a triple osteotomy for the left hip (case 1), which was followed by a right hip osteotomy the next year (case 2; Figure 2A, B). The follow-up period for the right hip was 6 years. Pre-operative JOAS in the left hip was 63 (pain 20, ROM 20, walking ability 5, ADL 18), whereas that in the right was 73 (30, 20, 5, 18). At the final follow-up examination, post-operative JOAS in the left and right hips was 95 (35, 20, 20, 20) and 95 (35, 20, 20, 20), respectively. Pre-operative HHS was 70 in the left hip and 80 in the right, whereas both the corresponding post-operative values were 100. The operating time for the left and right sides was 5 h 21 min and 6 h 28 min, respectively, whereas bloodloss was 340 mL and 220 mL, respectively, and elongation of the lower limbs 15 mm and 20 mm, respectively. Patient satisfaction scores for both hips corresponded to "well satisfied".

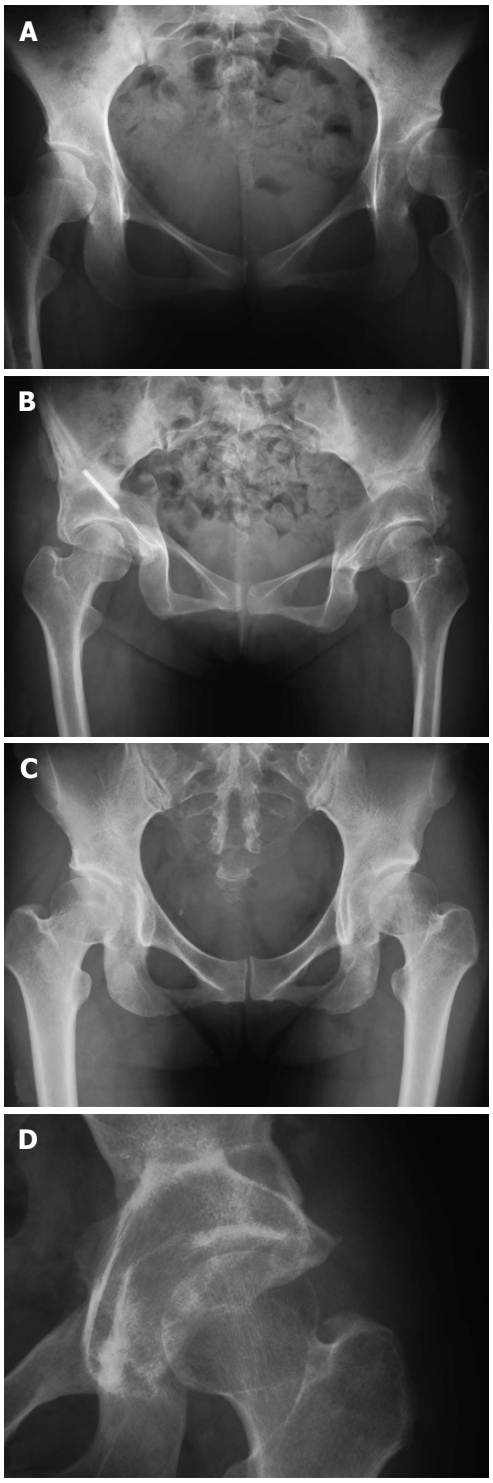

Figure 2 Anteroposterior X-ray images of cases 1, 2 and 5. A: Pre-operative anteroposterior (AP) X-ray images of cases 1 and 2 showing pre-osteoarthritis in a patient with bilateral developmental dysplasia of the hip (DDH); B: Post-operative AP X-ray image at the final follow-up examination. Three 3.0 mm K-wires were used for fixation of the acetabulum. One of the K-wire was remained at the right hip; C: Pre-operative AP X-ray image showing pre-osteoarthritis in a patient with bilateral DDH; D: Post-operative AP X-ray image at the final follow-up examination.

Case 5

Patient at age at the time of surgery was 43 years and the follow-up period was 3 years (Figure 2C, D). Triple osteotomy was performed on the left hip. Pre-operative JOAS was 80 (30, 20, 10, 20), whereas post-operative JOAS was 88 (30, 18, 20, 20). HHS values before and after surgery were 93 and 96, respectively. The operating time was 4 h 22 min, whereas blood loss was 830 mL,

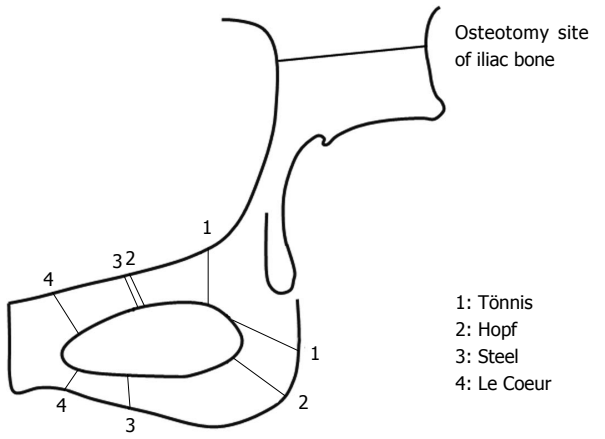

Figure 3 Several major modifications of triple osteotomy have been presented, and osteotomy line of the Bernese osteotomy and rotational acetabular osteotomy was also presented. In Steel's triple osteotomy, the pubic ramus and ischium in front of the tuberosity are osteotomized. The site of the ischial and pubic osteotomy in the method of Tönnis is closer to the acetabulum compared with Steel's osteotomy. In a Hopf triple osteotomy, the ischial tuberosity is osteotomized closer to the center of the hip joint than in Steel's procedure. In a Le Coeur osteotomy, the pubis and ischial ramus are osteotomized closer to the pubic symphysis as compared with Steel's procedure.

and elongation of the lower limbs was 8 mm. The values for the CE angle, acetabular index, Sharp angle, and AHI improved from 16, 14, 47, and 70.5 to 26, 2, 35, and 80, respectively.

THE HISTORY OF TRIPLE OSTEOTOMY

The first report of pelvic osteotomy as a treatment for DDH dates back to the classical report by Konig[17]. Long after this original report, Blavier *et al*[18] reported a circular osteotomy used to rotate the acetabulum over the femoral head. The concept of rotating the acetabulum over the femoral head developed into triple pelvic osteotomy first described by Le Coeur in 1965[19]. Hopf further developed the ideas of pelvic osteotomy and reported double osteotomy and triple osteotomy in 1965 and 1966, respectively[20]. Steel further modified the triple osteotomy procedure for the easier surgical access to the ischium[21].

Since then, a wide variety of studies on pelvic osteotomies for adult DDH have been reported, including the Chiari osteotomy[22-24], RAO[3], Bernese periacetabular osteotomy[2], eccentric RAO[25], curved periacetabular osteotomy[26], and a modification of the Ganz osteotomy[2]. The surgical sites of a triple osteotomy are the ilium, ischium, and pubis. The procedure provides improved coverage of the acetabulum along with biomechanical stability to the hip equivalent to that of an RAO.

MODIFICATION OF TRIPLE OSTEOTOMY

Steel's triple osteotomy reported in 1973 has probably been the most popular and has undergone substantial modifications (Figure 3). Tönnis invented a major modification of Steel's triple osteotomy[27], in which the site of the ischial osteotomy, closer to the acetabulum than in Steel's osteotomy, is just adjacent to the hip joint, allowing an easier rotation of the acetabulum. The contact area is superior to that of the Steel's osteotomy. Kotz's polygonal triple osteotomy was described[28-32], in which the osteotomy lines of the innominate and ischial are polygonal, and the axis of rotation of the acetabulum is parallel to the superior pubic ramus. The rotated acetabulum is relatively stable and fixed with an internal fixation plate. Wall reported an endoscopic triple pelvic osteotomy in 2001[33], whereas Lehman described an "almost" percutaneous triple pelvic osteotomy in 2004[34]. With those, a 2-incision surgical approach is employed and the iliac osteotomy is performed using a Gigli saw. They reported that their osteotomy method is safe and has a relatively shallow learning curve compared with other triple pelvic osteotomy procedures. Kumar *et al*[8] also reported a modified triple osteotomy, which adds a shelf procedure to the triple osteotomy to achieve further stability of the hip joint and coverage of the femoral head.

A variety of devices have been invented to provide stability of the osteotomy site. Eren reported an "incomplete" triple pelvic osteotomy[35], in which a greenstick fracture was created in the remaining portion of the ischial body without a total iliac osteotomy. This highly stable osteotomy allowed early weight bearing. In turn, Lipton reported a different modification of the triple osteotomy, in which a wedge osteotomy was performed at the proximal part of the ilium[36]. The resection of the wedge from the outer cortex created a slot, with the intact inner cortex serving as a stabilizing buttress where the distal posterior aspect of the ilium fits. This osteotomy allows for extensive coverage of the femoral head along with a greater stability.

We summarized the advantages and demerits of triple osteotomy in Table 4. After this paragraph, we in detail discussed these concerns point by point.

Table 4 The advantages and demerits of triple osteotomy

Advantages	Demerits
EAsier than Bernese osteotomy or RAO	Risk of non-union of pubis and ischium
Applicable regardless of whether the triradiate cartilage remains fused or not	Require the long period before weight bearing
Low risk Osteonecrosis of acetabulum Major vessel injury	Difficulty and limitation of sufficient acetabular correction and femoral head medicalization
No shortening of lower limb	Possibly narrowing the pelvic cavity for childbirth

RAO: Rotational acetabular osteotomy.

DEGREE OF CORRECTION AND ACETABULAR RETROVERSION

A number of the previous studies on triple osteotomy have reported good improvement of the radiological indices (Figure 1). Janssen *et al*[37] reported an increase of the CE angle[10] of 24.4° (10.2° → 34.6°) [37] and van Hellemondt *et al*[38] revealed an increase of 19° in CE angle

(9° → 28°)[38]. de Kleuver *et al*[39] reported a reduction of 12° in Sharp angle[12] (22° → 10°)[39]. Peters *et al*[1] revealed an increase of 20° in the CE angle (11° → 31°) and a reduction of 11° in Sharp (50° → 39°). Dora *et al*[40] showed an increase of 8.2° in the CE angle (7.8° → 36°) and a decrease of 15° in the Sharp angle (46° → 31°). Tönnis *et al*[15,16] reported an increase of 27.8° in the CE angle (-10° → 17.8°) and decrease of 18° in acetabular index angle[41] (36.7° → 18.5°)[15,16]. In our case series, the degree of acetabular correction for CE angle, acetabular index angle, and Sharp angle was +19.8°, -15.4°, and -17.3°, respectively. In addition, Hailer *et al*[42] reported that the median correction of lateralization in their study was approximately 0 mm. On the other hand, Dungl found 6 mm medialization in their young patients (average age 16.5 years)[6]. HLI in our series was 0.02; *i.e.*, no medialization of the femoral head was achieved.

Frick *et al*[7] performed detailed analysis by 3-dimensional computed tomography and reported that the acetabular fragment moved in the directions of adduction, anterior rotation (extension), and external rotation, thus improving femoral head coverage. They also found that the surgical procedure increased external rotation of the acetabulum and an excessive external rotation was noted in 22% of all cases. Exaggerated external rotation of an osteotomized acetabulum increases the risk of non-union by producing gaps at the pubic and ischial osteotomy sites[28,43]. Wenger *et al*[44] reported that a "figure-of-four" maneuver, often used to improve the mobility of osteotomized acetabulum, should not be employed to avoid excess external rotation of the acetabulum.

Tönnis *et al*[45] reported a case of painful hip due to over-correction. Acetabular retroversion is a cause of hip pain[14,46] and Kim *et al*[47] reported that retroversion of the acetabulum was likely to cause an early onset of coxarthrosis. Femoroacetabular impingement was first described as an anterior impingement after a Bernese periacetabular osteotomy by Myers *et al*[48] in 1999. Dora *et al*[40] also reported retroversion of the acetabulum after the Salter and triple osteotomy procedures, and found that a retroverted acetabulum was present in 27% of their cases, with an average angle of -15°. A retroverted acetabulum was more frequent and pronounced after a triple osteotomy than after a Salter osteotomy, *i.e.*, 60% *vs* 24%, respectively. Acetabular retroversion may further predispose the patient to osteoarthritis[14,46]. de Kleuver *et al*[49] reported that decreased coverage of the posterolateral quadrant of the femoral head would sacrifice walking ability and recommended not to overcorrect the acetabular rotation anteriorly only to improve anterior coverage.

ELONGATION OF LOWER LIMBS

Vukasinovic *et al*[5] reported that leg length may well influence patients' satisfaction. Hailer *et al*[42] reported that the average gain of limb length was +0.5 cm (0 to 4 cm). Dungl *et al*[6] reported an average gain of +1.8 cm, and speculated that the limb lengthening was due to a distal shift of the osteotomized acetabulum. In our cases, the average gain of limb length was +1.2 cm. In general, the length of the operated lower limb is increased following a triple osteotomy.

RANGE OF MOTION

Dungl *et al*[6] reported loss of hip flexion and internal rotation after a triple osteotomy. Hip flexion after the operation isrestricted because of the anterolateral tilt of the acetabulum, and the internal rotation becomes restricted in a similar manner. Faciszewski *et al*[50] studied 56 hips in their series, with an average age of 28 years and follow-up period of 7 years. They reported that patients had a slight decrease in hip internal rotation and abduction. A slight loss of ROM seems to be common in adults after a pelvic osteotomy because of lateral and external correction of the acetabulum. On the other hand, several authors have reported improvement in ROM. In a series of adult patients with mean age of 27.8 years, Kooijman *et al*[51] found that a moderately restricted preoperative ROM improved to full ROM with 47/51 (92%) hips becoming pain free at 2 years after the operation. In adolescents with an average age of 13.9 years, Kumar *et al*[8] reported that post-operative ROM in term of flexion and abduction recovered to the pre-operative ROM level with an average follow-up period of 6 years.

REHABILITATION AFTER TRIPLE OSTEOTOMY

Steel described the detailed postoperative treatment of a series of patients aged 7-17 years[4]. A cast was maintained for a period of 8-10 wk, after which the K-wires were removed. Passive and active motion was started, and then weight bearing began with crutches at 12-14 wk. Tönnis *et al*[15,16] reported that patients were immobilized in a long-leg spica cast for 6 wk and weight bearing was not allowed until sufficient consolidation of the osteotomy sites in the first series. The average age in their study was 19.8 years and 12-16 wk were needed before weight bearing began in adults. Weight bearing tended to be later, especially among those with osteoporosis or osteoarthritis.

Peters *et al*[1] noted that patients (average age 26 years) were limited to toe touching for 8 wk, at which time partial weight bearing was allowed if AP radiographs showed adequate osseous healing. Hip ROM and muscle exercises were also begun at 8 wk and full weight bearing was achieved after 36 mo. Hailer *et al*[42] reported that K-wires were routinely removed approximately 1 year after the operation, in patients whose average age was 23 years. Early mobilization on crutches without weight bearing was conducted for 6 wk and prophylaxis for deep venous thrombosis was performed until full weight bearing was achieved.

Janssen *et al*[37] reported that weight bearing was not allowed for 12 wk in their patients (average 38.6 years). During the early postoperative rehabilitation, ROM exercises over the following limits was prohibited: (1) joint

movement only up to 30° for abduction and adduction; (2) no external rotation; and (3) maximum flexion of 60°. When radiographic evidence of consolidation appeared 6 wk after surgery, flexion up to 90° and abduction were permitted. Thrombosis prophylaxis with low-molecular weight heparin was administered for the entire period of limited weight bearing. Vukasinovic *et al*[5] reported a young series (mean age 15.9 years), in which none of the patients were immobilized and post-operative skin traction was used in all for a mean period of 44.4 d. Rehabilitation began 8.8 d after surgery and weight bearing after 128.7 d. Eren *et al*[35] described post-operative rehabilitation results after incomplete triple pelvic osteotomy procedures in patients with an average age of 21.4 years. They reported that partial weight bearing (10 kg) with crutches and active motion of the hip were started on post-operative day 3, and full weight bearing with crutches was allowed approximately 6-8 wk after surgery.

FUNCTIONAL AND CLINICAL RATING

In Steel's original publication in 1973, the failure rate was 23% for 52 hips in 45 patients who were followed up from 2-10 years of age[4]. Furthermore, in 1977, Steel[21] reported the results of 175 hips in patients aged 6-35 years (70% aged 9-12 years) after a follow-up period of 3-13 years, which had an 86% success rate. de Kleuver *et al*[39] and van Hellemondt *et al*[38] reported the long-term results (mean follow-up of 15 years) of the triple osteotomy procedure in patients (mean age of 28 years) with pre-operative osteoarthritis stage grade 0 or 1. They performed triple osteotomy procedureson 51 patients (5 males, 38 females), 88% of did not undergo total hip arthroplasty (THA) and 83% reported no pain. Furthermore, there was no progression of osteoarthritis in 65% of the patients, and 64% had either "excellent" or "good" clinical scores. They concluded thata significant negative factor for good long-term results was the presence of advanced osteoarthritis designated by a fair or poor pre-operative clinical score.

Peters *et al*[1] found a significant relationship between osteotomy failure and pre-operative osteoarthritis. In their study (mean age: 26 years; mean follow-up duration: 9 years), 27% of the hips were classified as failures, out of which 20% needed to be converted to THA and 7% required THA. They concluded that a triple osteotomy is an alternative modality to THA, although the duration of the operation and postoperative treatment are much longer than that of THA. Dungl *et al*[6] (mean age at operation 16.5 years, mean duration of follow-up 12.5 years) reported that the results of the osteotomy procedure were excellent in the majority of cases (76% of the cases). In 8 patients (5%) with unsatisfactory results after the operation, THA was performed, whereas another 8 patients (5%) were candidates for THA. Vukasinovic *et al*[5] reported the occurrence of early osteoarthritis in 4 operated hips (5.3%), of which only 1 (1.3%) required an additional THA procedure 4.2 years later. von Bremen-Kühne *et al*[52] reported a conversion rate to THA of 2.6%, whereas van Hellemondt *et al*[38] had a conversion rate to THA of 11.7% after a mean follow-up period of 15 years. In general, long-term results of a triple osteotomy without osteoarthritis or with low-grade osteoarthritis are good[53].

Janssen *et al*[37] reported that a preoperative body mass index > 25 kg/m^2 and HHS < 70 resulted in a poor outcome or early conversion to a THA. They presented results of a triple osteotomy for only second-grade osteoarthritis (advanced stage) related to DDH (mean age at operation 38.6 years), with a long-term follow-up duration of 11.5 years. They concluded DDH even at an advanced stage can be treated with a triple osteotomy procedure.

PATIENT SATISFACTION

Peters *et al*[1] found that 98% of their patients would recommend the same procedure to other patients with similar symptoms. In contrast, Hailer *et al*[42] reported that 65% were satisfied with the procedure, whereas 35% were not, and 2 patients underwent THA after 11 years. The incidence of complications such as non-union at the osteotomy site influenced patient satisfaction. Their analysis showed that the "not satisfied" group was significantly older ($P = 0.005$) with significantly poorer clinical scores ($P < 0.0005$). The incidence of non-union ($P = 0.0017$) and that of other complications ($P < 0.0005$) was also significantly higher in the same group. They concluded that the occurrence of complications had a grave impact on patient satisfaction.

SURGICAL COMPLICATIONS

Non-union

Steel[21] reported no incidence of non-union in their original article, whereas Tönnis reported that 1 patient developed pseudoarthrosis in the pubic ramus (3%, 1/32)[41] and Vukasinovic *et al*[5] noted that 9.2% (7/76) experienced non-union. In the latter study, there was 1 (1.3%) case with triple non-unions of the ilium, pubis, and ischium, and 6 (7.9%) with double non-unions of pubis and ischium. However, all non-unions were asymptomatic and did not require an additional procedure. They also reported that non-union occurred more frequently when a saw was used (4/12) compared with when a chisel was used (2/64) ($P = 0.003$), suggesting that non-union may occur because of soft tissue interposition secondary to extensive bone resections. There was no statistically significant difference either between cases with 2 and 3 K-wire fixation, or among the levels of the osteotomy. On the other hand, non-unions tended to occur significantly more often in older patients; the average age in the non-union group was 20.2 ± 27.12 years, whereas that in the union group was 15.5 ± 4.67 years old ($P = 0.029$)[5].

Kirschner *et al*[54] presented 7 cases of pubis and ischium non-union in a series of 48 patients (14.6%). In turn, Dungl *et al*[6] reported non-union in 19 of 329 patients (5.4%), of whom 2 patients were triple non-union cases and 2 patients double non-union cases. All triple

non-union cases required osteosynthesis and bone grafting, whereas the double non-union cases also needed surgical intervention. Isolated non-union was seen in 15 patients (ischium 8, pubis 7). The most frequent site was the ischium, but isolated non-union was not considered to be indicative for re-operation. van Hellemondt *et al*[38] reported isolated non-union of the ischium in 3 patients out of 48 (6.25%) as well as an isolated non-union of the pubis in 1 patient out of 48 (2%). Their mean age at operation was 28 years. Their pre-operative grades for osteoarthritis were 0 and 1, and the non-union cases occurred in those with major acetabular correction. Peters *et al*[1] reported double non-union of the ilium in 2 patients out of 60 (3.3%), with a mean age at operation was 26 years and mean duration of follow-up was 9 years.

In 2003, Tschauner *et al*[55] reported cases of "painful non-union" after a triple osteotomy, and the mean age at operation of the patients was 25.7 years where as the mean duration of follow-up was 7.1 years. Their triple osteotomy utilized the Tönnis method with AO screw fixation. Partial weight bearing was permitted after 8 wk and full weight bearing after 16 wk. Isolated pseudoarthrosis of the pubis was seen in 8 patients (2%), though all were asymptomatic and no further surgical treatment was required. Five patients (1.2%) developed double pseudoarthrosis with non-union of the pubis and ischium, all of whom were symptomatic and required another operation including bone grafting, fixation, and excision at a mean duration of 19.4 mo after osteotomy. On the basis of their investigation of 409 triple osteotomies, they provided the following recommendation: (1) adequate bony contact should be ensured at all 3 osteotomy sites; (2) 2 or 3 screws should be used for the iliac osteotomy; (3) a long mediolateral screw should be used to stabilize the pubic osteotomy until union; (4) patients should not sit on the ipsilateral ischial tuberosity for 6 wk; and (5) patients should be informed that smoking is a risk factor for non-union. In general, the non-union rate seems to be approximately 7%.

Acetabular osteonecrosis

Tönnis reported no acetabular osteonecrosis in the first series[21], and van Hellemondt *et al*[38] later confirmed the absence of osteonecrosis. Few articles have provided details of acetabular osteonecrosis and, to the best of our knowledge, there are no reports of that complication in association with a triple osteotomy.

Infection

Steel reported 1 case of infection (2.2%) in their initial article[14], whereas Tönnis *et al*[15] and Dungl *et al*[6] reported none. Furthermore, Van Hellemondt reported superficial infections in 2 (4.2%) and deep infections in 1 (2.1%) out of 48 cases[11]. The prevalence of infection reported by Vukasinovic *et al*[5], Peters *et al*[1], and Hailer *et al*[42] was 1.3% (1/76), 3.3% (2/61), and 3.3% (2/61), respectively. In general, the rate of infection seems to be approximately 2.7%.

Nerve injury

Tönnis *et al*[15] reported that 1 patient in their series developed transient peroneal nerve palsy[15], whereas Vukasinovic *et al*[5] reported 2 peroneal nerve palsy cases (2/76 patients, 2.6%). Dungl *et al*[6] reported no serious neurovascular complications in their 329 patients. However, in 9% of those cases, loss of sensation in the region supplied by LFCN became permanent. Peters *et al*[1] also reported temporary irritation of LFCN in 6 of 32 cases (19%), and van Hellemondt *et al*[38] noted LFCN dysfunction in 9 (19%) and transient palsy of the sciatic nerve in 1 (2%) of 48 cases. In addition, Hailer *et al*[42] reported temporary sciatic nerve palsy in 2 of 61 patients (3.3%). In general, the nerve injury rate seems to be approximately 9.5%. Some authors found that a dorsal approach to the ischium has a higher level of safety as compared with an anterior approach[15,56,57].

Vascular injury

Few studies have investigated vascular injury in detail. Dungl *et al*[6] reported no neurovascular complications in their 329 patients, whereas Hailer *et al*[42] reported excessive bleeding from a branch of the internal iliac artery leading to discontinuation of a triple osteotomy in 1 case.

Other complications

In their initial article, Steel[21] reported that paralytic ileus occurred in 2 of 45 patients (4.4%) as an immediate postoperative complication, whereas skin necrosis appeared in 2 patients (4.4%). Janssen *et al*[37] reported 1case of external snapping hip syndrome in their 32 patients (3%). Hailer *et al*[42] noted 1 patient with a large hematoma (1.6%), 2 with heterotopic ossification (3.3%), 1 with complete insufficiency of the gluteal muscles (1.6%), and 1 with osteonecrosis of the femoral head (1.6%), though no other details were reported[39].

It is also important to discuss the procedure in relation to childbirth. Winklemann in 1984 observed narrowing of the birth canal after a triple osteotomy performed according to the method of Steel and Tönnis in the middle part of the pelvic cavity. That study recommended a caesarian section in all cases after a triple osteotomy[58]. In those cases, 95 (32%) became pregnant and 40% of those gave birth naturally, with 60% undergoing a Caesarian section. Lorder *et al*[59] reported that Salter, Sutherland, and Steel osteotomies all narrowed both the inlet and outlet of the pelvis. Female patients should be informed of these alterations and the possibility of a caesarian section for future pregnancies.

ADVANTAGES AND DEMERITS OF TRIPLE OSTEOTOMY

We summarized the advantages and demerits of triple osteotomy in Table 4. A biomechanical analysis performed by Hsin *et al*[60] revealed significantly smaller stress on the hip after a triple osteotomy and at the time of the latest

follow-up examination than that estimated after surgery. The decrease in stress was a direct result of a significant increase in the area of the weight-bearing surface of the hip. On the other hand, Huang *et al*[9] reported that patients who underwent an RAO were characterized by a better acetabular index angle than patients who underwent a triple osteotomy. However, the functional outcome based on HHS was better after a triple osteotomy than after an RAO, and patients who had a triple osteotomy tended to express better subjective scores.

Aminian *et al*[61] reported the freedom of the acetabular fragment on flexion (anterior femoral head coverage), abduction (lateral femoral coverage), and external rotation (acetabular retroversion) in several osteotomies using fresh-frozen male cadavers. Freedom of the acetabular fragment was evaluated with a Ganz osteotomy, Tönnis triple osteotomy, and Carlioz *et al*[62] triple osteotomy in the same article. The results revealed that maximum motion was achieved with the Ganz osteotomy, while "coupled motion" (external rotation during abduction) was most prominent with the Carlioz technique, and no coupled motion was seen with a Tönnis osteotomy. They considered the Tönnis osteotomy to be the safest and optimal for moving the acetabular fragment to improve abduction and flexion, such as the 20-20 rule.

CONCLUSION

In the present study, we present a detailed review of the relevant literature. We found that the clinical results of a triple osteotomy were satisfactory and it should be considered as an alternative candidate procedure for a pelvic osteotomy in older adults with DDH.

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Current concept in dysplastic hip arthroplasty: Techniques for acetabular and femoral reconstruction

Goran Bicanic, Katarina Barbaric, Ivan Bohacek, Ana Aljinovic, Domagoj Delimar

Goran Bicanic, Domagoj Delimar, Department of Orthopaedic Surgery, University of Zagreb, School of Medicine, 10000 Zagreb, Croatia
Goran Bicanic, Katarina Barbaric, Ivan Bohacek, Ana Aljinovic, Domagoj Delimar, Department of Orthopaedic Surgery, Clinical Hospital Centre Zagreb, 10000 Zagreb, Croatia
Author contributions: Bicanic G designed, prepared, partially wrote and revised manuscript; Barbaric K contributed to conception of the study, wrote part of the manuscript, helped with obtaining and drawing of figures; Bohacek I contributed in study design, wrote part of the manuscript, helped with references, editing and preparing the manuscript; Aljinovic A contributed to study conception, wrote part of the manuscript, helped with the references and figures and revised manuscript; Delimar D helped with design of the study and figures, helped in preparation and revision of the manuscript and editing; all authors approved final version to be published.
Correspondence to: Ivan Bohacek, MD, PhD, Department of Orthopaedic Surgery, Clinical Hospital Centre Zagreb, Salata 7, 10000 Zagreb, Croatia. gbic@mef.hr
Telephone: +385-1-2368911 Fax: +385-1-2379913
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Abstract

Adult patients with developmental dysplasia of the hip develop secondary osteoarthritis and eventually end up with total hip arthroplasty (THA) at younger age. Because of altered anatomy of dysplastic hips, THA in these patients represents technically demanding procedure. Distorted anatomy of the acetabulum and proximal femur together with conjoined leg length discrepancy present major challenges during performing THA in patients with developmental dysplasia of the hip. In addition, most patients are at younger age, therefore, soft tissue balance is of great importance (especially the need to preserve the continuity of abductors) to maximise postoperative functional result. In this paper we present a variety of surgical techniques available for THA in dysplastic hips, their advantages and disadvantages. For acetabular reconstruction following techniques are described: Standard metal augments (prefabricated), Custom made acetabular augments (3D printing), Roof reconstruction with vascularized fibula, Roof reconstruction with pedicled iliac graft, Roof reconstruction with autologous bone graft, Roof reconstruction with homologous bone graft, Roof reconstruction with auto/homologous spongious bone, Reinforcement ring with the hook in combination with autologous graft augmentation, Cranial positioning of the acetabulum, Medial protrusion technique (cotyloplasty) with chisel, Medial protrusion technique (cotyloplasty) with reaming, Cotyloplasty without spongioplasty. For femoral reconstruction following techniques were described: Distraction with external fixator, Femoral shortening through a modified lateral approach, Transtrochanteric osteotomies, Paavilainen osteotomy, Lesser trochanter osteotomy, Double-chevron osteotomy, Subtrochanteric osteotomies, Diaphyseal osteotomies, Distal femoral osteotomies. At the end we present author's treatment method of choice: for acetabulum we perform cotyloplasty leaving only paper-thin medial wall, which we break during acetabular cup impacting. For femoral side first we peel of all rotators and posterior part of gluteus medius and vastus lateralis from greater trochanter on the very thin flake of bone. This method allows us to adequately shorten proximal femoral stump, with possibility of additional resection of proximal femur. Furthermore, several advantages and disadvantages of this procedure are also discussed.

Key words: Hip; Arthroplasty; Dysplasia; Reconstruction; Techniques; Acetabulum; Femur; Osteoarthritis; Developmental dysplasia of the hip

Core tip: Total hip arthroplasty (THA) in adult patients with developmental dysplasia of the hip is technically demanding procedure. In this paper we present a vari-

ety of surgical techniques available for THA in dysplastic hips, their advantages and drawbacks, ending with the author's treatment method of choice.

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INTRODUCTION

Developmental dysplasia of the hip (DDH) is common cause of secondary hip osteoarthritis[1]. The prevalence of DDH varies among different ethnic groups; from 5.4 to 12.8% in the Danish population, 1.8% in Koreans, 2.4% in Turkish people and 7.3% in Singaporeans[2]. The aetiology of DDH is multifactorial, involving both genetic and intrauterine environmental factors. The group of patients at risk includes those with one or combination of the following risk factors: female gender, first born, positive family history or ethnic background, breech delivery, oligohydramnios, torticollis, and lower-limb deformity[3]. Despite new-born screening programs[4], some cases are missed, or incorrectly treated. These patients develop secondary osteoarthritis and eventually end up with total hip arthroplasty (THA) at younger age. Due to changed anatomy of dysplastic hips, THA in these patients is technically very demanding procedure[5-7]. Functional results after THA in dysplastic hips are often not excellent[8,9]. At the beginnings of modern arthroplasty it was considered that THA in these patients is not possible[10]. Better surgical techniques were developed over time to achieve a painless, stable and long-lasting hip endoprosthesis customized to increased functional needs of these young patients. In this paper we present a variety of surgical techniques available for THA in dysplastic hips, their advantages and drawbacks, ending with the author's treatment method of choice[7].

ANATOMY AND BIOMECHANICS OF DYSPLASTIC HIP

Anatomy of dysplastic hip is usually significantly altered. Acetabulum and femur are underdeveloped and femur is often displaced. Hip biomechanics is altered and there is no ideal stimulation for development of proper acetabulum and proper femoral head. Different morphological alterations are seen, not only on femur and acetabulum but also on pelvis[11-13]. In simplest degrees of dysplasia acetabulum is just a little bit shallower with lover acetabular angle but in the most complex cases of dysplasia acetabulum is underdeveloped, shallow and lacking bone stock medially. Since femoral head is situated more proximal (dislocated), a new acetabulum (neoacetabulum) is formed (Figure 1). Pelvic bone stock is rearranged and there is more bone thickness available more posteriorly in relation to the level of the true acetabulum[13]. Acetabular retroversion represents additional problem. Incidence of acetabular retroversion in dysplastic hips ranges from 1 in 6 according to Li *et al*[14] to 1 in 3 according to Mast *et al*[15]. Dysplastic femur has increased anteversion, shorter neck and narrower and straighter femoral canal[16,17]. Femoral head is elliptic which causes incongruity of the hip joint[17]. All of mentioned alterations in dysplastic hip anatomy are responsible for functionally "weaker" hip joint unable to withstand increased load. In short, dysplastic hips are incongruent, centre of rotation is displaced, hip abductors and flexors are shortened and weakened. If dysplasia is one-sided, pelvic disbalance is often present with limping and leg length discrepancy. All of these factors can increase forces in hip joint, which can cause quicker deterioration of cartilage and bone tissue with earlier onset of osteoarthritis of the hip joint[10,18].

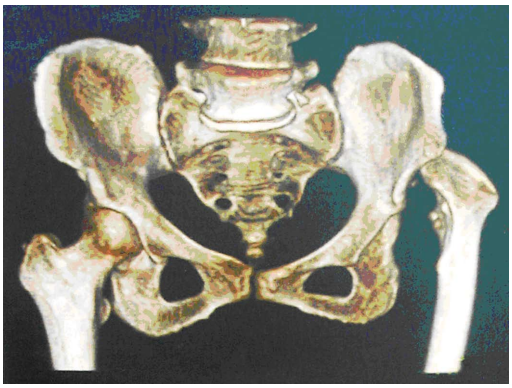

Figure 1 On the right side hip is normally developed and on the left side the acetabulum is underdeveloped, shallow and lacking bone stock medially and at the level of normal (ideal) acetabular roof. The femoral head is more proximal (dislocated) with increased anteversion, shorter neck and narrower and straighter femoral canal.

CLASSIFICATION OF DYSPLASTIC HIP

There are different classifications of dysplastic hips in adults. Those classifications are developed so that different treatments can be compared and so that the surgeon can plan and prepare operation and predict outcome based on the degree of dysplasia. Since in majority of the cases the diagnosis is formed based on the clinical exam and X-rays, most common classifications are based on X-rays of the pelvis and the hips. The most common is classification according to the Crowe[19] with 4 different degrees of dysplasia (Figure 2). There are more recent classification like Eftekhar[20] and Hartofilakidis *et al*[11,21] which take into account both femoral and acetabular side. Hartofilakidis *et al*[11] acknowledged importance at the acetabular side for operative treatment so in 1988 he based his classification on relations between femoral head and acetabulum and the difference between true and false (neo) acetabulum[11]. Then, in 2008, he additionally developed his classification by adding subtypes regarding to

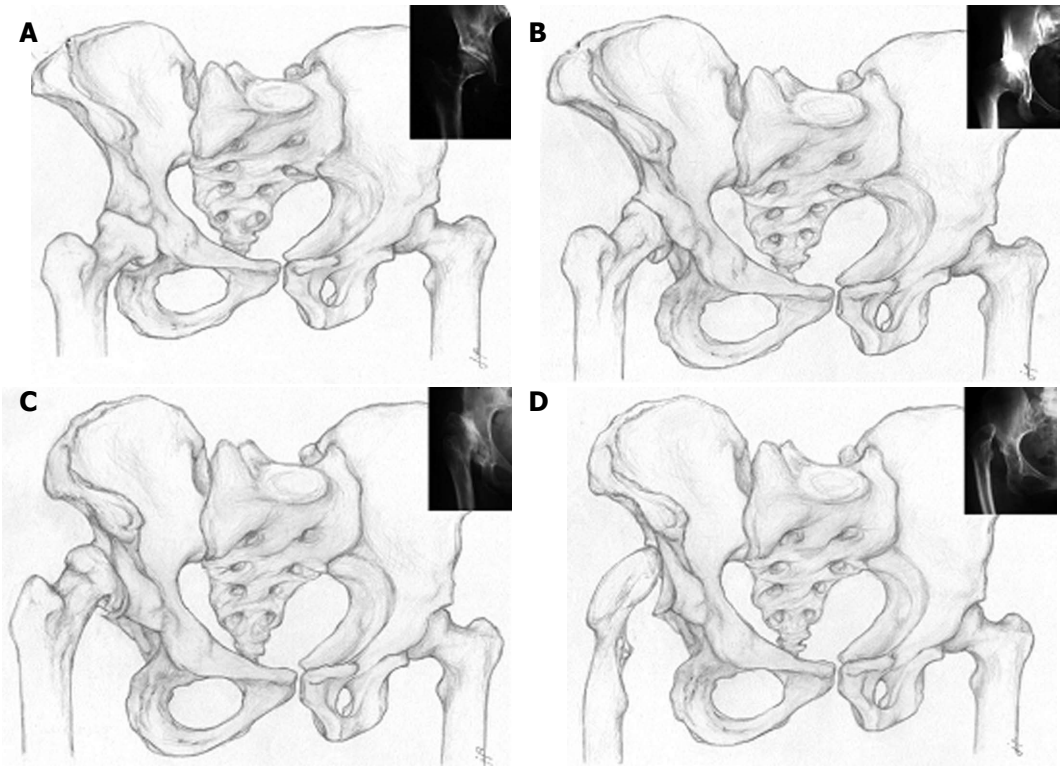

Figure 2 Left hip is normal, right hip is dysplastic. A: Crowe type 1-proximal head subluxation is less than 50% of vertical diameter of the femoral head (less than 10% of the pelvic height); B: Crowe type 2-proximal head subluxation is between 50% and 75% of vertical diameter of the femoral head (between 10% and 15% of the pelvic height); C: Crowe type 3-proximal head subluxation is between 75% and 100% of vertical diameter of the femoral head (between 15% and 20% of the pelvic height); D: Crowe type 4-proximal head dislocation with proximal movement of the femoral head for more than 100% of vertical diameter of the femoral head (head is moved proximally for more than 20% of the pelvic height).

the shape of the acetabulum[12]. This classification is very useful for surgeon but requires additional education and is more complicated. Special imaging modalities, including computed tomography (CT) of the hip, may be useful in complex hip arthroplasty. CT provides 3-dimensional information about anterior and posterior column deficiencies, socket size, thickness of the anterior and posterior walls and medial bone stock (thickness) at the level of the ideal acetabular roof which help us in preoperative planning[22]. Although Crowe classification is based on two-dimensional analysis of the pelvic X-ray and on, basically, just a vertical displacement of the femoral head, it is still predominant classification due to simplicity and availability.

OPERATIVE TECHNIQUES IN DYSPLASTIC HIP ARTHROPLASTY

Secondary osteoarthritis due to DDH occurs at a younger age because of abnormal anatomy (an average of 53 years according to Hartofilakidis *et al*[23]). The key point of surgical treatment is to ensure long-term stability of the endoprosthesis by restoration of anatomical and biomechanical relationships. This is not an easy task because total hip arthroplasty in DDH is technically demanding due to deficient acetabular bone stock, abnormal femoral anatomy with increased neck-shaft angle and valgus orientation, increased anteversion, muscle contracture and leg-length discrepancy[10,24]. Despite an initial discouraging statement that THR should be avoided in patients who have DDH, various techniques have been developed to approach this problem[10]. The surgeon has to address several issues. Distorted anatomy of the acetabulum and proximal femur is always a challenge. Then there is a leg length discrepancy. And finally, since majority of patients are at younger age, the soft tissue balance is of great importance (especially the need to preserve the continuity of abductors) to maximise postoperative functional result[7,25]. Technical options are numerous (Table 1).

Surgical alternatives to THA

There are also alternatives to THA in dysplastic hips such as pelvic osteotomies[14,26]. Pelvic osteotomies may provide excellent results for patients with early or no osteoarthritis and with moderate or no pain. The purpose of the pelvic osteotomy is to obtain an increased acetabular weight-bearing surface for the femoral head either by reshaping the acetabulum or by enlarging its margins. Different types of osteotomies are described in literature[14,26]. In the past, procedures such as the Chiari osteotomy or shelf augmentation of the acetabulum were used to treat adolescent and adult hip dysplasia but today realignment osteotomies would be used since they result with the reposition or acetabulum into a more favorable position over the femoral head and improve load distri-

Table 1 Different operative treatment options for total hip arthroplasty in secondary hip osteoarthritis in developmental dysplasia of the hip

Techniques for acetabular reconstruction	Techniques for femoral reconstruction
Standard metal augments (prefabricated)	Distraction with external fixator
Custom made acetabular augments (3D printing)	Femoral shortening through a modified lateral approach
Roof reconstruction with vascularized fibula	Transtrochanteric osteotomies
Roof reconstruction with pedicled iliac graft	Paavilainen osteotomy
Roof reconstruction with autologous bone graft	Lesser trochanter osteotomy
Roof reconstruction with homologous bone graft	Double-chevron osteotomy
Roof reconstruction with auto/homologous spongious bone	Subtrochanteric osteotomies
Reinforcement ring with the hook in combination with autologous graft augmentation	Diaphiseal osteotomies
Cranial positioning of the acetabulum	Distal femoral osteotomies
Medial protrusion technique (cotyloplasty) with chisel	
Medial protrusion technique (cotyloplasty) with reaming	
Cotyloplasty without spongioplasty	

bution. Their main advantage is that the femoral head is covered with hyaline cartilage instead of fibrocartilage. Their disadvantage is the complexity of the operations. Some of them are used only when the triradiate cartilage is open like Pemberton and Dega osteotomies. Others are single innominate osteotomy of Salter, the triple innominate osteotomies of Steel, Carlioz, and Tönnis and the periacetabular osteotomy of Ganz. The major disadvantage is that when there is advanced osteoarthritis of the dysplastic hip only THA can completely relieve the pain and restore the function of the hip joint.

Acetabular reconstruction

The major concern with total hip arthroplasty in DDH is the containment and incorporation of the acetabular cup. Placement of the cup is technically difficult because normal anatomic landmarks are obscured. There is a need for fine balance in adjusting the cup size, inclination, cup anteversion and coverage. A compromise can be made by setting acetabular component away from the ideal centre of rotation, but in such a way to ensure a good stability of the endoprosthesis. High placement of the acetabular component has been proposed (Figure 3A). Russotti *et al*[27] reports good long-term results with "high hip centre" acetabulum placement. Kaneuji *et al*[28] shows no differences in polyethylene wear with rotation centre placed 20 mm proximal from the figure of tears. However, according to Bicanic *et al*[29] one has to take into account that for every millimetre of proximalisation, load on the hip increases for about 0.1%. At this level bone stock is usually insufficient and the lever arm for body weight remains much longer than that of the abductors, resulting in excessive loading of the hip joint. In addition, at this level, shearing forces acting on the acetabular component may lead to an early loosening, and in unilateral cases a proximally placed acetabular component contributes to limping and limb-length discrepancy[23,30,31]. Placement of the acetabular component in the anatomical position and augmentation of the superior segmental defect with structural autologous graft (autograft) or allograft has also been proposed (Figure 3B). Cementless acetabular cups with 30% to 40% of uncoverage may be acceptable[32-34], more than that should be covered. Some authors recommend spongioplasty of the acetabular roof for smaller uncovered areas (Figure 3C)[35]. For larger defects structural autograft or allograft can be used. Autografts can be free or vascularized. For vascularized autografts it is expected to better integrate with iliac bone (Figure 3D)[36]. Usually vascularised iliac graft is used, although Fujiwara reported good outcome of acetabular roof reconstruction with free vascularized fibular graft[37]. Long-term survival rates of such bone grafts proved to be different in various studies. While some authors report good long-term results of free auto- or allografts[24,38,39] and vascularized autografts[37,40-42], others warn about graft resorption and secondary instability of acetabular component in structural bone grafting[43-45]. Acetabular bone stock deficiency can be managed with specially constructed acetabular components or using special 3-dimensional porous materials which simulates bone structure and allow faster and better endoprosthesis–bone integration (Figure 3F)[46-48]. For that purpose trabecular metal is used in form of acetabular cup or trabecular metal augments. That is manly used in revision surgery, but can be useful in dysplastic hip THA[48,49]. Potential advantage of trabecular metal is to avoid the use of structural bone grafts, avoid the need for custom shaped implants and provide excellent bone ingrowth on small contact area. Major disadvantage is potential difficulty if the cup should be removed because of infection. Oblong-shaped cementless implant (oblong cup) can be used for acetabular reconstruction. Abeyta *et al*[50] presented satisfactory long-term results in using oblong cup for reconstruction of the acetabulum. The reinforcement ring with the hook in combination with autologous graft augmentation has been designed for cases with severe bone-stock deficiencies (Figure 3E)[51,52]. This technique enables reconstruction of the anatomic hip centre by positioning the hook around the inferior margin of the acetabular floor (incisura acetabuli). The hook does not act as a fixation device but helps prevent high or lateral placement of the ring and helps adequate coverage of the polyethylene liner, regardless of the degree of anatomical deformity. Pitto *et al*[53] presented how reinforcement ring with hook

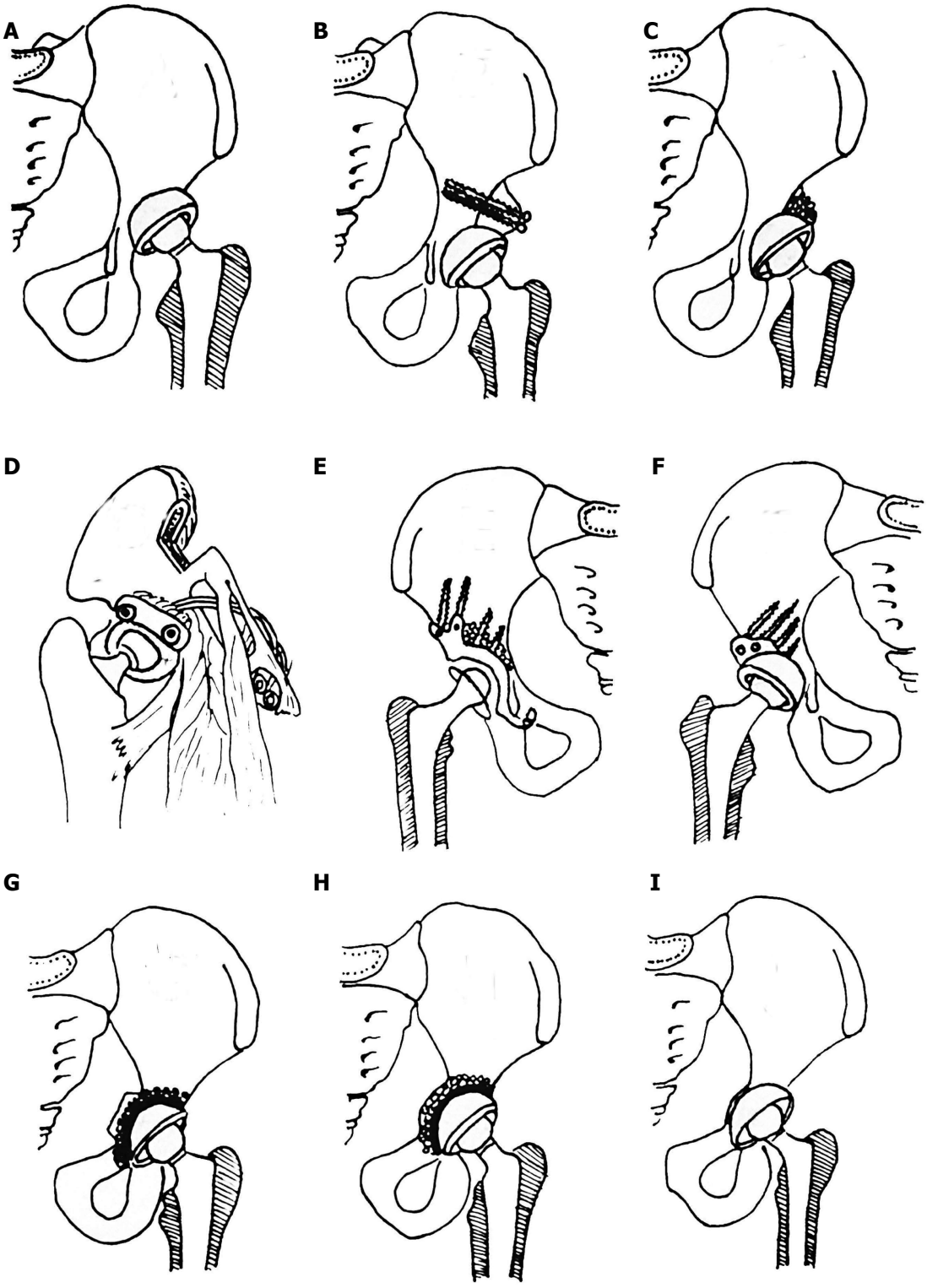

Figure 3 Different options for acetabular reconstruction. A: Higher placement of the acetabular cup; B: Placement of the acetabular component in the anatomical position and augmentation of the superior segmental defect with structural autograft or allograft fixed with screws; C: Placement of the acetabular component in the anatomical position and spongioplasty of the acetabular roof for smaller uncovered areas (30%-40%); D: Anatomical position of acetabular cup and augmentation of the superior segmental defect with vascularised iliac graft; E: Reinforcement ring with the hook in combination with autologous graft augmentation for cases with severe bone-stock deficiencies. Anatomic hip centre is reconstructed by positioning the hook around the inferior margin of the acetabular floor. The hook prevents high or lateral placement of the ring and helps adequate coverage of the polyethylene liner, regardless of the degree of anatomical deformity; F: Acetabular bone stock deficiency can be managed with specially constructed acetabular components or using special 3-dimensional porous materials which simulates bone structure and allow faster and better endoprosthesis-bone integration. For that purpose trabecular metal (tantalum) is used in form of acetabular cup or trabecular metal augments. Oblong-shaped cementless implants can be used for acetabular reconstruction; G: Cotyloplasty with chisel - intentional medial wall fracture using osteotome with cup placement beyond the ilioischial line with bone grafting; H: Cotyloplasty with reamer - first, perforation of the medial acetabular wall with a reamer is performed, then acetabulum is filled with a large amount of autogenous cancelous bone graft and cup is cemented in position without pressure; I: Cotyloplasty without spongioplasty - implantation of porous-coated cementless acetabular components without spongioplasty.

provides adequate stability in poor bone-stock settings and prevents bone graft resorption showing good mid-term results of this kind of treatment. According to fact that medialisation of acetabular cup decreases hip load and that satisfactory supero-lateral support of the component with host bone is a better option, a method named cotyloplasty was introduced. Later, in 2008 Bicanic *et al*[29] proved that every millimetre of lateral displacement of the acetabular cup (relative to the ideal centre of rotation) results with an increase of 0.7% in hip load, and for every millimetre of proximal displacement an increase of 0.1% in hip load should be expected (or decreased if displacement is medial or distal). That suggest acetabular placement as far medially as possible for optimal results. Cotyloplasty is a technique that involves making a perforation of the medial wall of a shallow acetabulum and then inserting an acetabular cup with the medial aspect of its dome beyond the Kohler's line. In 1976, Dunn *et al*[54] presented a method that involved intentional medial wall fracture using osteotome with cup placement beyond the ilioischial line, avoiding bone grafting but still achieving cemented acetabular cup stability (Figure 3G). At the meeting of the Greek Orthopaedic Association in 1984, technique of cotyloplasty for the preparation of the acetabulum was reported by Hartofilakidis *et al*[11]. This method involved the use of a T-handle curette to enlarge the socket. When the acetabulum was large enough they fracture the paper-thin medial wall using a deepening reamer. Acetabulum was filled with a large amount of autogenous cancelous bone graft and cup is cemented in position without pressure. Hartofilakidis *et al*[11,12] modified this method by perforating the medial acetabular wall with a reamer instead of an osteotome and called the technique cotyloplasty (Figure 3H). Satisfactory reports were published later concerning the results of implanting cemented cups using cotyloplasty. Dorr *et al*[55] reported good results when implanting porous-coated acetabular components using this technique. Cotyloplasty has advantages over other techniques of fixing an acetabular component in a dysplastic acetabulum. This technique has advantages over superior cup placement because it usually restores the normal hip joint biomechanics, it restores the leg length discrepancy and it has less chance of impingement that may lead to dislocation. Major disadvantage of the cotyloplasty is that it is difficult to control the amount of the medial wall fracture and complication such as fracture-dislocation of the cup inside the pelvis can occur.

Preoperative skeletal traction

According to fact that long term stability of the prosthesis with better abductor function and leg-length equalization is best achieved by placing the endoprosthesis near the normal anatomic level, some authors suggests iliofemoral distraction to reduce high congenital dislocation of the hip before THA[56,57] (Figure 4A). Grill was the first to describe the application of distraction between the ilium and femur before open reduction for DDH in children[58]. Lai *et al*[56] used Wagner's apparatus for distraction, and showed how laxity after distraction and close-to-normal position of the femur to the acetabulum made THA much easier than in those performed without distraction. Operative time, blood loss, and surgical complications were reduced, and the functional results were as good as those of ordinary THA. Holinka *et al*[57] modified surgical procedure according to Lai *et al*[56], with immediate femoral head resection and extensive soft tissue release prior to distraction and showed satisfying five-year results in unilateral and bilateral Crowe type IV high hip dislocations. Complications, such as pin tract infection, peroneal nerve palsy, cup protrusions are described for such procedures[57].

Femoral reconstruction

According to the Crowe classification, arthroplasty procedures performed on dysplastic hips that belong to Crowe I or Ⅱ class allow positioning of femoral head in optimal hip rotation centre without performing any of the femoral shortening procedures. In contrast, arthroplasty procedures performed on Crowe Ⅲ or Ⅳ dysplastic hips commonly require one of the femoral shortening procedures. However, here we have to emphasize that this is not a real "clear cut" division whether to perform femoral shortening or not since in Crowe I and Ⅱ dysplastic hips the complex deformities and variations of the dysplastic femur may be present and thus require femoral shortening procedure.

After placement of the acetabular component in anatomic position femur often becomes too long and needs to be shortened. Thus, shortening femoral osteotomies are developed, which further allow both: (1) hip arthroplasty without sciatic nerve stretching; and (2) correction of the proximal femoral anteversion. After these procedures are performed, abductor mechanism of the hip is restored with equal final leg length[59]. Femoral procedures can be roughly divided according to the level of procedure: proximal femur, femoral shaft and distal femoral procedure.

One of the most commonly performed procedures on proximal femur during THR includes trochanteric osteotomies. Trochanteric osteotomies in total hip arthroplasty were first introduced by Charnley[60] in 1972. Over long period of time several modifications of the initial procedure were developed such as changes in shape of skin incision, different approach to the hip, instrumentation etc. These procedures are nowadays reserved mainly for complex primary hip arthroplasty procedures (including arthroplasty in DDH) or complex revision procedures of THR. Trochanteric osteotomies have several major advantages. First, they provide excellent visualization of both, femur and acetabulum, *i.e.*, whole operating region. Second, by performing trochanteric osteotomy abductor mechanism of the hip is preserved and easily repositioned back to original position, altogether resulting in stable hip without risk for dislocation. An example of modified trans-trochanteric approach technique was

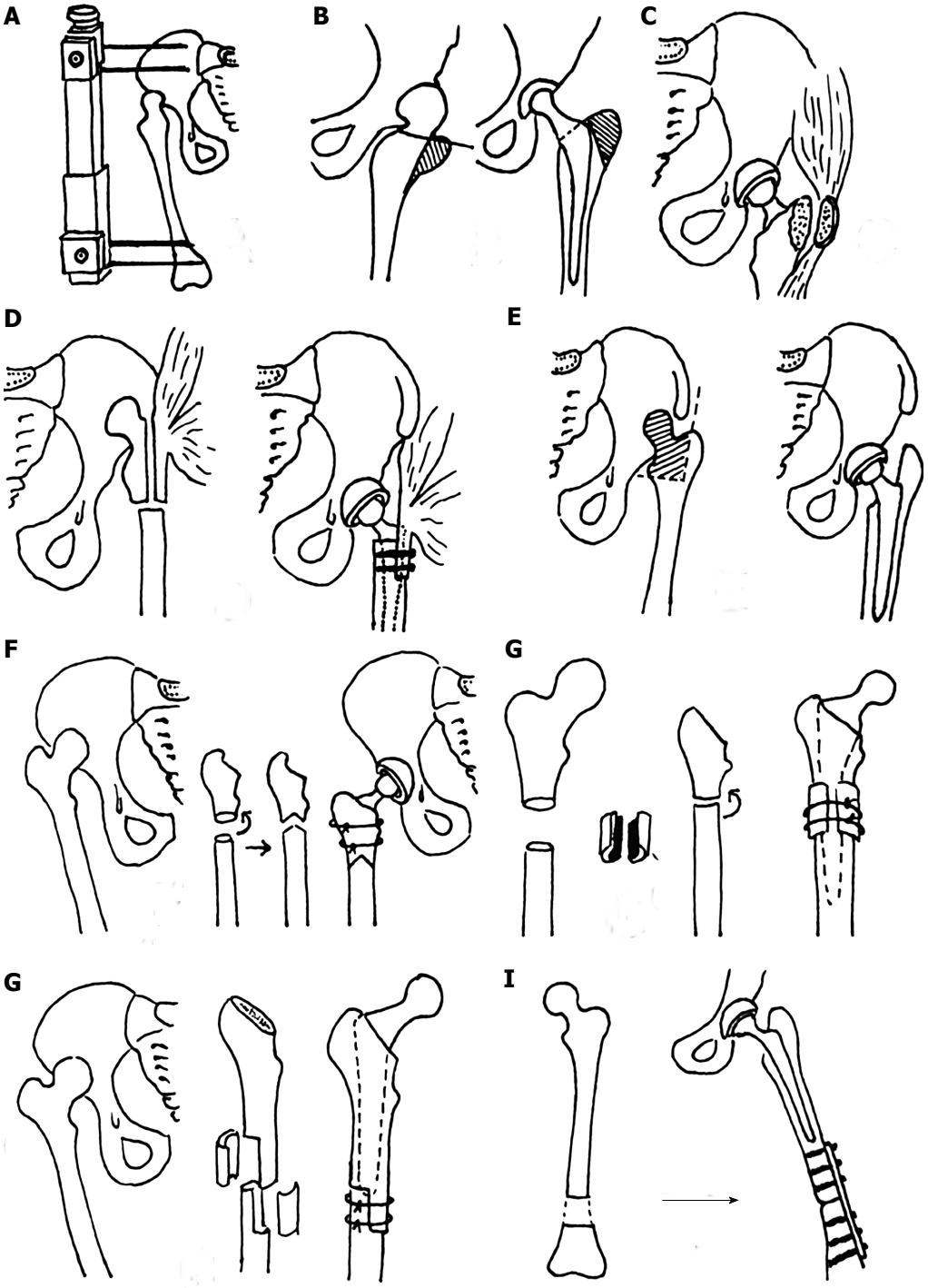

Figure 4 Different types of femoral reconstruction options. A: Wagner's apparatus for preoperative skeletal traction to reduce high congenital dislocation of the hip before total hip arthroplasty; B: Trochanteric osteotomy in total hip arthroplasty; C: Delimar *et al*[7] modification of the direct lateral approach to the hip. Anterior half of the continuous tendon is detached either by cautery or with a chisel. If the chisel is used, a thin layer of bone from the greater trochanter remains attached to the continuous tendon of the gluteus medius and the vastus lateralis. The posterior half of the continuous tendon of the gluteus medius and the vastus lateralis is always detached with the chisel leaving a bone flake of at least 2 to 3 mm thickness attached to tendons. In that way, the abductor muscles are stripped from the greater trochanter and there is no trochanteric osteotomy during the approach, which allows preservation of the continuity of the abductor muscles; D: Paavilainen's procedure of metaphyseal shortening osteotomy combined with distal sliding of the greater trochanter with intact attachment of the abductor muscles; E: Progressive femoral shortening at the level of lesser trochanter; greater trochanter remains intact, thus providing better functional results; F: Combined procedure of femoral subtrochanteric shortening with derotational double-chevron osteotomy. Transverse osteotomy was first performed, followed by rotational alignment in order to correct anteversion. Later, double chevron osteotomy was performed. Such method allows intraoperative derotation and shortening adjustment; G: Subtrochanteric osteotomy - modified technique; osteotomy sites were covered with onlay grafts of the excised fragments and fixed with two cerclage wires; H: Diaphyseal step-cut shortening osteotomy performed after reaming and stabilized with two to three cerclage bands with or without bone grafting. After stabile fixation, intramedullary reaming is done until optimal cortical contact is achieved, especially distal to the osteotomy site; I: Distal femur shortening procedure. First, total hip arthroplasty with acetabulum in anatomic position is performed followed by the femoral shortening that is done distal to stem so that the first screw of the plate would be more than 2 cm from the stem. Later, plate fixation of the femoral osteotomy site was performed.

presented by Kerboull *et al*[61] in 2007. These authors describe transtrochanteric approach as a method which allows easier hip dislocation with good visualization of the operating region and preserved hip abductory mechanism. This approach was also offered as one of the solutions in treatment of severe femoral deformities present in DDH. Namely, transtrochanteric approach allows performance of corrective osteotomies in the area of femoral metaphysis. Such procedure together with reposition of abductory muscles provide near-optimal anatomic relations in operated hip[61] (Figure 4B). Despite these evidences this approach is still controversial and under debate because of unclear conclusion about relatively high rate of around 6% of nonunion of greater trochanter after such procedures[61-64]. Paavilainen *et al*[32] reported procedure of femoral shortening on proximal femur during THR in DDH in 1990 - method included a cementless THR procedure where the acetabular cup is placed in anatomic position together with proximal femur shortening osteotomy with distal sliding of the greater trochanter (Figure 4D). Thorup *et al*[65] reported in 2010 a follow-up of 1.5 to 10 years after Paavilainen procedure on 19 hips with relatively low rate of complications reported after this procedure. Lesser trochanteric osteotomies represent method of progressive femoral shortening at the level of lesser trochanter in order to provide optimal positioning of acetabular cup in anatomic centre in patients with DDH (Figure 4E). Major advantage of this procedure is the fact that greater trochanter remains intact, thus providing better results and potentially lower rate of complications[66]. Bao *et al*[66], 2013 evaluated the efficacy of lesser trochanteric osteotomy for femoral shortening in total hip arthroplasty in treatment of 28 cases of Crowe Ⅳ DDH. After follow-up period of 55.3 mo method was proven to be safe and effective since complications were rare - sciatic nerve palsy was reported in two hips and positive Trendelenburg sign in two hips at the final follow-up. According to report of Bao *et al*[66] lesser trochanteric osteotomy could serve as valuable solution for femoral shortening in DDH; however, larger groups with longer follow-up are needed in order to bring up propper conclusion. In 2008 we described a modification of the direct lateral approach to the hip, which enables excellent exposure of both, femur and acetabulum and presents an optimal approach through which it is easy to shorten the proximal femur and neutralize leg length discrepancy[7] (Figure 4C). First, anterior half of the continuous tendon is mobilized either by cautery or with a chisel. If the chisel is used, a thin layer of bone from the greater trochanter remains attached to the continuous tendon of the gluteus medius and the vastus lateralis. The posterior half of the continuous tendon of the gluteus medius and the vastus lateralis is always detached with the chisel leaving a bone flake of at least 2 to 3 mm thickness attached to tendons. In that way, the abductor muscles are stripped from the greater trochanter and there is no trochanteric osteotomy during the approach, which allows preservation of the continuity of the abductor muscles. This approach eliminates the necessity for osteotomies of the trochanter and transverse cuts or detachment of the abductor muscles, thus reducing incidence of relatively often complications related to those method[7].

Shortening procedures performed on femoral metaphysis (subtrochanteric osteotomies) are the most frequently used procedures for femoral shortening in DDH. Double Chevron osteotomy was first described by Becker *et al*[67] in 1995, where total hip arthroplasty was combined with a femoral subtrochanteric shortening derotational double-chevron osteotomy in DDH. First results were promissing, but method of Becker and Gustilo did not allow any intraoperative changes and required complex and detailed preoperative planning that was sometimes hard to perform during surgery. Several modification of the first technique were reported so far, such as the one from Li *et al*[59] where transverse osteotomy was first performed, followed by rotational alignment in order to correct anteversion. Later, after vertical alignment (length) double chevron osteotomy was performed at the site of the previous transverse osteotomy (Figure 4F). Such method allowed more precise (intraoperative) derotation and shortening adjustment. Several authors with several differences in techniques described transverse subtrochanteric osteotomies. First, Reikeraas *et al*[68] presented transverse osteotomy in 25 cases, with the use of 4 cemented stems and 21 noncemented stems. The torsional stability was not performed with any fixation. Surprisingly, at 3-7 years later 96% satisfactory results were reported, with no revision procedures or mechanical complications and only 1 delayed union and 1 varus malunion. Similar to this procedure, Yasgur *et al*[69] reported in 1997 modified techique with enhanced torsional stability with noncemented fully porous-coated stems, press-fit into the diaphysis and augmented with allograft struts and cables on 9 patients. After 2-7 years period 1 patient suffered nonunion of the osteotomy site and one had failure of a distally ingrown porous device, which required revision. Later on, Masonis *et al*[70] supported the use of a transverse subtrochanteric femoral osteotomy in high DHH with secondary arthritis. 5 years after the procedure was performed a follow-up report was published where authors concluded that the transverse osteotomy union rate was identical to the report using a step-cut method[71]; with one important advantage - it allows intraoperative adjustment of femoral anteversion correction. On the other side, cemented total hip arthroplasty with subtrochanteric transverse osteotomy for Crowe group Ⅳ HDD was described by Kawai *et al*[72] in 2011. Authors descibed procedure where shortening osteotomy sites were covered with grafts of the excised fragments fixed with cerclage wires (Figure 4G). Authors presented good short-term results without significant complications. Bruce *et al*[73] reported in 2000 a femoral shortening technique with use of straight cylindrical prosthesis that acts as an intramedullary nail. Such prosthesis provides stability control of the distal fragment. First, femoral osteotomy was performed with prosthesis *in situ*, then,

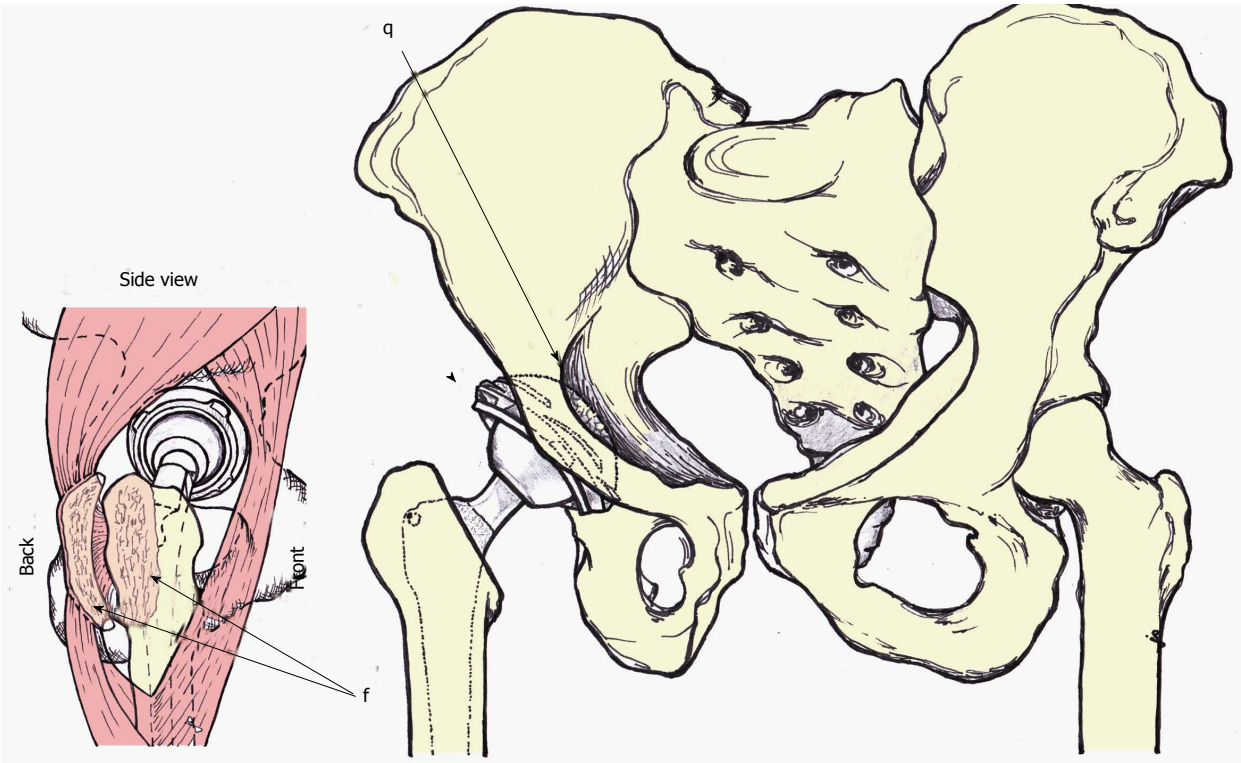

Figure 5 Anterior-posterior and latero-lateral (side) view of the author preferred method of treatment. Anterior-posterior view - acetabular cup is medialized (cotyloplasty) so that the dome of the cup is protruding beyond Kohler's line inside the pelvis (q marked with single arrow). Superolateral part of the cup is uncovered by the bone (marked with arrowhead). The cup is usually additionally secured with the screws (not show on the picture). latero-lateral (side) view-posterior part of the gluteus medius and vastus lateralis together with the external rotators are detached with the chisel on a thin flake of bone (f marked with double arrows). This is a modified direct lateral approach.

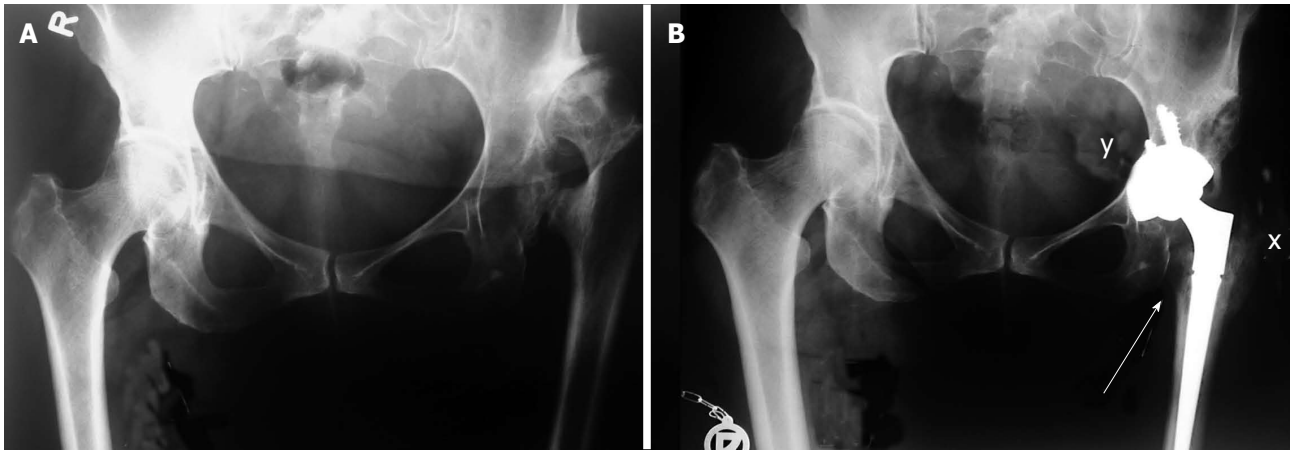

Figure 6 X-rays of patient with Crowe type 4 dysplasia on the left side and normal hip on right side. A: Preoperative X-ray with secondary osteoarthritis due to dysplasia, neoacetabulum formed superolaterally from original, true acetabulum and significant leg length discrepancy; B: Postoperative X-ray with implanted uncemented acetabular cup and femoral stem. Acetabular cup is protruding beyond the Kohler's line inside the pelvis (marked with y) and secured with 3 additional screws. Lesser trochanter is brought distally to the normal level so there is no leg length discrepancy postoperatively (marked with a single arrow). Modified direct lateral approach was used and posterior part of the gluteus medius and vastus lateralis together with the external rotators were detached with the chisel on a thin flake of bone, now they are completely attached and healed to greater trochanter (marked with x).

prosthesis was advanced distally and morcellized autologous bone-graft was applied to the osteotomy site. In that way, one of the most important complications after femoral shortening procedure: nonunion of the osteotomy site - was reduced to a minimun[69,72]. This method has all the characteristics of a simple, reliable and flexible surgical technique. Togrul *et al*[74] in 2010 presented a similar technique of femoral fixation that uses a transverse osteotomy for subtrochanteric shortening with the use of bone pegs prepared from the resected femoral segments which are then placed in the medullar canal around the stem thus providing femoral fixation. Authors reported 21 case with adequate union present in all cases, and early dislocation in only 2 cases.

Shortening procedures performed on femoral diaphysis were reported by Sener *et al*[71] in 2002, where proximal diaphyseal step-cut shortening osteotomy was performed after femoral reaming. Afterwards, step-cut was stabilised with two to three cerclage wires with the use of bone grafting. After fixation, intramedullary femoral reaming was continued until satisfactory cortical contact was achieved. Special attention was focused on the tight contact in distal fragment of the osteotomized femur (Figure 4H). Authors presented very good 5-year follow-up results. Results of very similar method with promising short-term to mid-term results for a Crowe's group IV DDH in adult patients were reported by Makita *et al*[75] in 2007. Later on, Neumann reported the results of very similar technique, but did not use any of the bone grafting techniques at the osteotomy sites[76].

Koulouvaris *et al*[77] reported in 2008 an interesting combined procedure where distal femoral shortening procedure was performed as an addition to THR of dysplastic and difficult-to-reduce hips. Authors used newer technologies such as the use of customized femoral implants and the use of 3D CT scan as an important tool in preoperative planning[77]. First, total hip arthroplasty with placement of acetabulum in anatomic position was performed. Then, femoral shortening procedure was performed on distal femur in the way that the first screw of the plate would be more than 2 cm separated from the femoral stem. The fixation of the femoral osteotomy was achieved with LC-DCP titanium femoral plate (Figure 4I). One of the major advantages of this technique is the possibility of conjoined correction of the ipsilateral knee valgus deformity, which can be performed simply by changing the shape of osteotomized fragment. In that case, regular fixation for valgus osteotomy of the knee was performed. Twenty-four patients were reported in the study, with follow-up period of 4.5 years. Authors reported excellent results: only 1 delayed union was observed, which resulted in malunion after 9 mo.

As shown above, large number of the femoral shortening procedures is described in literature. However, we have to emphasize that anatomical deformities on the femoral sides of dysplastic hip often require combined correction procedures that are frequently very challenging. According to our and other author's opinion, such procedures often require detailed preoperative planning combined with experienced surgeon's skills[78].

CONCLUSION

For severe dysplastic hips, Crowe type Ⅲ and Ⅳ, we perform THA through modified direct lateral approach[7] and then we clean and prepare the acetabulum at the level of the ideal centre of rotation. Even though advantages of the modified approach are numerous one has to take into account that this approach cannot be extended proximally more than 3-4 cm above the tip of greater trochanter and there are some patients that develop pain over greater trochanter. Since there is always lack of bone mass at the level of the ideal acetabular roof, we perform cotyloplasty leaving only paper-thin medial wall, which we break during acetabular cup impacting (Figure 3I and Figure 5). In this way our acetabular dome is always protruding beyond Kohler's line in the pelvis but with solid primary stability, which we additionally improve by placing 2-3 screws in the superior direction. One has to be aware, as mentioned before, that it is difficult to control the amount of the medial wall fracture and complication such as fracture-dislocation of the cup inside the pelvis can occur. Superolateral area of the acetabulum is left uncovered as much as needed, even more than 30%. Then we proceed with femoral shortening according to Delimar *et al*[7]. First we peel of all rotators and posterior part of gluteus medius and vastus lateralis from greater trochanter on the very thin flake of bone. Then we shorten proximal femoral stump as much as it is necessary. After femoral broaching and trial reposition we can additionally resect proximal femur. When final components are placed, abductors are sutured (anterior and posterior part one to another but not to the greater trochanter) and leg is lengthened. Postoperative X-rays are taken (Figure 6). Rehabilitation starts on the second day with the same rehabilitation protocol as for any standard THA (when elongation of more than 5 cm is performed than for the first few days extension is not forced). After 4 to 6 wk full weight bearing is allowed but muscle strengthening is continued for additional 6 mo.

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Anterior cruciate ligament reconstruction best practice: A review of graft choice

Daniel A Shaerf, Philip S Pastides, Khaled M Sarraf, Charles A Willis-Owen

Daniel A Shaerf, Philip S Pastides, Department of Trauma and Orthopaedics, Charing Cross Hospital, Imperial NHS Trust, London W6 8RF, United Kingdom
Khaled M Sarraf, Department of Trauma and Orthopaedics, Barnet General Hospital, Wellhouse Lane, Barnet EN5 3DJ, United Kingdom
Charles A Willis-Owen, Department of Trauma and Orthopaedics, Queen Elizabeth Hospital Woolwich, London SE18 4QH, United Kingdom
Author contributions: Shaerf DA and Pastides PS wrote the article; Sarraf KM reviewed and edited the manuscript; and Willis-Owen CA had the original idea and edited the manuscript.
Correspondence to: Philip S Pastides, PhD, Department of Trauma and Orthopaedics, Charing Cross Hospital, Fulham Palace Road, London W6 8RF,
United Kingdom. ppastides@hotmail.com
Telephone: +44-20-88366000 Fax: +44-20-88365819
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Core tip: There is no "ideal" graft to be used in anterior cruciate ligament reconstruction surgery and each of the four major graft choices has its advantages and disadvantages. Success or failure of the procedure depends heavily on surgical technique. Surgeons should be aware of the evidence behind the use of each graft and thus be able to make an informed decision of its appropriateness.

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Abstract

There is much literature about differing grafts used in anterior cruciate ligament (ACL) reconstruction. Much of this is of poor quality and of a low evidence base. We review and summarise the literature looking at the four main classes of grafts used in ACL reconstruction; bone-patella tendon-bone, hamstrings, allograft and synthetic grafts. Each graft has the evidence for its use reviewed and then compared, where possible, to the others. We conclude that although there is no clear "best" graft, there are clear differences between the differing graft choices. Surgeon's need to be aware of the evidence behind these differences, in order to have appropriate discussions with their patients, so as to come to an informed choice of graft type to best suit each individual patient and their requirements.

INTRODUCTION

Anterior cruciate ligament (ACL) reconstruction is a common operation[1]. The aim of surgery is to restore functional stability to the ACL deficient knee. The functional stability provided by the normal ACL is both in resisting anteroposterior translation as well as rotational subluxation. ACL reconstruction can be performed using a variety of different surgical techniques as well as different graft materials.

The choice of whether to operate or not is multifactorial and is highly dependent on patient's degree of symptoms and requirements in terms of activity level and participation in pivoting sports[2]. Many patients can become asymptomatic following a course of proprioceptive rehabilitation[3]. Timing of any ACL reconstruction is also crucial, it is commonplace to allow the acutely

injured knee to settle, giving time for resolution of effusion, restoration of range of motion and recovery from of concomitant ligamentous injuries[4]. Furthermore a delayed reconstruction allows patients to trial conservative therapy to see if surgery is indicated.

The three categories of commonly used grafts are autograft, allograft and synthetic graft[5]. Autografts usually consist of either hamstrings tendons (HS) or Bone-patella tendon-bone (BPTB). Allografts are varied but can consist of tibialis posterior tendon, Achilles tendon, tibialis anterior tendon, BPTB and peroneus longus tendon[6,7]. Synthetic grafts have been developed over the years and are currently on their "third generation" but have encountered considerable problems in the past[8-11]. Currently the most widely accepted synthetics are the Ligament Augmentation Reconstruction System (LARS; Corin, Gloucestershire, England) and the Leeds Keio (Xiros plc, Neoligaments, Leeds, United Kingdom) however their use remains somewhat controversial[12-15].

The surgical technique used during ACL reconstruction varies widely not only from country to country but even within departments of the same hospital. Different techniques include arthroscopic *vs* open surgery, intra *vs* extra-articular reconstruction, femoral tunnel placement, number of graft strands, single *vs* double bundle and fixation method[16-20]. This heterogeneity of techniques makes comparison of graft choice difficult.

The choice of which graft and which technique to use are often dictated to the surgeon by the patient's anatomy, previous surgical history, concomitant injuries as well as patient choice. Surgeon's choice is dictated by a combination of factors including perceived functional outcome, rehabilitation speed, graft incorporation, graft availability and donor site morbidity. Surgical familiarity also dictates which technique is used as well as the graft choice.

Much research has been done in trying to identify which particular graft or technique is best. Some of this research has been of good quality including meta-analyses, systematic reviews and randomised controlled trials (RCT). Yet, there continues to be wide variation in the choices made by surgeons. Long-term outcomes are not immediately available for newer techniques which fuels further debate.

Our aim is to bring together current literature in order to allow surgeons to make decisions based on current evidence.

DISCUSSION

The question of how best to assess results has been recently addressed by a review from the Dutch Orthopaedic Association. They recommended the use of a combination of physical examination using Lachman, pivot shift and anterior drawer tests, level 1 evidence, together with the following outcome scores-International Knee Documentation Committee Subjective Knee Evaluation Form Score (IKDC), Knee Injury and Osteoarthritis Outcome Score (KOOS) or Tegner Score from level 2 evidence[21].

Graft choice

Hamstring tendon grafts: Hamstring tendons are one of the more commonly used grafts for ACL reconstruction since Lipscombe in 1982 and arthroscopically assisted four stranded grafts by Friedman in 1988. The semi-tendinosus tendon with or without the gracilis tendon is harvested, typically from the ipsilateral leg. The resultant tissue is fashioned into a four strand graft which is then used to reconstruct the ACL as per the surgeon's favoured technique. It is common for the tendons to be folded over each other in order to increase the thickness of the donor graft. In order for the folded tendons to act a one unit they are sutured together using a whipstitch technique. The donor graft is then fed through the tibial tunnel and into the femoral tunnel and secured using a variety of fixation methods including screws, suspensory apparatus and transfixion devices which may be metallic, polymer or bio-absorbable.

Morbidity specifically associated with HS grafts include decreased knee flexion strength and tibial rotation although these do not usually translate into noticeable deficits in patients[22]. Other complications include sciatic or saphenous nerve damage, although again this is rare and may resolve with time[23].

The long term follow-up results of HS grafts are sparse and many studies use differing outcomes to report success and/or failure. Recently the 14 year results of 74 patients with HS graft reconstruction were reported by Leiter *et al*[24] looking at patient outcome scores as well as re-rupture rates. They used the IKDC Score and found that 75% of patients scored normal or nearly normal, however radiographic changes of Kellgren-Lawrence grade 3 were 19% in operated knees compared to 4% in the contralateral knee, this finding reached significance even after controlling for medial meniscal surgery. They found re-rupture rates of the reconstructed ligament at 9% compared to contralateral ACL ruptures at 5%. Other studies of HS tendons with similar follow-up are uncommon. Leys *et al*[25] reported results from a cohort study with 15 years follow-up comparing HS to BPTB. In the HS arm they had 15 year results on 51 patients. Re-rupture rates were 17% in the HS group and 12% in the contralateral knee. Re-ruptures were more common in men, patients with non-ideal tunnel position. Mean IKDC Subjective symptom scores were 90 (out of 100) and mean functional scores 9.1 (out of 10). Shorter term studies but with larger study group sizes are available. Streich *et al*[26] reported a single blinded evaluation of 40 patients with 4 strand HS grafts at 10 year follow-up. They report 8% re-rupture rate and an IKDC score of 90.3 and all joints were either grade A or B (normal or nearly-normal). Asik *et al*[27] reported the results of 271 patients with 4 strand HS grafts fixed using a transfix pin. Their follow-up length was a mean of 6.8 years and 86% scored normal or nearly normal on IKDC score. Re-rupture occurred in 1.5% of patients in this shorter follow-up study. Maletis *et al*[6] reported retrospectively from the prospective Kaiser Permanente ACL Recon-

struction Registry revision rates after HS grafts in 3012 patients was 1.56% (1.1% revision rate per 100 years of observation), however follow-up was short at a mean of 1.5 years. No assessment of patient outcome/satisfaction was performed.

BPTB grafts: BPTB grafts for ACL reconstruction have been around since the pioneering work of Franke in 1969 and are still very popular in certain countries and in specific patients. BPTB has historically been considered the gold standard for ACL reconstruction. The method of harvest includes a horizontal or longitudinal skin incision followed by resection of the mid-portion of the patella (inferior pole) and tibial tuberosity with the intervening tendon as a complete unit. Thus the graft has bone block at both ends which allows potentially superior integration of the graft into the tibial and femoral tunnels. The graft is then detached and fed through the tibial tunnel into the femur in the same way as a hamstrings graft. Fixation can take place using a variety of different methods ranging from an interference fit with no fixation device to screw or suspensory fixation[28].

There are many reports of the morbidity and complication associated with BTPB grafts. Complications include patella tendon rupture, patella/tibial fracture, quadriceps weakness, loss of full extension, anterior knee pain and difficulty kneeling[29,30]. Typically the cosmetic result is inferior to hamstrings harvest which may be of concern for some patient groups.

Long term results after BTPB graft reconstructions have been studied by many authors. Mihelic *et al*[31] retrospectively studied outcome of 33 operated BTPB grafts with 17 to 20 year follow-up with 83% of patients having stable knees with normal or near normal IKDC grades and an IKDC score of 83.15, they do not however report re-rupture rates. Gerhard *et al*[32] report 16 year mean follow-up of 63 patients after BTPB ACL reconstruction with 84% returning to previous sporting levels with 78% normal or near normal IKDC grades and a KOOS score of 84. Nineteen percent of patients had radiographic evidence of moderate to severe osteoarthritic changes, worse with meniscal injury at the time of ACL reconstruction. One point six percent of patients needed revision ACL reconstruction but a total of 33% needed further knee surgery during follow-up. Leys *et al*[25] who compared HS to BTPB showed in the BTPB arm of their study that there was no significant difference to HS in overall IKDC grade, whereas radiographic evidence of osteoarthritis was significantly more common in BPTB. Ahn *et al*[33] looked at 117 patients with mean 10.3 year follow-up after BTPB reconstruction and showed 90.6% normal or nearly normal IKDC subjective scores. Re-rupture rates were 5.1% and all were reported after additional injury. They did also report other complications including arthrofibrosis, limited range of motion, synovitis and patella fracture. Ninety-four point eight percent of patients complained of pain when kneeling on soft ground and 61.5% complained of knee pain on walking. Pernin *et al* reviewed 24.5 year data on 100 patients after a combination of BTPB reconstruction with lateral extra-articular augmentation with iliotibial band. IKDC subjective scores at final follow-up were 74.7, however overall only 46% had IKDC grades A or B. They report 19.5% clinical failures of which 72.2% had a meniscal injury at the time of first operation. It is important to note that they acknowledge a drop-out rate of 75% from initial enrolment which may bring a large bias into the results. Maletis *et al*[6] reported from 2791 BTPB autograft patients a revision rate of 1.18% at 1.5 years (or 0.66% per 100 years observation) which was favourable in comparison to both HS and Allograft.

Allografts: Donor site morbidity particularly in BTPB grafts has led to the search for alternatives. Also in the case of revision surgery where autograft options have already been exhausted an alternative graft choice may be required. The use of allograft is appealing particularly to the complete lack of donor site morbidity, reasonably good availability and a range of graft sizes with the options of bone blocks attached to the graft. Allograft material does come with its own unique risks including risk of an immunogenic reaction or disease transmission and is an expensive option when compared to autograft which costs nothing in monetary terms.

The most commonly used allograft tendons are tibialis posterior/anterior and Achilles tendon allografts however patellar tendon and HS are also widely available in some countries. Sterilisation has been an issue for allografts and older studies often used high dose irradiation or ethylene glycol which led to structurally inferior grafts. Cost availability, variability in graft tissue and storage are all important issues with allograft.

Long term results are not readily available yet, however, Almqvist *et al*[34] report 10.5 year follow-up of 50 patients with a mean IKDC score of 97. Graft failure rate was quoted at 5.45% and all were due to new significant knee trauma. Edgar *et al*[35] compared 47 patients after allograft ACL reconstruction with autograft with 48 mo average follow-up. They reported IKDC grades A or B in 82.6% of patients with subjective scores of 86.8%, which were similar to autograft. They reported a revision rate of 4.3% for allograft reconstructions. Kleipool *et al*[36] again compared small numbers 26 autograft *vs* 36 BPTB with 46 mo follow-up and reported 85% IKDC grade A or B compared to 70% in the autograft group, however, these results were not statistically significant. Foster *et al*[37] performed a systematic review of allograft *vs* autograft and found little difference between the two and reported pooled results of 82.9% IKDC grades A or B (compared to 87.2% for autograft). They also pooled failures and showed a graft failure rate of 8.2 per 100 reconstructions which performed poorly compared to 4.7 per 100 reconstructions for autograft. However none of these trends reached statistical significance. Siebold *et al*[38] compared two different allografts in ACL reconstruction, fresh frozen patella tendon *vs* Achilles tendon. In total they evaluated 251 patients with a mean follow-up of 37.7 mo. IKDC grades were normal or nearly normal

in 75.3% and 76.2% of patients undergoing patella and Achilles allografts respectively. Whilst this was not significant there was a significant difference in re-rupture with 10.4% of patella grafts re-rupturing compared to 4.8% of Achilles grafts. They do further note that these rates were high in comparison to autograft studies with similar length follow-up. In the recent study by Maletis *et al*[6], they included 4014 allograft patients and reported a re-rupture rate of 1.74% for allograft (1.23% per 100 observation years). A ready supply of allograft tissue requires a well co-ordinated and reliable human tissue bank with a consistent tissue cleaning and decontamination processes. The cost of providing this is typically high and is limited to the most developed healthcare systems.

Synthetic grafts: The concerns over both autograft and allograft have led to the development of synthetic alternatives which ideally have no risk of donor site morbidity but also lack the risks associated with allograft of possible disease transmission, can be widely available with a long shelf life and simple storage and inventory arrangements. Synthetic ligaments are now into their third generation. First generation ligaments were knitted, woven or braided. These early ligaments were subject to early breakage and tended to elongate. Second generation ligaments had additional longitudinal and transverse fibres woven into the braid or knit. The materials also advanced to use Polyethylene Terephthalate or Dacron to act as a permanent replacement and allow fibroblastic ingrowth. These ligaments also suffered with wear, fraying and low abrasion resistance. Both first and second-generation synthetics were plagued with problems related to wear debris and subsequent catastrophic synovitis. This led of large cohorts of patients with problematic knees and a general aversion to the use of synthetics for ACL reconstruction in the soft tissue knee surgery community. Third generation ligaments such as the LARS are similarly constructed of Polyethylene Terephthalate, however, they are now designed to specific indications. The ACL replacement has a knitted extra-articular portion with free longitudinal fibres which resist elongation but without any braids to cause intra-articular wear and the generation of biologically active wear debris.

The latest generation of synthetics have different indications from conventional graft choices. The design rationale is that the synthetic is used to augment the healing of a freshly injured ACL. Surgery should take place as soon as possible aft the acute injury and every effort must be made to preserve the native ACL stump and draw the stump up to its femoral attachment using the synthetic to then protect the graft whilst tissue ingrowth and healing occur. Thus the synthetic is used as an augmentation device alongside biological tissue, not as a substitute graft in isolation.

As well as availability, convenience, lack of disease transmission risk and cost, the other advantage of synthetic graft reconstruction is the potential for dramatically accelerated rehabilitation with return to sport significantly earlier than for autograft and allograft. This is because biological grafts require prolonged period (probably at least one year) for incorporation of the graft tissue into the host bone.

The results of first and second generation ligaments are not applicable to third generation ligaments due to the substantial re-design. A large scale systematic review was performed by Newman *et al*[39] which led to only 9 out of 156 articles being included. This study looked at data from 675 LARS ACL reconstructions and found an overall failure rate of 2.5% of which many of these were reported to be associated with technical errors in tunnel placement. Synovitis, which had plagued earlier synthetic grafts only occurred in only one patient in the included studies. This data suggests the third generation of synthetics have largely solved the problems of synovitis that led to the disrepute of the first and second generation. Dericks[40] described his experience of 220 patients reported 3 infections (1.4%) and 9 ligament ruptures (4.1%) with 83% of patients returning to full sports by 6 mo (and 61% by as early as 4 mo). The largest published study of LARS ACL reconstructions is by Gao *et al*[41] who retrospectively report on 159 reconstructions. They describe 94% of patients achieving IKDC grade A or B at a mean of 50 mo follow-up. All patients achieved return to sports by 6 mo with a re-rupture rate of only 1.9%. Nau *et al*[42] report the 24 mo results of a randomised controlled trial comparing BTPB and LARS ACL reconstruction in 27 and 26 patients respectively. They found no significant differences at final follow-up in the results of either graft with respect to IKDC, KOOS or Tegner scores. They also did not report and ruptures but did list patients lost to follow-up and other complications, with no significant difference. The only difference that they reported is a trend to earlier return to sport in the LARS group possibly allowing a faster rehabilitation protocol. Pan *et al*[43] report retrospective follow-up of a minimum of 4 years in 32 LARS reconstructions and compare these to 30 BPTB reconstructions. IKDC grades and Tegner scores were similar in both groups, the LARS group had A or B grading in 87.5% and a score of 6.16 respectively. No re-ruptures were reported in either group.

COMPARATIVE STUDIES

There are numerous studies that have compared BPTB grafts to HS grafts for ACL reconstruction. Many of these studies are well summarised by Li *et al*[44] in their recent systematic review of the available RCT. After using thorough methods of identifying and processing available data they identified 9 RCTs with useable outcome data. They performed meta-analysis of data where available and showed significant differences between the outcome of BPTB and HS grafts in respect to pivot shift (RR = 0.87 in favour of BPTB), anterior knee pain (RR = 0.66 in favour of HS), kneeling pain (RR = 0.49 in favour of HS) and extension loss (RR = 0.63 in favour of HS). Graft failure was slightly more common in the HS group, however this did not reach significance (RR = 1.37, P = 0.38). IKDC scores pooled from the available data

showed normal or nearly normal results in 206/266 HS reconstructions and 169/225 BPTB reconstructions (P = 0.41). Interestingly they concluded from this data that HS grafts restore knee joint function in a similar fashion to BTPB, however they comment that they were inferior with respect to restoration of stability.

In the multicentre study of 9817 patients by Maletis *et al*[6] they compared revision rate only and found a tendency to increasing revision rates from BPTB to HS to Allograft (1.18%, 1.56% and 1.74% respectively) with 2.7 year survival rates of 98.0%, 96.9% and 96.0% respectively. The other significant findings were increasing revision rates of 3.02 comparing Allograft to BPTB, and 1.82 comparing HS to BPTB grafts. Interestingly there was a 2.26 increased risk of revision in females with HS grafts compared to BPTB which was not reproduced in men. They also reported a protective effect of age of 7% per year which may well be an activity related phenomenon. The data they used to analyse was only related to crude failure and revision rates and no information was given on functional outcome.

The largest comparative study of LARS *vs* HS grafts, Liu *et al*[45] retrospectively compared 28 LARS and 32 HS grafts and found no significant differences between the two except in KT-1000 examination results showing the LARS to be more stable (1.2 mm *vs* 2.4 mm). However there were no differences in IKDC or revision rates. Similarly when comparing LARS to BTPB Pan *et al*[43] found no significant differences in functional outcome or examination findings between the two groups (30 BPTB and 32 LARS). In a large RCT of HS *vs* fresh frozen allograft with 7.8 year follow-up Sun *et al*[46] showed that apart from a shorter operative time for allograft procedures they showed no significant differences between the groups and both had similar outcome scores (IKDC 90 Allograft *vs* 89 Autograft). Interestingly they reported no ruptures and no complications apart from two superficial wound infections in the allograft group.

Several studies have investigated the relationship between muscle strength and isokinetic measurements after ACL reconstruction. In a series of patients by Condouret *et al*[47], the outcome of quadriceps and hamstring strength based on the type of graft used (BoB *vs* hamstrings), was evaluated. The review of 127 patients included isokinetic muscle tests, concentric and eccentric extensors/flexors but also internal rotators/external rotators with analysis of mean work and mean power. In their series, the average muscles deficit at two years was 10% for the flexors and extensors. The type of reconstruction (patellar tendon *vs* hamstrings) had an influence on the muscle deficit. For extensors, the recovery was the same in the two groups. For flexors, residual deficits were significantly higher in the hamstrings group on the three studied parameters whatever the speed and the type of contraction (concentric or eccentric) with an average deficit of 14% to 18%, while, in the patellar tendon group, there was a dominance over the opposite side of 2% to 3% in concentric contraction. For internal rotators, a significantly higher deficit is observed in eccentric contraction for the hamstrings group. The residual hamstrings deficits were related to the number of tendons harvested: -7% when there was no harvest, 7% with one tendon harvested and 17% with two tendons harvested.

A systematic review by Dauty *et al*[48] reporting on isokinetic results following ACL reconstruction included 53 studies; 29 reported isokinetic results after ACL reconstruction with patellar tendon graft, 15 reported isokinetic results after ACL reconstruction with hamstring graft, and 9 studies compared the two surgical procedures. Comparing the two graft choices, they found that BOB *vs* hamstring resulted in a larger knee extensor deficit but less knee flexion weakness for up to two years. They found no difference in isokinetic parameters between the two groups. These findings are supported by another metanalysis conducted by Xergia *et al*[49].

CONCLUSION

All the different types of grafts used in current everyday practice for the reconstruction of a ruptured ACL have a place in this complex field of surgery. There are good data to support all of them. There is no clear "best" graft to use. However there are some clear advantages with respect to the different grafts. Donor site morbidity has been a problem for the BTPB graft, however it appears to have consistently good results particularly with respect to graft stability and return to high level sports. HS grafts appear to be a good all-round graft choice with fewer donor site complications and good results, both sources of autograft are readily available in most patients and cost nothing, but do have some technical demands for safe and efficient harvest. Allograft generally has slightly poorer results in terms of re-rupture rates, however can be invaluable in certain patient groups, particularly those with multi-ligament deficiencies or in the revision scenario. Allografts are expensive, but save time and undoubtedly remove one of the more technically demanding stages of ACL reconstruction surgery. They remove the potential for donor site morbidity but do not permit faster return to sport. Synthetic grafts are slowly regaining popularity as these too show good general results with no donor site morbidity and the ability to perform multi-ligament reconstructions without compromising the patella or hamstrings. They offer an off the shelf solution which shortens operative time and renders the surgical procedure is somewhat less complex and no graft harvest is required however the surgery it technically different, and should ideally be performed on a different time scale form conventional ACL surgery. Graft choice, therefore, needs to be made after an educated discussion with the patient regarding their requirements and expectations with regards to donor morbidity and speed of rehabilitation as well as the surgeon's personal experience and the surgical units experience and access to graft options. Certainly there is no one-size-fits-all graft yet, however, surgeons should offer the differing graft options and inform their patients of the differences as well as their own personal results with each graft suggested.

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Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis

Egemen Ayhan, Hayrettin Kesmezacar, Isik Akgun

Egemen Ayhan, Department of Orthopaedics and Traumatology, Mersin University, Mersin 33110, Turkey
Hayrettin Kesmezacar, Isik Akgun, Kaktus Health Center, Istanbul 34394, Turkey
Author contributions: Ayhan E, Kesmezacar H and Akgun I contributed to this paper for conception and design, acquisition of data, and interpretation of data, drafting the article and revising it critically for important intellectual content, and final approval of the version to be published.
Correspondence to: Egemen Ayhan, MD, Department of Orthopaedics and Traumatology, Mersin University, Mersin 33110, Turkey. egemenay@yahoo.com
Telephone: +90-532-6363693 Fax: +90-324-3374305
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Abstract

Osteoarthritis (OA) is a complex "whole joint" disease pursued by inflammatory mediators, rather than purely a process of "wear and tear". Besides cartilage degradation, synovitis, subchondral bone remodeling, degeneration of ligaments and menisci, and hypertrophy of the joint capsule take parts in the pathogenesis. Pain is the hallmark symptom of OA, but the extent to which structural pathology in OA contributes to the pain experience is still not well known. For the knee OA, intraarticular (IA) injection (corticosteroids, viscosupplements, blood-derived products) is preferred as the last nonoperative modality, if the other conservative treatment modalities are ineffective. IA corticosteroid injections provide short term reduction in OA pain and can be considered as an adjunct to core treatment for the relief of moderate to severe pain in people with OA. IA hyaluronic acid (HA) injections might have efficacy and might provide pain reduction in mild OA of knee up to 24 wk. But for HA injections, the cost-effectiveness is an important concern that patients must be informed about the efficacy of these preparations. Although more high-quality evidence is needed, recent studies indicate that IA platelet rich plasma injections are promising for relieving pain, improving knee function and quality of life, especially in younger patients, and in mild OA cases. The current literature and our experience indicate that IA injections are safe and have positive effects for patient satisfaction. But, there is no data that any of the IA injections will cause osteophytes to regress or cartilage and meniscus to regenerate in patients with substantial and irreversible bone and cartilage damage.

Key words: Intraarticular injections; Corticosteroid; Hyaluronic acid; Platelet rich plasma; Knee osteoarthritis; Viscosupplementation

Core tip: Intraarticular (IA) corticosteroid injections can be considered as an adjunct to core treatment for short term reduction of moderate to severe pain in people with osteoarthritis (OA). IA hyaluronic acid (HA) injections might have efficacy and might provide pain reduction in mild OA of knee up to 24 wk. But for HA injections, the cost-effectiveness is an important concern that patients must be informed. Although more high-quality evidence is needed, recent studies indicate that IA platelet rich plasma injections are promising for relieving pain, improving knee function and quality of life, especially in younger patients, and in mild OA cases.

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INTRODUCTION

Osteoarthritis (OA) refers to a clinical syndrome of joint

pain with multifactorial etiopathogenesis that is characterized by the gradual loss of articular cartilage, osteophyte formation, subchondral bone remodeling, and inflammation of the joint[1]. OA is a major source of disability owing to pain and loss of function. It is the most common form of joint disease, and among the top 10 causes of disability worldwide[2]. With aging of the population and increasing obesity, OA arises as a major public health problem and an important financial burden for the global economy[3].

For the knee OA, various conservative treatment modalities are recommended by clinical guidelines[2,4,5]. The non-pharmacological modalities are patient education and self-management, exercises, weight reduction, walking supports (crutches), bracing, shoe and insoles modification, local cooling/heating, acupuncture, and electromagnetic therapy. Pharmacologic therapies can be summarized as paracetamol, non-steroidal anti-inflammatory drugs, opioids, and slow-acting drugs (glucosamine and chondroitin sulfate). If orally administered drugs are ineffective, intraarticular (IA) injection (corticosteroids, viscosupplements, blood-derived products) is the last nonoperative modality that can be preferred[5,6]. The major contraindication for IA injections is septic arthritis. In addition, in the presence of overlying soft tissue infection, there is risk of iatrogenic seeding to the joint.

When the various potential conservative treatment modalities and the uncertainty in regards to evidence-based recommendations are considered, it is inevitable that some inconsistencies exist between clinical guidelines[2,4,5]. However, the consensus occurs in two points: (1) The optimal conservative management of knee OA requires a combination of pharmacological and non-pharmacological treatment modalities customized to individual patient needs; and (2) The main goals of conservative management are to reduce pain, improve function and quality of life, and limit disease progression.

Etiopathogenesis of OA

To refer OA as "degenerative joint disease" would be a misnomer because OA is not simply a process of "wear and tear" but rather a much more complex disease driven by inflammatory mediators within the affected joint[7-11]. Recent researches supports that, OA is a "whole joint" disease[7-9]. Although cartilage destruction is the hallmark of the disease; synovitis, subchondral bone remodeling (thickening, bone collapse, bone cysts), degeneration of ligaments and menisci, and hypertrophy of the joint capsule take parts in the pathogenesis of OA[1].

The loss of articular cartilage is probably initiated as a focal lesion, which may progressively extend and produce changes in loading, thereby increasing loss of cartilage. This pathoanatomical description of cartilage loss process involves morphologic and metabolic changes in chondrocytes, as well as biochemical and structural alterations in the ECM, under the influence of complex mechanical, biological, biochemical, molecular, and enzymatic feedback loops[1]. In OA, chondrocytes, which are responsive to mechanical (*e.g.*, malalignment, articular cartilage incongruity, …) and inflammatory stimulation, become activated to produce inflammatory mediators, similar to an injury response[8,12]. Also, subchondral bone cells response in a similar way, and may take role in degradation of the deep layer of cartilage[13]. As articular cartilage matrix proteins are fragmented, these fragments feedback and stimulate further matrix destruction[8]. On the other hand, aging-related changes in chondrocytes (*i.e.,* accumulation of advanced glycation end-products) make the cartilage more brittle and lead to increased production of cytokines and chemokines by aged chondrocytes[14]. Therefore, increased age also arises as an important risk factor for OA.

Synovial inflammation plays a critical role in the symptoms and structural progression of OA. Soluble inflammatory mediators, such as cytokines and chemokines, are increased in synovial fluid (SF) in OA and promote synovitis[8]. Recent histological researches demonstrated that synovitis occurs even in early stages of disease, but the prevalence of synovitis increases with advancing disease stage[15,16]. The cause of synovial inflammation in OA is still unclear but hypothesized either as a result of foreign body reaction of synovial cells to degraded cartilage products inside the joint, or as a primary trigger of OA process[7,8,17,18]. Whatsoever, synovial cells are thought to produce inflammatory mediators, activate chondrocytes, and propagate cartilage breakdown[7]. Supporting this, synovitis has been shown to correlate with symptom severity and rate of cartilage degeneration[9,18-20].

Inflammatory mediators play a pivotal role in the initiation and continuation of the OA process. The source of such mediators may be local from joint cells, as previously mentioned, but also may be systemic from other tissues such as adipose tissue (*i.e.*, adipokine) released in blood flow and then reaching the joint via the subchondral bone vasculature[7,21]. The risk of hand OA is increased two-fold in obese patients[22]. This finding explains the theory of obesity as a risk factor for OA; not only because of mechanical overload, but also because of systemic factors. It was reported that adipokines, secreted mainly from abdominal adipose tissue, contribute to the low-grade inflammatory state of obese patients and may directly affect cartilage homeostasis[10,21].

Currently, it has become evident that the inflammatory mediators contribute significantly to the development and progression of structural changes in the OA joint. Because the induction of proinflammatory mediators in cartilage, synovial membrane, and subchondral bone and their signaling pathways are interlinked and overlapped, it therefore remains controversial whether inflammatory mediators are primary or secondary regulators of cartilage damage and defective repair mechanisms in OA[10]. Nevertheless, compounds that regulate cytokine synthesis or activity, or both, are considered as favorable targets for future OA therapy[11].

Pain

The hallmark symptom of OA is pain. The early stages

of OA is characterized by activity related pain, thereafter, with the advancing disease, the pain gets the chronicity character and converts to a more constant nature with accompanying intense pain attacks[3]. Genetic predisposition was associated with development of chronic pain in knee OA[23]. Weight has been shown as a potential factor contributing not only to OA risk, but also to pain[24].

Adult articular cartilage is avascular and aneural, so that cartilage is incapable of directly generating pain or inflammation, at least early in the disease course prior to potential neurovascular invasion that may occur in late or end-stage disease[25,26]. Pathologic changes to non-cartilaginous joint tissues are of particular interest in understanding the source of pain generation in OA. The subchondral bone, synovium, joint capsule, periarticular ligaments, and periarticular muscle are all richly innervated and are the likely source of pain in OA[25].

During inflammation or cartilage degradation, inflammatory mediators are released and sensitize primary afferent nerves. Thereby, the subchondral bone and pain receptors are exposed because of stripped cartilage, and there appears vascular congestion of subchondral bone which increases intraosseous pressure. Walsh *et al*[27] have observed sensory nerve fibers in the vascular channels associated with osteochondral angiogenesis and speculated that they could be a potential source of symptomatic pain.

Synovitis and effusion is frequently present in OA and correlates with pain and other clinical outcomes[28,29]. Synovial causes of pain include stimulation of nociceptors within the synovium from osteophytes and inflammation[30]. Histologically, the infiltrations of macrophages and lymphocytes, and villous hyperplasia in advanced disease, are observed in synovitis with knee OA[31]. Recently, an increase in vascularity accompanied by increased sensory nerves has been noted also in OA menisci, which may relate the otherwise painless menisci, as a source of pain in knee OA[32]. In a recent review, Mapp *et al*[33] emphasized that during OA, angiogenesis is increased in the synovium, osteophytes and menisci and leads to ossification in osteophytes and the deep layers of articular cartilage. The authors concluded that angiogenesis contribute to structural damage and pain in OA, and they suggested the angiogenesis as a potential target for new treatments. Finally, impairments in periarticular muscle function affect joint loading and arises as a source of pain in people with OA[34].

In conclusion, although the relationship of changes in bone marrow lesions and in synovitis with fluctuation in pain presence and severity were demonstrated in the study of Zhang *et al*[35], the extent to which structural pathology in OA contributes to the pain experience is still not well known, this is probably because of co-existence of the structural pathologies and variations in personal pain perception[36]. On the other hand, angiogenesis arises as a reasonable target for future treatment modalities in OA.

CORTICOSTEROID INJECTION

Agents

There are 5 injectable corticosteroids that have a current Food and Drug Administration (FDA) label for IA injections. These consist of methylprednisolone acetate, triamcinolone acetate, betamethasone acetate and betamethasone sodium phosphate, triamcinolone hexacetonide, and dexamethasone.

A few trials have been published comparing functional outcomes after different IA corticosteroid (CS) injections[37-39]. However, the results were inconclusive. Although, further research is needed, it seems that any agent have similar potency provided with correct indication, dosage, timing, and application[40].

Mechanism of action

Corticosteroids have both anti-inflammatory and immunosuppressive effect, but their mechanism of action is complex. Corticosteroids act directly on nuclear steroid receptors and interrupt the inflammatory and immune cascade at several levels. By this means, they reduce vascular permeability and inhibit accumulation of inflammatory cells, phagocytosis, production of neutrophil superoxide, metalloprotease, and metalloprotease activator, and prevent the synthesis and secretion of several inflammatory mediators such as prostaglandin and leukotrienes[41,42]. The clinical anti-inflammatory reflections of these actions are decreases in erythema, swelling, heat, and tenderness of the inflamed joints and an increase in relative viscosity with an increase in hyaluronic acid (HA) concentration[41,43].

Indications and efficacy

IA CS injections are frequently used to treat acute and chronic inflammatory conditions. Especially during the OA flare, when there is evidence of inflammation and joint effusion, CS injections decrease acute episodes of pain and increase joint mobility[44]. Also, when the correlation of chondrolysis with the OA flare is considered, the IA CS injection for the short-term treatment of disease flares is recommended[9,18-20].

From randomized controlled trials in OA patients there is evidence that IA corticosteroids are effective, but their benefit over placebo may be relatively short-lived, up to four weeks. In a 2006 Cochrane Review, the short term efficacy of corticosteroids in knee OA has been confirmed[45], and recently, the short-term effect was also highlighted in a systematic review by Hepper *et al*[46] and in a meta-analysis by Bannuru *et al*[47]. One more recent study also found IA corticosteroids to be superior to placebo on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total subscale scores at four weeks[48]. Moreover, some studies suggest a possible benefit of up to 26 wk[49,50]. On the other hand, in the 2006 Cochrane Review, it was also stated that there was a lack of evidence for efficacy in functional improvement

(*e.g.*, stiffness, walking distance, quality of life) at any time point with IA CS injections[45].

The clinical predictors for IA CS injection efficacy were studied. In 1995, Gaffney *et al*[51] reported that joint effusion and successful aspiration of SF at the time of CS injection were related with better pain reduction at one week. Promoting this study, in a more recent research, Arden *et al*[50] concluded that presence of an effusion and a lesser radiographic severity of knee OA are predictors of a good response to treatment with CS injections up to 26 wk. However, in a very recent systematic review about clinical predictors of response to IA CS injection in knee OA, no consistent predictors of response were identified[52]. The authors concluded that predictor factors were poorly studied in previous trials, which may be partly the cause of this result.

IA injection of CS has rare side effects. The infrequent reactive flares to IA administration may begin 6–12 h after injection and resolve spontaneously in 1 to 3 d[53]. Early studies in rodents reported the possibility of cartilage destruction[54-56]. However, subsequent studies showed that even multiple IA injections of steroids showed no significant evidence of knee cartilage degradation[57-59].

The American College of Rheumatology subcommittee on OA recommends CS injections as an effective method of decreasing pain[60]. However, American Society of Orthopedic Surgeons work group interpreted the evidence to be inconclusive as to the benefit of IA corticosteroids and were unable to recommend for or against the use of IA corticosteroids in their guideline for patients with symptomatic OA of the knee[4].

To sum up, the research evidence demonstrates that IA CS injections provide short term reduction in OA pain and can be considered as an adjunct to core treatment for the relief of moderate to severe pain in people with OA[2].

HYALURONIC ACID INJECTION (VISCOSUPPLEMENTATION)

Agents

HA is produced either from harvested rooster combs or via bacterial fermentation in vitro[61]. The injectable hyaluronan products that are approved by FDA are sodium hyaluronate, Hylan G-F 20, and high-molecular-weight hyaluronan. Injection schedules vary from 1 to 5 injections and patients are generally advised to repeat the injection schedule by 6 mo if they are satisfied with the previous injection course.

Although the basic science evidence studies seem to suggest that the use of both low molecular weight hyaluronic acid and high molecular weight hyaluronic acid (HMWHA) have disease modifying effects, comparative clinical studies and meta-analyses tends to favor the efficacy of HMWHA for knee OA[62-66]. Nevertheless, the current literature is inconclusive because of heterogeneity of studies[63-65,67].

Mechanism of action

HA is a naturally occurring glycosaminoglycan and a component of SF and cartilage matrix. Synovial cells, fibroblasts and chondrocytes synthesize HA and secrete into the joint. HA enhances viscosity and elastic nature of SF. SF with normal HA concentration acts as a viscous lubricant during slow joint movements and as an elastic shock absorber during rapid joint movements[68]. The adaptive ability reduces stress and friction on cartilage[69]. It also forms the backbone for the proteoglycans of the extracellular matrix. HA functions through anti-inflammatory, anabolic, analgesic, and chondroprotective mechanisms[70]. In the osteoarthritic joint, synovial inflammation leads to increased permeability of the synovial membrane for HA. Also, the elevated SF levels of free radicals, inflammatory cytokines, and proteolytic enzymes in osteoarthritic knees impair HA function and contribute to the progression of OA[71,72]. Therefore in OA, both the molecular weight and the concentration of HA are decreased[71-74].

The IA injection of HA is thought to restore normal viscoelastic properties of the pathologically altered SF, which explains the term of the approach: "viscosupplementation"[71]. It is thought that HA temporarily restores the lubricating and shock-absorbing effects of SF. Moreover, several studies suggest that viscosupplements also have disease modifying effects, such as reduction of synovial inflammation[67,75-79], protection against cartilage erosion[80,81], and promotion of IA HA production[62,74,82,83]. Although the precise in vivo mechanisms of action are poorly known in the joint, HA promotes tissue remodeling in other tissues, as well. It is used to optimize tissue restoration and minimize scarring in ophthalmic, thoracic and plastic surgery[84,85], and is also used to prevent postoperative peritoneal and intrauterine adhesions[86,87]. Lastly, HA have indirect and direct analgesic activity within the joints. Indirect effect is via the anti-inflammatory properties of HA. Direct effect is by the direct inhibition of nociceptors and the decreased synthesis of bradykinin and substance P[74,82,83,88].

Indications and efficacy

Viscosupplementation is widely applied to improve biomechanical function by replacing the reduced HA of osteoarthritic knee and pain management based on potentially therapeutic physicochemical properties[71,74,89].

However, despite many clinical trials, the efficacy of HA is a matter of debate with markedly discordant interpretations of the data[90]. Among the published meta-analyses, two concluded an overall beneficial effect for HA injections[63,91], four reported a small benefit[66,90,92,93], and two found no evidence to support HA injection therapy for knee OA[94,95]. Rutjes *et al*[96] found overall no clinically important benefit for pain intensity or frequency of OA flares in 89 trials involving 12667 patients. On the other hand, Bannuru *et al*[90] reported that HA asserts modest positive effect for certain clinical situations up to 24 wk, but its cost-effectiveness is advised to be re-

evaluated. Supporting this, National Health Service in Wales and England (NHS) reported in their guideline for management of OA that despite the evidence seems to suggest a benefit for reducing pain up to three months after a series of three to five injections, the cost-effectiveness estimate of HA injections is outside the realms of affordability[2].

When reviewed individually, most trials reported positive effects of HA, but there were considerable heterogeneity in the clinical research methodology[6,66,77]. Populations with variable OA severity, variable inclusion, exclusion and assessment criteria, different molecular weights of HA, different injection schedules were included in the trials. Also, there exists the potential for publication bias and the differences about interpretation of the clinical importance of the observed treatment effects[66].

In a very recent review, Printz *et al*[97] investigated financial conflicts of interest in studies on the therapeutic effects of IA HA injections for treatment of knee OA. The results demonstrated that 63% of studies were industry funded. None of the studies with at least one company employee as an author reported an unfavorable conclusion about the efficacy of HA in the treatment of knee OA. The authors concluded that the conclusions in studies on HA injections for knee OA were commonly associated with industry authorship. The authors advised the clinicians to be aware of the potential financial conflicts of interest of the authors reporting on this topic and carefully evaluate the recommendations from these studies based on the objectivity of the study design.

IA injection of HA is safe for use in patients with knee OA[66,98]. The only adverse effects of significance are transient local reactions in the injected joint observed at a rate of 2% to 4%[89,99,100].

The American College of Rheumatology subcommittee on OA has no recommendations regarding the use of IA hyaluronates[60]. However, American Society of Orthopedic Surgeons does not recommend using IA HA for patients with symptomatic OA of the knee. Work group interpreted the quality of the supporting evidence is high and the strength of recommendation is strong against the use of IA HA in their guideline[4].

To sum up, the research evidence demonstrates that IA HA injections are safe and might have efficacy and might provide pain reduction in mild OA of knee up to 24 weeks. But, the cost-effectiveness is an important concern that patients must be informed about the efficacy of these preparations. Therefore, beside patient expectations, cost-effectivity must be considered before deciding on this treatment.

PLATELET RICH PLASMA

Agents

Platelet rich plasma (PRP) is prepared from autologous blood by centrifugation to obtain a highly concentrated sample of platelets, which is four to five times higher than that of normal blood[101]. The platelets undergo degranulation to release growth factors (GFs). The plasma is the acellular portion of mixture including cytokines, thrombin, and other GFs.

Different preparation methods for PRP can yield products with different compositions and characteristics. Dohan Ehrenfest *et al*[102] described three methods of producing PRP: (1) the double-spinning method, that yields a four to eight fold change in platelet concentration over baseline levels and also concentrates leucocytes; (2) the single-spinning method, that yields a one- to three fold change in platelet concentration over baseline levels; and (3) selective blood filtration. Based on their leukocyte and fibrin content, different PRP formulations are such as: pure PRP, leukocyte-rich PRP, pure platelet-rich fibrin, and leukocyte- and platelet-rich fibrin[102]. Although some data show better results with PRP formulations with leucocyte depletion, the superiority of one PRP formulation over another for clinical effectiveness has not been established[103].

Mechanism of action

The platelet concentrate is activated by addition of calcium chloride, and this results in the formation of platelet gel and the release of growth factors and bioactive molecules[104]. Thereby, platelets actively participate in healing processes by delivering a broad spectrum of GFs (insulin-like growth factor, transforming growth factor b-I, platelet derived growth factor, and many others) and other active molecules (*e.g.*, cytokines, chemokines, arachidonic acid metabolites, extracellular matrix proteins, nucleotides, ascorbic acid) to the injured site[105]. These factors altogether contribute to comprehensive roles of PRP, including chondrogenesis, bone remodeling, proliferation, angiogenesis, antiinflammation, coagulation and cell differentiation[106,107].

In experimental studies on animal models with OA, PRP was related with decreased chondrocyte apoptosis, increased proteoglycans in the articular cartilage, and prevention against OA progression[108-114]. The effects were related to severity of OA[112]. However, PRP formulations are complex, and many of the questions about PRP mechanisms of action in a joint with OA remain unanswered[103,115]. In a recent review, Andia *et al*[116] concluded that although the effectors mediating the beneficial effects of PRPs have not been identified and research is complex because platelets contain more than 300 proteins, this therapy could act as an endogenous source of chondroprotection by interfering with the early catabolic and inflammatory events and by subsequently promoting anabolic responses.

Indications and efficacy

PRP is a blood product that allows in a simple, low cost, and minimally invasive way to obtain a concentration of many of growth factors and biologically active molecules and its use is associated with reduced inflammation, pain relief, improved function, and possible cartilage regeneration. The major problem is mechanisms underlying this

potential therapeutic effect of PRP remain poorly understood. Furthermore, interpatient variability and the lack of biochemical and imaging biomarkers to improve diagnosis specificity of OA make demarcating PRP therapies difficult. Therefore, strong evidence from well-designed clinical trials to support PRP therapy for OA of the knee is needed[115].

Sánchez *et al*[117] was first to describe the IA injection of plasma rich in growth factors to treat an articular cartilage avulsion in a soccer player. Next, in a retrospective study, the similar study group reported preliminary results of an autologous preparation rich in growth factors injection for knee OA, suggesting the safety and usefulness of this treatment approach[118]. Sampson *et al*[119] performed three sets of IA PRP injections at four weeks intervals for 14 patients affected by knee OA and reported a favorable outcome in most of the patients at 12 mo of follow-up. Kon *et al*[120] performed three sets of IA PRP injections at 21-d intervals to 115 osteoarthritic knees, and reported significant improvement at 6- and 12-mo of follow-up. However, they reported a worsening of the results after 6 mo of follow-up, even if still significantly was higher by the 12th-month with respect to the basal level. The similar study group performed a 2 year's follow-up evaluation and although they observed an overall worsening of the results, the results still showed improved quality of life for the patients[121]. In this study, the results showed 9 mo of median duration of the beneficial effects and were better in young patients with lower degrees of OA. Similar results were confirmed in recent studies[122-128].

In clinical studies to date, PRP is safe, with no serious complications reported. Minor adverse events associated with repeated IA injections have been moderate pain, swelling and mild effusion that lasted a few days[121,122,125-127,129].

American Society of Orthopedic Surgeons work group interpreted the evidence to be inconclusive as to the benefit of IA PRP injection and were unable to recommend for or against the use of IA PRP injection in their guideline for patients with symptomatic OA of the knee[4].

To sum up, studies indicate that PRP is promising for relieving pain, improving knee function and quality of life[115,119,121,128,130]. But, there is no data that PRP will cause osteophytes to regress or cartilage and meniscus to regenerate in patients with substantial and irreversible bone and cartilage damage. More promising results are shown in younger patients, and in mild OA cases. Despite the interesting preliminary findings and the increasing clinical application of this attractive treatment approach, extensive clinical use of PRP in OA is not supported by high-quality evidence of a clear clinical improvement[6]. But its low cost, the simple preparation technique, safety, and biologically active content have led to high acceptance both by patients and physicians.

Comparative studies

In the Cochrane reviews of trials comparing IA HA injections with IA corticosteroids, there were no significant differences 4 wk after injection but IA HA was shown to be more effective 5-13 wk post injection[45,91]. This is further supported by a meta-analysis of seven randomized controlled trials in patients with knee OA in which IA HA was compared directly with IA CS[47]. In the first two weeks, corticosteroids were more effective in relieving pain, but at week 4, both were equally effective, and from week 8, HA was more effective to last assessment at 26th week. Analyses of the results for other outcomes such as reduction in stiffness and improvement in function following IA HA were similar.

In the recent studies comparing PRP and HA, Kon *et al*[122] studied PRP versus HA injections in 150 patients, with PRP treatment giving better results than HA in reducing pain and symptoms and recovering articular function up to 6 mo. In this study, PRP showed a better performance compared with HA in younger patients affected by cartilage lesions or early OA. However, PRP and HA treatments offered similar results in patients aged over 50 years and in the treatment of advanced OA. Also, Spakova *et al*[129] compared 120 patients receiving IA injection of either HA or PRP. The authors reported that statistically significantly better results in the scores were recorded in a group of patients who received PRP injections after a 3- and 6-mo of follow-up. Say *et al*[131], compared IA HA and PRP injections in their prospective study and concluded that the application of single dose PRP to be a safe, effective and low-cost method for treating OA. Finally, in very recent three Level 1 studies, two randomized HA controlled clinical trials[125,126] and one placebo-controlled trial[127], PRP decreased pain and improved function in all three trials better than HA or placebo.

CONCLUSION

The current literature and our experience indicate that IA injections are safe and have positive effects for patient satisfaction. But, we are not sure that what ratio of this worthy outcome derives either from the real disease modifying effect or from the placebo effect of these drugs. When the unclear etiopathogenesis and the heterogeneity of OA are considered, it is hard to categorize the patients and their level of disease for IA injection choice. In regards to our experience, patient characteristics, symptoms, and clinical findings may indicate a practical approach for IA injections. The CS choice is reasonable in acute and persistent synovitis for patients that cannot be operated. The corticosteroids are effective in short-term. We prefer HA for obese patients who are older than 60 years and for patients with extremity malalignment. The supposed long-term effect of HA is attractive for these patients who are not willing to be operated. We prefer PRP for patients who are younger than 60 years, with mild OA and body mass index < 30, and for patients that do not have any extremity malalignment. If the patients are older than 60 years, or their body mass index > 30,

or they have moderate OA, we still apply PRP injection, which is followed by a supplementary single dose of HA injection 2 to 4 wk after PRP injection.

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Degenerative meniscus: Pathogenesis, diagnosis, and treatment options

Richard Howell, Neil S Kumar, Nimit Patel, James Tom

Richard Howell, Neil S Kumar, Nimit Patel, James Tom, Department of Orthopedic Surgery, Drexel University College of Medicine, Hahnemann University Hospital, Philadelphia, PA 19102, United States
Author contributions: Howell R, Kumar NS, Patel N and Tom J designed the research, performed the research, analyzed the data; Howell R, Kumar NS and Patel N wrote the paper; all the authors approved the final manuscript.
Correspondence to: Richard Howell, MD, Department of Orthopedic Surgery, Drexel University College of Medicine, Hahnemann University Hospital, 245 N. 15th Street, Philadelphia, PA 19102, United States. howellrichards@gmail.com
Telephone: +1-215-7622663 Fax: +1-215-7622663
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Abstract

The symptomatic degenerative meniscus continues to be a source of discomfort for a significant number of patients. With vascular penetration of less than one-third of the adult meniscus, healing potential in the setting of chronic degeneration remains low. Continued hoop and shear stresses upon the degenerative meniscus results in gross failure, often in the form of complex tears in the posterior horn and midbody. Patient history and physical examination are critical to determine the true source of pain, particularly with the significant incidence of simultaneous articular pathology. Joint line tenderness, a positive McMurray test, and mechanical catching or locking can be highly suggestive of a meniscal source of knee pain and dysfunction. Radiographs and magnetic resonance imaging are frequently utilized to examine for osteoarthritis and to verify the presence of meniscal tears, in addition to ruling out other sources of pain. Non-operative therapy focused on non-steroidal anti-inflammatory drugs and physical therapy may be able to provide pain relief as well as improve mechanical function of the knee joint. For patients refractory to conservative therapy, arthroscopic partial meniscectomy can provide short-term gains regarding pain relief, especially when combined with an effective, regular physiotherapy program. Patients with clear mechanical symptoms and meniscal pathology may benefit from arthroscopic partial meniscectomy, but surgery is not a guaranteed success, especially with concomitant articular pathology. Ultimately, the long-term outcomes of either treatment arm provide similar results for most patients. Further study is needed regarding the short and long-term outcomes regarding conservative and surgical therapy, with a particular focus on the economic impact of treatment as well.

Key words: Meniscus; Degenerative joint disease; Meniscal tear; Osteoarthritis; Arthroscopy

Core tip: The healing potential of chronic degenerative menisci remains poor. Persistent hoop and shear stresses create complex tears in the posterior horn and midbody. Conservative treatment with anti-inflammatory medications and physical therapy may provide pain relief and improve mechanical knee function. For patients refractory to conservative therapy, arthroscopic partial meniscectomy can provide short-term pain relief when combined with a physiotherapy program. Surgery, however, is not a guaranteed success, especially in the presence of articular pathology. Long-term outcomes of surgical or non-surgical treatment have been shown to be similar for most patient subsets.

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INTRODUCTION

Of the multitude of etiologies for knee pain, meniscal degeneration plays a significant role. The meniscus degenerates microscopically and macroscopically with the aging process, resulting in pain and knee dysfunction. This paper reviews the degenerative process of the meniscus as well as diagnostic modalities and treatment options.

ANATOMY

Gross anatomy

The human menisci are C-shaped or semicircular fibrocartilaginous structures with bony attachments on the tibial plateau. The menisci are essential for joint stability, shock absorption, distribution of contact forces, joint lubrication, and proprioception[1]. The medial meniscus is C-shaped, approximately 3 cm wide, and 4 to 5 cm long[2]. The posterior horn is larger than the anterior horn and various studies have described the different bony attachments. The anterior horn of the medial meniscus generally has a firm, bony attachment. Studies have shown that 3%-14% of medial menisci have no bony attachment for the anterior horn[3,4]. The insertion of the posterior horn lies anterior to the posterior cruciate ligament. The capsular attachments of the medial meniscus onto the tibia are known as the coronary ligaments, with a thickening along the midportion referred to as the deep medial collateral ligament[5].

The lateral meniscus is semicircular in shape and covers a larger portion of the tibial articular surface than the medial meniscus. It is approximately 3 cm wide and 3 to 4 cm in length[2]. The lateral meniscus is anchored anteriorly and posteriorly; however, the capsular attachment is not as well developed as the medial side. As a result, there is increased translation and movement of the lateral meniscus throughout all ranges of motion[6]. The anterior horn inserts just adjacent to the anterior cruciate ligament. The posterior horn inserts behind the intercondylar eminence, anterior to the insertion site of the posterior horn of the medial meniscus. The posterior horn also has meniscofemoral ligaments known as the ligament of Humphries and ligament of Wrisberg, which connect posterior horn to the lateral aspect of the medial femoral condyle[7].

Microstructure and composition

Water makes up approximately 70%-75% of the normal meniscus[8]. The dry weight is comprised of collagen (60%-70%), noncollagenous proteins such elastin (8%-13%), and proteoglycans (1%). The majority of collagen is type 1 (90%) with type Ⅱ, Ⅲ, Ⅴ, and Ⅵ making up smaller amounts[8,9]. The orientation of collagen fibers is predominantly circumferential. A smaller amount of radially oriented fibers are located at the surface. In addition, a collagen fibrillar network organized into a mesh like matrix is at the surface to aid in distribution of shear forces[8,9].

Fibrochondrocytes are the predominant cell type in the meniscus, producing collagen and its extracellular matrix[8,9]. Along the inner avascular zone, cells are morphologically similar to articular chondrocytes; on the periphery, cells are more similar to fibroblasts. Arnoczky *et al*[10] demonstrated that the outer 10% to 30% of the medial meniscus and 10% to 25% of the lateral meniscus is vascular. The medial and lateral geniculate arteries form a perimeniscal capillary plexus the supplies the outer surface of the menisci. The menisci have intrinsic innervation, which is most abundant on the periphery and the anterior and posterior horns[9]. Proprioception is believed to be obtained from free nerve endings that are activated on the anterior and posterior horns during flexion and extension of the knee[11,12].

Tear types

Meniscal tears can be classified as acute or degenerative. Acute tears are from excessive force applied to a normal knee and meniscus. This is different from a degenerative tear, which results from repetitive normal forces acting upon a worn down meniscus. Tears can also be described based on pattern and location. These tear patterns include vertical longitudinal, oblique, transverse (radial), horizontal, meniscal root, bucket-handle, and complex. Tears can located in the avascular or vascular zone (*i.e.*, white, red-white, red-red), which influences healing potential either spontaneously or after surgical repair[13]. Degenerative tears generally have a complex tear pattern and are predominantly found in the posterior horn and midbody[14]. Previous studies have shown an increase in articular cartilage changes in the presence of degenerative meniscal tears[15,16]. In 44 patients, Mesiha *et al*[17] showed that degenerative meniscal tears were associated with the presence of Outerbridge Ⅱ chondral degeneration more than 85% of the time, compared to 12% for flap tears and 0% for longitudinal tears. Likewise, in a prospective study of 497 consecutive knee arthroscopies in patients with meniscus tears, Christoforakis *et al*[18] found that patients with complex or horizontal tears were significantly more likely to have Outerbridge types Ⅲ and Ⅳ chondral lesions. Additionally, patients with complex tears were significantly more likely to have a second chondral lesion than patients with flap, radial, or bucket handle tears. The literature; however, is not conclusive. In a multicenter cohort study, Badlani *et al*[19] showed that the rate of medial meniscus degenerative tear was not significantly higher in those who developed osteoarthritis. However, meniscal extrusion and tears with a large radial involvement were, in fact, significantly associated with osteoarthritis. Osteoarthritis and degenerative meniscal tears share many of the same risk factors and biological processes. Therefore, it is difficult to definitively determine if one condition precedes the other, or if they both occur independently and/or simultaneously.

DIAGNOSIS

Presentation

Degenerative meniscal pathology typically presents as

knee pain accompanied by mechanical symptoms. Patients are typically over the age of 30 and often complain of insidious onset of symptoms with no known traumatic event. One should have a low threshold to consider meniscal injury in patients with knee osteoarthritis; Wang *et al*[20] diagnosed a 40% concomitant prevalence determined by arthroscopy. Typical mechanical symptoms include painful clicking, popping, locking, catching, and giving way. In addition, Lange *et al*[21] found meniscus tears to result in decreased walking endurance and balance performance.

Physical exam

Several findings are suggestive of meniscus injury including joint line tenderness, positive McMurray's test, locking, and palpable or audible clicking. The examiner should also examine the contralateral knee for comparison. Initial visual inspection of the knee should investigate for evidence of infection or trauma, such as erythema, wound, ecchymosis, or gross deformity. Patients with degenerative meniscus pathology rarely present with joint effusion, unlike after acute meniscus or ligamentous injury. Range of motion may be decreased due to a physical block caused by displaced meniscal material. Most often, passive and active range of motion is full and equivalent to the contralateral knee. With range of motion, clicking may be heard or felt; this is suggestive of meniscal pathology, although osteoarthritis, patellafemoral syndrome, and loose bodies also cause this sign. Joint line tenderness and a positive McMurray test are described as highly suggestive of meniscus injury, though study results vary regarding their sensitivity and specificity. Joint line tenderness sensitivity ranges from 63%-87%, while specificity ranges from 30%-50%[22,23]. A positive McMurray test has a sensitivity of 32%-34% and specificity of 78%-86%[22,23]. Ercin *et al*[24] found physical examination by an experienced practitioner to have better specificity (90% *vs* 60%), positive predictive value (95% *vs* 83%), negative predictive value (90% *vs* 86%), and diagnostic accuracy (93% *vs* 83%) than MRI for medial meniscal tears. They assert that physical examination is sufficient to diagnose a meniscus tear and proceed with arthroscopy. Currently, however, most surgeons choose to obtain advanced imaging prior to arthroscopy.

Radiology

Radiographic examination of the knee is of limited value in the patient suffering from degenerative meniscal pathology, as the menisci are not visualized with standard radiography. This modality is primarily used to exclude other sources of knee pain, such as osteoarthritis, which frequently occurs concurrently with meniscal degeneration. Traditionally, sonography has had low utilization as a tool in the diagnosis of degenerative meniscal pathology. However, De Flaviis *et al*[25] reported dynamic ultrasound to have 82% sensitivity for detecting degenerative meniscus changes based upon findings of border irregularity, cystic cavities, or calcification. Rutten *et al*[26] reported a sensitivity, specificity, and accuracy of sonography in the depiction of meniscal cysts as 97%, 86% and 94%, respectively. The accuracy of ultrasound is dependent on technologist skill. In addition, sonography cannot examine deep structures of the knee with high accuracy. In centers where dynamic sonography is available and the patient's clinical presentation is specific for meniscal pathology, ultrasound presents a viable cost saving option.

Ultimately, magnetic resonance imaging (MRI) is the gold standard for soft-tissue imaging of the knee. MRI has an accuracy of 90%-95% for detecting meniscal injury[27]. Meniscal structure is well evaluated on proton density and T1 sequencing, while pathology is best identified on T2 sequencing. MRI signal changes indicative of meniscus pathology are graded Ⅰ through Ⅲ[28]. Grade Ⅰ signal change is intrasubstance, globular, and does not intersect the articular surface. Grade Ⅱ signal change is intrasubstance, linear, and does not intersect the articular surface. Grade Ⅰ and Ⅱ signal changes represent intrasubstance degeneration in adults or vascularity in children. Traditionally, grade Ⅰ and Ⅱ changes were not thought to correlate with a true tear. However, recent studies have found that some grade Ⅱ changes may represent a true tear[29]. Grade Ⅲ changes intersect the superior or inferior articular surface, or both, and represent a true tear. von Engelhardt *et al*[29] evaluated the sensitivity and specificity of 3 Tesla MRI using arthroscopy as the reference standard. It was found that accuracy varied based upon lesion grade. Grade Ⅰ lesions identified by MRI were not associated with a torn meniscus at arthroscopy. In 24% of patients with a Grade Ⅱ lesion, a true tear was identified by arthroscopy. Grade Ⅲ lesions had an overall sensitivity and specificity of 79% and 95%, respectively: 86% and 100%, respectively, for the medial meniscus, and 57% and 92%, respectively, for the lateral meniscus. It should be noted that an MRI obtained postoperatively may be less accurate secondary to post surgical changes[27]. One must always remember to evaluate and treat the patient based upon the clinical presentation along with diagnostic findings, not by imaging alone. Fukuta *et al*[30] found a 50% incidence of grade Ⅲ signal changes in clinically asymptomatic patients over the age of forty with osteoarthritis. Thus, the finding of a meniscal tear on MRI in a patient without clinical symptoms should not prompt the surgeon to proceed with arthroscopy.

TREATMENT

Conservative and surgical modalities can be utilized in the treatment of the painful degenerative meniscal tear. No matter the method, the ultimate goal remains the same: to relieve acute symptomology and limit future recurrence. Nonoperative therapy is often times the mainstay of treatment, while surgical procedures are reserved for patients with symptoms resistant or recurrent to conservative management.

Non-operative therapy

The initial focus of non-surgical supportive care is the relief of knee pain. Patients should limit activities that instigate or exacerbate symptoms, however complete rest is

not advised, as stiffness may result. Patients often present with incomplete symptom relief after non-steroidal anti inflammatory drug (NSAID) use on an as-needed basis. If tolerable, such cases may warrant routine use over a period of up to 6 wk. Muscle relaxants and analgesics can also be used, although usually for a shorter period of time. Physical therapy and rehabilitation is a central aspect of conservative treatment, with exercises focused on maintaining range of motion (ROM), improve hip and hamstring flexibility, increase quadriceps and hip strength, and retain knee proprioception. Gait therapy, whether by exercise or supportive orthoses, may also improve knee function and provide pain relief[31]. A supervised exercise regimen lasting 8 to 12 wk, when combined with a home program, can provide immediate short-term benefits. In a small series, Østerås *et al*[32] reported that with 36 sessions over a 3 mo period improved pain scores, quality-of-life scores, and reduced anxiety at 3 mo follow-up. Stensrud *et al*[33] described a 3 mo protocol focused on dynamic neuromuscular training, which resulted in improved patient-reported outcomes and muscle performance up to 1 year. Physiotherapy can also reduce mechanical symptoms in addition to providing pain relief. In a prospective trial, 52 patients with degenerative meniscal tear underwent an exercise regimen; mechanical symptoms and knee pain were significantly reduced at final 2 year follow-up, even despite some advancement of osteoarthritic degeneration[34]. The benefits of physical therapy, even with radiographic evidence of worsening degeneration, has been found in studies with up to 3 year follow-up[35,36]. Herrlin *et al*[37] followed 47 patients in a prospective trial up to 5 years. Visual analog scale (VAS) scores and knee function significantly improved at 2 and 5 years, however no difference was found between these two follow-up points. Ultimately, a regimented physiotherapy program can reduce knee pain and improve function in the presence of degenerative joint disease progression.

Arthroscopic partial meniscectomy

While non-operative therapy provides some degree of symptom relief over the long-term, these benefits may wane with continued meniscal degeneration[38]. In such patients, arthroscopic partial meniscectomy can be effective in improving patient quality of life. A thorough arthroscopic examination of the chondral surfaces, joint spaces, and menisci are critical to document cartilage health, identify loose bodies, and localize meniscal tears. Partial meniscectomy attempts to debride the unstable degenerative tear in order to create a stable tear or a smooth rim of the remaining meniscus. The surgeon is tasked to remove the meniscal tear while simultaneously maintaining as much healthy meniscus as possible. Meniscectomy undoubtedly alters joint biomechanics; excessive debridement may lead to unnecessary load-induced chondral wear and shear-induced subchondral fracture, furthering joint and meniscal degeneration[39]. Relief from knee pain and improvement of function can be obtained quickly, as soon as 3 mo post-operatively[32]. Yim *et al*[34] found significant improvement in knee pain, knee function, and patient satisfaction scores in 50 patients at 2 years after arthroscopic partial meniscectomy; these results, however, were tempered by the finding that there was no difference at final follow-up in comparison with non-operatively treated patients. In another prospective study, Herrlin *et al*[37] noted significant improvement in VAS and knee function scores up to 5 years post-operatively. They also found that a significant portion, one-third, of patients treated non-operatively required arthroscopy secondary to incomplete pain relief. Similar to Yim *et al*[34], however, Herrlin*et al*[37] found no difference in pain and function scores at any point between operatively and nonoperatively treated patients. At this juncture, the long-term value of arthroscopic partial meniscectomy compared to non-operative physiotherapy is unknown.

Post-operative rehabilitation

Most surgeons recommend a program of physical therapy post-operatively to reduce pain and swelling, promote full range-of-motion, and improve knee function. Modalities such as icing, joint mobilization, and massage can provide short-term pain relief and reduce swelling[40]. Beyond the immediate postoperative symptoms, extensor weakness remains the primary concern after surgical treatment of the degenerative meniscal tear. Moffet *et al*[41] described the importance of physical therapy focused on extensor weakness, findings significant benefits in 31 patients. Østerås *et al*[42] described a specific 3 mo postoperative rehabilitation program in a prospective study utilizing bicycling, resisted quadriceps exercises, and squats. They noted better pain relief, knee function, and strength at 1 year compared to patients without postoperative physiotherapy. Even with dedicated rehabilitation, recovery or preoperative extensor strength may take 4 to 6 wk, and can still be deficient compared to the non-operative extremity[43]. This discrepancy may place the active patient at risk for injury on return to sporting activity. Generally, the active patient may return to practice at 80% strength, typically 3 to 6 wk postoperatively, and return to game competition at 90% strength, typically 5 to 8 wk postoperatively[40,44].

CONCLUSION

The symptomatic degenerative meniscus continues to be a source of discomfort for a significant number of patients. Patients with clear mechanical symptoms and meniscal pathology may benefit from arthroscopic partial meniscectomy, but surgery is not a guaranteed success, especially with concomitant articular pathology. Patient history, physical examination, and radiographic imaging are critical to determine the true source of pain, meniscus or cartilage degeneration, and to eliminate other potential aggravants. Non-operative therapy focused on NSAID anti-inflammatories and physical therapy may be able to provide pain relief as well as improve mechanical function of the knee joint. For patients refractory to conservative therapy, arthroscopic partial meniscectomy can provide short-term gains regarding pain relief, es-

pecially when combined with an effective, regular physiotherapy program. Ultimately, the long-term outcomes of either treatment arm provide similar results for most patients. Further study is needed regarding the short and long-term outcomes regarding conservative and surgical therapy, with a particular focus on the economic impact of treatment as well.

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Treatment for cartilage injuries of the knee with a new treatment algorithm

Ahmet Özmeriç, Kadir Bahadır Alemdaroğlu, Nevres Hürriyet Aydoğan

Ahmet Özmeriç, Kadir Bahadır Alemdaroğlu, Nevres Hürriyet Aydoğan, Department of Orthopedics and Traumatology, Ankara Training and Research Hospital, 06340 Ankara, Turkey
Author contributions: Özmeriç A contributed to data review, drafting of paper; Alemdaroğlu KB contributed to review and approval of paper; Aydoğan NH was the consultant supervisor.
Correspondence to: Ahmet Özmeriç, MD, Department of Orthopedics and Traumatology, Ankara Training and Research Hospital, Sukriye Mahallesi Ulucanlar Caddesi No:89 Altindag, 06340 Ankara, Turkey. aozmeric77@yahoo.com
Telephone: +90-532-5052520477 Fax: +90-312-3633396
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Abstract

Treatment of articular cartilage injuries to the knee remains a considerable challenge today. Current procedures succeed in providing relief of symptoms, however damaged articular tissue is not replaced with new tissue of the same biomechanical properties and long-term durability as normal hyaline cartilage. Despite many arthroscopic procedures that often manage to achieve these goals, results are far from perfect and there is no agreement on which of these procedures are appropriate, particularly when full-thickness chondral defects are considered.Therefore, the search for biological solution in long-term functional healing and increasing the quality of wounded cartilage has been continuing. For achieving this goal and apply in wide defects, scaffolds are developed.The rationale of using a scaffold is to create an environment with biodegradable polymers for the in vitro growth of living cells and their subsequent implantation into the lesion area. Previously a few numbers of surgical treatment algorithm was described in reports, however none of them contained one-step or two –steps scaffolds. The ultimate aim of this article was to review various arthroscopic treatment options for different stage lesions and develop a new treatment algorithm which included the scaffolds.

Key words: Chondral lesion; Microfracture; Osteochondral transplantation; Autologous chondrocyte implantation; Scaffolds

Core tip: This paper discusses the current arthroscopic treatment options of cartilage injuries. Over 1 cm^2 full thickness chondral lesions are seen in 4%-5% of patients under 40 years undergone arthroscopy. Conventional arthroscopic treatment may not have successful results although chondral defects are observed with such a high incidence. Addition of novel scaffolds to conventional methods will provide beneficial effects on healing of articular cartilage lesions with hyaline. We now formulate a new treatment algorithm with scaffolds under the light of existing literature. In future, we expect the widespread use of arthroscopic surgery in chondral defects.

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INTRODUCTION

Articular injuries that are related to trauma or overuse have plagued those afflicted for more than 200 years and are still problematic to treat. In 1743, Hueter[1] stated, "From Hippocrates down to the present age, we shall find, that an ulcerated cartilage is universally allowed to be a very troublesome disease; that it admits of a cure with more difficulty than carious bone; and that, when destroyed, it is not recovered".

Articular cartilage is vulnerable to both irreversible traumatic injury and degenerative disease[2]. The ability of

damaged articular cartilage to recover with normal hyaline cartilage is limited because of two main factors: the absence of a vascular response and the relative absence of an undifferentiated cell population to respond to injury[3]. If patients with previous cartilage deformation (chondral defects) have not been treated properly, the osteoarthritis symptoms can be seen radiographically after 10 years and primary gonarthrosis related with osteoarthritis develops 10 years early[4,5]. Therefore, it can be said that cartilage deformation leads to osteoarthritis and chondral defects in weight-bearing regions that are at risk of developing osteoarthritis[6].

It is questionable whether every chondral defect results in osteoarthritis. A defect size under 10 mm does not increase the pressure in peripheral healthy cartilage. However, 64% more pressure is exerted on cartilage with a defect size greater than 10 mm[5]. After a 14-year follow-up of 10 mm sized defects, it has been reported that the joint gap was observed to be 50% narrower[7]. In animal studies where the treatment of cartilage defects has been evaluated, some artificial defects regenerated spontaneously. The defect sizes which do not regenerate without treatment are called "critical sized defects". The sizes determined for every animal model can not be estimated for humans. In a clinical study, critical defect size was suggested to be 2 cm^2[8]. Therefore, defect size is not the only factor for defect resolution. Three major factors must be taken into consideration when making the treatment decision. The first factor to be considered involves defect-specific factors such as size, depth, location, and degree of containment. The second includes patient-specific factors such as patient age, current and desired level of activity and patient expectations. The third area is joint-related factors, including alignment, stability and the status of the meniscus.

Some form of cartilage healing has been proven given certain conditions, although the terms "healing and repair" are rather non-specific. Most often, the repaired articular cartilage is unsuccessful in replicating the structure, composition and function of healthy articular cartilage. Today, there are various surgical procedures to treat articular injuries.

GOALS, INDICATIONS AND CONTRAINDICATIONS FOR SURGICAL TREATMENT

Candidates for surgical treatment are patients who have documented articular damage and those with an associated ligamentous or meniscal injury that requires surgery. Today, the main purpose of surgical treatment of articular cartilage pathology is to lessen the pathology-related symptoms, stop the progression of articular damage, restore the articular surface anatomy and start a healing or repair process in order to transform damaged tissue into healthier new tissue. Currently, most surgical procedures lead to the formation of a fibrocartilage tissue replacement, which has an inferior biomechanical composition to normal hyaline cartilage. Surgical treatment of these articular lesions ultimately aims to replace the damaged tissue with normal hyaline cartilage that has an equivalent composition to that of the preexisting tissue. For this aim, indications are ranged according to chondral treatment options, however generally, distal femoral condyles lesions, symptomatic cartilage lesions, and asymptomatic lesion in patient who has an additional injury undergoing to surgical treatment . Contraindications of surgical treatment for articular cartilage lesions are wide-spread degenerative arthritis (including 3 compartment), systemic inflammatory or collagen vascular diseases, active infection in the related joint, body mass index > 30, opposed (kissing) full-thickness cartilage injury, untreated malignment and instability[9].

CLASSIFICATION OF CARTILAGE DEFECTS

It is important and necessary to throughly document and grade chondral lesions when treating patients with articular cartilage defects. In 1961, Outerbridge[10] described the simplest scale by directly observing damaged patellas during arthrotomy. The Outerbridge grading system is widely accepted, although it has size, depth and lesion locale descriptive limitations. Many other classification systems have been established to indicate the severity and type of articular cartilage. The international cartilage research society (ICRS) grading system observes the importance of subchondral osseous involvement and is used to describe the defect (area, depth, location)[11]. Table 1 shows the classification systems (Outerbridge, modified outerbridge grading system and ICRS) of articular lesions by severity[12,13].

SURGICAL TREATMENT OPTIONS AND RESULTS

During surgery, chondral defects in the knee joint are often observed. Those lesions do not always trigger symptoms. However, full thickness chondral lesions greater than 1 cm^2 have been reported at 4%-5% in arthroscopy performed on patients aged under 40 years[14,15]. In chondral defects, while cartilage is treated, the problem causing the chondral defect should also be detected and resolved[16].The detection and treatment of the chondral problem influences the success of the treatment of the lesion[17]. During arthroscopic surgery, the defect is generally seen to be greater than as observed on magnetic resonance imaging (MRI)[18].

In a retrospective review of over 31000 knee arthroscopies, in all age groups, chondral lesions were found in 63% of patients, with an average of 2.7 lesions per knee. 19% of those were focal (not widespread) chondral or osteochondral lesion, 5.2% were grade Ⅲ or grade Ⅳ and only focal cartilage lesions required treatment[14]. Most chondral defects (58%-80%) are seen in the medial femoral condyle, followed by the patella and tibial pla-

Table 1 Classification of articular lesions by severity

Grade	Outerbridge	Modified outerbridge	ICRS
0	Normal cartilage	Intact cartilage	Intact cartilage
I	Softening and swelling	Chondral softening or blistering with intact surface	Superficial (soft indentation or superficial fissures and cracks)
II	Fragmentation and fissures in area less than 0.5 inch in diameter	Superficial ulceration, fibrillation, or fissuring less than 50% of depth of cartilage	Lesion less than half the thickness of articular cartilage
III	Fragmentation and fissures in area larger than 0.5 inch in diameter	Deep ulceration, fibrillation, fissuring or chondral flap more than 50% of cartilage without exposed bone	Lesion more than half the thickness of articular cartilage
IV	Exposed subchondral bone	Full-thickness wear with exposed subchondral bone	Lesion extending to subchondral bone

ICRS: International Cartilage Repair Society.

Table 2 Treatment options for articular cartilage lesions

Procedure	Indications	Outcome
Arthroscopic debridement and lavage	Minimal symptoms	Palliative
Marrow stimulation	Smaller lesions, low-demand patient	Reparative
Osteochondral autograft	Smaller lesions, low-or high-demand patients	Restorative
Osteochondral allograft	Larger lesions with bone loss, low-or high-demand patients	Restorative
Autologous chondrocyte implantation	Small and large lesions with and without bone loss, high-demand patients	Restorative
Genetic engineering	Investigational	Restorative

From Garrick JG, editor: Orthopaedic knowledge update: sports medicine, 3rd ed, Rosemont, IL, 2004, American Academy of Orthopaedic Surgeons.

teau. Defects in the lateral condyle, trochlea and medial tibial plateau are observed at lower incidence rates[15].

The main goal of arthroscopic surgical management of symptomatic chondral defects is to lessen symptoms, improve joint congruence and prevent additional cartilage deterioration. Options can be characterized as palliative, reparative or restorative for those lesions. For lesions discovered incidentally or symptomatic lesions in low-demand patients with a preponderance of mechanical symptoms or signs of meniscal pathology, palliative procedures such as debridement and lavage are used. In the area of the defect, reparative procedures promote a fibrocartilage healing response. Restorative techniques replace the damaged cartilage with new articular cartilage; these include autologous chondrocyte implantation, osteochondral autografting and fresh osteochondral allografting (Table 2).

Debridement and lavage

Over 60 years ago, Magnusson[19] described the benefits of knee joint debridement to relieve arthritic symptoms. Jackson *et al*[20] became a proponent of arthroscopic palliative procedures such as debridement and lavage for the treatment of a symptomatic arthritic knee with the arrival of arthroscopy. The purpose of this technique is to debride the loose chondral tissues. Removal of loose intra-articular tissue debris and inflammatory mediators generated by the synovial lining leads to acceptable short-term results for both acute and degenerative chondral lesions. Lavage most often provides short-term symptomatic relief. This procedure is appropriate for older sedentary patients, but when an active population is considered, the results are generally insufficient[21].

Evidence based analyses indicate that lavage and debridement is accepted as an effective technique in the short-term (up to 12 mo) in terms of pain management in patients with early osteoarthritis and those with mechanical symptoms. However, in patients with moderate to advanced osteoarthritis the results are contradictory[22].

Marrow stimulating techniques

The concept of penetrating the subchondral bone to allow for the release of blood, growth factors and mesenchymal cells into the chondral defect was popularized by the Pirdiean[23] open technique in 1959 and was then modified for arthroscopic use by Johnson[24]. Marrow-stimulating techniques such as abrasion arthroplasty, subchondral drilling and microfracture are the three described techniques used to penetrate the subchondral bone. All these techniques are used to stimulate fibrocartilage in growth into the chondral defect.

Abrasion arthroplasty: This technique involves debridement of the articular defect circumferentially using a motorized burr to remove 1-3 mm of subchondral bone[23]. However, excessive trauma to the underlying bone and thermal necrosis can be potentially more destructive than helpful. Therefore this technique is not used in current practice[11].

Subchondral drilling: This procedure is an extension of the abrasion arthroplasty technique in which the subchondral bone is drilled with multiple drill holes penetrating into the bone marrow to stimulate a vascular response. Considering the efficacy of this procedure, questions still remain due to poor access, thermal necrosis and long-term results[25]. On the other hand, a recent study indicated that drilling does not cause thermal injury

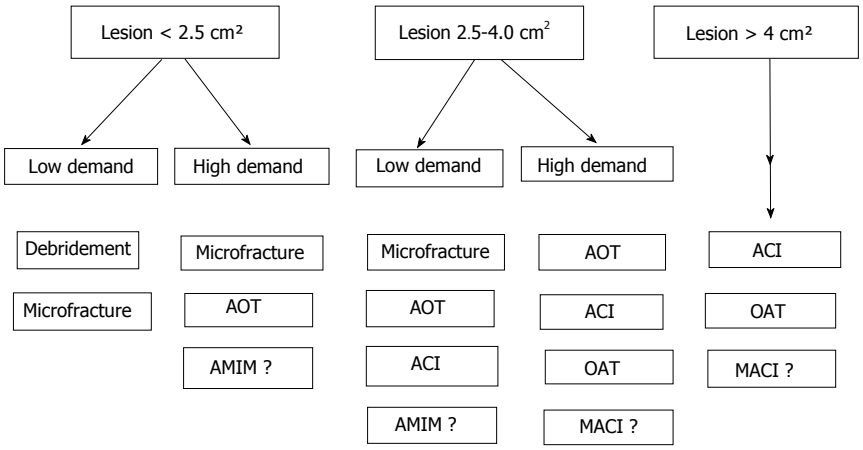

Figure 1 In small defects in high-demand patients, autologous osteochondral transplantation seems to be a reliable treatment alternative. AOT: Autologous osteochondral transplantation; ACI: Autologous chondrocyte implantation; MACI: Matrix-induced chondrocyte implantation; OAT: Osteochondral allograft transplantation; AMIM: Acellular matrix-induced microfracture.

and the drill holes actually allow more consistent channels for cell migration compared to microfracture holes that may be partially blocked with bony debris. Therefore, although less commonly used than microfracture, drilling is another alternative technique within the scope of marrow stimulating techniques[26].

Microfracture: In 1994, Steadman *et al*[27] developed the microfracture technique, which is now the currently preferred marrow-stimulation method. It includes arthroscopic debridement of the cartilage defect down to the subchondral bone but not through it. Damage to the subchondral bone should be avoided in over-aggressive shaving of the soft articular cartilage. When the subchondral bone is identified, an arthroscopic tapered awl is carefully used to make multiple drill holes approximately 3 to 4 mm apart and 4 mm in depth across the exposed surface of the lesion. The use of arthroscopic awls as opposed to subchondral drilling is thought to produce less thermal necrosis in creating the holes.

In spite of progression in chondral defect treatment, the current most widely-used therapy option is the chondral repair technique[28]. This technique is performed extensively as the first treatment choice due to its minimally invasive properties, technique simplicity, lower surgical morbidity and cost- effectiveness in focal chondral defects (< 2.5 cm^2) in patients under 45 years old with a low level of activity[27,29,30]. After less than 2 years follow-up of small, full thickness chondral defects treated with the microfracture technique, 75% of patients reported a decrease in pain, increased function and good-excellent clinical results[27,29]. Other arthroscopic treatment options of autologous osteochondral transplantation (AOT) and autologous chondrocyte implantation (ACI) have been compared with microfracture and after 5 years follow-up, there were no differences in functional scores and postoperative MRI grades between the groups. Microfracture is the first therapy choice because of the simplicity and cost-effectiveness compared to AOT and ACI[31].

However in a recent review of microfracture techniques, Goyal *et al*[32] emphasised that in young patients and smaller lesions, better results were seen in the first five years, but after 5 years the results worsened and resulted in osteoarthritis regardless of the defect size. Thus, with the aim of improving the quality of repair tissue with the microfracture technique and the management of long-term functional healing, biological solutions are being investigated[33].

Recent meta analyses and systematic review studies have indicated that microfracture technique is effective in smaller lesions (up to 4 cm^2) with short-term follow up. The major short comings have included poor hyaline repair, variable cartilage volume and long-term functional deterioration[34] (Figure 1).

Acellular matrix induced microfracture: Natural and artificial structure implants such as scaffolds have been developed for the improvement of the quality of repair tissue and treatment of wide defects with the microfracture technique[35]. Structure implants are implanted in 3 dimensional or liquid/gel-formed acellular materials to improve marrow inducement with the microfracture technique. The chondroconductive or osteoconductive properties of those implants do not contain vital cells.

In combination with microfracture this can stabilize the fibrin and provide an environment for mesenchymal root cells, keep them in place and support tissue differentiation. This type of microfracture has a scaffold to obtain hyaline chondral repair tissue.The advantages of the method are the placement of implants in single-stage surgery and no need for expensive cell production technology. Scaffolds are cost effective and non time-consuming devices. They are invaded by host tissue cells and resorb over time and are replaced with repair tissue. Chondrotissue®, Hyalofast®, AMIC®, CAIS®, Alginate Beads®, Trufit®, Maioregen® are examples of implanted one-step scaffold implants[36].

Siclari *et al*[37] reported that 52 patients, aged 25-65 years, treated with scaffold implants demonstrated an improvement in functional scores and the histological evaluation of 13 biopsy samples showed homogeneous hyaline-like chondral repair tissue. In a recent study, Gille *et al*[38] implanted scaffold membrane combined with microfracture in 27 patients with a mean defect size of 3.4 cm^2 (range 1-12 cm^2) and 87% of patients demonstrated significant clinical healing after a 37-mo follow-up period.

Current literature do not contain evidence-based researches or meta-analysis. Thus, to come to a decision with limited evidence, it could be speculated that one-step cell-free approaches have been developed to avoid the problems related to the *ex vivo* chondrocyte culture and expansion in a scaffold. Besides this, they reduce the costs and surgical time. Finally, osteochondral scaffolds have been proposed to treat lesions where the subchondral layer is also involved in the pathologic process and have shown promising preliminary results.

AOT

AOT is the cartilage restoration procedure which produces true hyaline articular cartilage. Osteochondral autografts can fill the articular defect with human articular cartilage tissue transplanted into damaged areas from areas of less weight-bearing on the femoral condyle as either a single large bone plug or multiple small plugs (mosaicplasty). The term mosaicplasty is reserved to describe the use of multiple, smaller diameter grafts. Autograft harvesting and transplantation techniques have the advantages of using the patient's own tissue and immediate transplantation from the donor site to the recipient site without any additional cost to the patient.

The upper age limit for mosaicplasty is under 50 years and it can be performed on patients with high physical expectations and 1-5 cm^2 focal chondral defects. Hangody *et al*[39] stated that 1-4 cm^2 sized defects are ideal for mosaicplasty. According to Ollat *et al*[40], defects of 2 cm^2 or less and to Solheim *et al*[41], 3 cm^2 or less, showed better results. Good prognostic factors are male gender, young age and small defects. Therefore, in small defects in high-demand patients, AOT seems to be a reliable treatment alternative (Figure 1).

Haklar *et al*[42] claimed that mosaicplasty is a reliable procedure in the treatment of full-thickness chondral lesions because it is minimally invasive, can be performed at a single session, and has a low complication rate and is cost effective.

Gudas *et al*[43] performed microfracture on 22 patients and AOT on 25 patients with a mean age of 24.3 years (range 15-40 years) and a follow-up period of 10 years. Patients treated with microfracture demonstrated good results immediately after surgery, which then worsened over time. The patients with AOT had better results compared with the microfracture group and a high rate of sportsmen in the AOT group were able to resume their previous sporting activities.

Osteochondral grafts in restorative techniques can be complicated by dislodgement of the graft from the transplant site, but this is rare with the press-fit technique. Additionally, graft collapse can occur through biomechanical overload or biological failure of the chondral or subchondral components.

Osteochondral allograft transplantation

The technique of osteochondral autograft plugs was first introduced by Yamashita[44] in 1985 and universalized by Hangody *et al*[45]. Fresh osteochondral allograft transplantation includes the implantation of a composite cadaveric graft that involves the subchondral bone and overlying hyaline cartilage in the site of the chondral defect with a single-stage procedure, and is not limited by its size. Osteochondral allograft transplants are used for medium to large articular lesions (up to 3 cm^2) in relatively high-demand patients. These grafts are generally used on the femoral condyles but can also be used for the patella, trochlea, medial and lateral tibial plateau along with the donor meniscus. There is no donor site morbidity involved in the use of allografts. In addition, allografts may be taken from younger, healthier patients with better quality bone and cartilage. Allografts can also be used in large sized defects. In a study by Giorgini *et al*[46] 11 patients were treated and followed up for mean 26.5 mo between 2006-2011. The average defect size was 10.3 cm^2 (range 3-20 cm^2). The results of this study determined success in 10 patients who showed pain regression and functional recovery. It was emphasized that this technique had better results in lesions smaller than 8 cm^2, although larger lesions also showed good results.

In another recent study, Chahal *et al*[47] conducted a systematic review of clinical outcomes after osteochondral allograft transplantation in the knee. There were 19 eligible studies with 644 knees in total. The mean age was 37 years and the mean follow-up period, 58 mo. The mean defect size across the studies was 6.3 cm^2. The methods of procurement and storage time included fresh (61%), prolonged fresh (24%) and fresh frozen (15%). It was emphasized that osteochondral allograft transplantation for focal and diffuse (single compartment) chondral defects leads to predictably favorable outcomes and high satisfaction rates at intermediate follow-up. The major drawback of this technique is the use of fresh allogenic tissue, which has the potential for disease transmission. Cost and size mismatch are other issues, which should also be considered.

Autologous chondrocyte implantation

As an alternative for the treatment of articular cartilage injuries with a hyaline-like cartilage repair, Brittberg *et al*[48] were the first to report Autologous chondrocyte implantation (ACI) in 1994. Being a two-stage technique, the first stage in ACI involves an arthroscopic evaluation of the chondral lesion and biopsy by harvesting of chondrocytes. In this stage, cartilage is taken from lesser weight-bearing regions of the knee. The preferred locations are the lateral edge of the intercondylar notch or the superomedial trochlea. The total size of the biopsy should be between 200 and 300 mg. The cartilage specimens are sent to the laboratory for the chondroyctes to be isolated from the harvested cartilage. The cells are cultured for 2 wk to increase the number of cells as the implanted cartilage cells require a stable environment in which to heal. This procedure comes 6 wk after the biopsy. Following this, the second stage involves implantation through a mini-arthrotomy. Coverage is obtained by a periosteal patch sewn according to the defect size with 6-0 Vicryl sutures and sealed with fibrin glue. The aim is to achieve

a more durable "hyaline-like" repair tissue that resembles hyaline articular cartilage.

ACI can be used as the primary treatment choice in over 4cm^2, focal, ICRS grade Ⅲ and Ⅳ lesions of the knee joint and in patients with chondral defects who have a high activity demand, excellent compliance and are aged 15-55 years. It can be indicated as a second treatment in patients with 2.5 cm^2 unhealed lesions where microplasty or microfracture has been previously performed.

In a systematic review, Bekkers *et al*[49] concluded that for defects over 2.5 cm^2 in young patients, ACI can be performed successfully. In another study by Harris *et al*[50] microfracture (n = 271), mosaicplasty (n = 42) and ACI (n = 604) were compared in 917 patients. The clinical results of mosaicplasty were similar to those of ACI in the short term but worsened over a period of two years. In defects over 4 cm^2 in size, ACI was found to be superior to all the other treatments.

The ACI technique has better results in 70%-80% of patients not only in the short term but also in mid and long-term follow-up[51]. Moseley *et al*[52] showed that 69% of patients maintained the successful treatment results over 6-10 years. In a 5-year follow-up study, ACI was found to be better than microfracture in patients whose complaints had been ongoing for less than 3 years[53]. Mosaicplasty and ACI were compared in a 10-year follow-up study and the functional outcome of patients with a surviving graft was significantly better in patients who had undergone ACI compared with the mosaicplasty group[54].

Matrix induced chondrocyte implantation

In the ACI process, complications, such as graft hypertrophy seen while using periosteal patches, have led to increased interest in utilizing bioabsorbable covers as an alternative. One such technique is matrix-induced chondrocyte implantation (MACI). The MACI membrane involves a porcine-derived collagen bilayer, which is seeded with the patient's harvested chondrocytes. MACI is a two-stage technique, which includes an arthroscopic evaluation of the chondral lesion and biopsied arthroscopically in the first stage and implanted generally through an arthrotomy in the second stage which is also applied by arthroscopic surgery[55]. During implantation, the graft is secured to the defect by fibrin glue alone, without sutures. Although there are several implants, Cares®, Hyalograft®, NeoCart®, Novocart®, Bioseed C®, Chondron®, Cartipatch®, Atelocollagen® are examples of implants containing autologous chondrocytes, which have produced satisfactory clinical results[36].

Marlovits *et al*[56] reported 2 failures from 21 patients treated with ACI after 5 years and with MRI evaluation it was observed that in 80% of patients,defects had totally healed and integrated with peripheral chondral tissue. Eber *et al*[57] reported successful results in 20 patients treated with arthroscopic surgical technique and MACI after 2 years. The follow-up MRI showed 90% defect healing and 70% integration. Vijayan *et al*[58] observed good results in deep lesions > 8 mm with MACI, bone graft and double layer MACI. Several studies have compared MACI with current treatment options[59,60]. Basad *et al*[59] performed microfracture in 20 patients and MACI in 40 patients with a defect size over 4 cm^2 and reported that MACI was superior to microfracture in the treatment of articular defects over 2 years. The MACI technique represents a significant advance in terms of reproducibility, safety, and reduced invasiveness. Zeifang *et al*[60] found no difference in clinical results between ACI and MACI in 21 patients after 2 years. Both treatments had similar results but MACI had significantly better scores in chondral healing when evaluated by MRI.

CONCLUSION

Appropriate patient selection for articular cartilage lesion treatment is paramount to reduce symptoms and successfully improve function. In smaller lesions of up to 2.5 cm^2 in size, and in larger (up to 4 cm^2) lesions in low-demand patients, debridement and microfracture are the most commonly used techniques. In lesions up to 4 cm^2, and in high demand patients, AOT is a reliable method. Although indications of the use of microfracture plus scaffolds are not clear, this technique is commonly used in high demand patients with lesions of up to 4 cm^2. However, in larger lesions more sophisticated cell based techniques such as ACI or MACI should be use.

In this article a treatment algorithm were formulated to help guide the decision.

Cartilage restoration techniques will most certainly evolve over the next several decades. With the addition of biological scaffolds and gene therapy techniques, the future holds much promise for patients for the natural healing of articular cartilage lesions. Alternative tissue techniques will be available to replace damaged articular cartilage or modifications of existing technology will lead to better results or fewer complications. Moreover, continued advances in arthroscopic techniques will allow procedures,which are commonly performed through an open arthrotomy, to be performed arthroscopically.

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Muscle force and movement variability before and after total knee arthroplasty: A review

Jessica W Smith, Jesse C Christensen, Robin L Marcus, Paul C LaStayo

Jessica W Smith, Paul C LaStayo, Department of Bioengineering, University of Utah, Salt Lake City, UT 84108-1290, United States
Jessica W Smith, Jesse C Christensen, Robin L Marcus, Paul C LaStayo, Department of Physical Therapy, University of Utah, Salt Lake City, UT 84108-1290, United States
Paul C LaStayo, Department of Orthopedics, University of Utah, Salt Lake City, UT 84108-1290, United States
Paul C LaStayo, Department of Exercise and Sport Science, University of Utah, Salt Lake City, UT 84108-1290, United States
Author contributions: Smith JW contributed significantly to the intellectual content, review of the literature, and overall organization of the manuscript, as well as wrote the majority of the manuscript; Christensen JC contributed significantly to the intellectual content, review of the literature, and overall organization of the manuscript, and assisted in the writing of the manuscript; Marcus RL and LaStayo PC contributed to the intellectual content and interpretation of data.
Correspondence to: Jessica W Smith, PhD, Department of Bioengineering, University of Utah, 201 Presidents Cir, Salt Lake City, UT 84108-1290, United States. j.smith@utah.ed
Telephone: +1-801-5567360 Fax: +1-801-6067441
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Abstract

Variability in muscle force output and movement variability are important aspects of identifying individuals with mobility deficits, central nervous system impairments, and future risk of falling. This has been investigated in elderly healthy and impaired adults, as well as in adults with osteoarthritis (OA), but the question of whether the same correlations also apply to those who have undergone a surgical intervention such as total knee arthroplasty (TKA) is still being investigated. While there is a growing body of literature identifying potential rehabilitation targets for individuals who have undergone TKA, it is important to first understand the underlying post-operative impairments to more efficiently target functional deficits that may lead to improved long-term outcomes. The purpose of this article is to review the potential role of muscle force output and movement variability in TKA recipients. The narrative review relies on existing literature in elderly healthy and impaired individuals, as well as in those with OA before and following TKA. The variables that may predict long-term functional abilities and deficits are discussed in the context of existing literature in healthy older adults and older adults with OA and following TKA, as well as the role future research in this field may play in providing evidence-based data for improved rehabilitation targets.

Key words: Osteoarthritis; Elderly; Total knee arthroplasty; Movement variability

Core tip: Muscle force output and movement variability are important aspects of identifying individuals with mobility deficits, central nervous system impairments, as well as future risk of falling. These correlations have primarily been investigated in elderly healthy and impaired adults, as well as in adults with osteoarthritis (OA), but the question of whether the same correlations also apply to those who have undergone a surgical intervention such as total knee arthroplasty (TKA) are still being investigated. The variables that may predict long-term functional abilities and deficits are discussed in the context of existing literature in healthy older adults and older adults with OA and following TKA.

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INTRODUCTION

Knee osteoarthritis (OA) is the most common type of arthritis, affecting over 37% of Americans 60 years and older[1]. Of these, approximately 12% have symptoms[1] that frequently include pain and loss of motion, resulting in restricted activity, decreased neuromuscular control, impaired proprioceptive acuity, and loss of independence during activities of daily living[2,3]. When symptoms become severe as in late stages of OA, many individuals seek additional treatment interventions that often include the total knee arthroplasty (TKA) surgical procedure. Not surprisingly, the increasing prevalence of knee OA coincides with a growing demand for TKA procedures, with an expected 6-fold increase in surgeries by the year 2030[4]. In light of this heightened demand, the need for evidence-based rehabilitation protocols that maximize long-term physical and muscle function is critically important.

TKA is often effective for pain relief, but the outcomes of this surgical procedure do not often achieve similar, long-term improvements in both physical and muscle function[5-7]. To counteract these deficits, it is important to better understand how TKA may influence various physical and muscle performance parameters that predispose an individual to impaired function post-operatively. Muscle atrophy, muscle weakness, and neuromuscular activation deficits are all factors associated with functional impairments in adults with OA and there is a growing body of evidence suggesting that impairments in theses areas lead to variability in muscle force output and movement patterns both pre- and post-operatively. The implications of muscle force output and movement variability in the ability to perform functional tasks is underappreciated in the literature, but could hold value in understanding the ramifications of functional impairments, as well as developing focused rehabilitation protocols that improve long-term functional outcomes in the OA and TKA patient populations.

The purpose of this narrative review is to expose and summarize the current evidence related to variability in muscle force output and movement patterns that occur in older individuals with knee OA before and after TKA. The implications of variable muscle force output and movement during common mobility tasks will be highlighted. Further, the concept that variability may have advantages and disadvantages in individuals with knee OA and following TKA will be explored.

For the purposes of this review, variability is described in two contexts: (1) as the variability an individual displays in muscle force output measured by the amplitude of force fluctuations; and (2) as the intra-subject variability during mobility tasks such as level walking. The former includes tasks involving an isolated muscle group, such as the quadriceps, and the latter includes synergistic activities that involve coordinated involvement of several muscle groups such as required during level walking and stair stepping. More specifically, variability in muscle force output is measured as the force fluctuations relative to a given submaximal force target while performing a specific task. This concept applies not only to measures of muscle function, such as during isolated tasks that aim to evaluate fluctuations of motor output, but to functional tasks such as gait and stair stepping that aim to evaluate fluctuations of temporal, spatial, and kinematic outcomes. For instance, variability during level walking is a measure of the fluctuation in gait characteristics from one step or stride to the next, while variability in negotiating stairs can be witnessed when stepping from one step to the next. These concepts of variability are applicable to both muscle and physical function, as there are studies that have investigated measures of purely muscle force output variability, and others that have investigated movement variability. The one common theme, however, is that both types of investigations have aimed to identify links between the respective measures of variability and the ability to perform functional tasks efficiently[8-11]. Heretofore, the implications of greater or reduced variability relative to healthy controls, in older adults with OA before and after TKA, have not been previously reviewed.

The initial review of the literature for this narrative review involved a general internet search, as well as a search of PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) using several search terms. The initial search was performed to identify the breadth of information regarding variability of motor output, as well as during various movement tasks. Following this review, a more focused search strategy was used that included several keywords (*e.g.*, motor output, gait variability, muscle function, muscle force steadiness, arthrogenic muscle inhibition, stair stepping, TKA, and OA), which were applied to the CINAHL and MEDLINE databases. No specific filtering strategy was used for the types of article, although limits were used to include research in humans only, the English language, as well as dates between 1990 and 2013. Of the articles returned, related articles were also reviewed for relevancy, resulting in a review of articles published prior to 1990.

MUSCLE FORCE OUTPUT VARIABILITY

Diminished quadriceps strength in knee OA and following TKA is coupled to the ability to perform functional tasks that require adequate muscle strength and motor control to perform accurately and within a specified trajectory[12-14]. Neuromuscular activation deficits accompanied by declines in proprioception[15] and kinesthetic awareness are common manifestations of knee OA, and contribute to these strength deficits, as well as slower movement patterns[16-18] and reduced force steadiness[19-21] before and after TKA[7,14,18]. These adaptations result in diminished ability to exert a steady force output during submaximal efforts, such as those that are required during activities of daily living, as well as greater variability in movement patterns[14,20,22]. The importance of understanding how these impairments are altered following TKA is relevant to identifying variables that may be ben-

eficial targets of post-operative rehabilitation.

Arthrogenic muscle inhibition

A significant component of impaired muscle function is the presence of arthrogenic muscle inhibition (AMI), or the inability to fully activate the quadriceps muscle[23]. Quadriceps AMI is associated with changes in the discharge of afferent, articular sensory receptors resulting from swelling, inflammation, joint laxity, and damage to knee joint afferents, all of which are common symptoms of OA[24]. Swelling, in particular, has been shown to independently alter joint afferent discharge by increasing the firing frequency and recruitment of group Ⅱ afferents[25-27]. Not surprisingly, in the presence of swelling, the greatest muscle inhibition occurs at the extremes of motion, where intra-articular pressure and afferent discharge are the highest[28-34]. In turn, these changes in neuromuscular control are implicated in the ability to control motor output.

Inflammatory responses and joint laxity also contribute to quadriceps AMI by increasing joint afferent discharge; inflammation *via* sensitization of free nerve endings innervated by group Ⅲ and Ⅳ afferents[35-37], and joint laxity *via* increases in the activation of mechanoreceptors and nociceptors[24,38]. While nociceptive influences have some correlation to AMI, the relationship between AMI and pain is inconsistent[24] in patients with OA[39] as well as following TKA[40,41]. Indeed, research suggests that while the presence of pain may accompany AMI, inhibition occurs in the absence of pain as well[24,34]. Although this research has been useful in clarifying the role of nociceptive influences on AMI, the overall effects on muscle force output variability, as well as movement variability during specific functional tasks have not been identified.

In addition to the increases to joint afferent discharge discussed thus far, as described by Rice *et al*[24] these disruptions may be accompanied by simultaneous decreases in afferent output due to damage to articular receptors[38,42-44] and subsequent effects on reflex pathways within the spinal cord. The potential contributors to these reflex pathway adaptations include group Ⅰ nonreciprocal (Ib) inhibitors[45], interneurons associated with the flexion reflex[46-48], and dysfunction of the gamma (γ)-loop[24], with the overall effect being inhibition of the quadriceps α-motoneuron pool[38,43,44,49]. Research suggests that all of these pathways contribute to AMI, with the relative contributions dependent on factors such as the extent and location of joint damage, swelling, inflammation, and laxity[24,34].

In individuals with OA, the different neural mechanisms described above involve a series of complex innervation strategies that contribute to quadriceps AMI, motor output variability, and associated force control. Total knee arthroplasty, by nature, results in disruption of the joint capsule and ligamentous structures [either anterior cruciate ligament (ACL) or ACL and posterior cruciate ligament (PCL)], as well as alterations to joint motion and as a result, would be expected to influence mechanisms that contribute to AMI that rely specifically on afferent discharge from these structures. Although TKA has been shown to reverse some of the pre-operative impairments by improving proprioception and joint stability, similar improvements in muscle and mobility deficits following TKA persist. The significance of these neuromuscular changes in individuals that undergo TKA is not well understood. That is, the factors that influence the extent to which these changes affect muscle force output variability and movement variability following TKA have not been thoroughly investigated[34].

Muscle force steadiness

Lower extremity muscle force steadiness (MFS) has been identified as a potential marker of impairment during functional tasks such as walking endurance, chair rising and stair climbing[13]. Moreover, correlations between concentric and eccentric quadriceps force steadiness and aging, as well as between eccentric steadiness and falling in elderly adults have been reported[50]. Although these studies were not performed in subjects with OA, they provide a basis for understanding the relationship between force steadiness and functional abilities, and subsequently, insight into how they may be altered by deficits common in OA. A summary of research that has focused specifically on lower extremity motor output variability, also reported as force steadiness, in elderly adults, and in OA before and after TKA is included in Table 1.

In elderly adults, the ability to control lower extremity submaximal muscle forces has been shown to be an independent risk factor for increased risk of falling[13,50]. Carville *et al*[50] compared force steadiness between young and older adults and found that the younger, non-fallers were steadier than older fallers, with eccentric contractions showing the strongest correlation with falling. This finding was consistent with another study that showed that the CV of force steadiness for both isometric and anisometric (*i.e.*, concentric and eccentric) force output was greater in older adults compared to young adults[58]. Hortobágyi *et al*[52], however, showed increased muscle force variability in older adults during concentric and eccentric contractions, but not in isometric contractions. Furthermore, Tracy *et al*[22] showed a reduction in MFS during isometric, but not concentric and eccentric contractions in healthy older adults compared to young adults. The differences in these findings may be due to inconsistencies in the speed of contraction, as well as in the proportion of the target force relative to the subjects' MVIC. While these discrepancies may appear relatively minor, it is evident that they can have large consequences on the efficiency and control of motor output[13,53]. As an example, Seynnes *et al*[13] reported isometric steadiness was an independent predictor of chair-rise time and stair-climbing power, while Manini *et al*[53] demonstrated no correlation between isometric force steadiness and functional tasks including chair-rise time or time to ascend and descend stairs in older adults. The differences in these studies persist regardless of the fact that both employed an isometric force-matching task at 50% of

Table 1 Summary of the literature addressing muscle force output variability in older adults and those with osteoarthritis before and after total knee arthroplasty

Study	Population	Purpose/hypothesis	Variables assessed	Significant findings
Older adults with native, non-arthritic knees				
Carville *et al*[50], 2007	*n* = 44 (Young adults; Age range = 18-4 yr) *n* = 78 (Older adults; Age range > 70 yr)	To investigate isometric and anisometric quadriceps contractions in healthy you and older adults	Muscle strength; CV of isometric force steadiness at 10%, 25%, and 50% of MVC; and SD of acceleration of anisometric steadiness during concentric and eccentric contractions against two external loads of 1 and 5 kg	1. Non-significant trend for younger subjects to be most steady and fallers least study 2. Isometric force steadiness was unaffected by the level of force output. 3. Fallers were less steady than both young and non-fallers 4. Older adults were less steady during eccentric contractions than the younger adults and fallers were the least steady
Christou *et al*[51], 2002	*n* = 24 (Young, active adults; Mean age = 25.3 yr) *n* = 24 (Older active adults; Mean age = 73.3 yr)	To examine the ability to control knee-extension force during discrete isometric, concentric, and eccentric contractions	Muscle strength; Isometric force steadiness at 90 degrees of knee flexion; and Concentric and eccentric force steadiness at 25 deg/s	1. CV of force steadiness for all contractions was greater in older subjects than younger subjects 2. Muscle strength was similar for all three types of contractions Young subjects were stronger than older subjects
Hortobágyi *et al*[52], 2001	*n* = 27 (Older adults; Mean age = 72 yr) *n* = 10 (Young adults; Mean age = 21 yr)	To compare the effects of low- and high-intensity strength training o maximal and explosive strength and on the accuracy and steadiness of submaximal quadriceps force in elderly humans	Muscle strength Quadriceps force accuracy and steadiness during isometric, concentric and eccentric contractions performed at 25 N target force	1. Older subjects had significantly more force variability (*i.e.*, were less steady) during eccentric and concentric, but not isometric contractions 2. Force variability and accuracy were correlated with each other, but not with maximal strength 3. Training significantly improved force accuracy and variability during eccentric and concentric contractions
Manini *et al*[53], 2005	*n* = 50 (Healthy, older adults; Mean age = 76.2 yr)	To determine how knee extensor steadiness during an isometric task is related to performing four everyday tasks that included chair rising, walking at a fast pace, and stair ascending and descending	Isometric knee extensor steadiness at 50%MVC; Chair rise time Time to ascend and descend stairs; and Walking velocity	Isometric quadriceps force steadiness was not a predictor of functional performance in older subjects
Schiffman *et al*[54], 2001	*n* = 19 (Healthy older adults; Mean age = 71.8 yr) *n* = 20 (Healthy young adults; Mean age = 25.8 yr)	To investigate the effects of motion on submaximal force control abilities in the knee extensors	Isokinetic force variability at two different force levels; 20% of MVC and 60% of MVC	1. Isokinetic submaximal force control was equally diminished in both young and older adults compared to isometric force control 2. As the force level increased, force variability decreased for both young and older adults
Tracy *et al*[22], 2002	*n* = 10 (Healthy young adults; Mean age = 22 yr) *n* = 10 (Healthy older adults; Mean age = 72 yr)	To compare the steadiness and EMG activity of young and old adults while they were performing submaximal isometric and anisometric contractions with the knee extensor muscles	Muscle strength; EMG of quadriceps muscles during experimental tasks; and Isometric, concentric, and eccentric force steadiness for 10-12 s at 2%, 5%, 10%, and 50% of MVC	1. Steadiness of old adults was reduced compared with young adults during isometric, but not during concentric and eccentric contractions 2. Decline in steadiness was not associated with differences in EMG magnitude
Tracy *et al*[55], 2004	*n* = 26 (Healthy, older adults; Mean age = 77.7 yr)	To determine the effect of strength and steadiness training with heavy loads by old adults on the fluctuations in force and position during voluntary contractions with the quadriceps femoris muscles	Muscle strength (MVC); Force fluctuations during isometric contractions at 2%, 5%, 10%, and 50% of MVC; Force fluctuations during concentric and eccentric contractions at 5%, 10%, and 50% of MVC; EMG activity of the quadriceps muscles during	1. Force fluctuations during submaximal isometric contractions did not change with training 2. Force fluctuations during submaximal anisometric contractions with a 50% load declined for both heavy and light training groups

			experimental tasks; and Physical function tasks including gait speed, chair rise, and stair ascent and descent	
Seynnes *et al*[13], 2005	*n* = 19 (Healthy older women; Mean age = 77.9 yr)	To assess the relationship between knee-extensor force-control capacity, as measured by isometric force steadiness and accuracy, and functional limitations in healthy older adults	Isometric quadriceps force steadiness at 50% of MVC; MVC Rate of torque development; EMG activity; and Functional performance measures including walking endurance, chair rising, and stair climbing	1. Isometric steadiness independently predicts chair-rise time and stair-climbing power 2. None of the accuracy measures were significantly associated with any of the functional performance tests Walking endurance was related to muscle strength, but not steadiness
Older adults with osteoarthritic knees				
Hortobágyi *et al*[56], 2004	*n* = 20 (Older adults with OA; Mean age = 57.5 yr) *n* = 20 (Controls; Mean age = 56.8 yr)	To characterize the distribution of error in knee joint proprioception, quadriceps force accuracy and steadiness and muscle strength in patients with knee OA	Quadriceps force accuracy and steadiness during a force target-tracking task during anisometric contractions. Muscle strength was measured during eccentric, isometric, and concentric contractions	1. Knee OA subjects needed 67% more time to complete functional tasks, produced 82% more proprioception errors, and 89% more errors in accurately matching target forces 2. Knee OA subjects had 155% more force variability, with eccentric contractions being particularly unsteady
Sørensen *et al*[57], 2011	*n* = 41 (Older adults with OA; Mean age = 62 yr)	To investigate the relationship between quadriceps force steadiness and knee adduction moment during walking in patients with knee OA	Submaximal isometric quadriceps force steadiness during a force target-tracking task. Peak knee adduction moment during ambulation	Quadriceps force steadiness does not predict peak knee adduction moment
Older adults following total knee arthroplasty				
Smith *et al*[14] ,2013	*n* = 13 (Older adults with TKA; Mean age = 62.7 yr) *n* = 11 (Controls; Mean age = 62.2 yr)	To compare muscle force steadiness of submaximal quadriceps force output in individuals with knee OA before and after TKA, and to a group of age-matched controls with native knees	Muscle strength; Quadriceps muscle force steadiness (MFS) during anisometric eccentric and concentric contractions at 50% MVIC	1. Pre-operatively, quadriceps force steadiness for both concentric and eccentric contractions was significantly higher in the OA group relative to controls; and 2. Post-operatively quadriceps force steadiness for both concentric and eccentric contractions was significantly lower in the OA group relative to controls Muscle strength was significantly lower in the TKA group both pre- and post-operatively compared to controls

CV: Coefficient of variation; MVC: Maximal voluntary contraction; OA: Osteoarthritis; TKA: Total knee arthroplasty; EMG: Electromyographic signal.

MVIC. These discrepant findings underscore the need for further research to identify the associations between the ability to control submaximal muscle forces and specific functional tasks in order to identify specific rehabilitation targets.

To shed more light on potential relationships between force steadiness and functional performance, Hortobágyi *et al*[56] investigated lower extremity steadiness during submaximal isometric and anisometric contractions and showed that knee OA was associated with 155% more force variability and 67% more time to complete functional tasks than a group of age- and sex-matched controls without OA. In contrast, Sørensen *et al*[57] identified no relationship between quadriceps force steadiness and peak knee adduction moment during level walking in subjects with knee OA, suggesting that submaximal isometric MFS and knee joint loads during walking represent two distinctive pathways with independent influences on knee OA pathogenesis. These studies lend support for potential relationships between the ability to control submaximal muscle forces and functional tasks in individuals with OA, but the specific correlations remain to be clarified. Consequently, it must also be considered that MFS may represent a distinctive pathway that does not have broader applicability to functional tasks.

Thus far, MFS in both older adults and those with knee OA have been discussed and while the methodologies, level of force exerted, and type of contractions vary between studies, there appears to be an overall trend that some aspect of force steadiness is worse in both elderly individuals and those with OA compared to healthy young and age-matched controls. In this regard, Enoka *et al*[12] described mechanisms that may contribute to the amplitude of force fluctuations between young and old adults as being primar-

ily dependent on the behavior of motor units; namely, the motor unit force and discharge rate variability.

Total knee arthroplasty, by nature, involves the removal of damaged structures and has been reported to positively affect proprioceptive feedback in individuals with OA[14,59,60]. Additionally, evidence suggests that following TKA, - which type of prosthesis - PCL retaining or PCL sacrificing? How long after surgery? what was the rehabilitation program after surgery regarding physio? there is a significant improvement in MFS to a level that exceeds a group of healthy, age-matched controls without OA[14]. In this study, subjects were examined within one month prior to surgery and at 6-mo post-operatively and were not stratified by ligament retention status or type and extent of post-operative rehabilitation. The authors of this study showed that while quadriceps force steadiness was significantly worse before TKA compared to an age-matched, symptom-free group of controls, following TKA, steadiness improved to a level that exceeded healthy controls[14]. These results raise an important question about motor output variability, *i.e.*, is there a level of steadiness that is too low and corresponds to impaired, rather than improved movement ability, and that may have implications for functional tasks? Certainly, a better understanding of how these changes in force control and steadiness following TKA correlate with other functional performance parameters could direct the development of future intervention strategies and improve long-term TKA outcomes.

MOVEMENT VARIABILITY

Similar to MFS, greater movement variability in elderly individuals as well as in those suffering from OA, is generally considered representative of a pathological or impaired state and has been associated with reduced function and future risk of mobility deficits[61,62]. For example, Brach *et al*[62] used stance time variability (STV) during level walking to identify an optimal level of gait variability, above which was an indicator of prevalent mobility disability. And although these findings are well-correlated in the literature, the implications of reduced variability relative to healthy, age-matched controls have received little attention. The next section aims to explore the implications of both increased and decreased movement variability in those with OA before and after TKA. To assist in this review, Table 2 presents an overview of the current literature regarding movement variability during level walking in these patient populations.

Level walking variability

Gait is a multifaceted and complex task that requires coordinated movement between both central and peripheral neuromuscular control mechanisms. And while variability during gait has been shown to be associated with incident fall risk in elderly adults[66], and predict mobility deficits in different populations[62,66]_ENREF_62 , there are conflicting reports on which variables are associated with these functional parameters. These inconsistencies only serve to propagate the lack of consistent and effective rehabilitation protocols for both individuals with knee OA as well as following TKA.

Muscle function and proprioceptive deficits associated with knee OA have been suggested to contribute to altered, spatio-temporal, kinematic, and kinetic gait patterns compared to individuals without OA[61,71-75]. The resulting gait pattern is characterized by slower gait speed and cadence, reduced stride length, and altered movement patterns that are particularly evident during the loading phase of the gait cycle[61,73,75]. However, since OA represents an increased level of pathology with associated neuromuscular changes beyond those that may be associated with aging alone, it is important to first clarify the changes in movement variability that may occur in older adults without OA.

Researchers have investigated several measures of gait variability in older adults to identify meaningful changes that may be associated with disability or impairment, which included the standard deviations (SD) of step width, stance time, swing time, and step length[61,63]. The results showed that increased STV is a predictor of central nervous system impairments[61] and mobility disability in elderly community-dwelling adults[62,64]. In a similar study, variability of gait was assessed in 100 frail community-dwelling adults by using velocity and cadence, as well as the CV of stride time, step width, double support time, and stride length as the predictor variables. The authors found that regulation of gait was impaired in older adults and that frailty was associated with higher variability of all gait parameters[76]. Callisaya *et al*[66] also investigated gait variability in older adults, but with the purpose of correlating gait measures with risk of falling. The authors assessed the relationship between the SD of velocity, cadence, step length, step width, step time, and double support phase with incident fall risk and found non-linear associations between velocity, cadence, and step time variability with multiple falls, although, none of the variables predicted risk of single falls[66].

The breadth of literature regarding gait variability in older adults is largely consistent across studies; *i.e.*, greater variability equates to greater impairment, and based on the known deficits that accompany OA, these findings would be expected to be consistent in individuals with OA. In fact, gait variability has been correlated with severity of OA[9,71]_ENREF_75, as well as risk of future falls and gait instability before and after TKA[11,69,72,77]. As an example, Lewek *et al*[10] investigated 15 subjects with unilateral OA and 15 age and gender-matched controls to quantify frontal plane, knee motion variability, which was assessed by the phase angle (knee angle *vs* angular velocity) during early stance phase of level walking. The authors found that despite altered involved side knee kinematics and kinetics, there were no differences between frontal plane variability between the two groups. In fact, the variability in the involved limb was significantly lower than the variability of the uninvolved knee's mo-

Table 2 Summary of the literature addressing gait variability in older adults and those with osteoarthritis before and after total knee arthroplasty

Study	Population	Purpose/hypothesis	Variables assessed	Significant findings
Older adults with native, non-arthritic knees				
Brach *et al*[62], 2012	*n* = 552 (Older adults; Mean age = 79.4 yr)	1. Determine the magnitude of STV that discriminates individuals who currently have mobility disability. Determine the magnitude of STV that predicts a new onset of mobility disability at 1 yr	Gait Variability: Stance time variability Self-reported walking disability	1. Values of STV may be useful in recognizing mobility disability and future disability 2. Recommend using 0.034 s as the cutoff
Brach *et al*[63], 2010	*n* = 241 (Older adults; Mean age = 80.3 yr)	1. To estimate clinically meaningful change in gait variability over time. Greater gait variability is a predictor of future falls and mobility disability	Gait Variability: Step width, Stance time, Swing time, Step length	Preliminary criteria for meaningful change are 0.01 s for stance time and swing time variability, and 0.25 cm for step length variability
Brach *et al*[61], 2008	*n* = 558 (Older adults; Mean age = 79.4 yr)	1. CNS impairments will affect motor control and be manifested as increased stance time and step length variability. Sensory impairments would affect balance and manifest as increased step width variability	Gait Variability: Step width, Stance time, Step length, Strength Measures: Grip strength, Repeated chair stands	CNS impairments affected stance time variability especially in slow walkers, while sensory impairments affected step width variability in fast walkers
Brach *et al*[64], 2007	*n* = 379 (Older adults; Mean age = 79 yr)	To determine if gait variability adds to the prediction of incident mobility disability independent of gait speed	Gait speed, Step length, Stance time, STV	1. After adjusting for gait speed and other comorbidities, only stance time variability remained an important indicator of disability 2. STV of 0.01 s was associated with a 13% higher incidence of mobility disability
Brach *et al*[65], 2005	*n* = 503 (Older adults; Mean age = 79 yr)	To examine the linear and nonlinear associations between gait variability and fall history in older persons and to examine the influence of gait speed	CV of step width, CV of step length, CV of step time, CV of stance time, Gait speed, Fall history	1. Step width variability had the highest correlation with fall history, which only existed in subjects that walked > 1.0 m/s 2. Step length, stance time, and step time variability were not associated with fall history
Callisaya *et al*[66], 2011	*n* = 411 [Older adults; Mean age = 72.6 yr (lost to follow-up); 71.2 yr (no falls); 72.3 yr (single fall); 73.9 yr (multiple falls)]	To investigate the associates of gait and gait variability measures with incident fall risk	Gait Variability: Step length, Step width, DSP, Gait speed, Cadence, Step time	Associations with multiple falls were present for gait speed, cadence and step time variability
Maki *et al*[67], 1997	*n* = 75 (Older adults; Mean age = 82 yr)	To determine whether specific gait measures can predict the likelihood of experiencing future falls or whether they are more likely to be indicative of adaptations associated with pre-existing fear of falling	Gait Variability: Stride length, Stride width, Stride period, Double-support, Stride velocity	1. Stride-to-stride variability in gait is a predictor of falling 2. Wider stride does not increase stability but does predict an increased likelihood of experiencing falls
Older adults with osteoarthritic knees				
Lewek *et al*[10], 2006	*n* = 15 (Older adults with OA; Mean age = 48.7 yr); *n* = 15 (Controls; Mean age = 48.4 yr)	Quantify the variability of knee motion in patients with medial knee OA	Joint kinematics and kinetics, Knee motion variability, Knee joint laxity, Co-contraction index	Patients with medial knee OA displayed altered kinematics and kinetics
Kiss *et al*[68], 2011	*n* = 90 (Older adults with moderate or severe OA; Mean age = 68.9 yr) *n* = 20 (Controls; Mean age = 70.7 yr)	To clarify how the variability of gait parameters is influenced by the severity of knee OA	Gait variability: Stride length, Stride width, Speed, Cadence, Duration of double-support, Duration of support	1. Variability of gait associated with knee OA is gender-dependent 2. Severity of OA affects step length, duration of support and cadence

Older adults following total knee arthroplasty				
Kiss *et al*[69], 2012	*n* = 45 (Older adults with TKA; Median age = 68.3 yr) *n* = 21 (Controls; Median age = 76 yr)	To evaluate the influence of different surgical techniques on gait variability and stability	Gait Variability: Stride length, Stride width, Speed, Cadence, Duration of double-support, Duration of support	1. Type of surgical technique influences gait variability and stability 2. Differences in the variability of angular parameters predict gait instability and increased risk of falling after TKA
Fallah-Yakhdani *et al*[11], 2010	*n* = 16 (Older adults with TKA; Mean age = 62.3 yr) *n* = 12 (Healthy, older adults; Mean age = 62.0 yr)	To evaluate treadmill walking at various speeds in OA patients pre- and post-TKA, to assess dynamic stability and variability of sagittal knee movements	Knee motion variability as measured by the angular velocity of sagittal knee movements; Walking speed; and Variability of knee movements	After TKA, knee motion variability decreased and was related to a reduction of fall risk. Stability control was also improved after surgery
Fallah-Yakhdani *et al*[70], 2012	*n* = 14 (Older adults with TKA; Mean age = 62.3 yr) *n* = 12 (Healthy, older adults; Mean age = 62.0 yr) *n* = 15 (Healthy, young adults; Mean age = 22.9 yr)	To identify the determinant of co-contractions during gait in patients with knee OA before and 1 year after TKA	Gait speed at seven different speeds (0.6-5.4 km/h) EMG activity Variability of angular velocity of sagittal knee movements over the first 30 strides at each speed	1. Variability of sagittal plane knee movements (measured in deg/s) increased with speed; 2. Pre-operatively, the patients' affected and unaffected legs were less variable than those of the young controls and the affected leg was less variable than the healthy peers 3. Post-operatively, variability in the knee OA group was further decreased to a level significantly below both control groups

CV: Coefficient of variation; OA: Osteoarthritis; TKA: Total knee arthroplasty; STV: Stance time variability; CNS: Central nervous system.

tion. Fallah-Yakhdani *et al*[11] also showed reduced variability during level walking in a study of individuals with OA before and after TKA. In this study, measurements of the variability in knee angular velocity in the sagittal plane before and at 1 year following TKA were performed. The results showed a positive correlation between reduced stride-to-stride variability and reduced risk of falling, and pre-operatively, OA subjects had reduced variability, which was even more pronounced post-operatively, compared to the healthy controls. The pre-operative findings, which appear contrary to expectations, were hypothesized as being the results of a strategy to avoid falling, as opposed to a sign of pathology. The authors, however, did not have a definitive explanation for the continued decline in variability post-operatively. Even so, these results were supported by findings by Kiss *et al*[69], who found that in individuals with unilateral OA, variability of articular motion decreased post-operatively compared to healthy controls, and similarly, Smith *et al* (unpublished data from the author's lab) showed that gait variability, as assessed by the CV of STV, declined in subjects with OA from the pre- to 6 mo post-operative time points and was significantly lower than a group of healthy controls at the 6 mo post-operatively. Although it is recognized that the specific measures of variability were different between these studies, the relevance of the findings are not diminished in that there appears to be a consistent pattern of decreased movement variability post-TKA relative to pre-operative values and healthy controls.

DISCUSSION

Based on the current evidence, both motor output and movement variability appear to be underappreciated outcome measures that could be linked to physical function both pre- and post-operatively. The evidence in elderly individuals, as well as in those with OA trends toward greater variability equating to greater mobility impairments. However, the alternative question of whether reduced variability, *i.e.*, variability that is less than a healthy, age-matched cohort, also indicates pathology remains unanswered. While data are present that suggest a trend toward reduced motor output and gait variability following TKA, this has not been correlated with functional outcomes, and in fact, some data suggest that reduced variability is associated with a reduced fall risk. Yet, this correlation is only present in older adults with and without OA prior to surgery; the relationship following TKA has not been established.

The question of reduced variability is an interesting one, in that it appears there may be a natural frequency for which individuals move, which serves a specific strategy to optimize balance and proprioception, and reduce the risk of falling. This strategy is likely affected by a variety of factors that may include age, sex, strength, activity level, and degree of pathology.

When considering the ability to respond to sudden balance perturbations, such as those that may occur when walking down stairs, it is theorized that a greater flexibility and available range of motion may be beneficial, thus suggesting that variability that is less than a group of healthy, age-matched controls, may equate to some level of pathology as well. Another potential explanation for the reduced variability following TKA is the influence of co-contraction of antagonist muscles during movement[10]. Evidence suggests that in individuals with medial knee OA, co-contraction is used as a stabilization strategy during gait to reduce joint excursions. However, this level of co-contraction does not persist following surgery; Fallah-Yakhdani *et al*[70] showed that following TKA, co-contraction is similar to that of healthy controls. Although, additional analysis revealed a negative regression between the affected side variability and unaffected side co-contraction time, leading the authors to surmise that at least some relationship exists between increased co-contraction and decreased variability. Thus, while it makes sense that this strategy may persist post-operatively, the correlation is notably weak and suggests the influence of other potential mechanisms to control motion and improve balance, when the quadriceps have not yet achieved a level of strength that is commensurate with age-matched controls.

When considering knee implant design, the obvious rigidity of the joint compared to a natural joint may impair the ability to respond to rapid perturbations and hence, may reduce movement variability, although, this cannot be elucidated from the available data. Nonetheless, the development of knee implant designs that incorporate greater range of motion in all planes lends support for this theory and may provide a way to test this hypothesis in the future.

CONCLUSION

Muscle force output and movement variability are important outcome variables that can be used to understand the effects of not only pathological conditions, but surgical interventions such as TKA as well. Movement variability has implications for identifying those at risk of future mobility deficits, fall risk, as well as correlating with severity of OA. In both elderly individuals and those with OA, increased motor output variability tends to implicate greater pathology, which would imply that greater variability, particularly during level walking, has a negative impact on physical function. While the evidence mostly supports this conclusion, it does not answer the question of how reduced variability, below that of an age-matched group of controls, may relate to the same deficits. There are limited data in individuals with knee OA who have undergone TKA, but research that has investigated this population, shows a general trend of reduced post-operative MFS and variability during level walking compared to healthy, age-matched controls. Indeed, if the variability in healthy, age-matched population is considered normal or ideal to optimize mobility function and efficiency, the reduced variability in a TKA population may imply impairment, similar to those with greater variability. Additional research investigating this link may provide an important rehabilitation target, or direct development of different implant designs.

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Perioperative pain control after total knee arthroplasty: An evidence based review of the role of peripheral nerve blocks

Thomas Danninger, Mathias Opperer, Stavros G Memtsoudis

Thomas Danninger, Stavros G Memtsoudis, Department of Anesthesiology, Hospital for Special Surgery, Weill Medical College of Cornell University, New York, NY 10021, United States
Mathias Opperer, Department of Anesthesiology, Perioperative Medicine and Intensive Care Medicine, Paracelsus Medical University, Salzburg 5020, Austria
Author contributions: Danninger T, Opperer M and Memtsoudis SG contributed equally to this work.
Correspondence to: Stavros G Memtsoudis, MD, PhD, FCCP, Department of Anesthesiology, Hospital for Special Surgery, Weill Medical College of Cornell University, 535 East 70th Street, New York, NY 10021, United States. memtsoudiss@hss.edu
Telephone: +1-212-6061206 Fax: +1-212-5174481
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Abstract

Over the last decades, the number of total knee arthroplasty procedures performed in the United States has been increasing dramatically. This very successful intervention, however, is associated with significant postoperative pain, and adequate postoperative analgesia is mandatory in order to allow for successful rehabilitation and recovery. The use of regional anesthesia and peripheral nerve blocks has facilitated and improved this goal. Many different approaches and techniques for peripheral nerve blockades, either landmark or, more recently, ultrasound guided have been described over the last decades. This includes but is not restricted to techniques discussed in this review. The introduction of ultrasound has improved many approaches to peripheral nerves either in success rate and/or time to block. Moreover, ultrasound has enhanced the safety of peripheral nerve blocks due to immediate needle visualization and as consequence needle guidance during the block. In contrast to patient controlled analgesia using opioids, patients with a regional anesthetic technique suffer from fewer adverse events and show higher patient satisfaction; this is important as hospital rankings and advertisement have become more common worldwide and many patients use these factors in order to choose a certain institution for a specific procedure. This review provides a short overview of currently used regional anesthetic and analgesic techniques focusing on related implications, considerations and outcomes.

Key words: Regional anesthesia; Peripheral nerve blockade; Total knee arthroplasty; Perioperative pain control; Postoperative outcome

Core tip: Over the last decades, the number of total knee arthroplasty procedures performed has increasing dramatically. This very successful intervention, however, is associated with significant postoperative pain, and adequate postoperative analgesia is mandatory in order to allow for successful rehabilitation and recovery. The use of regional anesthesia and peripheral nerve blocks has facilitated and improved this goal. In contrast to patient controlled analgesia using opioids, patients with a regional anesthetic technique suffer from fewer adverse events and show higher patient satisfaction. This review provides a short overview of currently used regional anesthetic and analgesic techniques focusing related implications, considerations and outcomes.

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INTRODUCTION

Over the last decades, major orthopedic procedures have been increasingly performed throughout the United

States. Specifically, total knee arthroplasties (TKA) have risen in volume by 154% between 1993 and 2011[1]. Projections suggest that the same trend will continue over the next decades, resulting in a demand of 3.48 million TKAs in 2030[2]. In order to appropriately meet this demand and provide comprehensive patient care physicians performing TKA need to keep in mind that this procedure is associated with severe postoperative pain and effective postoperative analgesic care is therefore mandatory. Regional anesthesia, and specifically the application of peripheral nerve blocks, has undergone significant developments over the last decade while proving its effectiveness and superiority over other traditional techniques. In this context it must be mentioned that the use of peripheral nerve blocks for TKAs remains underutilized[3], thus pointing to a significant potential for growth and expansion. Most recently, the use of ultrasound guidance has become more popular, resulting in the refinement of many nerve block techniques and more expansive utilization. Numerous publications have documented advances in respect to increases in safety, the use of decreased volumes of local anesthetics as well as improved onset times, prolonged duration of the blockade and/or a reduced length of stay[4-8]. Moreover, imaging technique and other necessary resources such as needles, catheters or infusion pumps have been improved in regard of their design as well as the material used[9-11].

Despite this progress, there is an ongoing discussion in the literature which type of block (or combinations thereof) is best for preventing postoperative pain, while facilitating rehabilitation and postoperative mobilization, reducing time to hospital discharge, enhancing cost effectiveness, and reducing the risk for complications (*e.g.*, inpatient falls) in TKA patients[12-14]. Various approaches to the performance of peripheral nerve blocks for postoperative pain control in patients undergoing TKA have been described in the literature; this includes the lumbar plexus block, the femoral nerve block, with or without a concomitant sciatic nerve block and the saphenous nerve block[12,15-19]. In addition, there is still a conflicting discussion in the regional anesthesia community whether a peripheral nerve block should be performed as a single-shot or as a continuous peripheral nerve block using a catheter.

This review aims to give an overview of peripheral nerve blocks currently used for postoperative analgesia in patients undergoing TKA, while assessing their impact on various outcomes. While some variations of the blocks discussed in this article exist; this review will focus on the most commonly used block techniques. Furthermore, we may summarize benefits and drawbacks for different approaches (*e.g.*, single shot *vs* continuous approach) in regard of side effects, complications and economic factors, such as cost effectiveness. In order to provide a focused discussion on the topic, the article, will only focus on peripheral blocks and not engage the field of neuraxial anesthesia and analgesia, which is also considered a regional anesthetic approach, but is more commonly although not exclusively used for effective intraoperative anesthesia.

PERIPHERAL NERVE BLOCKS USED FOR TKA

Lumbar plexus block

In the early 1970s, Winnie and colleagues introduced 2 different approaches to the lumbar plexus[20,21]. While the anterior approach failed to provide blockade of the obturator or lateral cutaneous femoral nerve, the posterior approach provided sufficient analgesia of the lumbar plexus[18]. The latter approach has been modified using various lumbar levels as a landmark for needle insertion as well as different distances from the spinous process[22]. Moreover, the use of ultrasound for regional anesthesia has become more widely available, thus providing and alternative to the traditional landmark guided approach towards the lumbar plexus block[23].

Technique: The L4 approach was described by Capdevila *et al*[24] and modified by the New York School of Regional Anesthesia, and includes the following landmarks: the spinous processes serve to define the midline at the level of the iliac crest (intercristal line, level of L4), the needle is inserted 4 cm lateral to the intersection of the midline and the iliac crest using nerve stimulation. A successful block will be achieved when local anesthetic is injected in the fascial plane of the psoas compartment; twitches of the quadriceps muscle using the nerve stimulator indicate the appropriate depth[25]. In 2001, Kirchmair *et al*[23] published a detailed description of the sonoanatomy of the lumbar plexus. They introduced a paramedian sagittal scan technique to identify the psoas muscle between L3-5. The needle is again inserted approximately 4 cm from the midline. The ultrasound guided technique described above, thus uses a similar approach as the landmark guided technique; it does, however, provide the benefits of ultrasound guidance including visualization of the needle as well as of the local anesthetic spread during injection.

Implications, considerations and outcomes: In regard to the use of a lumbar plexus block for total knee arthroplasty, some drawbacks have to be considered (Table 1). The block represents a clinically advanced technique with the potential for serious complications[26]. The main risk is derived from the close relation of important anatomical structures to the lumbar plexus, *i.e.*, proximity of the epidural space, the retroperitoneum or the kidney. Epidural spread leading to high neuraxial anesthesia, mislead catheters (epidural space) as well as kidney injuries have been reported[26-28]. Moreover, this technique should be avoided in anticoagulated patients to the lumbar plexus' location within the psoas muscle and risk of hematoma formation and subsequent nerve injury[29,30]. A large volume of local anesthetic is needed to provide sufficient anesthesia and postoperative analgesia; this fact may be one reason for reports of local anesthetic toxicity associated with lumbar plexus blocks[31]. Furthermore, when using ultrasound guidance, the user should have advanced skills as it may be challenging to obtain optimal images according to the

Table 1 Overview of block characteristics

Block	Landmarks	Ultrasound guidance	Catheter technique	Benefits
Lumbar plexus block	Spinous process iliac crest (L4) needle insertion 4 cm from midline	Paramedian sagittal L3-L5 identification of psoas muscle needle insertion 4cm from midline	Not widely used not practical	Some evidence for benefit in regard of early recovery and opioid consumption
Femoral nerve block	Inguinal ligament inguinal crease femoral artery	Transverse direction femoral crease identification of femoral artery and femoral nerve	Superior to single shot after 24 h	Easy to learn safe to use
Saphenous nerve block	United States guidance preferred	Midthigh identifying sartorius muscle anteromedial to femoral artery		Easy to learn safe to use
Sciatic nerve block	Classic approach: greater trochanter posterior superior iliac spine needle insertion 4 cm distal to the mid of the drawn line	Anterior approach: proximal end of medial thigh nerve beneath aducctor magnus muscle and femur	FNB catheter neccesary classic approach not well suited for catheters	Classic approach - easy to perform - high success rate

depth of the plexus and the anatomical structures in the neighboring area.

Following TKA, early remobilization and physiotherapy is a crucial part of the recovery process. The downside of this practice still lies in dreaded complications like inpatient falls. Therefore, the goal of regional anesthesia in this context must be a balance between the most effective pain relief and-at the same time–a minimal amount of motor blockade. In terms of postoperative outcomes, only very limited data for lumbar plexus blocks for total knee arthroplasty are available[32,33]. There is at least some evidence that the use of a continuous lumbar plexus blockade may be beneficial for early recovery. Watson *et al*[32] reported improved early recovery of patients receiving a continuous lumbar plexus block while simultaneously achieving a reduction in morphine consumption when compared with a single shot blockade. Lee *et al*[33] provided similar results; they compared pain scores over 48 h [continuous lumbar plexus block *vs* intravenous patient controlled analgesia (Ⅳ PCA)]. There were no differences in the first 6 h, whereas significant lower pain scores were found at 24 and 48 h, respectively. Consequently, nausea and sedation occurred more frequently in the Ⅳ PCA group. A difference in rescue analgesic consumption was however not observed. Indeed, lumbar plexus block might be used as an approach for regional anesthesia in patients undergoing TKA; there is however a potential for serious complications, moreover, advanced skills to perform the block are necessary. As a consequence, this block is not widely used.

Femoral nerve block

The femoral nerve block (FNB) is currently deemed to be the analgesic of choice when used for postoperative analgesia in patients undergoing TKA. It was first described in the 1920's by Labat[15]. FNBs are well studied and used in patients undergoing TKA to provide sufficient postoperative analgesia; this may be due to some advantages of this technique. Regardless if a single shot or continuous approach is chosen, a FNB is relatively simple to perform and therefore easy to learn; it has shown to have high success rates and carries a low risk for complications. FNBs can be performed using either nerve stimulator technique or ultrasound guidance; the latter technique has evolved over the last decade and is gaining popularity rapidly.

Technique: In contrast to lumbar plexus blocks, there is a well-defined insertion site for the FNB[34]: it is based on 3 landmarks: inguinal ligament, inguinal crease, and femoral artery. Using a nerve stimulator, the needle is inserted at the lateral margin of the artery in a sagittal, slightly cephalad plane; patella twitches, indicating quadriceps muscle stimulation and consequently the correct injection site, must be obtained before administrating the local anesthetic. For placing a nerve catheter, the technique is similar; however, a reduced insertion angle of the needle may facilitate advancement of the catheter. Using ultrasound guidance, it is however not necessary to palpate the femoral pulse as the artery needs to be visualized[35]. The transducer is positioned in a transverse direction, close to the femoral crease. After identifying the femoral artery and the femoral nerve using an in-plane technique, the needle is advanced towards the nerve. As soon as the needle tip is adjacent to the nerve, a small dose is administered to confirm the correct position by visualization of adequate spread. If the spread of local anesthetic is confirmed surrounding the nerve, the complete volume can be injected. A nerve stimulator may be used in addition to ultrasound guidance. Inserting a nerve catheter in the ultrasound guided setting, may be facilitated through a helper, as the catheter position should be visualized during advancement.

Implications, considerations and outcomes: An abundant amount of literature is available on the use of FNBs, for both regarding single shot blockade and continuous catheter techniques. Much of the literature suggests that a FNB facilitates recovery, improves early mobilization and reduces morphine consumption during the perioperative period when compared with other approaches[19,36]. It has shown that a single shot FNB can provide sufficient analgesia for pain with activity during the first 24 h, thereafter a continuous catheter technique is of advantage if

prolonged analgesia is desired compared to a single shot blockade[37]. The use of an indwelling catheter in an inpatient setting after TKA has been well described while it may be challenging to provide continuous FNB catheters in an outpatient setting[38,39]. More resources, such as a well-trained acute pain team or on call anesthesiologists are needed. One of the major drawbacks may consist in a belated awareness of complications[40]; moreover falls may occur more frequently if the patient is discharged home early. Some institutions, including leading centers for regional anesthesia, do not provide such services on an ambulatory basis due to those limitations. In contrast, the use of FNB catheters in an inpatient setting is well established. However, catheter dislodgment, nerve injury or prolonged motor weakness resulting in falls may also occur during the course of the patient's recovery[13,41,42]. Although exceedingly rare and with limited consequences if treated, an increased infection rate for catheters may be of concern; bacterial contamination is common 48 h after placement[43].

In terms of block safety, FNB is associated with a low complication rate and a low incidence of related long-term adverse effects. In general, neurologic complications after peripheral nerve blocks are low with a range reported between 0.3% and 2.07%[44-47]. Data on long-term outcomes beyond 6 mo are very limited, mainly due to limitations in study design (*i.e.*, follow up period) and high numbers needed to identify these already rarely occurring adverse effects. Moreover, neurological complications, which are attributable to the peripheral nerve block, are likely to be resolved within one year after the procedure. Recently, Widmer *et al*[41] reported an incidence of nerve injury of 1.94% in a retrospective analysis, ranging in the upper zone, which was previously described for femoral nerve blocks. The neurological symptoms lasted on average longer (25 mo) than previous studies have suggested. Interestingly, patients receiving a nerve catheter reported significantly fewer neurological adverse events than those receiving a single shot technique (0.93% *vs* 2.66%, P = 0.01). There are, however, some limitations to this study (retrospective, small sample size to determine rare adverse events) and data therefore have to be interpreted with caution. As an additional consequence of a FNB, a reduction in the quadriceps muscle strength of up to 80% can be observed[48]. Various attempts to counteract this effect, including a reduction in volume and/or dose of local anesthetic administered, blockade on a more distal level (saphenous nerve, see below) or manipulation of the location of the catheter tip have been performed with variable success[49-51]. Ilfeld *et al*[13] re-analyzed and pooled the data of three separate trials, which have – analyzed independently–not shown a significant difference between sham FNB and active FNB in regard to inpatient fall risk, which is viewed as a major complication associated with potential quadriceps weakness. However, in the pooled analysis a significantly higher fall rate for active FNB has been encountered. It remains, however, the subject of current research if a peripheral nerve block indeed is a strong contributor to inpatient falls. In a recent population based analysis including more than 190000 patients, Memtsoudis *et al*[52] did not find an increase in the odds for inpatient falls when a peripheral nerve block was placed, suggesting that in real world practice with the existence of fall prevention programs and other precautionary measures the reduction in muscle strength may be adequately considered and managed. One can conclude that a careful choice of the anesthetic technique is always warranted and the decision has to be made after carefully weighing pro/contra of each technique.

Saphenous nerve block

The saphenous nerve block (SaphNB, also referred to as adductor canal block) is a modification of the FNB discussed above[53]. The SaphNB has been gaining popularity in the anesthesia community over the last few years, particularly supported by the increased use of ultrasound. The saphenous nerve is the terminal sensory branch of the femoral nerve. It is located within the adductor canal in conjunction with a branch of the femoral artery; it further divides into two branches, the infrapatellar branch supplies the anteromedial area of the knee, the sartorial branch travels further distally and provides innervation of the medial area of the leg and ankle[54]. Motor weakness, which has been traditionally linked with regional anesthesia with FNB, is still under suspicion to contribute to dreaded complications like inpatient falls[13]. Therefore, a more sensory specific approach may have its advantages provided the analgesic potency is equally comparable to other block techniques. Mansour provided one of the first descriptions for a more sensory specific block (rather than a FNB) for orthopedic surgery using the subsatorial approach in the 1990ies[55]. He described a landmark technique including the use of a nerve stimulator. The development of the technique and the success rate of the SaphNB were facilitated through the emerging use of ultrasound.

Technique: The SaphNB is typically performed using ultrasound guidance[56]; higher success rates and better performance measures have been reported[57]. Nerve stimulation may be used in addition to confirm the correct needle position, by showing absence of motor activity. The transducer is placed on the mid-thigh identifying the sartorius muscle. It is then moved to an anteromedial position with the goal of identifying the branch of the femoral artery. As soon as the course of the femoral artery is confirmed, the needle is advanced towards the femoral artery using an in-plane technique. The needle tip should be visualized right next to the femoral artery. After careful aspiration, a small amount of local anesthetic is injected to confirm the correct needle location. As the saphenous nerve is rarely visualized, the local anesthetic solution is administered periarterially.

Implications, considerations and outcomes: The SaphNB provides some advantages over a conventional

FNB (Table 1). If performed at the proper level, motor weakness of the quadriceps muscle, *i.e.*, vastus medialis muscle, might be reduced or even be non-existent. The branch of the femoral nerve innervating the vastus medial muscle lies, however, also within the adductor canal[58]; it exits the canal more proximally. The correct needle insertion site as well as low volume of local anesthetic is therefore mandatory to avoid motor weakness. By using ultrasound guidance, the SaphNB has a low complication rate[59]; the block itself is relatively easy to learn and shows a high success rate. It is however not yet clear if the SaphNB has the equal anesthetic potency compared with a FNB; moreover, the theoretically possible reduction in motor weakness is not yet confirmed. A recent clinical trial by Jaeger *et al*[51] shows however promising results. More randomized controlled clinical trials are needed to determine whether those advantages may be provided through the SaphNB.

Sciatic nerve block

The sciatic nerve block (SNB) has undergone a controversial debate in the literature in regard of its usefulness for patients undergoing TKA. It is most commonly considered to treat posterior knee pain after TKA. The posterior approach to the sciatic nerve was first described by Labat[15]. Since then, it has been modified multiple times, however, the clinical impact of those modifications remains uncertain[60-63]. Nonetheless, the classic posterior approach remains to be used most commonly and will be referred to for the purposes of the review.

Technique: The landmark guided approach for the classic SNB includes the greater trochanter and the posterior superior iliac spine[64]. The needle insertion point may be found approximately 4 cm distal to the mid of a line drawn between the two anatomic landmarks. The needle is inserted perpendicular to the skin and advanced slowly. Twitches of the gluteal muscle are observed first; as soon as a response to the sciatic nerve (hamstring, calf, foot or toes) is obtained, the current is decreased. After negative aspiration, the local anesthetic may be injected slowly. Similar to most other nerve blocks, the posterior approach to the sciatic nerve may also be performed using ultrasound guidance[65]. Alternatively, the anterior approach using ultrasound guidance can be used[65]. This technique may be advantageous when the patient cannot be positioned in the lateral position. The ultrasound probe is positioned on the proximal end of the medial thigh. The sciatic nerve can be visualized as a hyperechoic structure beneath the adductor magnus muscle medially to the femur. Nerve stimulation can be used to further confirm the needle position. A different approach of blocking the sciatic nerve would be a high popliteal sciatic block. Perlas[66] recently showed that an ultrasound-guided block through the paraneural sheath at the site of the bifurcation of the sciatic nerve is a simple and safe alternative compared to 2 single injections; moreover block onset times were reduced by approximately 30% compared to the conventional technique. However, it has to be determined in randomized controlled clinical trials if this would be a feasible approach for postoperative analgesia in TKA patients.

Implications, considerations and outcomes: The SNB itself, especially the posterior approach, is relatively simple to perform. Moreover, it has shown a high success rate (Table 1). In terms of a continuous blockade, the SNB in addition to a FNB nerve catheter can be challenging for patients. First, managing two different pumps may be logistically difficult; second, the needle insertion site, especially within the classic approach for the SNB, is not well suited for a nerve catheter, and third, the anterior approach to the sciatic nerve is an advanced technique and is therefore not widely available. However, Morin *et al*[67] reported reduced opioid consumption with a combined FNB and SNB catheter technique compared to a continuous FNB alone. The authors used the anterior approach for the SNB resulting in a relatively high failure rate, which may be in part attributable to the lack of ultrasound guidance as well as to the approach chosen in general. Of even higher concern may have been the fact that physiotherapists reported "… active exercise was more difficult to perform and walking were more insecure with patients who had the combined FEM/SCI catheter because of more pronounced motor weakness...". There was no measurement for motor strength of the quadriceps muscle; therefore one can only hypothesize on the impact on recovery. A systematic review article by Abdallah *et al*[12] found no evidence for a beneficial analgesic effect of a SNB beyond 24 h. This was also true when a continuous nerve catheter was used. They concluded that the area innervated by the sciatic nerve might be of minor importance in contributing to postoperative pain following TKA. Of note, within 24 h after TKA, a SNB has provided better pain relief and has reduced the opioid consumption within the majority of the trials that have been included into the systematic review. Therefore the question arises if a continuous catheter technique is (still) needed at times when the analgesic duration achieved with a single shot of local anesthetics tends to be prolonged, either through the choice of long acting anesthetic or the addition of additives.

Patient satisfaction and cost effectiveness

Peripheral nerve blocks in general have contributed to improving patient satisfaction, shortening length of stay in the recovery unit and while remaining cost effective.

Patient satisfaction: Hospital rankings and advertisement have become more common worldwide; especially in the United States many patients use these factors in order to choose a certain institution for a specific procedure. A similar trend has started and is expected to continue in many other countries over the next years as well. However, these rankings seem to always include some measure of patient satisfaction. High levels in pa-

tient satisfaction might resemble an institution's ability to meet the patient's needs and meet or even exceed the patient's expectations. This is important, as with a change in the reimbursement policy, the Centers for Medicare and Medicaid will account for patient satisfaction rating when reimbursing hospitals for their expenses[68]. In this context it is important to note that regional anesthesia and peripheral nerve blocks have shown the potential to significantly contribute to a higher overall level of patient satisfaction[69]. In the successful multimodal analgesic model, regional anesthesia plays one of the most important roles. Therefore, it seems prudent that when medically indicated peripheral nerve blocks should be considered whenever possible in TKA patients.

Cost effectiveness: Cost-effectiveness has become a major factor in most health care systems around the world when providing medical care. In this regard, it has been shown that peripheral nerve blocks are associated with cost savings when used for postoperative pain management after TKA. In a retrospective analysis, Ilfeld *et al*[70] demonstrated a 34% reduction in hospital cost for patients receiving continuous FNB after conventional TKA. Regarding the use of ultrasound guidance, it has been shown to be a cost-effective alternative compared to a nerve stimulator technique for a continuous sciatic nerve block despite initially high acquisition costs[71]. A limitation for this and all other studies evaluating the costs for ultrasound usage are overhead costs which are not reflected within these trials. This includes the cost for education and training for users. Moreover, most trials do not take multiple clinical applications of ultrasound machines into account which may have a cost sparing effect as well.

CONCLUSION

Regional anesthesia, in specific the use of peripheral nerve blocks, has significantly improved the perioperative (pain) management of patients undergoing TKA. Early mobilization and rehabilitation, improved patient satisfaction and a reduced length of stay have been accomplished by using regional anesthesia and therefore peripheral nerve blocks are becoming ever more popular. The providers' skill as well as the institution's resources might however influence the specific choice of the peripheral nerve block used. It must be stressed, that health care providers utilizing peripheral nerve blocks need to be knowledgeable regarding possible complications such as risk nerve damage, bleeding, infection and inpatient falls, and take precautions to reduce such risk.

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Common controversies in total knee replacement surgery: Current evidence

Vasileios S Nikolaou, Dimitrios Chytas, George C Babis

Vasileios S Nikolaou, Dimitrios Chytas, George C Babis, 2nd Department of Orthopaedics, Athens University, 15124 Athens, Greece

Author contributions: Nikolaou VS collected data and wrote the manuscript; Chytas D contributed to data analysis and manuscript preparation and writing; Babis GC had the final checking and proof editing of the manuscript.

Correspondence to: Vasileios S Nikolaou MD, PhD, MSc, 2nd Department of Orthopaedics, Athens University, 21 Dimitriou Ralli Str, Maroussi, 15124 Athens, Greece. vassilios.nikolaou@gmail.com

Telephone: +30-69-32543400 Fax: +30-21-08020671

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Abstract

Total knee replacement (TKR) is a widely used operation that has radically improved the quality of life of millions of people during the last few decades. However, some technical details, concerning the surgical procedure and the rehabilitation following total knee arthroplasty, are still a matter of a strong debate. In this review of the literature, we have included the best evidence available of the last decade, in an effort to shed light on some of the most controversial subjects related to TKR surgery. Posterior-stabilized or cruciate-retaining prosthesis? To use a tourniquet during operation or not? Do patients need continuous passive motion for their post-surgery rehabilitation? To resurface patella or not? These are some of the most controversial topics that until now have been persistent dilemmas for the orthopedic surgeon. Results of this systematic review of the literature are highly controversial. These conflicting results are an indication that larger and more well conducted high quality trials are needed in order to gain more secure answers. At the same time, it is becoming apparent that a meticulous operative technique, respecting the soft tissue envelope and knowing the principles of alignment and soft tissue balancing, are some of the parameters that might contribute more to achieving the optimal results for the patients.

Key words: Total knee replacement; Controversy; Literature review; Patella resurfacing; Patella eversion; Posterior stabilized; Cruciate retaining; Tourniquet; Continuous passive motion

Core tip: A literature review has been conducted in an effort to present the best available evidence of the last decade and to shed light on some of the most controversial subjects related to total knee replacement surgery. Patella resurfacing or not? Posterior cruciate retaining or sacrificing? Continuous passive motion or not? Tourniquet or not? These are some of the most debatable topics that until now have been persistent dilemmas for the orthopedic surgeon. Results of this systematic review of the literature are highly controversial. These conflicting results are an indication that larger and better conducted high quality trials are needed in order to gain more secure answers.

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INTRODUCTION

Knee osteoarthritis (OA) is a very common condition with prevalence increasing with age. Recent studies estimated that the global burden of radiologically confirmed, symptomatic knee OA in 2010 was estimated to be 3.8%. This is a huge number, considering the world population, and it is expected to increase as the population ages[1].

Total knee arthroplasty (TKA) is a widely used operation that has radically improved the quality of life of millions of people suffering from symptomatic knee OA during the last decades[2]. Studies have shown that TKA is one of the most common procedures performed during hospital stay, and according to the national registries, there is a continuously increasing number of operations performed worldwide each year[3]. It has been estimated that, by 2030, the demand for primary TKA is projected to increase to 3.4 million surgeries performed annually in the United States alone[4].

Indeed, studies have shown that TKA is one of the most rewarding surgical procedures both for patients and surgeons[2]. However, other studies have shown that there is still a percentage of patients that remains dissatisfied with their clinical outcome[5-7]. As a result, there is an ever increasing effort in research and development in the field of knee arthroplasty aiming to improve patient safety and outcomes.

Several techniques have been described according to the patient's particular characteristics, and each of them has its own pros and cons, indications and contraindications. More specifically, some technical details, concerning the surgical procedure and the rehabilitation following TKA, are still a matter of a strong debate, despite the extensive investigations in the literature about their use. For example, the use of a posterior-stabilized or cruciate-retaining prosthesis, the necessity for a tourniquet and for continuous passive motion (CPM), the necessity for patella resurfacing or eversion during surgery, are some of the most controversial topics that until now have been persistent dilemmas for the orthopedic surgeon.

Thus, we tried to shed some light into these controversies, by extracting from the literature high quality papers that have as an object the answer to the previously reported questions.

An extensive search was conducted in MEDLINE (PubMed), Web of Science, and the Cochrane database for high quality. Prospective. randomized trials and meta-analyses. In order to be up-to-date and present the most recent findings, we preferred to include in our study only the papers published in the last decade. Initially, one reviewer conducted the literature search and retrieved the references for evaluation. A second reviewer independently selected the trials to be included in the review and also screened the reference lists of the selected articles in order to identify studies that were missed in the initial search.

POSTERIOR STABILIZED *VS* CRUCIATE RETAINING TKA

Retaining the posterior cruciate ligament (PCL) or not still remains a matter of a strong controversy among the orthopedic surgeons. Numerous studies have yielded conflicting results. In this review, we were able to identify 8 relevant studies (6 prospective randomized trials and 2 meta-analyses).

The high quality papers that we collected began with the review of Jacobs *et al*[8] in 2005, who concluded that sacrificing the PCL leads to superior results concerning the range of knee motion, although they mention that the methodological quality of the studies that were included was highly variable and the results should be interpreted with caution. In 2008, Harato *et al*[9] performed a prospective randomized trial, with a minimum follow-up of 5 years, which confirmed the superiority of sacrificing the PCL (prosthesis Genesis Ⅱ), for postoperative knee motion, but no significant difference was reported in knee function, postoperative complications and patient satisfaction. The randomized controlled trial by Chaudhary *et al*[10] also in 2008, is another study that finished with the conclusion that posterior-stabilized TKA does not have different outcomes with the posterior-retained one regarding pain, knee function, and quality of life scores. Furthermore, in contrast with the previously reported trials, the authors found that the range of knee motion 2 years after surgery was similar for the 2 kinds of TKA[10]. Kim *et al*[11] in 2009, in a prospective randomized study (minimum follow-up of 2 years), compared high-flexion posterior-retained with high-flexion posterior-stabilized prosthesis and also did not notice a difference in range of knee motion, clinical and radiographic results. However, in 2011, Seon *et al*[12] published another prospective randomized study which also compared high-flexion posterior-stabilized TKA with high-flexion posterior-retained TKA and disagreed: the former prosthesis proved superior to the latter in weight-bearing maximum flexion and posterior femoral roll-back, although no difference was noted in clinical outcomes. Yagishita *et al*[13] performed a prospective randomized study in 2012, with a minimum follow-up of 5 years, which indicated that posterior-stabilized prosthesis showed better results in postoperative knee motion, posterior knee pain at passive flexion and patient satisfaction, but no significant difference was found between the 2 types of TKA regarding Knee Society Score. On the other side, in 2012, Li *et al*[14] in a meta-analysis of randomized controlled trials, compared the 2 types of knee prosthesis and reported similar outcomes in postoperative knee pain, function, complications and prosthesis survivorship. Finally, the meta-analysis of randomized and quasi-randomized controlled trials by Verra *et al*[15] in 2013, confirmed that there was no difference between posterior-stabilized and posterior-retained TKA regarding pain, and clinical and radiological outcomes, despite the fact that the range of motion and Knee Society Score were found higher with the former type.

Thus, we can conclude that, generally, in the literature, neither the one nor the other prosthesis has been proved to offer clear clinical advantages. Nevertheless, we cannot neglect the fact that the studies that reported differences between the 2 types of TKA found superiority of posterior-stabilized knee prosthesis mainly with regard to range of motion (Table 1).

Is it necessary to use a tourniquet?

A strong debate is found in the literature about the

Table 1 Studies comparing posterior cruciate retaining *vs* posterior cruciate sacrificing total knee replacement methods

Ref.	Type of study	Outcome
Verra *et al*[15]	Meta-analysis of randomized and quasi-randomized controlled trials, comparing retention with sacrifice of the PCL in primary TKR	No clinically relevant differences found. Range of motion was 2.4° higher in the PCL sacrificing group
Li *et al*[14]	Meta-analysis of randomized controlled trials comparing posterior cruciate-retaining with posterior stabilized TKA	No differences between the 2 designs
Yagishita *et al*[13]	Prospective, randomized study comparing high-flexion CR design implanted in one knee and high-flexion PS design implanted in the other knee in simultaneous bilateral TKA	PS prosthesis better in postoperative knee motion, posterior knee pain at passive flexion and patient satisfaction
Seon *et al*[12]	Prospective randomized trial, comparing *in vivo* kinematics, range of motion, and functional outcomes in patients who received either a high-flexion cruciate retaining or a high-flexion cruciate substituting TKR	No differences in clinical outcomes. PS TKR superior to CR TKR in weight-bearing maximum flexion and posterior femoral roll-back
Kim *et al*[11]	Prospective randomized trial, comparing ROM and functional outcome in knees receiving either a high-flexion posterior cruciate-retaining or a high-flexion posterior cruciate-substituting TKR	No differences among groups
Chaudhary *et al*[10]	Prospective randomized study comparing range of motion of posterior CR *vs* posterior cruciate-substituting (PS) (TKA)	No differences among groups
Harato *et al*[9]	Prospective, randomized clinical trial comparing midterm outcomes of posterior CR *vs* posterior cruciate-substituting (PS) procedures using the Genesis Ⅱ (TKA)	No significant difference in knee function, postoperative complications and patient satisfaction. Superior ROM in the PS group
Jacobs *et al*[8]	Systematic review and meta-analysis of prospective randomized trials	Range of motion 8° higher in the posterior-stabilized group compared to the PCL retention group

TKR: Total knee replacement; TKA: Total knee arthroplasty; PCL: Posterior cruciate ligament; PS: Posterior stabilized; CR: Cruciate retaining; ROM: Range of motion.

usefulness of the tourniquet in TKA. We were able to identify 11 studies (4 meta-analyses and 7 prospective randomized trials) which aimed to answer this question.

The high-quality papers that we found in the last decade began with the prospective randomized study by Ishii *et al*[16] in 2005 about the optimal time of tourniquet deflation in cementless TKA. The authors concluded that tourniquet release before wound closure caused a significant increase in total blood loss. Consequently, they recommended that the tourniquet should be released after wound closure and that a compressive dressing should be applied[16]. Moreover, on the same subject, a meta-analysis of randomized controlled trials by Rama *et al*[17] in 2007, indicated that early tourniquet release for hemostasis increases blood loss, but also decreases the risk of regional postoperative complications (wound complications, symptomatic deep venous thrombosis and knee stiffness requiring manipulation) and the risk of reoperation. The first high-quality study that we noted in the last decade concerning the dilemma about the use of a tourniquet or not is the prospective randomized trial of Li *et al*[18] in 2009. A tourniquet was not recommended because it caused significantly increased blood loss, lower free hemoglobin levels, more extensive postoperative swelling, and ecchymosis. Also, straight leg raising and knee flexion in the early period after surgery were negatively influenced by the use of a tourniquet, which, therefore, was clearly discouraged by the authors[18]. To strengthen this point of view, Smith *et al*[19] in 2010, with their meta-analysis and systematic review, concluded that the use of a tourniquet was combined with significantly greater incidence of pulmonary embolism, blisters, deep vein thrombosis, superficial wound healing disorders, hematoma, peroneal nerve palsy, and greater intraoperative blood loss, but no significant difference in total blood loss. On the other hand, in 2012, we noted a randomized controlled trial by Tai *et al*[20], which supported the use of a tourniquet. It was proved that it significantly reduced total blood loss, excessive postoperative inflammation, and muscle damage, but caused slightly more postoperative pain, which, nevertheless, did not affect postoperative recovery. Alcelik *et al*[21], in a meta-analysis of randomized controlled trials in the same year, agreed that the use of a tourniquet restricted total blood loss, but was accompanied by a significantly higher rate of minor complications and did not affect the time of surgery and the incidence of thromboembolism. However, Ledin *et al*[22] in their randomized study, also in 2012, were not in favor of the use of a tourniquet, claiming that it did not improve the fixation of the components of TKA (as was indicated by the measurement of their migration with radiostereometric analysis), increased postoperative pain, and reduced the range of knee motion (the follow-up was up to 2 years after surgery). Additionally, in 2012, Mittal *et al*[23] performed a randomized controlled trial to investigate the possible advantages of tourniquet application only during cement fixation: the authors noted a significantly higher risk of transfusion and no functional benefit up to 1 year after surgery and, therefore, did not present restricted application of a tourniquet around the cement fixation as the optimal solution. Another interesting randomized controlled trial in 2012, by Olivecrona *et al*[24], demonstrated that measuring the limb-occlusion pressure before surgery reduced cuff pressure during surgery without influencing the quality of the bloodless field. Furthermore, the authors did not note differences in the parameters of postoperative pain, knee motion, and wound-related complications between the groups and came to an important secondary finding: in patients with a cuff pressure less than 225 mmHg, there were no postoperative infections and a lower rate

Table 2 Studies investigating the usefulness of tourniquet use in total knee replacement

Ref.	Type of study	Outcome
Molt *et al*[27]	Prospective randomized controlled trial. To use a tourniquet or not. To evaluate the early migration, measured by RSA, of cemented knee prosthesis	No differences between the groups regarding the translation or rotation of the components as measured by RSA
Tarwala *et al*[26]	Randomized trial. To use a tourniquet only during cementation or up to wound closure	No differences in surgical time, pain scores, pain medicine requirements, range of motion, hemoglobin change, or total blood loss
Li *et al*[25]	Meta-analysis of randomized controlled trials. To use a tourniquet or not	Tourniquet effective for reducing intraoperative blood loss but not for reducing the postoperative blood loss and total blood loss
Olivecrona *et al*[24]	Randomized controlled trial. Tourniquet cuff pressure based on the patient's systolic blood pressure or based on the measurement of the limb occlusion pressure	No differences between the groups regarding postoperative pain or complications. Tourniquet cuff pressure based on measurement of the limb occlusion pressure had less wound complications
Mittal *et al*[23]	Double-blind, randomized controlled trial. Tourniquet application only during cement fixation or continually	Higher risk of transfusion in the short tourniquet use group. No difference in the Oxford knee score or rate of recovery
Ledin *et al*[22]	Randomized trial of cemented TKR. To use a tourniquet or not	Tourniquet increased postoperative pain and reduced the range of knee motion. Tourniquet group had less overt bleeding
Alcelik *et al*[21]	Systematic review and meta-analysis of selected randomized controlled trials. To use a tourniquet or not	Tourniquet restricted total blood loss, but was accompanied with significantly higher rate of minor complications
Tai *et al*[20]	Prospective randomized trial. To use a tourniquet or not	Tourniquet effectively reduced blood and avoided excessive postoperative inflammation and muscle damage. Tourniquet group had slightly more post-op pain
Smith *et al*[19]	Meta-analysis of randomized and non-randomized trials. Tourniquet use or not	No advantage to using a tourniquet in knee replacement surgery for reduction of transfusion requirements
Rama *et al*[17]	Meta-analysis of randomized trials. Tourniquet release either before or after wound closure	Tourniquet release before wound closure increases the blood loss. However, tourniquet release after wound closure can increase the risk of early postoperative complications requiring another operation
Ishii *et al*[16]	Randomized trial in patients who had undergone cementless TKA. Tourniquet release either before or after wound closure	Tourniquet release before wound closure caused a significant increase in total blood loss

RSA: Radiostereometric analysis.

of wound complications[24].

In 2013, Li *et al*[25] performed a meta-analysis of randomized controlled trials and concluded that the use of a tourniquet significantly decreased the intraoperative blood loss but did not influence total blood loss. Besides, patients with a tourniquet did not have neither a higher risk of thromboembolic complications nor significant difference in the time of surgery compared with patients without a tourniquet[25]. Also, in 2013, Tarwala *et al*[26] in a randomized trial, examined the outcomes of the use of a tourniquet only during cementation and found that it offered bloodless bone for fixation, and did not influence the surgical time, pain, range of knee motion and total blood loss. Consequently, they recommended this method, claiming that it may restrict the possible risks related to prolonged tourniquet use[26]. Finally, the prospective randomized study by Molt *et al*[27] in 2013, underlined that tourniquet use did not affect the stability of the tibial tray of cemented TKA in a 2-year follow-up, as was demonstrated by a radiostereometric analysis.

In conclusion, we can see that the answer to the complicated dilemma "tourniquet or not?" is still difficult despite the extensive research on this subject. It is evident that several questions emerge about tourniquet use, related, for example, to the optimal timing of its release, the ideal cuff pressure, and the stages of surgery in which it should be inflated. Thus, further research is required to clarify these ambiguous aspects of tourniquet use and to construct definite guidelines. Table 2 summarizes the findings of the previous studies.

CPM: TO USE OR NOT TO USE?

We were able to identify 11 studies (3 meta-analyses and 7 prospective randomized trials) investigating the usefulness of CPM post TKR surgery.

The meta-analysis of Brosseau *et al*[28] in 2004 is the first high quality study that we noted in the last decade, concerning the question about the use of CPM. The authors concluded that there was a significant improvement in active knee flexion and analgesic use up to 2 wk postoperatively, while the average hospital stay was decreased, as was the need for knee manipulations under anesthesia[28]. However, the authors also highlighted the need for further research about the use of CPM, because of its inconvenience and expense, and put the question about the determination of protocols concerning the duration and intensity of CPM application[28]. Following this study, Leach *et al*[29] in 2006 published a prospective randomized trial, with a 1-year follow-up, in which they concluded that CPM does not offer significant benefits in range of knee motion and pain, after the application of a specific CPM protocol. This publication initiated a series of high-quality studies, which, since then, have contested the use of CPM after TKA. More specifically, in 2007, Postel *et al*[30] in their review of level I and II studies, noted that CPM offered short-term benefits concerning postoperative pain, swelling and knee motion, but claimed that long-term benefits were not established, and underlined the necessity for investigation of different CPM modalities and comparison with alternative intermittent mobiliza-

Table 3 Studies investigating the usefulness of continuous passive motion after total knee replacement

Ref.	Type of study	Outcome
Maniar *et al*[35]	Prospective randomized trial. To use or not to use continuous passive motion post TKR	No benefit from CPM use in immediate functional recovery post-TKR and postoperative ROM. The postoperative knee swelling persisted longer in the CPM group
He *et al*[34]	Meta-analysis of randomized trials (Cochrane). CPM or not against VTE	No evidence that CPM reduces VTE after TKR
Harvey *et al*[33]	Meta-analysis of randomized trials (Cohrane). CPM use or not	CPM increases passive knee flexion ROM by mean 2 degrees and active knee flexion ROM by mean 3 degrees. This effect is too small to clinically justify the use of CPM. Weak evidence that CPM reduces the need for manipulation under anesthesia
Alkire *et al*[32]	Prospective randomized study. CPM use or not for computer-assisted TKA	No statistically significant difference in flexion, edema or drainage, function, or pain between groups 3 mo post-surgery
Lensenn *et al*[31]	Randomised controlled trial. Effectiveness of prolonged CPM use *vs* in hospital only use of CPM	No long term difference in ROM or any of the outcome assessments
Leach *et al*[29]	Prospective randomized trial investigating the effect of CPM on range of knee flexion, lack of extension, pain levels and analgesic use after TKR	No differences among studied groups
Brosseau *et al*[28]	Meta-analysis of studies examining the effectiveness of CPM	Significant improvement in active knee flexion and analgesic use 2 wk postoperatively with the use of CPM and PT compared with PT alone

CPM: Continuous passive motion; VTE: Venous thromboembolism; PT: Physiotherapy; TKR: Total Knee replacement; ROM: Range of motion.

tion techniques for safer conclusions. Moreover, in 2008, Lensenn *et al*[31] in a randomized controlled trial, came to agree that CPM improved short-term range of knee motion but they did not recommend its prolonged use as an adjunct to physiotherapy, because their long-term results did not confirm their initial conclusion. To the previously mentioned papers, which were about conventional TKA, Alkire *et al*[32] added a prospective randomized trial in 2010 which examined the effectiveness of the use of CPM in computer-assisted TKA: they concluded that CPM did not offer any significant benefit concerning the range of knee motion, pain, swelling, and knee function[32]. Additionally, the use of CPM was discouraged by the review of randomized controlled trials by Harvey *et al*[33] also in 2010, who supported that, in the patients who participated, range of knee motion, pain, swelling, quadriceps strength, length of hospital stay, and incidence of manipulation under anesthesia, did not show significant improvement after the use of CPM[33]. Another interesting parameter of the possible effectiveness of CPM was investigated by He *et al*[34] with their review of randomized controlled trials concerning the possible prevention of venous thromboembolism. They claimed that CPM did not significantly reduce this risk. Finally, Maniar *et al*[35] in a prospective randomized trial in 2012, further discouraged the use of CPM after TKA, supporting that it not only did not significantly improve immediate functional recovery, but also had a negative impact on postoperative swelling.

From the previously reported data, we can conclude that there is no recent high-quality published study that is in favor of the use of CPM during rehabilitation after TKA and, therefore, remaining extensive use of routine CPM should probably be reconsidered (Table 3).

PATELLA RESURFACING OR NOT?

Patellar resurfacing during TKA is another subject about which orthopedic surgeons express different points of view and is a matter of long-standing debate. We were able to identify 10 studies (5 prospective randomized trials and 5 meta-analyses), aiming to answer the question of resurfacing the patella or not.

In 2007, Burnett *et al*[36] performed a prospective randomized trial with a minimum follow-up of 10 years and noted similar results for patellar resurfacing and nonresurfacing regarding the patient's pain, satisfaction, knee motion, and revision rate. A few years later, Burnett *et al*[37] in 2009, published the updated data from the previous randomized trial. Results confirmed the previously reported findings for the same parameters. A well conducted systematic review of the literature, which reported significant advantages of patellar resurfacing, was published by Calvisi *et al*[38] and merits mention. The authors concluded that this procedure reduced the risk of anterior knee pain, pain during stair climbing, and the patella-related reoperation rate, while increasing patient satisfaction and did not significantly influence knee motion[38]. However, they were not clearly in favor of the method of patellar resurfacing[38]. More recently, in 2011, Breeman *et al*[39] in a randomized controlled trial with a 5-year follow-up, found that this method did not have a significant impact on functional outcomes, reoperation rate, and total healthcare cost. Also in 2011, Pavlou *et al*[40] expressed the same opinion by performing a meta-analysis which indicated that patellar resurfacing did not significantly affect anterior knee pain and functional outcomes. The authors noted more reoperations in the non-resurfacing group, but they considered this result as possibly artificial, because secondary patellar resurfacing offers a surgical option for the therapy of anterior knee pain[40]. Furthermore, Fu *et al*[41] in 2011 published a meta-analysis in which they did not support patellar resurfacing as a matter of routine, as they did not notice a marked advantage, although they did note that this method reduced the

Table 4 Patella resurfacing *vs* non-resurfacing in primary total knee replacement

Ref.	Type of study	Outcome
Chen *et al*[48]	Meta-analysis of randomized controlled trials Patellar resurfacing *vs* nonresurfacing in primary TKR	Patellar resurfacing reduces the risk of reoperation after TKR. No difference between the 2 groups in terms of anterior knee pain, knee pain score, Knee Society score and knee function score
Pilling *et al*[44]	Meta-analysis of randomized controlled trials. Patellar resurfacing *vs* nonresurfacing in primary TKR	The reoperation rate due to anterior knee pain, and the patella-femoral complication rate was significantly higher in the resurfacing group. The knee component of the Knee Society Score was higher in the resurfacing group. No significant difference was observed for the function component of the Knee Society Score or for any other reported knee score
Beaupre *et al*[43]	Randomized controlled trial. Patellar retention *vs* patellar resurfacing in primary TKR	No differences among the studied groups
Liu *et al*[46]	Randomized prospective trial. Patellar reshaping *vs* resurfacing in TKR	No significant differences between the 2 groups in terms of total Knee Society score, Knee Society pain score, Knee Society function score and anterior knee pain rate
Fu *et al*[24]	Meta-analysis of randomized controlled trials. Patellar resurfacing *vs* nonresurfacing	Patellar resurfacing reduce the risk of reoperation after TKR. No difference in anterior knee pain
Breeman *et al*[39]	Multicenter, randomized controlled trial. Patellar resurfacing or not	No significant difference between the 2 groups regarding functional outcome, reoperation rate, and total health care cost at 5 yr post TKR
Pavlou *et al*[40]	Meta-analysis of Level-I randomized controlled trials. Patellar resurfacing or not	No significant differences between groups with regard to the incidence of anterior knee pain. Higher rate of reoperations was observed in the non-resurfacing group
He *et al*[34]	Meta-analysis of randomized trials. Patellar resurfacing or not	Reoperation for patella-femoral problems significantly more likely in the nonresurfacing group. No difference between the 2 groups in terms of anterior knee pain rate, knee pain score, knee society score and knee function score
Burnett *et al*[37]	Prospective randomized trial. Patella resurfacing *vs* nonresurfacing in patients undergoing bilateral TKA	No differences regarding the studied parameters
Burnett *et al*[36]	Prospective randomized trial. Patella resurfacing *vs* nonresurfacing in patients undergoing bilateral TKA	No differences with regard to range of motion, Knee Score, satisfaction, revision rates, or anterior knee pain

TKR: Total knee replacement; TKA: Total knee arthroplasty.

risk of reoperation. Additionally, Li *et al*[42] also in 2011, in a meta-analysis of randomized controlled trials, reported that, despite the fact that the risk for reoperation due to patella-femoral problems was significantly reduced by patellar resurfacing, there was no difference in pain and knee function. Beaupre *et al*[43] in 2012, performed a randomized controlled trial, with a follow-up of 5-10 years, in which they agreed that patellar resurfacing showed no difference with non-resurfacing regarding knee specific outcomes, like pain, stiffness, and function. Also in 2012, Pilling *et al*[44] in a meta-analysis of randomized controlled trials, highlighted the advantages of this method in the field of preventing additional surgical procedures and patella-femoral complications, but, nevertheless, reported no difference in operative time, infection rate, radiographic appearance, patient satisfaction, and anterior knee pain.

Of note, Altay *et al*[45] in 2012, investigated the subject of patellar denervation only, without patellar resurfacing: their prospective randomized study demonstrated that patellar denervation could significantly restrict anterior knee pain with satisfactory clinical and radiological outcomes, without patellar resurfacing[45]. Another alternative solution was presented by Liu *et al*[46] in a prospective randomized trial in the same year, compared patellar resurfacing with patellar reshaping, *i.e.*, removing the partial lateral aspect of the patella and the surrounding osteophytes and trimming the patella to match the trochlea of the femoral component. In a minimum follow-up of 7 years, the authors did not find a difference between the 2 methods regarding pain, radiographic findings, and functional knee scores, but recommended patellar reshaping, because it retained sufficient patellar bone stock and could easily be converted to patellar replacement in the case of recurrent anterior knee pain[46].

In 2013, the randomized controlled trial by Pulavarti *et al*[47] shed more light on the subject of patellar denervation without resurfacing: the method appeared safe, and improved patient satisfaction and range of knee flexion but did not ameliorate validated knee scores in a follow-up of 2 years[45]. Finally, Chen *et al*[48] also in 2013, published a meta-analysis of randomized controlled trials which supported the point of view that patellar resurfacing reduced the risk of reoperation and, moreover, gave better results in Knee Society Score in a follow-up of 5 years or more, but the overall benefits of the method were not sufficient to convince the authors to prefer this method over patellar non-resurfacing[48].

In conclusion, it is clear that patellar resurfacing as a common practice is not supported enough by the high-quality trials of the last decade, although some benefits have been adequately documented. More specifically, current evidence tends to suggest that patellar resurfacing may reduce the reoperation rate due to patello-femoral problems. Several alternative methods have been recommended with promising results, but future research will further clarify whether the advantages of patellar resurfacing are strong enough to encourage its use among the

Table 5 Patellar eversion *vs* subluxation

Ref.	Type of study	Outcome
Umrani *et al*[52]	Prospective randomized trial. Patellar eversion or not (mid-vastus approach)	No statistical differences between 2 groups throughout the follow-up periods in recovery of quadriceps force or power and clinical data
Arnout *et al*[51]	Prospective randomized study. Medial parapatellar arthrotomy with patellar eversion *vs* same approach without eversion	Patellar dislocation without eversion improved range of motion at 1 yr postoperatively. All other studied parameters were not significantly different
Dalury *et al*[50]	Prospective randomized trial. Patellar eversion and anterior tibial translation *vs* patellar subluxation and no tibial translation	No significant differences between the treatment groups at 6 wk, 12 wk or 6 mo after surgery
Walter *et al*[49]	Prospective, randomized, blinded study. Mid-vastus split with or without patellar eversion *vs* median parapatellar arthrotomy or a mid-vastus split both without patellar eversion	Significantly earlier return of straight leg raise was noted when patellar eversion was avoided
Reid *et al*[53]	Prospective randomized double-blinded study. Patients undergoing TKA through a standard medial parapatellar approach assigned to either retraction or eversion of the patella groups	No significant clinical differences in the early to medium term. With patella retraction, there may be an increased risk of damage to the patellar tendon and increased risk in implant malpositioning

orthopedic community (Table 4).

PATELLAR EVERSION OR NOT?

Patellar eversion during TKR surgery has traditionally been used to facilitate exposure and component positioning. More recently, the theory that avoiding patella eversion results in better range of motion and earlier quadriceps recovery has gained popularity. However, controversy regarding this technique still exists. Few high-quality trials (more specifically, 5 prospective randomized studies) have been published in the literature during the last decade concerning the usefulness of patellar eversion in TKA. Initially, in 2007, Walter *et al*[49] performed a study which led them to the conclusion that avoiding patellar eversion led to earlier return of quadriceps function and a decrease in the length of patient stay in hospital. On the other hand, in 2009, Dalury *et al*[50] claimed that patellar eversion and anterior tibial translation showed no significant difference to patellar subluxation and avoiding tibial translation on range of knee motion, quadriceps strength and patient's knee preference, up to 6 mo after surgery. Furthermore, Arnout *et al*[51] in 2009, in a prospective randomized study, concluded that patellar dislocation without eversion improved the active and passive range of knee motion up to 1 year postoperatively and recommended this procedure as safe. Umrani *et al*[52] in 2013, found that patellar eversion did not significantly affect quadriceps recovery after TKA up to 1 year after surgery. In the most recent study, Reid *et al*[53] in 2014 found that patients who underwent TKR with patella eversion had similar clinical outcome 3 mo and 1 year postoperatively with patients who had TKR with patellar subluxation. They also noted that patellar subluxation may lead to an increased risk of damage to the patella tendon and increase in tibial component malpositioning.

As a conclusion, we could say that the available evidence is not strong enough to support either patellar eversion or subluxation, as a standard technique during TKR surgery. More high-quality trials need to be performed for stronger evidence. Table 5 summarizes the available evidence.

CONCLUSION

Results of this review of the literature are highly controversial. We have tried to extract the best and most up-to-date evidence available regarding some of the most debatable aspects of TKR surgery regarding the everyday surgical technique of thousands of orthopedic surgeons around the world. These conflicting results indicate that larger and more well conducted high quality trials are needed in order to gain more secure evidence. At the same time, it is apparent that, irrespective of the variations in the operative techniques, certain parameters may contribute more to long-term successful results after TKR surgery. A meticulous operative technique, respecting the soft tissue envelope, and knowing the principles of alignment and soft tissue balancing are some of the parameters that may be of major relevance in achieving optimal results for TKA patients.

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Flap reconstruction of the knee: A review of current concepts and a proposed algorithm

Andreas Gravvanis, Antonios Kyriakopoulos, Konstantinos Kateros, Dimosthenis Tsoutsos

Andreas Gravvanis, Antonios Kyriakopoulos, Dimosthenis Tsoutsos, Department of Plastic Surgery-Microsurgery and Burn Center, General State Hospital of Athens "G Gennimatas", 15343 Athens, Greece
Konstantinos Kateros, Orthopedic Surgery Department, General State Hospital of Athens "G Gennimatas", 15343 Athens, Greece
Author contributions: Gravvanis A designed the study and wrote the manuscript; Gravvanis A and Kateros K performed the majority of clinical cases; Kyriakopoulos A and Tsoutsos D contributed to the collection and critical review of the pertinent literature.
Correspondence to: Andreas Gravvanis, MD, PhD, FEBOPRAS, Department of Plastic Surgery-Microsurgery and Burn Center, General State Hospital of Athens "G Gennimatas", Patroklou 10, Agia Paraskevi, 15343 Athens, Greece. gravvani@yahoo.com
Telephone: +30-69-44455575 Fax: +30-21-07709851
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Abstract

A literature search focusing on flap knee reconstruction revealed much controversy regarding the optimal management of around the knee defects. Muscle flaps are the preferred option, mainly in infected wounds. Perforator flaps have recently been introduced in knee coverage with significant advantages due to low donor morbidity and long pedicles with wide arc of rotation. In the case of free flap the choice of recipient vessels is the key point to the reconstruction. Taking the published experience into account, a reconstructive algorithm is proposed according to the size and location of the wound, the presence of infection and/or 3-dimensional defect.

Key words: Knee reconstruction; Local flap; Pedicled flap; Free flap; Recipient vessels

Core tip: There is much controversy in the literature regarding the optimal management of skin necrosis around the knee. Muscle coverage remains the standard to which all other flaps should be compared. Perforator flaps have recently represented a true revolution in the soft tissue reconstruction around the knee, with peculiar advantages due to their low donor morbidity and long pedicles. In the case of free flap the choice of recipient vessels is the key point to the reconstruction. With meticulous preoperative planning, by identifying the reconstructive needs and by understanding the reconstructive algorithm, the surgeon should be able to manage knee defects with high success rate.

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INTRODUCTION

The around the knee skin and soft tissue defects represents a challenge to the plastic surgeon. A thin, pliable coverage of the knee joint is a prerequisite to promote wound healing and to any concomitant orthopedic procedure. As a rule, the upper one third of the tibia can be covered effectively with rotational muscle flaps[1]. Nevertheless, complex lower limb wounds are best managed with a distant flap, because avoids additional skin incisions to the already damaged with impaired perfusion limb. Moreover, introduces a well-perfused tissue from an uninjured area, thus facilitating wound healing[2]. On the other hand, the free tissue transfer is more challenging option for around the knee, due to the difficulties in

recipient vessel selection positioned deeply around the knee[3].

The purpose of this article is to analyze the reconstructive challenges and reconstructive options for around the knee defects and to propose a reconstructive algorithm.

REVIEW OF THE LITERATURE

The literature search revealed 138 articles related to the reconstruction of soft tissue defects around the knee, whereas 124 articles consider the open and/or infected knee joint salvage with flaps. Thirteen articles are related to the use of local flaps and 51 articles are related to the use of pedicled flaps in peri-knee soft tissue reconstruction. Forty-one articles discuss the use of free flaps whilst 11 articles discuss the recipients' vessels that can be used.

Five review articles have been identified in English literature: 3 related to wound complications in total knee arthroplasty and flap reconstruction[4-6], 1 related to the recipient vessel selection[3], and 1 related to lateral genicular artery flap[7].

One article proposes an algorithm of treatment of the exposed total knee prosthesis[8], but no article has been identified proposing a reconstructive algorithm of the around the knee defects.

THE CAUSES AND RISK FACTORS OF THE SOFT TISSUE DEFECT AROUND THE KNEE

Apart from posttraumatic defects[9,10] and oncological resections[11-14] knee soft tissue defects may arise from chronic infection, post surgical radiation[15], or surgical release of postburn flexion contractures[16]. Moreover, can be caused by multiple previous operations[6,17,18]. Wound complications following total knee arthroplasty can occur up to 20% of patients, and are related to skin/soft tissue necrosis and possible exposure of the implant. Gross infection may lead to loss of the prosthesis or even of the limb[6,17,19].

Risk factors for knee wound complications could be related to the patient's general status and to local wound factors[20]. Diabetes is associated with dehiscence and infection[19], smoking is related to bleeding complications and infection[2], obesity may induce dehiscence and deep-venous thrombosis[2].

Local factors predisposing to complications are previous scars, major vessel trauma, hematoma, local infection, tension at the skin closure, and previous irradiated skin[20].

RECONSTRUCTIVE CHALLENGES

The knee is a hinge type synovial joint, which permits flexion and extension about a transverse axis, and a small medial and lateral rotation about the axis of the lower leg in the flexed position[21]. The total range of motion is dependent on several parameters such as active insufficiency, hamstring tightness and soft-tissue restraints. The overlying skin is thin and pliable with remarkable distensibility. The size of the skin defect should be estimated with the knee at maximum flexion, and the "like tissue replacement" principle should be ideally applied. In other words the defect should be replaced with plenty pliable skin from the adjacent area. In extensive or complex defects local flaps may not be available, therefore it requires either a distant muscle flap[2] or microvascular tissue transfers to aid in soft tissue reconstruction[22,23]. Distant muscle flaps are associated with variable morbidity and further trauma in the already traumatized limb, but is a fast procedure that requires less reconstructive expertise. Free tissue transfers offers less donor and recipient site morbidity, have the advantage of single stage, but requires expertise and infrastructure[22]. However, the main challenge is the proper selection of recipient vessels[3]. Some surgeons prefer to choose the suitable recipient vessels first allowing this choice to direct the proper flap choice[24,25]. Others advocate the selection of the proper flap first (according the size and depth of the defect), influencing the recipient vessels choice[26]. The fact is that in the severely damaged limb the recipient vessel selection is the main challenge and will determine the success of the reconstruction[3].

OPTIONS OF TREATMENT

The treatment of choice depends on the wound dimensions and geometry, presence of gross contamination and/or infection, and most importantly if there is bone, tendon or implant exposure[8]. The options are conservative wound management or debridement with reconstruction in the presence of necrotic tissues[23,25]. The cornerstone of the treatment is the thorough debridement and removal of any devitalized and infected tissue and/or infected foreign material.

In cases of small split-thickness skin loss, early skin grafting is preferable to secondary healing, in order to avoid hypertrophic or contracted scars. In deep wounds (without exposure of the patella, bone or implant) associating the vacuum assisted closure (VAC) therapy reduces the wound exudate, controls the microbial load and the speeds the granulation tissue formation, thus facilitating secondary skin grafting[26].

Nevertheless, if the resulting defect is deeper with exposed bone or hardware, or infection is documented, a flap is needed[23]. If the defect is associated with intra-articular infection, drainage through an arthrotomy and continuous irrigation could be indicated[27].

LOCAL FASCIOCUTANEOUS AND PERFORATOR FLAPS

Local skin are used in small skin defects (less than 4 cm). The prerequisite is the absence of infection and no bone or prosthesis exposure[23]. More recently, local perforator flaps have been used, with significant advantages due to

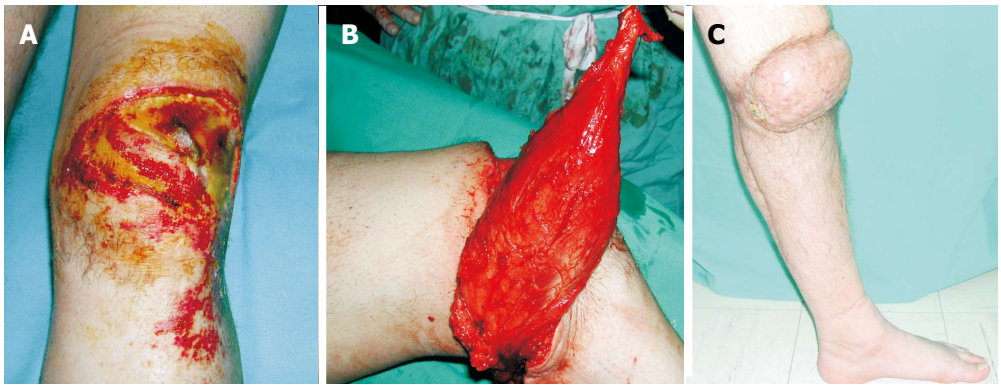

Figure 1 A 28-year-old man suffered a postburn unhealed wound around the right knee that was managed with pedicled gastrocnemius flap. A: The exposed patella was associated with flexion contracture; B: A medial gastrocnemius muscle flap was elevated as an island flap based on the medial sural artery. The muscle was freed from its origin and its motor nerve, as well, to allow greater arc of rotation; C: Four weeks postoperatively, gait without external supports was achieved. From the cosmetic point of view, although the muscle was denervated, a bulky pivot point was present that resulted in a cosmetic deformity.

their low donor morbidity and better esthetic outcome[2]. Panni *et al*[4], in their review paper, emphasized on the use of a flap from the inferomedial thigh based on perforators arising from the descending genicular artery. The preoperative investigation of the perforator vessels with color doppler is essential[28]. Occasionally the flap may suffer from venous congestion, and an additional venous microanastomosis with a local vein could be valuable. The flap presents wide arc of rotation and may cover the whole knee[29].

PEDICLED MUSCLE AND MUSCULOCUTANEOUS FLAPS

Pedicled muscle and musculocutaneous flaps still represent the workhorse for coverage of knee defects, because of the straightforwardness, and are specifically indicated more complex soft defects with joint and/or prosthesis exposure. Muscle flaps obliterate the three-dimensional defect and provide rich blood supply to the wound that facilitates the antibiotics delivery.

Although, gastrocnemius flap was introduced since 1978[30] is still the most commonly used flap for knee coverage, due to its reliable axial blood supply and ease of dissection. The gastrocnemius flap is a type I (single vascular pedicle) according to the Mathe *et al*[31] classification with dominant vessel in most patients the media sural artery. The medial gastrocnemius is greater than the lateral one, with longer vascular pedicle and greater arc of rotation, reaching the knee easily and thus is more frequently used (Figure 1). The lateral gastrocnemius carries the risk of damaging the peroneal nerve while it turns around the neck of the fibula, and is used for lateral knee defects. The medial half musculotendinous unit has been used to reconstruct in one stage the extensor apparatus and to provide soft tissue cover in open knee joint[10]. The combined "gastrocnemius with soleus bi-muscle flap" has been introduced for large patella/infrapatella defects, and is based on the perforators of the distal half of the gastrocnemius muscle to the soleus muscle[32]. The soleus muscle (Type Ⅱ: dominant pedicles branches from popliteal artery, proximal two branches of posterior tibial, proximal two branches of peroneal artery and minor pedicle 3 or 4 segmental branches of the posterior tibial[31]), based proximally, can be reliably carried to a point approximately 5 cm above its tendinous insertion, thus to cover the lower portion of the knee[32] The soleus is a "slow" muscle that aids in posture stabilization and slow gait. Transfer even of the entire soleus muscle creates little if any functional deficit. Gastrocnemius flap has been the workhorse in exposed total knee prosthesis with variable but generally good results[33-35].

Recently, gracilis muscle that is also associated with negligible donor site morbidity has been described for knee resurfacing. Gracilis muscle is type Ⅱ (dominant pedicle medial circumflex femoral artery and minor pedicle 1-2 branches from superficial femoral artery) according to the Mathes and Nahai classification[31]. The reversed gracilis pedicle flap has been suggested as a substitute to, or combination with a gastrocnemius for the treatment of large patella or suprapatella defects[36].

The Sartorius muscle flap was first used in 1978 to close an exposed knee joint. The blood supply to this muscle is by numerous segmental vessels from the femoral artery (type Ⅳ according to the Mathes and Nahai classification[31], and the main feeding vessel is located about 8 cm below the inguinal ligament[37]. The distally based Sartorius is best prefabricated by denervation and vascular delay and then transposed based on the distal pedicle to cover the defect[38]. In 2012 Shen *et al*[39] presented 12 cases of covering proximal tibia by the sartorius flap based on the rich anatomotic network of the descending genicular artery, together with the perforators of the posterior tibial artery and the medial inferior genicular artery.

Arnold *et al*[40] in 1981 were the first to publish an article for Vastus medialis flap (type II: dominant pedicle branch from superficial femoral and minor pedicle branches of descending genicular artery[31]) to cover an exposed knee joint, and Swartz *et al*[41] in 1987 evaluated the blood supply to the vastus lateralis by dye injection

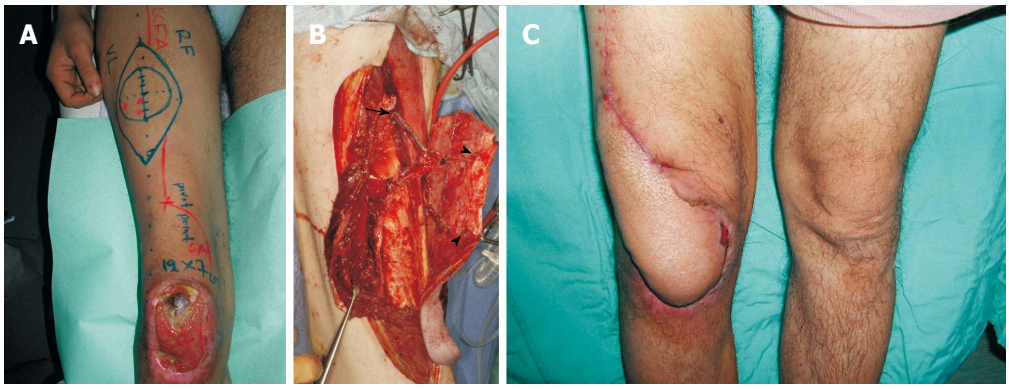

Figure 2 A 24-year-old man suffered from skin and soft tissue defect over the right knee with exposure of the patella that was managed with a distally based anterolateral thigh flap. A: An anterolateral thigh flap was designed; B: The distally based flap was elevated, based on 2 perforators (arrowheads). Note the 20 cm length of the pedicle (perforator and descending branch of LCFA), as well as, the preservation of the proximal end of the LCFA (arrow) that was added to the flap; C: Satisfactory healing and contour achieved.

techniques in fresh cadaver type Ⅱ: dominant pedicle descending branch of lateral circumflex femoral artery and minor pedicle branches of lateral superior genicular artery[31]). Thereafter, the authors have used successfully the distally based vastus lateralis muscle flap to cover defects above the knee. These two papers were the precursors of distally based antromedial and anteromedial thigh perforator flap, respectively[40,41].

PEDICLED PERFORATOR FLAPS

Zhang was the first to introduce the reversed anterolateral thigh island flap, and reported that the flap is reliable based on the anastomoses of the lateral superior genicular artery with the descending branch of the lateral circumflex femoris artery[42]. Nevertheless, Yildirim *et al*[16] reported that the reliability of the flap is questionable. Gravvanis *et al*[43] comparing the option of distally based ALT *vs* gastrocnemius flap concluded that the technical complexity of the former flap is justified by the greater flexibility of size and shape, and by the better color and texture match. ALT is less bulk as compared to gastrocnemius, has longer arc of rotation to reach above and below the knee defects, and provides enough skin to resurface the whole knee[44] (Figure 2). However, the authors emphasized that the reconstructive surgeon should always be alert for vascular compromise of the distally based flap, and thus for flap recharging[43]. Later, Gravvanis *et al*[45] presented the successful use of a distally based ALT flap with a venous supercharge, to reconstruct the tibial tuberosity. They recommended the venous supercharging of this flap as a routine procedure because could eliminate any vascular problems[45].

The Anteromedial thigh perforator flap is based on perforator of the descending branch of the lateral circumflex femoris artery that is perforating the rectus femoris muscle (instead of the vastus lateralis in the case of the ALT)[46] As a knee defect coverage was presented in 2010 by Hupkens *et al*[47] in a study on cadavers. Lu *et al*[48] in 2011 applied this flap on eleven cases covering the exposed knee joint.

Peroneal Artery perforator flap based on perforators from the peroneal artery running in the posterior intermuscular septum can be designed and transferred in a propeller fashion to cover inferior knee defects. Yoshimura *et al*[49] in 1985, first described this flap for knee defects and Ruan in 2009 presented the extended peroneal artery perforator (EPAP) flap[50,51]. The limitation of the peroneal flap in knee reconstruction is the variable number and location of the perforators. A dominant perforator should be located proximal enough to allow an adequate arc of rotation to cover the knee. Thus, a preoperative study with duplex ultrasound or CT-angiography is mandatory.

Li *et al*[52] in 1990 was the first to describe the coverage of the knee with the lateral sural flap, based on sural cutaneous artery, preserving all the big vessels of the lower leg. Umemoto *et al*[53] followed in 2005, and Shim *et al*[54] in 2006 presented the medial sural artery flap on six patients, covering knee defects.

Nguyen *et al*[55] described on cadaveric studies the lateral supragenicular pedicled perforator flap, and subsequently they used successfully this perforator flap in two patients with exposed knee joint.

Likewise, Rad *et al*[56] described the anterior tibial artery perforator flap on cadavers, and then reported the management of four patients with good results. Adhikari *et al*[57] has used the same flap to reconstruct post-burn flexion contractures in seven patients with excellent outcomes.

The introduction of free-style local perforator flaps[58] and propeler flaps[59] presented another reliable and predictable technique to cover skin defects over the knee with a low morbidity rate. The method is based on the use of Echo-Doppler Tracing of good perforator vessels around the knee defect and the administration of Free-style supero-medial or supero-lateral flaps[59].

FREE FLAPS

Free flaps are used for more extensive soft tissue defects. In the case of a complex, three-dimensional defect a free flap is a better option, because it avoids further scaring and trauma to an already injured limb. This well-perfused

tissue from outside the zone of injury brings stability to the wound and promotes healing. When considering free tissue transfer for around the knee defects, the recipient vessel selection is the main difficulty and challenge[3].

RECIPIENT VESSELS

The use of various vessels has been reported, however each has drawbacks. The popliteal artery, the continuation of the femoral, is the main vessel in the knee region, and divides into anterior tibial, posterior tibial and peroneal. Popliteal artery gives of branches such as sural, superior genicular, middle genicular and the inferior genicular artery. The size, position and depth of the soft tissue loss will change the normal anatomy of the region and will drive the surgeon to different options according to the quality of the available vessels.

The popliteal artery is a reliable choice of recipient vessels[60], but is risky for free tissue transfer to the anterior surface of the knee-joint[3] due to potential compression of the vascular pedicle and/or microanastomosis. End-to-side anastomosis is necessary to preserve the distal flow of the major artery, and is associated with limb ischemia during microanastomosis. Tibial arteries can be used as recipient vessels but the anterior tibial artery is frequently involved in trauma as compared with the posterior artery[61]. Nevertheless, the smaller branches can reliably provide inflow, thus one does not have to isolate the popliteal or tibial system in the majority of cases.

The sural arteries are two branches that arise from the popliteal artery across the knee joint, and can be used as recipients when popliteal vessels are absent or severly damaged[62]. In trauma cases the gastrocnemius muscle heads may protect the sural vessels from injury. Therefore are preserved as reliable recipient vessels to simplify the required microanastomoses in an end-to-end fashion, instead of end-to-side to the popliteal system. Hallock proposed a medial approach to the sural vessels that permits the patient to remain in a supine or lateral position for simultaneous dissection of the donor and recipient site[63]. Beumer *et al*[24] has proved that the interruption of medial sural artery has no subsequent functional effect to the gastrocnemius head, and indicated that should be used with confidence as recipient vessel for free flap to the knee.

In either side of the politeal artery, two superior genicular arteries arise and wind around the femur above the condyles in front of the knee joint. Park *et al*[25] used them successfully in four cases of soft tissue defect in the posterior region of the knee. Rees-Lee *et al*[64] further popularized their use for anterior and medial knee defects. The middle genicular artery arises from the anterolaterar surface of the popliteal artery, and generally presents short, intraarticular course. The descending genicular artery arise from the femoral artery and descents between the vastus medialis and the adductor magnus, and is used as a recipient vessel for the anterior knee defects[25,65]. Remarkably, Chien *et al*[66] has used this vessel as recipient for an ALT free flap in reverse flow pattern.

The descending branch of the lateral circumflex femoral vessels can be dissected out and serve as a recipient vessel after being placed adjacent to the defect for free tissue transfer to the difficult areas of the lower extremity[67-69] (Figure 3). However, the descending branch has variable anatomy and size, especially at its distal end, thus a meticulous preoperative imaging with duplex ultrasound and/or CT-angiography is mandatory.

The distal superficial femoral arterial branch was used as recipient vessel for a free flap reconstruction involving knee and proximal tibia[70].

Suprafascial perforators of the knee area were also introduced as recipients, but this approach demands advanced microsurgical expertise. The random perforators were traced with Doppler sonography, computer tomography angiography or magnetic resonance angiography in 25 different cases[71].

In high-energy injuries all superficial sited vessels may be are involved, consequently their use is unreliable. Such cases require the use of vein grafts or long arteriovenous fistulas that are associated with higher failure rate[72]. Alternatively, the Superficial Femoral can be used as an ultimate recipient vessel. Gravvanis *et al*[73] described a reproducible technique to use femoral vessels before the adductor canal as recipients (Figure 4). The femoral present substantial advantages: constant anatomy, ease of dissection and learning curve, and most-importantly well-protected anastomoses that are not positional depended (*e.g.*, cannot be compressed due to the limb's position). The few drawbacks are: deep recipient vessel position that requires long pedicle or long flap to reach the defect and the temporal occlusion of limb's perfusion during anastomoses[73].

FREE MUSCLE FLAPS

Free muscle flaps traditionally have been used to reconstruct lower extremity defects and are generally covered with skin grafts. They confront better the three-dimensional defect; they control infection and bring stability to the wound. On the other hand they are associated with variable donor site morbidity, and shorter vascular pedicle (as compared to perforator flaps). The latter may restrict the free tissue transfer, given that in the mobile knee area the selection of recipient vessels is critical.

The latissimus dorsi muscle flap (type V: dominant pedicle thoracodorsal artery and secondary segmental branches of posterior intercostal and lumbar artery[31]) is probably the most popular free flap in knee coverage, in the literature[26,74-79], followed by rectus abdominis[76,79] (type Ⅲ two dominant pedicles: superior and deep inferior epigastric artery) and fascia lata[80] (type I single vascular pedicle: ascending branch of lateral circumflex femoral artery). Rectus femoris muscle as a functional graft for restoration of knee extension and defect coverage after trauma was published by Wechselberger *et al*[81] in 2006. Tibial composite bone and soft tissue defects of

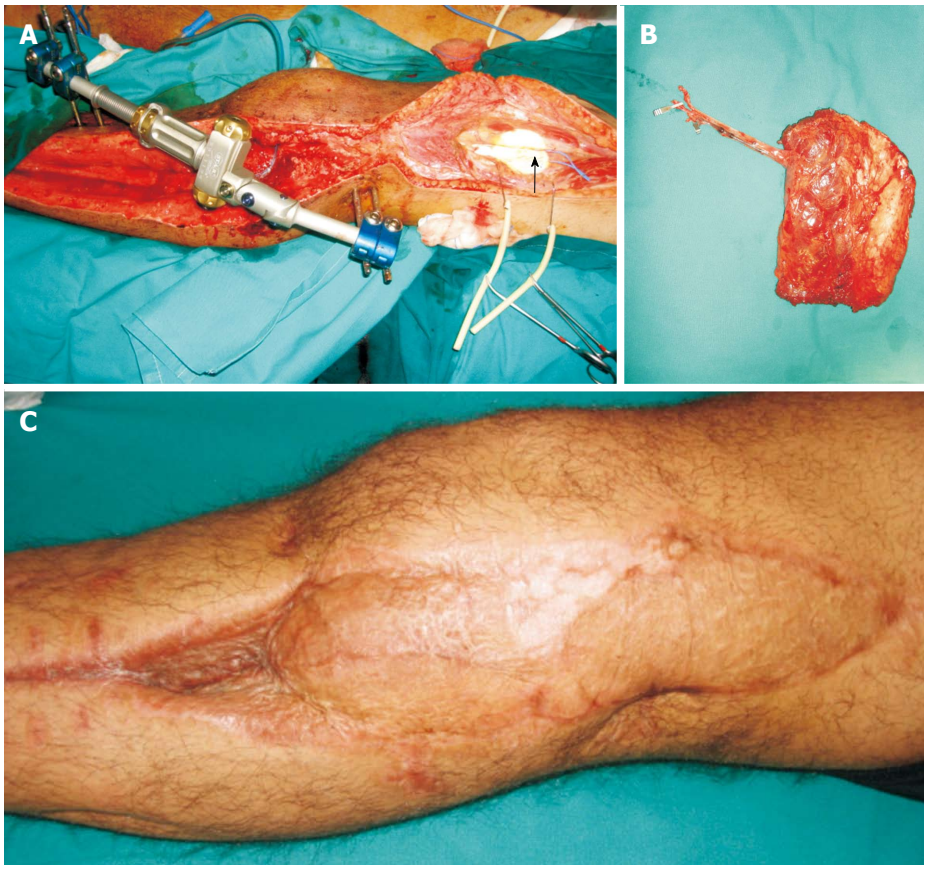

Figure 3 Patient with anterior compartment syndrome and vascular (femoral-popliteal) bypass, presented with skin and soft tissue defect over the lateral aspect of the knee. A: The descending branch of the lateral circumflex femoral vessels was dissected as recipients (arrow); B: The contralateral vastus lateralis muscle was dissected as a free flap and was anastomosed in end-to-end fashion to the distal end of the descending branch of the lateral circumflex femoral vessels; C: Satisfactory healing and contour achieved.

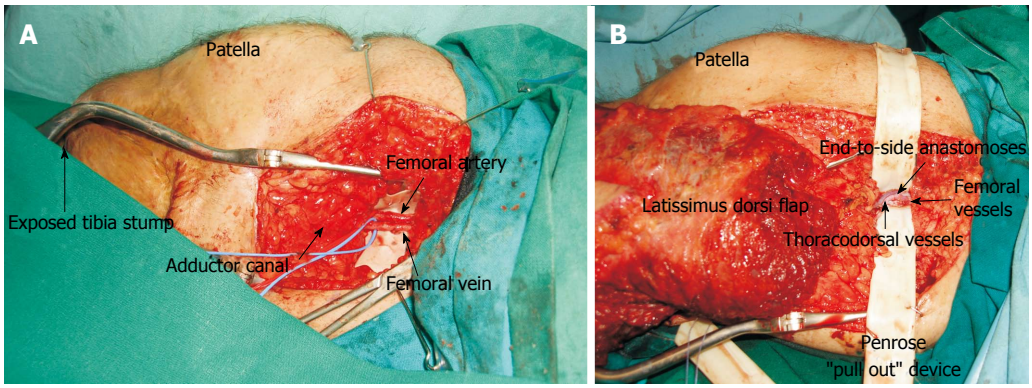

Figure 4 The use of superficial femoral vessels as recipient in free tissue transfer for around the knee defects. A: Femoral vessels skeletonised and dissected free from surrounding fat of the area; B: Penrose "pull out" device in place facilitated the end to side anastomoses.

the knee were reconstructed with free composite serratus anterior and rib flaps by Lin *et al*[82] in 1997.

Taking into account the considerable morbidity of the aforementioned flaps, muscles with documented less morbidity can be used in the majority of cases. Vastus lateralis muscle flap[83] can be used in extended defects (Figure 3) instead of latissimus dorsi and gracilis muscle[84] can be used in smaller defects instead of rectus abdominis. Both muscles can be used as functional muscles for knee extension.

FREE PERFORATOR FLAPS

Free perforator flaps are cutaneous flaps without muscle that gave another rebirth to reconstructive surgery. The most commonly used in knee coverage are ALT (anterolateral thigh, Figure 5), TDAP (thoracodorsal artery perforator), and superficial iliac circumflex perforator

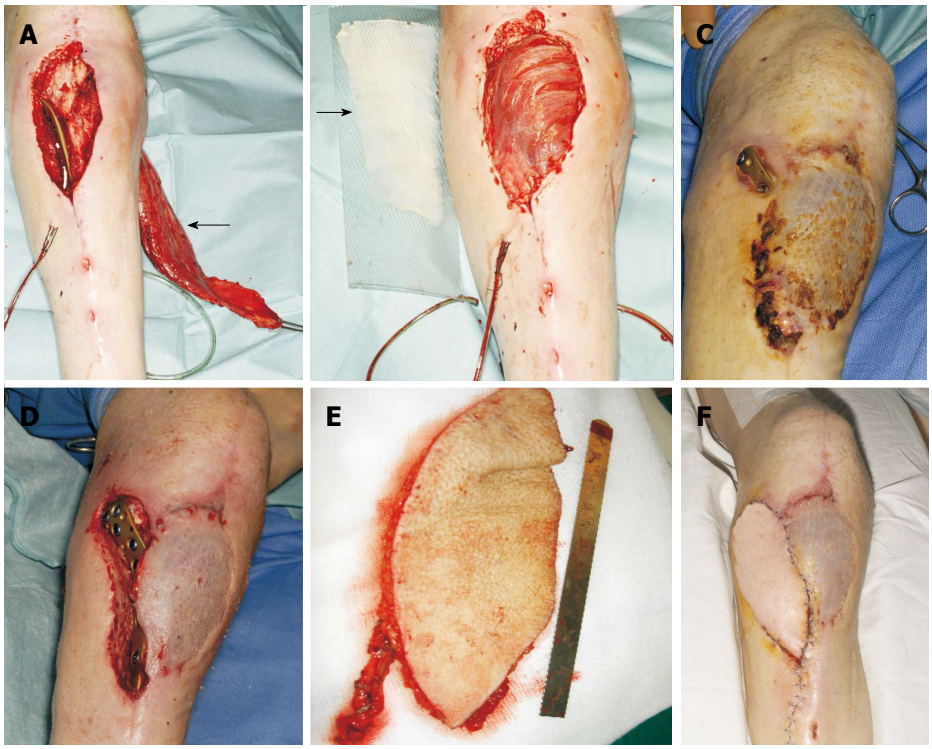

Figure 5 Infrapatellar exposure of a poorly placed plate in a 60-year-old man. A: Due to the questionable viability of the lateral gastrocnemius head, the medial head was dissected (arrow); B: The flap was medially rotated and covered the defect. The muscle was resurfaced with a split-thickness skin graft (arrow); C: Two months later, the plate was exposed in a more proximal position; D: Defect following thorough debridement; E: A free Anterolateral thigh flap based on a single perforator was raised; F: The free flap was anastomosed on end-to-end fashion to the anterior tibial vessels, and a satisfactory healing was achieved.

flap[85]. Cavadas *et al*[86] reported the use of the medial sural artery perforator free flap and Herrera *et al*[70] the superficial artery epigastric flap. Among their advantages are reliability and the long pedicle that enables to easily reach the recipient vessels facilitating microanastomosis. Most importantly, perforator flaps are associated with low donor site morbidity[87], given that no muscle is sacrificed and typically the donor site is closed directly resulting in a linear scar. They present great versatility and adaptability. They can be safely thinned in the plane immediately under the superficial fascia, in order to provide thin pliable coverage. On the other hand, if there is a three-dimensional defect or a grossly contaminated wound, part of the underlying muscle (*e.g.*, vastus lateralis, latissimus dorsi) may be included in a chimeric fashion[88]. Most importantly, complex knee trauma with knee joint exposure and patellar tendon deficiency can be reconstructed in a single stage with ALT myocutaneous flap combined with vascularized fascia lata[88].

RECONSTRUCTIVE ALGORITHM

Successful salvage of the lower extremity following flap reconstruction ranges from 75% to 100%, while salvage of the knee prosthesis is achieved in 75%-85% of patients[23]. Although effective treatment options of the exposed knee joint are available today, there is still no universally accepted management. This is mainly due to the lack of soft tissues over the knee joint that precludes the use of local flaps frequently, and due to the challenging selection of recipient sites for microanastomoses. The optimal management of knee defects is still debated, depending on the size of the wound, location of the wound, presence of deep infection, and the level of microsurgical expertise. The decision either for pedicled or free flap should be based on the existing vascular anatomy, thus a meticulous preoperative vascular study either with Duplex ultrasound[28] or CT angiography[89,90] should be done.

Taking into account all the existed literature, a reconstructive algorithm is proposed (Figure 6).

For small (< 4 cm) defects without exposure of the patella, split thickness skin grafts with or without Vacuum Assisted Closure (VAC) therapy is the treatment of choice.

For deeper wounds with exposure of the patella, bone or the artificial joint, flap coverage is mandatory. For small defects (< 4 cm) without infection, skin flaps present the advantages of less morbidity, pliability and better cosmetic outcomes. Perforator flaps such as free style propeller perforator flaps and medial sural artery perforator flap are indicated for suprapatellar and patellar defects, whilst peroneal artery perforator flap is indicated for infrapatellar defects. Nevertheless, perforator flaps are more technically demanding and needs a significant amount of microsurgical expertise.

Therefore, pedicled muscle flaps have been the workhorses for decades. Moreover, muscle flaps are better indicated for deep infection because they obliterate the dead space arising from the debridement and bring stabil-

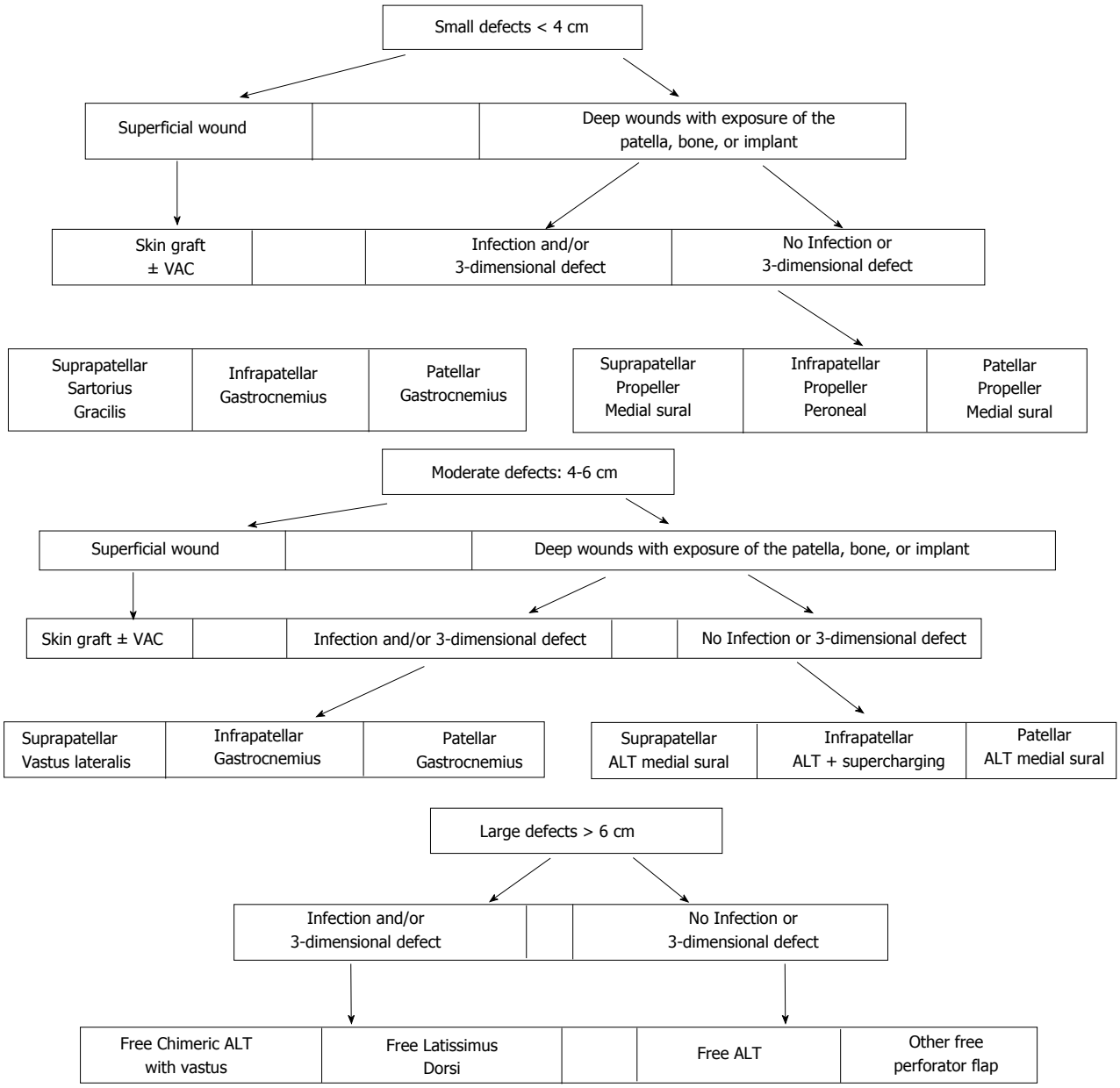

Figure 6 Knee reconstructive algorithm. VAC: Vacuum assisted closure; ALT: Alanine aminotransferase.

ity to the wound. Gastrocnemious flap has been proved to be reliable, safe and easy surgical option. Medial gastro head is more suitable for patellar, infrapatellar defects and tibial tuberosity. Lateral gastro head is more suitable for lateral defects. Distally based thigh muscle flaps, such as sartorius and gracilis, are suggested in the case of suprapatellar infected wounds or absent/traumatised sural arteries (not reliable gastrocnemius flap).

For moderate defects (4-6 cm) not excessively deep, medial sural artery perforator flap and distally based ALT flap is indicated. If the defect is extended to the infrapatellar area, ALT flap supercharging of the flap is considered. If the defect is deep and there is a space to fill gastrocnemius flap and distally based vastus lateralis musle flap are suggested.

For large defects (> 6 cm) or severely damaged limb, a free flap is better solution. Anterolateral thigh as a perforator flap for superficial wounds or as a chimeric flap (with part of vastus lateralis muscle) for deeper wounds will be the flap of choice in the majority of cases. If the thickness of ALT is not suitable, vastus lateralis (associated with minimal morbidity) or latissimus dorsi muscle (associated with considerable morbidity) flap will reconstruct large, deep and infected wounds. The recipient vessel of choice will be identified by the preoperative vascular imaging[28,89,90]. If the study suggests a smaller branch (such as sural, genicular arteries) close to the defect with good inflow and outflow, this choice will enable straightforward end-to-end microanastomoses. Occasionally, smaller branches are absent or traumatized, then Superficial Femoral Vessels can be used in an end-to-side fashion. The choice of the recipient vessels may direct the choice of the most suitable flap, in order to ensure the highest success rate.

Above-the-knee amputation is considered only for life-threatening sepsis or massive bone and soft tissue loss in elderly patients.

CONCLUSION

With the meticulous preoperative planning, by identifying the reconstructive needs, and by understanding the reconstructive algorithm, the surgeon should be able to manage knee defects with high success rate.

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Neuromuscular interactions around the knee in children, adults and elderly

Eleftherios Kellis, Lida Mademli, Dimitrios Patikas, Nikolaos Kofotolis

Eleftherios Kellis, Lida Mademli, Dimitrios Patikas, Nikolaos Kofotolis, Laboratory of Neuromechanics, School of Physical Education and Sport Sciences at Serres, Aristotle University of Thessaloniki, Serres 62100, Greece
Author contributions: Kellis E contributed to the conception and design and final editing and approval of the whole article and the literature search, drafting and revision of the Introduction, the Conclusion Sections and the section "common mechanisms" of this article; Mademli L contributed to the design, literature search and writing of the Section "Elderly", as well as the final approval of the article; Patikas D contributed to the design, literature search and writing of the section "children", as well as the final approval of the article; Kofotolis N contributed to the literature search, drafting and revision, and final editing of the injury-related sections of the article and the final approval of the article.
Correspondence to: Eleftherios Kellis, PhD, Associate Professor in Sports Kinesiology, Laboratory of Neuromechanics, School of Physical Education and Sport Sciences at Serres, Aristotle University of Thessaloniki, TEFAA, Serres 62100, Greece. ekellis@phed-sr.auth.gr
Telephone: +30-2310-991053 Fax: +30-23210-64806
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Abstract

Although injury and neuromuscular activation patterns may be common for all individuals, there are certain factors which differentiate neuromuscular activity responses between children, adults and elderly. The purpose of this study is to review recent evidence on age differences in neural activation and muscle balances around the knee when performing single joint movements. Particularly, current evidence indicates that there are some interesting similarities in the neuromuscular mechanisms by which children or the elderly differ compared with adults. Both children and elderly display a lower absolute muscle strength capacity than adults which cannot fully be explained by differences in muscle mass. Quadriceps activation failure is a common symptom of all knee injuries, irrespective of age but it is likely that its effect is more evident in children or adults. While one might expect that antagonist co-activation would differ between age categories, it appears that this is not the case. Although hamstring: quadriceps ratio levels are altered after knee injury, it is not clear whether this is an age specific response. Finally, evidence suggests that both children and the elderly display less stiffness of the quadriceps muscle-tendon unit than adults which affects their knee joint function.

Key words: Knee stability; Knee joint; Stiffness; Electromyography; Strength imbalance; Aging, Co-activation; Age; Injuries

Core tip: Children and elderly display a lower absolute muscle strength capacity than young adults. This may be due to a higher quadriceps activation failure as well as a more compliant quadriceps muscle-tendon in children (probably due to maturation) and elderly (due to age effects on neuromuscular system) than adults which, in turn, leads to an altered strength capacity. In contrast, age differences in muscle co-activation are not age dependent. Current evidence precludes any conclusions on whether muscle strength balance ratios are age specific.

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INTRODUCTION

The well documented benefits of physical activity and

exercise for health include an increase in physical competency and psychosocial interaction as well as decreased health risks[1,2]. However, physical activity also carries a risk of injury[3,4].

The knee joint is one of the most common injured joints[5]. Alteration of normal neuromuscular function around the knee is considered as a significant contributor to injuries. For this reason, restoration of neuromuscular function represents a fundamental aim of post-injury rehabilitation.

Although injury and neuromuscular activation patterns may be common for all individuals, there are certain factors which differentiate neuromuscular activity responses between children, adults and elderly. The effects of growth and maturation on neuromuscular function have not been thoroughly investigated but there is evidence that children display different neuromuscular profiles compared with adults. It is also known that aging has a significant impact on the force generation capacity of the muscular system which is accompanied by changes in neuromuscular activation patterns. The purpose of this study is to review current and recent evidence on neural activation and muscle strength balances around the knee in children, adults and aged individuals. The main research question was whether there are similarities in neuromuscular interaction during single joint tests across the life span.

There are numerous techniques to evaluate neuromuscular function depending on the scope of assessment and the applied methodology. Evaluation may help in the understanding of the causes of knee injury, and aid in the development of more effective training and rehabilitation programs[6,7]. After providing a brief introduction on knee injury epidemiology, age differences in four different areas of neuromuscular function will be examined. First, the ability of the central nervous system to provide the essentially stimuli for muscular activation are examined. This is translated into quantification of the extent the central nervous system is able to activate the entire motor pool. Second, muscle co-activation which is defined as the simultaneous activity of various muscles acting around the knee will be examined. This is achieved mainly by comparing electromyography (EMG) signals of the antagonistic muscle groups of the knee. Third, muscle strength imbalances around the knee will be examined, mainly refereeing to the hamstrings (H) to quadriceps (Q) moment ratio (H:Q ratio) during isometric or isokinetic tests. Forth, factors related to the properties of the muscle-tendon units of the knee joint and their role for knee joint function will be presented. This study will focus on experimental evidence from single joint movements rather than multi-joint activities.

RESEARCH

A worldwide review of published work on neuromuscular interactions during single joint movements was conducted. Studies were selected for this review if they were written in English, they focused on neuro-muscular or musculo-tendinous strategies during knee joint tests. The literature search was performed from date of inception until end of November 2013 on the following electronic databases: Scopus (1995-2013), Web of Science (1970-2013), PubMed (1948-2013), Proquest, CINAHL, EBSCO, Embase, and Cochrane. The use of key words "knee", "age-related", "neuromuscular", "children" "knee flexors", "knee extensors", "activation level", "neural adaptation", "ageing", "muscle strength", "antagonist", "coactivation", "co-contraction", " tendon stiffness" "injury mechanisms". Studies excluded were non-English language papers, conference abstracts, research reports, personal correspondence. A total of 831 studies that met the inclusion criteria were assessed by two co-authors followed by blind assessment by a third co-author with respect to: (1) sample size; (2) reliability of measurement protocols; and (3) clear data presentation. Case studies or studies which did not report the reliability of their protocol or their data were not clearly presented were excluded from the analysis.

KNEE INJURY EPIDEMIOLOGY: A SHORT OVERVIEW ON AGE DIFFERENCES

The current literature on knee injuries is extensive and it cannot be fully presented in this review. Nevertheless, it is worthwhile to provide a brief overview on potential similarities and differences in knee injury profiles across lifespan.

Knee injuries are frequently seen in the everyday clinical practice of orthopaedic surgeons and general practitioners. In the general population, the incidence is suggested to be 11 cases per 1000 person-years[8]. In a recent study, Gage *et al*[9] examined 6664324 knee injuries and they found that individuals aged 15 to 24 years displayed the highest injury rate while children younger than 5 years had the lowest rate which is confirmed by similar studies in this area[8,10,11].

The most common injury is a knee sprain without clearly identifiable internal derangement, and the most common diagnoses are anterior cruciate ligament (ACL) tear (20.3%), medial meniscus tear (10.8%) and chondral lesion (10.6%)[10]. Other frequent diagnoses include acute patellar dislocation (22%) and collateral ligament tear (9%)[12].

There are various factors which have been considered to increase the risk for knee joint injury. In general, a higher age increases the risk of disabling knee injuries[13]. However, it appears that risk factors act in combination with other factors rather than individually. For example, higher age, obesity, and poor physical conditioning are frequently suggested to be risk factors for musculoskeletal injuries as a whole[13-15]. In another example, a higher age combined with higher weight increase the risk for deeper chondral lesions[15] as well as knee injuries in general[12]. The number of chondral lesions increases with age[16].

Systematic participation in sports and gender are ad-

ditional factors which are also related to a higher injury risk. It is not surprising that current literature focuses primarily on young athletes[3,10,17-19]. For example, knee injuries are reported to account for 60% of high school sports-related surgeries[17,20]. Patellar dislocations typically occur in young adults during sports[21]. Risk factors for acute patellar dislocations are suggested to be higher height and weight[12,22]. Participation in sports, quadriceps muscle weakness, and female sex are associated with ACL tears[23-26] while all these factors acting in combination with older age increase the risk for meniscal tears[5,27]. Further, female athletes have been reported to be four to six times more likely to sustain a major knee injury[17,20].

Individuals 65 years and older sustained a higher proportion of injury due to stairs, ramps, landings, and floors (42.0%), compared to adults and children[9]. Furthermore, ageing is a well-defined risk factor for knee osteoarthritis, as the risk for osteoarthritis increases by 2 to 10 times in people between 30 and 60 years of age and even more for individuals above 60 years[28,29]. Knee arthritis is more common among men below the age of 50, while it is more frequent among women above this age[30]. Obesity and overweight are also known risk factors for knee osteoarthritis, due to mechanical overload of the knee joints[30-33]. Occupations requiring repetitive weight-lifting and squatting[34] as well as repetitive knee torsion[35] and knee bending have been associated with knee osteoarthritis.

To summarize, it appears that knee injury rates are higher in young adults than children and the elderly. Adults suffer mostly from ligamentous injuries chondral lesions and sprains, children display less serious injuries while arthritis represents a characteristic injury of older individuals. Knee injury risk factors, such as obesity, gender, body mass index and poor physical conditioning or systematic participation in sports contribute to injury, irrespective of age.

COMMON NEUROMUSCULAR MECHANISMS AROUND THE KNEE

Arthrogenic muscle inhibition

Knee injury or surgery or arthritis lead to weakness of the quadriceps muscle group[36-40]. One of the factors responsible for this atrophy is an on-going neural inhibition that prevents the quadriceps from being fully activated, a process known as arthrogenic muscle inhibition. This inhibition has been quantified using EMG or the interpolated twitch technique. In addition, activation failure can be induced by experimentally creating an effusion (*via* saline injection into the joint) which is typically seen after knee surgery[41].

Even early after injury, quadriceps weakness can be substantial, despite little time for atrophy[36]. Quadriceps EMG signal reduction ranges from 50% to 70% in the first few hours after meniscectomy; it then increases up to 80% for the next 3 d and it remains at high levels up to 15 d[42]. The reduction in the quadriceps EMG is somewhat lower after total knee arthroplasty reaching 30% in the first 4 wk after surgery[43]. Following ACL surgery, activation failure continues for approximately 6 mo[44,45] but it is gradually reduced to 6% deficit 18 mo after[46]. Similarly, total knee arthroplasty is followed by significant quadriceps inhibition up to 6 mo[47] and 24% decline 33 mo[47] after surgery.

The magnitude of quadriceps failure depends on the severity of joint damage, especially in individuals with ACL problems. For example, Urbach *et al*[48] found a lower central activation deficit in 30 patients with isolated rupture of the ACL compared with that displayed by patients with ACL rupture and accompanying joint damage. ACL rupture leads to a 3%-8% decline in quadriceps activation[36,49] while ACL rupture with simultaneous damage in other joint structures leads to a higher decline[48,50].

Central activation failure can also affect the uninvolved side[36,49-51]. Becker *et al*[51] showed that patients who underwent partial meniscectomy displayed a 20% failure in the injured side and 17% failure in the contralateral side. Similar results were reported for individuals who experienced an ACL injury[49] which led the authors to conclude that the difference between ACL injured patients and controls is due to a reduction in muscle size and activation failure. Chmielewski *et al*[36] also reported a decline in central muscle activation of 21% in both limbs post ACL-surgery[36]. Would this indicate a generalized activation failure and not solely a preferential one? The implication for testing and rehabilitation after knee surgery is that using strength measurements of the uninvolved limb as targets for rehabilitation of the involved limb may set lower strength targets than needed. In fact, Urbach *et al*[48] reported that due to contralateral deficits in central activation, the mean underestimation of the isometric muscle-force deficit ranged from 22% to 48%. Therefore, the validity of tests for the assessment of muscle function when using the uninjured side as reference was questioned. Others, however, did not find a quadriceps inhibition of the contralateral limb[52] proposing that rehabilitation protocols after knee joint injury should focus on ipsilateral and not bilateral neuromuscular and mechanical alterations that occur as a result of joint damage.

There are several factors which may contribute to activation failure such as swelling[53], pain[54], inflammation[55] and damage to joint receptors[56]. For example, activation failure may be due to swelling[53] and an associated increase in intraarticular pressure[57]. Since intraarticular pressure is higher towards knee extension, inhibition will be greater near extension rather than flexion[58]. For these reasons, in the acute stages after injury or surgery, isometric quadriceps exercises should be performed in 30 to 50° of knee flexion, where intraarticular pressure is the lowest[40].

The mechanisms responsible for arthrogenic inhibition vary and include both central and peripheral nervous system. In a recent review, Rice *et al*[40] identified three spinal pathways which may affect arthrogenic inhibition. First, inhibition of group I nonreciprocal interneurons

which receive inputs from tendon organs. Second, an enhanced flexion reflex that inhibits agonist activity and facilitates antagonist muscle activation[59]. Third, a deficit in the transmission of Ia input to the motoneuron pool, termed γ-loop dysfunction may be observed after ACL injury[60,61]. In addition, to the above spinal mechanisms, the role of corticomotor excitability as a contributor to activation failure was also examined. Interestingly, Heroux and Trenblay[62] reported a higher excitability of corticomotor projections targeting muscles in ACL deficient individuals. It has been proposed that this increase in corticospinal excitability may serve to counteract a-motoneuron inhibition by spinal reflex pathways[40].

In summary, athrogenic muscle inhibition represents a common symptom seen after many knee injuries. In many instances, clinicians consider reduced quadriceps strength as a result of muscle atrophy. However, the presence of inhibition after injury indicates that interventions employing only muscle strengthening exercises are not entirely appropriate to enhance neuro-muscular function. The use of techniques to increase quadriceps activation, such as electrical stimulation, has the potential to increase the effectiveness of rehabilitation programs.

Muscle co-activation

Neuromuscular function is not only related to the ability to recruit the entire motor unit pool of a certain muscle but also to the ability to achieve an optimal activation of all muscles acting around the knee. Muscle co-activation has been examined by comparing the surface electromyographic (EMG) signal of the involved muscles expressed as percentages of reference EMG values[63-67] or by using the EMG signals to calculate a co-contraction index[68]. Numerous studies have examined antagonist co-activation levels during various activities[69-72]. Antagonist co-activation of the hamstrings in most movements ranges from 5% to 10% and increases in more demanding activities such chair up and down exercises[69].

Early evidence indicated that hamstrings co-activation represents a reflex response to ACL loading which is also accompanied by quadriceps inhibition[64]. The presence of mechanoreceptor input provided by the cruciate ligaments have been confirmed in healthy individuals[73] but it is absent following surgical ACL reconstruction[74]. This was supported by several studies showing a higher hamstring EMG in ACL deficient patients during the impact phase of the side-step cutting manoeuvre[75], walking[76,77] or landing[78] although such patterns have not always been confirmed[79,80]. In addition, some studies have reported an earlier onset of muscle activity during the late stance phase of walking after ACL injury[76,77,79]. The increased and earlier hamstring and gastrocnemius activation in ACL deficient individuals aims to maintain the knee joint stable by preventing anterior subluxation as the ground reaction forces increase upon heel contact[76-77]. In addition, increased level of antagonist co-activation increases joint active stiffness[69]. This is also related with proprioception deficits often observed in ACL deficient knees[81].

More recent evidence indicates that non-contact ACL injuries are more likely when total hamstring pre-activation is much less than the corresponding quadriceps pre-activity during side cutting[82]. Furthermore, a higher hamstring coactivation near terminal knee extension was observed in ACL deficient individuals compared with uninjured individuals[83]. The observation that co-activation is found in both uninjured and injured individuals led Alkjaer *et al*[83] to suggest that antagonist co-activation is not only a reflex response but it may be modulated by central motor programming. Some evidence seems to support this statement[84,85], although, clearly more concrete evidence is necessary.

Using mathematically or EMG-driven models, research studies have estimated the antagonist moment in healthy subjects[86,87] and in ACL deficient subjects[83-84] as well as its effect on joint forces[73,86,88,89]. Isolated contraction of the quadriceps increases shear force between the tibia and the femur at the last 20° of knee extension which is partly counteracted by hamstring activation[86,88,89]. This results also in a wider pressure distribution along the articular surfaces of the joint and prevents early tissue damage and osteoarthritis[73] while it may reduce ACL strain at angles near full extension[90]. This notion is supported by modeling data by Yangawa *et al*[91], which confirms that coactivation of the hamstring muscles during isolated dynamic (isokinetic) knee extension effectively reduces anterior tibial translation. Further evidence seems to confirm these findings as a higher hamstring coactivation and moment near terminal knee extension was observed in ACL deficient individuals compared with uninjured individuals[83]. The elevated antagonist hamstring moment observed in the ACL deficient subjects may reflect a compensatory neuromuscular adaptation to counteract the increased laxity of the knee joint[83]. However, others have not found any difference in antagonist hamstring moment between ACL deficient, ACL reconstruction, and uninjured individuals[84]. Methodological issues in EMG - moment data treatment may account for these variations[83] which guarantees further research in this area.

Strength imbalances

Since neuromuscular activation is altered in knee pathological conditions, then changes in force generation capacity of the surrounding musculature may be observed. These are also accompanied by alterations in size of the muscle as a result of injury or subsequent immobilization. Muscular imbalances around the knee refer mainly to the relationship between absolute muscle strength developed by antagonistic muscle groups. The H:Q peak moment ratio takes into consideration the function of two opposing (agonist-antagonist) muscle groups and it represents the most frequent parameter used to estimate muscle strength balance[6,7,92].

The methods used to calculate the H:Q strength ratios vary. Early research studies have mainly examined the concentric H:Q ratios, frequently defined as "conventional" ratios[93,94]. A theoretical value of 0.6 of the ratio ob-

tained frequently under isometric or slow isokinetic concentric tests is often considered as "normal"[95]. However, conventional ratios have been gradually been replaced by the "functional" ratios which involve the calculation of eccentric H: concentric Q (H_{ecc}:Q_{con}) muscle strength ratio[6,7,92,93,96].

There has been a long debate on the usefulness of antagonist to agonist strength ratios as an injury predictor or as a target for restoring normal knee muscle function[97]. A methodological approach is to measure H: Q ratio in athletes in the pre-season period and follow this for the forthcoming seasons. It has been found that athletes with a Hcon:Qcon ratio closer to 1.0 may have a reduced risk of hamstrings strain[98]. Also, a Hcon: Qcon ratio closer to 1.0 in athletes with ACL injury has been suggested to reduce the risk of an anteriolateral subluxation of the tibia[99]. Croisier *et al*[100] identified a lower H_{ecc}:Q_{con} ratio in players with a previous hamstring injury during the pre-season assessment and applied a rehabilitation program to restore the ratio into normal values. They then followed the players for 12 mo. Their results showed that none of the players experienced a re-injury. Further, epidemiological evidence in 462 players followed for one season showed a total of 35 hamstring injuries, most of which were experienced by players with lower Hcon:Qcon and Hecc:Qcon ratios[101]. Recently, Kim *et al*[95] found an association of lower than 0.6 of the H_{con}:Q_{con} ratio at 60°/s and non-contact leg injuries in National College American Association athletes. In an almost parallel study, Fousekis *et al*[102] reported that professional soccer players with Hecc strength asymmetries were at greater risk of hamstring strain while players with Qecc strength and flexibility asymmetries were at greater risk of quadriceps strain.

Other studies have examined the ability of H:Q ratio to identify individuals with knee joint problems from uninjured ones. Early studies have identified[79,92] a significantly lower isokinetic Q moment in patients with ACL deficiency compared to healthy subjects while H_{ecc} and H_{con} moment deficits were not as significant. This is in line with later studies[103,104] who reported a higher H:Q ratio in subjects with ACL reconstruction[103,104] compared with uninjured individuals. Similar findings have been reported when comparing individuals with knee osteoarthritis with controls[105,106] which may indicate that compensation strategies with regards to antagonist to agonist muscle balances are more generic than solely ACL problems.

Knee related injuries may also be due to differences in strength between the two legs. Furthermore, strength levels of the unaffected limb frequently represent a reference value against which restoration of strength of the affected limb. Evidence on bilateral leg differences in soccer players is unclear as some studies have reported no differences[107] whereas others reported a 10% difference in both Q and H strength in favor of the non-dominant leg[108]. Others, however, have shown that bilateral leg differences exist only in the hamstrings but not in the quadriceps (players displayed weaker hamstrings in the dominant leg than the non-dominant one)[109,110]. The existence of muscle specific bilateral differences in strength led researchers to explore whether H:Q ratios differ between limbs. Again, there is some evidence that the non-dominant or non-preferred limb shows somewhat higher ratios than the dominant one but still this evidence is not always statistically significant[108,111] or differs between tested speeds[110]. However, a lower H_{ecc} moment in the injured limb compared to the contralateral limb continues even after ACL reconstruction surgery[112]. It is not clear whether such deficits pre-existed or they were due to ACL injury or reconstruction.

Although functional ratios have been considered as better indicators of muscle balance, there is still not sufficient evidence supporting their use. A problem associated with the use of H:Q ratios is that they were assessed using peak force values during a maximum voluntary effort[113-115]. This raises two issues: (1) that injuries occur at a specific joint angle while the H:Q ratio is calculated using peak force values irrespective of joint angle. The value of calculating the H:Q ratio at a specific joint angle, the one which is closer to the injury mechanism of the specific knee structure would be higher[116] (Figure 1). Particularly, peak moment H/Q ratio ranges from 0.5 and 0.6[96,117] and increases near full knee extension exceeding values of 1.0[117,118]. This increase was attributed to a relative dominance of the H near full extension[118] in order to stabilize the knee joint when the strain on the ACL is the greatest[90]. The shift of H_{ecc}/Q_{con} ratio at angles of knee extension was also attributed to a limitation in knee extensor motor unit recruitment at joint angles of greatest ACL strain[118]. Nevertheless, whether H:Q ratio at a specific joint angle can discriminate knee injured individuals from uninjured ones or to predict injury is still unclear; (2) during explosive movements, such as soccer match play situations, the time available to stabilize the knee joint is frequently very short (< 50 milliseconds)[119]. However, during a standard isometric test the peak force occurs within 400-500 ms from onset of contraction. This suggests that in most explosive movements there is no time available for maximum force generation. Thus, the relevance of using Hcon:Qcon and H_{ecc}:Q_{con} based on peak values has been questioned[120]. In one of the first studies, Aagaard *et al*[115] proposed that rate of force development (RFD), defined as the rate of rise in force at the onset of contraction, may be a better index of neuromuscular activity around the knee. Based on these aspects, Zebis *et al*[120] have recently assessed the H:Q ratio using the RFD values obtained during maximum isometric contraction in twenty three soccer players. They reported that two female players who sustained an ACL injury had a normal H: Q peak force ratio but a low RFD H:Q ratio.

Gender differences

Male and female relative H:Q ratio profiles differ significantly during and following puberty[121]. Isokinetic dynamometer measurements show that male athletes demonstrate significantly greater hamstrings peak torques with

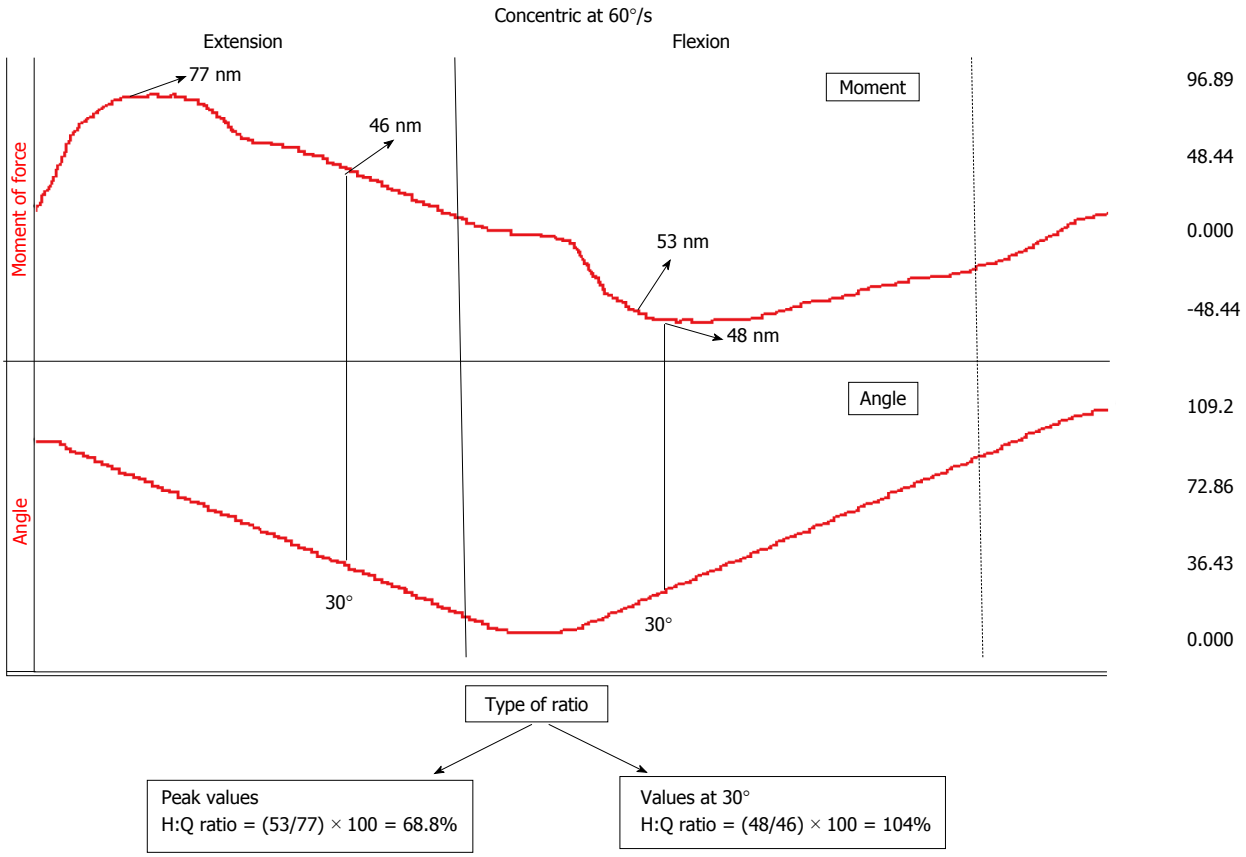

Figure 1 An example of different methods to calculate the hamstrings:quadriceps ratio. The raw data from moment of force (upper line) and angular position (lower line) as recorded from an isokinetic concentric knee extension-flexion trial. Using peak moment values results to a different ratio value compared with that obtained using values at a knee flexion angle of 30°. H: Hamstrings; Q: Quadriceps.

increasing maturity, while peak hamstrings torque remains stable with increasing maturational stage in female athletes[121]. Thus, it appears that lower hamstrings strength and H:Q ratios of female athletes relative to males may be related to the development of neuromuscular imbalances associated with the onset on maturation. These neuromuscular imbalances may increase injury risk in pubertal and post pubertal female athletes[121,122]. In a thorough review, Hewett *et al*[123] analysed 23 research studies and reported that isokinetic H:Q ratios do not differ between genders at slow velocities. As angular velocity increases, males display higher H:Q ratio than females. The authors commented that this difference may be related to females' decreased ability to dynamically control the knee joint during sports activities. However, more recent studies have reported an increase in both conventional and functional ratios in female athletes with increasing angular velocity[124,125], which is not in line with the above conclusion. This might be due to differences in the characteristics of the samples examined, as both these studies referred to trained female athletes whilst data examined by Hewett *et al*[123] included mainly sedentary or untrained individuals.

Gender differences in knee injury occurrence are also related to more global neuromuscular differences that lead to injury than solely H:Q ratios. Muscle co-activation can decrease the dynamic valgus motion of the knee, which potentially places the knee at increased risk of injury[123,126]. Individuals with chronic ACL deficiency showed lower internal/external rotation strength ratios than controls and acute ACL deficient subjects, indicating a compensatory mechanism developed by the patients to unload the ACL[103]. In contrast, ACL reconstruction patients showed fewer deficiencies compared with controls[103].

Gender differences in hamstring and quadriceps muscle co-activation have also been examined. Palmieri *et al*[127] reported that females displayed lower co-activation than males and that medial co-activation had a linear relationship with external knee abduction moment in females only. A higher knee abduction moment is considered as a risk factor for ACL injury[128]. Therefore, it appears that females display a greater risk for ACL injury than males. Similar results were reported by Rozzi *et al*[129] upon landing from a jump. There is no single explanation on why females display deficits only on lateral muscles and not on the medial part. There are suggestions that lateral muscles may co-activate more than the medial ones to resist internal rotation moments which may increase ACL loading[130]. However, more evidence is necessary.

NEUROMUSCULAR INTERACTIONS AROUND THE KNEE IN CHILDREN

Muscle strength increases during maturation, in terms

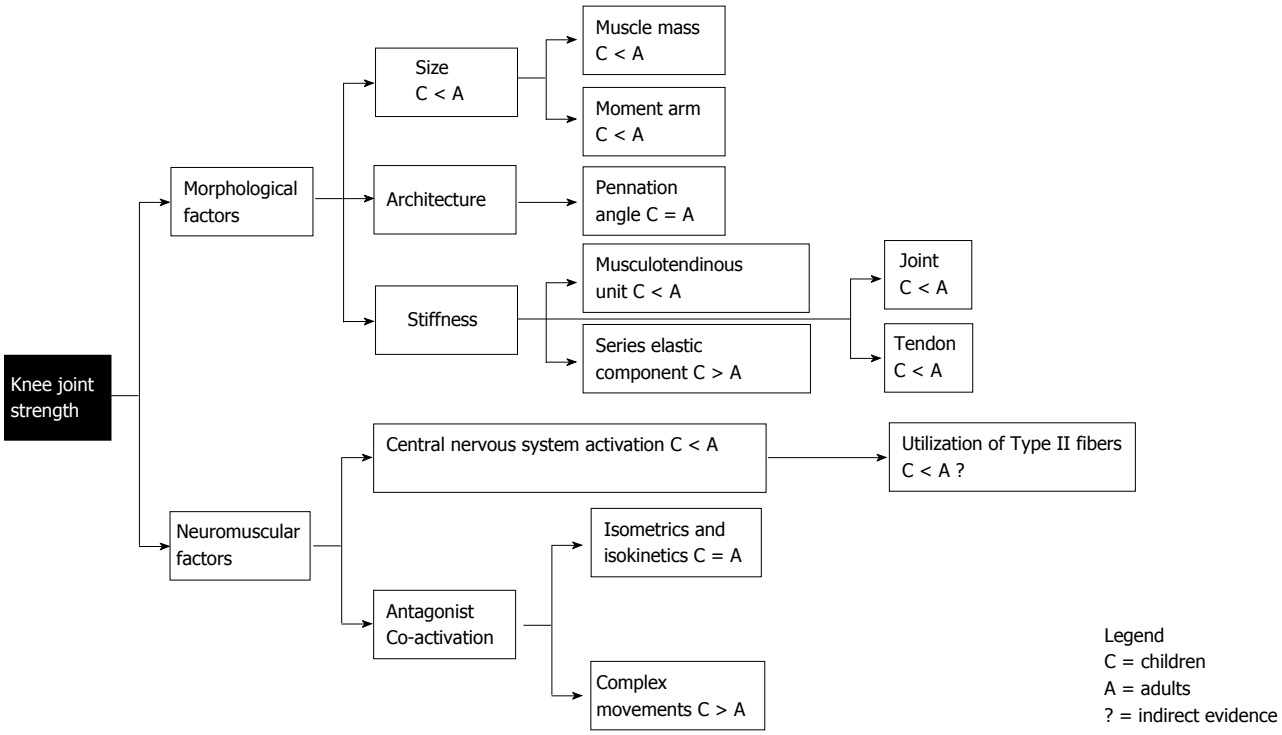

Figure 2 Schematic summary of comparison between children (C) and adults (A) regarding factors influencing knee joint strength.

of joint moment. This development is primary a consequence of hormonal changes which result in muscle mass augmentation (hypertrophy)[131], and in limb size increase (moment arm)[132]. However, differences in strength between children and adults cannot be fully explained by these parameters[133]. This designates the possible contribution of neuromuscular factors that could play a role in force deficit observed in children compared to adults. There are two main issues to mention regarding the neuromuscular aspect: Firstly, the level of central activation, *i.e.*, to what extent the central nervous system is able to activate the entire motor pool, and secondly, the level of antagonist co-activation, which reduces the net amount of moment produced around the joint. Hence, strength gain observed during developmental ages could be partly attributed to neural adaptations. In addition to this, differences between children and adults in muscle tendon unit (MTU) architecture and stiffness might also play a role on the force development around the knee joint (Figure 2).

Earlier studies have shown that the isokinetic strength normalized to cross sectional area (CSA) and thigh length is lower in 6-9 years old children compared to young adults[131]. The fact that this difference was more profound when the angular velocity was increasing reveals that muscle and limb size could not be the only factor affecting force production. This could be explained by findings supporting that children might have lower proportion of type-Ⅱ muscle fibers[134], which have fast contractile properties. However, several studies revealed no significant differences in muscle-fiber composition between children and adults[135,136].

This raises the question whether children and adults possess similar proportion of muscle fibers types, but the former are not capable of fully recruit the fast ones. It has been shown that especially in large muscle groups, such as the quadriceps, children are incapable to fully recruit their motor units[137]. More recent studies using the twitch interpolation technique with magnetic or electric stimulation demonstrated that children activate their motor units in lesser extent than adults during knee extension[138], and this is particularly evident in girls when compared to women[139]. This finding observed in children could at least partially account for their force deficit compared to adults. Furthermore, assuming that the size principle is valid for children too (*i.e.*, the higher the level of activation, the larger in size -and thus faster- motor units are recruited), it would be expected that children utilize in lesser extent type-Ⅱ (fast) motor units compared to adults. This assumption is supported by experimental findings for the knee extensors, revealing that children have lower rate of torque development under isometric[140] and dynamic conditions[141].

Despite the simplicity of using the anatomical CSA for the estimation of muscle size of children and adults, the most appropriate measure is the physiological CSA, which accounts for the pennation angle and is calculated as the ratio of muscle volume to fascicle length[138]. However, no difference between 8-10 years old children and adults is observed in the pennation angle of all quadriceps heads[138]. To our knowledge, no respective data exist in the current literature, regarding the pennation angle for the hamstring muscles in children and adults. This piece of information could have important implications, since

the pennation angle influences the shortening velocity of a muscle (and the force capacity of a muscle), and might affect the torque H:Q ratio at different contraction velocities.

Decreased torque H:Q ratio is an indicator for potential increased probability of lower extremity injury[142]. More particularly, it has been shown that collegiate athletes with isokinetic at 180 deg/s peak torque H:Q ratio less than 0.75 have higher incidence of injury[143]. According to cross-sectional studies, the isokinetic torque H:Q ratio at 60 deg/s remains unchanged from the age of 7 to 18 years, although the CSA H:Q ratio increases gradually after the age of 10 years[144]. On the other hand, post-pubescent athletes demonstrate a close correlation between the hamstrings and quadriceps CSA and the flexion and extension torque, respectively[145]. Furthermore, during puberty strength improvement of the knee flexors is diverged from the extensors, particularly for the females[121]. Although in males the hamstrings and quadriceps isokinetic peak torque increases proportionally during growth[107,121], in females the peak torque of hamstrings does not follow the improvement achieved in quadriceps[121]. This deficit in knee flexion torque observed in females results in a decreased torque H:Q ratio. Further gender specific imbalances are observed on the level of knee anterior/posterior and medial/lateral muscle activation[146] during dynamic multijoint tasks. Females activate their quadriceps more compared to males[147-150] and this could contribute to the decreased H:Q ratio in torque output. Furthermore, decreased medial to lateral quadriceps[151] and hamstrings[129] activation ratio observed in females, could increase valgus, and varus laxity. These observations regarding the imbalances in activation level and torque output of the thigh muscles could increase the risk for ACL injury because hamstrings function synergistically with the ACL, especially at knee joint angles less than 45 degrees[64].

A factor that could modify the torque H:Q ratio is the level of antagonist co-activation. However, no significant differences between children and adults have been observed[152,153]. Furthermore, in isometric contractions, the antagonist co-activation is even lower and still not significant between age groups[139,154]. On the other hand, co-activation is higher in children compared to adults when performing tasks involving multiple joints such as gait[155] and jumps[156,157]. This implies that movement coordination and learning factors might be an issue during developmental ages[133], considering that the process of maturation of the corticospinal tract in terms of conduction velocity is not complete until the age of 11 years[158] and that the pyramidal system attains full functionality during puberty[159].

Regarding the passive component of stiffness, Lebiedowska and Fisk[160] have shown that passive knee stiffness increases with stature, within an age range between 6 and 18 years. Furthermore, Kubo *et al*[161] measuring the tendon elongation of the vastus lateralis during isometric knee extension, concluded that the tendon of younger boys was more compliant than older boys and young men. In line with the idea that the MTU is more compliant in children, Asai *et al*[162] demonstrate that children had longer electromechanical delay compared to adults. This could also contribute to their reduced capacity to produce high rate of force development[140-141]. In contrast, series elastic component, quantified with quick-released movements in the knee extensors, revealed decreased stiffness with age[163]. The above differentiations in MTU stiffness between children and adults might influence the force/length relationship of the muscles acting around the knee joint. Stiffer MTU favors more direct force translation from the muscle to the bone[164], whereas the opposite situation requires greater shortening velocity of the contractile apparatus, in which children are inferior[140,141]. The concept of differences in MTU stiffness that are reflected to changes in the joint torque/angle relationship has been supported[165] but also questioned[139] in previous studies, and therefore requires further investigation. More particularly, Marginson *et al*[165] demonstrated that children demonstrate their maximal knee extension torque at more flexed joint angle (longer muscle) than adults, whereas O' Brien *et al*[139] showed no difference in the optimal joint angle between children and adults.

It is apparent that the function of the knee depends on multiple factors, which are influenced during the developmental ages. Despite this complexity, O'Brien *et al*[138] concluded that children's and adults' specific tension (the ratio between muscle strength and size) of the quadriceps is the same, taking into account differences in physiological cross sectional area, moment arm, level of activation, and co-activation. This implies that the muscle tissue is qualitatively very similar in children and adults. It is concluded that regardless of structural differences in muscle size, moment arm-joint angle relationship, central voluntary activation, H:Q ratio, and muscle-tendon stiffness, children's neuromuscular system is highly adaptive, although further systematic research with longitudinal studies are required to improve our understanding on the effects of growth and development in the force and power output of children.

NEUROMUSCULAR INTERACTIONS AROUND THE KNEE IN THE ELDERLY

The aging process is associated with a significant decline in muscle strength (dynapenia) and strength development that might be caused by alterations of skeletal muscle properties as well as by neural modulations[166,167]. Regarding the knee joint, the reported age-related decrease in the measured isometric muscle force/moment of the knee extensors ranges from 19% to 38% when comparing groups of similar physical activity level[166,168-173] (Table 1). Even greater differences (50% or more) have been reported for people in their ninth decade and beyond[166]. When comparing the specific tension of the knee extensors between young and old women, a reduction of 17% during isometric contraction has been reported[174] (Table 1).

Table 1 Information provided by cited articles about age-related reduction in muscle force

Ref.	Age-related reduction in muscle force/torque	Age of participants, yr	Testing condition	Physical activity level
Baroni *et al*[171]	30%-36%	y: 30 ± 6	Isometric KE	No systematic training
	40%-53%	o: 69 ± 5 yr	Concentric KE (60-360°/s)	No systematic training
Laudani *et al*[173]	36.9%	y: 28 ± 2	Isometric KE	Sedentary adults
		o: 70 ± 3		
Karamanidis *et al*[169]	21%	y: 21-32	Isometric KE	Endurance runners
	18.9%	o: 60-69	Isometric KE	Not active
Mademli *et al*[170]	28%	y: 30 ± 7	Isometric KE	Physically active
		o: 65 ± 3		
Savelberg *et al*[172]	33%	y: 23 ± 2	Isometric KE	Active runners
	43%	o: 65 ± 3	Isometric KF	Active runners
Macaluso *et al*[174]	17%	y: 23 ± 6	Isometric KE	Active
	30%	o: 70 ± 2	Isometric KF	Active
Frontera *et al*[195]	15.5%-22%	12-yr longitudinal study, initial mean	Isokinetic KF (60 and 240°/s)	Healthy
	17%-23%	age 65 ± 2	Isokinetic KE (60 and240°/s)	Healthy

KE: Knee extension; KF: Knee flexion; Y: Young; O: Old.

The age-related decline in muscle strength is gender specific, with men losing almost twice as much strength as women[175]. Nevertheless, in absolute values, older women demonstrate significantly lower strength than men[176,177], which can be explained predominantly by their higher fat mass[176]. Indeed, when investigating the decline in muscle quality of the knee flexors and extensors, *i.e.*, peak torque per unit of muscle mass, it was found that the rate of the decline was the same for both genders[178]. The higher proportion of body fat in women may put them at significant biomechanical disadvantage for greater disability in old age[176]. It seems that due to their gender-related lower average strength, old women may be at greater risk than old men of becoming impaired in certain motor tasks[177].

Furthermore, when measuring knee extensor moments at different knee angle positions, the percentage loss of muscle strength was different at the different positions[168,179]. Karamanidis *et al*[168] found that the aging process revealed a clear reduction in maximal knee extension moment at intermediate knee joint angles (140° and 110°), but there was virtually no age effect at more extended (160° and 170°) or flexed (80°) knee joint positions. The authors proposed among other, two potential explanations for this phenomenon: (1) The discrepancy in the age-related reduction in muscle strength within the quadriceps muscles, with greater decline in Vastii (monoarticular) than in rectus femoris (biarticular) muscle[172]. It has been reported that, while the moment-knee-joint angle relationship of the Vastii muscles described by a parabolic curve having its vertex (maximum value) between 100° and 120°, the rectus femoris demonstrates a rather flat joint-moment-length curve[172]. Thus, it is possible that the relative contribution of the rectus femoris to the total knee extension moment is higher at more extended or flexed knee joint positions[172], where no age-related effect on quadriceps muscle strength was found; and (2) The modulation of the EMG activity. In their study, Karamanidis *et al*[168] found that older adults have an increased quadriceps femoris EMG activity at more extended (160° and 170°) as well as at moreflexed (80°) knee joint angles in comparison to younger adults. This was not the case at intermediate knee joint angles (110° and 140°).

Knee flexors have been reported to demonstrate similar decline as knee extensors due to the aging process[166]. Nevertheless, Ogawa *et al*[180] found no significant change in muscle volumes and average CSA for the hamstring muscles between young and old adults, whereas quadriceps muscle volume and average CSA were 20% and 16% lower, respectively. This resulted to greater age-related decline in the specific tension for the knee flexors compared to knee extensors (Table 1)[174,180]. In contrast to the knee extensors, for the knee flexors the strength reduction is mainly caused by deterioration of the biarticular muscles, and not of the monoarticular muscles[172]. Furthermore, for the knee flexors, the age-related reduction of joint moment is almost invariant to joint angle[172], something that does not hold for the knee extensors, as already mentioned above.

Age-related muscle weakness is associated with the well described decline of skeletal muscle mass. Yet, more recent studies have shown that this relationship is less robust than once believed[167]. Goodpaster *et al*[175], when measuring knee extensor strength by isokinetic dynamometry, found that although the loss of muscle mass is associated with the decline in strength of older adults, this strength decline is much more rapid than the concomitant loss of muscle mass. Moreover, they reported that maintaining or gaining muscle mass does not prevent aging-associated reduction in muscle strength. Furthermore, there are age-related alterations in torque production capability that are not explained by a reduction in muscle mass, including reduced specific tension and slower rate of isometric torque production (expressed relative to peak torque)[167]. The altered neuromuscular activation is another critical component of the weakness observed in senescence[167].

Nevertheless, the studies focusing on the underlying neuromuscular mechanisms of age-related reduction in knee extensors force generation capacity are limited. Moreover, the reported results are partially conflicting, especially the ones concerning alterations in neural drive to the quadriceps muscle. While some studies find greater activation deficit in the elderly, compared to young adults[181,182], other studies do not find any significant differences between young and old in the ability to activate the knee extensor muscles to a high degree (93%-96%)[183-186]. Harridge *et al*[187] found that very old adults (85-97 years) demonstrated significant impairment in central activation, with mean knee extensor voluntary activation level of only 81% (range: 69%-93%)[187]. This outcome suggests that deficits in the neural drive essentially contribute to the weakness of the knee extensor muscles observed in very old age[188]. On the contrary, Miller *et al*[189] found that the ability to activate the quadriceps muscle was generally very high, and there was no significant difference between older (96%) and younger (98%) subjects. The study was conducted on 20 moderately active older subjects (mean age 75 years) and 12 younger (mean age 25 years). The above described inconsistency in reported findings may be primarily related to methodological limitations and differences in the techniques used to estimate muscles voluntary activation[181], as well as to different physical condition of participants[188]. Mau-Moeller *et al*[181] estimated the neural drive to the knee extensor muscles during maximal isometric contractions by means of both interpolated twitch technique and the root mean square of the EMG signal normalized to maximal M wave[181]. Both techniques led to the same outcome, *i.e.*, there was an age-related decline in the neural drive to the muscle which resulted in muscle weakness. Regarding the knee flexor muscles, to our knowledge there is no study investigating their voluntary activation.

Another neuromuscular mechanism of age-related reduction in knee extensors force generation capacity, regards the age-related changes in antagonistic muscle coactivation. The mechanical opposition to the agonist action can contribute to the reduced exerted moment at the knee joint. Studies investigating the effect of aging on the coactivation during knee extension are limited and their findings lack of consensus. Laudani *et al*[173] found that old (mean, 70 years) and young (mean, 28 years) adults with similar physical activity level do not demonstrate significant difference in the coactivation during maximum isometric contractions (26.2% ± 22.8% *vs* 29.6% ± 20.5%). The increased standard deviation in their measured values indicates high intra-group variability, assigning to coactivation a rather person-dependent instead of age-related nature. Regarding dynamic contractions, no association was found between normalized antagonist activation and velocity, indicating that changes in coactivation cannot be responsible for age-related deficit in force production[190]. On the contrary, Tracy *et al*[191] found that old subjects (mean, 71.5 years) exhibited during submaximal isometric and anisometric contractions, greater coactivation of antagonist muscle compared to young ones (mean, 22 years). Similar findings have been reported for measurements over women during isometric knee extension contraction[174]. Furthermore, there is a highly determinant effect of coactivation on the capacity to produce isometric force on a short period of time[192]. However, significantly higher antagonistic coactivation was only found during contraction of the knee extensors and not during knee flexion[174]. During knee flexion, the co-contraction of knee extensors was found to be significantly lower for both old and young adults[173].

The transfer of force between the muscular and skeletal systems may be affected by age-related changes in muscle architecture, as well as in the length and compliance of tendons[167]. An age-related reduction in vastus lateralis tendon and aponeurosis stiffness has been reported[168-170] (Figure 3). Thus, the greater compliance of the aged tendon and aponeurosis can influence the force-length and force-velocity relationship of the muscle (contractile element) and consequently its force generating potential[193]. The result is a more deteriorate function of the knee extensor muscles in the older population.

The above mentioned age-related alterations in neuromuscular interactions around the knee joint lead to differences in the way old adults perform activities of daily living. For example, when older adults descend and ascend stairs and ramps, they demonstrate an altered control strategy compare to young adults, causing a redistribution of the mechanical load at the tibiofemoral joint[194]. This has effects on the initiation and progression of knee osteoarthritis in the elderly, which in turn makes movement even more difficult[194].

CONCLUSION

In this review, we attempted to provide a global view of the neuromuscular mechanisms associated with knee joint injuries across lifespan. It is certain that neuromuscular strategies and mechanisms differ between children, adults and the elderly. However, there are some interesting similarities in the mechanisms by which children or elderly differ compared with adults.

Both children and elderly display a lower absolute muscle strength capacity than adults. This deficit may be due to a lower muscle mass (especially of the quadriceps) displayed by children and elderly, obviously for different reasons. The effects of a lower muscle mass are more evident in older individuals. However, when variations in muscle mass are taken into consideration, there are still differences between different age categories.

Quadriceps activation failure is a common symptom of all knee injuries, irrespective of age. However, for those individuals who have a lower quadriceps strength capacity, it is reasonable to suggest that functional impairment will also be higher. If we assume that knee injury conditions (swelling or pain and inflammation) are constant amongst different age groups, an initial differ-

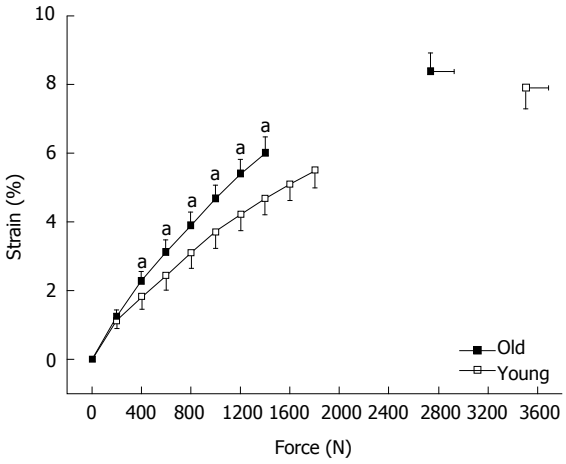

Figure 3 Strain-force curves of the vastus lateralis tendon and aponeurosis. The strain values at every 200 N and at maximum calculated tendon force during maximal voluntary isometric knee flexion contraction are displayed. The curves end at 1400 N for the old adults and at 1800 for the young ones, these values correspond to the maximum common force achieved by all subjects in either group, old and young adults. Y: Young (n = 12); O: Old adults (n = 14); Means and SEM; Age effect: ($^{a}P < 0.05$) *vs* young.

ence in the ability to recruit the entire motor unit pool of the muscle would also contribute to a higher impairment after injury. Our review indicates that this is the case for both children (probably due to maturation) and elderly (due to age effects on neuromuscular system).

Another factor which might have affected the impaired ability to produce maximum muscle strength is a higher antagonist co-activation. Although co-activation levels may contribute to a high joint stability and stiffness, it appears that co-activation levels do not differ between children and adults or between elderly and adults, at least during isolated (static or dynamic) joint strength testing conditions. This indicates that it is the reduced muscle mass and central activation of the agonist muscles rather than higher co-activation by the antagonists that contributes to age related differences in absolute strength. It follows, that this particular neuromuscular mechanism, central or peripheral, is not age specific.

While extensive research has examined the strength balance around the knee through the H:Q ratio, there is a marked difference in the amount of research performed in adults compared to that performed in children and the elderly. Nevertheless, it appears that H:Q ratio levels are altered after knee injury mainly as a result of a lower quadriceps muscle strength. Current evidence does not indicate whether H:Q ratio differs between different age groups. Sparse data indicate that hamstring muscle strength tends to be relatively less affected by age compared with quadriceps muscle strength, but this is only a speculation.

It appears that stiffness of the muscle-tendon units around the knee differs between age groups. Interestingly, there is a common pattern regarding age variations in muscle-tendon stiffness: both children and the elderly display less stiffness of the quadriceps MTU than adults. While in children this may be due to sexual maturation and in elderly due to deterioration of tissue, it could be suggested that the main characteristic is similar: both children and elderly show a more compliant muscle-tendon unit. It seems that tendons adaptations follow muscle's force capacity. Muscle force determines the strain of tendon cells, *i.e.*, the higher the force applied to tendon the higher its deformation. There is evidence that strain of tendon cells is an important regulator for the homeostasis of connective tissues. The resulted more compliant tendon in children and elderly affects both the force-length and force-velocity relationship of their muscles and, in turn, leads to an altered strength capacity.

Finally, an interesting question is whether age-related differences in neuromuscular strategies around the knee depend on gender. There have been no studies that specifically addressed such a question. Neverthless, current evidence indicates that females display a higher injury rate than males. Such variation is observed from an early age where, there is evidence that muscle strength and co-activation profiles may place girls to a greater injury risk than boys. Similar results are also reported for older individuals, where additional factors, such as body mass, also contribute to gender variations.

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Identification and preoperative optimization of risk factors to prevent periprosthetic joint infection

Seung-Hoon Baek

Seung-Hoon Baek, Department of Orthopedic Surgery, Kyungpook National University Hospital, Daegu 700-721, South Korea
Author contributions: Baek SH contributed to conception design and drafted as well as revised the article, and final approval of the version
Supported by The grant of Research Institute of Medical Science, Catholic University of Daegu (2011)
Correspondence to: Seung-Hoon Baek, MD, Department of Orthopedic Surgery, Kyungpook National University Hospital, 130 Dong-duk Ro, Jung-gu, Daegu, 700-721, South Korea. insideme@paran.com
Telephone: +82-53-4205633 Fax: +82-53-4226605
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Abstract

Despite significant improvements over the past several decades in diagnosis, treatment and prevention of periprosthetic joint infection (PJI), it still remains a major challenge following total joint arthroplasty. Given the devastating nature and accelerated incidence of PJI, prevention is the most important strategy to deal with this challenging problem and should start from identifying risk factors. Understanding and well-organized optimization of these risk factors in individuals before elective arthroplasty are essential to the ultimate success in reducing the incidence of PJI. Even though some risk factors such as demographic characteristics are seldom changeable, they allow more accurate expectation regarding individual risks of PJI and thus, make proper counseling for shared preoperative decision-making possible. Others that increase the risk of PJI, but are potentially modifiable should be optimized prior to elective arthroplasty. Although remarkable advances have been achieved in past decades, many questions regarding standardized practice to prevent this catastrophic complication remain unanswered. The current study provide a comprehensive knowledge regarding risk factors based on general principles to control surgical site infection by the review of current literature and also share own practice at our institution to provide practical and better understandings.

Key words: Total joint arthroplasty; Periprosthetic joint infection; Prevention; Risk factors; Preoperative optimization

Core tip: Despite general success in joint arthroplasty, periprosthetic joint infection remains a serious challenge. With the accelerated incidence and increased charges, PJIs are expected to impose substantial medical and socioeconomic burden in the future. There is no debate that the prevention is the first and the best strategy to minimize this catastrophic complication and the specific strategies for prevention should be integrated into and be in accordance with the general principles to control surgical site infection. Thus, we provide a comprehensive approach based on these general principles as well as own specific practice at our institution for better understandings.

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INTRODUCTION

Although significant improvements have reduced the rate of periprosthetic joint infection (PJI) in the past decades[1-3], PJI still remains the leading cause of revision after total knee arthroplasty (TKA) ranging from 0.4% to 4.0%, and it is the third most common complication afflicting 0.3% to 2.2% following total hip arthroplasty

(THA)[4-7]. A study performed in the United States using the Nationwide Inpatient Sample database estimated that the number of primary TKA and THA would increase by 673% and 174%, respectively from 2005 to 2030[8]. With increasing number of arthroplasties performed every year, the corresponding increase in the number of PJIs is also expected. The authors predicted that the burden of PJI would increase from 1.4% to 6.5% after THA and from 1.4% to 6.8% after TKA, respectively during same period.

Prevention is the first and best strategy to minimize this catastrophic complication. With the recent emerging interests in prevention, several reviews have described the strategies, but most of them put emphasis on intra- or post-operative measures[3,9-19]. Although each reviews provided invaluable information, the strategies to minimize PJI should start from identifying and optimizing preexisting risk factors. The understanding of these risk factors can help identifying patients at high risk and proper screening for prior medical conditions is essential to develop appropriate interventions for those patients. Moreover, those interventions should be integrated into and be in accordance with the general principles for surgical site infection (SSI). Therefore, the purpose of this article is to provide comprehensive knowledge on identifying and optimizing risk factors to minimize PJI based on recommendations on such as a guideline for prevention of SSI by the US Centers for Disease Control and Prevention (CDC) (Table 1)[20]. Also we will provide individualized practice at our institution for practical and thus, effective understanding.

Demographic characteristics such as gender are seldom changeable and will be explored first. Others that increase the risk of PJI, but are potentially modifiable should be optimized prior to elective arthroplasty. In the following sections, demographic characteristics that increase the risk of PJI, will be presented and followed by preexisting comorbidities potentially modifiable

DEMOGRAPHIC CHARACTERISTICS

Specific demographic characteristics such as male gender[4,21,22] and low socioeconomic status[4,22,23] are associated with increased risk of PJI. Female had a significantly lower risk of PJI by 17% after THA[4] and 24% after TKA[22]. The first year following THA, the annual incidence was relatively stable up to 10 years follow-up at 0.3% for female and 0.4% for male[4]. Patients receiving public assistance for Medicare premium, a national social insurance program employed in United States, were at elevated risk for developing PJI by 34% after THA[4] and 27% after TKA[22]. A hypothesis explaining these increased risk is that low socioeconomic status may reflect the level of nutrition, smoking status or preexisting comorbidities, all of which would contribute to the risk of PJI[4] or other complications such as mortality[24] and poor functional outcome[25].

PREEXISTING COMORBIDITIES

Controversies remain regarding some of these risk factors due to lack of prospective studies of high quality as well as low incidence of PJI. Studies using Medicare administrative claims data providing up to 10 years of follow-up identified the following independent risk factors for PJI (in decreasing order of significance): congestive heart failure, chronic pulmonary disease, preoperative anemia, diabetes, depression, renal disease, pulmonary circulation disorders, obesity, rheumatologic disease, psychoses, metastatic tumor, peripheral vascular disease, valvular disease in THA[26] and rheumatologic disease, obesity, coagulopathy and preoperative anemia in TKA[27]. Among retrospective studies with fewer subjects from a single institution, Keats[28] reported higher American Society of Anesthesiologists (ASA) score, morbid obesity, bilateral arthroplasty, knee arthroplasty, allogeneic transfusion, postoperative atrial fibrillation, myocardial infarction, urinary tract infection and longer hospitalization as risk factors for developing PJI within the first year after TJA[5]. ASA score ranks patients for risk of adverse events during an operative procedure and this classification is usually used as a surrogate for underlying severity of illness[29]. Lai *et al*[30] also reported that diabetes, absence of prophylactic antibiotics, previous operations, remote infection and total number of medical comorbidities including cardiovascular, respiratory, gastrointestinal, genitourinary, metabolic/endocrine, neurologic and hematologic conditions had a cumulative effect on the likelihood of developing PJI and each medical comorbidity increased the risk of PJI by 35%. In the following sections, risk factors that are commonly encountered will be discussed separately:

Cardiac disorder

The adjusted hazard ratio (HR) after TKA in patients with congestive heart failure is 1.28, for valvular disease 1.15, and pulmonary circulation disorders 1.42[26]. Patients with cardiac disorders have a higher chance of receiving aggressive anticoagulation, an independent risk factor for developing PJI due to post-operative hematoma[31]. Patients with serious cardiac disorder are generally more sick and older and have slower wound healing resulting in later infection[5]. Thus, the patients at higher risk should be referred to a cardiologist for a pre-operative evaluation. We currently give no aggressive anticoagulation to these patients.

Preoperative anemia

Patients with preoperative anemia are at increased risk for developing PJI, HR of 1.36 after THA[27] and HR of 1.26 after TKA[26]. Patients with preoperative anemia undergoing arthroplasty are more likely to receive allogeneic blood transfusions[32], increasing the risk of postoperative infection[33]. Preoperative prescription of medication such as recombinant human erythropoietin can decrease the need for transfusion, lessening the risk of PJI[34]. Because of high cost, however, we currently do not prescribe preoperative erythropoietin, but instead, evaluate any possible causes of anemia such as poor nutrition, another risk factor for developing PJI[27]. We don't withhold nec-

Table 1 Risk factors for periprosthetic joint infection

Risk factors	Grade of recommendation by CDC[20]
Demographic characteristics	
Gender	-
Socioeconomic states	-
Preexistent comorbidities	
Cardiac disorder	-
Preoperative anemia	-
Obesity	-
Diabetes	Category Ⅰ B
Smoking	Category Ⅰ B
Malnutrition[1]	No recommendation. Unresolved issue
Rheumatologic disease and	No recommendation. Unresolved issue
Cessation of Steroid use[2]	
Coagulopathy	-
Malignancy	-
Depression and Psychosis	-
Treat remote or coexistent infection prior to operation	Category Ⅰ A

[1]Enhance nutritional support for surgical patients solely as a means to prevent infection; [2]Taper or discontinue systemic steroid use (when medically permissible) before elective operation. CDC: Centers for Disease Control and Prevention. Category Ⅰ A: Strongly recommended for implementation and supported by well-designed experimental, clinical, or epidemiological studies; Category Ⅰ B: Strongly recommended for implementation and supported by some experimental, clinical, or epidemiological studies and strong theoretical rationale; Category Ⅱ: Suggested for implementation and supported by suggestive clinical or epidemiological studies or theoretical rationale. No recommendation. Unresolved issue. Practices which insufficient evidence or no consensus regarding efficacy exists.

essary blood products from surgical patients as a means to prevent infection

Obesity

Obese patients are at higher risk of PJI after THA (HR of 1.73) than after TKA (HR of 1.22)[26]. The attributed risk of obesity for PJI has been reported at 2.7% after THA[27]. Patients with a BMI more than 20% of their ideal weight are also at increased risk of developing an infection due to "paradoxical malnutrition"[35,36]. Although obesity is frequently difficult to modify, weight reduction prior to elective arthroplasty should be recommended to minimize PJI. Even when patients are considering surgical management for weight reduction such as gastric bypass, this counsel should come first to pursue the benefit of weight reduction. Although morbid obesity is rare in Asians, obese patients are routinely counseled for weight reduction prior to elective arthroplasty and surgical procedures for weight reduction are rarely performed at our institution.

Diabetes

According to the study using Medicare administrative claims data, 22% of patients undergoing TKA had diabetes and those with diabetes were at increased risk with HR of 1.19 for developing infection after TKA[26]. Currently, our policy is that we do not perform elective arthroplasty in patients with uncontrolled glucose levels and hemoglobin A1C levels that reflect long-term glucose control should be normalized (under 6.9%) in diabetic patients, especially when combined with anemia.

Peripheral vascular disease and smoking

Vascular insufficiencies are at increased risk of PJI, especially after TKA with HR of 1.13[26]. Also, smoking is associated with a higher rate of developing infection after TKA[37]. Smoking has deleterious effects including decreased tissue oxygenation, impaired neutrophil defense and resultant retardation of wound healing[38-40]. Following CDC guidelines, we currently enroll smokers in a smoking cessation program and instruct them to abstain for at least 30 d before elective arthroplasty. Working with patients and an appropriate consultant together is often beneficial to optimize this risk factor and reduce the risk of PJI.

Malnutrition

Although theoretical arguments can be made for a belief that preoperative malnutrition should increase the risk of PJI, the CDC reported that benefits of preoperative nutritional repletion of malnourished patients in reducing SSI risk were unproven and concluded that randomized clinical trials would be necessary to determine if nutritional support alters SSI risk in specific patient-operation combinations (Table 1)[41]. The diagnosis of malnutrition can be made if serum transferrin levels are less than 200 mg/dL, serum albumin less than 3.4 g/dL, and total lymphocyte count less than 1500 cells/mm^3[42]. Greene *et al*[35] reported that preoperative lymphocyte count of less than 1500 cells/mm^3 was associated with a five times greater frequency of developing a major wound complication and an albumin level of less than 3.5 g/dL had a seven times greater risk. At our institution, the level of serum albumin and total lymphocyte count can be easily obtained from routine blood test and elective arthroplasty is delayed in any patients in whom malnutrition is diagnosed until nutritional status improves and medical underlying conditions are optimized.

Rheumatologic disease and immunosuppressant

Patients with rheumatoid arthritis are at increased risk of developing PJI[4,26,27] and the independent attributable risk for developing PJI has been reported up to 5.5% with HR of 1.71 after THA[27] and HR of 1.18 after TKA[26]. The increased risk seems mainly due to the immunosuppressive disease modifying drugs and use of systemic steroids for extended periods[30,36,37]. The CDC reported that data supporting this relationship were contradictory (Table 1)[41], but these controversies may originate from imbalance between suppressive effect of inflammatory disease process and deleterious effect of immune suppression by long-term use of immunosuppressive agents. We currently taper or discontinue systemic steroid use when medically permissible or unless flare is apparent.

Coagulopathy

Coagulopathy including high international normalized ra-

tio (INR), can lead to a higher chance of intra-operative bleeding and subsequent hematoma formation[21,31,36,43] and is an independent risk factor with an attributable risk of 2.7% as well as HR of 1.58 after THA[27]. Recently, increased compliance for venous thromboembolism (VTE) prophylaxis has led to unintended bleeding and increased infections after THA[44]. We routinely use intermittent pneumatic compression device, but reserve chemoprophylaxis against VTE for selective patients with positive ultrasonographic findings because the prevalence of VTE in Korean patients without thromboprophylaxis is reported to be low[45].

Malignancy

Berbari *et al*[46] suggested that the presence of a malignancy is associated with an increased risk of PJI in a matched case-control study and Bozic *et al*[26] reported metastatic tumor as a risk factor with HR of 1.59 as well. At our institution, optimization after evaluating immune function as well as nutritional status are important steps in these patients in whom elective arthroplasty is scheduled.

Depression and psychosis

Depression and psychosis are risk factors of developing PJI after TKA with HR of 1.28 for depression and with HR of 1.26 for psychosis[26]. Depression may be associated with poor nutritional status, an important risk factor for the development of PJI[47]. At our institution, evaluation of coexisting depression is integrated with the initial medical screening and often, management of depressive mood itself improves the clinical symptoms of osteoarthritis. Consequently, we can avoid unnecessary arthroplasty in early stage[47]. Also, we rarely perform elective arthroplasty in patients with psychosis.

Remote or coexistent infection

It is critical to make sure that the patient has no other remote or concurrent infections such as a urinary tract infection and those with remote infections should be optimized by eradication of the infection prior to elective arthroplasty with appropriate antibiotic therapy[5,20]. Human immunodeficiency virus (HIV) is a risk factor for developing PJI and those with HIV should be placed on regimens to maintain the viral load under detectable level[48,49]. In our institution, these infections should be eradicated via appropriate antibiotic therapy prior to elective arthroplasty except hemiarthroplasty for patients with femur neck fracture. We don't have an experience of arthroplasty in those with HIV because of low prevalence in our country.

Other comorbidities

Patients with chronic renal insufficiency should have normal creatinine value before the elective arthroplasty[50]. Although the creatinine values may be optimized, patients with chronic renal failure are still at high risk of mortality and morbidity including PJI (HR of 1.38 after TKA)[26,51,52]. General skeletal abnormalities and combined multiple comorbidities in these patients may explain the increased risk for developing PJI. However, among 32 THAs performed in 18 patients with chronic renal failure (five patients received kidney transplantation later) at our institution, two patients (4 hips) died at two and four years after THA. At the average follow-up of 147 mo, there were two cup revisions due to aseptic loosening, and the remaining 14 patients who have survived have no infection or no revision yet.

Prior history of infection or steroid injection at the same joint was reported as a risk factor for developing PJI that is seldom modifiable[53,54]. We routinely delay TKA in patients with a history of recent injection into the knee joint within 4 weeks and use antibiotic-impregnated cement when performing TKA in these patients.

INTEGRATION OF MULTIPLE RISK FACTORS AND MEDICAL CLEARANCE

The risk factors mentioned above are all important for developing PJI. Measures like the modified Charlson Comorbidity Index[55] or ASA score are of value to quantify overall health of the patient. Patients with an ASA score more than 2[5] or 3[23] are at significantly higher risk for developing infection following THA. Also, those with a Charlson index score greater than 4 are at 157% increased risk of infection after THA and 116% after TKA compared to those with a score of 0[4,22,23]. While these measures help imagine overall pictures of the patients, they are often of limited value at the time of counseling with evaluating the individual-specific risks for developing PJI[27]. An easily accessible electronic risk calculator has recently been developed to provide the individualized risk for PJI after THA integrating interactions between and synergistic effect of these risk factors, especially in patients who have multiple comorbidities[56].

We currently start preoperative medical screening with questionnaires regarding individual background medical history and preoperative routine tests including electrocardiography, chest radiography, blood test and urinalysis. In addition to history taking and laboratory test, we conduct a thorough clinical evaluation with observation of clinical signs or symptoms and physical examination. This is especially important in Asian countries, where acupuncture or moxa cautery is in common use. Also, skin ulceration implies vascular insufficiency or neuropathy, and a patient with any skin problems is not an ideal candidate for elective arthroplasty. These patients are referred to a dermatologist and surgery is delayed until the skin lesion improves. Once any medical comorbidity is identified, they are optimized by a medical consultant prior to elective arthroplasty and the consultant continues to follow the patients during postoperative period as well.

CONCLUSION

Thorough understanding of risk factors in individual patients and attentive application of the general principle

for preoperative optimization are paramount to reduce overall incidence of periprosthetic joint infection. Even though some risk factors such as demographic characteristics are seldom changeable, they allow more accurate expectation regarding individual risks of PJI and thus, make proper counseling for shared preoperative decision-making possible. Others that increase the risk of PJI, but are potentially modifiable should be optimized prior to elective arthroplasty. Although remarkable advances have been achieved in past decades, many questions regarding standardized practice to prevent this catastrophic complication remain unanswered. Randomized controlled trials incorporated with general principles for preventing surgical site infection are necessary to determine the best approach.

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Complications of hip fractures: A review

Pedro Carpintero, Jose Ramón Caeiro, Rocío Carpintero, Angela Morales, Samuel Silva, Manuel Mesa

Pedro Carpintero, Rocío Carpintero, Samuel Silva, Department of Orthopaedic, University Hospital Reina Sofía, 14004 Córdoba, Spain
Jose Ramón Caeiro, Department of Orthopaedic, University Hospital Santiago de Compostela, 15006 La Coruña, Spain
Angela Morales, Department of Anesthesia, University Hospital Reina Sofia, 14004 Córdoba, Spain
Manuel Mesa, Orthopaedic Department, Hospital Valle de los Pedroches, 14400 Pozoblanco, Spain
Author contributions: All the authors contributed to the conception and design of the work, revised carefully the content and approved the final version of the manuscript.
Correspondence to: Pedro Carpintero, MD, PhD, Department of Orthopaedic, University Hospital Reina Sofia, Menendez Pidal Avenue, 14004, Córdoba, Spain. pcarpinterobe@hotmail.com
Telephone: +34-957-218248 Fax: +34-957-218248
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Abstract

Nowadays, fracture surgery represents a big part of the orthopedic surgeon workload, and usually has associated major clinical and social cost implications. These fractures have several complications. Some of these are medical, and other related to the surgical treatment itself. Medical complications may affect around 20% of patients with hip fracture. Cognitive and neurological alterations, cardiopulmonary affections (alone or combined), venous thromboembolism, gastrointestinal tract bleeding, urinary tract complications, perioperative anemia, electrolytic and metabolic disorders, and pressure scars are the most important medical complications after hip surgery in terms of frequency, increase of length of stay and perioperative mortality. Complications arising from hip fracture surgery are fairly common, and vary depending on whether the fracture is intracapsular or extracapsular. The main problems in intracapsular fractures are biological: vascularization of the femoral head, and lack of periosteum -a major contributor to fracture healing- in the femoral neck. In extracapsular fractures, by contrast, the problem is mechanical, and relates to load-bearing. Early surgical fixation, the role of anti-thromboembolic and anti-infective prophylaxis, good pain control at the perioperative, detection and management of delirium, correct urinary tract management, avoidance of malnutrition, vitamin D supplementation, osteoporosis treatment and advancement of early mobilization to improve functional recovery and falls prevention are basic recommendations for an optimal maintenance of hip fractured patients.

Key words: Hip fracture; Complications; Morbidity; Mortality; Anesthesia

Core tip: Over 90% of hip fracture patients are older than 65-year-old and have preexisting medical comorbidities. Both factors have an important influence in its prognosis and treatment. Even with optimal care, elderly trauma patients suffer a higher morbidity and mortality rate when compared with the general population, and often demand for expensive hospital aftercare. Because of that, surgical treatment of hip fracture in these patients has exceptional clinical challenges, and needs strategies to optimize patient care. Acute orthogeriatric units, with medical co-management of these patients, offer the best chance for a successful outcome.

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COMPLICATIONS OF HIP FRACTURES

Overall importance

Nowadays, hip fracture surgery represents a large quota

Table 1 Medical complications after hip fracture surgery

Medical complications		Perioperative incidence	Intervention/recommendation[1]
Cognitive and neurological	Cognitive alterations	10%	Preventive interventions in high-risk patients
	Postoperative delirium	13.5%-33%	Preventive role of antipsychotics (haloperidol)
Cardiac and vascular	Arrhythmia		Evaluation and care of patients with previous heart affectation
	Heart failure/Myocardial ischemia	35%-42%	Restoration of fluid status to euvolemic. Beta-blockers if necessary
	DVT/PE	27%/1.4%-7.5%	Thromboembolism prophylaxis Early mobilization
Pulmonary	PPCs (exacerbation of chronic lung disease, atelectasis, respiratory failure, PE, ARDS)	4%	Evaluation and care of patients with previous lung disease Adequate postoperative fluid balance and pain control
	Hospital-acquired pneumonia	7%	Thromboembolism prophylaxis Timely diagnosis, adequate antibiotic treatment and accurate monitoring
Gastrointestinal	PGICs (dyspepsia, abdominal distension, reflexes ileum and constipation)	5%	Adequate postoperative fluid, diet, pain and medication management
	Gastrointestinal postoperative stress ulcer/ gastrointestinal bleeding	1.9%	Gastrointestinal bleeding prevention with pump inhibitors
Urinary tract	Urinary retention Urinary tract infections	12%-61%	Urinary catheters should be taken out as soon as possible, preferably within 24 h after insertion Timely diagnosis and adequate antibiotic treatment Preventive identification of pre, peri or postoperative medical or surgical risk factors
	AKI (prerenal, renal or postrenal)	11%	Timely diagnosis, adequate treatment and accurate monitoring
Hematologic	Anemia	24%-44%	Preventive identification of pre, peri or postoperative medical or surgical risk factors Correct hemoglobin level to $\geqslant$ 10 g/dL before surgery In anticoagulated patients, correct international normalized ratio to $\leqslant$ 1.5 preoperatively Timely diagnosis, adequate treatment and accurate monitoring
Endocrino-metabolic	Protein-caloric malnutrition	20%-70%	Nutritional supplements in peroperative period
	Diabetes	17%	Maintain glucose levels between 100 and 180 mg/dL
	Vitamin D insufficiency-deficiency		Vitamin D supplementation
Other	Pressure scars	7%-9%	Early surgery fixation (within 24-48 h in stable patients) Alternating pressure mattresses, pressure-relieving beds and equipment, aggressive skin care and proper nutrition, prevention-focused nursing

DVT/PE: Deep vein thrombosis/pulmonary embolism; PPCs: Postoperative pulmonary complications; PGICs: Postoperative gastrointestinal complications; AKI: Acute kidney injuries. [1]Each patient needs a preoperative functional assessment, joint orthopedic-geriatric care is of benefit, reducing inpatient complications, length of stay and mortality.

of the orthopedic surgeon activity, and normally has associated major clinical and social cost implications[1]. Though hip fracture incidence has declined in many countries during the last decade, it still represents around 1/4 of the geriatric fractures that require hospital admission, and in spite of the enhancements in both surgical and medical services, its morbidity and mortality remains elevated[2]. Over 90% of hip fracture patients are older than 65 years old and have preexisting medical comorbidities. Both factors have an important influence in its prognosis and treatment[3]. Even with optimal care, elderly trauma patients suffer a higher morbidity and mortality rate when compared with the general population, and often demand for expensive hospital aftercare. Because of that, surgical treatment of hip fracture in these patients has exceptional clinical challenges, and needs strategies to optimize patient care. Acute orthogeriatric units, with a medical co-management of these patients, offer the best chance for a successful outcome[4-6], with some studies demonstrating a decrease in postoperative complications and mortality[7-9]. Early surgical fixation, the role of anti-thromboembolic and anti-infective prophylaxis, good pain control at the perioperative, detection and management of delirium, correct urinary tract management, avoidance of malnutrition, vitamin D supplementation, osteoporosis treatment and promotion of early mobilization to improve functional recovery and falls prevention are basic recommendations for an optimal care of hip fractured patients.

Medical complications of hip fractures

Though a retrospective cohort study has reported that most patients have no medical problems after hip fracture repair[10], postoperative complications of this procedure are still relevant, and may affect around 20% of patients with hip fracture[11]. Cognitive and neurological alterations, cardiopulmonary affections (alone or combined), venous thromboembolism, gastrointestinal tract bleeding, urinary tract complications, perioperative anemia, electrolytic and metabolic disorders, and pressure scars are the most important medical complications after hip surgery in terms of frequency, increase of length of stay and perioperative mortality[6,12] (Table 1).

The American Society of Anesthesiologists (ASA)

classification can be a useful risk-stratification system for aged patients who have a hip fracture. In a retrospective study, medical complications were more usual in patients in ASA class 3 and 4 ($P \leqslant 0.001$) than those in ASA class 2, having respectively 3.78 and 7.39 times greater probability of suffering complications of this type[13]. With a similar clinical usefulness, a recent prospective study has demonstrated that advanced age (OR = 1.09), poor Barthel index (OR = 2.21) and low hemoglobin at admission (OR = 0.76) are factors associated with the development of medical inpatient complications[12].

Cognitive and neurological complications

Cognitive complications appear in approximately 10% of patients after hip fracture surgery, being more common in elderly (> 65 years) than younger patients. Most of them suffer mild problems after surgery (inability to concentrate, write, read a book, *etc*.) but are able to overcome activities of daily living[14].

The physiopathology of postoperative cognitive problems has not been yet clearly elucidated. Probably, its responsible mechanisms are heterogeneous and multifactorial, and may be related to preoperative health status, level of cognition (cognitive reserve), the neurotoxic effects of anesthetic agents and perioperative events related to the surgery itself[15]. In this sense, the use of acrylic cement for prosthetic implantation can cause an inflammatory response that may possibly be associated with the occurrence of postoperative cognitive complications[16]. Upcoming research must be focused on actions to prevent and treat postoperative cognitive complications in patients at high-risk[14].

Postoperative delirium in patients with hip fracture appears normally after surgery, and affects 13.5% to 33% of these patients[17]. It has a variable presentation, and patients may reveal hyperactive, hypoactive, or mixed cognitive and motor statuses. While hyperactive patients present augmented psychomotor activity (pressured speech, irritability and uneasiness), hypoactive ones normally exhibit quiet appearance, carelessness, reduced mobility and trouble to answer simple questions about themselves and/or special-temporal orientation[18]. Hypoactive delirium may be misdiagnosed as depression or fatigue[14]. Causes of postoperative delirium are multifactorial and include advanced age, history of cognitive impairment, history of alcohol abuse, preoperative medication (especial attention to unrecognized benzodiazepine use), type of anesthetic used during surgery, infection, urinary retention and fluid or electrolyte disturbance[15,19]. Postoperative delirium amplifies the risk of poorer outcomes, medical complications, mortality and institutionalization in patients with hip fracture[6], being necessary to establish early prevention and treatment interventions to reduce its incidence in high-risk patients.

Regional anesthesia (especially spinal anesthetic with very light sedation) probably reduces the incidence of delirium early after surgery[20]. Supplemental oxygen (3-4 L/min) continually till day 2 post-surgery, or while patient's oxygen saturation is not $\geqslant$ 95% without oxygen, have proven to reduce delirium risk[21]. Because pain can contribute to delirium, an adequate postoperative analgesia minimizing the use of sedative drugs and anticholinergic medications seems to decrease its risk. It is necessary to take in count that narcotics also produce sedation and may contribute to its appearance. Though the preventive role of certain medications (antipsychotics, sedatives and cholinesterase inhibitors) has not been yet clearly elucidated[6], some studies have proven that low doses of haloperidol are effective in delirium prevention in this patient population.

Cardiac and vascular complications

A report of the American College of Cardiology and the American Heart Association (ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery) estimates at less than 5% the risk of cardiac complication in postoperative after orthopedic major surgeries, but the 1-year recorded mortality exceeds 20% in patients with hip fracture[22].

The main reasons of in-hospital cardiac related mortality after hip fracture are heart failure and myocardial ischemia, which normally come out quick after fracture in patients with previous heart affectation[23]. The general incidence of perioperative myocardial ischemia in aged patients suffering hip fracture surgery has been informed to be 35% to 42%[24]. Deep venous thrombosis (DVT) is one of the principal causes of perioperative morbidity and mortality. In lack of thromboembolism prophylaxis, the prevalence of venography-detected proximal DVT ascend to 27% of patients[25]. The incidence of fatal pulmonary embolism oscillates between 1.4% to 7.5% of patients within 3 mo of hip fracture surgery[25]. Thromboembolism prophylaxis reduces the rate of DVT by approximately 60%[26]. Regional anesthesia significantly reduces as well these complications, probably in relation with its capability to generate peripheral vasodilatation and to maintaining venous blood flow in the lower extremities, as well as to promote a local inhibition of platelet aggregation and stabilization of endothelial cells[27].

Pulmonary complications

Postoperative pulmonary complications (PPCs) were defined as anomalies of the lung resulting in an identifiable disease with adverse impact in the clinical course of the patient[28]. They are quite common (4% of patients) and suppose an increase length of stay, morbidity and mortality, in patients who had undergone hip fracture surgery. For those reasons, PPCs occurrence may predict long-term survival, particularly among patients older than 70-year-old[28]. Clinical important PPCs after hip fracture surgery comprise exacerbation of chronic lung disease, atelectasis, respiratory failure, pneumonia, pulmonary thromboembolism and acute respiratory distress syndrome[28].

A high number of PPCs risk factors have been identified, such as disorders of central nervous system, medication reducing alertness, treatment with dopamine antagonists, *etc*. Adequate postoperative fluid balance

and pain control may help to diminish PPCs by enabling earlier ambulation and improving the patient's ability to take deep breaths. Hospital-acquired pneumonia has a high incidence and an important clinical relevance in-between PPCs, being currently the second most frequent nosocomial infection[6]. In addition to other PPCs risk factors, this entity is associated to immunosenescence, a change in the immune response associated with increased age, which causes higher rates of infection and impaired wound healing[29]. Moreover, age-related changes of the lung epithelium contribute to the higher susceptibility to chest infections, since fibrillation frequency and clearance of the respiratory epithelium decrease with higher age[28]. If a chest infection occurs after hip fracture surgery, timely diagnosis, treatment and accurate monitoring are required[21].

Gastrointestinal complications

Common postoperative gastrointestinal complications after hip fracture surgery include dyspepsia, abdominal distention, reflexes ileum and constipation[6]. Gastrointestinal postoperative stress ulcer and secondary bleeding are well documented as a medical complication after hip surgery[6], especially in patients with a history of previous gastroduodenal ulcers. Prevention of gastrointestinal bleeding with pump inhibitors, antacids, *etc*. is extremely important in this clinical situation, in order to minimize the morbidity and mortality associated with it.

Urinary tract complications

The most common postoperative urinary tract complications after hip surgery are urinary retention, urinary infections and acute kidney injuries[6].

Controlled trials have found that patients who had scheduled intermittent catheterization immediately after surgery or their catheter removed the morning after surgery, had lower rates of urinary retention[30]. For those reasons, urinary catheters should be removed as soon as possible, though the evidence is already limited[6].

Urinary tract infections are the leading cause of nosocomial infection and affect 12% to 61% of all patients with hip fractures[31]. Urinary tract infections are considered an important delirium factor risk, and are responsible to prolong the hospital stay for another 2.5 d and even a higher mortality rate[21]. Urinary catheters are the single most important risk related to this type of postoperative infection. Therefore, indwelling catheters should be preferably removed within 24 h after insertion[32].

The incidence of acute kidney injuries (AKI) among aging patients undergoing arthroplasty for femoral neck fractures ranges from 16% to 24.4%[33]. Postoperative AKI (prerenal, renal or postrenal acute failure) is often multifactorial and may be related to pre, peri or postoperative medical or surgical factors (age, emergency surgery or longer preparation time, dehydration, malnutrition, nephrotoxic drug use, including NSAID, type of surgical procedure, chronic obstructive pulmonary disease, congestive heart disease, peripheral vascular occlusive disease, chronic kidney disease, *etc*.)[33].

If an AKI occurs after hip fracture surgery, timely treatment and accurate monitoring are required, in order to minimize the risk of permanent kidney damage[33].

Hematologic complications

The prevalence of perioperative anemia in hip fractured patients ranges from 24% to 44%, being even higher if consider only the postoperative one (51% to 87%)[34].

Oscillation of hemoglobin during a hip fracture hospital stay can be attributed to several causes. Preoperative ones are normally related to the fracture itself, because blood loss from a hip fracture can be up to 500 mL[35], while intraoperative ones comprise fluid shifting and significant blood loss during surgery. Postoperative anemia can happen from repeated phlebotomy or hemodilutional anemia[34].

Perioperative anemia has been consistently connected to adverse events in patients undergoing hip fracture surgery. It is related to other medical complications and increased hospitalization duration, rate of readmission and death. Risk factors linked up with this bigger rate of complications include age, inadequate pre-fracture functional level, cardiovascular or pulmonary diseases, low hemoglobin, fracture type, anesthetic type (neuraxial anesthesia and associated sympathetic blockade reduces intraoperative bleeding even under normotensive conditions), length of surgery, and the degree of intraoperative bleeding[15]. Values of hemoglobin concentration $\leqslant$ 10 g/dL at admission are an independent predictor of increased mortality at 30 d in patients with hip fractures[36].

Endocrine-metabolic complications

Malnutrition, which is in general prevalent among the elderly population, is even more frequent among patients hospitalized for hip fracture, with rates ranging from 20% to 70%[6]. Malnutrition affects many organs and corporal systems, causing sarcopenia and impairing mental, cardiac and immune function. Consecutively, patients with a protein-caloric malnutrition have higher medical and surgical complication rates (including pressure scars and perioperative infectious complications), lower functional capability and a higher mortality[6,37].

Lower values of Body Mass Index and/or triceps skinfold, albumin, retinol binding protein and cholesterol are related to malnutrition and increase in a dependent way the risk of mortality in institutionalized elderly patients[38]. Men with hip fractures have normally inferior nutritional status than women, which may be one of the factors that explain their increased mortality[38]. Several studies have found a lower acute mortality in patients with hip fracture whom a nutritional supplement is administered in the perioperative period[6].

Diabetes, either type 1 or 2, is frequent in patients with hip fracture. In fact, type 2 diabetics are 70% more likely to suffer this type of fracture. Diabetes decompensation is a quite common preoperative complication of patients that undergo hip fracture surgery, and is associated with both increased risk of asymptomatic coronary heart disease and perioperative infection.

Other complications

Pressure scars result from an imbalance between extrinsic mechanical forces acting on skin and soft tissue, and the intrinsic susceptibility to tissue to collapse. Acute hip fractures are their most frequent causes. Close to 35% of decubitus ulcers occur at the conclusion of the first week of hospitalization.

Risk factors of pressure scars include age, malnutrition, history of smoking and systemic illnesses[34]. The use of foam or alternating pressure mattresses, special beds and equipment to relieve pressure, aggressive skin care, nursing focused on prevention, and good nutrition help prevent the evolution to ulceration[34].

Per and postoperative mortality

Hip fracture has an overall 1 year mortality rate that varies from 14% to 36% among patients aged 65 or above, being higher among men and women, especially after 5 to 10 years after fracture[15,39], and in addition, the survivors have a shorter life expectancy[34]. Mortality is significantly influenced by preoperative cognitive state, medical comorbidities and mobility. Dementia, chronic obstructive pulmonary disease, chest infection, heart failure, anemia, abnormal sodium (low or raised), elevated urea, elevated creatinine and malignancy, have all been described as risk factors for increased mortality in the months following a hip fracture. Patients with an acute heart failure or a postoperative chest infection had a high 30-d mortality of 65% and 43%, respectively[6]. However, postoperative complications increase short and long-term mortality[3].

From the anesthetic and surgical point of view, patients with a high ASA score and patients treated non-operatively have a higher mortality rate[40]. Patients operated within 48 h appear to have a better outcome than those with a delayed surgical intervention. However, in medically unstable patients, a delay of surgery does not result in a statistically significant difference in mortality compared to patients treated surgically[15].

The Nottingham Hip Fracture Score has been validated as a useful tool to predict hip fracture mortality at 30 d. Independent predictors of mortality in patients with hip fracture included masculine sex, age > 86-year-old, two or more comorbidities, anemia, and a mini mental test score ⩽ 6 of 10[36].

Clinical and surgical decision making may be personalized to each patient according to an accurate mortality risk assessment[13]. Complication and mortality scoring systems may allow a better informed discussion between doctors and patients.

Anesthetic complications of hip fractures

The incidence of anesthetic complications during hip fracture surgery is influenced not only by the anesthetic technique used, but also by patient comorbidities, the delay between admission and operation, and the surgical technique employed.

A number of meta-analyses report that an operative delay of over 48 h leads to increased morbidity (*e.g.*, pressure scars, pneumonia, thromboembolic phenomena) and even to increased mortality[41-43].

The most frequently-encountered anesthetic complication is arterial hypotension, defined as a preoperative drop in mean arterial blood pressure of more than 30%, or a presurgical pressure reading of 60-70 mmHg[44]. Arterial hypotension has been reported in 15%-33% of patients during the first 20 min after spinal anesthesia induction. This form of anesthesia prompts a sympathetic nervous system block, leading to decreased venous return and thus to impaired peripheral vascular resistance. But hypotension may arise independently of the anesthetic technique used: patients are often hypovolemic due to a fracture-induced loss in blood volume, to the ingestion of diuretics, or to inappropriate fluid intake resulting from immobility, dementia or other causes. All these factors can enhance the hypotensive effect of anesthetics.

Around 25% of hip fracture patients display at least one episode of cognitive dysfunction during hospitalization[42]. A systematic review published by Cochrane in 2004 suggests that the use of spinal anesthesia may reduce the incidence of postoperative confusion. Since spinal anesthesia is also associated with a lower incidence of deep venous thrombosis, recent meta-analyses recommend this as the technique of choice for hip fracture repair, as long as it is not contraindicated[42,43].

Another complication which, though much less common, may prove fatal, is the use of bone cement, which can give rise to the so-called bone cement implantation syndrome (BCIS)[42,45]. Clinical features of this poorly-understood syndrome include hypoxia, hypotension, cardiac arrhythmias, lung hypertension, and a decline in cardiac output. The cardiopulmonary complications of BCIS can be reduced through modern cementing techniques, appropriate anesthesia interventions, and adequate patient preparation, as well as by avoiding the use of cement altogether.

In short, it is impossible to apply a single protocol for hip fracture repair, valid for all patients. The protocol has to be adjusted to reflect patient comorbidities, with a view to minimizing complications. It would seem to be generally accepted, nonetheless, that hip fracture surgery should be performed within 48 h of the patient's admission to hospital, and that the patient should be provided with an appropriate analgesic, bearing in mind that in most cases the best analgesic is surgical treatment[42].

Surgical complications of hip fractures

Complications arising from hip fracture surgery are fairly common, and vary depending on whether the fracture is intracapsular or extracapsular. The main problems in intracapsular fractures are biological: vascularization of the femoral head, and lack of periosteum -a major contributor to fracture healing- in the femoral neck. In extracapsular fractures, by contrast, the problem is mechanical, and relates to load-bearing.

Though age, comorbidities, ASA classification and delay in surgery are correlated with both medical and surgical postoperative complications and a significantly prolonged hospital stay, there is not a well-designed study

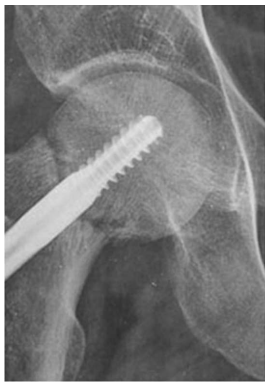

Figure 1 Intracapsular fracture. Non-union.

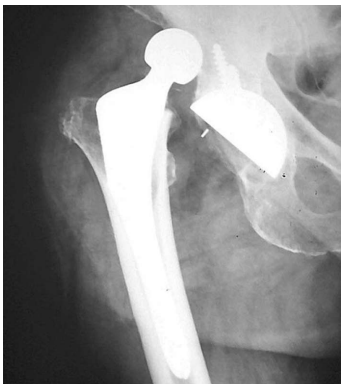

Figure 3 Total hip arthroplasty. Dislocation.

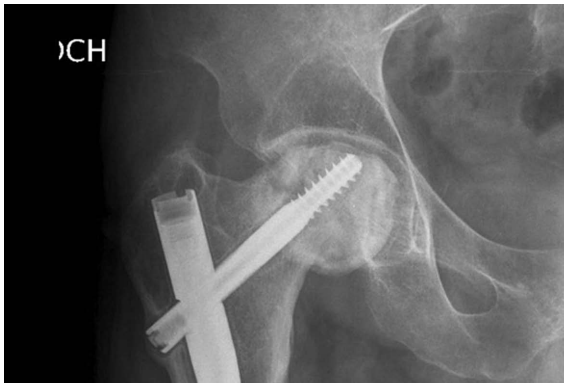

Figure 2 Femoral head necrosis.

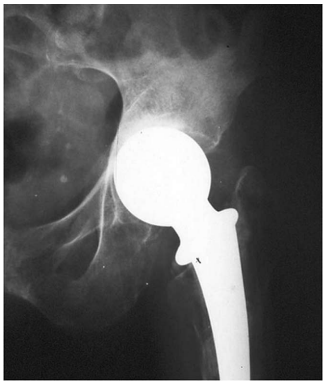

Figure 4 Acetabular erosion.

that demonstrates a relation between precisely medical complications with particularly surgical ones. Nevertheless malnutrition and diabetes seem to be clearly related to deep infections. Despite the fact that osteoporosis and poor bone quality are related to some surgical complications, the most frequent concomitant osteoporotic fractures (radial and humeral fractures) seem not influence in length of hospitalization, in-hospital mortality, complication rate, and function[46].

Intracapsular fractures

Two major complications may arise following treatment of an intracapsular fracture by osteosynthesis: non-unions and avascular necrosis.

Factors influencing the appearance of non-unions include patient age, degree of displacement, fracture line, degree of comminution and quality of reduction; non-unions are reported in between 10% and 45% of patients undergoing osteosynthesis[47] (Figure 1).

Avascular necrosis of the femoral head occurs in 9%-18% of patients, between two and eight years post-fracture; risk factors include the degree of fracture displacement, patient age and delay in surgical treatment[48-50] (Figure 2).

In view of the high complication rates recorded among patients undergoing osteosynthesis, often leading to repeat surgery, several works have compared arthroplasty with osteosynthesis to treat intracapsular fractures. The results indicate significantly ($P < 0.001$) lower complication and reoperation rates in patients undergoing arthroplasty[47,48]. A number of authors therefore recommend arthroplasty for the treatment of all intra-articular fractures in elderly patients. However, arthroplasty to treat the femoral neck fracture is associated with a number of complications. Dislocation (Figure 3) is most commonly seen in total hip arthroplasty. Acetabular erosion often occurs in active patients undergoing hemiarthroplasty (Figure 4); to avoid this complication, many experts recommend total arthroplasty in these patients[51]. Thigh pain is more frequently reported in uncemented arthroplasty[52]. Moreover, though uncemented arthroplasty may result in higher hip scores, it appears to carry an unacceptably high risk of later femoral fractures[53] (Figure 5).

Extracapsular fractures

A number of postoperative complications have been reported following surgery for extracapsular fractures. The three most common are screw cut-out, femur fracture and implant failure.

Screw cut-out (Figure 6) occurs in between 1.1% and 6.3% of patients treated for an extracapsular fracture, and accounts for 85% of fixation failures[54]. The main causes of cut-out are fracture instability[55], and especially, the incorrect placement of the lag screw. The greatest predictor for the appearance of cut-out is the distance

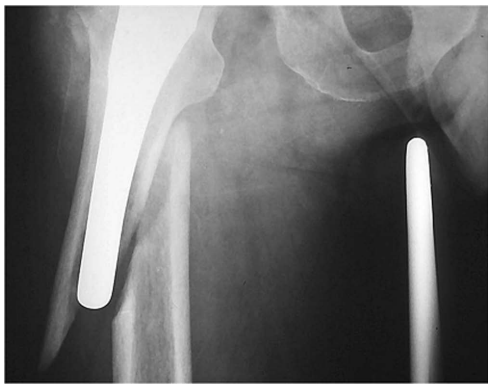

Figure 5 Uncemented hip arthroplasty. Femoral fracture.

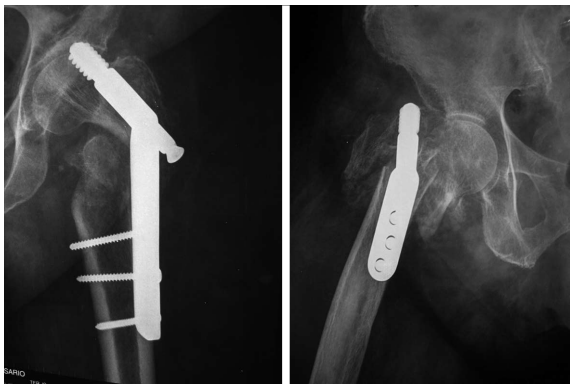

Figure 6 Cut-out.

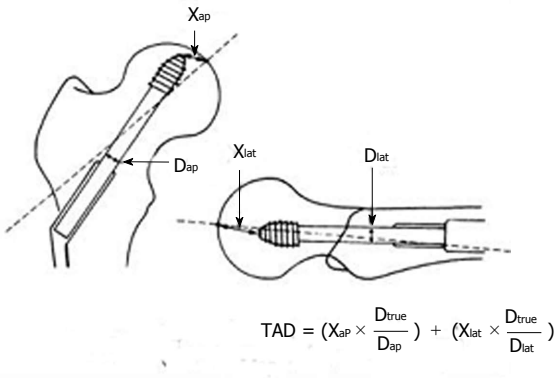

Figure 7 Tip-apex distance.

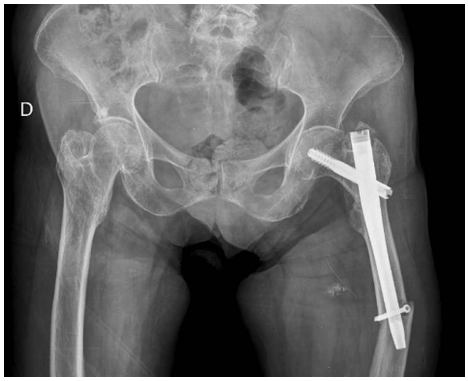

Figure 8 Femoral fracture in intramedullary nail.

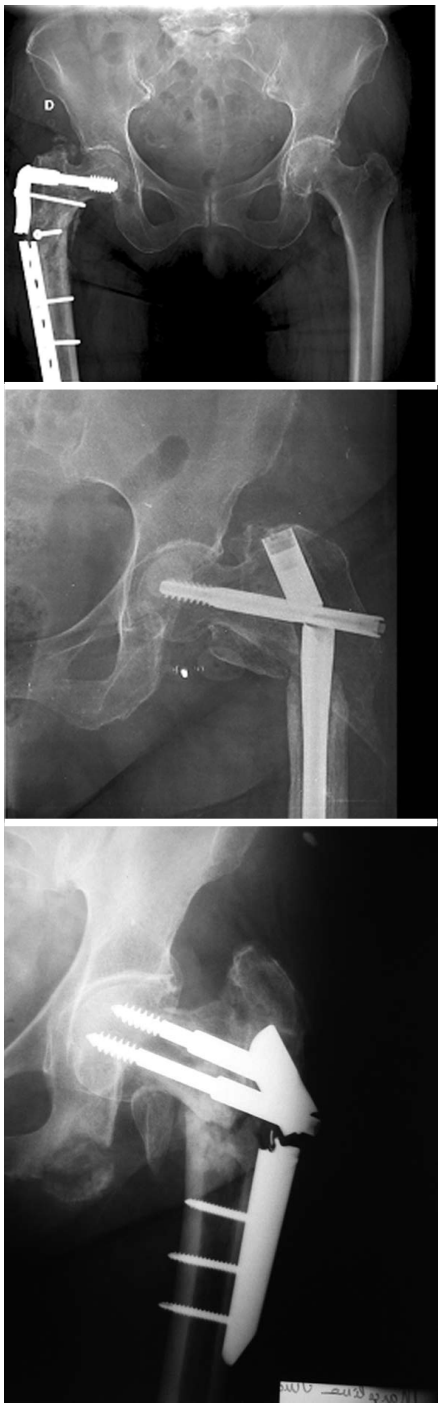

Figure 9 Different implant failures.

from the screw tip to the subchondral bone. Baumgaertner *et al*[56], have demonstrated the importance of screw placement and tip-apex distance (TAD) (Figure 7): when TAD was greater than 35 mm, the cut-out rate was 30%, while when TAD exceeded 45 mm, the cut-out rate rose to 60%. The best results have been reported with a TAD of less than 5 mm[49]. Equally important is the positioning of the lag screw in the femoral head, the ideal position being center-center; any other position of the screw tip leads to a higher cut-out rate, which a reportedly rise to 58%[49]. To avoid serious implant failure due to screw cut-out is largely conditioned by the ability of the surgeon

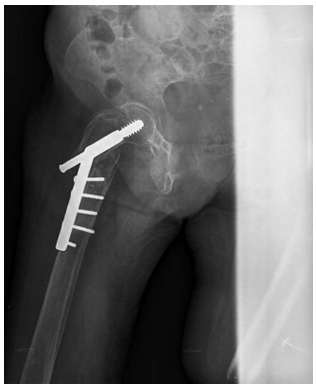

Figure 10 Excessive screw sliding.

to positioning the lag screw in the femoral head.

Femoral shaft fracture occurs much more frequently in patients treated with intramedullary nails, and particularly with first-generation nails with a larger distal diameter; according to one meta-analysis, these nails were associated with a femoral fracture rate of 5.3%[57] (Figure 8). Second-generation intramedullary nails, with reduced distal diameter and reduced valgus offset, have prompted a considerable decline in the incidence of femoral fractures[58]. Special mention should be made of reverse obliquity intertrochanteric fractures, in which extramedullary devices are associated with a failure rate of 36%, compared to only 5% for intramedullary nails, since the latter offer improved load-bearing capacity[59]. It should be borne in mind that reverse obliquity fractures of the proximal femur have biomechanical characteristics different from those of other intertrochanteric fractures. It is not yet clear whether nail length influences healing in these fractures[60].

Implant failure usually appears as a result of poor fracture reduction, mechanical stress or fracture instability, but may also be caused by technical error. Implant failure is more common when there is greater rigidity of the fraction fixation device (Figure 9).

Other complications are less frequently reported. Excessive screw sliding (Figure 10) has been linked to impaired postoperative mobility: patients with > 187 mm of sliding display the least postoperative mobility[54]. Thigh pain appears mainly in patients receiving first-generation intramedullary devices, and is linked to the use of two distal interlocking screws. Non-unions are much less common in extracapsular than in intracapsular fractures, and are reported mainly in severely comminuted fractures with bone loss.

CONCLUSION

Even with optimal care, elderly trauma patients suffer a higher morbidity and mortality rate when compared with the general population, and often demand for expensive hospital aftercare. Because of that, surgical treatment of hip fracture in these patients has exceptional clinical challenges, and needs strategies to optimize patient care. Preoperative early clinical assessment helps to identify patients at high-risk and to prevent unnecessary delays. Orthogeriatric units, with a medical co-management of these patients, offer the best chance for a successful outcome, reducing length of stay, in-patient problems and mortality, allowing the patient to recover his previous ambulatory state.

Further research is necessary to evaluate those interventions and recommendations that improve medical management of aged patients with hip fractures, in order to achieve a reduction in morbidity and mortality in these at risk population.

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Treatment of acute periprosthetic infections with prosthesis retention: Review of current concepts

Jesse WP Kuiper, Robin Tjeenk Willink, Dirk Jan F Moojen, Michel PJ van den Bekerom, Sascha Colen

Jesse WP Kuiper, Center for Orthopaedic Research Alkmaar, Medical Center Alkmaar, 1815 JD, Alkmaar, The Netherlands
Jesse WP Kuiper, Department of Surgery, Spaarne Hospital, 2134 TM, Hoofddorp, The Netherlands
Robin Tjeenk Willink, Sascha Colen, Department of Orthopaedic Surgery, University Hospitals Leuven, 3212 Leuven, Belgium
Dirk Jan F Moojen, Michel PJ van den Bekerom, Department of Orthopaedic Surgery and Traumatology, Onze Lieve Vrouwe Gasthuis, 1091 AC, Amsterdam, The Netherlands
Sascha Colen, Department of Orthopedic Surgery and Traumatology, Sint Bonifatius Hospital, 49808 Lingen, Germany
Author contributions: Kuiper JWP, van den Bekerom MPJ and Colen S designed the study; all authors performed research, wrote the manuscript and revised the manuscript
Correspondence to: Jesse WP Kuiper, MD, Center for Orthopaedic Research Alkmaar, Medical Center Alkmaar, Wilhelminalaan 12, 1815 JD, Alkmaar, The Netherlands. jwp.kuiper@gmail.com
Telephone: +31-72-5482503 Fax: +31-72-5482168
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Abstract

Periprosthetic joint infection (PJI) is a devastating complication after total joint arthroplasty, occurring in approximately 1%-2% of all cases. With growing populations and increasing age, PJI will have a growing effect on health care costs. Many risk factors have been identified that increase the risk of developing PJI, including obesity, immune system deficiencies, malignancy, previous surgery of the same joint and longer operating time. Acute PJI occurs either postoperatively (4 wk to 3 mo after initial arthroplasty, depending on the classification system), or *via* hematogenous spreading after a period in which the prosthesis had functioned properly. Diagnosis and the choice of treatment are the cornerstones to success. Although different definitions for PJI have been used in the past, most are more or less similar and include the presence of a sinus tract, blood infection values, synovial white blood cell count, signs of infection on histopathological analysis and one or more positive culture results. Debridement, antibiotics and implant retention (DAIR) is the primary treatment for acute PJI, and should be performed as soon as possible after the development of symptoms. Success rates differ, but most studies report success rates of around 60%-80%. Whether single or multiple debridement procedures are more successful remains unclear. The use of local antibiotics in addition to the administration of systemic antibiotic agents is also subject to debate, and its pro's and con's should be carefully considered. Systemic treatment, based on culture results, is of importance for all PJI treatments. Additionally, rifampin should be given in Staphylococcal PJIs, unless all foreign material is removed. The most important factors contributing to treatment failure are longer duration of symptoms, a longer time after initial arthroplasty, the need for more debridement procedures, the retention of exchangeable components, and PJI caused by *Staphylococcus* (*aureus* or coagulase negative). If DAIR treatment is unsuccessful, the following treatment option should be based on the patient health status and his or her expectations. For the best functional outcome, one- or two-stage revision should be performed after DAIR failure. In conclusion, DAIR is the obvious choice for treatment of acute PJI, with good success rates in selected patients.

Key words: Arthroplasty; Prosthesis; Infection; Periprosthetic joint infection; Retention; Debridement antibiotics and implant retention; Debridement; Acute

Core tip: Acute periprosthetic joint infection (PJI) is a major complication after total joint arthroplasty, and occurs either postoperatively or via hematogenous spreading. Debridement, antibiotics and implant retention (DAIR), the primary treatment for acute PJI, should be performed as soon as possible after the development of symptoms, and has success rates around 60%-80%. Whether single or multiple debridement procedures are more successful remains unclear. Sys-

temic treatment, based on culture results, is important for all PJI treatments. Various factors for treatment failure can be identified. For acute PJI, DAIR has good success rates, especially in selected patients.

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INTRODUCTION

With an average infection rate of approximately 1%-2%, periprosthetic joint infection (PJI) is a relatively frequent and devastating complication after performing joint arthroplasty[1,2]. It is especially debilitating for patients, as it requires prolonged hospitalization and often multiple surgical procedures. Besides the clinical impact of PJI, there is a high economic impact with tremendously increased health care costs[3]. With a rising population and overall increasing age, the number of total hip arthroplasties performed are expected to increase significantly thereby having a growing effect on the number of PJIs and, subsequently, on overall health care costs[4].

Most PJIs are caused by intra-operative contamination and cause either early or delayed infection[1]. Hematogenous seeding is less common, and is most often seen years after the initial arthroplasty[2,5]. Although these types of infection have a different pathogenesis, both early postoperative and hematogenous infection usually have an acute onset and, therefore, both attribute to "acute infection", based on similar symptoms and treatment options[6]. Chronic late infections are usually caused by less virulent microorganisms, and although these are also thought to occur from intraoperative contamination, symptoms develop very slowly. Therefore, patient complaints are often similar to those seen in aseptic arthroplasty loosening[2,7].

Although recent guidelines published by Osmon *et al*[2] have provided some directive, classification of acute PJI remains difficult in borderline cases. For early postoperative PJI, the period after initial arthroplasty is reported, in literature, as being between 0-4 wk[5] and 0-3 mo[1]. For acute hematogenous infections, the (vague) definition encompasses acute symptoms in "a previously well-functioning prosthesis", which can occur at any time postoperatively[2,5,8].

Micro-organisms causing PJI are mainly *Staphylococcus aureus* and coagulase negative *Staphylococcus*, accounting for up to half or even three quarters of the infections[9,10]. Other micro-organisms responsible include *Streptococcus* species, *Enterococcus* species, and gram negative bacteria[9,10]. The microbiological profile for acute *vs* chronic PJI is reported by only a limited number of authors, and shows that acute PJI is more often caused by *S. aureus* and *Streptococcus* species[5,11-13]. In comparison, chronic infections are more often caused by coagulase negative *Staphylococcus* and *Propionibacterium acnes*[5,11-13].

In this review we will focus on acute PJI, both early postoperative as well as acute hematogenous PJI, after an initial symptom free period in which the arthroplasty functioned properly. First we will clarify the definition of these infections. Which diagnostic tools can be used? Which risk factors are associated with developing PJI? Which micro-organisms are a predominant cause of acute PJI? What kind of treatment options exist and what is the outcome of each of these treatment options? Finally we will discuss the risk factors associated with failure of these treatments.

DEFINITION OF A PROSTHETIC JOINT INFECTION

Several definitions of PJI have been used in the past decades. The Workgroup of the Musculoskeletal Infection Society published a well restricted definition[14]. In their definition the diagnosis of PJI can be made if: (1) there is a sinus tract communicating with the prosthesis; or (2) a pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint.

In patients presenting without such clear indications four of the following six criteria have to be present to prove the presence of PJI: (1) elevated serum erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) concentration; (2) elevated synovial leukocyte count; (3) elevated synovial polymorphonuclear neutrophil percentage (PMN%); (4) presence of purulence in the affected joint; (5) isolation of a microorganism in one culture of periprosthetic tissue or fluid; and (6) more than five neutrophils per high-power field in five high-power fields observed from histological analysis of periprosthetic tissue at × 400 magnification.

Other authors have described similar definitions, of which some are used more frequently, either directly or slightly adapted[5,15,16]. There are yet other studies which use a less well-contained definition, for example only mentioning the diagnosis ("staged revision for septic loosening")[3], or mentioning only that the diagnosis was made based on several laboratory values and culture results[17].

DEFINITION OF ACUTE, LATE CHRONIC AND ACUTE LATE PJI

Two classification systems are most often used to determine whether or not there is an acute, late chronic or acute late PJI. Tsukayama *et al*[5] suggested a system which divides the occurrence of infection into four groups: positive intra-operative cultures (at time of implantation of the prosthesis), early postoperative infection (< 4 wk), late chronic (> 4 wk, indolent onset), and acute hematogenous (acute onset). This system was adapted by Toms *et al*[18] to early postoperative (type I , acute, < 6 wk), chronic (type

Ⅱ, chronic, indolent onset) and acute hematogenous (type Ⅲ, acute onset in a well-functioning prosthesis, secondary to hematogenous spread). The other commonly used classification, proposed by Zimmerli *et al*[1], defines the PJIs as early (occurring within 3 mo postoperatively), delayed (3-24 mo) and late (> 24 mo).

Parvizi *et al*[19] also mentioned a period of 3 mo after performing arthroplasty as the cutoff to determine whether the infection can be regarded as being acute or not, however, they referred to an article only including patients undergoing aspiration within 6 wk postoperatively[20].

DIAGNOSIS

Classical cornerstones of PJI diagnosis are, as for any disease, a thorough patient interview and physical examination. This includes evaluation of the patient's history and comorbidities, medication use, postoperative wound problems and duration of infectious symptoms[2].

In addition to this, different diagnostics, such as infection parameters in the patient's blood (ESR and CRP), pre-operative joint aspiration results (cell count, cell differentiation and culture) and intra-operative tissue and fluid culture results are equally important in order to determine the diagnosis of PJI[2,14].

Blood analysis

Blood leukocyte count is unable to differentiate between the absence or presence of PJI[1]. ESR and CRP have a more discriminating ability, and ESR higher than 30 mm/h, and CRP higher than 10 mg/L are suggestive for the presence of PJI[14]. However, shortly after surgery (such as in early infections), these parameters generally remain elevated for a prolonged period (30-60 d)[14]. Thus, a single high value is difficult to interpret, and serial measurements are recommended to aid in diagnosing PJI[1].

Several other serum markers have been studied for this purpose, such as interleukin-6. Studies have shown promising results, with high sensitivity and very high specificity, but it has not yet been included in recently published guidelines[2,21,22].

Pre-operative joint aspiration

When PJI is suspected, preoperative aspiration is recommended in almost all cases, the exceptions being when it will not change further choice of treatment (*e.g.*, presence of a sinus tract), and when the diagnosis (including the causative microorganism) has already been established[2]. The synovial fluid should be sent for culture, cell count and differentiation, for the determination of the percentage polymorphonuclear leukocytes.

Gram staining has a limited role in PJI diagnosis according to most authors[23-26]. Despite the fact that its specificity and positive predictive value are high, false positive results have also been mentioned. Furthermore, with a sensitivity of 20%, many PJIs are missed[23-26].

Recent studies have focused on two new synovial fluid diagnostics including synovial CRP levels[27,28] and the use of leukocyte esterase strips (also used to diagnose urinary tract infections)[27-29]. These diagnostics appear to be promising in the diagnosis of PJI, but are not yet widespread.

Intra-operative samples

For the definitive diagnosis of PJI, multiple intra-operative samples should be obtained. It is recommended that between 4 to 6 samples should be sent for bacterial culturing[2]. The incubation period should be at least 7 d, but preferably 14 d[30]. The samples should be tissue samples or samples obtained from dislodging the bacterial biofilm from the prosthetic parts[2]. For dislodging, sonication is the preferred method[31]. Scraping the biofilm from the foreign material has a lower yield of micro-organisms[32]. A relatively new but promising method is the use of dithiothreitol (DTT), an agent that has the ability to dislodge bacteria while also keeping them alive[33]. In addition to the culture samples, it is recommended that at least one sample is sent for histopathological determination of acute inflammation[2]. For a positive result, the average presence of 1 or more neutrophil polymorphs per high power field in at least 10 high power fields is required[34].

RISK FACTORS FOR (ACUTE) PJI

Considering the substantial incidence of PJI it is important to recognize certain risk factors associated with the development of such an infection (risk factors associated with debridement, antibiotics and implant retention (DAIR) treatment failure will be discussed further on in this review).

Chen *et al*[35] performed a meta-analysis regarding risk factors for total knee arthroplasties. Patient related factors that increase PJI risk include high body mass index (> 30), diabetes mellitus, hypertension, steroid use and rheumatoid arthritis. Everhart *et al*[36] support these risk factors and found that revision surgery, tobacco abuse, MRSA colonization and infection and (a history of) bone cancer also play an essential role in PJI development. They claim, however, that super obesity (*i.e.*, A BMI > 50) is a critical risk factor. Choong *et al*[15] found that there is a direct correlation between a BMI ⩾ 30 and an increased risk of infection. This correlation also exists if there are more than 2 co-morbidities present.

According to Liabaud *et al*[37] there is a significant, linear correlation between BMI and operating time which is in line with Willis-Owens's results claiming that "prolonged operating time and male gender are associated with an increased incidence of infection"[38]. Luessenhop *et al*[39] also found that a patient diagnosed with rheumatoid arthritis (and subsequent use of steroids) has a greater risk for developing PJI.

Berbari *et al*[40] showed that a patient with a system surgical patient risk index score of 1 or 2, the presence of a malignancy, and a history of joint arthroplasty are

also risk factors.

TREATMENT

For acute infections with a stable implant and adequate soft tissue mass, the latest guidelines recommend implant retention treatment (also referred to as DAIR: debridement, antibiotics and implant retention) for PJI occurring within 30 d after arthroplasty, or with less than 3 wk of symptoms[2]. Osmon *et al*[2] noticed that DAIR may be used in patients who do not meet these criteria, but state that worse results can then be expected.

When patients do not meet the criteria to undergo DAIR treatment, revision surgery is the preferred treatment, either in one stage (when tissue quality and microorganism susceptibility allow for direct exchange) or in multiple stages. Mere medical treatment should be reserved for patients in whom surgery is not the most preferred option or when it is medically irresponsible. Resection arthroplasty (without reimplantation), arthrodesis and amputation are options for difficult to treat and chronic PJI, and these treatment options only very rarely have a role in acute PJI cases[1,2].

DAIR

DAIR treatment is probably the most widely performed initial treatment option for acute PJI, although the exact data on the number of such procedures performed is yet unknown. When acute PJI is suspected (or confirmed by the previously mentioned criteria) a debridement procedure should be performed as soon as possible, meanwhile keeping in mind that patient health optimization should also be maintained. For example, it has been seen that factors such as hyperglycemia and malnutrition adversely affect outcome after total joint surgery[41,42].

The procedure includes acquiring multiple tissue samples, excessive debridement and removal of all infected (and necrotic) tissue, exchange of modular components and extensive irrigation[2,6]. Compared to arthroscopic washout, DAIR is associated with higher success rates: Byren *et al*[43] reported a success rate of 47% for arthroscopic washout, *vs* 88% for open washout, with a hazard ratio of 5.4. Retention of modular components is also associated with a higher failure risk. A recent study including hip and knee arthroplasties showed higher success rates for exchange of modular components: 59% for exchange *vs* 44% for retention (HR = 1.54)[44]. Another study showed 53% success for exchange *vs* 0% success for retention of modular parts for infected knee arthroplasties[45].

Success rates of DAIR treatment in general also show a great variety. Most small studies report success in approximately 60%-80% of the cases, but these are selected groups. When looking at cohorts with more than 100 patients (including both hip and knee PJI), success rates lie between 31% and 78% (Table 1). A recent meta-analysis showed a combined success rate of 46% for DAIR with one debridement procedure (n = 710), and 52% for multiple procedures (n = 175)[49].

Single vs multiple debridement procedures

Different strategies regarding debridement surgery can be divided into either performing only one debridement, single debridement with repeat surgery on indication, or standard repeated debridement procedures[49]. Traditionally, when only local antibiotic cement beads were used, especially popular in Europe, the strategy of multiple debridements was necessary, because these beads always had to be removed again after initial insertion. However, when using resorbable local antibiotic carriers or no local antibiotics, a single debridement might be a sufficient alternative. Although the authors do not specifically mention it in their publication, in the Zimmerli algorithm a single open debridement seems to be favored as well[1].

Two studies on combined groups of total hip and knee patients suggest that a repeat debridement on indication increases the infection eradication rate compared to a single debridement[6,50]. There are also two studies that show good results using the strategy of routine multiple debridements[51,52]. Unfortunately, to date, no comparative studies between different strategies are available and therefore no hard recommendations regarding which one to use can be made. For every strategy different studies are published with results ranging from poor to excellent (21% to 90% success rate)[49,52-54]. All of them are retrospective case-series, which are often quite heterogeneous regarding inclusion, exact treatment and outcomes.

Local antibiotic treatment

Carriers for local antibiotic release include antibiotic loaded bone cement (polymethylmethacrylate, PMMA), beads and dissolvable sponges[55]. The rationale for using local antibiotic treatment is to achieve a high local concentration of antibiotic agents, thereby killing the causative microorganism, without the side-effects of high systemic concentrations.

Beads are usually loaded with gentamicin, but vancomycin and tobramycin are also used. The beads are most often fabricated in chains of 30 beads. Locally, concentrations of around 300 μg/mL are achieved, far above minimum inhibitory concentration (MIC) values for most micro-organisms[55-57]. A disadvantage of antibiotic beads is the additional removal surgery that is necessary, and their capability of forming a foreign body on which a biofilm can develop, after the antibiotic release (10-14 d)[57]. Their use in DAIR treatment has been reported in a few studies, with relatively high success rates. Tsukayama *et al*[5] (n = 20, success 75%), Tintle *et al*[58] (n = 9, 100% success), Estes *et al*[51] (n = 20, 90% success), and Geurts *et al*[59] (n = 89, 83% success). Kuiper *et al*[53] also mentioned a subgroup treated with beads, albeit with lower success rates (n = 12, 33% success).

Gentamicin loaded collagen sponges, which are dissolvable, do not need removal surgery. Due to the quick expansion of the collagen, when water is added, the release of gentamicin is fast, resulting in a very high local antibiotic concentration in the first hours, up to 3800 μg/mL[55,60]. The addition of hydrophobic gentamicin salt (gentamicin crobefat) has shown a longer release pattern,

Table 1 Characteristics of studies on debridement antibiotics and implant retention treatment with over 100 patients

Ref.	Type	Selection	*n*	Hip	Knee	Other	Success	Success rate	Mean fup (m)
Azzam *et al*[6]	Retrospective cohort	-	104	51	53	-	46	44%	68
Odum *et al*[17]	Retrospective cohort	-	150	53	97	-	46	31%	n.m.[1]
Byren *et al*[43]	Retrospective cohort	-	112	52	51	9	92	82%	27
Lora Tamayo *et al*[44]	Retrospective cohort	*Staphylococcus aureus* PJI	345	146	195	4	199	55%	n.m.
Cobo *et al*[46]	Prospective cohort	Early infections (< 30 d)	117	69	53	17	67	57%	24
Buller *et al*[47]	Retrospective cohort	-	309	62	247	-	160	52%	34
Koyonos *et al*[48]	Retrospective cohort	-	138	60	78	-	48	35%	54
El Helou *et al*[73]	Prospective cohort compared to 2 retrospective cohorts	Staphylococcal PJI	101	40	61	-	69	68%	12
Tornero *et al*[81]	Retrospective cohort	Staphylococcal PJI	106	39	67	-	81	76%	46

[1]Minimum 2 yr, n.m.: Not mentioned; PJI: Periprosthetic joint infection.

resulting in high concentrations (approximately 1000 μg/mL) for the first 40 h. Up to 3-5 sponges can be used in patients, without reaching toxic serum concentrations[61]. A disadvantage of gentamicin sponges might be prolonged and increased wound secretion[59] The clinical success rate of antibiotic loaded sponges in DAIR treatment for hip PJI has only been reported in one retrospective study, with a success rate of 70%[62].

Local continuous irrigation with an antibiotic pump or catheter is another option for local delivery. Its main advantage is that the agent can be changed, as well as the fact that it drains the intra-articular fluid. However, the burden for the patient is very high[63]. Reported success rates vary from 18%-85%[63-66].

Systemic antibiotic treatment

In general, to eradicate PJI, both surgical and medical treatments are necessary[1,2]. Antibiotic treatment is recommended in all cases, and involves systemic administration of one or more antibiotic agents, based on the microorganism causing the PJI, for a period of at least three months[2]. Usually, in the first two to six weeks of treatment, antibiotics are administered intravenously, to achieve a better penetration of periprosthetic tissues, and thus a higher local concentration. Depending on the culture results, the intravenous administration might be switched to oral administration. This is a possibility if the microorganism is susceptible to an agent which reaches high tissue concentrations upon oral intake[2].

Culture results are the leading factor when choosing the appropriate antibiotic agent. Zimmerli *et al*[1] already described a medical treatment protocol in 2004, pointing out the best (combination of) antibiotic agents per causative organism. This algorithm was adapted by recent guidelines, with the addition of several newer antibiotics, such as daptomycin for Staphylococcal or Enterococcal PJI[2]. None of the two studies make a distinction between joints involved[1,2].

All recommendations are based on the knowledge of the causative microorganism. What to do when PJI is suspected, but culture results are not yet known, is not mentioned in the guidelines. Only one study provides a treatment algorithm for empirical antibiotic therapy[67]. They advise the use of vancomycin for acute PJI caused by an unknown microorganism, and to switch to carbapenem if gram-negative bacteria are found[67]. Another study, on culture negative PJI, mentioned the parenteral use of cefazolin in 69%, and vancomycin in 13% of culture negative cases, but this is a selected group, with many patients that were already treated with antibiotics prior to surgical treatment[68].

In almost all cases of DAIR, the addition of rifampin is useful. Rifampin is thought to penetrate the biofilm, and is recommended in all cases of Staphylococcal PJI treated with DAIR[1,2]. Several studies describe the success rates of a regimen including rifampin[15,69-71], but only one prospective clinical study has been performed, which also observed higher success rates when rifampin was added to the antibiotic regimen[72]. Another, more recent study, compared a prospective rifampin group with a retrospective rifampin and a retrospective non-rifampin group[73]. They found higher success rates with the use of rifampin, but the groups were small, and included more knee rather than hip PJI. Despite the limited evidence, the use of additional rifampin is recommended in the most recent guidelines[2].

RISK FACTORS FOR DAIR TREATMENT FAILURE

Several studies mention risk factors associated with a higher chance of treatment failure. PJI caused by a *Staphylococcus* infection is the most well documented and influential risk factor. Azzam *et al*[6] state that any *Staphylococcus* infection, high American Society of Anesthesiologists score and intra-articular purulence, contribute to a substantial increase in failed treatments. They state that when "none or only one of these risk factors was present, a success rate of at least 67% was attainable". Vilchez, Choi and Deiermengian all specifically mention *S. aureus* as being much more virulent than other micro-organisms (possibly due to their biofilm production) and having a significant, negative influence on treat outcome[45,74,75]. Peel *et al*[76] specifically state MRSA infections as leading to a significant decrease in treatment success whereas Kuiper *et al*[53] report that coagulase negative *Staphylococcus*

PJI has a higher risk of failure. Martínez-Pastor *et al*[77] claim that a fluoroquinolone susceptible mico-organism leads to a better chance of treatment success. This is in line with Jaén *et al*[78] who claim fluoroquinolone resistant bacteria to being risk factors for failure.

Another important risk factor appears to be the number of debridement procedures necessary, although the exact cut-off number varies. Vilchez *et al*[74] and Lora-Tamayo *et al*[44] state that the need for ⩾ 2 debridements leads to an increased likelihood of failure, whereas Peel *et al*[76] set this number at > 4. Specifically in knee PJI, lack of component exchange together with a *S. aureus* infection leads to much lower infection control rates, according to Choi *et al*[45]. Lora-Tamayo confirm the importance of component exchange, stating that this "is an independent predictor of (treatment) success"[44].

The duration of the presenting symptoms and the time after initial surgery are also important contributors to treatment success, or failure. Some studies state that treatment outcomes decline when the patients undergo a debridement a mere > 2 d after onset of symptoms[79], whereas other studies claim the cutoff is at 7 d[53], 21 d[47] or even 28 d[62,80]. The time after index surgery showed an even greater scope, ranging from 15 d[81] to two years[82].

A patient's BMI and the presence of co-morbidities was only statistically significant in one study; Choong states that a BMI > 30 and having > 2 co-morbidities are substantial risk factors[15]. Buller *et al*[47] and Byren *et al*[43] both claim having a history of infection of the same joint as being associated with treatment failure. Byren *et al*[43] also state arthroscopic washout as a risk factor. A higher ESR is a potential risk factor[47], whereas a lower preoperative CRP, of ⩽ 15mg/dL, leads to a better outcome[77]. Lora-Tamayo *et al*[44] confirm this, stating that the degree of complexity of the infection (polymicrobial, bacteremic, or presenting with high CRP levels) and immunosuppression were independent predictors of failure. Kuiper *et al*[53] also state rheumatoid arthritis as a significant risk factor.

OUTCOME AFTER DAIR FAILURE

As described above, DAIR treatment for PJI has a success rate of approximately 70%, which may even be higher in selected patients, *e.g.*, those with a shorter duration of symptoms and without co-morbidities. The use of multiple debridement procedures remains up for discussion.

The definition of DAIR treatment failure, just like the PJI definition, is not uniformly well described in the literature. Most studies do, however, consider DAIR as having failed when one or more of the following criteria are met after both surgical and medical treatment[15,62,52,83]: (1) presence of local or systemic infectious symptoms; (2) laboratory signs suggesting presence of PJI (*e.g.*, CRP higher than normal laboratory values, usually 5 or 10 mg/L); (3) the use of chronic suppressive antibiotics; (4) signs of loosening on radiography; (5) positive intraoperative culture result in a subsequent procedure; (6) if the arthroplasty has been resected or replaced; or (7) death, resulting from PJI.

In the majority of the studies, after DAIR failure, most patients were treated with two-stage revision, but one-stage revision, resection arthroplasty without reimplantation and chronic suppression with antibiotics were described as well[15,16,52,62,83-85].

One-stage and two-stage revisions are preferred if function and eradication are important, but the patient must then endure one or more additional elaborate surgical procedures. For knee PJI, two studies suggest that two-stage procedures may have worse results if DAIR already has been attempted[86,87], but this has not yet been described for hip PJI. If patient health status is poor, or his or her expectations are not high, an acceptable situation may be achieved with resection arthroplasty (Girdlestone arthroplasty) or the use of chronic suppressive antibiotics[2].

The choice of treatment after DAIR failure in the abovementioned cohorts was based on individual patient characteristics, if mentioned[15,62]. The recent IDSA (Infectious Diseases Society of America) guidelines advise individual judgment in all cases, but endorse the use of treatment algorithms when DAIR has failed, since it has been proven that their use increases treatment success[2]. Unfortunately, the current algorithms do not offer help after the initial treatment choice[1,2,88,89]. If the symptoms remain and the tissue status progressively worsens, it may be possible to move down the algorithm thereby choosing an alternative treatment plan. However, in our opinion, it is much more important to choose a treatment method that fits the patient's and the doctor's expectations in regard to revalidation time, mobility of the patient and the chance of PJI eradication.

DISCUSSION

This review is intended to provide a concise summary of all the currently available literature regarding acute periprosthetic joint infections. The various classifications, definitions and diagnostic tools used to make the diagnosis of PJI, as well as the use of DAIR were collected and analysed in order to provide a series of solid treatment recommendations.

The initial difficulty researchers and clinicians face is how to properly make the correct diagnosis. Patient interview and physical examination, together with a blood analysis, pre-operative joint aspiration and intra-operative samples are of equal importance and must all be employed. Despite the fact that different authors use different criteria, in general all of these criteria and definitions are useful. The exact definition and cut-off of an acute infection remains unclear, however, due to the fact that some authors claim this be less than 4 wk whereas other implement less than 6 wk or even less than 3 mo. Literature remains unclear whether a period of 3 mo has worse outcome than 4 wk.

Most of the risk factors for developing PJI are the same as the risk factors associated with DAIR treatment failure. A BMI of more than 30 kg/m^2, MRSA and the

presence of multiple co-morbidities put all patients at an extra risk, for both infection development and subsequent treatment failure. However, there are some specific risk factors for failure of DAIR, like the number of debridements and the time between presenting symptoms and initial surgery. The sooner the DAIR is carried out, the better.

DAIR (with modular component exchange) remains the preferred initial treatment choice, before one- and two stage revisions, mostly due to its less invasive character. Unfortunately DAIR has a lower success rate than one- and two-stage revision, respectively 70% *vs* higher than 90%[90]. There is no consensus regarding the optimal number of debridements necessary.

The use of local treatments such as beads, cement and sponges loaded with antibiotics appear to be promising, though only a handful of studies have been published, all of which analysed a relatively small patient population.

Systemic antibiotic treatment is complementary to surgical treatment. The antibiotic used for PJI is based on the acquired culture results, potentially combined with rifampin in the case of a Staphylococcal infection. However, too few studies have been published regarding the choice of antibiotics when the cultures are not yet known. Vancomycin appears to be a possible antibiotic option though a definite recommendation cannot be made. The duration of antibiotic administration is currently reported to be three months[1,2]. If the PJI cannot be eradicated using minimally invasive approaches, one- and two stage revisions are eventually the preferred treatment.

Despite many studies providing information about PJI, much evidence is missing. In order to provide stronger scientific evidence additional multicenter prospective and randomized trials must be carried out, using a single, uniformly agreed upon definition of APJI based upon equal criteria and diagnostic tools.

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New perspectives for articular cartilage repair treatment through tissue engineering: A contemporary review

Giuseppe Musumeci, Paola Castrogiovanni, Rosalia Leonardi, Francesca Maria Trovato, Marta Anna Szychlinska, Angelo Di Giunta, Carla Loreto, Sergio Castorina

Giuseppe Musumeci, Paola Castrogiovanni, Marta Anna Szychlinska, Carla Loreto, Sergio Castorina, Department of Bio-Medical Sciences, Human Anatomy and Histology Section, School of Medicine, University of Catania, 95123 Catania, Italy
Rosalia Leonardi, Department of Medical and Surgical Sciences, II Dental Unity, University of Catania, 95123 Catania, Italy
Francesca Maria Trovato, Department of Medical and Pediatric Sciences, Internal Medicine Division, University of Catania, 95123 Catania, Italy
Angelo Di Giunta, Sergio Castorina, Fondazione Mediterranea "G.B. Morgagni", 95125 Catania, Italy
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Author contributions: Musumeci G researched the area and identified papers, wrote and structured the review; Castrogiovanni P, Loreto C, Szychlinska MA and Trovato FM reviewed and edited the paper; Di Giunta A provide the surgical materials; Leonardi R and Castorina S structured the paper.
Correspondence to: Giuseppe Musumeci, PhD, Department of Bio-Medical Sciences, Human Anatomy and Histology Section, School of Medicine, University of Catania, 95123 Catania, Italy. g.musumeci@unict.it
Telephone: +39-095-3782043 Fax: +39-095-3782034
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Abstract

In this paper review we describe benefits and disadvantages of the established methods of cartilage regeneration that seem to have a better long-term effectiveness. We illustrated the anatomical aspect of the knee joint cartilage, the current state of cartilage tissue engineering, through mesenchymal stem cells and biomaterials, and in conclusion we provide a short overview on the rehabilitation after articular cartilage repair procedures. Adult articular cartilage has low capacity to repair itself, and thus even minor injuries may lead to progressive damage and osteoarthritic joint degeneration, resulting in significant pain and disability. Numerous efforts have been made to develop tissue-engineered grafts or patches to repair focal chondral and osteochondral defects, and to date several researchers aim to implement clinical application of cell-based therapies for cartilage repair. A literature review was conducted on PubMed, Scopus and Google Scholar using appropriate keywords, examining the current literature on the well-known tissue engineering methods for the treatment of knee osteoarthritis.

Key words: Cartilage; Repair; Mesenchymal stem cells; Scaffolds; Tissue engineering; Osteoarthritis

Core tip: In this paper review we describe benefits and disadvantages of the established methods of cartilage regeneration that seem to have a better long-term effectiveness. We illustrated the anatomical aspect of the knee joint cartilage, the current state of cartilage tissue engineering through mesenchymal stem cells and biomaterials and in conclusion we provided a short overview on the rehabilitation after articular cartilage repair procedures.

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INTRODUCTION

The knee is one of the largest and most complex joints in

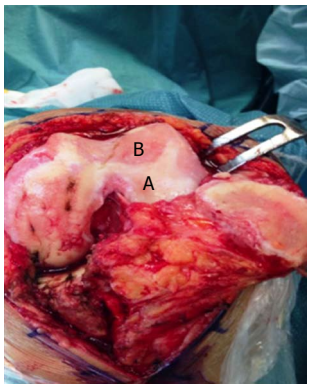

Figure 1 Macroscopic signs of osteoarthritis knee hyaline cartilage. A: Healthy cartilage; B: Osteoarthritis cartilage.

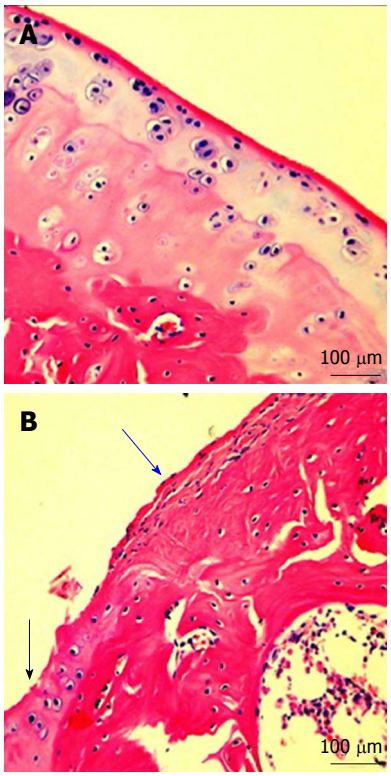

Figure 2 Microscopic signs. A: Microscopic signs of healthy knee hyaline cartilage. The histological (HE staining) analysis of cartilage from normal donor, showed a preserved morphological structure with no sign of cartilage degradation. Moreover, the surface of healthy hyaline cartilage appears white, shiny, elastic and firm. Magnification x 20; Scale bars: 100 μm; B: Microscopic signs of osteoarthritis (OA) knee hyaline cartilage. The histological (HE staining) analysis of cartilage from OA donor. The donor demonstrated joint swelling and oedema, horizontal cleavage tears or flaps, the surface becomes dull and irregular and had minimal healing capacity. Magnification x 20; Scale bars: 100 μm. Moderate OA cartilage (black arrow), the structural alterations included a reduction of cartilage thickness of the superficial and the middle zones. The structure of the collagen network is damaged, which leads to reduced thickness of the cartilage. The chondrocytes are unable to maintain their repair activity with subsequent loss of the cartilage tissue. Severe OA cartilage (blue arrow), demonstrated deep surface clefts, disappearance of cells from the tangential zone, cloning, and a lack of cells in the intermediate and radial zone, which are not arranged in columns. The tidemark is no longer intact and the subchondral bone shows fibrillation.

our body. It plays an essential role in movement related to carrying the body weight in horizontal (running and walking) and vertical (jumping) directions[1]. The knee joint consists of two articulations, one between the femur and tibia, and one between the femur and patella[1]. The knee is a mobile angular ginglymus or troclear, which permits flexion and extension as well as a slight medial and lateral rotation[2]. The joint is bathed in synovial fluid, which is contained inside the synovial membrane called the joint capsule. Ligaments join the knee bones and tendons connect the knee bones to the leg muscles, providing stability to the knee. Since in humans the knee supports nearly the whole weight of the body, it is vulnerable to both acute injury and chronic development of osteoarthritis. Two C-shaped pieces of cartilage called the medial and lateral menisci lie between the articular surfaces of the femur and tibia[3-5]. The menisci are shock absorbers of the load and make concordant the articular surfaces between the femoral condyles and the tibial plateau[3-5]. During flexion the menisci slide forward, during extension slide back[2]. The menisci are divided into outer rim, inner rim and core[3-5]. The inner rim is the most delicate part, because it is not vascularized. The lateral meniscus has the form of an almost complete circle and adheres to the two cruciates[3-5]. The medial meniscus has the form of a half moon and is more extensive than lateral, with its extremities adhering to anterior and posterior intercondylar areas. Between the two menisci, the medial meniscus is more subject to trauma, because it is less mobile than the lateral for the presence of the semimembranosus tendon, but also because usually we tend to have a slight valgus during gait[3-5]. Numerous bursae, or fluid-filled sacs, are located between the bones and tendons. This anatomical structure helps to reduce the friction between the bones during movement, for helping the knee to move smoothly. The joint capsule of the knee is strengthened by different ligaments, important for the stability of the joint, they are: the patellar ligament or patellar tendon, the lateral and medial retinaculum of the patella, the medial and lateral alar ligaments, the medial and lateral collateral ligaments (preventing the femur from sliding side to side), the popliteal ligaments and the anterior and posterior cruciate ligaments.

Articular cartilage is a form of hyaline cartilage that covers the articulating surfaces of long bones and sesamoid bones within synovial joints[6,7], and in the growth plate of the metaphysis, the zone between diaphysis and epiphysis[8,9]. Cartilage is a porous, viscoelastic composite that relies on a complex interaction and organization of its constituents to provide the resilient load-bearing, energy-dissipating lubrication and frictional properties[6,7]. The impressive load-bearing capacity of this tissue reflects in part the intrinsic matrix toughness and turgidity, as the ability of the tissue to swell is opposed by the internal structure. The degradation, loss, or breakdown of this unique relationship between the collagenous matrix and heavily hydrated charge-carrying proteoglycans caused by trauma or chronic and progressive degenerative joint disease (*e.g.*, osteoarthritis or rheumatoid arthritis) has great functional, biomechanical, clinical, and social implications[10]. Knee osteoarthritis (Figures 1, 2) is the most common type of osteoarthritis[10]. Early diagnosis and

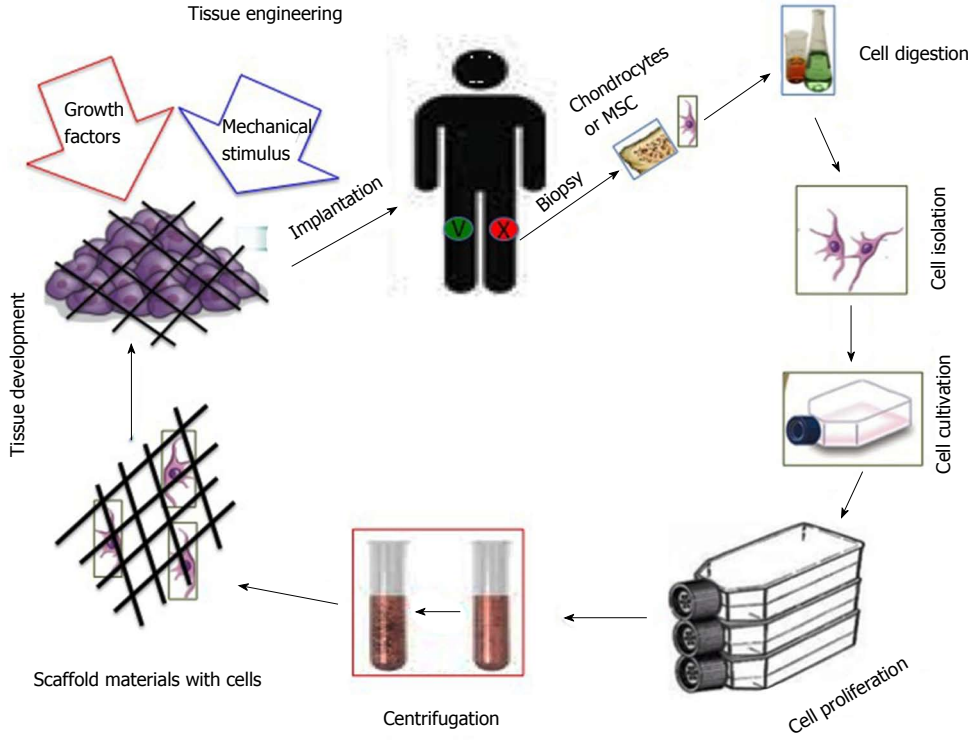

Figure 3 Graphic representation of the cartilage tissue engineering. MSC: Mesenchymal stem cell.

treatment may help to manage its symptoms. Deterioration of articular cartilage is the main problem associated with knee osteoarthritis. The condition can be caused by: previous knee injury like fractures, ligament tears and meniscal injury or repetitive strain on the knee which can affect alignment, obesity, and genetics which make some people more likely to develop knee osteoarthritis[11]. Medical history, physical examination, and X-rays are used to diagnose knee osteoarthritis. The evidence of joint space narrowing on X-rays is crucial for the diagnosis and rules out other causes of knee pain[12]. If more detailed imaging is needed, an MRI may be ordered[12]. Arthroscopic knee surgery is another way to view the condition of the knee[12]. Knee osteoarthritis typically develops gradually over a period of years. The primary symptoms include: pain (mild, moderate, or severe), stiffness, limited range of motion in the knee, localized swelling. Knee osteoarthritis pain is usually worse following activity, especially overuse of the affected knee[10-13]. Stiffness can worsen after sitting for prolonged periods of time. As knee osteoarthritis progresses, symptoms generally become more severe. Then pain can become continuous rather than only when weight-bearing. The consequence in many cases is an inability to work and often the substitution of the diseased joint with an artificial implant becomes inevitable[6,7]. Joint replacement also called knee arthroplasty has had a major impact on the management of OA. After injury, articular cartilage is unable to naturally restore itself back to a functional tissue, and, because of this, a widely studied alternative to avoid the knee replacement surgery for osteoarthritis is tissue engineering[11-13].

TISSUE ENGINEERING

Tissue engineering (Figure 3), is the use of a combination of cells, biochemical and physio-chemical factors, engineering and biomaterials to improve or replace biological functions[14-16]. While it was once categorized as a sub-field of biomaterials, having grown in scope and importance it can be considered as a field in its own right. While most definitions of tissue engineering cover a broad range of applications, in practice the term is closely associated with applications that repair or replace portions of or whole tissues (*i.e.*, bone, cartilage, blood vessels, skin, muscle, nerve *etc.*)[14-16]. Often, the tissues involved require certain mechanical and structural properties for proper functioning. The term regenerative medicine is often used synonymously with tissue engineering, although those involved in regenerative medicine place more emphasis on the use of stem cells to produce tissues[14-16]. Tissue engineering of natural cartilage tissue has become an attractive new area of research. For this reason, we discuss briefly the most widely used techniques in the treatment of cartilage lesions to solve the problem of the management of cartilage defects. In recent years, surgeons and researchers have been working hard to elaborate surgical cartilage repair interventions for patients who suffer from articular cartilage damage. They provide pain relief, helping patients to return to their original lifestyle (regaining mobility, going back to work and even practicing sports again), while at the same time slowing down the progression of damage or considerably delaying joint replacement. Though these

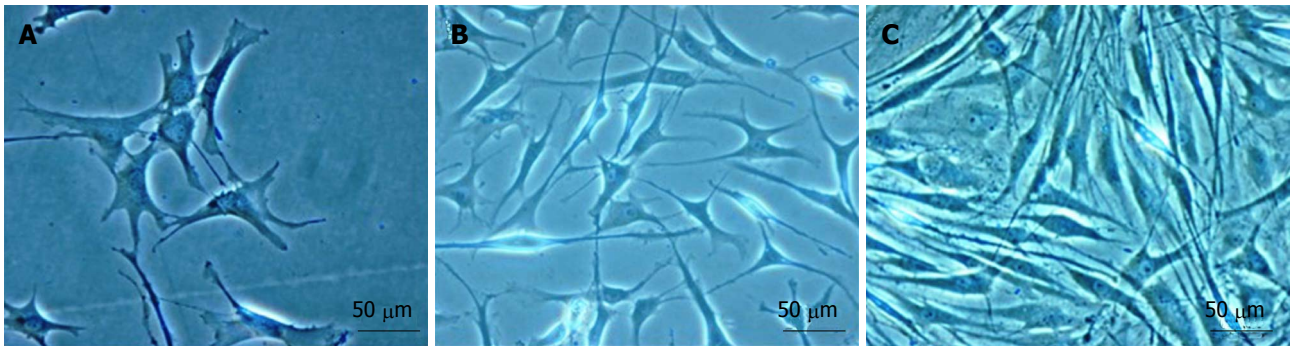

Figure 4 Mesenchymal stem cells development. A: First day of culture; B: Third day of culture; C: One week of culture. Magnification x 40; Scale bars: 50 μm.

solutions do not perfectly restore cartilage, some of the latest technologies start to bring very promising results in repairing cartilage from traumatic injury or chondropathies. Although initially considered a tissue with a simple structure, reproducing the finely balanced structural interactions has proven to be difficult. Tissue engineering is able to create live tissue to replace, repair or strengthen harmed tissue. It is based on cell and genetic therapy and offers some of the most promising strategies of tissue repair, including articular cartilage repair. Although it has concentrated on finding therapies for focal lesions, it has now developed sufficiently to begin considering the challenge of finding novel solutions for the extensive joint damage seen in osteoarthritis.

At the present time, a variety of clinical methods is available for repairing a chondral defect: marrow stimulation, autologous chondrocyte implantation (ACI), and most recently, next-generation ACI involving scaffolds or cell-seeded scaffolds, microfracture, osteoarticular transfer system (OATS) or mosaicplasty, penetration of the subchondral bone, osteochondral plug transplantation and matrix-induced autologous chondrocyte implantation (MACI)[6,7]. The cartilage repair procedure seeks to restore the surface of an articular joint's hyaline cartilage and to replace the defect with an optimal repair tissue, mechanically stable, in order to prevent further degeneration. Today almost none of the mentioned procedures prove capable of generating hyaline cartilage and the clinical outcome needs to be further improved. ACI procedures take place in three stages. First, chondrocytes are extracted arthroscopically from the patient's healthy articular cartilage that is located in a nonload-bearing area of either the intercondylar notch or the superior ridge of the femoral condyles. Then these extracted cells are transferred to an "*in vitro*" environment in specialized laboratories where they grow and replicate, for approximately four to six weeks, until their population has increased to a sufficient amount. Finally, the patient undergoes a second surgery where the "*in vitro*" chondrocytes are applied to the damaged area. In this procedure, chondrocytes are injected and applied to the damaged area in combination with either a membrane or a matrix structure. These transplanted cells grow in their new environment, forming new articular cartilage[6,7]. Increasing the source of cells for artificial repair of cartilage defects is becoming a problem[6,7]. The limited supply of cartilage, as a source of chondrocytes, requires a phase of expansion in monolayer culture. Chondrocyte differentiation and the maintenance of function require both transient and long-lasting control through humoral factors, particularly under stress, repair and regeneration *in vivo* or *in vitro*. To date, humoral factors from all major classes of molecules are known to contribute: ions (calcium), steroids (estrogens), terpenoids (retinoic acid), peptides (PTHRP, PTH, insulin, FGFs) and complex proteins (IGF-1, BMPs)[17]. BMP-4, a stimulator of chondrogenesis, both *in vitro* and *in vivo*, is a potential therapeutic agent for cartilage regeneration. BMP-4 delivery can improve the healing process of an articular cartilage defect by stimulating the synthesis of the cartilage matrix constituents: type Ⅱ collagen and aggrecan. BMP-4 has also been shown to suppress chondrogenic hypertrophy and maintain regenerated cartilage. Use of an appropriate carrier for BMP-4 is crucial for successful reconstruction of cartilage defects[18].

Chondrocyte expansion is complicated by the fact that monolayer-cultured chondrocytes de-differentiate, lose their characteristic phenotype and synthesize type Ⅰ (typical of fibrocartilage) rather than type Ⅱ collagen (typical of hyaline cartilage)[8]. Osteochondral plug transplantation, or ostechondral autograft transfer system (OATS), usually applied for mid-sized defects[19], immediately recovers the joint surface. Small sized articular lesions are commonly addressed arthroscopically by penetration of the underlying subchondral bone[20-22] to promote a fibrous scar within the defect by invasion of adult mesenchymal stem cells. However, the reparative tissue does not withstand repetitive mechanical forces because of its poor quality, consisting mainly of collagen type Ⅰ, and clinical outcome deteriorates over time[23,24]. This has led to investigation into the use of mesenchymal stem cells (MSCs). MSCs (Figure 4) can be relatively easily harvested and the procedures using them are less invasive or destructive than articular cartilage harvesting procedures.

The inherent ability of MSCs to self-renew opens the possibility that cell expansion may be achievable post-implantation[25]. The differentiation of MSCs into different cell types, in this case to produce cartilage tissue, is reliant on the local microenvironment, and growth factors, extracellular matrix and mechanical forces[25,26]. MSCs are easily available from bone marrow, synovial membrane,

Table 1 Natural and synthetic materials

Natural and synthetic materials	Materials	Advantages
Natural	Natural Silk, collagen, gelatin, fibrinogen, hyaluronic acid, alginate	Biodegradable Easily available Bioactive, interact with cells
Synthetic	PEG, PGA, PMMA, PLGA	Facilitate restoration of structure of damaged tissues Inert Long shelf-life Easily tailored for desired porosity and degradation time Predictable and reproducible mechanical and physical properties

PGA: Polyglycolic acid; PLGA: Poly (lactic-co-glycolic acid); PEG: Polyethylene glycol; PMMA: Polymethyl methacrylate.

adipose tissue[27,28], *etc*., so then, we can get a variable number of cells from a different tissue[29,30]. MSCs show a high proliferation and differentiation potential, although coming from different tissue, and have an uneven chondrogenic differentiation capacity probably related to the special cytokines, growth factor and induction molecules composition of the medium[31,32].

Marrow stimulating techniques attempt to solve articular cartilage damage through an arthroscopic procedure. Firstly, damaged cartilage is drilled or punched until the underlying bone is exposed. By doing this, the subchondral bone is perforated to generate a blood clot within the defect. Studies have shown that marrow stimulation techniques often have insufficiently filled the chondral defect and the repair material is often fibrocartilage (which is not as good mechanically as hyaline cartilage)[6,7,33]. The blood clot takes about 8 wk to become fibrous tissue and it takes 4 mo to become fibrocartilage. This has implications for the rehabilitation[2]. Further on, it is common that only 1 or 2 years after the surgery symptoms start to return as the fibrocartilage wears away, forcing the patient to reengage in articular cartilage repair. This is not always the case and microfracture surgery is therefore considered to be an intermediate step. An evolution of the microfracture technique is the implantation of a collagen membrane onto the site of the microfracture to protect and stabilize the blood clot and to enhance the chondrogenic differentiation of the MSCs[6,7]. One of the cons of chondrocyte transplantation is the dedifferentiation process that these cells suffer when they are treated *in vitro* and the limited ability to redifferentiate them[34]. On the contrary, MSCs are very stable and they do not suffer this dedifferentiation process and have a high differentiation capacity[35]. Beside the characteristics of MSCs expounded above, these cells have self-renewal potential as well as multilineage differentiation potential[36,37], including chondrogenesis[25]. A defined medium for *in vitro* chondrogenesis of MSCs was first reported by Johnstone *et al*[25] in 1998, who used micromass culture with TGF-β and dexamethasone. To date, the micromass culture is widely used to evaluate chondrogenic potential of MSCs "*in vitro*". However, this "*in vitro*" chondrogenesis does not imitate cartilage formation during development. During micromass culture, MSCs increase expressions of both collagen type Ⅱ (chondrocytes marker) and X (hypertrophic chondrocytes marker)[25]. Other cytokines such as insulin like growth factor (IGF), bone morphogenetic protein (BMPs) and parathyroid hormone related peptide (PTHrP) had been tried for better differentiation of the cells, but it is still difficult to obtain "*in vitro*" MSC-based cartilage formation comparative to native cartilage tissue[25]. Those molecules may reach chondrocytes *via* free diffusion or may be bound to collagens or proteoglycans on extracellular matrix superstructures, becoming available after metabolic processing of collagens and/or proteoglycans. Depending on their position in the metabolic cascade controlling chondrocyte development and homeostasis, they may be used in tissue engineering and regenerative approaches towards cartilage repair by direct application, carrier-mediated release or genetic delivery[17].

BIOMATERIALS

Recently a huge expansion in biomaterial technologies, scaffolds, cell sources, and molecular and genetic manipulations took place to create functional tissue replacements to treat cartilage injuries or osteoarthritis[38-40]. A new generation of materials is being developed and it is influenced by the knowledge of the anatomical and structural complexity of articular cartilage. The increasing capacity to design and synthesize materials with molecular resolution that ranges across organizational levels is generating great excitement in the biomaterials community[25]. The combination of technological advances and an increased knowledge in the fields of molecular and cell biology are generating new biomaterial scaffolds with many desired properties[25]. In addition to being biocompatible and accommodating cell adhesion, proliferation, and matrix synthesis, an ideal biomaterial scaffold for cartilage regeneration can now be bioactive, biomimetic, biodegradable and bioresponsive, providing signaling with spatiotemporal control and response that is selective to defined stimuli. Scaffolds analogous to the natural three-dimensional extracellular matrix may provide important microenvironmental clues to cells. A wide array of materials has been used in various "*in vitro*" and "*in vivo*" studies for articular cartilage engineering (Tables 1-3). Scaffolds that are most often studied in cartilage tissue engineering

Table 2 Overview of advantages and disadvantages of various scaffolds

Scaffold	Advantages	Disadvantages
Porous scaffolds	High porosity Interconnected structure Simple and easy to manufacture	Use of highly toxic solvent Low pore interconnectivity Difficulty in homogenous cell seeding post scaffold fabrication Highly porous scaffolds can have weak mechanical properties Lack of control over scaffold thickness
Fibrous scaffolds	Fiber meshes and fiber bonding are simple techniques Large surface area-volume ratio High inter-fiber distances for nutrition and gas exchange	Fiber meshes lack mechanical integrity Fiber bonding lacks control over porosity and pore size Small pore sizes produced during fabrication processes such as electrospinning limit cell infiltration and 3-D cellular integration with host tissue after implantation
Hydrogels	Can form stable and highly ordered scaffolds using self assembly Tissue like flexibility Viscoelasticity	Higher cost Non-adherent and usually need to be secured by a secondary dressing, for *in-vivo* testing
Custom scaffolds (Computer-aided design technique)	Intestinal flow and diffusive transport Controlled matrix architecture: size, shape, interconnectivity, branching, geometry and orientation Can control pore and pore size Controlled mechanical properties and degradation kinetics	Natural polymer hydrogels like collagen gelatin, alginate and agarose may evoke inflammatory responses Low resolution of current systems Selective polymeric materials can only be used
Microspheres	Reproducible architecture and compositional variations Used as cell carriers, when fabricated using biodegradable and non-toxic materials Large surface area for cell attachment and growth	Difficult to remove once injected or implanted Unknown toxicity associated with microsphere/beads
Native/ Extracellular matrix scaffolds	Applicable for 3-D cell culture in a stirred suspension bioreactor Simulates the cell's natural microenvironment in terms of composition, bioactive signal and mechanical properties	Difficult to control degree of decellularization and retain all ECM Non-uniform distribution of cells Immunogenicity upon incomplete decellularization

Table 3 Overview of advantages and disadvantages of various scaffolds

Cells	Material	Results
Chondrocytes	Poly(epsilon-caprolactone)-block-poly(L-lactide)	Applicable for cartilage tissue engineering
Rabbit marrow mesenchymal stem cells	Oligo(poly(ethylene glycol) fumarate) with encapsulated cells and gelatin microparticles loaded with TGF-β1	Maintained viability of cells for 14 d Differentiation of cells into chondrocyte-like cells
Chondrocytes	Gelatin microparticle aggregates, +/- TGF-β1	Supported viability and function of chondrocytes Applications in cartilage-engineering
Human adipose derived stem cells	Genipin-crosslinked cartilage derived matrix	Using genipin resulted in contraction free biomaterial. Chondrogenesis
Human mesenchmal stem cells	Poly(epsilon-caprolactone)	Cell colonization, proliferation and osteogenic differentiation were related to the micro-architecture of the pore structure
Human chondrocytes	Blend of poly (lactic-co-glycolic acid) and polyvinyl alcohol	Supported cell adhesion and growth After implantation, there was better bone in-growth and bone formation inside the scaffold.
Bone marrow stem cells	Polyglycolic acid, poly (lactic acid)	Cell infiltrated the scaffold Good cellular compatibility Applicable to repair craniomaxillofacial bone defects

TGF: Transforming growth factor.

include hydrogels made from poly(ethylene glycol) diacrylate (PEGDA)[7,11-13,41,42], collagen[43], fibrin[44,45], agarose, and synthetic peptides[46,47]; sponge-like scaffolds manufactured from materials such as collagen, polyglycolic acid, polylactic acid[48], and polyurethane[49]; materials with a naturally-occurring porous structure, such as coral, devitalized articular cartilage[50], and hyaluronan based scaffolds[51]. The three-dimensional scaffold provides the structural support for cell contact and matrix deposition prevents dedifferentiation of autologous chondrocytes even after long periods and promotes the expression of chondrocyte-specific markers[52]. Advantages of this procedure are a more uniform cell distribution, avoidance of periosteal harvest and implantation, and increased technical ease without the need for suturing to adjacent articular cartilage. These scaffold-less platforms develop a robust ECM framework of their own and permit long-term maintenance of phenotype, at least in long-term *in*

vitro culture, and can improve biophysical properties by mechanical loading. Scaffold-free constructs using alginate as an intermediate step have also been produced[53] and subjected to mechanical loading[54]. The challenge with such scaffold-free systems is producing them in a cost-effective and timely manner for clinical use, especially with autologous cells. This is also true for scaffold-based systems, but they have biomechanical properties that are immediately functional "*in vivo*", showing the ability to direct growth; further they can be designed to deliver relevant bioactive factors[25].

REHABILITATION

Mechanical stimuli are of crucial importance for the development and maintenance of articular cartilage[55]. Rehabilitation, following any articular cartilage repair procedure is crucial for the success of any articular cartilage resurfacing technique[2]. The rehabilitation is often long as it takes a long time for the cartilage cells to adapt and mature into repair tissue. Cartilage is a slow adapting substance, indeed where a muscle takes approximately 35 wk to fully adapt, cartilage only undergoes 75% adaptation in 2 years. If the rehabilitation period is too short, the cartilage repair might be put under too much stress, causing the repair to fail[2]. Over the years a variety of cartilage restorative procedures have been developed for athletes to address focal, full-thickness cartilaginous defects in the knee joint[56]. In most rehabilitation protocols, continuous passive motion or range of motion exercises are performed within the first day after injury or surgery. Ice, compression, elevation, weight-bearing activities, and electrical stimulation are also started immediately, and the intensity and repetition of these exercises increases as the rehabilitation program progresses. In addition, exercises to address the complimentary musculoskeletal system are also introduced, especially if distinct asymmetries are noted[57]. The type of mobilization exercises used depends on the injury. Experimental and clinical studies demonstrate that early, controlled mobilization is superior to immobilization for primary treatment of acute musculoskeletal soft-tissue injuries and postoperative management[58]. Early mobilization helped return the patients more quickly to physical activity, reduce persistent swelling, restore stability, restore range of motion, and improve patient satisfaction with the rehabilitation outcome[58]. Postoperative rehabilitation programs following articular cartilage repair procedures will vary greatly among patients and need to be individualized, based on the nature of the lesion, the unique characteristics of the patient, and the type and detail of each surgical procedure[59]. These programs are based on knowledge of the basic science, anatomy, and biomechanics of articular cartilage as well as the biological course of healing following surgery[59]. The goal is to restore full function in each patient as quickly as possible by facilitating a healing response without overloading the healing articular cartilage[2]. A patient, lesion, and sports-specific approach is required on the part of the trainer or physical therapist to gradually restore knee joint function and strength so that the athlete may be able to return to competitive play[56]. In this paper review we also take the opportunity to remind readers of the importance of a healthy lifestyle, including physical activity (mild exercise) and balanced diet such as Mediterranean Diet, in the medical therapy to prevent OA disease, in order to preserve the articular cartilage and then the entire joint[59].

CONCLUSION

In conclusion, the treatment of articular cartilage defects can be approached by different procedures in relation to cartilage lesions. Further "*in vivo*" and "*in vitro*" studies must be carried out in order to confirm their successful clinical outcomes.

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Treatment of meniscal tears: An evidence based approach

Simon C Mordecai, Nawfal Al-Hadithy, Howard E Ware, Chinmay M Gupte

Simon C Mordecai, Nawfal Al-Hadithy, Chinmay M Gupte, Imperial College NHS Trust, St Mary's and Charing Cross Hospitals, London W21NY, United Kingdom
Howard E Ware, Chinmay M Gupte, The Wellington Hospital, The Knee Surgery Unit, London NW8 9LE, United Kingdom
Author contributions: Mordecai SC and Al-Hadithy N wrote the manuscript; Ware HE and Gupte CM provided specialist input and edited the manuscript.
Correspondence to: Dr. Simon C Mordecai, Imperial College NHS Trust, St Mary's and Charing Cross Hospitals, Praed St, London W21NY, United Kingdom. simon.mordecai@gmail.com
Telephone: +44-020-33130970 Fax: +44-020-33130971
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Key words: Meniscus; Meniscectomy; Meniscal tear; Meniscal repair; Arthroscopic surgery

Core tip: Meniscal tears are a common orthopaedic pathology. Selecting the correct treatment can be challenging and involves multiple factors. This review explores the evidence for managing meniscal tears and when to consider each treatment option based on current available evidence.

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Abstract

Treatment options for meniscal tears fall into three broad categories; non-operative, meniscectomy or meniscal repair. Selecting the most appropriate treatment for a given patient involves both patient factors (*e.g.*, age, co-morbidities and compliance) and tear characteristics (*e.g.*, location of tear/age/reducibility of tear). There is evidence suggesting that degenerative tears in older patients without mechanical symptoms can be effectively treated non-operatively with a structured physical therapy programme as a first line. Even if these patients later require meniscectomy they will still achieve similar functional outcomes than if they had initially been treated surgically. Partial meniscectomy is suitable for symptomatic tears not amenable to repair, and can still preserve meniscal function especially when the peripheral meniscal rim is intact. Meniscal repair shows 80% success at 2 years and is more suitable in younger patients with reducible tears that are peripheral (*e.g.*, nearer the capsular attachment) and horizontal or longitudinal in nature. However, careful patient selection and repair technique is required with good compliance to post-operative rehabilitation, which often consists of bracing and non-weight bearing for 4-6 wk.

INTRODUCTION

Meniscal tears are the most common pathology of the knee with a mean annual incidence of 66 per 100000[1]. Historically it was believed that the menisci served no functional purpose and they were often excised with open total meniscectomy[2]. McMurray[3] described that insufficient removal of the meniscus was the cause of failure of meniscectomy. In 1948 Fairbank[4] reported the clinical outcomes of 107 patients after total meniscectomiesand found that the majority had progressive flattening of the condyle, narrowing of the joint space and ridge formation. This study significantly changed our approach to dealing with meniscal tears. More recent studies have shown that function of the knee was directly related to the amount of meniscal tissue that remained[5]. Increased knowledge of the long term consequences and altered biomechanics in the knee post meniscectomy has placed greater emphasis on meniscal preserving techniques. This review explores the evidence

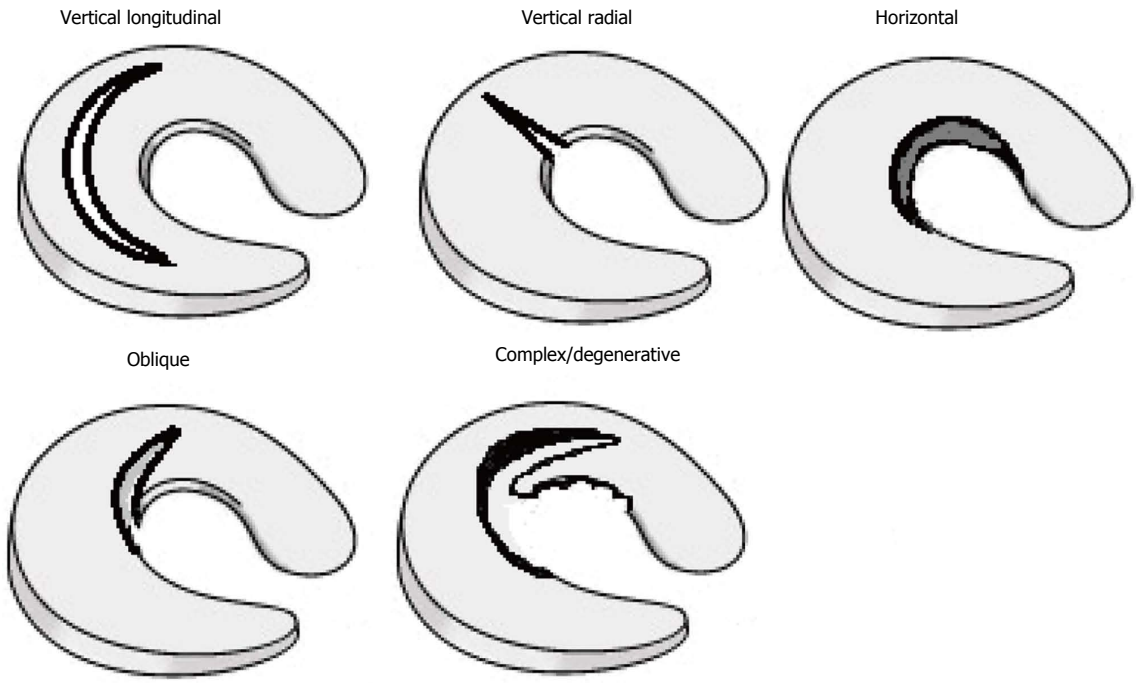

Figure 1 Meniscal tear patterns.

for managing meniscal tears and when to consider each treatment option based on current available evidence.

ANATOMICAL STRUCTURE

The menisci are wedge shaped fibrocartilagenous structures located between the femoral condyles and tibial plateau. The medial meniscus is "U" shaped covering around 60% of the medial compartment whereas the lateral meniscus is more "C" with a shorter distance between its anterior and posterior horns covering 80% of the lateral compartment[6]. Meniscal tissue consists mainly of water and type I collagen fibres[7]. These fibres run circumferentially from the anterior horn insertional ligament to the posterior horn insertional ligament with predominance in the outer third. The fibres help to absorb the energy by converting axial loading forces across the joint into hoop stresses within the tissue. There are also radial fibres which prevent longitudinal splitting of the circumferential fibres[8]. The structure of these fibres are important clinically when deciding which meniscal tears are stable or which are unstable and warrant resection or repair.

The blood supply to the menisci is of high relevance having important implications for the potential healing of a meniscal repair. Supply is from the periphery *via* the medial and lateral geniculate arteries. A cadaveric study has demonstrated that only the peripheral 10%-25% of the meniscus benefits from a blood supply in the mature skeleton[9]. Two distinct zones have been termed, the red-red vascular zone in the periphery and the white-white avascular zone centrally. They are separated by a red-white region with attributes from each zone. Tears located in the white zone are unlikely to generate a healing response.

CLASSIFICATION OF MENISCAL TEARS

Meniscal tears are often classified according to their orientation. They can be vertical longitudinal, vertical radial, horizontal, oblique or complex[10] (Figure 1). Longitudinal tears are more common medially, whereas radial tears are more frequently seen laterally[11].

Vertical longitudinal tears occur between the circumferential collagen fibres. The biomechanics of the knee is therefore not always disrupted and these tears may be asymptomatic. Complete vertical tears can sometime twist within the joint known as "bucket handle" tears. These are unstable tears which cause mechanical symptoms or true locking of the knee. Vertical radial tears disrupt the circumferential collagen fibres and affect the ability of the meniscus to absorb tibiofemoral load[12]. These tears are usually not amenable to repair. Partial meniscectomy does not restore complete function and accelerated degenerative changes are likely to occur[13]. Horizontal tears split the meniscus into an upper and lower part and can exist without clinical symptoms[14]. They are usually mechanically stable but may give rise to flap tears. Their frequency increases with age and often accompanied by meniscal cysts[15]. Oblique tears give rise to flaps which are mechanical unstable and associated with mechanical symptoms. This pattern of tear requires resection to prevent propagation of the tear as the flap gets caught within the joint during flexion. Complex or degenerative tears are where two or more tear patterns exist. They are more common in the elderly and have associated osteoarthritic changes in the knee.

NON-OPERATIVE MANAGEMENT

Non-operative treatments for meniscal injuries have been

well documented, particularly for degenerative tears. Exercise has been shown to improve knee function and reduce joint pain[16,17]. Mangione *et al*[18] found that quadriceps strengthening with static cycling for twenty five minutes three times a week for ten weeks improved knee function by 35% in patients with osteoarthritis. Herrlin *et al*[19] extended this theory to patients with degenerative medial meniscal tears in a prospective randomised study. Ninety middle aged patients with non-traumatic MRI confirmed medial meniscal tears were split into two treatment groups[1], arthroscopic partial meniscectomy followed by supervised exercise or[2] supervised exercise alone. The aims of the exercise were to improve muscle strength, flexibility and proprioception for a period of eight weeks. Multiple outcome scores were performed at eight weeks and 6 mo. Significant improvements in all outcomes were found at follow-up. There were no significant differences in improvement between the groups suggesting that a combination of arthroscopic partial meniscectomy and supervised exercise does not necessarily lead to greater improvements than exercise alone in this patient group. Authors recommend a trial of supervised exercise alone as first line treatment. A follow-up study showed that the similarities between the groups were maintained at five years[20]. However, one third of the patients from the exercise group still had disabling knee symptoms after exercise therapy but improved to the same level as the rest of the patients after arthroscopic surgery with partial meniscectomy. These results were echoed by a multicentre randomised controlled study of 351 patients over 45 years of age with a meniscal tear and evidence of osteoarthritis[21]. No significant differences were found in the magnitude of improvement in functional status and pain between the partial meniscectomy and physical therapy aloneat twelve months follow up. It should be noted though, that there was also crossover from the physical therapy group to the surgery group in 35% of patients. The factors for this crossover were not defined and may have skewed the results. Functional outcomes of the crossover patients after 12 mo however, were similar to those patients who had surgery initially, suggesting that non-operative treatment is a reasonable first line strategy.

Yim *et al*[22] compared non-operative strengthening exercises with meniscectomy for degenerative horizontal tears of the posterior horn of the medial meniscus. Satisfactory clinical results were found in each group at 2 years follow up with no significant difference in terms of pain, function and patient satisfaction. All clinical data was obtained using questionnaires which can be very subjective. Another study[23] following the effect of supervised exercise therapy on 37 patients with degenerative tears of the medial meniscus found improvement in functional knee scores up to 6 mo, after which there was decline and progression of osteoarthritis. The decline was also related to the patients' BMI.

Previous studies have suggested that early degenerative changes are more likely to occur after meniscectomy then non-operative management[24,25]. However the current evidence suggests that although non-operative management can be beneficial initially around a third of patients will go on to have a meniscectomy to achieve satisfactory pain relief and functional outcomes. Provided patients with degenerative tears have a robust and supervised exercise programme they can initially be managed conservatively. If symptoms persist they could then go on to have a meniscectomy. There were no studies reporting on non-operative management of acute meniscal tears in young patients.

MENISCECTOMY

It is now well known that the menisci serve an important role in the knee. Their main functions include load bearing, shock absorption and stabilisation. In addition they may have roles in joint lubrication, nutrition of the articular cartilage and proprioception[26].

Baratz *et al*[27] conducted a biomechanical cadaveric study and found that following total medial meniscectomy there is a decrease in intra-articular contact area of approximately 75% and the peak contact pressure increased by approximately 235%. Comparable results were found in a study by Ahmed and Burke[28]. Pressure on the meniscus increased by 85% during flexion and contact pressure by 100%-200% following total meniscectomy. Roos *et al*[29] report on a long term clinical study with follow-up of 21 years of patients after total meniscectomy compared to matched controls. They confirm that the increased pressure seen in the biomechanical studies leads to radiographic evidence of osteoarthritis with a relative risk of 14. It has also been shown that the risk of developing osteoarthritis after lateral meniscectomy is greater than the equivalent for the medial side[30,31]. This is due to the convexity of lateral tibial plateau mirroring the convexity of the distal femoral condyle. In the absence of a meniscus there is greater tendency to point loading. The medial tibial plateau is concave providing some degree of congruity even without a meniscus[32]. Furthermore as previously mentioned the lateral meniscus covers a greater percentage of the compartment and carries 70% of the compartment load compared to 50% medially adding to the risk of developing osteoarthritis[33]. Given the drastic changes in the biomechanics of the knee after total meniscectomy much interest has focused on the benefits of preserving as much meniscus as possible. Partial meniscectomy aims to remove only the torn piece of meniscus while retaining as much normal meniscus especially in the peripheral rim which is mostly responsible for the biomechanical function of the knee[34].

Northmore-Ball *et al*[35] compared arthroscopic partial meniscectomy with open partial and total meniscectomy in 219 knees. They reported that 90% of patients had either good or excellent satisfaction following arthroscopic partial meniscectomy compared to only 68% who had open total meniscectomy after 4.3 years follow-up. Burks *et al*[36] also found good or excellent results in 88% of patients after partial meniscectomy and Jaureguito *et al*[37] report 90% of patients report good or excellent results

with 85% resuming pre-injury level of activities at 2 years after surgery.

Short term results following partial meniscectomy are encouraging with around 90% showing satisfactory clinical results. Several long term studies show that partial meniscectomy may delay degeneration but not prevent it. In a study[38] looking at 136 patients following partial meniscectomy for isolated meniscal tears, at 8.5 years follow-up there was a re-operation rate of 22.8% and 53% of patients had osteoarthritic radiographic changes compared to only 22% in the unaffected control knee. A longitudinal study[39] of 147 athletes following meniscectomy for an isolated meniscal injuries were followed up at 4.5 years and then again at 14 years. At the first follow-up around half were asymptomatic but this reduced to around one third at final follow-up. Also the incidence of radiographic changes rose from 40% to 89% between follow-ups and 46% had given up or reduced their sporting activity. Radiographic degeneration was more frequently seen after lateral meniscectomy than medial.

Determining which patients will do well following partial meniscectomy is a challenging task and multiple factors need to be considered. Matsusue *et al*[40] conducted a retrospective analysis of 65 patients over forty years of age who had undergone partial medial meniscectomy. Patients were divided into two groups based on degree of articular degeneration. In the group with no pre-existing articular damage 87% had an excellent outcome, and only one patient had a poor result. In contrast, patients from the other group had significantly worse results, with only one knee having an excellent outcome, and four knees having poor results. Authors concluded that arthroscopic partial medial meniscectomy in patients older than 40 years is an acceptable and effective long-term treatment, particularly in patients without significant articular cartilage damage. Arthroscopic resection of flap tears from the posterior horn of the medial meniscus was also shown to have less favourable outcomes in the presence of chondromalacia in a review of 93 patients[41].

A randomised double blinded placebo controlled study published in The New England Journal of Medicine[42] looked at 180 patients who were randomly assigned to receive arthroscopic debridement, arthroscopic lavage or placebo surgery. Patients in the placebo group received skin incisions and simulated debridement. Patients were followed up multiple times over a 2 year period. Authors concluded that in patients with osteoarthritis the outcomes after arthroscopic lavage or debridement were no better than after a placebo procedure. Also function did not improve in any group.Although this is a very well designed study providing the highest level of evidence practice should not be changed on the basis of just one study as the authors suggest and certain limitations should also be taken into account. Firstly there is an element of selection bias. All patients were recruited from the Houston Veterans Affairs Medical Centre of which 97% were male. Even though response to surgery is not known to differ between sexes, osteoarthritis affects millions of people worldwide and results from just one single institution cannot be a true representation. Secondly there is no clear indication of the severity of the osteoarthritis in each case. Bernstein and Quach[43] in a critique of this paper believe the inclusion criteria were too broad and arthroscopy based these indications should be invalidated.Finally the authors' state that the billions of dollars spent on arthroscopies annually might be put to better use. If these patients were subjected to total knee replacements instead this carries a five times greater cost than arthroscopy. Also as the knee replacements will be done earlier they are more likely to need revision further adding to the costs.

Katz *et al*[44] reviewed 105 patients following partial medial meniscectomy with aim to establish multiple predictors of functional outcome. They identified that although partial meniscectomy generally had favourable outcomes, extent of cartilage damage as well as workers' compensation case pending and low preoperative physical function were predictors of poor outcome. Predictors of good outcomes in arthroscopic partial meniscectomy include age younger than 40 years, symptoms present less than 1 year, absent patellar symptoms, no preoperative radiographic evidence of degeneration and absence of ligamentous injury[45].

Despite selecting patients with characteristics for more favourable outcomes, long term studies have suggested that they will eventually go on to have accelerated degenerative changes. Table 1 summarises the factors influencing the risk of developing arthritis based on the evidence previously discussed.

MENISCAL REPAIR

Owing to the long term complications associated with meniscectomy, as well as the recognition of the functional importance of the meniscus, there has been increasing interest in avoidance of meniscectomy where possible and meniscal repair has gained popularity.

In the early 1980s animal studies were performed to evaluate the response of the meniscus to injury, and showed that meniscal tissue was capable generating a healing response particularly at its periphery. Cabaud *et al*[46] performed transverse medial meniscal lacerations and repair with a single Dexon suture on 20 canine and 12 rhesus knee joints. At just four months, 94% showed sufficient healing to protect the underlying articular cartilage. Only 6% failed to heal. Histology revealed that the scar tissue was composed of unorganised collagen without common ground substance components. Arnoczky and Warren[47] reported on the vascular response to complete midportion transaction of the medial meniscus in 15 dogs. They found that at ten weeks all of the lacerations healed with fibrovascular scar tissue. The response originated from the peripheral synovial tissues. Interestingly longitudinal incisions in the avascular portion of the meniscus all failed to heal.

The blood supply is fundamental to the success of

Table 1 Factors influencing the risk of developing arthritis following meniscectomy

Compartment involved	Greater risk with lateral meniscectomy
Volume of resection	Greater risk with larger resection volume
Orientation of tear	Greater risk with radial tear – destroys hoops tress function
Associated conditions	Greater risk with pre-existing chondral damage
	Greater risk with ACL insufficiency
Knee alignment	Varus malalignment → greater medial compartment load
	Valgus malalignment → great lateral compartment load
Body habitus	Greater risk for larger BMI
Patient age	Greater risk over 40-year-old
Activity level	Greater risk with lower preoperative activity level

BMI: Body mass index.

a meniscal repair. Only tears in the red-red or possibly the red-white zone are expected to heal. The absence of blood vessels in the remaining meniscus prevents widespread use of meniscal repair and patients are subjected to meniscectomy. Attempts have been made to encourage bleeding in otherwise avascular zones. Exogenous fibrin clots have been used to stimulate a reparative response in an avascular zone[48]. Five cases of posterolateral meniscal tears just anterior to the popliteus fossa that are devoid of penetrating blood vessels were repaired and enhanced with a fibrin clot. All patients returned to initial level of sports and second look arthroscopy showed healing of the periphery occurred in all cases. Trephination of vascular channels on the free meniscal edges has also been shown to improve healing rates. In a study[49] comparing meniscal repair plus trephination with meniscal repair alone, there was a significantly lower re-tear rate in the group who had additional trephination. Further evidence that bleeding can aid meniscal repair is from a study by Cannon and Vittori[50]. Patients with meniscal repairs in conjunction with anterior cruciate ligament reconstruction were compared with patient undergoing meniscal repair alone. They report a 93% healing rate in the anterior cruciate ligament reconstruction group compared to 50% in meniscal repair alone. Anterior cruciate ligament reconstruction involves tibial and femoral drilling, this delivers local growth and clotting factors which may account for the higher repair success rate. It was also noted that acute repairs within 8 wk of injury did better than the more chronic repairs.

Johnson *et al*[51] reviewed a consecutive series of 48 patients who had arthroscopically assisted repair of medial meniscal tears. Exclusion criteria was any other knee pathology or a tear less than 10mm. Clinical success was based on history of pain, physical examination and bilateral standing radiographs. The average follow-up period was just over 10 years. Authors found a clinical success rate of 76%. Furthermore radiographic examination revealed only 8% of operated knees had minimal joint changes compared to 3% in the contralateral knee. As patients were contacted on average 10 years following the procedure almost 30% were lost to follow-up. Another study[52] with long term follow-up over 10 years also report encouraging results. Thirty-three consecutive open meniscal repairs were evaluated. No patients were lost to follow-up. None of the 12 menisci in the stable knees sustained re-tears, compared with 7 of 21 (33%) menisci in nearly stable or unstable knees. Authors concluded a long term survival for 79% with radiographic evidence for the biomechanical function of successful meniscal repairs. A review[53] of sixty two meniscal repairs has shown that early repair within 3 mo of injury had better results than late repair (91% *vs* 58% success rate) and traumatic tears fared better than chronic tears (73% *vs* 42%). Authors concluded that isolated atraumatic medial meniscal tears appeared to do particularly poorly and may be better treated by meniscectomy.

Seo *et al*[54] performed second look arthroscopies in 11 patients who underwent arthroscopic repair of the posterior root attachment at 13.4 mo postoperatively and in none of them had the repair healed. A study[55] evaluating healing after meniscal repair using artho-CT scan also found that posterior segment healing rate was lower compared to middle portion tears. Despite this most patients still showed clinical improvement suggesting that the favourable results seen after meniscal repair do not necessarily correlate with the appearance of a normal looking meniscus.

Studies comparing meniscal repair with meniscectomy are limited. Defining whether or not a meniscal tear has healed post-operatively is difficult. MRI scans are only 80%-90% accurate at diagnosing meniscal tears initially and even less accurate post-operatively. High signal in the meniscal tissue can represent oedema, degeneration, an actual tear or a healing tear post repair[56]. Second-look arthroscopy to directly visualise the repair, requires an invasive surgical procedure and would be hard to justify. Furthermore randomising patients to receive either repair or resection would not be ethical as different tear patterns require different interventions. Stein *et al*[57]report on the long term outcome after arthroscopic meniscal repair versus arthroscopic partial repair meniscectomy for traumatic meniscal tears. Eight-one patients were assigned to either repair or resection. Meniscal repair was performed in full thickness and vertical longitudinal tears greater than 1cm or bucket handle tears in the red-red to red-white zone. Partial meniscectomy was for ruptures in the white-white zone, or for all tears considered non-

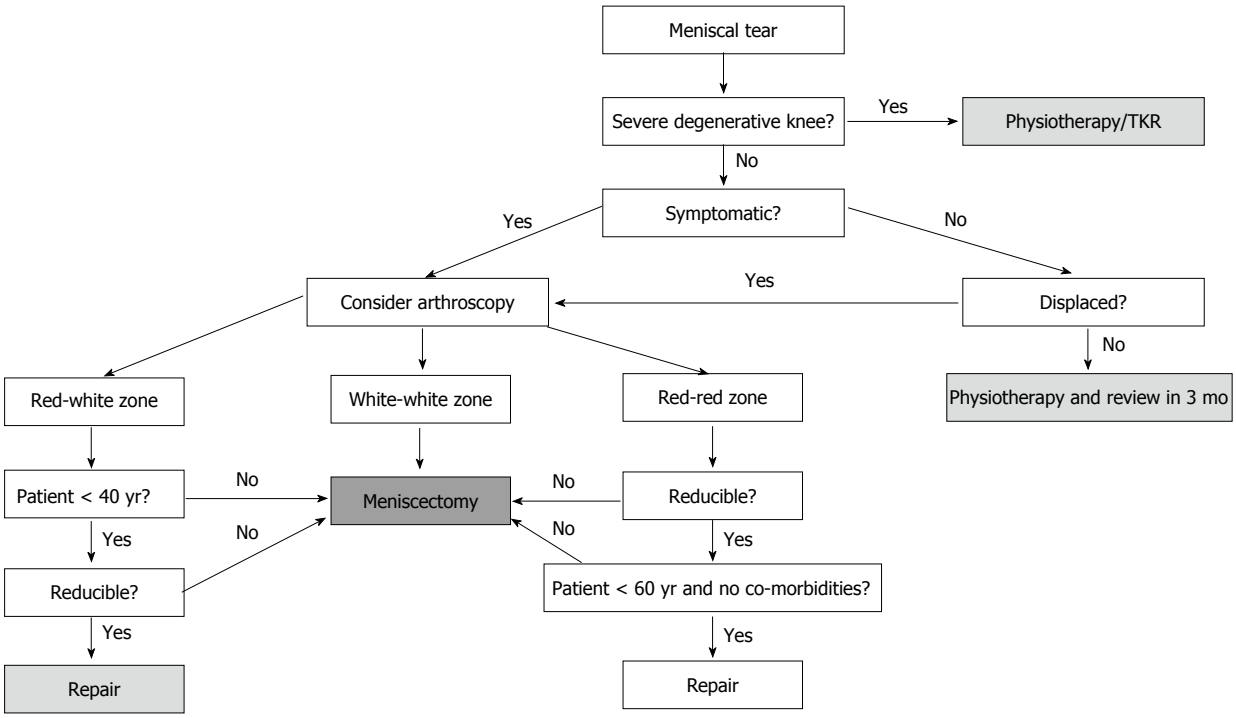

Figure 2 Meniscal tear management tree.

repairable due to type and size. Full rehabilitation was performed for all repairs. This included six weeks of protected weight bearing in motion limiting braces. At long term follow-up (8.8 years) no osteoarthritic progression was detectable in 80.8% after repair compared with 40.0% after meniscectomy. Pre-injury level of activity was achieved in 96.2% after repair compared with 50% after meniscectomy. Function score revealed no significant difference. An important point to note from this study is that all patients benefited from surgery. One cannot deduce that repair is better than resection as treatment was not randomised but specifically chosen depending on the type of tear. Also potential benefits of meniscal repair must be weighed up against significant differences in post-operative rehabilitation. Patients having simple meniscectomy can usually return to full work after a couple of weeks. However for a successful result following meniscal repair, patients are required to wear a hinged brace for up to 6 wk followed by extensive physiotherapy. Such restriction should be taken into account and evaluated on a patient by patient basis.

MENISCAL REPAIR TECHNIQUES

With the growing trend towards meniscal repair, naturally there have also been advances in repair techniques particularly since the introduction of arthroscopic surgery. Open meniscal repair through an incision posterior to the collateral ligaments is now rarely performed due to associated neurovascular injury. Rockbom and Gillquist[58] report on a 13 year follow-up of 31 patients who underwent open meniscal repair. They found an overall failure rate of 29%. Interestingly,although knee function was reduced in the repair group compared to an uninjured control group; there was no difference in incidence of radiological changes between groups. Other more commonly used techniques include inside-out, outside-in and all inside repairs.

Both inside-out and outside-in repair techniques involve passing a suture from either the inside or the outside of the knee *via* arthroscopy and tied beyond the joint capsule using a small incision. These techniques are particularly useful for anterior and middle third tears which are not easily accessed by an all-inside technique. However care of neurovascular structures in particular the saphenous nerve medially and the common peroneal nerve laterally must be taken when making the accessory incisions[59].

Advances in meniscal repair devices have allowed for all-inside arthroscopic meniscal repair techniques to evolve with the advantage of avoiding the need for accessory incisions. Initially rigid biodegradable devices were used. Gill *et al*[60] report on 32 meniscal repairs using the rigid biodegradable Meniscus Arrow (Bionx Implants, Blue Bell, PA). At 2.3 years follow-up they show a 90.6% success rate with only 3 patients requiring further surgery. However in a follow-up study[61] at 6.6 years, this success had declined to just 71.4%. A biomechanical study[62] of rigid biodegradable devices found that at 24 wk hydrolysis was responsible for a significant decrease in failure strength.

Suture based devices consisting of an anchor component and a sliding knot were the next generation to be developed in an attempt to avoid the complications associated with rigid devices and to allow and more flexible fixation of the meniscal fragments. Success rates

of 83%-88%[63,64] have been reported so far. Barber and Herbert[65] investigated load-to-failure strength of meniscal repair devices and found that suture based devices had superior pullout strength than rigid devices, with a double vertical suture being the strongest. Drawbacks associated with suture based devices include, increased costs, retained polymer fragments, chondral injury and a significant learning curve with a high rate of anchor pull-out during insertion[66].

Several studies have been published in order to establish the optimum repair technique. Grant *et al*[67] performed a systematic review comparing 19 studies looking at different repair techniques for isolated meniscal tears. They found no differences in clinical failure rate or subjective outcome between inside-out and all-inside meniscus repair techniques. Complications were associated with both techniques. More nerve symptoms are associated with the inside-out repair and more implant-related complications are associated with the all-inside techniques. Nepple *et al*[68] found similar results in a systematic review of 13 studies with a minimum of five year follow-up. A pooled rate of failure from 20.2% to 24.3% was found for all repair techniques. It was noted that modern all-inside repair devices were not included in the review and long term results are still awaited before firm conclusion on the best repair technique and device can be made.

CONCLUSION

Meniscal tears are a common orthopaedic pathology. Selecting the correct treatment can be challenging and involves multiple factors. Knowledge and understanding of the anatomical structure and vascularity of the meniscus as well as the pattern of tear is important. Evidence shows that non-operative treatment can be successful especially in the short term and in the presence of osteoarthritis. Partial meniscectomy can preserve some of the function of the meniscus and is beneficial for tears within the avascular white-white zone. Meniscal repair has grown in popularity and boasts excellent long-term results. This should be considered for all repairable tears provided the patient can comply with the post-operative rehabilitation. Figure 2 summarises the evidence discussed in this review as well as contributions from the senior author in a decision tree for dealing with meniscal tears.

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Enhanced microfracture techniques in cartilage knee surgery: Fact or fiction?

Stefan Bark, Tomasz Piontek, Peter Behrens, Sabreen Mkalaluh, Deike Varoga, Justus Gille

Stefan Bark, Sabreen Mkalaluh, Justus Gille, Department of Trauma and Reconstructive Surgery, University of Schleswig-Holstein, Campus Luebeck, 23562 Luebeck, Germany
Tomasz Piontek, Rehasport Clinic, 60-201 Poznań, Poland
Peter Behrens, Chirurgie, Unfallchirurgie, Notfälle und Orthopädie (CUNO) Hamburg, 22045 Hamburg, Germany
Deike Varoga, Department of Orthopaedic and Trauma Surgery, University Hospital Schleswig-Holstein, Campus Kiel, 24105 Kiel, Germany
Author contributions: All authors created clinical studies which are presented in this paper; Bark S wrote the paper and Gille J corrected it.
Correspondence to: Bark Stefan, MD, Department of Trauma and Reconstructive Surgery, University of Schleswig-Holstein, Ratzeburger Allee 160, 23538 Campus Luebeck, Germany. stefan.bark@uksh.de
Telephone: +49-451-5002642
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Abstract

The limited intrinsic healing potential of human articular cartilage is a well-known problem in orthopedic surgery. Thus a variety of surgical techniques have been developed to reduce joint pain, improve joint function and delay the onset of osteoarthritis. Microfractures as a bone marrow stimulation technique present the most common applied articular cartilage repair procedure today. Unfortunately the deficiencies of fibrocartilaginous repair tissue inevitably lead to breakdown under normal joint loading and clinical results deteriorate with time. To overcome the shortcomings of microfracture, an enhanced microfracture technique was developed with an additional collagen Ⅰ/Ⅲ membrane (Autologous, Matrix-Induced Chondrogenesis, AMIC®). This article reviews the pre-clinical rationale of microfractures and AMIC®, presents clinical studies and shows the advantages and disadvantages of these widely used techniques. PubMed and the Cochrane database were searched to identify relevant studies. We used a comprehensive search strategy with no date or language restrictions to locate studies that examined the AMIC® technique and microfracture. Search keywords included cartilage, microfracture, AMIC®, knee, Chondro-Gide®. Besides this, we included our own experiences and study authors were contacted if more and non published data were needed. Both cartilage repair techniques represent an effective and safe method of treating full-thickness chondral defects of the knee in selected cases. While results after microfracture deteriorate with time, mid-term results after AMIC® seem to be enduring. Randomized studies with long-term follow-up are needed whether the grafted area will maintain functional improvement and structural integrity over time.

Key words: Cartilage; Microfracture; Autologous, Matrix-Induced Chondrogenesis; Knee; Chondro-Gide®

Core tip: Articular cartilage has a limited healing potential which presents a well-known circumstance in orthopedic surgery. This fact has led to a variety of surgical techniques for treating articular defects and currently the microfracturing presents the most commonly used procedure. The aim of this article is to give an overview about actual studies regarding microfracture and the AMIC® technique in cartilage knee surgery and to show recent developments.

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INTRODUCTION

Articular cartilage has a limited healing potential which presents a well-known circumstance in orthopedic surgery[1]. The affected patients suffer from pain, stiffness and loss of quality of life. This fact has led to a variety of surgical techniques for treating articular defects and currently the microfracturing presents the most commonly used procedure[2]. Pridie recognized the potential of mesenchymal stem cell (MSCs) stimulation for the aim of cartilage repair in the 1950s while Steadman *et al*[3] described further developments of penetrating the subchondral bone for the recruitment of MSCs in the 1990s. In microfracture (MFx) the MSCs migrate in the fibrin network of the blood clot and this clot is transformed into repair tissue by the contained bone marrow components. In this context the blood clot is not mechanically stable to withstand tangential forces[4,5]. Therefore Benthien *et al*[6] developed the Autologous, Matrix-Induced Chondrogenesis (AMIC®) technique. This procedure uses a natural collagen Ⅰ/Ⅲ scaffold (Chondro-Gide®, Geistlich Pharma AG, Switzerland) which covers the microfractured area and stabilizes the formed blood clot. Several clinical results of AMIC® have already been published[6-9].

The aim of this article is to give an overview about actual studies regarding microfracture and the AMIC® technique in cartilage knee surgery and to show recent developments.

PRE-CLINICAL RATIONALE

The potential of mesenchymal stem cell (MSCs) stimulation for the aim of cartilage repair was first described by Pridie[10]. Steadman developed out of this the microfracture technique[3]. Both techniques have similarities including focal penetration of the subchondral plate to expose cartilage defects to the benefits of cellular and growth factors influx, as well as improving anchorange of the new tissue to the underlying subchondral bone and to some extent surrounding cartilage. However, while functional outcomes have been reported, there is a paucity of data on the histological, biochemical and molecular changes in human patients[3,11].

Regarding the application of a collagen membrane in cartilage defects like used in AMIC®, Kramer *et al*[12] showed in an in-vitro work that a membrane consisting of collagen can retain cartilage building cells, like, *e.g.*, mesenchymal stem cells from bone marrow after microfracturing. In conclusion MSCs, found in the membrane, were successfully differentiated into adipogenetic, osteogenetic and chondrogenetic lineage. Dickhut *et al*[13,14] demonstrated in another in-vitro study that a biphasic carrier made of collagen type I/III, like for, *e.g.*, Chondro-Gide® (Geistlich Pharma AG, Switzerland) used for AMIC®, supports chondrogenesis of MSCs and further that in comparison to collagen-free-membrane the form stability of the repair tissue was enhanced.

Gille *et al*[15] tested in a sheep study with a follow-up period of 12 mo the addition of a collagen membrane to microfractured areas. The authors confirmed that the average thickness of the repair tissue was greater when a collagen Ⅰ/Ⅲ scaffold was used compared to microfracture alone.

CLINICAL STUDIES

Microfractures

While clinical efficacy of the MFx technique for articular cartilage repair in the knee has recently been subjected to an evidence-based systematic analysis (28 studies describe 3122 patients), the published data about AMIC is in comparison still limited[16].

In general diverse factors are known to influence the clinical outcome after microfractures: size and location of the defect, sex and age of the patient, surgical technique and postoperative rehabilitation program[17,18].

Regarding the size of the defect Gudas *et al*[19] showed in a prospective randomized clinical study that the International Knee Documentation Committee (IKDC) score in young athletes showed significant worse outcome in the microfractured group if the lesion was greater as 2 cm^2 and concluded that the lesion size affects the outcome of microfracture.

According to this, Knutsen *et al*[20] presented in another prospective randomized clinical study comparing autologous chondrocyte implantation with microfracture significant higher short form 36 (SF-36) scores in MFx group associated with lesions under 4 cm^2 and also concluded that the lesion size is associated with MFx outcome.

De Windt *et al*[21] analyzed in a prospective cohort study the prognostic value of the defect location (medial *vs* lateral) on clinical outcome 3 years after cartilage therapy for a focal cartilage lesion in autologous chondrocyte implantation (ACI) and MFx. The authors found a significant better Knee and Osteoarthritis Outcome Score (KOOS) for medial than for lateral lesions and therefore concluded that the defect location is related to clinical outcome of ACI and MFx. Another prospective cohort study by Kreuz *et al*[22] confirmed the effect of defect location for clinical outcome after microfracture procedure. IKDC and Cincinnati score as well as MRI findings showed significant better outcome when MFx was performed in femorale condyle versus tibia, trochlea and retropatellar regions.

In a prospective study by Mithoefer *et al*[23] a lower body mass index (BMI) correlated with higher scores for the activities of daily living and SF-36 after microfracture in 48 symptomatic patients with isolated full-thickness articular defects in the knee joint. Worst results were seen in patients with a BMI > 30 kg/m^2.

Highlighting the patients age, de Windt *et al*[21] showed in a prospective study treating 55 patients with MFx and ACI that the KOOS improvement was significantly better for patients under 30 years compared with older patients[21]. Data of a randomized controlled trial with 80 human subjects treated with ACI or MFx by Knutsen, are

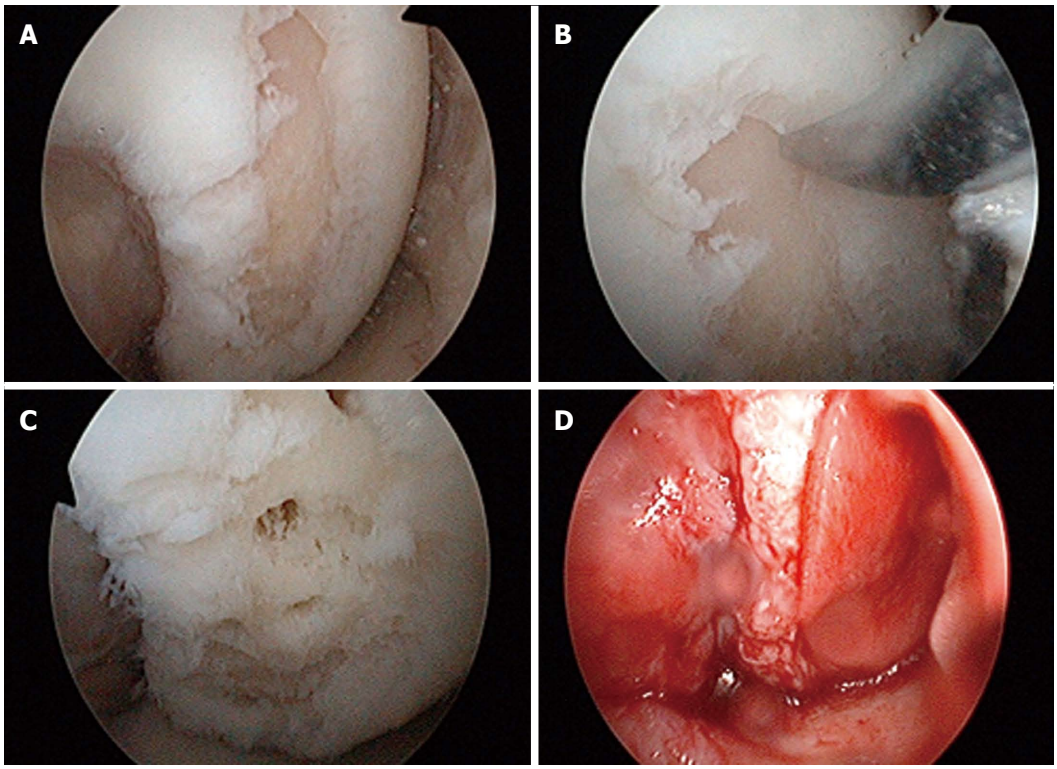

Figure 1 Twenty years old female with a chondral defect on the lateral condyl after trauma. The AMIC® technique was done arthroscopic assisted: after debridement of the chondral defect (A), numerous perforations of the subchondral lamina were performed (B, C). The implantation of the matrix was performed under dry, arthroscopic conditions, as published before (D)[27].

in accordance with findings from de Windt *et al*[21]. Both authors concluded that the patient age influences the clinical outcome of ACI as of MFx. In contrast we could not show a significant impact of age on the results after AMIC®[24].

Autologous, matrix-induced chondrogenesis

To overcome the shortcomings of the microfracture technique, an enhanced procedure was first described in 2005 by Behrens *et al*[25] and first initial results were presented by our study group. Figure 1 shows step-by-step an arthroscopically AMIC® procedure. In a prospective series, we investigated 27 patients with a follow-up-period up to 62 mo and a mean of 37 mo. The mean age of the patients was 39 years (range 16-50 years) and the mean defect size was 4.2 cm^2 (range 1.3-8.8 cm^2). 87% of the patients were subjectively highly satisfied and the outcome scores applied [Lysholm, International Cartilage Repair Society (ICRS), Meyer, Tegner, Cincinnati] showed significant increase up to 24 mo. Patients with lesions larger 8 cm^2 had greatly reduced scores. In this series, a potential gender-specific dimorphism was obvious; males had significantly higher values in the ICRS score compared with their female counterparts[24]. We couldn't approve these findings in a recent study evaluating 57 patients treated with AMIC[8]. In this study a significant decrease of pain in the visual analogue scale (VAS) from a mean of 7.0 preoperatively to 2.7 at 1 year and 2.0 at 2 years postoperatively was found (Figure 2). Improvement of the Lysholm score also showed significant results with a mean score of 50.1 preoperatively, 79.9 at 1 year and 85.2 at 2 years postoperatively (Figure 2). Younger patients with no ligamentous instability, meniscal deficiency or patellofemoral malalignement had the best outcome[8].

Kusano *et al*[26] presented clinical and radiographic results in a retrospective study with a mean follow-up of 29 mo of patients treated with AMIC for full-thickness cartilage defects of the knee. They found significant improvements in the IKDC, Lysholm, Tegner and VAS pain score. Moreover, the patients were satisfied while the MRI findings showed generally incomplete or inhomogeneous tissue filling.

A current randomized, controlled trial by Anders *et al*[7] compared the AMIC technique with microfracture during 1- and 2-year follow-up. The authors included 38 patients with a mean defect size of 3.4 cm^2 and mean age of 37 years. The clinical follow-up was performed with the modified Cincinnati and the IKDC score. MRI findings revealed a homogenous defect filling in the majority of patients (Figure 3). No significant statistical differences could be found between the groups but improvements in both scores were seen at 1- and 2-years postoperatively. It is open to debate if a significant difference of both groups has to be expected within the first 2 years of follow-up.

Modifications to the original AMIC technique may have a promising future. An arthroscopic approach of the AMIC® technique was published by Piontek *et al*[27]. Compared to open surgery, the described arthroscopic technique may offer advantages including minimal soft

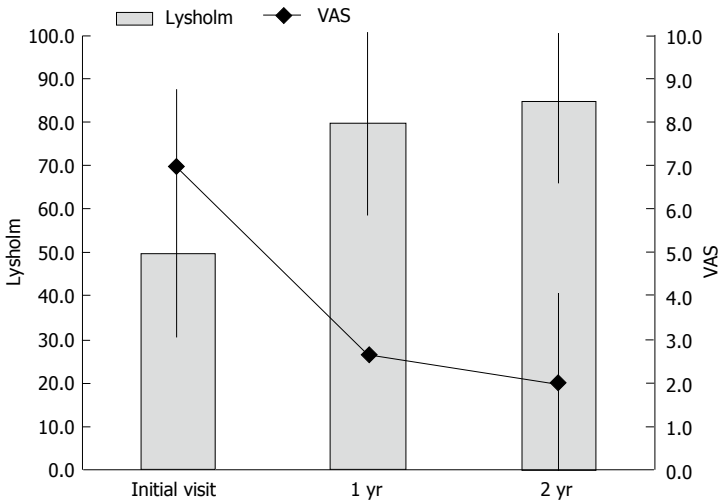

Figure 2 Significant improvements of the mean Lysholm and visual analogue scale score after 1 year and further increased values up to 2 years postoperatively in patients with cartilage knee defects treated with AMIC®[32]. VAS: Visual analogue scale.

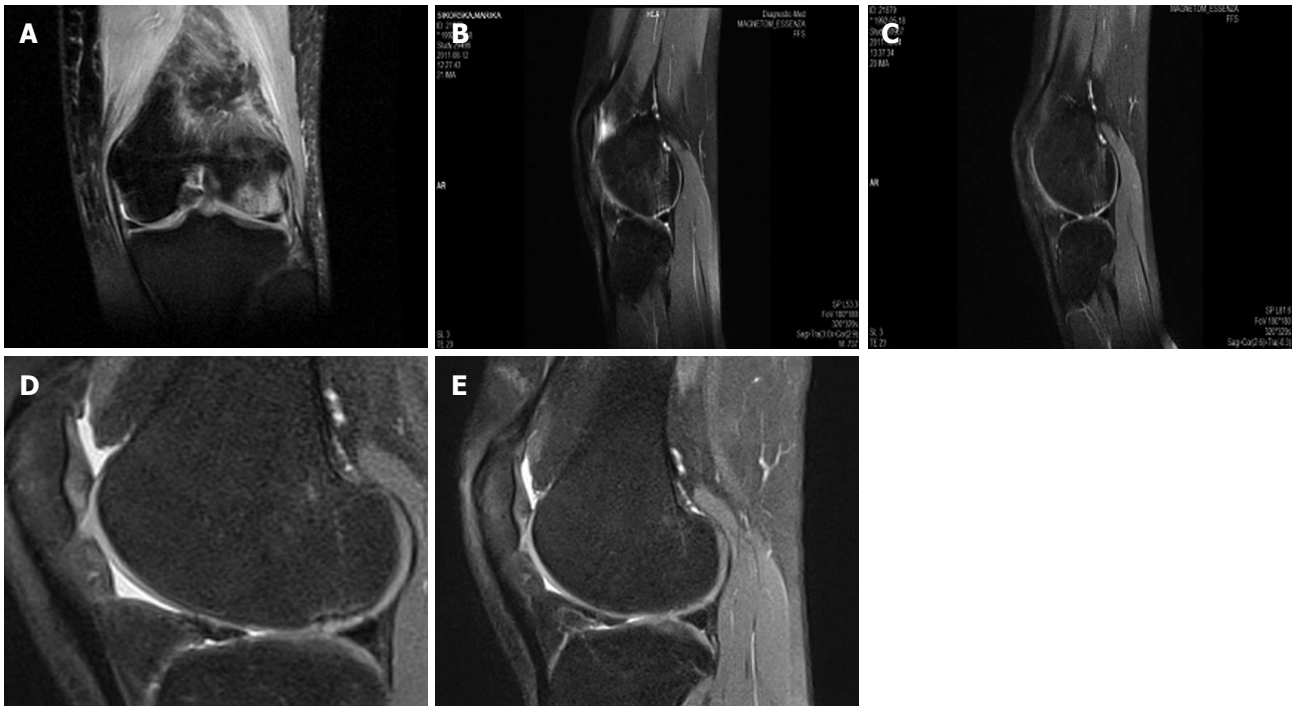

Figure 3 The same patient showing enhanced defect filling demonstrated by follow-up magnetic resonance imaging before surgery (A) and 3 (B), 6 (C), 12 (D) and 24 mo (E) after the index procedure.

tissue trauma and minimal blood loss. Dhollander *et al*[28] *e.g.*, performed a modified so called AMIC plus technique (AMIC plus platelet-rich-plasma gel) and were able to show clinical improvements. Emerging techniques, *e.g.*, the addition of concentrated bone marrow from the iliac crest or platelet rich plasma gel may be beneficial, but the impact needs to be proven in further studies[29]. Benthien *et al*[30] and Chen *et al*[31] presented in a recent study first results with a so called nanofracture®.

CONCLUSION

In conclusion both techniques (microfracture and AMIC®) present an effective and safe method of treating full-thickness chondral defects of the knee. While results after microfractures deteriorate with time, clinical outcome after AMIC® seems to be more enduring. By now, only one randomized trial has been published comparing microfractures and AMIC®. This limitation involves the extent to which the findings can be generalized beyond the cases studied. The number of cases is too small for broad generalizations. However, these limitations should be seen as fruitful avenues for future research along the same lines.

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Principles of postoperative anterior cruciate ligament rehabilitation

Tolga Saka

Tolga Saka, Department of Sports Medicine, Bezmialem Vakif University Medical Faculty Hospital, 34093 Fatih, Istanbul, Turkey
Author contributions: Saka T designed and performed the research and wrote the paper.
Correspondence to: Tolga Saka, MD, Associate Professor, Department of Sports Medicine, Bezmialem Vakif University Medical Faculty Hospital, Adnan Menderes Bulvarı, Vatan Caddesi, 34093 Fatih, Istanbul, Turkey. tolgasakamd@gmail.com
Telephone: +90-212-4531710 Fax: +90-212-6217580
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Abstract

It is known that anterior cruciate ligament (ACL) reconstruction needs to be combined with detailed postoperative rehabilitation in order for patients to return to their pre-injury activity levels, and that the rehabilitation process is as important as the reconstruction surgery. Literature studies focus on how early in the postoperative ACL rehabilitation period rehabilitation modalities can be initiated. Despite the sheer number of studies on this topic, postoperative ACL rehabilitation protocols have not been standardized yet. Could common, "ossified" knowledge or modalities really prove themselves in the literature? Could questions such as "is postoperative brace use really necessary?", "what are the benefits of early restoration of the range of motion (ROM)?", "to what extent is neuromuscular electrical stimulation (NMES) effective in the protection from muscular atrophy?", "how early can proprioception training and open chain exercises begin?", "should strengthening training start in the immediate postoperative period?" be answered for sure? My aim is to review postoperative brace use, early ROM restoration, NMES, proprioception, open/closed chain exercises and early strengthening, which are common modalities in the very comprehensive theme of postoperative ACL rehabilitation, on the basis of several studies (Level of Evidence 1 and 2) and to present the commonly accepted ways they are presently used. Moreover, I have presented the objectives of postoperative ACL rehabilitation in tables and recent miscellaneous studies in the last chapter of the paper.

Key words: Anterior cruciate ligament rehabilitation; Eccentric exercise; Proprioception; Strengthening; Postoperative; Anterior cruciate ligament

Core tip: In this topic highlight, I will review the answers given by some literature studies to questions in the literature about anterior cruciate ligament rehabilitation such as "could common ossified knowledge or modalities really prove themselves?", "is postoperative brace use really necessary?", "what are the benefits of early restoration of the range of motion?", "to what extent is neuromuscular electrical stimulation effective in protecting from muscular atrophy?", "how early can proprioception training and open chain exercises begin?", "should strengthening training start in the immediate postoperative period?"

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INTRODUCTION

Anterior cruciate ligament (ACL) reconstructions have to be combined with detailed postoperative rehabilitation in order for patients to return to their pre-injury activity levels. ACL reconstruction ensures structural ligament repair, whereas rehabilitation protects and maintains the lig-

Table 1 Goals of 0-1 mo (acute phase)

Education of patient
Pain control
Decrease effusion
Increase range of motion
Be able to do straight leg raise (1–2 d[1])
Be able to lift the leg in all directions without assistance (1–7 d)
Flexibility (hamstrings, calves)
Strengthening (quadriceps, hamstrings, hip, calf, core, upper body, non-injured leg)
Patellar mobilization
Proprioceptive/balance training (start walking with crutches)
Start cardiovascular fitness (arm ergometer)
Achieve and maintain near or full ROM in knee flexion and extension (full extension 1–5 d[1], full flexion 2-3 wk[1])
Achieve and maintain weight bearing gait (2 crutches 0-1 wk[1], 1 crutch 0-1 wk[1], no crutches 0-2 wk[1])
No apprehension when walking without a crutch
Home training program (2-3 h/d[1], therabands, ROM exercises, *etc.*)
Start bicycling (90°-100° in active flexion[1])
Start pool exercises (after suture removal, when wound is closed[1])
Start to fight with fear of re-injury physically and psychologically
Return to work (3-4 wk[1] if office work)
MD visit 1/wk

[1]Author's approach.

ament repair and the physical and psychological state and performance capabilities of the athlete. The above paragraph is maybe the summary of the one point on which there is consensus about ACL reconstruction. Different rehabilitation protocols post-ACL reconstruction exist in our country and all over the world at sports medicine departments of universities and sports medicine clinics, as indicated on their websites. This lack of consensus led to uncertainties, which resulted in aggressive and non-aggressive approaches. Studies in the literature tried to determine the earliest optimal time to start rehabilitation and how long it should take, considering all parameters of the rehabilitation process. Although there are many studies on this topic, there is a lack of consensus in the literature even about commonly accepted modalities. Today, specialists decide on the type of exercises that need to be prescribed, and when in the ACL rehabilitation process to start them on the basis of their experience and interpretation of the condition. Different interpretations lead to more questions, which in turn lead to more original articles. New trial outcomes modify and develop current protocols. Thus, it would not suffice to say that the required exercises or modalities should be performed in a specific period of time. The ACL rehabilitation objectives that I summarize in Table 1, Table 2, Table 3 and Table 4 do not indicate a precise time; the times may overlap and modifications have to be made on the basis of the criteria associated with the time schedule.

Protocols and interpretations may differ in ACL rehabilitation approaches, but what remains the same is the outcome that every sports medicine specialist tries to achieve. The overall objectives before a return to sports activities are control of pain and swelling, a full range of motion and flexibility, elimination of muscle atrophy, a normal gait, a return to work for non-athletes, a return to pre-injury muscular strength and endurance levels, maintenance of cardiovascular fitness, restoration of proprioception, a return of self-confidence and overcoming kinesiophobia. When all these objectives are achieved the athlete can return to sports activities.

Table 2 Goals of 1-4 mo (maintenance and acceleration phase)

Decrease and disappearance of effusion
Full and pain-free knee range of motion
Continue flexibility exercises
Continue strengthening exercises (add isokinetic hamstring exercises)
Swimming
Bicycling (indoor)
Core training progression
Proprioceptive progression (focus on weak positions)
Maintain cardiovascular fitness
Determine and manage hamstring, quadriceps strength deficits
Prepare physically and psychologically for jogging
Deep water running
MD visit 2/mo

My aim is a review of the most common modalities in ACL rehabilitation, such as postoperative bracing, early range of motion (ROM), neuromuscular electrical stimulation (NMES), proprioception, open/closed chain exercises and early strengthening; I preferred not to approach the subject from the basic definitions and historical perspective, and present in the last chapter recent miscellenous studies.

POSTOPERATIVE BRACE USE

The objectives of postoperative brace use are restriction and development of the ROM of the knee, resistance of the knee to medial and lateral stressors, knee stability, and protection from knee injuries, however its role in ACL rehabilitation is controversial.

McDevitt *et al*[1] reported in 2002 that there was no definite evidence of improvements in outcomes or protection from re-injuries associated with the use of a brace in postoperative ACL reconstruction.

Swirtun *et al*[2] stated that use of a brace in non-operated ACL-injured patients reduced the feeling of instability, but increased complaints during day-to-day activities. They also underlined in their trial that the positive effects were not supported by objective outcomes.

Wright *et al*[3] indicated in a systematic review in 2007 that wearing of a knee brace had no additional treatment value after ACL reconstruction. This conclusion was supported in 2009 by Andersson *et al*[4].

Birmingham *et al*[5] conducted a randomized controlled trial in 2008 to compare the outcomes of a rigid knee brace and a neoprene sleeve in 150 patients post-ACL reconstruction during exercise and all physical activities. The authors stated in the conclusion of their trial that the use of a rigid knee brace postoperatively was not superior to the use of a neoprene sleeve on the measured outcomes. Nevertheless, they stressed that the subjective

Table 3 Goals of 4-6 mo (sports-specific phase)

No effusion
Pain free jogging and running (no effusion)
Pain free landing (from double to single leg)
Pain free hopping (from double to single leg)
Functional strengthening (plyometrics, agility drills, *etc.*)
Sports specific proprioception training
Sport specific cardiovascular fitness
Training in the sports field
Adequate neuromuscular control
Continue fighting against fear of re-injury
Success in functional tests
MD visit 1/mo

Table 4 Month 4-6 (return to sports phase)

Flawless running
Good psychology
Maintain good results of functional tests
Adequate sports specific aerobic/anaerobic measures
Quadriceps and hamstring strength at least 85% of the normal leg
No swelling
No laxity
No fear

confidence rating of patients that used the rigid knee brace was higher than in the neoprene sleeve group[5].

Can the use of a brace attenuate pain, which is a significant problem in the postoperative period? Hiemstra *et al*[6] tried to answer this question in their randomized controlled trial from 2009. They carried out a comparative study of pain, use of analgesics, effusion and ROM parameters in 88 patients who were immobilized and non-immobilized post-ACL reconstruction. For immobilization, a soft, unhinged knee brace was used. They found no differences in pain or any of the secondary outcomes between immobilized and non-immobilized patients at any point during the first 14 d after ACL reconstruction[6].

Mayr *et al*[7] randomized 73 patients to compare the clinical outcomes of postoperative ACL rehabilitation using a water-filled soft brace to those using a hard brace. Braces were applied for 6 wk after the surgery. The soft brace group had significantly higher postoperative International knee documentation committee (IKDC) subjective ratings, Tegner activity scores and Lysholm knee scores and significantly less effusion. The hard brace group had significantly more extension deficits and no significant difference was reported between the groups on knee ROM, knee laxity and thigh atrophy parameters. The authors stated that the water-filled soft brace was easy-to-use and safe and might be an efficacious alternative to the hard brace[7].

In a recent study, Stanley *et al*[8] reported that the use of a knee extension constraint brace reduced the peak posterior ground reaction force when walking, but this effect was not observed when descending stairs and jogging. They concluded that the knee extension brace modified the lower extremity movement pattern which made re-injuries less possible and this is why it could be used for postoperative ACL rehabilitation[8].

Kruse *et al*[9] investigated the outcome of 11 studies in their systematic review and concluded that the postoperative use of a brace did not provide any additional benefits. Lobb *et al*[10] found in their systematic review strong evidence of no added benefit of the use of a brace for 6 wk postoperatively compared with standard treatment in the short term. Meuffels *et al*[11] reported in their study, which referred to the recommendations of the Dutch Orthopaedic Association, that a brace can be used in patients with instability symptoms who do not qualify or who do not want to qualify for operative treatment.

In our clinical approach, we do not use postoperative braces in many of our patients. We prefer using braces for only 1-2 wk in patients who find it difficult to regain their confidence or are temperamentally conservative and anxious. In our clinical experience, the most common complaints associated with postoperative brace use are too much restriction during motion and the desire to be able to move independently sooner. The question "is the use of a brace required?" is mainly answered with "No, it is not" by the literature. Nevertheless, as indicated in the introduction, optimistic specialists based on their clinical experience and referring to trials that find the use of braces beneficial continue using them in the postoperative period. I think that force vectors of the knee joints during movement need to be investigated and compared in future research studies in order to clarify this point.

EARLY RESTORATION OF ROM

Many investigators underline that the priority goal of postoperative ACL rehabilitation should be restoration of the full ROM[12-15].

Rubinstein *et al*[12] reported that full knee extension in the immediate postoperative period in 194 patients that underwent autogenous bone-patellar-tendon ACL reconstruction did not damage the graft or joint stability. Protection of the graft is important for both the patient and the orthopedist who performed the surgical procedure. Orthopedists refer their patients to those sports medicine clinics they are convinced will perform a rehabilitation modality that will not adversely affect the graft recovery process. It is obvious that patient compliance with the rehabilitation protocol will improve when patients trust the orthopedist who performed the surgical procedure, and orthopedists trust physicians responsible for the rehabilitation program.

An early start to quadriceps exercises in the postoperative period has been reported to improve early ROM development[13]. Another study found that restoration of symmetrical ROM in the early period of ACL rehabilitation was quite valuable for long-term ROM maintenance of the patients[14]. Early restoration of strength and ROM will accelerate early mobilization of the patient and more effective participation of the patient in the following rehabilitation phases. This in turn will allow for different training activities to be performed on the knee joints and long-

term ROM maintenance will be ensured. Previous studies have shown that patients who maintain normal ROM according to IKDC criteria have better outcomes after ACL reconstruction[16,17]. In their study of the long-term outcomes of postoperative ACL reconstruction, Shelbourne and Gray reported that the most important reason for low subjectivity scores of the patients was the absence of normal knee extension and normal knee flexion[17].

The reason for early ROM restoration brings to the fore the question of whether rehabilitation should be accelerated or non-accelerated. There is no consensus on this subject in the literature. Beynnon *et al*[18] reported that in postoperative ACL rehabilitation, accelerated programs were not significantly different from non-accelerated programs on knee laxity, clinical assessment, proprioception, functional performance and thigh muscle strength parameters. Shelbourne followed the recommendations regarding immediate full extension and maintenance and stated that, after ACL reconstruction graft remodeling, continued loss of ROM could be associated with long-term osteoarthritis modifications in radiography[15].

In a recent study, Christensen *et al*[19] found no differences between early aggressive and nonaggressive rehabilitation after ACL reconstruction on the primary outcomes of knee laxity and subjective IKDC score. In addition, they observed no differences in secondary outcomes between groups for differences in ROM and peak isometric force values. Kruse *et al*[9] stressed in the conclusion of their systematic review that further investigations were needed to clarify the effect of accelerated, aggressive rehabilitation on quick return to sports.

In the light of the above studies we can say that the importance of early ROM recovery in postoperative ACL rehabilitation is obvious. However it is still uncertain when to start ROM exercises in the early postoperative period. Early ROM of extension and flexion is known to reduce the risk of arthrofibrosis[20]. We target a full ROM in the first 2-3 wk in our patients. This can be accepted as the accelerated approach in the literature. In our experience, ROM recovery in the first 2-3 wk should be encouraged unless there is a problem with compliance of the patient with the treatment.

NEUROMUSCULAR ELECTRICAL STIMULATION

In the early phase, normal gait should be restored by controlling and synchronizing the quadriceps with the antagonist hamstring. Improvement of gait varies from person to person. Sensitivity to pain, anxiety and other factors can prolong this period. In this phase, in nearly all cases atrophy of the quadriceps caused by a knee effusisson that inhibits the quadriceps muscle is observed. Many studies have proven that electrical stimulation (ES) protects from muscle atrophy[21-23].

Sisk *et al*[24] examined the effect of prolonged daily ES on quadriceps strength in casted 22 patients during the 6 wk following anterior cruciate reconstruction. They found no difference in quadriceps strength between the two groups during the 7th, 8th, and 9th week postoperatively. The length of time (how much time per day and how many weeks) for the use of ES in the ACL rehabilitation process is not known yet.

Wigerstad-Lossing *et al*[21] in a 1988 study found that the effect of ES plus voluntary muscle contraction increased the isometric muscle strength more than control group. In the conclusion of their study they stated that ES combined with voluntary muscle contraction was significantly protecting from atrophy of the muscles. In a study in 1988 Delitto *et al*[22] compared the isometric torque values of an ES co-contraction group and voluntary isometric co-contraction group in postoperative ACL reconstruction. They found that isometric torque was significantly increased in the extensors and flexors in the ES group.

In a study in 1991, Snyder-Mackler *et al*[23] evaluated 10 patients who were randomized to ES with voluntary contraction *vs* only voluntary contraction. They found a significantly positive difference in the ES group on the values for cadence, walking velocity, stance time of the involved limb, and flexion-excursion of the knee during stance *vs* the voluntary exercise group. They emphasized that the ES group had stronger quadriceps muscles and more normal gait patterns than those in the voluntary exercise group[23].

In a study in 1995 Snyder-Mackler *et al*[25] investigated 110 patients in 4 groups, a high-intensity NMES group, a high-level volitional exercise group, a low-intensity NMES group, and a combined high- and low-intensity NMES group. They found that high intensity ES either alone or in combination with low intensity ES increased recovery of the opposite limb quadriceps strength.

Although most of the above-mentioned studies stressed the benefit of ES, Wright *et al*[26] reported in a systematic review in 2008 that the quality of these studies varied; many did not address randomization or were not blinded and their results were not evaluated by independent observers. In the light of these findings, they underlined that NMES helped the development of the quadriceps, but one could not conclude that NMES was certainly required for successful ACL rehabilitation[26].

In a study in 2011, Hasegawa *et al*[27] administered NMES from postoperative day 2 following ACL reconstruction until the 4th month. They reported that early NMES helped the recovery of knee extension strength measured at 3 mo postoperatively. Moreover, there was a significant increase in the vastus lateralis and calf thickness at 4 wk postoperatively in the NMES group *vs* the control group[27].

In an interesting recent study, NMES was found to modify gene expression in mice post-ACL surgery and delay atrophy of the muscles. NMES was reported to decrease atrogene and myostatin accumulation in the quadriceps muscle and protect from early atrophy on postoperative day 3 but did not affect atrophy on the 7th and 15th day[28]. Future human gene studies may be the key in answering the question of how long NMES and

other modalities should be applied postoperative.

Most of the above-mentioned studies report that NMES contributes to atrophy prevention in postoperative ACL rehabilitation[21-23,25,27], whereas some publications report no such effects[24,26]. When using NMES as part of our treatment we ask the patient to do voluntary muscle contraction each time. Even if we assume that NMES is not efficacious, we think that it could contribute to atrophy prevention when combined with voluntary muscle contraction.

PROPRIOCEPTION

Balance and proprioception training have a positive effect on joint position sense, muscle strength, experienced knee function, outcome of functional capacity, and return to full activity[29-32]. Hewett *et al*[33] stated that balance exercises on the balance board could start early in the postoperative period. Proprioceptive exercises actually begin when the patient steps on the ground early in the postoperative period. Early start of locomotion at a level tolerated by the patient will ensure early restoration of proprioception and facilitate progress in proprioceptive exercising.

Friden *et al*[34] reported in a review published in 2001 that despite the existence of many proprioception tests there were no standardized reference tests. They also underlined that the link between the conscious and non-conscious proprioceptive system and their specific roles was unknown. Additionally, they stated that information regarding how proprioceptive training restored sensorial defects was limited. Nevertheless, they reported that during rehabilitation each patient must create muscle strength, alertness, and stiffness in harmony with the disturbed mechanics of the knee, which were present both after nonoperative treatment of the ACL and after a reconstruction of the ACL[34].

In a systematic review published in 2003, Thacker *et al*[35] stated that neuromuscular and proprioceptive training was an important factor in protection from knee injuries. At the same time, they wrote that the studies reviewed were inadequate due to methodological mistakes, and more studies were needed to shed light on this topic in the future[35].

A study in 2005 investigated the effect of early proprioceptive coordination training on neuromuscular performance values post-ACL surgery. The authors stated they found a highly statistically significant correlation between the single leg stance, one leg hop, Lysholm, and Tegner tests at 6 wk, and 4, 6, 9 and 12 mo in the postoperative period[36].

In a randomized controlled study, Cooper *et al*[37] compared the effects of proprioceptive and balance exercises and the strengthening program in the early period post-ACL reconstruction. The investigators reported that the strengthening exercise group had better Cincinnati and patient specific functional scale scores than the proprioceptive group, and early postoperative strengthening training could be more beneficial than proprioceptive training[37]. It is difficult to clearly draw the line between muscle strengthening training and proprioceptive training. Each strength training has proprioceptive properties and most proprioceptive exercises have strength-associated properties.

Angoules *et al*[38] compared knee proprioception post-ACL reconstruction with hamstring *vs* patellar tendon autografts. They reported that there was no statistically significant difference in the joint position sense and threshold to detection of passive motion values between graft groups during any time period, and the knee proprioception returned to normal in postoperative month 6[38].

In a systematic review in 2011, Howells *et al*[39] tried to answer the question whether postural control could be restored postoperative ACL reconstruction. The authors stated that the results were not conclusive due to the limited number of studies on this topic and different methodologies applied in them. They stressed that deficits in dynamic tasks may be more relevant to people intending to return to sport following surgery due to the inherently dynamic nature of sport and should perhaps be the focus of future research[39].

In a recent study, athletes who underwent postoperative ACL reconstruction proved able to start balance training on the Biodex platform 4 wk earlier than with the use of the conventional approach. The authors concluded that the combination of classical rehabilitative techniques with balance training, Speed Court training, and training on the alpine ski simulator made it possible to begin special alpine ski training on the snow 2 mo earlier than with the use of conventional methods[40].

There is no clearly defined starting time for proprioceptive training. Regain of confidence, absence of pain and willingness to exercise are factors contributing to the start of balance training.

OPEN/CLOSED CHAIN EXERCISES AND EARLY STRENGTHENING

Closed chain exercises can be introduced in early rehabilitation due to their benefits, *e.g.*, reduction of shear and acceleration forces on the joints, development of dynamic early joint stability and stimulation of proprioceptors. The question is which open chain exercises can be used safely at which stage in the rehabilitation process. According to Fitzgerald, closed chain exercises are considered safer and more functional compared to open chain exercises[41]. Notwithstanding, Seto *et al*[42] stated that the open and closed chain exercises could co-exist in enabling rehabilitation and strengthening objectives. In their prospective randomized trial, Bynum *et al*[43] reported that closed kinetic chain (CKC) exercises were recommended to provide improved arthrokinematics in comparison with open kinetic chain (OKC) exercises for rehabilitation of ACL injury. Kvist *et al*[44] stated that CKC exercises produced a smaller magnitude of anterior tibial translation (ATT) than OKC activities.

Some studies[45,46] have reported that the kinematic ef-

fects, resulting from hamstring co-activation and increase in the joint compression force during CKC exercises, are not sufficient to reduce ATT significantly. There are also reports of larger ATTs and similar ACL strain during CKC compared with OKC exercises[45,47]. In the early phase of rehabilitation, closed-chain exercise therapy is likely to give fewer patello-femoral complaints and less laxity than open-chain exercises[4,26,31]. Heijne *et al*[48] aimed to evaluate physical outcome after ACL reconstruction with early *vs* late initiation of OKC exercises for the quadriceps in patients operated on either patellar tendon or hamstring grafts. They reported an exercise program with early OKC exercises (postoperative week 4) would lead to more laxity with hamstring grafts than late OKC exercises (postoperative week 12)[48].

Glass *et al*[49] published a systematic review about the effects of open *vs* closed kinetic chain exercises on patients with ACL-deficient or -reconstructed knees in 2010. In their conclusion, they wrote that CKC and OKC exercises seem to have similar outcomes on knee laxity, knee pain, and function and therefore could both be used during the rehabilitation of a patient with ACL deficiency or post-ACL reconstruction[49]. They stated that one article found positive significant effects with inclusion of OKC exercises in the rehabilitation program[50] and another found significant benefits with a combination of OKC and CKC exercises[51]. CKC exercises alone were not found by any studies to be superior to OKC exercises. Mikkelsen *et al*[51] found that using CKC and OKC exercises together led to greater quadriceps torque return and a quicker return to sport than CKC alone. Tagesson *et al*[50] reported that OKC exercises for quadriceps led to better gains in quadriceps strength than when using CKC exercises. In their systematic review, Glass *et al*[49] concluded that OKC exercises should be initiated after the 6th week of the postoperative period. Meuffels *et al*[11] stated that only the use of closed-chain exercises was recommended in early rehabilitation.

A recent study measured the amount of ATT of ACL-deficient knees during selective OKC and CKC exercises. The authors found no significant differences between the ATTs of the ACL-deficient and intact knees at all flexion angles during forward lunge and unloaded open kinetic knee extension. Nevertheless, they recommended that weight-bearing CKC exercise should be preferred over OKC knee extension exercises in ACL-deficient knees[52].

Fridén *et al*[53] stated that there were no clinical trials that evaluated outcomes of OKC exercises in a restricted ROM for pain, function, muscle strength, and anterior knee laxity at 1 year after surgery. The goal in their randomized controlled clinical trial was to determine if an early start of OKC exercises for quadriceps strength in a restricted ROM would promote a clinical improvement without causing increased anterior knee laxity in patients after ACL reconstruction. They concluded that an early start of OKC exercises for quadriceps strengthening in a restricted ROM did not differ from a late start in terms of anterior knee laxity.

In a study in 2005, Shaw *et al*[13] started isometric quadriceps exercises and straight led raises in a group immediately postoperative and compared the result with the non-exercise control group. In postoperative week 2, both groups were enrolled in the same rehabilitation system. They concluded that there was no significant difference in the 6th month postoperatively regarding knee laxity, hop tests, Cincinnati score and isokinetic quadriceps force measurements[13].

Gerber *et al*[54-56] compared the effects of progressive eccentric exercises started in 3rd and 12th week after ACL reconstruction. In their first study, eccentric exercises were performed in knees with full ROM at 20°-60° knee flexion. They reported no statistically significant difference between both groups on pain, effusion and anterior laxity parameters in the 14th week postoperatively[55]. In another study in 2009, they extended the follow-up period to 1 year and detected a statistically significant increase in the cross-sectional areas and volumes of the quadriceps and gluteus maximus muscles and in the quadriceps muscle strength in the group that started eccentric exercises early *vs* late[56].

Sekir *et al*[57] compared the outcomes of isokinetic hamstring strengthening exercises initiated in 3rd and 9th wk post-ACL reconstruction with patellar tendon autograft. The group that started early hamstring strengthening had a better quality of life, activities of daily living in the 1st month, and isokinetic hamstring strength performed at 60°/s angular velocity. Sekir *et al*[57] reported that early hamstring strengthening was not harmful at any point in time during the ACL rehabilitation process.

In a systematic review in 2012, Kruse *et al*[9] reported that immediate postoperative weight-bearing, knee ROM from 0° to 90° of flexion, and strengthening with closed-chain exercises were likely safe, and starting eccentric quadriceps strengthening and isokinetic hamstring strengthening at week 3 after ACL surgery might improve or accelerate strength gains.

In the literature, CKC exercises were proved to benefit the patient in the early postoperative period and new studies focus on the safest point in time to start OKC exercises in early ACL rehabilitation. This remains uncertain. We want to underline that in our clinical approach we are cautious when it comes to the initiation of early postoperative OKC exercises.

RECENT MISCELLANEOUS STUDIES

In this part, I have reviewed the outcomes of some recent interesting studies.

In a study published in 2013 patients that underwent ACL surgery were divided into 2 groups, smokers and non-smokers. The stability and functional scores of the smokers were found to be worse (less satisfactory) than those of the non-smokers. The Achilles tendon-bone allograft of the smokers group rendered the worst result *vs* the other autografts, and the bone-patellar tendon-bone autograft was reported to be more appropriate for ACL reconstruction in smokers[58].

A 15-year prospective, randomized, controlled trial published in 2013 compared the failure rate, knee injury osteoarthritis outcome score (KOOS) (pain, symptoms, Sport/Rec, quality of life, daily living function), Tegner activity scale, anterior knee pain-score, Lysholm score, Rolimeter laxity, extension deficit, single hop and crossover hop for distance outcomes of an iliotibial band autograft and bone-patellar-bone autograft. The authors concluded that the use of an iliotibial band graft could be a safe alternative[59].

In a recent study, Månsson *et al*[60] aimed to identify preoperative factors that had a positive affect on postoperative health-related quality of life. The study concluded that preoperative pivot shift, knee function, ROM and Tegner activity levels were significant factors for postoperative health-related quality of life[60].

A systematic review published in 2013 investigated the psychological predictors of postoperative ACL reconstruction. Self-confidence, optimism, and self-motivation factors were reported to have a predictive value for outcomes. They stated that postoperative emergence of knee symptoms and compliance with rehabilitation were adversely affected by preoperative stress and positively affected by social support[61].

In a randomized, controlled trial published in 2013, Frobell *et al*[62] followed-up 121 patients for 5 years who were part of the same rehabilitation program after ACL reconstruction. The trial concluded that early or late ACL reconstruction did not differ significantly in absolute KOOS4 score, all 5 KOOS subscale scores, SF-36, Tegner activity scale, meniscal surgery, and radiographic osteoarthritis parameters[62].

A retrospective comparative study published in 2013 investigated the return to sport rates after ACL reconstruction; 46% of 135 patients returned to their preinjury levels while 56% did not (non-returners). Half of the reasons why non-returners did not return to sport were related to fear of reinjury[63].

Fridén *et al*[64] reported that the impact of fear on self-report of function and performance following ACL reconstruction was less clear. The findings of this study lend further support to the theoretical application of the fear-avoidance model in knee rehabilitation, and identified fear of movement/reinjury as a potential target for ACL reconstruction rehabilitation guidelines.

Nyland *et al*[65] drew attention to the importance of kinesiophobia. They believed that increased self-efficacy and confidence and decreased kinesiophobia suggested a greater patient willingness to use the involved lower extremity. Ardern *et al*[66] stated that the single limb hop for distance and the crossover hop test scores served as indicators of an athlete's likelihood to return to sport.

On the other hand, in their systematic review, Narducci *et al*[67] underlined that although functional performance testing was valuable for the assessment of ACL injured patients, they did not identify any clinical test or battery of tests that predicted the athletes' ability to return to play sports.

In a cohort study in 2012, Logerstedt *et al*[68] stated that the outcomes of the single-legged hop tests conducted in the 6th mo after ACL reconstruction were valuable in predicting outcomes in the 1st postoperative year, whereas preoperative single-legged hop tests did not have a predictive value for the postoperative outcome. Moreover, they indicated the presence of minimal side to side differences in the crossover hop tests conducted in the 6th mo postoperatively could improve knee functions in the 1st year postoperative period if patients continued with the training program[68].

Two separate studies reported that the coordinated coactivation of the hamstrings and quadriceps might play a role in mitigating primary injury risk by reducing ligament strain[69] and promoting normal landing mechanics[70]. In a cross-sectional study in 2012, Begalle *et al*[71] reported that the most balanced quadriceps-hamstring coactivation ratios were identified in the single-limb deadlift, lateral-hop, transverse-hop, and lateral band-walk exercises which could be safely used in post-injury rehabilitation programs. They stressed that balanced agonist and antagonist coactivation might also protect the reconstructed knee against second ACL injury risk *via* similar protective mechanisms[71].

CONCLUSION

The basic approach in ACL rehabilitation is to ensure a return to sports activities at the 6th mo postoperatively. However, many studies have been and will be conducted with the purpose of shortening this period for all rehabilitation modalities. The objective is to find the optimal strengthening and maximal safe loading times and type of loading for all rehabilitation modalities without creating ACL re-injury. Although there are many studies in the literature on ACL rehabilitation that have not been mentioned in this review, they did not result in the setting of definite and clear criteria and standards, and the reason could be that these have touched upon the mere surface of the topic. As new studies are underway with the advancement of technology we hope to find out how modalities used in ACL rehabilitation affect genetic and biochemical pathways. Today postoperative ACL rehabilitation guidelines are time-focused. This approach makes implementation of the program easier, but does not cover all cases. Rehabilitation varies and should vary from person to person, so it would not be wrong to assume that future ACL rehabilitation guidelines will focus on rehabilitation techniques instead of time. I believe that, with the emergence of criteria-based guidelines, standardization will come.

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Utility of arthroscopic guided synovial biopsy in understanding synovial tissue pathology in health and disease states

Mihir D Wechalekar, Malcolm D Smith

Mihir D Wechalekar, Malcolm D Smith, Rheumatology Research Unit, Repatriation General Hospital, Daw Park SA 5041, Australia
Author contributions: Both authors contributed equally to this work.
Supported by National Health and Medical Research Council Medical and Dental Postgraduate Research Scholarship to Dr. Wechalekar, MD, No. APP1018009
Correspondence to: Malcolm D Smith, BSc (Hons), MBBS, FRACP, PhD, Professor of Medicine, Director of Rheumatology, Southern Adelaide Local Health Network, Rheumatology Research Unit, Repatriation General Hospital, Daws Road, Daw Park SA 5041, South Australia,
Australia. malcolm.smith@health.sa.gov.au
Telephone: +61-8-82751819 Fax: +61-8-83744276
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Abstract

The synovium is the soft tissue lining diarthrodial joints, tendon sheaths and bursae and is composed of intimal and subintimal layers. The intimal layer is composed of type A cells (macrophages) and type B cells (fibroblasts); in health, the subintima has few inflammatory cells. The synovium performs several homeostatic functions and is the primary target in several inflammatory arthritides. Inflammatory states are characterised by thickening of the synovial lining, macrophage recruitment and fibroblast proliferation, and an influx of inflammatory cells including lymphocytes, monocytes and plasma cells. Of the various methods employed to perform synovial biopsies arthroscopic techniques are considered the "gold standard", and have an established safety record. Synovial biopsy has been of critical importance in understanding disease pathogenesis and has provided insight into mechanisms of action of targeted therapies by way of direct evidence about events in the synovial tissue in various arthritides. It has been very useful as a research tool for proof of concept studies to assess efficacy and mechanisms of new therapies, provide tissue for *in vitro* studies, proteomics and microarrays and allow evaluation for biomarkers that may help predict response to therapy and identify new targets for drug development. It also has diagnostic value in the evaluation of neoplastic or granulomatous disease or infection when synovial fluid analysis is non-contributory.

Key words: Synovium; Synovial biopsy; Arthroscopy; Inflammatory arthritis; Synovial pathology

Core tip: The synovium is the soft tissue lining diarthodial joints, tendon sheaths and bursae. Arthroscopic synovial biopsy techniques have an established safety record. Synovial biopsy has been of critical importance in understanding disease pathogenesis and mechanisms of action of targeted therapies; it has been invaluable as a research tool in proof of concept studies to assess mechanisms and efficacy of new therapies. It also has diagnostic value when synovial fluid analysis is non-contributory.

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INTRODUCTION

The synovium is the soft tissue lining diarthrodial joints,

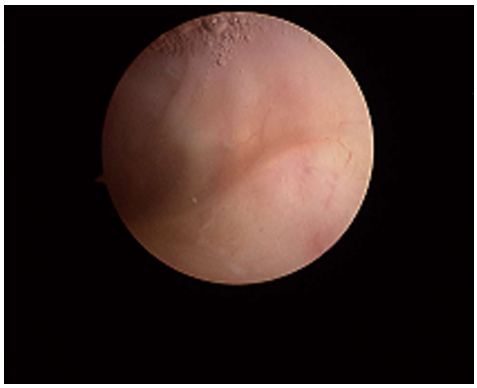

Figure 1 The normal synovium.

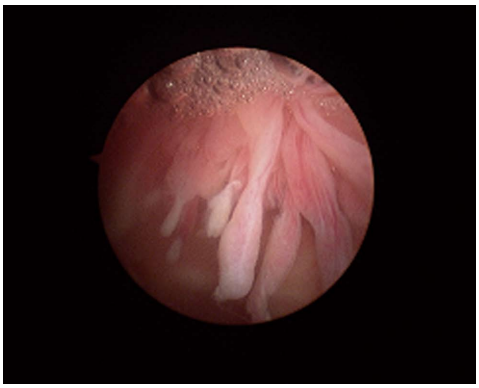

Figure 2 The synovium in rheumatoid arthritis. Note the villous appearance and straight vessels.

tendon sheaths and bursae. The normal synovium has intimal and subintimal layers and performs the critical homeostatic functions of non-adherence, control of synovial fluid volume and composition and contributes to chondrocyte nutrition. The synovial membrane is involved in several rheumatic diseases including rheumatoid arthritis (RA), osteoarthritis (OA), the spondyloarthritides and the crystal induced arthropathies; and is the primary target of inflammation in RA. Analyses of the synovial membrane have been central to our current understanding of the pathogenetic mechanisms in the inflammatory arthritides in addition to having provided insight into mechanisms of action of targeted therapies.

METHODS OF SYNOVIAL BIOPSY

The synovium is amenable to biopsy by arthroscopy or by using blind needle or ultrasound directed techniques[1]. Blind needle techniques have been established for decades and have a good safety and feasibility record[2]. They can be undertaken in an office setting, are relatively low-cost, and do not require special facilities. The major concerns of blind biopsy techniques lie in failure to obtain satisfactory samples, especially if the joint is clinically quiescent because of failure to visualize involved areas; in addition the joints that are amenable to biopsy by this technique are limited[2]. In one series with more than 800 Parker-Pearson biopsy procedures, sufficient tissue was obtained in about 85% of patients for histological examination; the authors found that the procedure failed especially in joints that were not swollen. There were no haemarthroses or infections reported in this series[3]. This failure rate, however would not be acceptable within the context of "proof of concept" phase I B or II RCTs in which arthroscopic synovial biopsy would be more acceptable[2].

Arthroscopic synovial biopsy (usually done with a small-bore arthroscope) is the "gold standard"[2]; it has the advantage of macroscopic examination, visually directed biopsies with better sampling from areas of interest, its major disadvantages being the need for a "learning curve" and the requirement of a sterile area and operation theatre facilities[2]. In addition arthroscopic biopsy techniques allow biopsies from sites adjacent to cartilage (the "cartilage-pannus junction"), an area that differs quantitatively and qualitatively from the synovium as opposed to needle biopsies in which this area is difficult if not impossible to access[1]. Complications with arthroscopies performed by rheumatologists are similar to those reported in the orthopaedic literature: in a study evaluating 16532 arthroscopies in which 50.5% and 49.5% of the arthroscopies had a clinical and research indication respectively revealed a complication rate of joint infection in 0.1%, wound infection in 0.1%, haemarthrosis in 0.9%, deep venous thrombosis in 0.2% and neurological damage, thrombophlebitis and other complications in 0.02%, 0.08% and 0.06% respectively. Irrigation volume correlated with wound infection rate and centres that performed cartilage biopsy had a higher rate of haemarthrosis[4]. Further information on details of arthroscopic synovial biopsy performed as a day procedure has been reviewed elsewhere[5].

Ultrasound guided synovial biopsy is a relatively recent technique which combines the advantage of being minimally invasive, enables sampling under guidance, and may be of particular utility in synovial biopsy of small joints[6,7].

MACROSCOPIC APPEARANCE OF THE SYNOVIUM

Macroscopically, the normal synovium (Figure 1) looks bland and devoid of villi, granularity or increased vascularity. In contrast, synovium in RA (Figure 2) has a distinct vascularity pattern with straight vessels as opposed to tortuous vessels or a mixed pattern seen in spondyloarthritides (SpA), reactive arthritis and psoriatic arthritis (Figure 3). The macroscopic appearance may predict histological changes (albeit with only a very moderate correlation) and clinical parameters with the straight pattern portending a worse outcome. However there is no widely accepted scoring system or well-validated method of description of macroscopic changes, and no reliable method to predict microscopic features, especially in an individual patient[1,6,8].

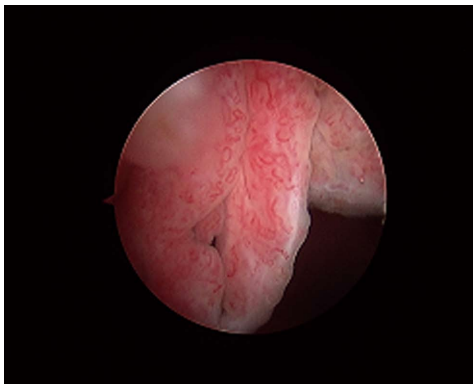

Figure 3 The synovium in psoriatic arthritis. Note the hypervascular villous hypertrophy and tortuous vessels.

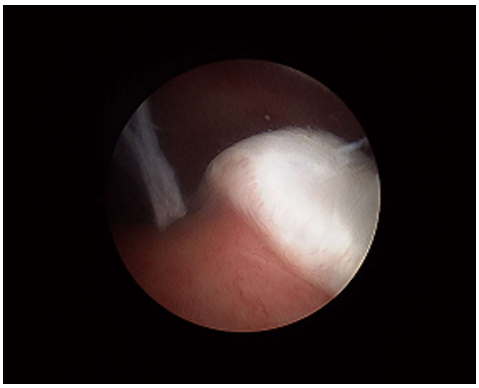

Figure 4 The cartilage-pannus junction.

THE UNDERLYING DISEASE PROCESS AND REPRESENTATIVENESS OF SYNOVIAL TISSUE

A single study[9] has examined arthroscopic synovial biopsies from the knee joint and wrists or metacarpophalangeal joints in a small number of patients and found that the numerous biopsy specimens correlated well with regards to qualitative and quantitative markers of cellular infiltrate.

Various studies have also looked at whether there was significant variability of synovial tissue within regions of the same joint; this distinction is particularly relevant in the context of inflammatory arthritis such as RA where the cartilage-pannus (which is the inflamed tongue of abnormal synovium at the junction of the cartilage and bone and is thought to be central in causing bone destruction known as erosions; see Figure 4) junction may have a different cellular and cytokine profile as compared to synovium elsewhere. While some differences in certain cellular populations can be recognised, in general the features of inflammation and expression of mediators of inflammation and destruction are thought to be largely similar, though cellular markers responsible for bone destruction may be one notable exception[2,10,11].

To minimise intra-joint variability and to maximise reliability it has been demonstrated that a minimum of six synovial biopsy specimens are necessary[2].

HANDLING OF SYNOVIAL TISSUE

The handling and processing of synovial tissue is largely dictated by the indication for the synovial biopsy. For routine histopathology by light microscopy, synovial biopsy samples should be fixed in 4% formalin and then embedded in paraffin. If infection is suspected, the tissue should be transported in suitable culture media. For detection of bacterial DNA using the PCR, it is critical to avoid contamination of the samples by foreign DNA and the samples should be snap frozen in liquid nitrogen[6]. The latter method is also preferred for synovial sample processing and storage in the research setting, and enables immunohistochemical staining to be performed without the need for antigen retrieval. For detection of crystals, synovial tissue needs to be sent in absolute alcohol (as crystals dissolve in most other fixatives)[6].

METHODS OF QUANTIFICATION OF CELLULAR, CYTOKINE, CHEMOKINE AND RECEPTOR EXPRESSION IN SYNOVIAL BIOPSIES

The histological assessment of synovium in RA includes intimal thickness and density and composition of the cellular infiltrate[1]. The preferred method to analyse cellular infiltrate, cell phenotype, cell surface receptor expression and cellular adhesion molecule expression is by immunohistochemical techniques. Quantification can be performed using either manual counting (reliable but time consuming), semiquantitative scoring (the fastest of all techniques with proven intra- and inter-observer reliability) or digital image analysis (expensive and time consuming but has been validated with regards to inter- and intra-observer reliability for the widest range of biological variables including cytokines, metalloproteinases, vascular markers, adhesion molecules and chemokines)[2]. The synovium can also be subject to analyses, by real time quantitative polymerase chain reaction (PCR) for gene expression profiling, and to potentially analyse all genes, expression microarrays can be used; the latter method has revealed considerable heterogeneity and identified molecularly distinct forms of RA[12,13].

NORMAL SYNOVIUM

The normal synovium has an intimal layer, which is 20 to 40 μm thick in cross section, and an areolar subintima, which can be up to 5 mm in thickness; considerable variability in this pattern exists and three main types of synovia have been described on the basis of their subintima: fibrous, areolar and adipose[14]. Of these, areolar synovium (Figure 5) is the most specialized form. Often crimped into folds, the lining consists of 2-3 layers of cells. Beneath this layer are capillaries and further down

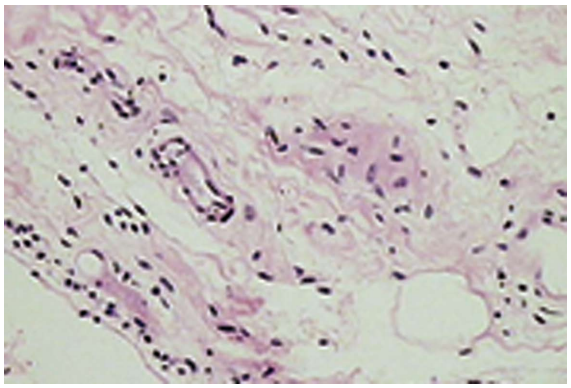

Figure 5 The normal (areolar) synovium.

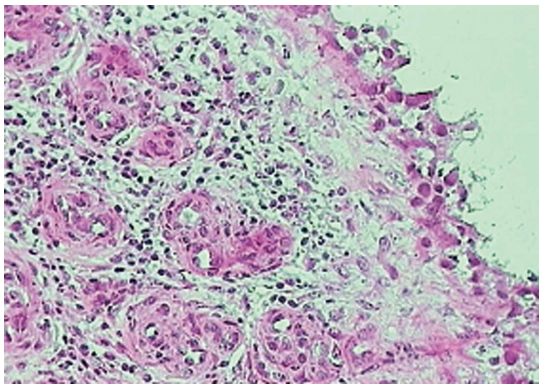

Figure 6 Lymphoid follicles in rheumatoid arthritis.

a network of arterioles, venules and lymphatic vessels. Nerve fibres are present in association with blood vessels. The supporting tissue matrix is rich in type I collagen which forms the physical membrane. Still deeper is a loose layer that enables the synovial membrane to move freely[15-18]. The adipose synovium occurs as fat pads and within villi; the deeper tissue is fat, there is a superficial net of capillaries and a complete intimal layer. Fibrous synovium can be difficult to accurately define and consists of fibrous tissue such as ligament or tendon on which lies an intimal layer of cells.

The synovium is devoid of a true basement membrane. Most of the soluble components and proteins in synovial fluid exit the synovial microcirculation through pores or fenestration in the vascular endothelium, traverse the interstitium and then enter the joint space. A rich microvascular network lies beneath the synovial surface with the larger venules, arterioles and lymphatics forming an anastomosing quadrilateral array[15,17,18]. The subintima in health, is generally devoid of inflammatory cells apart from a few macrophages and mast cells.

Recent evidence[19] from an animal model suggests that cadherin-11 (cadherins are cell-cell adhesion molecules controlling animal morphogenesis) on synovial fibroblasts may be critical in the development of a recognisable synovial lining by facilitation of cellular organization, compaction, and matrix development and may be critical for normal synovial tissue development.

Synovial intimal cells are of two types: type A cells (macrophages) and type B cells (fibroblasts). Evidence suggests that synovial macrophages are true macrophages derived from bone marrow derived precursors in contrast to synovial fibroblasts which are locally derived. In health, synovial fibroblasts are the dominant population (in disease states, macrophages may constitute as much as 80% of the intimal cells)[20-24]. Synovial fibroblasts are adapted to hyaluronan production and demonstrate high activity of the enzyme uridine diphosphoglucose dehydrogenase which is essential for synthesis of hyaluronan[25]. Synovial intimal fibroblasts express CD55; this feature distinguishes them from CD68 positive (but CD55 negative) intimal macrophages.

SYNOVIUM IN DISEASE STATES

RA

Microvascular changes occur very early in the course of the disease. As noted above, synovial blood vessels in RA are relatively straight in contrast to tortuous and bushy appearance in early psoriatic arthritis and SpA[26].

As early as four to six weeks following the onset of symptoms of RA, synovial lining layer thickening of up to 10 cells is noted along with vascular proliferation and diffuse subintimal inflammatory infiltrate consisting of macrophages, lymphocytes, neutrophils, mast cells and dendritic cells (DCs)[27]. Synovial fibroblast proliferation and macrophage recruitment are both thought to be contributors to the lining layer thickening[28] and are of particular importance as they are both implicated in engendering joint damage[29-31]. Importantly, cellular changes in joints are well evident and established before the clinical onset of disease[32] and asymptomatic joints also show cellular changes mainly in the form of lining layer hyperplasia, though to a lesser degree than in clinically involved joints[33]. While most of the cellular subtypes (including monocytes, macrophages, lymphocytes and plasma cells thought to be more typical of established disease) are similar in early and late disease (including the degree of lymphocytic, plasma cell and neutrophil infiltration), lymphoid follicles (Figure 6) are generally a feature of established RA as compared to early disease[26,34,35]. Of note, "early" arthritis is a clinical and not a histological definition and changes at the synovial level precede clinical symptoms by an undetermined period of time[36].

In general, there is no definite evidence to suggest a distinct histopathological pattern in early as opposed to late disease; the differences observed may relate not to disease duration but how active the disease was at the time of sampling: this was illustrated in a well-designed study[37] that included 16 patients with early RA (and similar numbers with late RA, early SpA and OA). In this study except for maximal synovial lining thickness, no difference was found between early and late RA, though differences were found between RA and SpA/OA.

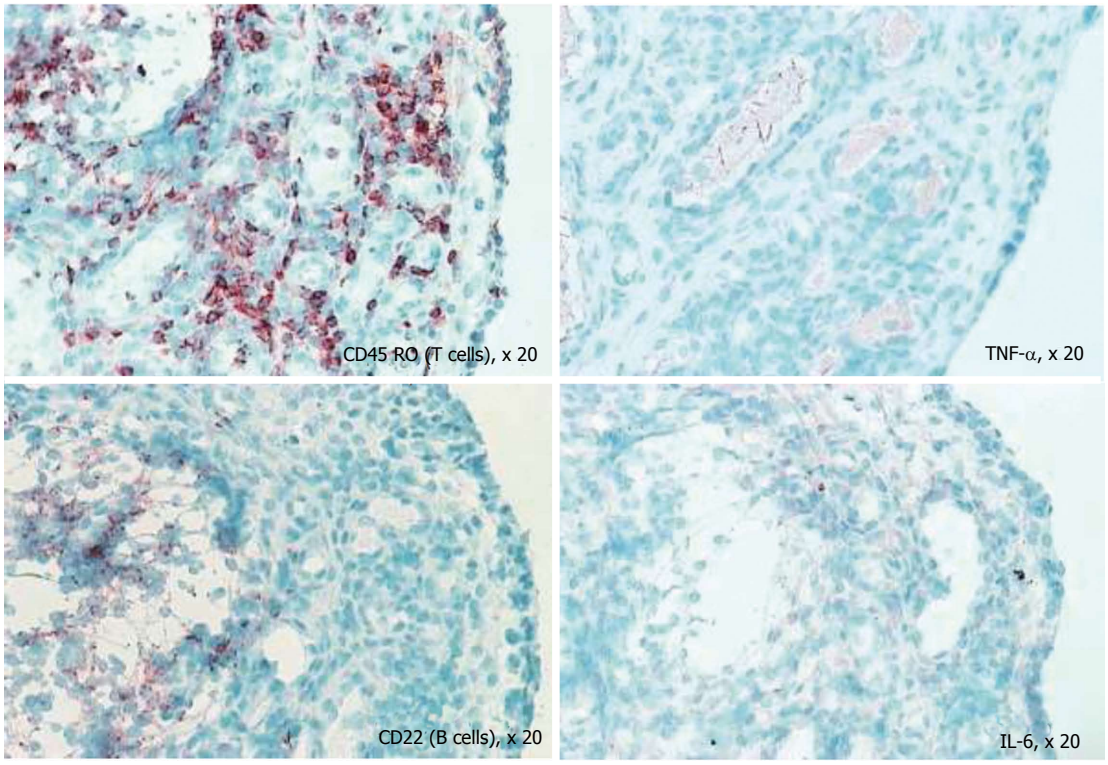

Figure 7 Differential staining of synovial biopsy for T cells, tumour necrosis factor, B cells (CD22), and interleukin-6 in a patient with active rheumatoid arthritis prior to disease-modifying therapy. TNF: Tumour necrosis factor; IL: Interleukin.

Spondyloarthritides including psoriatic arthritis

In the study alluded to above[37], patients with SpA showed similar degree of synovial villous hypertrophy in RA *vs* SpA, with a clear difference in vascular pattern. The mean synovial intimal layer thickness was similar. On microscopy vascularity was increased and few had lymphoid follicles. Another study[38] confirmed the increased vascularity of the psoriatic arthritic synovium as compared to RA and found less intimal layer hyperplasia, fewer macrophages but similar numbers of B cells, T cells and T cell subsets. There has been increasing interest recently in the Th-17 T cell pathway and related cytokines in the spondyloarthritides; despite therapeutic success of drugs targeting this pathway[39] and demonstration of increased frequency of IL-23 positive cells in facet joints of ankylosing spondylitis[40], this pathway probably has diverse roles in the pathogenesis of psoriatic SpA, with little or no expression of IL-22 in the psoriatic synovium[41].

Synovium as an immunologic target; synovial response to therapy in the inflammatory arthritides and targeted therapy

Despite the fact that the synovium is the primary target of many inflammatory arthritides, synovial tissue specific antigens that may elicit an immune response *per se* are virtually unknown; when the rheumatic diseases are associated with autoantibodies, the antigens involved are ubiquitous. One of the most important reasons in undertaking a study of the synovium in health and disease is to gain insight into immunopathologic processes that may suggest a therapeutic target in the inflammatory arthritides and identify biomarkers to predict outcomes in individual patients. Several studies have used serial synovial biopsies to attempt to identify biomarkers; these studies have evaluated responses to corticosteroids, gold, methotrexate, leflunomide, tumour necrosis factor inhibitors and rituximab, among others[42-46]. It is now well established that the inflammatory arthritides are very heterogeneous; indeed RA is now considered to be an umbrella term encompassing multiple disease subtypes with different phenotypes correlating to different genotypes. This heterogeneity[13,47] perhaps explains the variable response to therapy. It remains unexplained why some patients with RA fail to respond to standard and biologic disease modifying therapy; in addition, a proportion of patients initially respond only to lose response later. The exact reasons for this remain elusive. Studies in our laboratory (Figure 7) show that at the level of the synovial cellular infiltrate, the dominance of infiltrate is markedly heterogeneous and therapeutic selections that are not individualised may be one explanation for primary or secondary non-response to therapy.

Synovial proliferative conditions

Pigmented villonodular synovitis (PVNS) is a nodular and villous thickening of the synovial membrane that affects males and females equally with the knee being the most commonly involved joint[48]. Microscopy reveals synovial intimal cells overlying a lobular and sheet-like

arrangement of mononuclear rounded (containing large hemosiderin granules) and epithelioid cells, multinucleated osteoclast-like giant cells, and lipid rich cells; an extra-articular analogue of PVNS is the giant cell tumour of the tendon sheath. Haemosiderotic synovitis (which usually happens as a complication of chronic intra-articular haemorrhage in haemophiliacs) differs from PVNS; the synovium lacks the thickened fronds and nodules of PVNS and becomes thickened and opaque due to repeated scarring[48].

Synovial chondromatosis is characterised by multiple nodules of metaplastic hyaline cartilage that are present in the synovial sublining and often have foci of calcification or endochondral ossification[48].

Crystal induced synovial disease: Gout and Calcium pyrophosphate dehydrate deposition disease (pseudogout)

Monosodium urate crystal deposits in the synovium appear as creamy white tophi (which demonstrate needle shaped crystals that are strongly negatively birefringent on polarised light microscopy) and lead to membrane opacification and papillary thickening; histological examination of the synovial membrane in acute gout shows lining layer hyperplasia and intense infiltration with neutrophils, mononuclear cells and lymphocytes[48-50]. Synovial sections can also be stained with the DeGolantal stain for urate to identify gouty synovitis[6]. Calcium pyrophosphate dehydrate (CPPD) disease, in contrast also involves cartilage; CPPD crystals are rhomboid shaped and positively birefringent on polarised light microscopy. Synovial deposits are usually smaller than gout, are associated with foci of metaplastic cartilage and usually elicit a histiocytic reaction[48].

Infectious and granulomatous, infiltrating and other deposition diseases

Synovial biopsies can assist in diagnosing bacterial species when blood and synovial cultures are negative especially when antibiotic treatment has been initiated[51] before culturing synovial fluid and with fastidious and difficult to grow bacteria[52]. Synovial biopsies may also help in diagnosis of granulomatous, infiltrating and deposition diseases including amyloidosis, sarcoidosis, arthritis caused by foreign body material and Erdheim-Chester disease[6].

CONCLUSION

Synovial biopsy is a safe and generally well-tolerated procedure; of the several methods used to obtain synovial biopsies, arthroscopic techniques, though more complicated, allow macroscopic examination and have a consistent and higher yield especially after effective therapy when synovial tissue volume has reduced.

Analyses of the synovial membrane provides useful insight into the etiopathogenesis of and direct evidence about events in the synovial tissue in various arthritides; in particular, evaluation of serial biopsy specimens has been very useful in understanding the effects of targeted therapies. In addition, synovial biopsies have a role in the diagnostic evaluation of neoplastic or granulomatous disease or infection when synovial fluid analysis is non-contributory. Finally, synovial biopsies are invaluable as a research tool for proof of concept studies to assess efficacy and mechanisms of new therapies, provide tissue for in-vitro studies, proteomics and microarrays and allow evaluation for biomarkers that may help predict response to therapy and identify new targets for drug development.

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Painful sesamoid of the great toe

Alex L Sims, Harish V Kurup

Alex L Sims, Department of Orthopaedics, University Hospital of North Tees, Cleveland TS19 8PE, United Kingdom
Harish V Kurup, Department of Orthopaedics, Pilgrim Hospital Sibsey Rd, Lincolnshire PE21 9QS, United Kingdom
Author contributions: Sims AL wrote the paper; Kurup HV wrote and edited the paper.
Correspondence to: Alex L Sims, MBBS, MSc, MRCS, Department of Orthopaedics, University Hospital of North Tees, Hardwick Rd, Stockton-on-Tees, Cleveland TS19 8PE, United Kingdom. asims@nhs.net
Telephone: +44-1642-617617 Fax: +44-1642-624814
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Abstract

The painful sesamoid can be a chronic and disabling problem and isolating the cause can be far from straightforward. There are a number of forefoot pathologies that can present similarly to sesmoid pathologies and likewise identifying the particular cause of sesamoid pain can be challenging. Modern imaging techniques can be helpful. This article reviews the anatomy, development and morphological variability present in the sesamoids of the great toe. We review evidence on approach to history, diagnosis and investigation of sesamoid pain. Differential diagnoses and management strategies, including conservative and operative are outlined. Our recommendations are that early consideration of magnetic resonance imaging and discussion with a specialist musculoskeletal radiologist may help to identify a cause of pain accurately and quickly. Conservative measures should be first line in most cases. Where fracture and avascular necrosis can be ruled out, injection under fluoroscopic guidance may help to avoid operative intervention.

Key words: Sesamoid; Pain; Great toe; Management; Forefoot

Core tip: This paper is a review article examining available evidence on the anatomy, function and common variation in the sesmoids of the great toe. There is discussion of the presentation, history, examination, investigations and subsequent management of the patient with a painful sesamoid. We discuss the role of operative intervention. We recommend early use of magnetic resonance imaging and discussion with a musculoskeletal radiologist to assist in diagnosis. Conservative management should be the first line in most cases.

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INTRODUCTION

Origins

The term sesamoid comes from the Arabic word, semsem, meaning sesame seed. Galen named these small rounded bones in reference to their similarity to sesame seeds[1]. The anatomic locations of some sesamoid bones are constant but others are variable.

Anatomy

The two sesamoid bones of the big toe metatarsophalangeal joint are contained within the tendons of Flexor Hallucis Brevis and forms portion of the plantar plate. There are two sesamoids, tibial (medial) and fibular (lateral) sesamoids. The sesamoids articulate on their dorsal surface with the plantar facets of metatarsal head[2]. A crista or intersesamoid ridge separates the medial and lateral metatarsal facets. The crista provides intrinsic stability to the complex. In severe cases of hallux valgus the intersesamoid ridge atrophies and can be obliterated. The sesamoids are connected to the plantar aspect of proximal phalanx through plantar plate[3] which is continuation

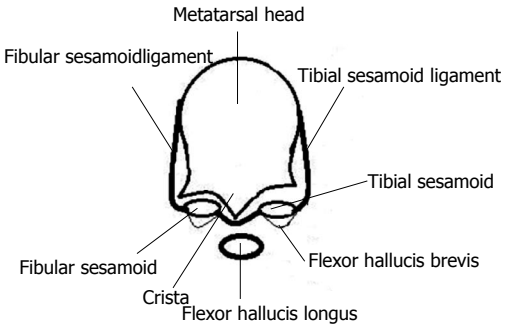

Figure 1 Diagrammatic representation of a cross section through the distal metatarsal and sesamoids.

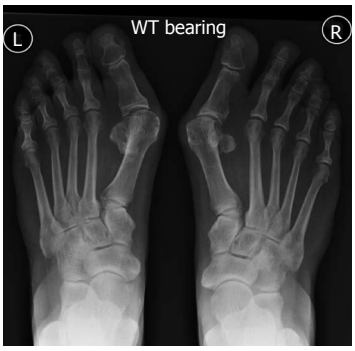

Figure 2 X-ray to demonstrate a case of sesamoid coalition.

of the flexor hallucis brevis tendon[4]. The inferior surface of the sesamoid is covered by a thin layer of flexor hallucis brevis tendon and superior surface is articular. The sesamoids are suspended by a sling like mechanism; sesamoid ligaments to the corresponding aspect of metatarsal head (Figure 1). There is no direct connection between sesamoids and flexor hallucis longus tendon that runs between them. The abductor hallucis and adductor hallucis tendons have fibrous insertions into the tibial and fibular sesamoids respectively. The deep transverse metatarsal ligament attaches to the fibular sesamoid[5].

Function

The function of sesamoids is to distribute weight bearing of first ray, increase mechanical advantage of the pull of short flexor tendon and stabilize the first ray. The tibial sesamoid normally assumes most of the weight bearing forces transmitted to the head of the first metatarsal[6]. When a person is in standing position sesamoids are proximal to the metatarsal heads. With dorsiflexion of first ray they however move distally thereby protecting the exposed plantar aspect of metatarsal head. When a person rises on to the toes, sesamoids (especially tibial) act as the main weight bearing focus for medial forefoot. Tibial sesamoid is more prone for pathology due to increased loading on this by the first metatarsal head[7].

Perfusion

Sesamoids have a tenuous blood supply and this is often variable as well. Blood supply to sesamoids enters mostly from proximal part and distal part has more tenuous blood supply. This can lead to delayed or unsuccessful healing following injury[8].

The bipartite sesamoid

Sesamoids ossify between the ages of 6 and 7. Ossification of sesamoids often occurs from multiple centres and this is the reason for bipartite sesamoids. Bipartite sesamoids are a normal anatomical variant. Studies quote the incidence of bipartite sesamoids to be between 7 and 30[9-11]. Ninety percent involve tibial sesamoid and 80%-90% are bilateral[10]. Bipartite sesamoid has narrow and distinct regular edges and also are usually larger than single sesamoid. Some of these divided sesamoids do undergo osseous union with time. The synchondrosis between the sesamoid fragments can also disrupt with injury leading to symptoms and makes it difficult to distinguish whether some of these partite sesamoids are actually ununited fractures[12]. A Bone scan or magnetic resonance imaging (MRI) scan may help in differentiating between the two[13]. Bipartite sesamoids can predispose to hallux valgus deformity as twice higher incidence is noted in patients with Hallux Valgus[14].

Abnormalities of the sesamoids

Other variations with sesamoids include congenital absence (reported widely in literature)[15-17] and also changes in shape. Hypertrophy can cause a projection on the plantar surface leading to hyperkeratotic lesion. Exostoses of sesamoids have been reported and these can cause keratosis or ulcerations. Hypertrophied fibular sesamoid can cause pain in the first intermetatarsal space due to local irritation or nerve compression. Coalition of sesamoids can also occur and give rise to symptoms (Figure 2)[18].

HISTORY AND EXAMINATION

Pain is typically during toe off phase of gait. Careful history taking should include examination of footwear used in past and present, leisure activities to identify causation, occupation and treatment taken so far. Occupational factors include running, ballet dancing and jumping from a height[19-21]. The wearing of high heels and a high arched foot type also has an aetiological association. Previous injections to the area and smoking status should be asked for. Patients tend to avoid weight bearing on the involved sesamoid and load the lateral aspect of foot.

Findings include restricted and painful range of metatarsophalangeal joint motion, tenderness (Figure 3), and diminished plantar flexion strength. With long standing overloading, an intractable plantar keratotic lesion may develop beneath the affected sesamoid. Any tendency for hallux valgus, varus or clawing should be looked for. Examination of sensory nerves is important to rule out digital nerve compression[11].

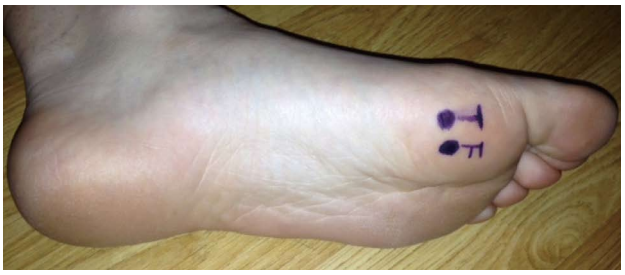

Figure 3 Photograph to show surface markings of the tibial (T) and fibular (F) sesamoids.

INVESTIGATIONS

Radiographs

Routine AP and lateral radiographs provide limited information. The tibial sesamoid can be better imaged with a medial oblique view and the fibular sesamoid can be visualised better with a lateral oblique view. An axial sesamoid view will provide a better profile of both sesamoids with their metatarsal articulations (Figure 4)[22].

Isotope bone scan

Isotope bone scanning can demonstrate altered uptake before radiographs show changes. It shows increased uptake prior to development of radiological changes such as sclerosis, fragmentation. Bone scanning may be of use in differentiation of the fractured sesamoid from the congenital bipartite sesamoid[23].

MRI

Pathologies affecting the hallucal sesamoids may have overlap of both history and examination. For this reason, imaging is a useful tool that can differentiate causes of sesamoid pain where a diagnosis may not otherwise be easily made[20]. It can also distinguish between bipartite sesamoids and fracture non-unions. This is currently the investigation of choice for most sesamoid pathology[20,24].

DIFFERENTIAL DIAGNOSIS

Intractable plantar keratosis

Intractable plantar keratosis may form under the heads of the metatarsals. This can often be as a result of repeated abrasion or increased activity. It is important to differentiate IPK from verruca. Radiographs may help to identify causative osseous abnormality. This may include deformity of an underlying sesamoid. Management may involve activity modification, padding of pressure areas, use of orthosis or shaving of the keratosis. For persistent cases, condylectomy or osteotomy may be required[25].

Bursitis

Bursitis may affect the intermetatarsal bursae or the adventitial bursae. magnetic resonance imaging may help to diagnose the location of the affected bursa. Should conservative measures fail, bursectomy alone or in combination with sesamoidectomy or metatarsal osteotomy may provide relief[26].

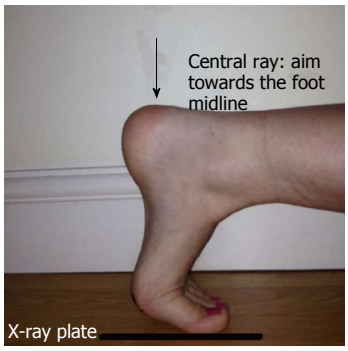

Figure 4 Photograph to show patient positioning to obtain a sesamoid axial view.

Nerve compression

Plantar medial and plantar lateral digital nerves travel near to the corresponding sesamoids and can be a source of pain. Nerve compression at these sites can cause altered sensation, pain and a positive Tinel's sign. Surgical decompression may be indicated in the resistant case[5].

Osteoarthritis

This may be associated with Hallux rigidus or localized to the sesamoid metatarsal articulation. This can develop secondary to trauma, chondromalacia or sesamoiditis. If conservative treatment fails where disease is restricted to one sesamoid resection of the involved sesamoid may help. When both sesamoids are involved excision can lead to clawing, hence MTP fusion is more appropriate[18].

Infection

Infection of sesamoids is uncommon. Direct trauma with puncture wound or breakdown of skin in those with peripheral neuropathy are the common mechanisms. Should antibiotic therapy prove ineffective, excision of the sesamoid can be considered. Care should be taken when excising the sesamoids to preserve the surrounding structures to prevent development of intrinsic minus deformity[11].

Fracture of sesamoid

An acute fracture of unipartite sesamoid can be differentiated from a congenital bipartite sesamoid using bone scan or MRI. Bipartite sesamoids can also fracture following trauma when the synchondrosis between the two sesamoid fragments prevents healing. Rest in a non-weight bearing cast for 6 to 8 wk is the first line of treatment. Symptomatic non-union may be treated with percutaneous screw fixation, open fixation or open bone grafting (Figure 5)[27]. Surgical excision may be reserved for revision surgery.

Subluxation/dislocation of sesamoids

As hallux valgus develops, first metatarsal drifts medially. The sesamoids maintain their relationship to the second metatarsal due to tethering by transverse metatarsal

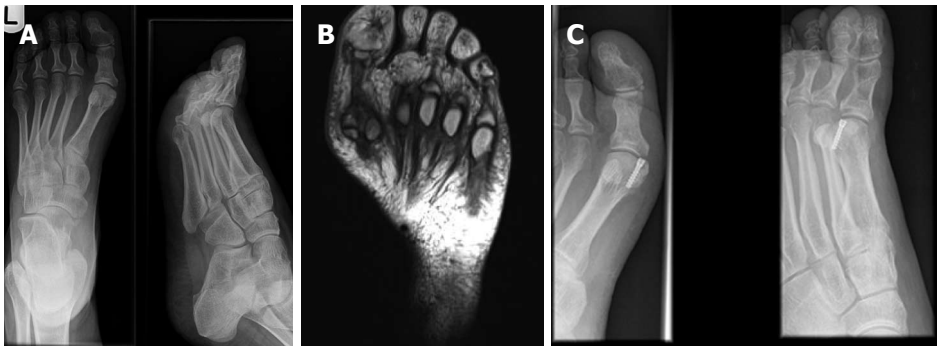

Figure 5 Symptomatic non-union may be treated with percutaneous screw fixation, open fixation or open bone grafting. A: X-ray to show a symptomatic non-union of a sesamoid fracture; B: Magnetic resonance imaging scan demonstrating fracture of the sesamoid; C: Post-operative X-ray following fixation of a non-union sesamoid fracture.

ligament and adductor hallucis tendon. There is often erosion of the crisita and increased weight bearing by the tibial sesamoid. Fibular sesamoid is spared as it is displaced into the first intermetatarsal space[28].

Osteochondritis/avascular necrosis

Sesamoids have a tenuous circulation making them vulnerable to avascular necrosis. In cases of avascular necrosis trauma may be an aetiological factor. Radiographs may show fragmentation with areas of increased bone density. MRI is also helpful in diagnosis. Excision of the sesamoid is reserved for cases where conservative management is ineffective[11].

Sesamoiditis

Sesamoiditis is a diagnosis of exclusion once other causes of sesamoid pain have been excluded. Sesamoiditis is a painful condition affecting the sesamoids and can occur with or without trauma. This may be due to cartilage abnormalities similar to chondromalacia of patellofemoral joint[29] or inflammation of peritendinous structures. This condition is typically seen in younger women. The tibial sesamoid is more often involved. Radiographs are usually normal and bone scan and MRI may help in diagnosis. Conservative treatment involves decrease in activity. Low heels reduce pressure on sesamoids. Offloading custom made insoles are often helpful. Injections can be helpful and when everything fails excision is treatment of choice.

MANAGEMENT

Conservative management

Initial attempts at management include a period of non- or reduced weight bearing, providing wide shoes with a reduced heel height, orthotics or padding[30]. The toes may be taped in plantar flexion or neutral to avoid excessive dorsi-flexion. Clinical evidence confirming resolution of symptoms with simple, conservative measures is often possible[31]. Non-steroidal anti-inflammatory drugs may also help to provide relief.

Injection

Steroid and local anaesthetic injections can be both diagnostic and therapeutic. Injections are usually done under radiological guidance to improve accuracy of needle placement. Steroid injections should not be used in presence of a sesamoid fracture or avascular necrosis[3].

SURGERY

Sesamoid shaving

In the presence of an intractable plantar keratosis due to prominence of a tibial sesamoid, shaving of the plantar half of the sesamoid may provide relief without excision of the complete sesamoid. This should only be attempted in the presence of normal mobility at the first metatarsal[32].

Sesamoidectomy

Surgical excision of a sesamoid should be considered only when other treatment modalities have failed. Only one sesamoid may be excised, excision of both is likely to lead to a cock-up deformity or a claw toes deformity[30]. The sesamoid to be excised will dictate the surgical approach. For tibial sesamoidectomy a medial approach is preferred to avoid injury to plantar medial nerves. In one study, ninety-percent of patients were able to return to normal pre-morbid levels of activity following tibial sesamoidectomy[33]. A dorsolateral approach is preferred for fibular sesamoidectomy as a plantar approach is likely to encounter the neurovascular bundle and flexor hallucis longus tendon, making access difficult[11]. Painful plantar scar is a difficult problem to resolve and should be avoided.

Percutaneous screw fixation

In cases of fracture of the sesamoid unresponsive to conservative management, percutaneous fixation of the sesamoid may provide improvement of symptoms. In one study of nine patients managed this way, all patients had dramatic relief from pain at three months post-operatively[27].

CONCLUSION

A range of conditions can lead to sesamoid pain. Careful history examining occupation and hobbies alongside a thorough examination and use of appropriate imaging modalities are likely to identify aetiology. Our recommendations are that early consideration of MRI and discussion with a specialist musculoskeletal radiologist may help to identify a cause of pain accurately and quickly. Conservative measures should in most cases be first line. Where

fracture and avascular necrosis can be ruled out, injection under fluoroscopic guidance may help to avoid operative intervention. Operative intervention used only in resistant cases operative morbidity should be considered and explained to patients.

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Cartilage repair techniques of the talus: An update

Mike H Baums, Wolfgang Schultz, Tanja Kostuj, Hans-Michael Klinger

Mike H Baums, University of Göttingen Medical Centre, Aukamm Klinik GmbH, D-65191 Wiesbaden, Germany
Mike H Baums, Wolfgang Schultz, Hans-Michael Klinger, Department of Orthopaedic Surgery, University of Göttingen Medical Centre (UMG), Georg-August-University, D-37099 Göttingen, Germany
Tanja Kostuj, Institute of Medical Biometrics and Epidemiology, University of Witten/Herdecke, D-58448 Witten, Germany
Author contributions: Baums MH idealed, concepted and wrote the manuscript; Schultz W corrected the manuscript and graphical material; Kostuj T literature research in databases, epidemiological support; Klinger HM literature research in databases, correction of manuscript.
Correspondence to: Dr. Mike H Baums, PhD, Assistant Professor, University of Göttingen Medical Centre, Aukamm Klinik GmbH, Leibnizstr. 21, D-65191 Wiesbaden, Germany. mbaums@t-online.de
Telephone: +49-611-572120 Fax: +49-611-1899705
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Abstract

Symptomatic chondral or osteochondral defects of the talus reduce the quality of life of many patients. Although their pathomechanism is well understood, it is well known that different aetiologic factors play a role in their origin. Additionally, it is well recognised that the talar articular cartilage strongly differs from that in the knee. Despite this fact, many recommendations for the management of talar cartilage defects are based on approaches that were developed for the knee. Conservative treatment seems to work best in paediatric and adolescent patients with osteochondritis dissecans. However, depending on the size of the lesions, surgical approaches are necessary to treat many of these defects. Bone marrow stimulation techniques may achieve good results in small lesions. Large lesions may be treated by open procedures such as osteochondral autograft transfer or allograft transplantation. Autologous chondrocyte transplantation, as a restorative procedure, is well investigated in the knee and has been applied in the talus with increasing popularity and promising results but the evidence to date is poor. The goals of the current article are to summarise the different options for treating chondral and osteochondral defects of the talus and review the available literature.

Key words: Cartilage defect; Talus; Repair techniques; Arthroscopy; Marrow stimulation; Mosaicplasty; Autologous chondrocyte implantation

Core tip: The goals of the current article are to summarise the different options for treating chondral and osteochondral defects of the talus and review the available literature.

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INTRODUCTION

In contrast to other joints of the lower extremity, chondral and osteochondral lesions of the talus are frequently being recognised as being caused by traumata. The impact of shear and compression forces causes a cartilage contusion and is often transmitted to the subchondral bone, thus causing subchondral microfractures. In addition to trauma other causes include endocrine or metabolic factors genetic predisposition, vascular or synovial abnormalities, localised hyperpressure, or chronic microtrauma[1-3].

Irrespective of their aetiology, these lesions remain important problems (Figure 1), a consequence of the limited reparative potential of human cartilages. During

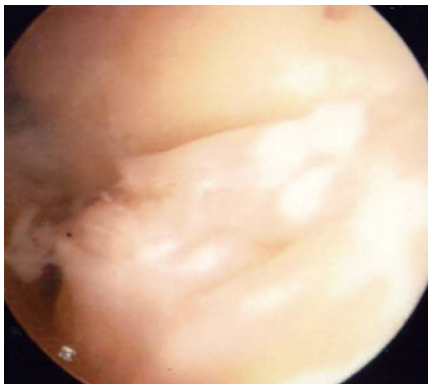

Figure 1 Arthroscopic view of an osteochondral lesion of the lateral shoulder of the talus.

repair, the cartilage usually produces a fibrocartilaginous tissue that has inferior mechanical properties and may deteriorate gradually[4]. For these lesions, diverse treatment options have been published in the last decades[5-10].

The goals of the current article are to summarise the different options for treating chondral and osteochondral defects of the talus and review the available literature.

Special characteristics of talar cartilage

Many recommendations for the management of talar cartilage defects are based on approaches for the knee. However, some well-known and important attributes clearly distinguish the cartilage of the talus from other cartilage, especially from that of the knee joint.

First, the ankle is a highly congruent joint, which is important to know when using different methods for cartilage repair, such as autologous osteochondral transplantation. Additionally, the nature of the joint will affect the development of pain in osteochondral defects of the talus[11]. Of note, the average thickness of the talar articular cartilage is approximately 0.89 mm whereas knee cartilage thickness reaches 6 mm[12,13]. Moreover, the tensile stiffness of healthy talar cartilage has only minimal topographical variability and the dynamical stiffness is higher than in the knee[14,15]. A further difference is the lower contact area and the lack of absorbability that makes the cartilage able to tolerate higher maximum loads[16]. Additionally, its metabolic activity appears to be greater than that of the knee, with a higher turnover as well as a higher level of proteoglycan synthesis[16].

Finally, the capability to maintain its mechanical properties more successfully during ageing appears to be more favourable in the talar articular cartilage compared to other joints[17].

TREATMENT OPTIONS

Conservative treatment

The intended purpose of a non-operative approach is to unload the injured cartilage and thereby allow the subchondral oedema to resolve, prevent osseous necrosis, or enable healing of a minimal detached fragment. Unfortunately, the reasons for choosing this treatment are not always clearly described[18]. Additionally, the overall results of the non-operative treatment of cartilage lesions of the talus indicate only a low success rate[19,20].

Despite this fact, conservative management may be considered and favourable for some types of lesions. Non-operative treatment is appropriate in fresh cartilage injuries that are non-displaced and have a potential for healing, depending on their size and location as well as on patient parameters, such as age, socio-professional context, or smoking[1]. Asymptomatic lesions, minimally symptomatic lesions that involve cartilage alone or show an intact cartilage surface, and low-grade osteochondritis dissecans lesions in children may recover using temporarily protected weight-bearing with or without joint immobilisation[1,3,21].

Surgical treatment

Marrow stimulation techniques: Human articular cartilage has a limited reparative capability because of its avascularity, among other reasons. Although the basic purpose of the surgical treatment is to re-vascularise the bony defect, many cartilage defects of the talus can be treated arthroscopically using bone marrow stimulation methods involving drilling or microfracture.

These techniques attempt to promote the development of a fibrocartilageous formation over the defect, which may suffice for small lesions. The principle is to breach the subchondral plate at multiple intervals to allow the subsequent inflow of serum factors as well as to stimulate chondroprogenitor cells of the marrow into the base of the defect site[22] (Figure 2A and B). The release of fatty drops from the created fracture apertures provides a clinical indicator that the depth of the microfracture is adequate. To remove the calcified layer and to obtain stable edges of vital cartilage, it is recommended that the procedure be supplemented by excision and curettage[23,24] (Figure 3).

Of note, a recent study of 2nd look arthroscopy at 12 mo postoperatively revealed incomplete healing of osteochondral lesions treated using these techniques in 40% of the patients[25]. Interestingly, good clinical results were achieved, which agrees with most series demonstrating pain relief and optimisation of function[26-28]. O'Driscoll[29] summarised that this technique may be best for the treatment of small (< 6 mm), shear-type lesions with minimal subchondral involvement.

Increased age has been considered to be an independent risk factor for a poor outcome, but has not been confirmed by recent studies[27,30]. In contrast, a higher body mass index, a history of trauma, and the presence of degenerative changes will certainly worsen the outcome[5,27]. Moreover, the defect's size is a predictor of clinical outcome: a defect dimension larger than 150 mm^2 appears to result in a significantly higher failure rate[5,31].

Tissue transplantation

Autologous osteochondral transplantation: The un-

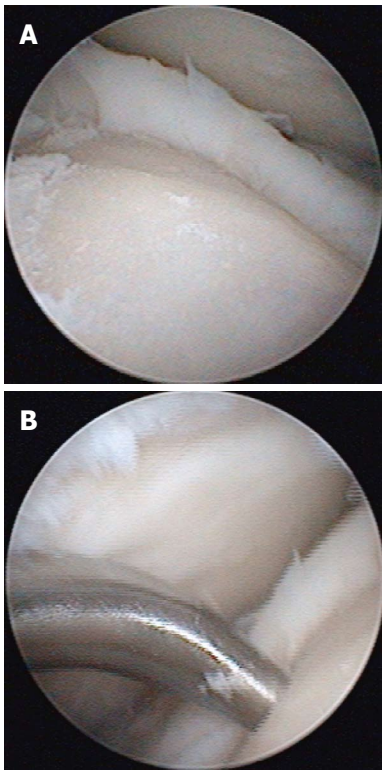

Figure 2 Chondral defect grade Ⅳ (A) of the lateral aspect of the talus, breaching the subchondral plate with an awl (B).

certain value of bone marrow stimulation techniques for defects larger than 150 mm^2 has encouraged the search for alternative resurfacing procedures, such as autologous osteochondral transplantation. This technique was developed principally to treat focal cartilage defects of the knee[32].

This procedure involves autologous grafting using one or more cylindrical components consisting of cartilage and its underlying bone. The components were harvested from a less weight-bearing part of the femur of the ipsilateral knee. Hangody *et al*[8] introduced this mosaicplasty to treat large cartilage defects using a one-step procedure. This can be performed using an open approach or, in special cases, arthroscopically. The size of the defect determines whether more than one osteochondral plug is needed: the plugs may vary in size and are placed in a side-by-side configuration into the prepared defect site. Distinctive cystic lesions could be treated using the osteochondral autograft transfer system (OATS)[3]. Several authors reported favourable results based on short- to mid-term follow-up[8,33-35]. Good results may be expected for a moderate talar dome defect of approximately 2 cm^2 in size and more than 5 mm in depth[36]. Others recommend this treatment for lesions that are 4 cm^2 or smaller[3].

In contrast to bone marrow stimulation the aim of osteochondral transplantation techniques is to resurface the defect with a viable hyaline cartilage. Therefore, this procedure attempts to reproduce the mechanical, structural, and biomechanical characteristics of the primary hyaline talar cartilage[18].

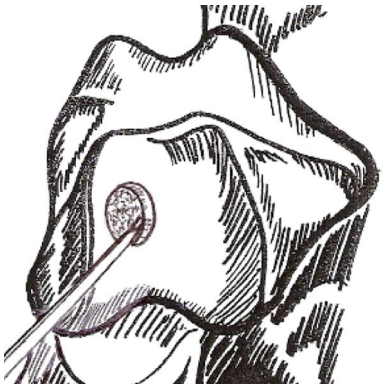

Figure 3 Schematic drawing: It is necessary to obtain a vertical and stable border of healthy cartilage after debridement of the cartilage defect.

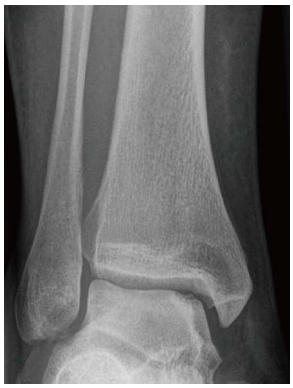

Figure 4 A.-P. radiograph of the ankle showing an osteochondral defect of the medial shoulder of the talus.

Despite these advantages, some disadvantages must be considered when planning osteochondral autografts. Only a circumscribed surface can be treated anatomically due to the limited number of suitable donor sites, which is primarily due to differences in the surface curvature between the graft and the host tissue[4] (Figure 4). Additionally, restoring lesions of the talar shoulder can be difficult[17]. Any type of surface incongruity or irregularity caused by differences in thicknesses of the grafts or differences between the size of the graft and the size of the defect should be carefully avoided. These surface differences often result in an uneven surface or the development of "dead spaces" between each graft that is filled only with a fibrous regrind. Therefore, circular lesions could often be resurfaced better than elliptical defects[17].

Based on the location of the lesion and depending on the approach needed a malleolar osteotomy is necessary. In some patients the use of an osteotomy may worsen the clinical outcome and affect the potential benefit of cartilage resurfacing[37], but this does not appear to cause widespread concern[38]. Several techniques were described for performing the osteotomy[39]. However, the surgeons have to be aware of potentially related problems. First, it is essential to be conscious of a proper level to avoid violating the articular surface as well as to gain optimal visibility of the defect[40]. Second, one must focus on a

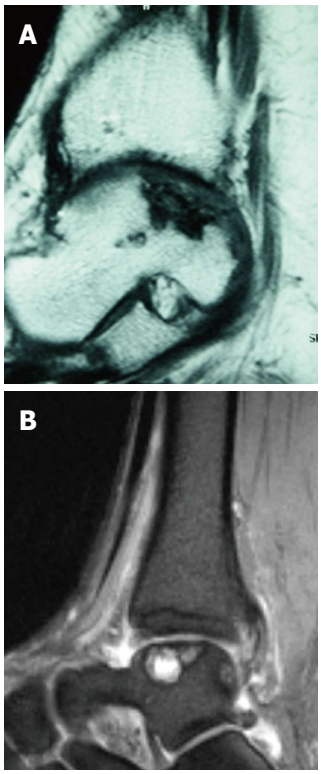

Figure 5 Sagittal T1 and T2-weighted magnetic resonance imaging scan. A: Sagittal T1-weighted magnetic resonance imaging scan demonstrating deep osteochondral defect of the posterior aspect of the talus; B: Sagittal T2-weighted magnetic resonance imaging scan showing the several cystic lesions of the talus in addition to an osteochondral defect.

precise reduction and sufficient fixation to avoid a fibrous non-union or malunion[3]. For example, Lamb *et al*[41] described a chevron-type medial malleolar osteotomy that appears safe and reduces the risk of non-union. At a median follow-up of 34.5 mo 94% of the patients were non-symptomatic. The median time to radiographic healing was six weeks.

Donor-site knee morbidity could pose problems for patients, but it is not discussed in any of the published series[17]. Therefore, some authors suggest harvesting the osteochondral plugs from the talus itself to avoid donor-site knee pain, stiffness, or even arthritic changes[42]. Two series specifically addressed donor-site morbidity[43,44]. In a retrospective study of 11 patients, Reddy *et al*[44] showed that the number of grafts obtained had no effect on clinical outcome. Paul *et al*[43] found that a high body-mass index influenced the outcome score negatively.

Osteochondral allograft transplantation: The use of fresh osteochondral allografts is a different technique especially designed to reconstruct massive osteochondral defects that have substantial loss or cystic degeneration of subchondral bone[40] (Figure 5). Indications for choosing this method for reconstruction are similar to those for osteochondral autologous transplantation, but without limitations based on size[36]. In patients with severe tibiotalar arthritis, the use of bipolar osteochondral allografts has been described[45].

In osteochondral allografts, a cadaver graft, consisting of both articular cartilage and its underlying bone, is transplanted into the defect site. An advantage of this technique is that the transplanted allograft can be tailored to match the shape of the defect precisely, which is particularly necessary due to the above-mentioned high congruity of the ankle joint. Therefore, even severe defects that involve the talar shoulder can be treated successfully[46]. Regardless, a malleolar osteotomy is required in some cases. A viable articular cartilage is provided and graft harvesting from a healthy knee joint is not needed; these are other advantages of this method.

Nevertheless, the success of such allografts is related to the percentage of chondrocytes that remain viable after graft procurement[47]. The storage of a fresh human allograft for more than fourteen days was revealed to substantially decrease the viability, cell density, metabolic activity of the chondrocytes, and lead to an approximately 30% decrease in viable chondrocytes after 28 d[47,48]. Despite these drawbacks, the biomechanical characteristics appear not to be affected by storage for this time interval[39]. However, many tissue banks need almost one month for screening to minimise the risk of disease transmission via the graft[36]. To date, the authors are not aware of any viral transmission via such allografts; however, the screening period is necessary and patients have to be informed of this hypothetical risk.

An immunologic reaction that adversely affects the chondrocytes, the limited availability of grafts, and the acceptance of costs may be further disadvantages[47]. Several authors have investigated the treatment of large osteochondral defects of the talus using osteochondral allograft transplantation in case series[7,46,49-52]. The overall clinical results were promising, especially considering the size of the defects. However, in certain of these studies, only a few patients were reported to be symptom-free[51]: some patients needed further surgical treatment, or the procedure failed[46,49,51].

In summary, the evidence for the use of osteochondral allograft transplantation has to be interpreted carefully. Most series included a small number of patients, studied patients retrospectively, had only a short- or mid-term follow-up, or presented no description of the underlying size of the defect[7,46,49,50,52,53]. Additionally, in several of these investigations, patients were lost to follow-up or were excluded because of graft failure[46,50,52].

Autologous chondrocyte transplantation/ implantation: Brittberg *et al*[54] implemented the technique of autologous chondrocyte transplantation in 1987. The first results were published in 1994 after treating chondral defects of the knee with this technique. Since then, it has become a promising tool for the repair of cartilage defects. Several long-term trials have provided strong evidence of the efficacy of this procedure, primarily studying its application in the knee[55-57]. Young patients suffering from a single focal cartilage defect with only a short duration of symptoms should expect good re-

Table 1 Indications and contraindications for autologous chondrocyte transplantation of the talus (modified to[61])

Indication	Contraindication
symptomatic full-thickness chondral/osteochondral lesions	Osteoarthritis/rheumatoid arthritis
focal lesion > 1.5 cm^2 in size	so-called kissing lesions
lesion with necrotic bone/fibrous tissue base	ligamentous instability (can be corrected in conjunction with the ACT procedure)
failed previous traditional surgery	axial malalignment
(*i.e.*, drilling or microfracture)	(should be previously corrected)
patients younger than 45 yr of age	children/teenagers
	patients older than 45 yr of age

ACT: Autologous chondrocyte transplantation.

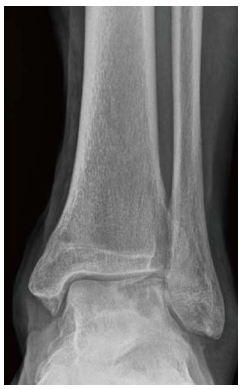

Figure 6 A.-P. radiograph of the ankle demonstrating a distinctive cystic lesion due to an osteochondral defect of the lateral shoulder of the talus.

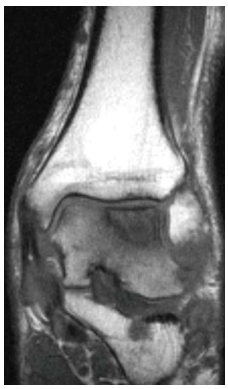

Figure 7 Sagittal T1-weighted magnetic resonance imaging scan demonstrating an osteochondral defect of the wholelateral aspect of the talus and a consecutive talar edema.

sults[58]. However, to our best knowledge, equivalent data do not exist regarding the treatment of the talus. Additionally, a clearly recommendation regarding the defect size in which this procedure works best cannot be given: reported defect sized vary between 2 cm^2 and 12 cm^2[59].

Autologous chondrocyte transplantation (ACT) is a cell-based, two-stage procedure that involves the transplantation of viable and cultured chondrocytes into a defect. In the first step, cartilaginous material is harvested from the knee or the ankle itself[10,40]. In some cases, the cartilage was harvested from a detached osteochondral fragment without any reported adverse effect on the chondrocytes' viability[60]. Usually, the second-stage of the procedure is performed after three to four weeks of cell culturing.

The aim of ACT is to promote the development of a regrind that meets the requirements of human hyaline cartilage or, at best, will facilitate a hyaline-like repair tissue. The ideal indication for an ACT is a full-thickness cartilage defect with an intact subchondral plate with stable edges of the surrounding cartilage[59]. The conditions for its application do not differ from that of the above-mentioned techniques: all pathologic cartilage should be carefully debrided to achieve vertical and stable edges surrounding the defect[10,61]. In case of an osseous deficiency (Figures 6 and 7), concomitant bone-grafting is suggested to provide a sufficient bony base[61]. Indications and contraindications are summarised in Table 1.

A method using a periosteum-covered ACT is called the first generation of this technique. A periosteal flap is harvested, *i.e.*, from the distal part of the tibia, and then placed over the defect with the cambium layer facing toward the aforementioned prepared bed[40,61]. Then, the cultured cell suspension is injected beneath the sutured flap. However, this technically demanding procedure induced complications, such as delamination, uneven distribution of cells within the defect, cell leakage, or periosteal hypertrophy[38].

Due to these complications, a second generation of ACT, using matrix-associated techniques, was developed. In matrix-induced autologous chondrocyte implantation/transplantation (MACI/MACT), cells are embedded into a bioabsorbable, porcine type- Ⅰ/Ⅲ collagen membrane[62]. In the second stage of the procedure this membrane is placed over talar cartilage defect. Advantages of MACI/MACT are the avoidance of periosteal graft harvesting and a more even cell distribution potentially delivering more viable cells to the defect[17].

Furthermore, a third-generation of ACT, a three-dimensional, biomaterial-free MACT with chondrospheres, is available[63]. To apply it entirely arthroscopically and therefore reduce morbidity is a further advantage. However, to date, it is unclear whether the chondrospheres will remain securely in the defect because they are placed without coverage.

Analysing of the literature reveals various trials of ACT of the talus[4,40,43,63,64]. Although, many of the reports publicised promising results, the available evidence is of poor quality. A recent meta-analysis showed that many

Table 2 Summary of treatment options for cartilage repair of the talus

Procedure	Concept	Indication	Potential Advantage	Worth knowing	Evidence
Conservative	Unload injured cartilage	Low-grade OD in children	Healing without surgical risk	Results in literature low but recommended first-line treatment in low-grade lesions	Poor
Marrow stimulation techniques	Recruits mesenchymal stem cells from bone marrow Stimulates differentiation of repair tissue	Lesions < 150 mm^2 with none/minimal subchondral involvement	Can be administered arthroscopically Can be done repeatedly	Fibrocartilaginous repair tissue Results deteriorate over time	Fair
Autologous osteochondral transplantation	Resurfaces defect with viable hyaline cartilage + underlying bone	Osteochondral defects (2-4 cm^2)	Reproduces mechanical, structural, biomechanical characteristics of primary cartilage One-stage procedure	Donor site morbidity Potential need for osteotomy	Fair
Osteochondral allograft transplantation	Resurfaces defect with viable hyaline cartilage + underlying bone	Large-volume/ cystic lesions	No limitations based on size of defect One-stage procedure	Potential decrease in viable chondrocytes due to disease screening	Poor
Autologous chondrocyte transplantation (ACT)	Cultured chondrocyte-like cells will stimulate a hyaline-like repair tissue	Second-line treatment in large defects (> 2 cm^2)	Nearly perfect fit with defect (no "dead spaces")	Adverse effects of 1st generation MACT with better cell distribution Osseous defect has to be grafted before ACT	Poor
Further treatment options (hyaluronic acid, PRP, mesenchymal stem cells)	Not clear May function as an biological adjunct	Not clear May be added to repair techniques	Not clear May improve final outcome	Mode of function not completely understood	Insufficient

ACT: Autologous chondrocyte transplantation; MACT: Matrix-associated autologous chondrocyte transplantation; OD: Osteochondritis dissecans; PRP: Platelet rich plasma.

publications address ACT of the talus[65]. However, only 16 of 54 studies could be included in this systematic review. Due to the use of several products for ACT, several "generations" of ACT, the low case numbers, inhomogeneous indications, and the use of different outcome parameters, it was not possible to draw any conclusion about what type of ACT is superior[65]. Additionally, there were no controlled studies available. Therefore, a safe and significant superiority of other techniques of cartilage repair could not be estimated until now.

Further treatment options

Further methods to optimise techniques for cartilage repair have been introduced, but most of them are in the early stages of development or are only described in isolated case series. In summary, there is insufficient evidence to support recommending their use. However, they are mentioned below for completeness.

Mesenchymal stem cells may be able to differentiate into articular cartilage and may be used as an adjunct to microfracture treatment[6]. However, to date, the only relevant investigations were either animal or uncontrolled trials[66,67].

Additionally, platelet-rich plasma (PRP) may function as a scaffold for cultured cells and provide a reservoir of growth-stimulating factors[9,68].

Finally, viscosupplementation therapy using of hyaluronic acid has great popularity despite the lack of convincing outcomes[3]. In a recent study, after arthroscopic debridement and microfracture in osteochondral defects of the talus, hyaluronic acid was added postoperatively. Functional and pain scores were significantly improved compared to the group treated with microfracture alone[53].

CONCLUSION

In summary, no technique appears to be superior to the others, and treatment of chondral/osteochondral lesions of the talus remains controversial. Patients should be analysed rigorously. Before selecting an appropriate procedure, the socio-professional context and the patient's compliance, as well as the characteristics of the patients job-related or sports activities, have to be considered.

Based on the evidence available as well as our own experience we agree with others that, depending on the lesion's size, arthroscopic treatment using marrow stimulation and debridement may be a reasonable strategy to treat these lesions effectively[3,18,38]. Therefore, this approach can be recommended as first-line treatment.

For larger lesions, autologous osteochondral transplantation can be utilised as primary treatment with good success as well. Moreover, it can be recommended as second-line treatment in cases in which the bone marrow stimulation technique fails.

Patients with large-volume or cystic lesions who cannot be treated with the standard autograft procedures due to evidence of poor quality results, should be chosen for osteochondral allograft transplantation carefully.

Finally, autologous chondrocyte transplantation techniques should be individualised and applied to cautiously selected patients in whom the above-mentioned first-line treatment methods have failed. Table 2 gives an overview

about the different treatment options.

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Worldwide spread of the Ponseti method for clubfoot

Lior Shabtai, Stacy C Specht, John E Herzenberg

Lior Shabtai, Stacy C Specht, John E Herzenberg, International Center for Limb Lengthening, Rubin Institute for Advanced Orthopedics, Sinai Hospital, Baltimore, MD 21215, United States
Author contributions: Shabtai L, Specht SC and Herzenberg JE solely contributed to this paper.
Correspondence to: John E Herzenberg, MD, FRCSC, International Center for Limb Lengthening, Rubin Institute for Advanced Orthopedics, Sinai Hospital, 2401 West Belvedere Avenue, Baltimore, MD 21215,
United States. jherzenberg@lifebridgehealth.org
Telephone: +1-410-6010894 Fax: +1-410-6019575
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Abstract

The Ponseti method has become the gold standard for the treatment of idiopathic clubfoot. Its safety and efficacy has been demonstrated extensively in the literature, leading to increased use around the world over the last two decades. This has been demonstrated by the increase in Ponseti related PubMed publications from many countries. We found evidence of Ponseti activity in 113 of 193 United Nations members. The contribution of many organizations which provide resources to healthcare practitioners in low and middle income countries, as well as Ponseti champions and modern communication technology, have helped to spread the Ponseti method around the world. Despite this, there are many countries where the Ponseti method is not being used, as well as many large countries in which the extent of activity is unknown. With its low rate of complication, low cost, and high effectiveness, this method has unlimited potential to treat clubfoot in both developed and undeveloped countries. Our listing of countries who have not yet shown presence of Ponseti activity will help non-governmental organizations to target those countries which still need the most help.

Key words: Ponseti; Clubfoot; World; Organization; Children

Core tip: The Ponseti method has become the gold standard for the treatment of idiopathic clubfoot. With its low rate of complication, low cost, and high effectiveness, this method has unlimited potential to treat clubfoot in both developed and undeveloped countries. Our listing of countries who have not yet shown presence of Ponseti activity will help organizations to target those countries which still need the most help.

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INTRODUCTION

Ponseti developed his method for the conservative treatment of clubfoot at the University of Iowa in the 1950's, but it remained largely confined to Iowa until around 1997. It has since spread widely around the world.

Clubfoot (CF) is a common congenital deformity affecting approximately 1-2 per 1000 live births. The traditional treatment of congenital clubfoot has been mainly performed through complex surgical release procedures[1,2]. Common complications related to this extensive surgery included recurrence of the deformity, overcorrection, long-term joint stiffness, and pain[3,4]. The disappointing long term results inspired some to seek out less invasive, more conservative treatments typified by the Ponseti method, which involves serial casting and percutaneous Achilles tenotomy of the affected feet followed by bracing to maintain the correction.

Today, this method has become the de facto gold standard for the initial treatment of clubfoot. Its safety and efficacy has been demonstrated extensively in the literature[5-14].

We performed a systematic review to determine the

Table 1 Ponseti method journal articles and abstracts published between 1972 and 10/31/2013: Countries of origin (41)

Albania	Malawi
Australia	Mexico
Austria	Nepal
Bangladesh	New Zealand
Belgium	Norway
Bosnia and Herzegovina	Pakistan
Brazil	Poland
Canada	Portugal
China	Romania
Czech Republic	Russian Federation
Egypt	Saudi Arabia
France	Spain
Germany	Sudan
India	Sweden
Iran	Taiwan
Ireland	Tunisia
Israel	Turkey
Italy	Uganda
Japan	United Kingdom
South Korea	United States
Kuwait	

exact penetration of the Ponseti method worldwide, and to examine the factors that lead to this spread. The additional goal of this study is to determine which countries are currently not using the Ponseti method, in order to help agencies such as Ponseti International and Miracle Feet to target new countries for expansion.

LITERATURE SEARCH

The following databases were used for this search through October 31, 2013: The United States National Library of Medicine National Institutes of Health (PubMed), the Cochrane Library and the Excerpts Medical Database (EMBASE). We used "Ponseti" and "Ponseti method clubfoot" as key words in our search. We included publications in all languages where an English abstract was available. We used Google scholar to search for abstracts presented at various conferences such as the "5th and 6th International clubfoot congress". Additionally, we searched in the web sites of "Ponseti International", "Global Clubfoot Initiative", "Miraclefeet" and "Cure Clubfoot" to determine which countries are using the method, though have not yet published their results[15-18] (Table 1). Additionally, "Ponseti method" and each of the 193 United Nations (UN) acknowledged countries were used as search words in Google to ensure that our information was as complete as possible.

Our results were separated into 2 categories: (1) Countries practicing the Ponseti method who have published results, in either paper or abstract form; and (2) Countries who demonstrate evidence of using the Ponseti method, though without publication of results.

Published articles were then categorized by number, year, and region.

Although the 193 members of the UN represent the vast majority of countries in the world, independent countries such as Vatican City and Kosovo are not included. For the purpose of this review, we included only those 193 countries recognized by the UN.

RESEARCH

We found more than 265 published papers discussing the Ponseti method for the treatment of clubfoot from 1950 until October 31, 2013. These papers originated from only 34 of the 193 UN countries using PubMed, the Cochrane Library and EMBASE. There were an additional 7 countries with abstracts from the 5th and 6th International Clubfoot congress (Table 1), and another 72 countries, so called, "low and middle income countries in which there was evidence of activity according to the "Ponseti International", "Global Clubfoot Initiative", "Miraclefeet" and "Cure Clubfoot" association websites. In these cases, we relied on confirmation from colleagues who are leaders in the dissemination of the Ponseti method globally.

With this evidence, we conclude that a total of 113 countries are currently using the Ponseti Method clinically. We further categorized those countries with published papers according to when the treatment occurred. These four epochs include; up to 2000, from 2001 to 2005, from 2006 to 2010 and after 2011 (Figure 1).

The number of publications across a wide variety of countries in PubMed has increased significantly over the past two decades suggesting an increase in those who are trained and using the method (Figure 2).

There are some countries where we know for certain the Ponseti method is being used, but could not find publications or Internet evidence (Table 2).

DISCUSSION

Since Ponseti first introduced his method for the treatment of clubfoot in the 1950's, the method was relatively isolated and confined to Iowa until 1996 when Ponseti published his textbook. Since 1997, the efforts of Ponseti champions have led to a steady increase in clinical use and publication worldwide, especially over the last decade. This conservative method has been shown to be effective, safe, and cost-effective[5-14]. As this method is largely non-surgical, and requires only basic medical supplies, its potential to spread to both developed and undeveloped countries is unlimited. With proper training, this method can effectively be performed by a wide variety of medical personnel, including physiotherapists and orthopedic officers.

Despite the benefits of this technique, we found that only 34 of 193 (18%) UN countries have published their experience using the Ponseti method. In another 7 countries we found abstract submissions related to this topic and another 72 countries where the Ponseti method is apparently performed on a clinical basis. This total of 113 countries represents only 59% of the countries in the world.

One of the weaknesses of this study is that large

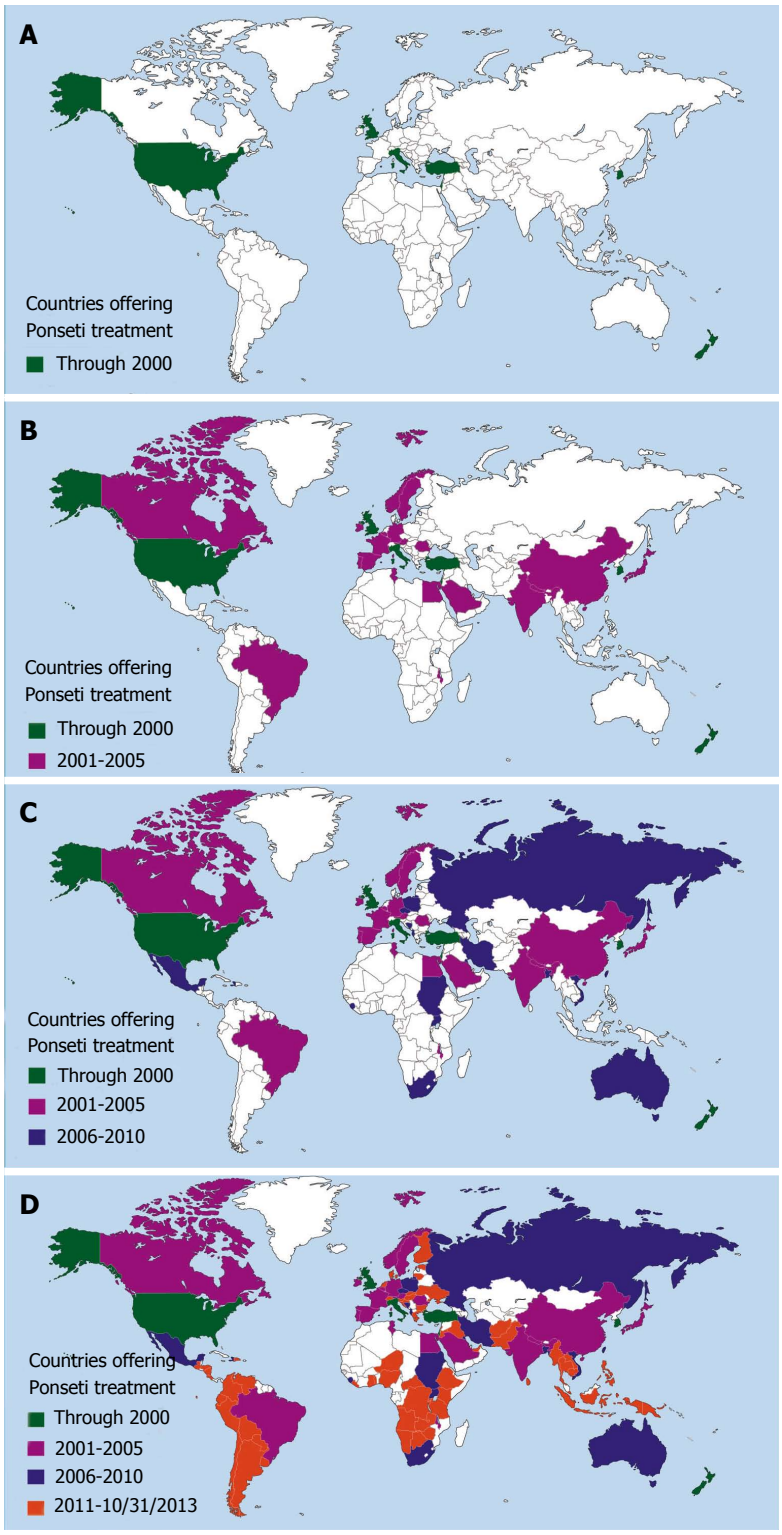

Figure 1 Represents the world with the order of appearance of the Ponseti method. A: Through 2000; B: Through 2005; C: Through 2010; D: Until 10/31/2013. The countries still depicted in white are those that can be targeted for further penetration of the Ponseti method.

countries such as China and Russia have shown evidence of activity but the actual extent or penetrance of activity is unknown. Also, although various information gathering methods were used, it's possible that we omitted countries that may be already practicing the Ponseti method. For this we apologize and await remonstrative letters to the editor correcting our inaccuracies. Further studies need to be done to provide further information about the extent within these countries that the Ponseti method is being used.

More than 220000 children in developing countries are born with clubfoot every year[15-18]. Despite the efforts of some non-profit organizations, there are still many children with neglected clubfoot and disability caused by untreated or wrongly treated clubfoot. With proper training and education, we feel this method could be further spread, successfully treating patients in both developed and developing countries around the world. This review gives us some idea where this future training and education could be best targeted.

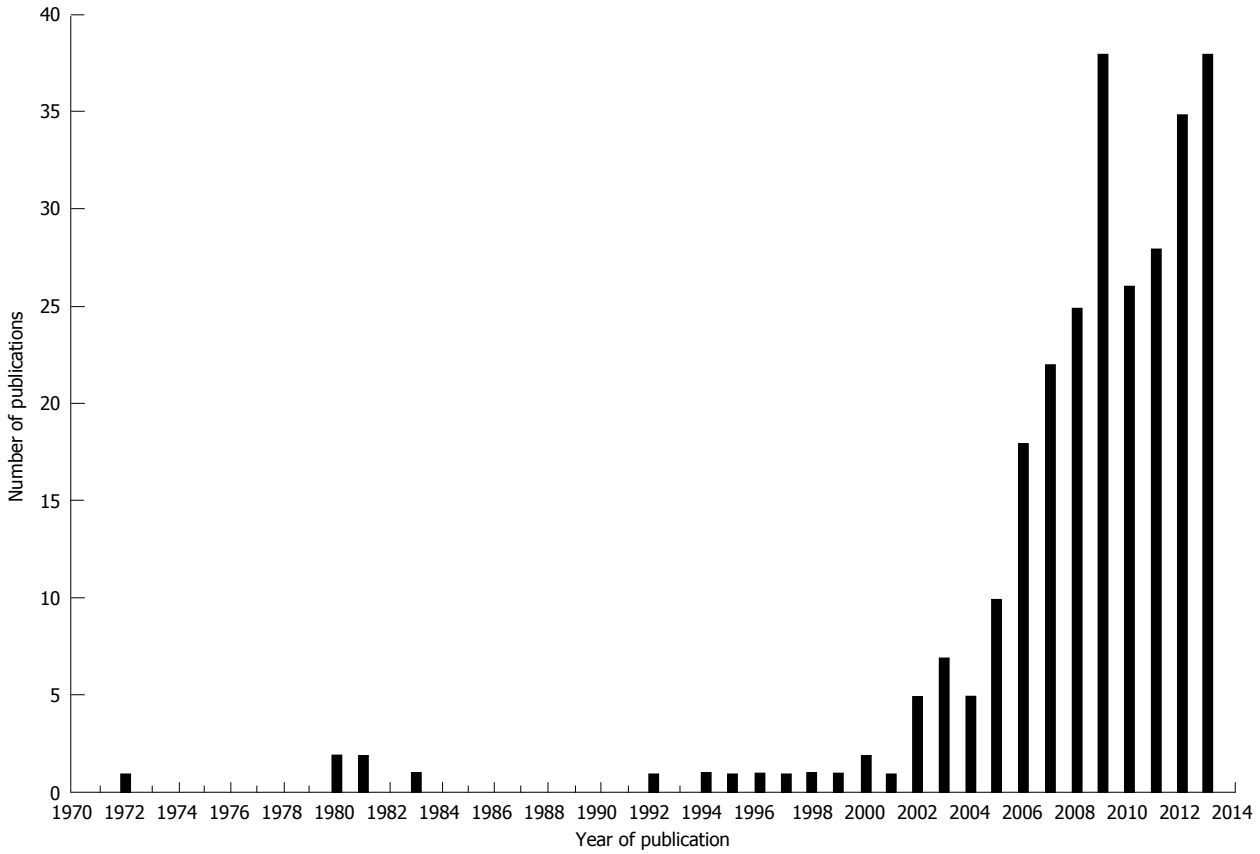

Figure 2 Demonstrates the increase in the number of Ponseti related articles in PubMed during the last two decades.

According to the Ponseti clubfoot management book[19]: more than 100000 downloads of the PDF edition in more than 30 languages have been performed in more than 150 countries.

What has helped this method to spread? (1) Evidence based results (publications) which detail the success of this method, in a wide variety of clinical practices. The Ponseti method was proven to be the gold standard treatment for CF patients; therefore many countries adopted this method as the initial treatment for newborn patients (Figure 2); (2) Recent studies have shown good results when the Ponseti method was performed by trained clinical specialists in either a teaching hospital setting or in the developing world. In countries in which there are fewer orthopedic surgeons, especially in low income countries, specially trained non-physician staff can successfully perform this method in a non-surgical environment[20-22]; (3) Non-governmental organizations such as the Global Clubfoot Initiative and the Ponseti International Association provide resources to health care practitioners in low and middle income countries[15-18]; (4) Ponseti champions, such as Jose Morcuende, Shafiq Pirani, Norgrove Penny, Fred Dietz, John Herzenberg and many others have made contributions by traveling to, and training staff in developing countries; (5) Technological advances such as the Internet helped to spread this method in two ways. First, parents today frequently searched the Internet for new, effective, minimally invasive techniques[23]. Second, physicians now can read free articles and learn the method by watching demonstration videos. The internet is also a tool for transmission of the Ponseti method by the "Ponseti Virtual Forum" (PVF), which demonstrated its effectiveness in low income countries[24]; (6) The treatment is affordable as it uses inexpensive casting materials as its primary treatment. The Achilles tenotomy is typically done as an office procedure, thereby avoiding expensive surgical costs[25]; (7) Clubfoot: Ponseti Management book. This book provides information on all aspects of Ponseti management of Clubfoot, and is available as a free download in more than 30 different languages. More than 100000 downloads of the PDF have been performed in more than 150 countries; and (8) Meetings and training courses are available to practitioners in the United States and around the world. Jayawardena *et al*[26] demonstrate the effectiveness of these courses in a study in which an online survey was sent to the participants in these training courses from 2001 to 2011. They found that prior to the course, surgical release was the primary method of treatment. Ninety-seven percent of respondents changed their practice as a result of attending the course.

CONCLUSION

Since approximately 2000, there has been a spectacular increase in number of countries using the Ponseti method. The Internet, training courses, individuals and organizations have all helped to educate health care professionals as well as patients, increasing its impact worldwide.

Table 2 Countries without evidence that the Ponseti method is being practiced

Country	Population	Country	Population
Algeria	37900000	Swaziland	1250000
Morocco	33113600	Bahrain	1234571
Uzbekistan	30183400	Djibouti	873000
Yemen	25235000	Fiji	858038
North Korea	24895000	Guyana	784894
Ivory Coast	23202000	Bhutan	741920
Syria	21898000	Comoros	724300
Madagascar	21263403	Montenegro	620029
Angola	20609294	Solomon Islands	561000
Burkina Faso	17322796	Luxembourg	537000
Senegal	13567338	Suriname	534189
Chad	12825000	Cape Verde	491875
Cuba	11167325	Malta	416055
Somalia	10496000	Brunei	393162
Benin	10323000	Bahamas	351461
Belarus	9467200	Iceland	325010
Azerbaijan	9235100	Maldives	317280
Tajikistan	8000000	Belize	312971
Libya	6202000	Barbados	274200
Kyrgyzstan	5747000	Vanuatu	264652
Slovakia	5412008	Samoa	187820
Turkmenistan	5240000	São Tomé and Príncipe	187356
Central African republic	4616000	Saint Lucia	166526
Georgia	4483800	Saint Vincent and Grenadines	109000
Oman	3929000	Kiribati	106461
Moldova	3559500	Grenada	103328
Mauritania	3461041	Tonga	103036
Armenia	3024100	Micronesia	101351
Mongolia	2754685	Seychelles	90945
Jamaica	2711476	Antigua and Barbuda	86295
Lesotho	2074000	Andorra	76246
Qatar	2068050	Dominica	71293
Macedonia	2062294	Marshall Islands	56086
Latvia	2008700	Saint Kitts and Nevis	54000
Gambia	1849000	Liechtenstein	36942
Guinea-Bissau	1704000	Monaco	36136
Gabon	1672000	San Marino	32509
Equatorial Guinea	1622000	Palau	20901
Trinidad and Tobago	1328019	Tuvalu	11323
Mauritius	1257900	Nauru	9945

This review identifies where this method is currently being used, as well as those areas (Table 2) that could benefit from targeted education and training. With its low rate of complication, low cost and high effectiveness, this method has unlimited potential for the treatment of clubfoot in both developed and undeveloped countries.

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Hallux rigidus: Joint preserving alternatives to arthrodesis - a review of the literature

Hans Polzer, Sigmund Polzer, Mareen Brumann, Wolf Mutschler, Markus Regauer

Hans Polzer, Mareen Brumann, Wolf Mutschler, Markus Regauer, Munich University Hospital, Foot and Ankle Surgery, Department of Trauma Surgery-Campus Innenstadt, 80336 Munich, Germany
Sigmund Polzer, Department of Hand, Ellbow and Footsurgery, ATOS Clinic Heidelberg, 69115 Heidelberg, Germany
Author contributions: Polzer H and Polzer S concepted designed and drafted the manuscript; Brumann M and Regauer M acquired and analysed the literature and finalized the manuscript; Mutschler W gave substantial input concerning the conception and design and critically revised the manuscript; all authors gave final approval of the article to be published.
Correspondence to: Hans Polzer, MD, Munich University Hospital, Ludwig-Maximilians-University, Foot and Ankle Surgery, Department of Trauma Surgery-Campus Innenstadt, Nussbaumstrasse 20, 80336 Munich,
Germany. hans.polzer@med.uni-muenchen.de
Telephone: +49-89-51602511 Fax: +49-89-51602662
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Abstract

Hallux rigidus describes the osteoarthritis of the first metatarsophalangeal joint. It was first mentioned in 1887. Since then a multitude of terms have been introduced referring to the same disease. The main complaints are pain especially during movement and a limited range of motion. Radiographically the typical signs of osteoarthritis can be observed starting at the dorsal portion of the joint. Numerous classifications make the comparison of the different studies difficult. If non-operative treatment fails to resolve the symptoms operative treatment is indicated. The most studied procedure with reproducible results is the arthrodesis. Nevertheless, many patients refuse this treatment option, favouring a procedure preserving motion. Different motion preserving and joint sacrificing operations such as arthroplasty are available. In this review we focus on motion and joint preserving procedures. Numerous joint preserving osteotomies have been described. Most of them try to relocate the viable plantar cartilage more dorsally, to decompress the joint and to increase dorsiflexion of the first metatarsal bone. Multiple studies are available investigating these procedures. Most of them suffer from low quality, short follow up and small patient numbers. Consequently the grade of recommendation is low. Nonetheless, joint preserving procedures are appealing because if they fail to relief the symptoms an arthrodesis or arthroplasty can still be performed thereafter.

Key words: Hallux rigidus; Osteoarthritis; First metatarsophalangeal joint; Joint preserving; Operative treatment; Osteotomy

Core tip: If nonoperative treatment fails to relieve the symptoms of hallux rigidus surgery is indicated. The procedure with the most evidence for success is the arthrodesis of the first metatarsophalangeal joint. Nevertheless, many patients prefer treatment options which preserve the joint motion. The evidence for different arthroplastic procedures is of low quality. Furthermore, in case the procedure fails to relieve the symptoms to perform an arthrodesis after resection of the joint is much more difficult and may require bone graft. Consequently, joint and motion preserving osteotomies are of great interest for treatment of hallux rigidus. We here provide a review of the different joint and motion preserving alternatives for treating hallux rigidus and the studies available investigating these procedures.

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INTRODUCTION

The term "hallux rigidus" refers to the osteoarthritis of the metatarsophalangeal joint (MTPJ) of the first toe. This disease was first reported in 1887 by Davies-Colley[1]. He suggested the name "hallux flexus". Shortly thereafter Cotterill was the first to introduce the term "hallux rigidus"[2]. Since then multiple names have been suggested, such as metatarsus primus elevatus, dorsal bunion, hallux dolorosus, or hallux malleus, to describe the same diagnosis. It is one of the most common problems of the great toe[3].

ETIOLOGY

Hallux rigidus is a common form of osteoarthrosis in the foot[4]. Radiographic signs for the disease can be recognized in 10% of people aged 20-34 years and 44% of people over the age of 80 years[5]. The exact cause for hallux rigidus is controversial. Coughlin *et al*[6] (2003) demonstrated that 80% of all patients suffering from bilateral hallux rigidus have a family history. Furthermore, in a long term study they could depict that most patients develop a bilateral hallux rigidus over time[6]. Some authors blame poor shoewear[1], a tight achilles tendon[7] or believe in a spontaneous onset[8]. Another popular concept is that an elevated first ray, the so called metatarsus primus elevatus, leads to hallux rigidus. While many authors are in favour of this theory[9-13], there are multiple surgeons opposing it[14-16]. Coughlin *et al*[6] even propose that the metatarsus primus elevatus might be a secondary change due to hallux rigidus. Taken together, the exact cause leading to hallux rigidus remains controversial. Nevertheless, it is known that females show a higher incidence[10,14,17,18] and that it mainly occurs after the age of 40 years[6]. The most common cause for unilateral hallux rigidus is believed to be traumatic, either by isolated injury or repetitive microtraumata[14,19,20]. These can cause chondral injury and lead to progressive arthritic changes. However, most of these concepts are theoretical and lack scientific evidence.

CLINICAL FINDINGS

Hallux rigidus is characterised by arthralgia, which is usually worsened by walking. With time the joint enlarges and the symptoms become more pronounced with pain at the dorsal bony prominence of the first MTPJ[6] and decreased range of motion, especially dorsiflexion. In this process the destruction of the cartilage commonly starts at the dorsal portion of the metatarsal head[21] and the bony prominence might impinge against the proximal phalanx (Figure 1). Physical examination usually shows a painful, tender and swollen first MTPJ with limited motion and pain usually when dorsiflexed.

RADIOGRAPHIC FINDINGS

Radiographic examination should include weight-bearing anteroposterior and lateral radiographs[22]. The typical radiographic findings are asymmetric joint narrowing and a flattened metatarsal head (Figure 1). With advancement of the disease more of the joint surface is involved and subchondral cysts, sclerosis and bony proliferation at the joint margins occur and the joint narrowing progresses[22,23].

GRADING

Multiple different grading system for hallux rigidus have been introduced differentiating between two and five different grades[11,12,21,22,24-30]. A classification system should aid the decision on treatment and allow a meaningful comparison of different treatment strategies. Furthermore, in order to compare the results of different studies and procedures a consistent classification is crucial. Beeson *et al*[31] (2008) performed a systematic review of the literature to critically evaluate the different classification systems for hallux rigidus. The authors criticize, that none of the classification systems has been tested in regard to reliability and validity. Taking this shortcoming into account they consider the classification system by Coughlin *et al*[22] to be the closest to a "gold standard". These authors base their classification on subjective and objective clinical and radiographic findings (Table 1).

NONOPERATIVE TREATMENT

Nonoperative treatment of hallux rigidus should be applied in accordance to the degree of symptoms. Anti-inflammatory medications and strapping of the toe might be sufficient. Furthermore, shoe modification or the use of rigid shoe inserts and modification of activities might be beneficial[22,32]. Little evidence is available for injection of sodium hyaluronate, but it seems to be beneficial only in the early state[33,34]. Zammit *et al*[35] performed a systematic review and identified only one high class randomised controlled trial evaluating conservative interventions for hallux rigidus. Shamus *et al*[36] compared physical therapy alone to physical therapy combined with sesamoid mobilization, flexor hallucis strengthening exercises, and gait training. The authors concluded that combined multifaceted physical therapy reduces pain and restores function more sufficiently. When nonoperative treatment fails to provide relief, surgery should be performed.

JOINT DESTRUCTIVE SURGICAL TECHNIQUES

Arthrodesis

The best evidence available is in support of arthrodesis for the first MTPJ. When compared to total arthroplasty[37], hemiarthroplasty[38], resection arthroplasty[39], interpositional arthroplasty or cheilectomy[40,41], arthrodesis yielded better reduction of pain, better functional satisfaction, shorter hospital stays, lower revision rates and faster return to normal activity[42]. Nevertheless, joint and motion preserving operations are appealing, because

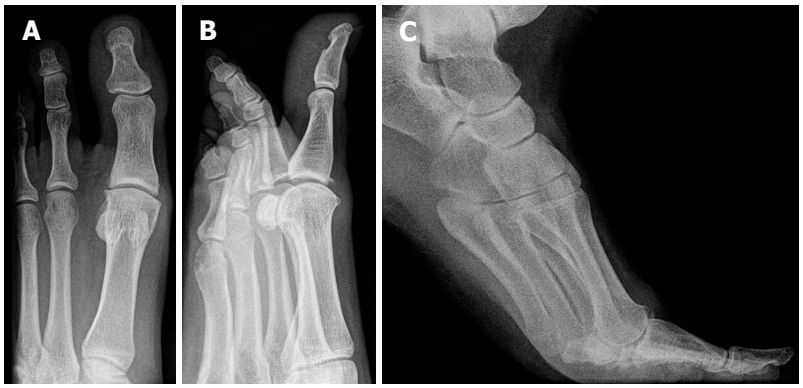

Figure 1 Radiographic images of a hallux rigidus grade 2. A: Dorso-plantar view; B: Oblique view; C: Stress radiographs in dorsiflexion revealing bony impingement.

Table 1 Clinical and radiographic grading for hallux rigidus

Grade	Dorsiflexion	Radiographic findings	Clinical findings
0	40°-60° and/or 10%-20% loss compared with normal side	Normal	No pain; only stiffness and loss of motion
1	30°-40° and/or 20%-50% loss compared with normal side	Dorsal osteophyte (main finding), minimal joint space narrowing, periarticular sclerosis, flattening of metatarsal head	Mild or occasional pain and stiffness, pain at extremes of dorsiflexion and/or plantar flexion
2	10°-30° and/or 50%-75% loss compared with normal side	Dorsal, lateral, and possibly medial osteophytes (flattened metatarsal head) < 1/4 of dorsal joint space involved (lateral radiograph), mild to moderate joint-space narrowing and sclerosis, sesamoids not involved	Moderate to severe pain and stiffness that may be constant; pain just before maximum dorsiflexion and maximum plantar flexion
3	⩽ 10° and/or 75%-100% loss compared with normal side. Notable loss of plantar flexion (often ⩽ 10°)	Same as in Grade 2 but with substantial narrowing, possibly periarticular cysts, > 1/4 of dorsal joint space involved (lateral radiograph), sesamoids enlarged and/or cystic and/or irregular	Nearly constant pain and substantial stiffness at extremes of range of motion but not at mid-range
4	Same as in Grade 3	Same as in Grade 3	Same as in Grade 3 but definite pain at mid-range of passive motion

if they fail to relief the symptoms, an arthrodesis can still be performed.

Arthroplasty

Different methods of arthroplasty are available. The studies comparing arthroplasty using nontissue implants compared various different implants[37,43-45] and produced conflicting results[40]. Arthroplasty by resection also seems to be effective for treatment of hallux rigidus[39,41,46], although it could not be demonstrated that it is superior to other techniques. The same applies to the interpositional arthroplasty[40,46-48].

Cheilectomy

This procedure was introduced in 1979 by Mann *et al*[15]. In addition to the osteophytes of the base of the proximal phalanx 25%-30% of the dorsal metatarsal head are removed (Figure 2A). Consequently, the procedure must be classified as a partially joint sacrificing technique. Too aggressive resection may lead to a MTPJ subluxation. Furthermore, arthrodesis or arthroplasty are more difficult thereafter. Only retrospective trials are available comparing cheilectomy to other surgical interventions[40,41,44,49]. There is no consistent evidence that cheilectomy is superior to other operative interventions[42], while it was used mainly in low grades of hallux rigidus.

JOINT PRESERVERING SURGICAL TECHNICES

Proximal phalanx osteotomy (Moberg)

One of the main clinical findings in hallux rigidus is the painful limited range of motion, especially of dorsiflexion. Therefore, the concept of the proximal phalanx osteotomy is to reset the arc of motion by placing the toe into a more extended position (Figure 2B). This should better accommodate the need for dorsiflexion[50]. Bonney *et al*[51] were the first to describe this concept in 1952 and called it "greenstick extension osteotomy of the proximal phalanx". Kessel *et al*[52] and Moberg[3] were the first to perform retrospective case series reporting promising results and suggesting "that further testing of this method should be worthwhile". The only prospective trial investigating proximal phalanx osteotomy was performed by Kilmartin[53]. They compared the proximal phalanx osteotomy (49 joints) to different metatarsal decompression osteotomies (59 joints). Unfortunately the sample size for each procedure in the metatarsal decompression osteotomy group was decreased by mixing the proximal plantar displacement osteotomy, the modified Reverdin Green osteotomy and the shortening scarf osteotomy. In both groups a significant increase of the AOFAS score could be noted. A higher satisfaction rate and a lower

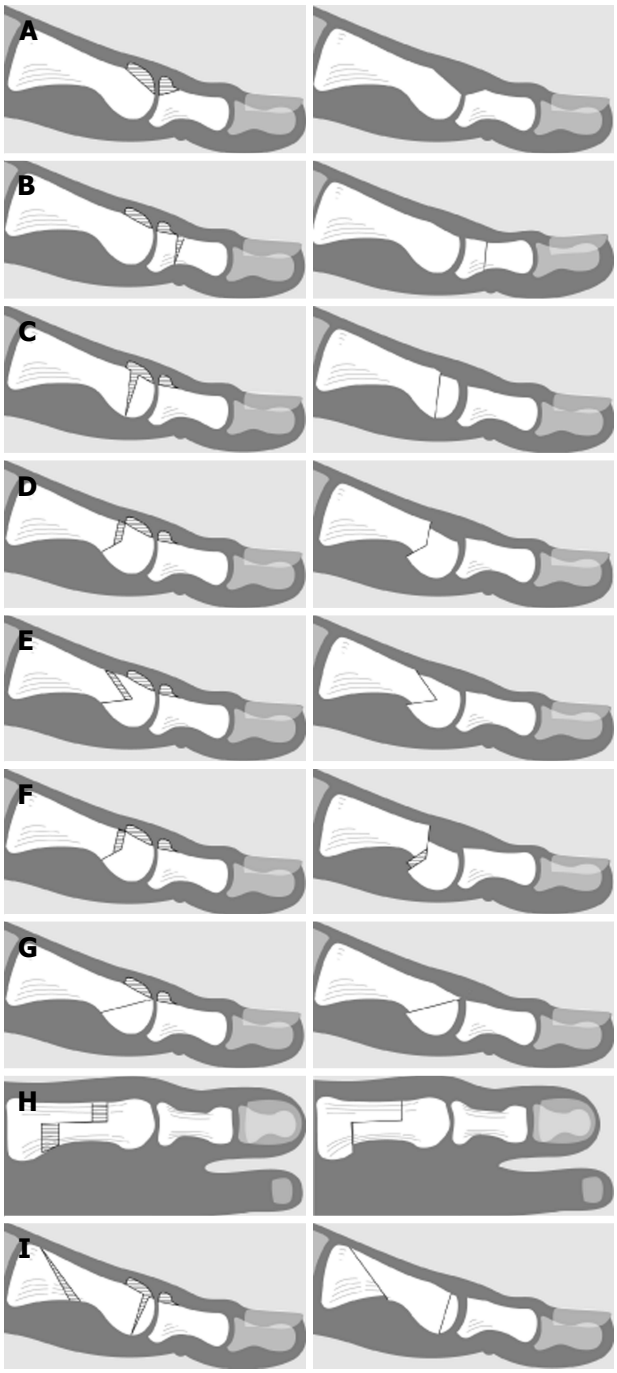

Figure 2 Diagrammatic presentations. A: A Cheilectomy; B: A proximal phalanx osteotomy (Moberg); C: A dorsal closing wedge osteotomy (Watermann); D: A Watermann Green procedure; E: A Youngswick procedure; F: A Reverdin Green osteotomy; G: A distal oblique sliding osteotomy; H: The Sagittal Z osteotomy; I: A Drago procedure.

complication rate were observed for the proximal phalangeal osteotomy although without significant differences. In a retrospective long term follow up study Citron *et al*[54] found complete pain relief shortly after the operation compared with 50% pain relief after an average follow up of 22 years (10 joints). Blyth *et al*[55] retrospectively analysed 18 osteotomies with a follow up period of four years and found significant improvement for pain, footwear difficulties and range of motion. Fourteen of the eighteen patients evaluated the result of the surgery as good or excellent. Southgate *et al*[56] retrospectively compared the proximal phalanx osteotomy (10 joints) to arthrodesis (20 joints) with an average follow up of 12 years. Without performing statistical analysis they found comparable results for both procedures, with less complications but greater changes of the foot pressure for the osteotomies. Mesa-Ramos *et al*[57] evaluated 26 minimal invasive procedures including a proximal phalanx osteotomy in combination with a capsular release and resection of bony spurs. The authors also found a good pain reduction with an increasing AOFSAS score and a high patient satisfaction. Furthermore, few low quality retrospective case series investigated either only the proximal phalanx osteotomy[55] or the combination with cheilectomy[58]. Due to the low quality the only conclusion from these trials is, that the procedure is safe and that it seems to provide relief of symptoms.

Taken together, the evidence available is not good enough to draw a definitive conclusion, whether the proximal phalanx osteotomy is superior to other operative techniques. Nevertheless, the procedure seems to be safe and to reduce pain.

Dorsal closing wedge osteotomy (Watermann)

Watermann was the first to report a dorsal closing wedge trapezoidal osteotomy of the distal metatarsal (Figure 2C)[59]. It was designed to relocate the viable plantar cartilage to a more dorsal location, thereby allowing more dorsiflexion of the hallux[60]. It further causes a decompression of the joint[61]. Cavolo *et al*[61] reported two cases and found an increased range of motion and a high patient satisfaction. To our knowledge there are no further studies available evaluating this technique. From our point of view the major disadvantage is that the osteotomy is relatively unstable due to the perpendicular orientation of the osteotomy in relation to the metatarsal shaft and the resulting difficult fixation[60]. Furthermore, some authors state that this procedure is contraindicated in metatarsus primus elevates, as it could increase the symptoms[60]. From the little evidence available, no recommendation for this procedure can be made.

Watermann Green

The name Watermann Green is misleading as the procedure originally was not designed to rotate the articular cartilage compared to the original Watermann procedure. The procedure describes a 2-arm osteotomy. The dorsal arm consists of two incomplete osteotomies 0.5 cm proximal to the articular cartilage of the first metatarsal head in order to shorten the first metatarsal. If these two cuts form a trapezoid, the proximal articular set angle can be changed. The plantar osteotomy of was originally angled 135 degrees to the dorsal arm and causes a plantar transposition (Figure 2D). This angle can be modified thereby changing the ratio of the first metatarsal shortening to the plantar transposition of the capital fragment. It is often combined with a cheilectomy. It is difficult to

clearly delineate this procedure from the Youngswick osteotomy as the angle between the two limbs can vary depending on whether the shortening or the plantar translation is more important[62] for both procedures resulting in comparable osteotomies.

Dickerson *et al*[63] also retrospectively analysed 28 Watermann Green procedures with an average follow up of four years. Ninety-four percent of all patients reported an extensive relief of pain and 75% experienced a subjective increase of the range of motion. Roukis *et al*[43] prospectively compared the periarticular osteotomy either according to Watermann Green or Youngswick (16 patients) to a resurfacing endoprosthesis (9 patients). The authors did not find significant differences for subjective and objective measures. The only difference found was a reduced metatarsal protrusion distance, but due to the limited follow up of one year, the importance of this finding could not be delineated. Furthermore, the authors do not state how many Watermann Green and how many Youngswick procedures were performed and do not evaluate the results for the two procedures independently. Consequently, the conclusions drawn are limited.

Youngswick

This procedure was introduced by Youngswick[64] in 1982 as a modification of the Chevron osteotomy. First a V-shaped osteotomy is performed with the apex directed distally and two diagonal arms are directed dorsal proximal and plantar proximal at a 60 degree angle. Then, a second osteotomy is performed parallel to the dorsal limb of the first osteotomy (Figure 2E). This results in a shortening of the first metatarsal thereby leading to a decompression of the first MTPJ. Further it tries to plantar translate the first metatarsal head which may decrease metatarsalgia and dorsal impingement.

Giannini *et al*[65] retrospectively evaluated eight patients with less severe hallux rigidus and found an improvement of both the AOFAS score as well as joint motion. Unfortunately no statistical analysis was performed and the results of this procedure were not clearly confined from the results of other osteotomies. Oloff *et al*[66] retrospectively evaluated the outcome of the Youngswick procedure in 28 feet in late stage hallux rigidus. The operation led to a significant improvement of pain, function, range of motion in pain, the AOFAS score and significant less shoe restrictions. The authors reported an overall patient satisfaction of more than 85%, with the patients' chief complaint alleviated in more than 75%. Yet, the authors included combinations of the osteotomy with or without cheilectomy and/or chondroplasty and do not specify the number of these adjunct procedures. This makes the interpretation of these results difficult. Roukis *et al*[43] conducted a prospective trial comparing the Youngswick as well as the Watermann Green osteotomy to a resurfacing endoprothesis. The authors did not find significant differences for the AOFAS scores between the two study groups, while the AOFAS score in both groups significantly increased from pre- to postoperatively. Main limitations of the study were, that it was not identified how many Youngswick and Watermann Green osteotomies were performed. Furthermore, they did not provide a detailed statistical analysis and only performed a follow up to twelve months. They concluded that further long-term studies are needed in order to draw a definitive conclusion. Bryant *et al*[67] demonstrated that the Youngswick procedure changes the plantar peak pressure distribution in the forefoot. Yet, the importance of this finding is still unclear.

Reverdin Green

The Reverdin Green osteotomy is a modification of the Youngswick procedure. After performing the V-shaped osteotomy a second osteotomy is performed parallel to the dorsal limb of the V-shaped osteotomy and the excised bone block is implanted in the plantar limb of the osteotomy to further translate the metatarsal head plantarwards (Figure 2F). The only prospective trial investigating the Reverdin Green osteotomy was performed by Kilmartin[53]. They included three different metatarsal decompression osteotomies, namely the Reverdin Green, the plantar proximal displacement and the shortening Scarf osteotomy and compared them to the proximal phalanx osteotomy. The authors performed 30 Reverdin Green osteotomies, but due to complications they instead continued with a plantar proximal displacement osteotomy. Unfortunately the authors do not state the nature of the complications. Furthermore, they do not report the results of the different osteotomies. The authors state that the decompression osteotomies resulted in a lower patient satisfaction rate and a higher complication rate when compared to the phalangeal osteotomy and conclude that neither of the procedures could be considered definitive for hallux rigidus.

We believe that the results of the Reverdin Green procedure cannot be judged due to the low quality of the data available. Nevertheless, the high rate of reported but not further specified complications must be noted.

Distal oblique sliding osteotomy

This osteotomy is carried out in a distal to proximal direction beginning slightly proximal of the articular surface in an angle of 35°-45° oblique to the sagittal plane. The capital fragment is then displaced proximally and thereby leading to plantar displacement (Figure 2G). Consequently this procedure leads to both a decompression of the first MTPJ and a plantar displacement of the first metatarsal head. Lundeen *et al*[13] initially introduced this concept for treatment of hallux valgus associated with hallux limitus, but it has been adopted for treatment of hallux rigidus only.

Giannini *et al*[65] retrospectively analysed ten joints with low grade hallux rigidus treated by distal oblique sliding osteotomy. The AOFAS score as well as joint motion could be improved. As stated above no statistical analysis was performed and the results of this procedure were not clearly confined from the results of the Youngswick osteotomy. Ronconi *et al*[68] retrospectively evaluated 30 osteotomies with a mean follow up of 21

mo. They demonstrated an increased range of motion of the first MTPJ and a high patient satisfaction rate, while the number of patients with excessive pressure on the second and third metatarsal head increased and the forefoot supination angle decreased postoperatively. Gonzalez *et al*[69] performed a retrospective study of 25 joints. They included less and more severe grades (Ⅱ-Ⅲ according to Drago *et al*[11]). The authors report a subjective satisfaction rate of 96% with a return to normal activity within two months for 80% of all patients and a significant increase of dorsiflexion of 41.2° in average, while 28% reported subjective limitation of joint motion. The authors do not comment on metatarsalgia of the lesser toes. Further limiting is the short follow up of twelve months only, consequently it cannot be evaluated whether this gain in motion can be maintained over time. Malerba *et al*[70] retrospectively analysed 20 joints treated with a distal oblique sliding osteotomy with an average follow-up of 11.1 years. They found a significant increase of the AOFAS score as well as in the range of motion and concluded that the procedure is safe and reliable and provides a high patient satisfaction. Kilmartin[53] operated 15 patients with grade Ⅱ hallux rigidus. The authors state that metatarsal decompression is associated with a high risk of transfer metatarsalgia, but as pointed out above they used three different techniques and do not state the results for each procedure individually. None of these authors observed severe complications such as head necrosis or non-union of the osteotomy.

Sagittal Z osteotomy

The sagittal Z osteotomy also aims at shortening and thereby decompressing the first MTPJ (Figure 2H). Further it allows plantarflexion of the MTPJ. The greatest advantages of this procedure are the high cross-sectional area for bone healing, the great shortening potential and the ability to be fixated with multiple screws in combination with a low risk for avascular necrosis[60]. This procedure was always performed in combination with a cheilectomy. This combinatory approach makes it difficult to determine the outcomes of the osteotomy and cheilectomy. The evidence for this procedure is low. Kissel *et al*[71] evaluated the results of the sagittal Z osteotomy in combination with cheilectomy and chondroplasty and found good patient satisfaction rate without performing statistical analysis. Viegas[72] performed 13 procedures and found only good and excellent results. Again the authors did not acquire objective measurements and consequently they could not perform statistical analysis.

Drago

Drago *et al*[11] presented a double osteotomy consisting of a Watermann procedure at the distal end of the first MT and a proximal plantarflexing osteotomy. The idea was to perform a proximal osteotomy in order to allow more plantarflexion compared to the distal osteotomy. The authors hypothezised, that this could lead to a dorsal jamming of the first MTPJ. In order to prevent this effect and to rotate the articular surface dorsally, they combined this osteotomy with a Watermann procedure (Figure 2I). To our knowledge no study has yet evaluated the results of this procedure.

Modifications

Furthermore, there are various modifications of the previously depicted osteotomies. All studies evaluating such procedures were retrospectively performed without a control group. Yet, all authors claim good results for their procedures.

Derner *et al*[73] presented a modification of the Youngswick procedure. Their first cut is straight in contrast to the V-shaped osteotomy by Youngswick. The second osteotomy is performed parallel to the dorsal two thirds of the first osteotomy. The authors report an increase of the range of motion of 38° with an excellent patient satisfaction of 85%.

Selner *et al*[74] performed a retrospective analysis of a tricorrectional osteotomy (18 joints) with an average follow up of 32 mo. It is basically a modified Youngswick procedure but it allows to change the orientation of the first MTPJ.

Kilmartin[53] performed a shortening Scarf osteotomy in 14 patients. They state that the increase in range of motion is limited but a high number of patients suffered from transfer-metatarsalgia without specifying these results. As depicted above this study suffers multiple shortcomings.

CONCLUSION

The evidence currently available investigating the different procedures is poor. Especially the clinical heterogeneity and the low number of prospective trials are the reason why it is not possible to compare outcomes for patients undergoing the different surgical procedures. Consequently the grade of recommendation for each procedure is low and the choice of the procedure still is an individual decision of the treating surgeon until better prospective trials are available. Nevertheless, joint preserving operations are appealing, because if they fail to relief the symptoms, joint sacrificing operations can still be performed.

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Impact of rheumatoid arthritis on sexual function

Antonio G Tristano

Antonio G Tristano, Rheumatology Department, Centro Médico Docente La Trinidad, 1080-A Caracas, Venezuela
Antonio G Tristano, Centro Medico Carpetana, 28025 Madrid, Spain
Author contributions: Tristano AG solely contributed to this paper.
Correspondence to: Antonio G Tristano, MD, MSc, FACP, Centro Medico Carpetana, Manuel Alvarez 3-4, 28025 Madrid, Spain. antoniotristano@yahoo.com
Telephone: +34-685-475345 Fax: +34-915-256422
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Abstract

Sexuality is a complex aspect of the human being's life and is more than just the sexual act. Normal sexual functioning consists of sexual activity with transition through the phases from arousal to relaxation with no problems, and with a feeling of pleasure, fulfillment and satisfaction. Rheumatic diseases may affect all aspects of life including sexual functioning. The reasons for disturbing sexual functioning are multifactorial and comprise disease-related factors as well as therapy. Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by progressive joint destruction resulting from chronic synovial inflammation. It leads to various degrees of disability, and ultimately has a profound impact on the social, economic, psychological, and sexual aspects of the patient's life. This is a systemic review about the impact of RA on sexual functioning.

Key words: Sexuality; Sexual functioning; Sexual dysfunction; Rheumatoid arthritis

Core tip: Sexual functioning is a neglected area of quality of life in patients with rheumatoid arthritis (RA) that is not routinely addressed by physicians or health professionals. Sexual functioning is also not part of questionnaires frequently used to assess physical function or quality of life. It is therefore important that physicians or any other health professionals in charge of handling these kinds of patients raise the subject of sexuality and discuss it with them. On the other hand, there are not enough studies comparing sexual functioning between RA patients and healthy controls and the impact of the treatments usually used in RA in improving sexual function. Because of the impact of this chronic inflammatory disease on sexual function and because there are not enough overviews about the impact of rheumatoid arthritis on sexual function, this systematic review is intended to cover this important but underestimated problem.

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INTRODUCTION

RA may affect all aspects of life including sexual functioning. These factors include: pain, fatigue, stiffness, functional impairment, depression, anxiety, negative body image, reduced libido, hormonal imbalance, and drug treatment[1].

The percentage of arthritic patients who experience sexual problems ranged in various studies from 31% to 76%[2-5]. The reasons for disturbing sexual functioning are multifactorial and comprise disease-related factors as well as therapy. It can occur before, during and after sexual activities, and can affect sexual health in different perspectives. Normal sexual functioning consists of sexual activity with transition through the phases from arousal to relaxation with no problems, and with a feeling of pleasure, fulfillment and satisfaction[6,7]. Sexuality and its expression

are important for healthy and ill individuals and therefore a crucial part of an individual's self-identity[8].

There are not enough studies comparing sexual functioning between rheumatoid arthritis (RA) patients and healthy controls. However, there is a tendency to find more sexual functioning problems in patients with RA. These patients could experience sexual disability and diminish sexual drive, with pain and depression being the most common symptoms.

SEXUAL FUNCTION IN RA PATIENTS

Sexual functioning is a neglected area of quality of life in patients with RA that is not routinely addressed by physicians or health professionals. Sexual functioning is also not a part of questionnaires frequently used to assess physical function or quality of life. In a recent survey of ten rheumatologists, only 12% of patients seen in their practice were screened for sexual activity. The reasons given by rheumatologists were time constraints, discomfort with the subject, and ambivalence whether such a screening is in their domain or not[9].

The sexual problems in RA could be attributed to physical and psychological variables. Physical variables include difficulties in performing sexual intercourse (sexual disability), while psychological variables include depression, altered body image, worries about partner interest, and diminished sexual drive reflected in both diminished desire and satisfaction[2,10-14]. Difficulty in assuming certain positions when hip or knee movements are limited, dyspareunia due to vaginal dryness in secondary Sjogren's syndrome, and joint pain and fatigue during intercourse are the principal manifestations of sexual disability; the latter is experienced by 50%-61% of RA patients[11,15,16].

The majority of patients with RA are female, and there are differences in sexual health between women and men with RA[17]. It has been shown that women with RA have fewer sexual fantasies and masturbate less than controls, and during intercourse, pain is the dominant problem, as well as limited joint mobility, but there are no differences in satisfaction[15,18].

On the other hand, in a study of male adolescents and adults with juvenile idiopathic arthritis (JIA) masturbation and intercourse were practiced equally between patients and controls, although joint pain during intercourse was significantly more frequent among patients. Moreover, although some patients experienced joint pain associated with greater functional disability as indicated by higher HAQ scores, overall sexual pleasure and satisfaction were preserved[19]. In contrast, van Berlo *et al*[18] found that adult males with RA felt less sexual desire than controls (healthy volunteers); however, patients do not differ from controls regarding sexual satisfaction.

Packham *et al*[20], in a study of 246 adult patients with long-standing JIA, found that 50% of them felt a detrimental effect on body image but only 28.2% of the patients experienced problems with their relationships. The percentage of patients who were sexually active or had had previous sexual experience was 83.3%; 58.3% of these had disease-related sexual problems. Hill *et al*[3] studied 58 adults an average of 14.5 years after the diagnosis of juvenile RA. They found that two thirds had mild to moderate disease, good sexual adjustment and "normal" educational achievement, employment history and lifestyle. One third had severe disease, often with progressive disability; this did not prevent sexual activity but caused some limitations.

A possible explanation of these differences between young and adult patients could be by the fact that JIA manifests in childhood before the establishment of definite links, relationships, and complete growth. Thus, these children are able and have the opportunity and possibility to learn and build up new strategies and developmental mechanisms, such as alternative movements, gestures, and sexual positions, indicating better adaptive skills related to their new reality and life aspects, including sexual functioning[19].

In contrast with this theory, Foster *et al*[21] evaluated quality of life (QOL) in adults with JIA, and they found that the SF-36 scores for bodily pain, general health, physical functioning, vitality, emotion, and social isolation were significantly worse in patients compared with controls, and this trend increased with increasing age of the patients and disease duration. Another important question is whether or not there is any difference between patients with early RA compared with RA patients with long-standing disease. Karlsson *et al*[22], found that patients with early RA were less satisfied with life as a whole at disease onset compared to patients with long standing disease. Patients with early RA also reported low levels of satisfaction with self-care activities, work and sexual life. Women reported that they were more satisfied than men. Notably, women report themselves as less satisfied with sexual life after two years of disease duration. Women with long-standing disease report even lower levels of satisfaction. No correlation was found between disease activity variables and satisfaction with life as a whole. There were, however, positive correlations between disease activity and both satisfaction with partnership and with family life after two years. In patients with early RA compared with those who have chronic RA, the early intervention in addition to the modern early pharmacological treatment practiced today will hopefully lead to a higher degree of life satisfaction.

On the other hand, it is recognized that androgenic status could be related to sexual function. However, hypogonadism or testicular dysfunctions do not necessarily reduce sexual activity. In a study by Gordon *et al*[4], it was shown that RA can cause hypogonadism with sexual dysfunction such as impotence and decreased libido.

IMPACT OF PHYSICAL AND PSYCHOLOGICAL VARIABLES IN SEXUAL FUNCTION IN RA PATIENTS

The two main sexual problems experienced in RA pa-

tients are: difficulties in performing sexual intercourse (sexual disability); and diminished sexual drive, reflected in both diminished desire and satisfaction.

Hill *et al*[23] found that 56% of RA patients reported that arthritis placed limitations on sexual intercourse mainly due to fatigue and pain. It has been shown that when the hip joint is severely affected, total hip replacement improves sexual disability to pre-disease levels in 50% of sexually active patients with RA[24]. On the other hand, diminished sexual drive is manifested by a decrease in desire in 50%-60% of RA patients, reduced frequency of intercourse in up to 73% of patients, increase in aversion to sexual interactions, and diminished sexual satisfaction over time compared to pre-disease levels[11,15,16].

Elst *et al*[25] showed that 50% of patients with RA lost sexual interest during the course of their disease and 60% were dissatisfied with quality of their sex life. However, Ostensen *et al*[26], in a study of patients with history of juvenile chronic arthritis (JCA), showed that in the younger age group and patients with inactive or less active disease, sexual activity and frequency of intercourse was not different from healthy, age-matched controls. Furthermore, female patients who shared characteristics of marital status with their healthy counterparts showed a similar attitude to sexual activity.

Other studies attributed sexual problems in RA to psychological variables such as depression, altered body image, and worries about partner interest[2,10-14].

Moreover, it has been found that in healthy females, anxiety is associated with reduced frequency of intercourse, whereas depression is an important factor in both loss of libido and loss of sexual satisfaction[13,14].

Kraaimaat *et al*[5] found that physical disability, pain, and depression all contribute to the intrusiveness of RA on sexuality. Gutweniger *et al*[27] found that morning stiffness in female RA patients plays an important role in their feelings of being a handicap. Female RA patients with a high degree of morning stiffness also had significantly more worries about body image and experienced more sexual dissatisfaction than females with lower degrees of morning stiffness.

Recently, Abdel-Nasser *et al*[28] studied 52 female patients with RA. They found that 32 patients had difficulties in sexual performance including 9 patients who were totally unable to engage in sexual intercourse because of arthritis. More than 60% of female RA patients experienced variable degrees of sexual disability and diminished sexual desire and satisfaction. Difficulties in sexual performance were related more to disability and hip involvement, while diminished desire and satisfaction were influenced more by perceived pain, age and depression. They also found that 27% of their patients had genital tract abnormalities that could influence sexual performance. However, these abnormalities can be easily controlled by prompt gynecological referral.

In another recent study, van Berlo *et al*[18] found that male patients felt less sexual desire, and female patients masturbated and fantasized less than controls. Differences in satisfaction were not found. Male and female patients did not experience more sexual problems than controls. Up to 41% of the men, and up to 51% of the women have troubles with several joints during sexual activities. Medications influencing ejaculation in men correlated with distress with orgasm.

Finally, El Miedany *et al*[29] showed that among 231 rheumatoid arthritis patients included, 49/91 (53.8%) men and 64/140 (45.7%) women reported sexual dysfunction. Erectile dysfunction in men, and problems with orgasm, arousal, and satisfaction in women, were the most prevalent manifestations.

IMPACT OF RA IN COUPLE'S RELATIONSHIP

Majerovitz *et al*[30], when the relationship between functional disability and sexual satisfaction for both rheumatic disease patients and their spouses was examined and their levels of sexual satisfaction to those of healthy comparison couples were compared, found that rheumatic disease and comparison couples did not differ in sexual dissatisfaction. However, greater functional disability was related to greater sexual dissatisfaction for patients and spouses.

Bermas *et al*[31], in a cross-sectional survey of 79 persons with RA and 78 spouses, correlated their marital satisfaction. They found that patients and spouses were generally satisfied with their marriages. Moreover, it was showed that lower marital satisfaction in patients was associated with higher education level, patient's greater use of escape into fantasy, patient's greater use of finding blame, and spouse's higher use of escape into fantasy. Spouses less satisfied with their marriages were more likely to use passive acceptance and less likely to find blame. Female spouses were less likely to be satisfied in their marriages than male spouses. They concluded that certain passive coping styles, more highly educated patients and female spouses are associated with lower marital satisfaction in persons with RA and their spouses.

Kraaimaat *et al*[5] studied whether physical disability, pain, depressive mood, and criticism by the spouse are differentially related to intrusiveness of RA on sexuality in male and female patients. They found that physical disability, pain, and, to a lesser extent, depression were found to contribute to intrusiveness of RA on sexuality. However, female patients, compared with male patients, appeared to have lower levels of mobility and self-care. They suggested that differences in sexual motivation between men and women might have been influential in the absence of gender differences in intrusiveness.

TREATMENT RECOMMENDATIONS

One of the most important issues about the treatment of sexual dysfunction associated to RA is the fact that neither the sexual functioning is routinely addressed by physicians or health professionals, nor is it part of frequently used

Table 1 Factors associated to sexual dysfunction in rheumatoid arthritis and recommendations for specific symptoms

Sexual dysfunction	Factors implicated	Recommendations
Sexual disability	Limited mobility	Change position
	Pain, fatigue	Analgesic, heat, and muscle
	Morning stiffness	Relaxation before activity surgery
Dyspareunia	Vaginal dryness	Vaginal lubrication, estrogen cream
Diminished desire	Anxiety, depression	Counseling, antidepressive
Diminished satisfaction	Altered body image	Drugs[1]
Impotence	Hormonal imbalance	Sidenafil, sex therapy

[1]Could decrease libido (Modified from Ref[33]).

questionnaires to assess physical function or quality of life. For example, in Europe, United Kingdom health professionals should monitor the sexual activity of RA patients; however, a recent study showed that 66% of RA patients were never asked about the impact of RA on their sexual lives[23]. The common problem is communication, so an open communication including inquiry about sexuality in routine care is the first step to improve the situation. To allow the patients to present problems and concerns without embarrassment is also important. After an open communication is achieved, the treatment will depend on the specific patient's symptoms (Table 1). However, there are some general recommendations including: discussion of the problems with the partner, principally about the partner's fear in causing pain or distress during sexual intercourse; exploring different positions; using analgesic drugs, heat, and muscle relaxants before sexual activity in order to decrease pain; exploring alternative methods of sexual expression; and physiotherapy[32-34].

CONCLUSION

Sexual function in patients with rheumatoid arthritis has not been well studied. There are not enough studies comparing sexual functioning between RA patients and healthy controls and the impact of treatments usually used in RA in improving sexual function.

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Perioperative management of the patient with rheumatoid arthritis

Megan L Krause, Eric L Matteson

Megan L Krause, Eric L Matteson, Division of Rheumatology, Department of Medicine, Mayo Clinic, Rochester, MN 55905, United States
Author contributions: Krause ML and Matteson EL solely contributed to this paper.
Correspondence to: Eric L Matteson, MD, MPH, Professor, Division of Rheumatology, Department of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States. matteson.eric@mayo.edu
Telephone: +1-507-2848450 Fax: +1-507-2840564
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Abstract

A multidisciplinary approach is required to care for patients with rheumatoid arthritis (RA) in the perioperative period. In preparation for surgery, patients must have a cardiovascular risk assessment performed due to the high risk of heart disease in patients with RA. Treatment of RA is with immunomodulatory medications, which present unique challenges for the perioperative period. Currently, there is no consensus on how to manage disease modifying antirheumatic drug (DMARD) therapy in the perioperative setting. Much of the data to guide therapy is based on retrospective cohort data. Choices regarding DMARDs require an individualized approach with collaboration between surgeons and rheumatologists. Consensus regarding biologic therapy is to hold the therapy in the perioperative period with the length of time dictated by the half-life of the medication. Special attention is required at the time of surgery for potential need for stress dose steroids. Further, there must be close communication with anesthesiologists in terms of airway management particularly in light of the risk for cervical spine disease. There are no consensus guidelines regarding the requirement for cervical spine radiographs prior to surgery. However, history and exam alone cannot be relied upon to identify cervical spine disease. Patients with RA who undergo joint replacement arthroplasty are at higher risk for infection and dislocation compared to patients with osteoarthritis, necessitating particular vigilance in postoperative follow up. This review summarizes available evidence regarding perioperative management of patients with RA.

Key words: Rheumatoid arthritis; Perioperative management; Disease modifying antirheumatic drugs; Tumor necrosis factor inhibitors; Postsurgical complications

Core tip: Patients with rheumatoid arthritis (RA) require specialized care in the perioperative setting. Special attention must be given to management of immunomodulatory therapies, temporarily suspending their administration in the perioperative period. Patients on corticosteroids may require stress doses. Anesthesiologists should be aware of the possibility of cervical spine disease and appropriate measures, including obtaining cervical spine radiographs preoperatively. Patient with RA are at heightened infection risk because of their disease and its treatment, requiring particular vigilance in the postoperative period.

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INTRODUCTION

Unique factors impact the perioperative care of patients with rheumatoid arthritis (RA). Not only does a patient with RA require routine perioperative management in the

setting of elective surgery, there are also disease specific management issues such as immunosuppressants and care of the cervical spine.

PREOPERATIVE EVALUATION

General preoperative evaluation

RA, both the disease itself as well as the medications used in therapy, can impact multiple organ systems beyond the joints. Prior to elective surgery, patients must be carefully evaluated for organ involvement that may impact their fitness for surgery including cardiovascular, pulmonary, hepatic, and hematologic.

Cardiovascular risk evaluation

Prior to elective surgery, the risk of perioperative cardiovascular events must be assessed. Overall, individuals with rheumatoid arthritis have a higher risk of myocardial infarction which is similar to individuals with diabetes mellitus or a person 10 years older than the age of the patient[1]. There is an increased risk of cardiovascular related death for patients with RA as compared to the general population[2]. Traditional risk factors do not completely explain the risk for cardiovascular disease in patients with RA[3]. To complicate evaluation further, patients with RA often present with fewer symptoms of angina and have higher rates of unrecognized disease[4]. While RA itself has not been demonstrated to be an independent risk factor for perioperative death or cardiovascular events, cardiovascular risk must be carefully evaluated[5].

As part of the American College of Cardiology/American Heart Association (ACC/AHA) perioperative guidelines, in the setting of emergent surgery, no additional cardiac evaluation is recommended. However, in the elective setting, first, active cardiac conditions must be identified which would require further cardiovascular evaluation prior to surgery including unstable coronary syndromes, decompensated heart failure, significant arrhythmias, or severe valvular disease.

If no active cardiac conditions are present, then the next step is to determine the risk of the procedure. Low risk procedures do not require further evaluation. Most orthopedic surgeries are considered moderate risk. In the setting of moderate risk procedures, identifying the clinical risk factors stratifies the perioperative risk and, therefore, the recommendations for further perioperative evaluation. If a patient is able to complete 4 metabolic equivalents (METs) then the perioperative risk is low enough to not require further evaluation[6]. Four METs could be equated to the ability to walk up a flight of stairs[6,7]. Unfortunately, patients with RA are often unable to be readily assessed for their functional capacity as a consequence of pain or disability related to arthritis[8].

In those with moderate risk procedures and inability or unknown ability to complete 4 METs, then further cardiovascular risk stratification is needed. Different risk calculators have been generated to predict perioperative cardiovascular risk. The Revised Cardiac Risk Index (RCRI), as incorporated into the ACC/AHA algorithm, includes ischemic heart disease, compensated or prior heart failure, use of insulin, renal insufficiency (creatinine > 2.0 mg/dL), and cerebrovascular disease as important comorbidities[9]. A more recent cardiac risk calculator has been demonstrated to perform better than the RCRI based on the type of surgery, functional status, abnormal creatinine, American Society of Anesthesiologists class, and age[10]. If risk is determined to be low, patients can proceed to surgery. If not, further consultations will be required[6].

Evaluation for cervical spine disease

RA can involve the cervical spine with important implications for perioperative management, particularly positioning for anesthesia. The prevalence of cervical instability based on radiographs differs among cohorts. The rates of cervical instability in patients undergoing elective joint replacement can be as high as 61%[11]. Anterior atlantoaxial subluxation has been estimated to range from 18%-49% with the majority of cohorts demonstrating approximately 20%[11-15]. Atlantoaxial impaction ranges from 12%-26%[11,13,14]. Subaxial subluxation has varying estimates of 9.0%-43.6%[11-15]. Evaluating the posterior atlanto-odontoid interval can help assess the risk of paralysis in patients with RA. A cut-off of ⩽ 14 mm is associated with increased risk of paralysis[16].

Older age, longer duration of RA, erosions, increased disease activity, and increased disability are associated with higher rates of subluxation[14]. Despite the advances in RA therapy, between 1983 and 2001 there were no changes in the number of hospitalizations for cervical spine disease related to RA[17]. Symptoms alone cannot be relied upon to signal the presence of relevant cervical spine disease, as in one cohort only 50% of those with radiographic abnormalities had evidence based on history or physical evaluation such as neck pain, neck stiffness, or radicular symptoms[11]. Even radicular pain occurred at similar rates between patients with or without subluxation[14].

In terms of the choice of imaging modality, the majority of studies are based on conventional radiography of the cervical spine. In one study evaluating computed tomography (CT) and plain radiographs, in 1 out of 12 patients, the CT demonstrated information not identified by plain radiograph. In that case, the plain radiographs identified posterior subluxation, but spinal cord impingement was only identified on CT[18]. Magnetic resonance imaging (MRI) findings including atlantoaxial spinal canal stenosis, atlantoaxial cervical cord compression, and subaxial myelopathy are associated with neurologic dysfunction[19]. However, MRI underestimates the degree of anterior atlantoaxial subluxation[20].

There are currently no guidelines regarding radiographic imaging in patients pursuing surgery. In routine clinical practice, there is variability regarding if and what imaging studies should be performed. In a retrospective review, 21% of patients undergoing their first surgery had

no cervical spine plain radiographs performed prior to surgery. Of the patients who did have plain radiographs performed, 36% were inadequate as defined by images of a lateral view of the neck in neutral position and frontal view of entire cervical spine only. Plain radiographs were felt to be complete if there were lateral views of neck in flexion and extension plus frontal view of entire cervical spine plus frontal open-mouth odontoid view. Complete views were only performed in 5% of patients. Adequate views as defined by lateral views of neck in flexion and extension plus frontal view of entire cervical spine were obtained in 59%[12]. In a more recent retrospective evaluation utilizing the same definitions of adequacy of plain radiographs, half of patients had no cervical spine plain radiographs performed within 2 years while 4% had complete plain radiographs, in contrast to 18% with inadequate studies[21].

In an attempt to optimize cost effective care, radiology imaging is most important if it impacts management. In an older retrospective cohort, there was a difference in the type of anesthesia in those known to have cervical instability in contrast to those without. In patients with known cervical instability, regional blocks and general anesthesia with flexible fiberoptic bronchoscope under local anesthesia were more commonly used than general anesthesia with spontaneous respiration with laryngeal mask airway or facemask or direct laryngoscopy[12]. In a more recent evaluation, neither completion of cervical spine plain radiographs nor radiographic abnormalities were associated with the airway management techniques[21].

While there are no clinical guidelines regarding preoperative imaging of the cervical spine in patients with RA, clinicians must be aware of the risk of cervical instability which may be asymptomatic. If performed, radiology imaging should include at least flexion-extension views of the cervical spine. Close communication between surgeons, anesthesiologists, and rheumatologists is critical to provide the best care for these patients.

Medication management

Patients with RA suffer higher rates of infection at baseline compared to other patients without RA[22]. This underscores the added importance of optimizing the use of immunosuppressants in the perioperative period. The risk of infection/delayed wound healing must be balanced with the risk of flare which if occurs may require an escalation of immunosuppressants such as corticosteroids.

Traditional, nonbiologic disease modifying antirheumatic drugs

Methotrexate: Methotrexate is widely considered the cornerstone of RA management[23,24]. The majority of data regarding the perioperative safety of methotrexate are from retrospective cohort studies. Five retrospective cohort studies did not demonstrate any difference in perioperative infection or wound complications between those who continued or discontinued methotrexate in the perioperative period[25-29]. In a retrospective evaluation of total joint replacements, 60 patients who had received methotrexate within 4 wk of surgery compared to 61 not receiving methotrexate, there was no difference in postoperative complications including infection or wound healing effects. The group who had received methotrexate within 4 wk of surgery was further divided into those who continued it throughout the perioperative time period and those who stopped; these 2 groups had no difference in postoperative complications. Of note, these patients were on low dose methotrexate, mean weekly dose 8 mg with a range of 5-12.5 mg. Further, it is unclear if the disease severity was similar among the 2 groups; they were similar in terms of duration of disease and concurrent prednisone dose[25].

Retrospective review of hand surgery in patients who continued on their routine treatment for RA including methotrexate, with median weekly dose of 10 mg, did not demonstrate an increased risk of infection[26]. Another retrospective review demonstrated no increased risk of infection in 66 patients who received methotrexate. The mean dose or details regarding discontinuation or continuation are not available[27]. In a retrospective chart review evaluating 42 patients with RA who underwent reconstructive surgery of the hand and wrist, 15 were on methotrexate at the time of surgery with mean dose 10.7 mg per week. None of these patients suffered from infection or delay in wound healing[28]. A further retrospective review of 122 patients undergoing 201 elective surgeries receiving low dose methotrexate, 2-8 mg/wk, did not demonstrate any difference in postoperative infection or rates of flare between those who continued or discontinued methotrexate perioperatively[29].

A prospective evaluation of 201 patients (94% of whom had RA) were enrolled to an open label study in which they continued their stable therapy of methotrexate, leflunomide, or anti-tumor necrosis factor-α (TNF-α) therapy during the perioperative time period. There was no increased risk of perioperative infection in those who continued on methotrexate[30]. A case-control study evaluating patients who underwent foot or ankle surgery did not demonstrate an association with methotrexate, with unclear dosing, and infection or wound healing complications[31].

Confounders that may have led providers to recommend holding versus continuing methotrexate can complicate interpretation of retrospective cohort and case-control studies. There are differing results from randomized trials regarding methotrexate. One randomized trial demonstrated no difference between those who continued or discontinued methotrexate in the perioperative period. In this randomized unblinded study regarding continuation versus discontinuation of methotrexate with a total of 89 cases, there were no postoperative infections in either group. There was no difference in prolonged wound healing, 6/50 (12%) in those who discontinued and 4/39 (10%) in those who did not discontinue methotrexate[32].

In contrast, in one randomized trial evaluating methotrexate continuation versus discontinuation, the surgical complications and infection frequency occurred less often in those who remained on methotrexate than those who discontinued. Further, there was an increased risk of rheumatoid arthritis flare, occurring in 8% of patients, in those who discontinued its use. However, it should be noted that the patients were doses of methotrexate (7.5-10 mg weekly) than usually prescribed for RA management[33].

One study demonstrated an increased risk of continuation of methotrexate in the perioperative period. This was a small prospective trial of 32 patients, in which patients were assigned either to continue methotrexate or hold for a total of 2 wk based on the preference of the patient's rheumatologist/orthopedic surgeon and therefore not randomized. The mean weekly methotrexate dose was 12.5-13.1 mg. No infections occurred in those who held the methotrexate while 4 infections occurred in those who continued methotrexate ($P = 0.03$). No patients suffered a flare of RA in either group[34].

Due to its frequent use, management of methotrexate in the perioperative period will be an issue commonly faced by clinicians. The majority of studies demonstrate safety of methotrexate in the perioperative period; however much of this data comes from retrospective cohort studies.

Leflunomide: Conflicting data are available regarding perioperative use of leflunomide. In one study, patients with RA treated with leflunomide were randomized to continue versus hold for 2 wk before and after hip, knee, or elbow arthroplasty. There was no difference in the number of infections between the groups. All patients who developed infection were also taking prednisone in addition to their leflunomide. However, corticosteroids were also not found to be associated with higher risk of infection[35]. In contrast, in another prospective study, patients with predominantly RA were prospectively followed as they continued leflunomide therapy during the perioperative time period. Leflunomide was associated with a higher risk of postoperative wound complication with an odds ratio of 3.48[30].

Cholestyramine can be utilized to facilitate leflunomide drug elimination if required in the setting of leflunomide associated adverse reactions[36]. However, advanced planning is required as protocols with cholestyramine require 11 d of therapy[37].

Hydroxychloroquine: Limited data is available regarding hydroxychloroquine and risk of perioperative infection. In one case-control study evaluating infectious complications, there was no difference in the use of hydroxychloroquine[31]. Further, an additional retrospective study did not demonstrate any association with risk of infection[27]. Expert opinion frequently recommends continuation of hydroxychloroquine in the perioperative period[8,38].

Other nonbiologic traditional DMARDs: There are only limited data regarding other DMARDs. In one retrospective study, azathioprine, while associated with infection in univariate analysis did not demonstrate the association with multivariate analysis[27]. Frequently, azathioprine is recommended to be continued in the perioperative time period with some physicians recommending holding the day of surgery[8,38]. Similarly, sulfasalazine is typically recommended to be continued perioperatively with some physicians holding it the day of surgery. In one retrospective study, sulfasalazine was associated with a lower risk of perioperative infection[39]. In all cases, renal function, which affects the elimination of many DMARDs, must be closely monitored[8,38].

The American College of Rheumatology does not provide recommendations on the perioperative management of nonbiologic DMARDs due to conflicting data[40]. Medication management requires a risk-benefit discussion between patients, surgeons, and rheumatologists.

Biologics

TNFα Inhibitors: Multiple studies have evaluated the perioperative risk of TNF-α inhibitors as compared to traditional DMARDs. A single prospective study demonstrated that TNF-α inhibitors compared to other DMARDs were associated with reduced complications of infection and wound healing with TNF-α inhibitor use[41]. In a retrospective cohort study, there was no difference in adverse events for surgical wounds, time for wound healing, or duration of fever when comparing TNF-α inhibitors and DMARDs. TNF inhibitors were held at the time of surgery[42]. In contrast, in a retrospective evaluation comparing patients who used traditional DMARDs versus TNF-α inhibitors, there was an increased risk of surgical site infection with TNF-α inhibitors, OR 21.8. All of these patients had stopped TNF-α 2-4 wk before surgery. Further, there was a higher rate of deep venous thrombosis[43].

A retrospective parallel cohort demonstrated no increased risk of infection with continuation of TNF-α inhibitor therapy perioperatively (8.7%) as compared to cessation (5.8%). The highest risk for perioperative infection in this study was previous surgical site infection[39]. In a cohort of patients treated with TNF-α inhibitors, there was no difference in rates of complications if the therapy was stopped greater than 5 half-lives prior to surgery versus not stopped. Also, there was no difference if it was stopped 2 half-lives before surgery as compared to less than 2 half-lives or not discontinued[44].

In a retrospective cohort of 16 patients all of whom were treated with TNF-α inhibitor therapy, there were no perioperative infections either in the group who continued the therapy or those who discontinued. There was a single episode of RA disease flare that occurred in a patient who stopped etanercept at the time of triple arthrodesis of the ankle[45]. In a retrospective evaluation of 30 patients who underwent 50 surgical procedures, there were no episodes of major infections in either patients who continued or discontinued the TNF-α therapy.

There were 3 cases which experienced delay in wound healing by 1-2 wk. It is not specified if these were in individuals who continued or discontinued their therapy. There were higher rates of flare in those who discontinued therapy at the time of surgery rather than those that continued (P = 0.02) with overall rate of 12% flares in the cohort[46].

A retrospective review of a cohort of patients treated with infliximab with mean of 4 wk between infliximab infusion and surgery revealed low rates of infection (3.8%, 2 cases). There was no association with the time duration of latest infliximab infusion and infection[47].

A separate retrospective analysis of 91 patients who underwent orthopedic surgery revealed that TNF-α inhibitor therapy was associated with serious postoperative infection (septic arthritis, osteomyelitis, or deep wound infection) in multivariate analysis, OR 5.3[48]. In a retrospective review of patients with RA who underwent total knee arthroplasty, a total of 268 replacements in 248 patients, the cohort included patients who were treated with TNF-α inhibitor therapy versus those who were not. Of those treated with TNF-α inhibitors, 87% were recommended to discontinue therapy in the perioperative period with the remaining 13% having no documentation regarding the recommendation. There were 10 episodes (4.3%) of infection with a single deep joint infection. There was no difference in the rates of infection[49].

A further retrospective evaluation of total hip and total knee arthroplasties reported that 5.7% of cases had superficial surgical site infections while 0.7% experienced infections requiring removal of the artificial joint prosthesis. In multivariate logistic regression, the use of biologic DMARDs (OR, 5.69) was associated with infection. When evaluating individual TNF-α inhibitors, infliximab (OR, 9.80) and etanercept (OR, 9.16) when adjusted for disease duration were associated with increased risk of infection. TNF-α inhibitors were stopped prior to surgery[50].

Cohorts of RA patients treated with and without biologics were compared in a review of patients in whom infliximab, etanercept, adalimumab, and tocilizumab had been stopped between 2-4 wk before surgery. There was no difference in complications of wound healing. The rates of infection were very low with 4 infections out of 554 surgeries and no association was found with biologic therapy[51].

Clinical guidelines vary in regard to their recommendations of TNF-α inhibitor management in the perioperative period[52,53]. Some guidelines do not provide specific details but rather recommend weighing the risks of infection/wound healing with risk of flare with discontinuation[54]. American College of Rheumatology guidelines recommend holding biologic therapy for at least 1 wk before and after surgery with further adjustment to that time frame depending on the pharmacokinetics of the individual agent[40].

Other biologic therapy: Less information is available regarding other biologic therapy in the perioperative setting. Tocilizumab was evaluated in the perioperative setting of 161 surgeries. Tocilizumab was held for mean of 23.5 d with range of 1-71. Three (1.9%) surgical site infections occurred. Wound healing delays occurred in 20 (12.4%). There were high rates of concurrent corticosteroid use (74.5%). Multiple logistic regression demonstrated corticosteroid use, foot surgery, and spinal surgery as risks for delayed wound healing[55]. In a smaller cohort of 22 patients treated with tocilizumab, no postoperative infections occurred. Surgery occurred in between infusions of tocilizumab with a mean of 16.1 d from the previous infusion. No patient required a delay in the next infusion[56].

Seven patients who underwent 8 surgeries were being treated with abatacept. The mean discontinuation time prior to surgery was 15.9 d with a total time of discontinuation of 33.1 d. None of these patients experienced surgical site infections or delays in wound healing[57].

Finally, a review of 133 patient undergoing 140 surgeries (including 94 orthopedic surgeries) on average 6.4 mo following a last rituximab infusion reported a postoperative infection rate of 6.7%, including one death due to septic shock[58]. With little data available to guide decisions, an individualized plan is required for management of non-TNF biologic therapy.

AT TIME OF SURGERY

Stress dose corticosteroids

Corticosteroid use is a major risk factor for infection in patients with RA[59]. This risk is dose related emphasizing the importance of balancing risks of adrenal insufficiency with infection[60]. Not all patients receiving corticosteroids require stress dosing to prevent adrenal insufficiency. There is not a single dose cut-off that can be utilized to determine which patients may be at risk, as even low dose corticosteroids can lead to disruption of the hypothalamic-pituitary axis[61]. An ACTH stimulation test when performed with a normal result is predictive of an appropriate response during surgery[62]. Using 250 μg of cosyntropin, a cortisol value at time point zero, 30 or 60 min following injection greater than or equal to 20 μg indicates a normal response[8].

In patients requiring stress dose corticosteroids in the perioperative timeframe, the does required depends on the type of surgery. Most orthopedic surgeries such as joint replacement are representative of a moderate surgical stress. Other examples of moderate surgical stress beyond arthroplasties include hemicolectomy. A severe surgical stress would include major cardiothoracic surgery. Examples of minor surgical stress include dental procedures, colonoscopy, and inguinal hernia repair. On the day of the procedure, hydrocortisone 50-75 mg or methylprednisolone 10-15 mg intravenously can be used with the does tapered to the routine corticosteroid dose in 1-2 d[63].

Airway management

Rheumatoid arthritis can result in wide ranging involve-

ment of the larynx including cricoarytenoid arthritis and rheumatoid nodules[64,65]. The use of laryngeal mask airway can exacerbate laryngeal rheumatoid arthritis, which may be undiagnosed prior to surgery[66]. This possibility must be included in the differential diagnosis in the setting of acute upper airway obstruction particularly following extubation[67]. An emergent cricothyroidotomy is sometimes required for treatment[68].

AFTER SURGERY

Postoperative complications

Patient with RA must be followed closely in the postoperative time period as well. Patients with RA suffer higher rates of prosthetic joint infections compared to matched controls with osteoarthritis (hazard ratio of 4). The risk is increased in the setting of revision arthroplasty and previous prosthetic infection[69]. Data from a large registry in Norway revealed the risk of revision of arthroplasty of the hip or knee for infection to be higher in patients with RA as compared to osteoarthritis[70].

Staphylococcus was the most likely infectious cause of total joint arthroplasty infection in the setting of TNF-α inhibitor therapy according to a case control study. In multivariate analysis, primary arthroplasty or revision within the previous year (odds ratio, OR, 88.3) and prednisone use (OR, 5.0 per 5 mg/d) were identified as risk factors for infection[71]. In 200 episodes of prosthetic joint infection, the rate of 5 year survival free of treatment failure was 56%. The rates of survival free of treatment failure were highest with 2-stage exchange (79%) followed by resection arthroplasty (61%) with the lowest rates occurring with debridement and retention of components (32%)[72].

A meta-analysis demonstrated the increased risk of total hip arthroplasty dislocation in patients with RA as compared to osteoarthritis, OR 2.74. In terms of overall rates of revision for hip arthroplasty, there was a higher rate of revision within 5 years of patients with RA as compared to osteoarthritis, OR 1.33. There was no difference in infection rates between 6-10 years following revision arthroplasty. After 10 years, there were lower rates of revision in patients with RA, OR 0.28. In terms of revision for knee arthroplasty, there was a higher rate in the first years for patients with RA with OR 1.24. There was no difference detected after 5 years. There was no difference in 90 d mortality or venous thromboembolism rates between patients with RA *vs* osteoarthritis[73].

Patients with RA require special attention because of their disease, treatments and comorbidities in the perioperative period. Despite the decreased rates of orthopedic surgeries for RA patients, surgery continues to be a modality that is required for some patients[74]. Successful perioperative management requires a multidisciplinary approach including orthopedic surgeons, rheumatologists, anesthesiologists and radiologists.

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Advances in the treatment of cervical rheumatoid: Less surgery and less morbidity

Grant W Mallory, Sasha R Halasz, Michelle J Clarke

Grant W Mallory, Sasha R Halasz, Michelle J Clarke, Department of Neurologic Surgery, Mayo Clinic, Rochester, MN 55905, United States
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Correspondence to: Michelle J Clarke, MD, Associate Professor of Neurosurgery, Department of Neurologic Surgery, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States. clarke.michelle@mayo.edu
Telephone: +1-507-7746840 Fax: +1-507-2845206
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Abstract

Rheumatoid arthritis is a chronic systemic inflammatory disease that often affects the cervical spine. While it was initially thought that cervical involvement was innocuous, natural history studies have substantiated the progressive nature of untreated disease. Over the past 50 years, there has been further elucidation in the pathophysiology of the disease, as well as significant advancements in medical and surgical therapy. The introduction of disease modifying drugs and biologic agents has reduced the amount of patients with advanced stages of the disease needing surgery. Advancement in instrumentation techniques has improved patient outcomes and fusion rates. The introduction of endoscopic approaches for ventral decompression may further lower surgical morbidity. In this review, we give a brief overview of the pertinent positives of the disease. A discussion of historical techniques and the evolution of surgical therapy into the modern era is provided. With improved medical therapies and less invasive approaches, we will likely continue to see less advanced cases of disease and less surgical morbidity. Nonetheless, a thorough understanding of the disease is crucial, as its systemic involvement and need for continued medical therapy have tremendous impact on overall complications and outcomes even in patients being seen for standard degenerative disease with comorbid rheumatoid.

Key words: Atlantoaxial instability; Cranial settling; Subaxial subluxation; Cervical; Surgery; Morbidity; Rheumatoid arthritis

Core tip: This review summarizes the pertinent features of cervical rheumatoid arthritis. A discussion of important preoperative considerations and surgical approaches in a modern era with advancing medical therapy is provided. The evolution of surgical techniques and outcomes are also highlighted.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic relapsing inflammatory disorder that primarily affects synovial joints with varying degrees of systemic involvement[1,2]. Although an awareness of the disease and its propensity to involve the cervical spine were appreciated as early as the 18th and 19th century[3,4], an observational approach was generally advocated until Matthew and colleagues' seminal natural

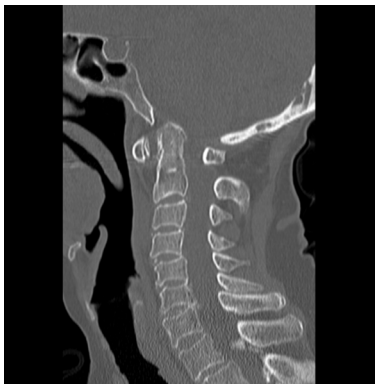

Figure 1 Sagittal computed tomography of the cervical spine of an 82-year-old female with rheumatoid arthritis and neck pain with cranial settling.

history study demonstrated clear radiographic and neurologic progression[5]. Several studies have since confirmed the progressive and grim natural history of untreated disease of the cervical spine[6-11]. Thus, a role for surgery was established, and it is now widely accepted that operative intervention should ideally occur before neurologic deterioration, particularly given poor outcomes with advanced disease[6]. With advancement in surgical instrumentation and newer medical therapies, however, there have been recent trends towards less surgery and less invasive approaches, along with a decrease in surgical volume as biologic agents have been shown to reduce the amount of de novo cervical lesions[12,13]. In this review, we provide an overview of the pertinent disease features of rheumatoid and important preoperative considerations for surgical planning. Finally, we briefly discuss the evolution of surgical therapies and modern techniques and emerging techniques and their impact on overall morbidity and surgical outcomes.

PRESENTATION

Rheumatoid arthritis typically presents in the 4th and 5th decades of life, and more often afflicts females than males (2-4 fold)[1]. The prevalence in the United States among whites is estimated to be 0.5%-1% (roughly 1.3 million adults)[14,15]. RA accounts for significant disability and loss of work force worldwide[16]. Half of those affected are unable to work within 10 years of disease onset and life time costs rival that of coronary artery disease and stroke[1].

In general, rheumatoid can manifest in any joint. However, the metacarpophalangeal and proximal interphalangeal joints of the hand, the metatarsophalangeal joints of the feet, and the wrists and knee are most often affected[17]. Given the systemic nature of the disease, patients can also present with constitutional symptoms or a myriad of extra-articular manifestations. Extra-articular manifestations have a higher incidence in those with an accompanying vasculitis and may range from subcutaneous nodules and nail bed thrombi to pleurisy, pulmonary fibrosis, and/or pericarditis[18-23]. Other peripheral complications include cutaneous ulcers and neuropathy[18,24]. The cervical region is the most frequently involved area of the spine and can show radiographic changes in up to 88%[25], though both the thoracic and lumbar spine can also be involved[26,27].

PATHOPHYSIOLOGY AND CERVICAL MANIFESTATIONS

A general understanding of RA pathophysiology can help explain its presentation in patients whose cervical spine is affected by the disease. While the precise etiology has yet to be fully elucidated, the prevailing hypothesis is that RA results from a humoral autoimmune response arising from exposure to an environmental agent (*i.e.*, Epstein-Barr Virus) in genetically predisposed individuals[28,29]. Following exposure to an environmental trigger, antigen presentation by macrophages (particularly in those with variants in HLA-DR4 and DR-1) initiates an inflammatory cascade and release of cytokines[30]. This is believed to result in both the formation of autoantibodies such as rheumatoid factor (present in 80% of individuals of the disease[18]) and an inflammatory infiltrate of synovial joints, otherwise known as a pannus. The synovial infiltrate is comprised of T cells (predominantly Th1 cells), B cells, plasma cells, natural killer cells, dendritic cells, and mast cells[31]. The autoantibodies lead to further activation of the complement system and neutrophils. Synovial fibroblasts, macrophages, and T cells secrete cytokines (interleukin-1, interleukin-17, tumor necrosis factor *etc*) and digestive enzymes (*e.g.,* matrix metalloproteinases, collagenases) that result in osteoclast activation and ultimately destruction of adjacent cartilage, tendons, and bone[32-35]. The ongoing inflammatory response leads to either progressive spinal instability from ligamentous laxity and facet involvement, direct neural compression (*i.e.*, pannus), or compromises in blood supply to the spinal cord in cases with cervical disease[36].

Classically, rheumatoid can manifest in the cervical spine as atlantoaxial subluxation, cranial settling (also termed "basilar invagination"), and/or subaxial subluxation (Figure 1). Other manifestations include a C1-2 pannus (present in up to 81% on MRI)[25], odontoid erosions or fracture[37], or rarely an inflammatory discitis[26]. In a moderate sized cohort (N = 106), Kawaguchi *et al*[27] found the overall rate of cervical spine involvement to be 65%, with atlantoaxial subluxation occurring most commonly (47%), followed by odontoid erosion (35%) and subaxial subluxation (20%). More subtle signs of early involvement include a neurocentral synovitis of superficial joints and erosion of the lateral disk margins, with little osteophyte formation[9,38,39]. Varying degrees of fibrosis and ankylosis are also not uncommon[40]. Histologic analysis has also confirmed the presence of fibrinoid changes in the apical and interspinous ligaments[41]. Finally, osteoporosis can also often accompany rheumatoid[41,42].

SIGNS AND SYMPTOMS OF CERVICAL SPINE MANIFESTATIONS

The aforementioned changes can result in a variety of symptoms in rheumatoid patients including pain (occipital headache and neck pain), myelopathy and cranial nerve palsies, or signs of vascular insufficiency (*i.e.*, Wallenberg syndrome or syncope)[43-45]. While pain is the most common symptom of cervical involvement and may suggest instability, it is nonspecific; Neva and colleagues found that 65% of patients in a rheumatoid cohort reported pain and had no evidence of radiographic subluxation[43]. Occipital headaches may indicate impingement of the greater or lesser occipital nerves and is present in 60% of patients with atlantoaxial subluxation and 90% with cranial settling[46]. Pain can be somewhat regionalized to the area involved. In other words, suboccipital pain can indicate atlantoaxial pathology, while mid to lower cervical pain can correlate with subaxial instability. Patients with C1-2 instability may report a "clunking" with movement, also termed the Sharp-Purser test[47]. Signs and symptoms of myelopathy include limb paresthesias, numbness, weakness, and bladder or bowel disturbances. Hand deformities and peripheral neuropathy can mask myelopathy in RA. Bell's cruciate paralysis has been described with cervicomedullary compression with cranial settling and describes upper motor neuron weakness greater in the arms than legs due to a more caudal decussation of the lateral corticospinal tracts supplying the legs[48]. Cranial nerve involvement (usually glossopharyngeal, vagus, and hypoglossal) can also result from cranial settling. Dysfunction of one or more cranial nerves has been reported in up to 20% of individuals[46]. Other signs of bulbar compression that can result include internuclear ophthalmoplegia, facial diplegia, nystagmus, loss of sensation in the trigeminal distribution, quadriparesis, sleep apnea, and locked-in syndrome[49]. Lastly, sudden death can result from direct brainstem compression or vascular insufficiency[50,51].

NATURAL HISTORY

The majority of the natural history studies for cervical rheumatoid were conducted in the 1980's, before the development of biological therapies such as anti-tumor necrosis factor agents. As previously mentioned, these agents have been shown to impede de novo involvement of cervical spine. However, they have not been shown to prevent further progression of instability once it has occurred[12,13]. Nonetheless, improved medical therapy has reduced the overall need for surgical intervention. Cervical disease usually develops within 2-10 years of disease onset[52]. Generally, it is felt that atlantoaxial subluxation precedes cranial settling, and that subluxation can falsely appear to reduce once this occurs[53]. The degree of progression has been shown to correlate with peripheral disease of the hands and feet[54]. Fujiwara *et al*[7] followed a moderate size cohort (N = 173), 29% of which had atlantoaxial subluxation. At 5 years of follow up, they found that 63% with atlantoaxial subluxation progressed and that 39% without prior evidence of disease developed de novo subluxation. Ten patients became myelopathic[7]. Similarly, Pellici noted worsening in subluxation in 80%, de novo subluxation in 27%, and an overall 5-year mortality of 17%[8]. Mikulowski *et al*[50] reported postmortem findings in 104 rheumatoid patients and found that 11 deaths were associated with cervicomedullary compression from atlantoaxial dislocation[50].

More advanced stages of the disease can have an even worse natural history. Out of 31 total patients, Marks and Sharp noted 15 deaths within 6 mo of presentation[9]. All patients who did not undergo treatment and 50% treated with a soft collar alone died. Casey and colleagues reported on patients with cranial setting (classified as Ranawat 3B or with the inability to walk or feed oneself)[6]. Three out 58 patients refused surgery and died at 1 wk, 2 mo, and 6 mo respectively. The 30-d mortality rate in those who underwent surgery was 13%, and 60% died within 4 years. Only 25% had a favorable outcome. Because of the poor natural history, a general consensus has arisen to intervene before cervical myelopathy or cranial settling occurs[6,10,11,46]. Approximately, 10% with cervical spine involvement will require surgery[8].

While a detailed description of specific medical therapies is beyond the scope of this review, we briefly mention the various medical agents as their cessation becomes important when considering surgical intervention. Commonly employed therapies include non-steroidal anti-inflammatory drugs (NSAIDs), oral steroids, disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate, sulfasalazine, hydroxychloroquine, and newer biologic agents such as tumor necrosis factor or interleukin-1 antagonists[55]. Other potential adjuncts include osteoporosis agents to improve bone density[56]. In an older series by Sunahara, 76% of patients showed further progression at six years despite medical therapy[51]. Although newer agents show less de novo disease, they are less effective at halting further cervical progression unlike with peripheral disease[57]. Mutilating disease, corticosteroid use, high seropositivity, vasculitis, rheumatoid nodules, and male gender are established risk factors for progression[58,59].

PREOPERATIVE EVALUATION

Radiographic evaluation and criteria for instability

Plain cervical X-rays are recommended for screening RA patients for cervical spine disease. Useful views for evaluation are upright AP and lateral, open-mouth (odontoid view), and flexion-extension for detection of instability (Figure 2). Plain radiographs can be limited, however, by bony erosion and inability to visualize soft tissue compression. CT is useful for determining overall bone quality and for surgical planning especially with C2 fixation techniques[60]. MRI has the highest sensitivity for detecting disease of all three modalities[61]. General recommen-

Table 1 Criteria for cranial settling in rheumatoid

Measurement/Criteria	Description	Definition of abnormal
McRae's line	Tip of the basion to opisthion	If any portion of the odontoid extends superior to this line
McGregor's line	Hard palate to caudal aspect of the opisthion	> 4.5 mm of the dens is superior to this line
Chamberlain's line	Hard palate to the midpoint of the opisthion	> 3 mm of the dens extends superior to this line
Ranawat's[1]	Distance from the C2 pedicle to a line bisecting the ring of C1	< 15 mm in males, < 13 mm in females
Redlund-Johnell and Peterson[1]	Distance from the inferior end plate of C2 to McGregor's palato-occipital line	< 34 mm in males, < 29 mm in females
Clark's station of the atlas[1]	Position of C1 with relation to the body of C2 (divided into thirds)	If C1 extends below the rostral third of C2

[1]Recommended criteria by Riew *et al*[79].

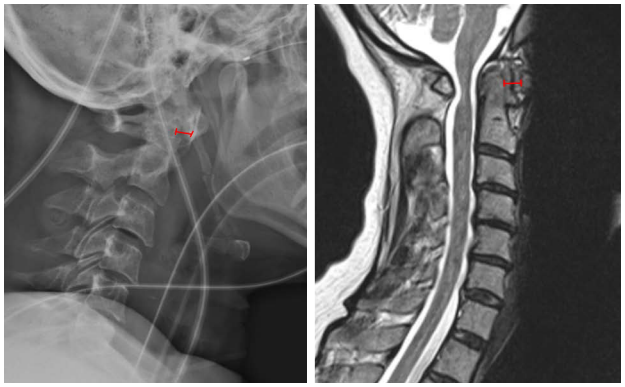

Figure 2 Lateral X-ray (left) and sagittal magnetic resonance imaging (right) of a 52-year-old with atlantoaxial subluxation. Left: Lateral X-ray; Right: Sagittal Magnetic resonance imaging. The anterior atlantodental interval is shown (red line).

dations for obtaining MRI are the presence of neurologic deficits, a predental space of 7 to 8 mm, and abnormal radiographic pathology (*i.e.,* cranial settling, odontoid erosion, or subaxial subluxation). Additionally, MRI can be useful for detecting pannus. While it was initially though that T2 hyperintensity correlates with regression after fusion, it has been since been shown that pannus regression is independent of MR signal and can resolve after posterior fusion despite its MR intensity (Figure 3)[62-64]. Lastly, preoperative CT and MRI are useful for preoperative planning and can be incorporated into the operative theater with intraoperative navigation to improve safety during transoral decompression[65].

Evaluating for atlantoaxial instability

Although the atlanto-dental interval (ADI) has been used as a measure for atlantoaxial instability, the posterior atlanto-dental interval (PADI) has been shown to be a more reliable indicator and correlates with neurologic improvement after surgery and the development of myelopathy. Normal ADI is defined as 0-3 mm, whereas values between 6-10 mm have been cited as cutoffs for instability and indications for surgery[37,66-69]. Cut-off values on lateral radiographs of 13 and 14 mm have been suggested for PADI[70-73]. These values correlate with anatomical studies at C1 showing the width of the cord, dura (anterior and posterior) and cerebrospinal fluid space of 10 mm, 1 mm, and 2 mm, respectively[71,74]. More recently, it has been shown that preoperative neurologic function is directly related to increased intramedullary T2 signal, which also corresponds to ADI and PADI on lateral radiographs[75]. Open mouth odontoid views are useful for detecting lateral subluxation, with a distance of greater than 2 mm being shown to correlate with spinal cord compression[37,76].

Evaluation for cranial settling

A variety of radiographic parameters have been used to identify cranial settling (Table 1). Classic indicators evaluate the location of the odontoid process with respect to the foramen magnum (McRae's line)[77] or with respect to the hard palate and the base (Chamberlain's line)[78] and midpoint of the opisthion (McGregor's line)[79]. Newer classifications describe the relation of C1 relative to C2 (*e.g.,* Ranawat's Criteria and Clark's station of the atlas) or the base of C2 relative the palatal-occipital line (Redlund-Johnell)[66,80,81]. While all can potentially be used, none have a sensitivity, specificity, or negative or positive predictive value of greater than 90%[79]. Riew and colleagues conducted a meta-analysis which found that combining Clark station, Redlund-Johnell criteria, and Ranawat criteria yielded a sensitivity and negative predictive values of 94% and 91%, and thus recommend the use of all three when evaluating for cranial settling[79].

Evaluation of the subaxial spine

Boden and colleagues define a cut off for critical stenosis as less than 14 mm in subaxial spine[71]. Other commonly used criteria on plain radiographs include White and Panjabi's, which uses a value of greater than 3.5 mm of vertebral translation or greater than 11 degrees between adjacent motion segments as markers for subaxial instability[82].

Cervicomedullary angle

The cervicomedullary angle measured on MRI or myelography is predictive of neurologic compression[83]. The cervicomedullary angle corresponds with the angle formed by the intersection of vertical lines drawn along the anterior surface of the brainstem and the spinal cord on sagittal MRI. The range in normal individuals is 135-175 compared to less than 135 degrees in those with

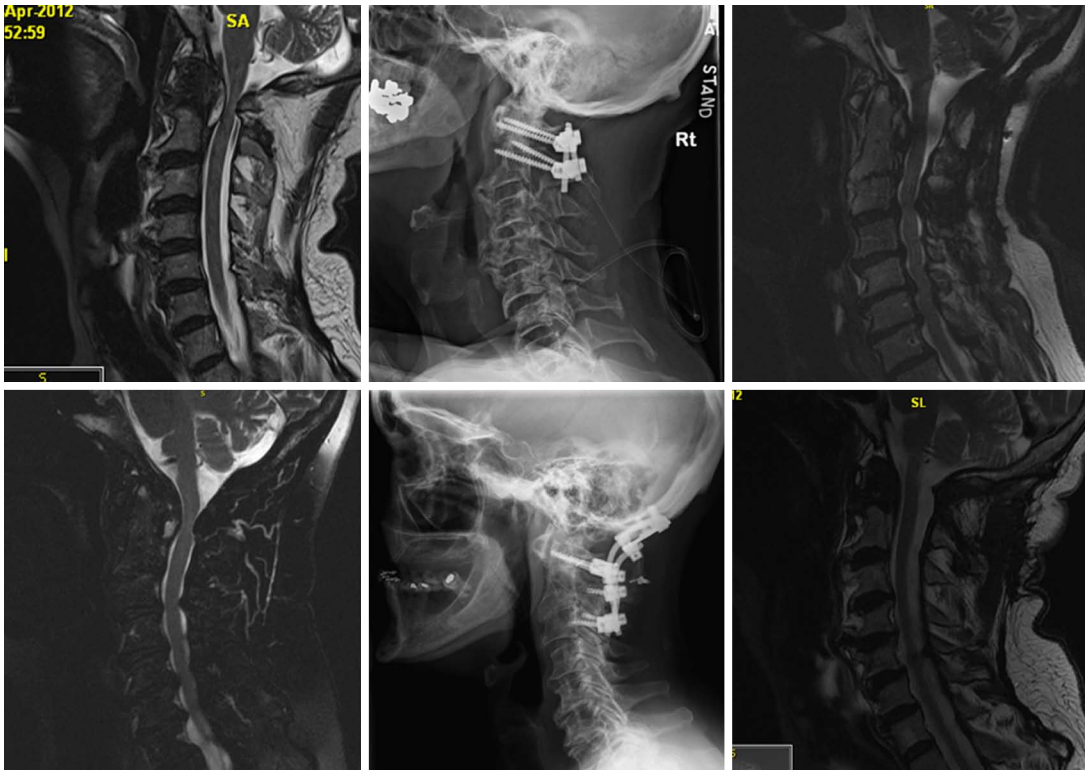

Figure 3 Resolving rheumatoid pannus after occipital cervical (top) and C1-2 fusion (bottom). Left: Preoperative magnetic resonance imagings; Middle: Postoperative lateral X-ray; Right: Postoperative magnetic resonance imagings.

Table 2 Common rheumatoid arthritis medications and perioperative considerations

RA medication	Preoperative action
NSAIDs	Discontinue 3-5 half-lives before surgery
Corticosteroids	Administer perioperative stress doses
Methotrexate	Discontinue for 6-8 wk if possible
Biologic agents (TNF-α and interleukin-1 antagonists)	Discontinue preoperatively and hold until 10-14 d post-surgery

RA: Rheumatoid arthritis; NSAIDs: Non-steroidal anti-inflammatory drugs; TNF-α: Tumor necrosis factor α.

myelopathy.

EFFECT OF RHEUMATOID MEDICATION ON SURGERY

The cessation or continuation of various rheumatoid medications is an important perioperative consideration (summary provided in Table 2). Because NSAIDs inhibit platelet function and thus increase the risk for intraoperative blood loss and postoperative hemorrhage, they should be discontinued 3 to 5 half-lives before surgery[84]. Additionally, NSAIDs have been shown to inhibit bone formation and should be withheld after surgery if possible. Corticosteroids impair bone and wound healing and can cause adrenal suppression in patients on an equivalent of 20 mg/d of prednisone or more. Perioperative stress doses should be given to these individuals[84,85]. While methotrexate has not been shown to increase in infection rates[86], it may affect bone healing[87] and should be discontinued for 6 to 8 wk if possible. Finally, biologic agents (tumor necrosis factor-α and interleukin-1 antagonists) increase the risk of opportunistic infections (11% reported by Giles *et al*[88]) and should be stopped preoperatively and held until 10 to 14 d after surgery[84,85].

OVERALL IMPACT OF RA ON SURGICAL COMPICATIONS AND OUTCOMES

There are several general considerations that should be noted about rheumatoid patients before considering any surgery. Because of the overall systemic effects of the disease, patients will have higher complication rates than would be expected for other indications that involve the same surgery. For example, patients with comorbid rheumatoid and lumbar pathology have been shown to have higher wound and implant related complications[89-91]. Similar findings have also been reported in other orthopedic procedures such as total hip arthroplasty[92,93]. Nonunion and instrumentation failures are impart related to baseline osteopenia or osteoporosis and also due to anti-

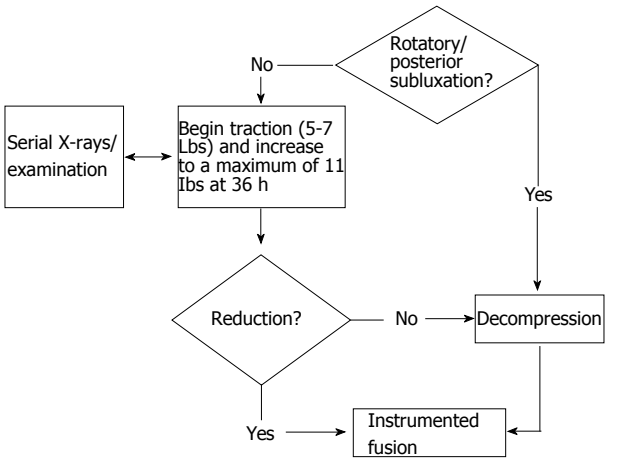

Figure 4 Preoperative traction and surgical approach to cervical rheumatoid.

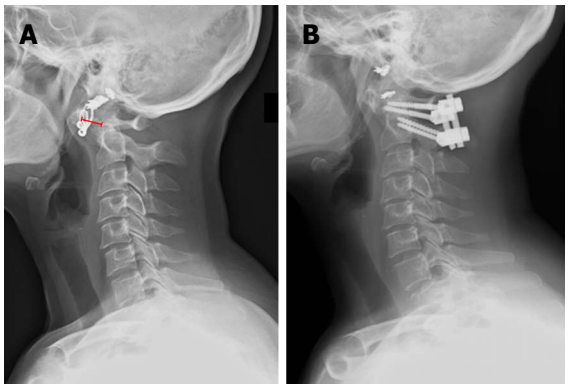

Figure 5 Lateral X-ray images of the spine before (A) and after (B) surgical intervention. The anterior atlantodental interval is shown (red line).

rheumatoid agents that impair fusion[88,89,91]. Rheumatoid patients are also more prone to develop infections[94-96]. In a large matched cohort with over 10 years of follow up, Doran *et al*[95] found that rheumatoid patients had higher overall incidence of infections with particular predilection for bone, joints, skin, soft tissues, and the respiratory tract. The higher infection rates were felt to be due to alterations in immunity from rheumatoid and immunosuppression from rheumatoid medication. Pulmonary involvement especially has an impact on overall morbidity with surgery and also increases the risk of premature mortality[93,97,98]. Increased morbidity and ongoing systemic disease result in higher resource utilization and worse outcome in rheumatoid patients[93,99,100]. Thus, it is imperative that these patients undergo thorough medical evaluation and preoperative optimization to mitigate these effects as much as possible. Lastly, outcomes are largely determined by preoperative neurologic function. Wolfs and colleagues performed a meta-analysis on 752 rheumatoid patients (25 studies) and found that those who were Ranawat class Ⅰ and Ⅱ rarely had deterioration in neurologic function. Whereas, patients with Ranawat class ⅢB function had significantly worse outcomes with 43% and 70% mortality rates at 5 and 10 years, respectively[101].

SURGICAL INDICATIONS

Indications for surgery include medically refractory pain, neurologic deficits (myelopathy or cranial nerve/bulbar dysfunction), and radiographic instability as defined previously[41,64,71,102-104]. The ultimate goals of surgery are to relieve neurologic compression and eradicate instability, thereby preventing further neurologic decline[44].

PREOPERATIVE TRACTION AND SURGICAL APPROACH

Prior to surgery both the reducibility of the lesion and vector of compression need to be considered (Figure 4). Atlantoaxial instability can often be reduced with positioning intraoperatively, and thus, preoperative traction is mostly used for cases of cranial settling. Traction is contraindicated only in cases of complex rotary subluxations and posterior occipito-atlantoaxial dislocations due to risk of distracting the vertebral artery[40]. Otherwise, traction can be initiated with 5-7 lbs. and gradually increased to a maximum of 10-11 lbs. by 36 h[40]. Periodic radiographs and serial neurologic examinations should be performed. Instrumented fusion can be performed in cases of cranial settling which reduce with traction. If no reduction occurs by 4 to 5 d, however, decompression in the vector of the offending pathology should be performed followed by instrumented fusion. Roughly 80% of cases will reduce[44]. Negative predictors for reduction include odontoid penetration beyond 15 mm through the foramen magnum, large pannus, odontoid fractures, and cranial settling complicated by lateral or rotatory subluxation[40].

FUSION AND DECOMPRESSION TECHNIQUES

Occipitocervical fusion is indicated for cranial settling or for fixed atlantoaxial subluxations with posterior cord impingement by C1 in which case a C1 laminectomy is also performed[105-107]. The technique was originally described by Foerster in 1927 and then modified by Hamblen with the addition of iliac crest grafts in 1967[108,109]. Ransford and Flint later popularized the loop-rod technique[110,111], which eventually became supplanted by occipitocervical plating as described by Grob[112,113] and Smith[114]. Occipitocervical plating is more rigid and commonly used today[112,115,116]. Typically occipitocervical fusions extend down to at least C2 with or without a C1 laminectomy (which is preferred by some even in reducible lesions). The fusion may need to extend further into the subaxial spine depending on the bone quality and screw fixation.

A C1-2 fusion is considered the surgery of choice for atlantoaxial subluxation (Figure 5). Historically, Gallie wiring and grafting techniques were used[117], which were further modified by Brooks and Jenkins[118], Wertheim

and Bohlman[119], and Clark and colleagues[66]. Halo immobilization was often used to supplement wiring techniques to improve arthrodesis rates, but still could have failure rates of 20%[69,120,121]. As instrumentation methods improved, however, these techniques have been replaced or combined with screw and rod instrumentation. Magerl originally described the use of C1-2 articular screws[122,123]. Goel would later describe plate and screw fixation for atlanto-axial subluxation which was further modified by Harms and Melcher to posterior C1 lateral mass and C2 pedicle or pars screws[124,125]. When using C2 fixation techniques it is paramount to consider the course of the vertebral artery which can be defined with preoperative CT or CT angiography[126]. A high riding vertebral artery or narrow C2 isthmus can be prohibitive to C2 transarticular screw fixation. Other contraindications include collapsed lateral masses or significant cranial settling, irreducible subluxations, poor bone quality, or loss of osseous integrity of C1 or C2. The C2 isthmus should be wide enough to accommodate a 3.5 mm screw. The starting point is 3 mm above the C2-3 facet articulation, 2-3 mm lateral to the medial border of the C2 facet, and the trajectory is 0-10 degrees medially aimed at the anterior arch of C1. Screw size is typically a width of 3.5 to 4.5 mm and 40 to 44 mm long. Optimally placed transarticular screws have a fusion rate of roughly 95%[127], though it can be difficult to capture both the C1 and C2 vertebrae. The Harm's technique involves placing polyaxial screws (3.5 mm) directly into the lateral mass of C1 and into the pars or pedicle of C2 bilaterally. C2 pedicle fixation can be performed provided the pedicle width is wide enough to accommodate a screw (at least 6 mm per Alosh *et al*[60]). Overall the literature suggests that incidence of vertebral artery injury is low with either transarticular or pedicle screw fixation techniques, and both have greater than 90% fusion rates[128-131]. Although no prospective comparisons have been conducted, pooled meta-analysis suggests that pedicle screws may have a lower risk of misplacement and vertebral artery injury[132]. In the authors' opinion, either technique is acceptable provided the surgeon has sufficient experience and a thorough knowledge of the patient's anatomy. Other C2 fixation techniques have been described to lower the risk for vertebral artery injury or for cases with unfavorable anatomy. Tokuhashi and colleagues describe an alternative technique that involves the use of Halifax interlaminar clamps to achieve intraoperative reduction and placement of an interference screw that is secured to a corticocancellous graft[133]. Intralaminar screws can also be used as an alternative method of C2 fixation when anatomy for pedicle or transarticular screws is unfavorable[134]. From a biomechanical perspective, C2 pedicle screws provide greatest overall stability[135]. Lapiswala *et al*[136] demonstrated superior lateral bending moments with pedicle and transarticular screws compared to intralaminar screws, though with wire supplementation, all have equivalent moments in flexion, extension, and axial rotation. The senior author prefers pedicle screw fixation in patients with favorable vertebral artery anatomy due to their increased biomechanical strength.

Subaxial fusion techniques have also evolved from wiring (Bohwman's triple wire technique) to plating and screws, to polyaxial lateral screws and rods[123,137,138]. Three variants of lateral mass screws have been described by An, Magerl, and Roy-Camille. While pedicle screws have been shown to have the highest pullout strength, we do not recommend their routine use due to a higher risk of vertebral artery injury[139,140]. Our personal preference is to use a modified An technique due to a lower rate of nerve root violation compared to other techniques[141], and to reserve other techniques as potential rescue methods.

For cases that are irreducible or in cases in which a pannus fails to regress, decompression is indicated. A standard C1 laminectomy is indicated for cases of posterior impingement of the cord. Ventral decompression has traditionally been performed through a transoral approach. These are often complicated by swallowing dysfunction and postoperative airway swelling, necessitating tracheostomy and percutaneous gastrostomy placement[142]. Because of a high failure rate of successful postoperative extubation, we often place a tracheostomy prior to transoral approach. We have also found it resourceful to use intraoperative navigation as an adjunct[65]. More recently, endoscopic approaches via a transnasal or transoral route have been advocated[143-145]. In addition to reducing swallowing dysfunction and the need for tracheostomy, these approaches may also allow for preservation of the anterior arch of C1 and perhaps obviate the need for posterior fixation in select cases[143-151]. A transcervical endoscopic approach is also feasible and may mitigate morbidity as demonstrated in a small cohort (N = 15) by Dasenbrock *et al*[152] in which all were able to avoid the need for postoperative tracheostomy. While these approaches potentially offer less invasive techniques for ventral decompression, further prospective and comparative studies will be necessary to determine their role in the management of rheumatoid patients.

OUTCOMES

Surgical outcomes are generally better in patients with less preoperative impairment. In a series of 28 patients, Schmitt-Sody *et al*[153] found that 7 out of 10 patients that were Ranawat class Ⅱ improved to class Ⅰ, whereas 1 out of 11 class ⅢA improved to class Ⅱ, and 2 patients deteriorated to Class ⅢB. Ranawat *et al*[154] noted that outcomes were particularly poor in non-ambulatory patients (Ranawat Class ⅢB). Other poor prognosticators include a spinal cord area of less than 44 mm^2 and PADI of less than 10 mm[154]. Boden *et al*[71] noted significant motor improvement in patients with had preoperative PADI of 14 mm or more. Advanced age, atlantoaxial instability, and postoperative complications have all been found to be predictors of mortality[39,155]. Lastly, intervening early and before cranial settling occurs has been shown to decrease the risk for future instability. Agarwal and colleagues

found that 5.5% of patients undergoing early intervention for atlantoaxial subluxation developed recurrent instability (mean 9 years) compared to 36% who underwent occipitocervical fusion cranial settling[156]. Clarke *et al*[157] found that 39% of rheumatoid patients undergoing surgery for atlantoaxial subluxation subsequently developed subaxial subluxation, 54% of which required further fusion.

CONCLUSION

The treatment of cervical rheumatoid has significantly evolved over the past 50 years. A disease with potentially grim outcomes has been improved with surgery. Additionally, the advanced stages of the disease are less commonly seen due to improved medical therapies. Significant advances in surgical instrumentation no longer require internal and external fixation, and fusion rates have improved. Finally, the use of endoscopic approaches may potentially lower the morbidity with ventral decompression, though further prospective study will be necessary to elucidate their role and whether they can obviate the need for fusion.

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Inflammation, lipid metabolism and cardiovascular risk in rheumatoid arthritis: A qualitative relationship?

Carmen García-Gómez, Maria Bianchi, Diana de la Fuente, Lina Badimon, Teresa Padró, Emili Corbella, Xavier Pintó

Carmen García-Gómez, Maria Bianchi, Department of Rheumatology, Consorci Sanitari de Terrassa (CST), Unitat Investigació Biomèdica CST-UAB (Universitat Autònoma de Barcelona), 08227-Terrassa, Barcelona, Spain
Diana de la Fuente, Department of Rheumatology, Hospital de Viladecans, 08840-Viladecans, Barcelona, Spain
Lina Badimon, Teresa Padró, Cardiovascular Research Center, CSIC-ICCC, Biomedical Research Institute Sant-Pau, 08025-Barcelona, Spain
Emili Corbella, Xavier Pintó, Lipid and Vascular Risk Unit, Department of Internal Medicine, Hospital Universitari de Bellvitge-IDIBELL, L'Hospitalet de Llobregat, Barcelona University, 08907 Fipec, CIBERobn ISCIII, Spain
Author contributions: García-Gómez C conception, design and draft of the manuscript, and initial outline of the illustrations; Bianchi M development of the illustrations and bibliographic research; de la Fuente D bibliographic research and reference order; Badimon L, Padró T and Pintó X correction and critical review with contributions to improve the scientific quality of the manuscript and provide novel categories; Corbella E acquisition of research articles and data.
Correspondence to: Carmen García-Gómez, MD, PhD, Department of Rheumatology, Consorci Sanitari de Terrassa (CST), Unitat Investigació Biomèdica CST-UAB (Universitat Autònoma de Barcelona), Ctra, Torrebonica S/N, 08227-Terrassa, Barcelona, Spain. ggcarme@gmail.com
Telephone: +34-93-7839488 Fax: +34-93-70003637
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Abstract

Life expectancy in patients with rheumatoid arthritis (RA) is reduced compared to the general population owing to an increase in cardiovascular diseases (CVD) not fully explained by traditional cardiovascular risk factors. In recent years, interest has been focused on the alterations in lipid metabolism in relation to chronic inflammation as one of the possible mechanisms involved in the pathogenesis of atherosclerosis of RA patients. Research regarding this issue has revealed quantitative alterations in lipoproteins during the acute-phase reaction, and has also demonstrated structural alterations in these lipoproteins which affect their functional abilities. Although many alterations in lipid metabolism have been described in this regard, these structural changes associated with inflammation are particularly important in high-density lipoproteins as they affect their cardioprotective functions. In this respect, excessive oxidation in low-density lipoprotein (LDL) and increased lipoprotein(a) with a predominance of smaller apolipoprotein(a) isoforms has also been reported. This article will discuss proinflammatory high-density lipoproteins (piHDL), oxidized LDL and lipoprotein(a). Elevated concentrations of these lipoproteins with marked pro-atherogenic properties have been observed in RA patients, which could help to explain the increased cardiovascular risk of these patients.

Key words: Rheumatoid arthritis; Cardiovascular disease; Lipoproteins; Proinflammatory high-density lipoproteins; Lipoprotein(a); Oxidized low-density lipoproteins; Lipid metabolism; Inflammation

Core tip: Inflammation plays a major role in the process of accelerated atheromatosis in rheumatoid arthritis patients by modifying the structural and functional properties of lipoproteins.

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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic disease of unknown etiology, which affects all ethnic groups at a rate of approximately 0.5% to 1% of the adult population, being more prevalent in North America than in Asian countries[1,2]. RA is characterized primarily by chronic inflammation of the joints, although it is increasingly recognized that comorbid conditions, especially cardiovascular disease (CVD), play a pivotal role in RA outcomes[3]. These patients have reduced life expectancy[4] owing to an increased mortality rate attributable mainly to CVD, primarily coronary heart disease[5], which results from a process of accelerated atherosclerosis[6], irrespective of the traditional cardiovascular risk factors[7], and is frequently silent and subclinical[8]. The excess risk observed in RA and other autoimmune diseases appears to be driven by a complex interaction between traditional and non-traditional cardiovascular risk factors, where inflammation plays an important role through direct or indirect mechanisms[9,10] such as damaging effects on the vasculature. Possible mechanisms involved include lipid metabolism disorders related to the inflammatory process itself[11].

LIPID ABNORMALITIES IN RA

Lipid abnormalities have been shown to contribute to accelerated atherosclerosis, leading to an increased risk for CVD[12]. For decades, increased low-density lipoprotein (LDL) levels have been recognized as strong predictors of CVD, and it is also known that high-density lipoproteins (HDL) usually protect from atherosclerosis. Data on dyslipidemia in RA are conflicting and it appears to be present in RA patients with both early and advanced disease. Although the exact mechanisms are unknown, changes in lipid profiles and acute-phase reactants are associated with early atherosclerosis in RA[13]. In this respect, it has been reported that active and untreated RA showed a proatherogenic lipid profile, with a decrease in high-density lipoprotein cholesterol (HDL-C) being a more convincing finding. This appears to be secondary to chronic inflammation rather than to primary metabolic alterations in RA[14], since lipid abnormalities can be improved by effectively treating RA without using a lipid-lowering agent[15]. Further, higher HDL values were reported by our group in RA patients treated with low doses of glucocorticoids than in those not treated with these drugs, with no increase in LDL cholesterol (LDL-C) or triglycerides[16], resulting in apparently beneficial effects on the cardiovascular system.

Apart from plasma lipid values, the size and density of these particles are also clinically important. Smaller HDL particles probably perform reverse cholesterol transport more successfully and therefore confer greater cardio-protection[17], whereas small dense LDL particles more readily infiltrate the endothelium and thus become more susceptible to oxidative changes[18]. In RA, higher levels of small dense LDL particles and lower levels of small HDL particles compared with controls have been reported[19]. Indeed, this increased level of small dense LDL seems to be common in drug-naïve patients with early RA[20].

Nevertheless, all this would probably still be insufficient to explain the increased cardiovascular risk in RA compared to the general population. In the context of inflammation, structural alterations of these particles, which undoubtedly affect their function, have also been described[11]. Similarly, other less established CVD risk factors such as elevated lipoprotein (a) [Lp(a)] may be implicated. In this respect, a high prevalence of hyperlipoproteinemia has been observed in RA patients[21,22]. All these aspects will be developed below.

HIGH-DENSITY LIPOPROTEIN

Heterogeneity and function of HDL

During the 1970s, numerous studies showed an inverse correlation between plasma HDL-C concentrations and cardiovascular risk. Decades later, HDL-C was recognized as an independent risk factor for coronary heart disease and incorporated into clinical practice. This lipoprotein is highly heterogeneous[23], with subfractions which can be identified by their density, size, charge and protein composition. During maturation of HDL in plasma (passage of nascent HDL, HDL2 and HDL3), this particle undergoes a series of modifications or renovations with redistribution of lipids among lipoprotein particles. This remodelling involves mainly the phospholipid transfer protein (PLTP), cholesteryl ester transfer protein (CETP) and hepatic lipase (HL). HDL2 is a larger particle that is rich in cholesterol and apolipoprotein AI (apo AI). HDL3 are small particles, lipid-poor and contain apo AI and apo AII. In general, controversy exits regarding the importance of HDL cholesterol subfractions, HDL2 and HDL3, in relation to the anti-atherogenic effect[17,24].

A variety of functions that may contribute to the cardiovascular protective effect have been attributed to HDL particles[25]. One of the most widely accepted mechanisms is that HDL facilitates the process known as reverse cholesterol transport[26], by which the non-esterified cholesterol from peripheral tissues is transferred to HDL and transported to the liver to be excreted in bile and feces. There are two main routes for liver uptake of transported HDL cholesterol: one is selective uptake via receptor type BI (SR-BI), very important in rodents that have no natural CETP pathway, and the second pathway, important in humans, which involves the transfer of cholesterol esters by CETP enzyme to Apo B-containing lipoproteins, which are taken up by the liver. In addition, specific qualitative aspects have been attributed to HDL particles such as the anti-inflammatory, antithrombotic and promoting antioxidant properties of nitric oxide, which render a molecule with pleiotropic functions. Regarding their antioxidant properties, HDL are involved in the inhibition of LDL oxidation and endothelial inflammation[27], effects due in part to paraoxonase 1 (PON1). PON1 is closely linked to HDL particles and confers on them antioxidant properties, which represent the main

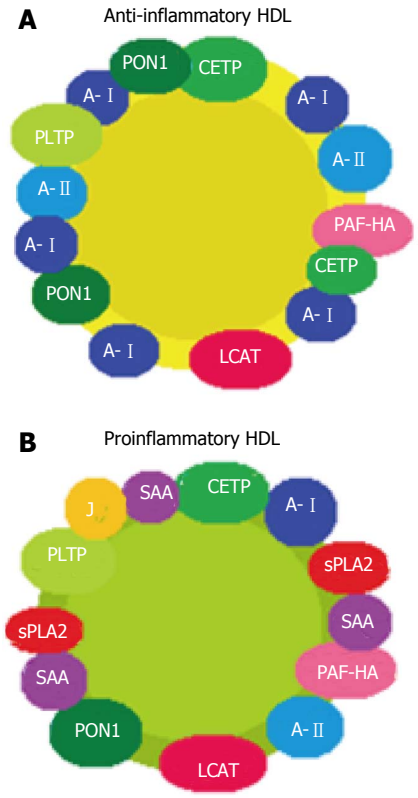

Figure 1 Structural change from normal protective anti-inflammatory high-density lipoproteins (A) to proinflammatory high-density lipoproteins (B) in the context of inflammation. A- Ⅰ: Apolipoprotein A Ⅰ; A- Ⅱ: Apolipoprotein A Ⅱ; J: Apolipoprotein J; PON1: Paraoxonase 1; PLTP: Phospholipid transfer protein; CETP: Cholesteryl ester transfer protein; PAF-HA: Hydrolyzes platelet-activating factor; LCAT: Lecitin cholesterol acil transferasa; sPLA2: Pancreatic phospholipase A2; SAA: Serum amyloid protein A.

mechanism of inhibiting the oxidation of LDL and HDL itself[28] (processes directly involved in the early stages of atherosclerosis), and also anti-inflammatory properties, through activating acetylhydrolase, the enzyme that hydrolyzes platelet-activating factor (PAF-AH), with a recognized proinflammatory effect.

Proinflammatory HDL

The role of HDL is not always predictable based on their quantitative values[29]. In healthy individuals, in the absence of oxidative stress and systemic inflammation, HDL is anti-inflammatory, *i.e.*, with cardioprotective properties. However, in patients with chronic diseases, which are characterized by oxidative stress and systemic inflammation, HDL may have proinflammatory properties (piHDL) and therefore lose their cardioprotective function[30]. During the acute-phase reaction, protein and enzymatic changes occur in HDL particles. Serum amyloid protein A, apolipoprotein J and pancreatic phospholipase A2 are present in serum at high concentrations and are incorporated into HDL, displacing the usual components thereof such as apo AI, CETP and LCAT (Figure 1). Furthermore, other variations in the enzymatic content of HDL have also been observed; these include a reduction in PON1 and elevated PAF-AH levels as a result of a decreased enzyme acetylhydrolase activity. Together, all these changes that occur during the inflammatory process will confer pro-atherogenic properties on HDL particles[31].

In accordance with this, it was observed that quantitative measurements of HDL were not predictive of subclinical or clinical atherosclerosis in any studies on patients with rheumatic diseases[13]. The importance of HDL to atherosclerosis in RA becomes apparent when qualitative rather than quantitative properties of HDL are measured. Autoimmune rheumatic diseases, being states of chronic inflammation, might be associated with piHDL and contribute as an additional risk factor to the development of atherosclerosis[32]. A recent publication showed lower activity and mass of CETP in RA patients on glucocorticoid therapy compared with those not taking glucocorticoids and controls[33], which could imply a functional impairment of HDL given that this enzyme plays a pivotal role in reverse cholesterol transport. Also, PiHDL have been reported to be present in approximately 45% of systemic lupus erythematosus (SLE) patients and 20% of RA patients compared to 4% of healthy controls, with statistically-significant differences[34]. Thus, it would be easy to deduce that controlling disease activity reduces inflammation and that normalization of the lipid profile is achieved. However, in the same study, interestingly, no correlation was found between SLE and disease activity (assessed by SLEDAI), nor was a fluctuation in piHDL levels observed over time, even if disease activity changed, thereby suggesting that in these patients there is a sustained low-grade level of inflammation that is adequate for altering HDL particles, or that genetic effects play a major role in determining whether an individual has protective or proinflammatory HDL.

Published articles regarding the effect of anti-rheumatic therapies or statins on HDL functionality are scant. It has been reported that anti-tumor necrosis factor (anti-TNF) agents and rituximab could have a beneficial effect on HDL antiatherogenic capacity[35]. Infliximab is able to improve HDL antioxidative capacity, even 6 mo after initiation of therapy[36]. Also, changes in the composition of HDL, rendering the molecule anti-atherogenic, have been described with adalimumab and etanercept[37], as well as in patients with good response to treatment with rituximab[38]. However, no difference in HDL antioxidative capacity was found after six weeks of tocilizumab and, to our knowledge, no studies have been published on the effect of abatacept on HDL function. Furthermore, some statins may improve anti-inflammatory and anti-oxidative actions of HDL in the general population[39], although only atorvastatin has been studied in RA and has proved to significantly reduce the anti-inflammatory capability of HDL[40]. However, it is unclear whether these changes would result in a lower incidence of cardiovascular events in these patients.

LOW-DENSITY LIPOPROTEIN

For decades, raised LDL levels have been recognized as

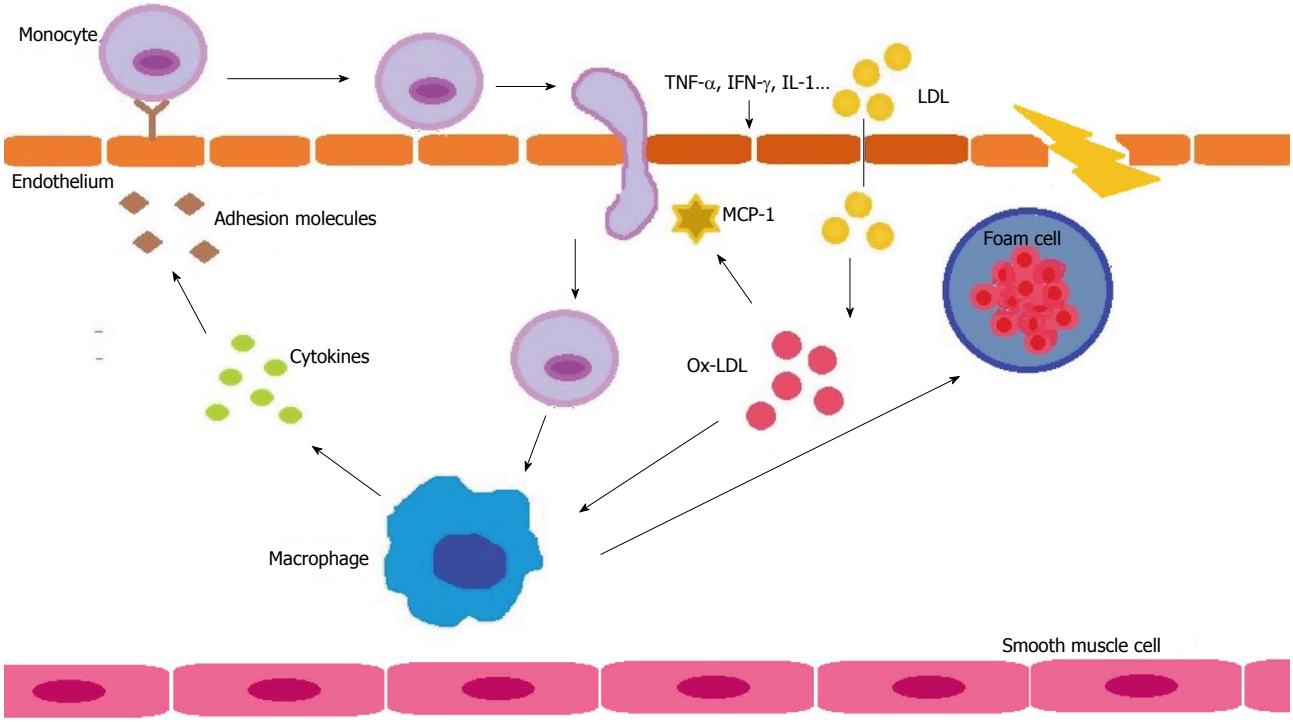

Figure 2 Oxidation of low-density lipoprotein in the context of inflammation to produce atherosclerosis (see text). Ox-LDL: Oxidation of low-density lipoprotein; MCP-1: Monocyte chemotactic protein-1; TNF-α: Tumor necrosis factor α; IFN-γ: Interferon γ; IL-1: Interleukin-1.

strong predictors of CVD, and guidelines developed to date have a reduction in LDL as the primary focus for lipid-lowering therapy[12]. LDL are sub-classified according to size and density, and the smallest and densest are those associated with greater CVD risk[41]. The main function of LDL is to transport cholesterol from the liver to tissues, essential as a basic structural element of the skeleton of cell membranes, precursor of some vitamins and hormones and as energy input. Nevertheless, an excess accumulation of cholesterol in tissues causes atherosclerosis. When the endothelial cells of the arterial wall are altered, increased space permits the entry of LDL, especially those small and dense, which are modified by the effects of oxidation and converted into oxidized LDL (Ox-LDL) (Figure 2).

Oxidized LDL

Oxidized LDL play a central role in the pathogenesis of atherosclerosis. They have the ability to activate endothelial cells as an initial step in the process of atherosclerotic disease to finally be engulfed by macrophages to form foam cells that are the nidus of plaque[42,43]. Increased oxidized lipids have been described during infection and inflammation[44,45]. Several mechanisms have been associated with increased LDL oxidation during the acute-phase response. PON1, an HDL-associated enzyme, protects LDL from oxidative stress by destroying biologically-active phospholipids, and a decreased PON1 activity during inflammation has been reported[40,46]. A further mechanism suggested is a possible rise in ceruloplasmin during inflammation, which has been shown to increase LDL oxidation[47]. Also, transferrin, a metal-binding protein associated with HDL, decreases during the acute-phase response, and less transferrin in HDL reduces their ability to protect against LDL oxidation *in vitro*[48].

Ox-LDL has been detected in the synovium and synovial fluids of RA patients[49,50]. Also, it has been reported that active RA patients had significantly increased serum Ox-LDL levels than inactive RA or age-matched controls[51]. Nevertheless, few studies have been conducted on the subject. Furthermore, although a few of those studies had conflicting results questioning the pathogenic role of Ox-LDL in increasing CVD in these patients[52], most confirmed that Ox-LDL are raised in RA[53]. Indeed, the relationship of Ox-LDL with the presence or not of subclinical atherosclerosis has been evaluated and a positive association of Ox-LDL levels with intima-media thickness has been demonstrated[54,55]. Less is known of the effect of treatment on Ox-LDL levels. To our knowledge, the sole study published reported that both anti-TNF and rituximab had increased Ox-LDL levels temporarily at three months[56], however the impact of these effects on future CVD events requires further studies.

LIPOPROTEIN (a) AND APOLIPOPROTEIN (a)

Lp(a) was first described by Berg in 1963 as an antigenic variant of LDL[57]. This lipoprotein is structurally similar to the LDL molecule which, in addition to apolipoprotein B100 (apoB100), has an additional protein, apolipoprotein (a) [apo(a)][58]. This apolipoprotein is a glycoprotein of the plasminogen family, which binds to apo B100 by a single disulfide bond. Apo(a) gives Lp(a) more atherogenic properties which mostly depend on its size (Figure

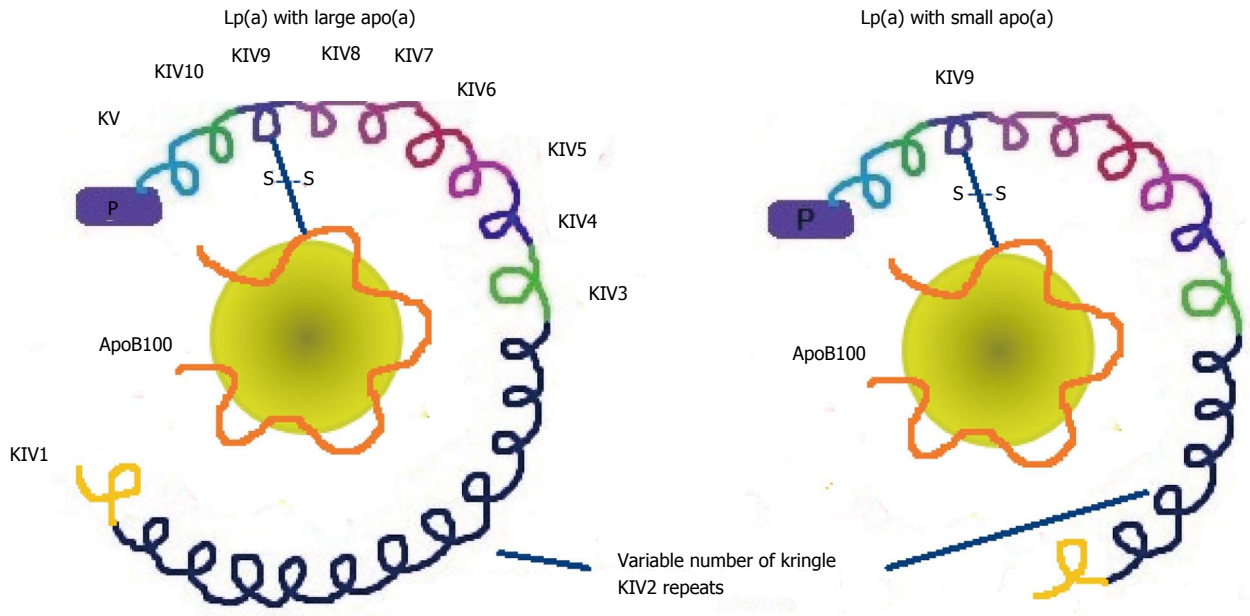

Figure 3 Outline of the different lipoprotein (a) sizes depending on apolipoprotein (a) size, which in turn depends on the number of copies of one of the domains of the protein, the Kringle Ⅳ type 2. Apo(a) is formed by 10 different types of plasminogen Kringle Ⅳ-like repeats and also contains other regions that are homologous to plaminogen, the Kringle Ⅴ and protease (P) regions. Fynally, apo(a) is linked in its kringle Ⅳ type 9 domain to the apolipoprotein B100 (apoB100) by a single disulfide bond (S-S). Lp(a): lipoprotein (a); Apo(a): Apolipoprotein (a); KV2: Kringle Ⅳ type 2.

3). The size heterogeneity of apo(a) is related to the variable number of copies of one of the protein domains, the Kringle Ⅳ type 2[59]. This variable number of copies confers marked heterogeneity on the molecular mass of apo(a) isoforms, which may vary from 200 to 800 kDa. The size of apo(a) isoforms has an inverse relationship with density and the plasma concentration of Lp(a)[60]. As the size of apo(a) increases, secretion by liver cells is more difficult and this leads to a lower Lp(a) concentration. Thus, individuals with small apo(a) are those with the highest Lp(a) concentrations and increased cardiovascular risk. Hence, Lp(a) may have different sizes mainly due to the structural polymorphism of apo(a), which has a strong genetic component[61]. Plasma levels of Lp(a) remain fairly stable throughout life, given its strong genetic component, and are not influenced by diet or treatment with standard lipid-lowering drugs, except niacin[62]. Presumably for the same reason, the differences observed in the population depend on race, with the lowest being in Caucasians, modest in Hispanics, Chinese and Japanese, and the highest in Blacks[63]. The particles of Lp(a) with smaller isoforms are considered more pathogenic because they seem to have increased ability to bind to oxidized phospholipids, are more likely to be located in the vascular wall due to their ability to bind to lysine and interact with fibrin, and appear to have a thrombogenic effect due to an increase in the inhibition of plasmin activity.

In recent years, the relationship between Lp(a) and cardiovascular risk has emerged reinforced as a key factor in the development of atherosclerosis owing to new genetic techniques[64]. Numerous studies confirmed this positive association between excess Lp(a), defined by a > 300 mg/L concentration, and increased CVD[65]. This may, in part, be due to the structural similarities with plasminogen, competing for its binding site. Thus, Lp(a) may competitively inhibit some physiologic actions of plasminogen in the coagulation and fibrinolytic cascade, and act as a procoagulant[66]. The other hypothesis as to why Lp(a) is believed to have atherogenic properties is based on the structural similarity of Lp(a) and LDL[67]. Lp(a), in contrast to LDL, binds very poorly to the LDL receptor, leading to an accumulation of tissue cholesterol. Lp(a) would be captured by macrophages through the scavenger pathway and transformed into foam cells, precursors of the formation of atheromatous plaque.

Although values remain fairly stable in individuals owing to the strong genetic component, increases in Lp(a) in acute stress situations or chronic inflammatory diseases have been described with behavior similar to an acute-phase reactant[22]. In this respect, some authors have reported elevated plasma Lp(a) levels in RA patients[21,22]; furthermore, a correlation between Lp(a) and high carotid intima-media-thickness[68] has also been observed in these patients. The significant increases in Lp(a) in RA may be due exclusively to a direct result of inflammation or perhaps to increased genetic expression. Interestingly, in our previous work[21], we showed that many of the lipid changes described in active and non-treated RA patients were reversible with treatment aimed at reducing inflammation, including glucocorticoids, disease-modifying agents and anti-TNF therapy, except for Lp(a) that remained consistently elevated despite antirheumatic therapy. No relationship with disease activity was found. These findings would reinforce the idea that the hyperlipoproteinemia (a) observed in these patients has a strong genetic involvement. On the other hand, other studies

showed that methotrexate or methotrexate combined with a anti-TNF appeared to significantly reduce Lp(a) in RA[69], and also that Lp (a) levels decreased significantly after treatment with tocilizumab in rheumatoid diseases[70]. Therefore, in contrast to the above, these other findings suggest that Lp(a) might be related to systemic inflammation, or that the examined drugs might reduce Lp(a) by other mechanisms. Nevertheless, despite these significant findings, the distribution of the apo(a) isoforms in RA remains unknown, a significant aspect that is related to the atherogenic potential of Lp(a). Furthermore, the role of the Lp(a) and different apo(a) isoforms in the atherosclerotic disease of these patients remains unclear.

CONCLUSION

RA patients are exposed to chronic systemic inflammation, which could explain the accelerated atheromatosis observed in these patients due in part to the structural and functional alterations in lipoprotein in relation to inflammation. Although future studies are required, qualitative aspects of lipoproteins should be considered in the estimation of cardiovascular risk in RA patients, since the quantitative values currently used underestimate the real risk in these patients.

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Rheumatoid arthritis: Nuclear Medicine state-of-the-art imaging

Paulo Henrique Rosado-de-Castro, Sergio Augusto Lopes de Souza, Dângelo Alexandre, Lea Mirian Barbosa da Fonseca, Bianca Gutfilen

Paulo Henrique Rosado-de-Castro, Sergio Augusto Lopes de Souza, Lea Mirian Barbosa da Fonseca, Bianca Gutfilen, Departamento de Radiologia, Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro 21941-913, Brazil
Dângelo Alexandre, Instituto Nacional de Traumatologia e Ortopedia, Rio de Janeiro 20940-070, Brazil
Author contributions: Rosado-de-Castro PH, Lopes de Souza SA, Alexandre D, Barbosa da Fonseca LM and Gutfilen B performed the literature review, drafted the article, revised the article critically for important intellectual content and finally approved for print.
Correspondence to: Bianca Gutfilen, PhD, Professor, Departamento de Radiologia, Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Ilha do Fundão, Rio de Janeiro 21941-913, Brazil. bianca.gutfilen@gmail.com
Telephone: +55-21-25622399 Fax: +55-21-25622399
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Abstract

Rheumatoid arthritis (RA) is an autoimmune disease, which is associated with systemic and chronic inflammation of the joints, resulting in synovitis and pannus formation. For several decades, the assessment of RA has been limited to conventional radiography, assisting in the diagnosis and monitoring of disease. Nevertheless, conventional radiography has poor sensitivity in the detection of the inflammatory process that happens in the initial stages of RA. In the past years, new drugs that significantly decrease the progression of RA have allowed a more efficient treatment. Nuclear Medicine provides functional assessment of physiological processes and therefore has significant potential for timely diagnosis and adequate follow-up of RA. Several single photon emission computed tomography (SPECT) and positron emission tomography (PET) radiopharmaceuticals have been developed and applied in this field. The use of hybrid imaging, which permits computed tomography (CT) and nuclear medicine data to be acquired and fused, has increased even more the diagnostic accuracy of Nuclear Medicine by providing anatomical localization in SPECT/CT and PET/CT studies. More recently, fusion of PET with magnetic resonance imaging (PET/MRI) was introduced in some centers and demonstrated great potential. In this article, we will review studies that have been published using Nuclear Medicine for RA and examine key topics in the area.

Key words: Rheumatoid arthritis; Nuclear medicine; Scintigraphy; Single photon emission computed tomography; Positron emission tomography

Core tip: In recent years, the use of nuclear medicine to characterize and diagnose infectious and inflammatory diseases has been rapidly increasing. In the case of rheumatoid arthritis (RA), the success of treatment requires improvement of early diagnosis and assessment of response to anti-inflammatory therapy. In this setting, Nuclear Medicine may be valuable in the assessment of early inflammatory activity in RA, foreseeing and monitoring response to treatment, and allowing the selection of optimal treatments for each patient. The development of new radiopharmaceuticals and hybrid imaging technologies may improve the potential of molecular imaging in the field.

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INTRODUCTION

For many years, the evaluation of rheumatoid arthritis (RA) has been restricted to conventional radiography, helping to establish the diagnosis and, subsequently, to monitor the progression of disease. However, this modality doesn't have good sensitivity in identifying the inflammatory process that occurs in the initial stages of the disease. In the past 20 years, new drugs (particularly biological agents) that greatly reduce the progression of RA have allowed a more efficient treatment. Therefore, an early diagnosis and an adequate follow-up of the disease have become major challenges for Rheumatology and Radiology, and better results can only be achieved if technologies from both specialties are developed together.

New imaging systems have been presented in the past years and digital technologies significantly transformed clinical practice. Here, we will review the different studies that have been published using nuclear medicine for evaluation of RA and discuss important aspects in the area.

CONVENTIONAL NUCLEAR MEDICINE

Conventional nuclear medicine techniques are divided basically into two-dimensional planar scans and three-dimensional single photon emission computed tomography (SPECT), which permits reconstruction of images in sagittal, coronal and axial planes[1-3]. SPECT images allow improved localization of the site of uptake (*e.g.*, for differentiating involvement of the facets or pedicle of a vertebra), and increases sensitivity and specificity[1-3]. Hybrid SPECT/computed tomography (CT) imaging, which allows morphological and functional data to be acquired and fused, increases even more the diagnostic accuracy of Nuclear Medicine studies because it provides anatomical localization of SPECT findings[4].

Different radionuclides, including Technetium-99m (^{99m}Tc), Gallium-67 (^{67}Ga), Indium-111 (^{111}In) and Iodine-123 (^{123}I) have been used in studies for RA and will be reviewed in the following sections.

^{99m}Tc-labeled diphosphonates

Amongst the different radionuclides available, ^{99m}Tc is presently the most commonly used[3,5]. For the evaluation of bone diseases, there are different radiopharmaceuticals available including ^{99m}Tc labeled hydroxy methylene diphosphonate (HDP), dicarboxy propane diphosphonate (DPD) and methylene-diphosphonate (MDP), with the latter being the most commonly used[1-3]. After intravenous injection, ^{99m}Tc-MDP circulates in the vascular system, then equilibrates to the extravascular space and, subsequently, accumulates in the bone. These three phases may be evaluated in a bone scintigraphy, which has high sensitivity but low specificity. In many cases, distinction between degenerative, inflammatory and metastatic bone processes may be difficult[1-3,6]. In RA, bone scintigraphy has a certain degree of usefulness and may allow identification of arthritic joints[7,8]. However, planar scintigraphy and SPECT have the limited spatial resolution in comparison to radiography and magnetic resonance imaging (MRI)[3,5].

Bachkaus *et al*[6] performed a prospective study comparing clinical evaluation, conventional radiography, ultrasound, three-phase ^{99m}Tc-MDP bone scintigraphy and MRI in 60 patients with different types of arthritis including RA, arthritis related to connective tissue disease and spondylarthropathy. They found that clinical assessment, scintigraphy, ultrasound and MRI were more sensitive than radiography in identifying inflammatory processes and destructive joint lesions. However, scintigraphy had limited specificity.

Recently, in an attempt to improve the specificity of SPECT images, Ostendorf *et al*[9] studied the application of a multipinhole SPECT (MPH-SPECT), originally created for small animal imaging[10]. Six human subjects were studied after injection of ^{99m}Tc-DPD: 3 with established RA, 1 with early RA, 1 with osteoarthritis (OA) and 1 healthy volunteer. The authors reported better identification of anatomic landmarks with MPH-SPECT in contrast to planar scintigraphies, but comparison with other methods such as MRI was limited.

In a second study by the same group, the clinically dominant hands of 13 subjects with initial RA, nine with initial OA and five control subjects were evaluated by MPH-SPECT and skeletal scintigraphy. MRI was carried out in RA subjects, and these images were later fused with MPH-SPECT. Bone scintigraphy identified 26 articulations with augmented uptake while MPH-SPECT detected 80 joints. MPH-SPECT indicated a central tracer uptake in RA (10 out of 13 patients) and an eccentric pattern in OA (7 out of 9 patients). Uptake in MPH-SPECT matched areas of marrow edema and destruction in MRI in 11 out of 13 patients.

Buchbender *et al*[11] compared 3 tesla MRI with ^{99m}Tc-DPD scintigraphies using MPH-SPECT in 10 early RA patients. Visual and region of interest (ROI) analyses of MPH-SPECT images were carried out. The authors reported that MPH-SPECT detected higher rates of inflammatory bone involvement compared to MRI.

^{67}Ga-citrate

The accumulation of ^{67}Ga-citrate into inflammatory is complex and involves different mechanisms. It binds to transferrin and suffers extravasation in areas of inflammation where vascular permeability is increased[12,13]. Moreover, ^{67}Ga suffers cross-chelation to lactoferrin, a protein released which is taken up by macrophages and also binds to siderophores, low-molecular-weight products of bacteria[12,13].

Even though ^{67}Ga-citrate scintigraphy has good sensitivity detection of inflammation and has been used in the evaluation of RA[3,13-15], there are numerous drawbacks with this technique. ^{67}Ga scintigraphy leads to relatively elevated radiation burden because of its physical half-life and high-energy gamma radiation (91-393 keV)[16]. It also has elevated background activity and slower imaging times. Additionally, it cannot precisely differentiate in-

flammation from infection or neoplasias[13].

^{99m}Tc and ^{111}In-labeled leukocytes

Leukocytes may be labeled with ^{99m}Tc or ^{111}In-oxine for detection of inflammatory and infectious diseases[3,17-20]. Al-Janabi *et al*[21] labeled leukocytes with ^{99m}Tc in subjects with RA and found a 50%-80% decrease in leukocyte uptake after local steroid injection into eight out of nine painful knees, which showed clinical response. Gaál *et al*[22] performed ^{99m}Tc-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO) labeled leukocyte scintigraphy in 21 patients with RA. A significant association was seen between the uptake in hands and feet and clinical evaluation. Thurlings *et al*[23] performed two scintigraphies after injection of ^{99m}Tc-HMPAO labeled monocytes in eight RA patients, with a two-week interval. Arthroscopic biopsies were performed one day after the second scintigraphy and synovial macrophage infiltration was evaluated by immunohistochemical staining. The number of scintigraphically positive joints was significantly associated with the number of activated macrophages in the synovium.

^{99m}Tc-labeled ciprofloxacin

Appelboom *et al*[24] investigated the use of ^{99m}Tc labeled ciprofloxacin (Infecton scintigraphy) in 106 patients, 17 of them with RA. Subjects received an intravenous injection of ^{99m}Tc-ciprofloxacin and whole body scans were acquired after 4 h. Augmented uptake was seen in 12 patients with RA. Association between clinically inflamed joints and articular ^{99m}Tc-ciprofloxacin uptake was observed. The authors concluded that the radiotracer was not specific for infection and could potentially identify the presence of inflammation in joints and monitor their response to treatment.

^{99m}Tc-labeled human immunoglobulin G

Labeling polyclonal human immunoglobulin G (HIG) with ^{99m}Tc allows evaluation of inflammation and infection. Different groups have suggested that these exams may have higher sensitivity than clinical assessment, bone scintigraphy and labeled leukocyte scintigraphy[25,26]. However, similar to radiotracers like ^{67}Ga, the exam has limited specificity.

^{99m}Tc and ^{111}In-anti-E-selectin

Chapman *et al*[27] evaluated the biodistribution of ^{111}In-labeled anti-E-selectin monoclonal antibodies in 14 subjects with RA and compared it with ^{111}In-labeled polyclonal HIG in 6 of these patients. ^{111}In-anti-E-selectin resulted in better sensitivity and image intensity and more focal localization in synovium.

The same group published another study where they used ^{111}In-anti-E-selectin and ^{99m}Tc-labeled polyclonal HIG in 11 patients with RA[28]. Scintigraphic images were compared with clinical scores. The authors reported that ^{111}In-anti-E-selectin had greater sensitivity and specificity than ^{99m}Tc-HIG. However, the necessity of performing 24 h images with ^{111}In-anti-E-selectin led to the development of a ^{99m}Tc-labeled tracer[29]. In this study, the authors performed scintigraphies 4 h and 20-24 h after ^{111}In- or ^{99m}Tc-anti-E-selectin injection in a group of 10 patients with RA. They concluded that they led to similar diagnostic accuracy, what favored the use of the ^{99m}Tc-labeled tracer. In another group of 16 RA patients, ^{99m}Tc-anti-E-selectin was compared with ^{99m}Tc-HDP 4h after injection. Although ^{99m}Tc-anti-E-selectin seemed to have *in vivo* instability, as indicated by thyroidal and intestinal uptake, ^{99m}Tc-anti-E-selectin was better than ^{99m}Tc-HDP (88% *vs* 57%) in terms of accuracy. Inactive or normal joints didn't show uptake of ^{99m}Tc-anti-E-selectin.

^{111}In-octreotide

Vanhagen *et al*[30] studied the articulations of 14 subjects with ongoing RA, 4 with intense OA, and 30 controls. The somatostatin analog ^{125}I-Tyr3-octreotide was used for *in vitro* somatostatin receptor autoradiography and the somatostatin analog ^{111}In-DTPA-D-Phe1-octreotide was used for scintigraphy. A total of 76% of tender and of augmented joints of the subjects with RA were identified by nuclear medicine scans. The authors found that joint uptake was associated with the amount of pain and swelling. *In vitro* autoradiography of the synovial membranes indicated somatostatin receptors in 2 of the RA patients. In subjects with OA, joint uptake was considerably poorer than in subjects with RA, while the ones of control subjects didn't exhibit uptake.

^{99m}Tc-anti-CD3

Marcus *et al*[31] studied the biodistribution of a ^{99m}Tc-labeled murine monoclonal antibody (Muromonab, Orthoclone OKT3®), specific for T lymphocyte glycoprotein CD3 receptor. Seven patients with RA and two with psoriatic arthritis were included. Scintigraphies of the whole-body and of the articulations were carried out. All joints with intermediate to intense pain showed intermediate to high uptake, while all asymptomatic joints and joints with mild or minimal pain had normal images. Of note, two patients had side effects (shaking chills and neck pain) after ^{99m}Tc-OKT-3 injection.

Our group of research developed another technique for labeling OKT3 with ^{99m}Tc and also investigated its use to evaluate disease activity in subjects with RA. A total of 38 patients with RA functional classes Ⅱ and Ⅲ according to American College of Rheumatology criteria were evaluated[32]. Planar anterior scans of the patients' metacarpophalangeal and interphalangeal joints, shoulders, elbows, wrists and knees were carried out 1 h and 3 h after the infusion of ^{99m}Tc-OKT3. Significant association ($P < 0.05$) was found between the ^{99m}Tc-OKT3 uptake and swollen or tender joints and the visual analogue scale. It was possible to distinguish subjects in remission from subjects with active synovitis. On the other hand, no association was seen between ^{99m}Tc-OKT3 uptake and the patients' duration of disease, gender and age or erythrocyte sedimentation rate.

In a continuation of the previous report, we have

studied 1232 joints from 44 patients with RA were evaluated 1 h and 3 h after injection of anti-CD3 antibody labeled with ^{99m}Tc and compared with another 812 joints from 33 patients with juvenile idiopathic arthritis (JIA), OA or gouty arthritis (GA)[33]. RA and JIA showed high uptake at the first scan, which augmented after 3 h. In OA, uptake was minimal or absent. Therefore, it was possible to distinguish RA and JIA from OA and GA. However, it was not possible to distinguish subjects with RA in remission from those with OA.

^{99m}Tc-anti-CD4

Becket *et al*[34] performed three-phase bone scans with ^{99m}Tc-HDP and scintigraphies with an anti-CD4 antibody named MAX.16H5 labeled with ^{99m}Tc. Six patients with RA were included prospectively and five of them received ^{99m}Tc-anti-CD4 scans after 1.5 h, 4 h and 24 h. In all patients, affected joints could be distinctively imaged at as early as 1.5 h. The authors reported that uptake in affected joints was associated with clinical signs and early ^{99m}Tc-MDP weakly uptake. However, it was not clear if late uptake of the radiotracer differed from control immunoglobulins.

To evaluate this aspect, the same group later included eight patients with severe, active RA to perform scintigraphies with ^{99m}Tc-labeled anti-CD4 or polyclonal HIG, with five of them receiving both radiotracers[35]. Scintigraphies of the whole-body and of the joints were carried out after 1, 4 and 24 h. The authors found that ^{99m}Tc-anti-CD4 had higher target-to-background ratio in knee and elbow joints, suggesting higher specificity than ^{99m}Tc-HIG.

^{99m}Tc-anti-CD20

Malviya *et al*[36] labeled Rituximab, an anti-CD20 antibody (MabThera®), with ^{99m}Tc in 20 patients with chronic inflammatory diseases and acquired scintigraphies after 6 h and 20 h. Five of the patients had RA and presented uptake of the radiotracer in known lesioned joints. Nonetheless, such uptake was variable and not all patients showed uptake in each clinically positive joint.

^{99m}Tc-anti-tumor necrosis factor-alpha

Chianelli *et al*[37] labeled Infliximab (Remicade®), a chimeric mouse/human anti-tumor necrosis factor alpha (anti-TNF-alpha) antibody, with ^{99m}Tc and included seven RA patients eligible to receive intra-articular Infliximab therapy for scintigraphic evaluation previously and 3 mo following the therapy. Planar scans of the joints were carried out 3, 6 and 24 h after intravenous infusion of ^{99m}Tc-Infliximab. Post-treatment scans indicated that the uptake disappeared in 1 joint, was reduced considerably in 2, was faintly in 4 and remained unchanged in 2. The authors suggested ^{99m}Tc-Infliximab could potentially aid in the choice of those subjects who would profit most from treatment with unlabeled Infliximab and provide a more objective assessment of immunotherapy efficacy.

A study from our group of research compared whole body and hand/wrist scintigraphies after injection of ^{99m}Tc-anti-TNF-α with clinical examination and MRI of wrists joints and hands in subjects with active RA[38]. Eight subjects with active RA and one healthy volunteer were included. With MRI considered as the gold standard, the sensitivity and specificity of scintigraphy was 89.9% and 97.3%, respectively, while pain and edema had sensitivity of 65.3% and 59.2% and specificity of 75.2% and 95.3%, respectively.

^{123}I-IL-1 receptor antagonists

Barrera *et al*[39] studied the biodistribution of ^{123}I labeled interleukin-1 receptor antagonist (IL-1ra) in four subjects with RA. A comparison of scintigraphies acquired with ^{123}I-IL-1ra and those acquired with a non-specific radiopharmaceutical was made. Although the authors found that labelled IL-1ra allowed the identification of synovial disease in subjects with RA this process did not seem to occur by specific binding.

POSITRON EMISSION TOMOGRAPHY

The radionuclides that have been used for Positron Emission Tomography (PET) include fluorine-18 (^{18}F), carbon-11 (^{11}C) and iodine-124 (^{124}I). PET has two to three times higher spatial resolution than SPECT and permits quantification of standardized uptake value (SUV)[40-42]. In the following sections the studies that used PET for RA monitoring are reviewed.

^{18}F- fluoro-D-glucose

2-deoxy-2-(^{18}F) fluoro-D-glucose (^{18}F-FDG) allows evaluation of tissue metabolism. ^{18}F-FDG accumulation in inflammatory and infectious diseases is based on its increased uptake by polymorphonuclear leukocytes, which adopt glucose after becoming activated. The transportation of ^{18}F-FDG is intermediated by glucose transporters (GLUT), which are also to a higher amount present on the cell membrane of inflammatory and infectious cells. RA is an autoimmune disease, which is associated with systemic and chronic inflammation of the joints, resulting in synovitis and pannus formation, both leading to increased ^{18}F-FDG uptake.

Polisson *et al*[43] published a seminal report where ^{18}F-FDG PET and MRI were carried out in 2 RA patients with active synovitis in the carpus at baseline and after 14 wk of treatment. In comparison with baseline, there was marked improvement in clinical parameters and decrease in synovial volume measured by MRI and ^{18}F-FDG uptake measured by PET.

The same group published later another study where ^{18}F-FDG PET and gadolinium-enhanced MRI of the wrist were carried out prospectively in 12 subjects under anti-inflammatory treatment in different moments: without drugs for 2 wk and after 2 and 12 wk of treatment[44]. They found that MRI and ^{18}F-FDG PET were strongly correlated with clinical findings in wrists, and concluded that these techniques permitted quantification of altera-

tions in joint inflammation. In addition to these reports, other articles have indicated the capability of ^{18}F-FDG PET to identify alterations in disease activity, but few have shown it can foretell clinical results[45,46].

Nonetheless, one of the most important breakthroughs in the field of Nuclear Medicine has been the advent of PET/CT hybrid imaging, which allows concomitant acquisition of morphologic and functional information, increasing both sensitivity and specificity of findings. Initial case studies suggested that ^{18}F-FDG PET/CT correctly identifies articular and extra-articular inflammatory areas[47-49]. Kubota *et al*[50] performed ^{18}F-FDG PET/CT in 18 subjects with RA and evaluated uptake in the atlanto-axial, shoulder, elbow, wrist, carpal, knee and hip joints and in axillary lymph nodes. The total uptake score for all joints was significantly associated with C-reactive protein level. Furthermore, ^{18}F-FDG uptake score of painful/swollen joints were greater than not painful/swollen joints and significantly distinct between subjects in remission and those with active inflammation. Roivainen *et al*[51] studied 17 subjects with active RA that started to receive disease-modifying antirheumatic drugs. Disease activity was clinically evaluated at screening, at baseline and after 2, 4, 8 and 12 wk of therapy, while ^{18}F-FDG PET/CT of all joints was carried out at baseline and after 2 and 4 wk of therapy. ^{18}F-FDG maximum SUV decreased in 76% and 81% at weeks 2 and 4 in comparison to baseline. The percentage of decline in ^{18}F-FDG activity was associated with disease activity at week 12 and with variations in C-reactive protein levels and erythrocyte sedimentation rate.

More recently, fusion of PET and MRI has been developed. Chaudhari *et al*[52] performed an extremity ^{18}F-FDG PET/CT immediately after MRI at baseline and 5 wk after TNF-alpha inhibitor therapy in a 57-year-old female with RA. CT was later used for PET/MRI fusion. The authors reported that PET uptake decreased significantly in the synovium and at sites of erosions and clinical exam at 3 mo corroborated a positive response to therapy. Then, Miese *et al*[53] reported on the first hybrid hand PET/MRI in intial RA, demonstrating augmented ^{18}F-FDG uptake occurred in synovitis.

^{11}C-choline

Roivainen *et al*[54] included 10 subjects with inflammatory disorders of the joints, two of them with RA, in a study that compared ^{11}C-choline and ^{18}F-FDG PET with contrast-enhanced MRI. The authors found that the uptake of ^{18}F-FDG as well as ^{11}C-choline had good correlation with synovial volume measured in MRI and suggested ^{11}C-choline could be a promising radiotracer for quantitative assessment of disease activity.

^{11}C-(R)-PK11195

^{11}C-(R)-PK11195 is a radiotracer that suffers macrophage binding. Van der Laken et *al*[55] studied the knees of 11 RA patients using ^{11}C-(R)-PK11195 PET imaging and arthoscopic assessment of the knee with greatest inflammation in all subjects. The authors found that ^{11}C-(R)-PK11195 had significantly increased uptake in inflamed joints. Moreover, uptake in non-inflamed knees of RA subjects was considerably greater than in the knees of controls, indicating the existence of subclinical RA activity.

^{124}I-anti-CD20

Tran *et al*[56] included six patients in a study to evaluate the distribution of ^{124}I labeled Rituximab. One patient was excluded due to adverse effects after injection of the unlabeled drug. Whole body PET/CT was carried out in 5 subjects at 10 min, 24 h, 48 h and 72-96 h. Evaluation was carried out based on visual analyses and correlated with disease activity. Accumulation in joints occurred only after 24 h, in 4 out of 5 patients. The authors reported that several exams had uptake in clinically normal joints while a few joints with clinical arthritis had no uptake, but no quantification or comparison with other imaging methods was performed.

CONCLUSION

The success of RA therapy requires improvement of early diagnosis and evaluation of response to anti-inflammatory treatment. New powerful and efficient medications are now offered that can change the natural history of the disease. Molecular imaging may be useful in the evaluation of early inflammatory activity in RA, predicting and monitoring response to treatment, and allowing the selection of optimal treatments for each patient. Nuclear Medicine techniques, particularly SPECT/CT, PET/CT and PET/MRI can deliver important molecular information that may be correlated with biological therapies. However, large prospective, controlled clinical trials comparing imaging methods are still needed to improve the understanding of the potentials of Nuclear Medicine in RA.

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Beyond the joint: Subclinical atherosclerosis in rheumatoid arthritis

Antongiulio Scarno, Fabio Massimo Perrotta, Francesca Cardini, Alessia Carboni, Gianmarco Annibali, Ennio Lubrano, Antonio Spadaro

Antongiulio Scarno, Francesca Cardini, UOC Medicina E, Dipartimento di Medicina Interna e Specialità Mediche, Sapienza - Università di Roma - Azienda Policlinico Umberto I, 00161 Rome, Italy
Fabio Massimo Perrotta, Alessia Carboni, Gianmarco Annibali, Antonio Spadaro, UOC di Reumatologia, Dipartimento di Medicina Interna e Specialità Mediche, Sapienza-Università di Roma - Azienda Policlinico Umberto I, 00161 Rome, Italy
Ennio Lubrano, Academic Rheumatology Unit, Department of Medicine and Health Sciences, University of Molise, 86100 Campobasso, Italy
Author contributions: All authors contributed to this paper.
Correspondence to: Antonio Spadaro, Professor, UOC Medicina E, Dipartimento di Medicina Interna e Specialità Mediche, Sapienza - Università di Roma - Azienda Policlinico Umberto I, Viale del Policlinico 155, 00161 Rome, Italy. a.spadaro.reuma@virgilio.it
Telephone: +39-06-49974642 Fax: +39-06-49974642
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Abstract

Rheumatoid arthritis is a chronic autoimmune inflammatory disease associated with increased cardiovascular risk and higher mortality in respect to general population. Beyond joint disease, inflammation is the major determinant of accelerated atherosclerosis observed in rheumatoid arthritis. We review the relationship between inflammation, atherosclerosis and cardiovascular risk in rheumatoid arthritis, focusing on the assessment of subclinical atherosclerosis by functional and morphological methods. These tools include flow mediated dilatation, carotid intima-media thickness, ankle/brachial index, coronary calcium content, pulse wave analysis and serum biomarker of subclinical atherosclerosis.

Key words: Atherosclerosis; Rheumatoid arthritis; Flow mediated dilatiation; Intima-media thickness; Inflammation

Core tip: In this paper we briefly review the role of subclinical atherosclerosis in rheumatoid arthritis, its relationship with inflammatory process and the current available method to detect early atherosclerotic changes.

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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease that affects synovial joints and lead to chronic pain, bone erosions and progressive disability. Approximately 1% of the adult population in the United States has RA, and the overall world prevalence range from 0.5% to 1%, qualifying it as the most common chronic inflammatory condition[1,2]. Beyond joint disease, evidences support the hypothesis that chronic inflammation could increase cardiovascular risk: patients with RA die earlier than the general population[3], in particular, mortality risk in RA patients is 1.5 higher than general population and occurs largely as a result of higher rates of cardiovascular death[4]. A recent meta-analysis shows that standardized mortality ratio (SMR) ranges from 0.99 to 3.82 for myocardial infarction and from 1.08 to 2 for cerebrovascular diseases[5], while risk to develop peripheral arterial diseases is 2.35 in a large cohort of United States patients. Risk to develop non fatal cardiovascular and cerebrovascular diseases, that lead to significant disability care cost is also increased in RA. These diseases are strictly related to an accelerated atherosclerotic pro-

cess and, although several factors contribute independently to the heightened cardiovascular risk observed in patients with RA, systemic inflammation contributes importantly[6]. Different authors suggested in fact that the higher prevalence of cardiovascular events in RA patients could be explained by other mechanisms than the classic atherosclerotic risk factors[7-10].

We briefly review the role of subclinical atherosclerosis in RA, its relationship with inflammatory process and the non-invasive methods to detect early atherosclerotic changes and to estimate risk of cardiovascular events.

INFLAMMATION AND ATHEROSCLEROSIS IN RA

Atherosclerosis and RA share a number of similarities, including T-cell and mast cell activation, production of pro-inflammatory cytokines such as tumor necrosis factor (TNF) alpha and interleukin (IL)-6, and increased expression of leukocyte adhesion molecules[11].

Patients with RA have elevated levels of the acute-phase reactant C reactive protein (CRP), a marker of inflammation associated with increased cardiovascular risk. Moreover, CRP causes endothelial dysfunction by decreasing endothelial nitric oxide synthase, a potent anti-atherogenic factor[12].

Patients with RA with elevated erythrocyte sedimentation rate (ESR) have a higher rate of cardiovascular death than those without elevated ESR. This inflammatory marker also increases linearly with increased carotid artery intima-media thickness in both patients with RA and healthy controls[6].

Immune system plays an important role in the progression and development of atherosclerotic disease and associated complications. Atherosclerosis is in fact now considered as an autoimmune disease[6,13,14]. The presence of inflammatory cells, such as macrophages and activated lymphocytes within atherosclerotic plaque, is a strong indicator of immune system involvement. Furthermore, the inflammatory burden in RA and other rheumatologic diseases increases the process of oxidation of low density lipoproteins (ox-LDL), responsible for the formation and progression of atherosclerotic plaque[15]. ox-LDL amplifies the inflammatory response through the expression of adhesion molecules by endothelial cells and through the production of pro-inflammatory cytokines (TNF alpha, IL-1, IL-6) by macrophages[13,16]. Mature dendritic cells (DC) express CCL17 that favoring T-lymphocytes recruitment; moreover the presence of modified or native LDL, induce up-regulation of co-stimulatory molecules on DCs that lead to T-lymphocyte proliferation. Modified LDL determine the formation of new antigenic epitopes which can be presented by DCs and brought to clonal expansion of LDL-specific T-lymphocytes. Indeed, about 10% of all T-lymphocytes detectable in human atherosclerotic plaques specifically recognize modified or native LDL. Of note, LDL-specific T-lymphocytes are also present in the circulation[17]. The elevated levels of pro-inflammatory cytokines can elicit a systemic inflammatory state that could lead to pro-atherogenic phenotype: cytokines, in addition to their role in regulating immune responses, mediate a number of metabolic effects that, in the short term, mediate appropriate responses to injury or infection, but on a chronic basis prove detrimental: systemic release of IL-1, IL-17, IL-6, and TNF-α, produced in synovial tissue in RA patients, promotes a number of pro-atherogenic functions of the liver, adipose tissue, skeletal muscle, and vascular endothelium, including insulin resistance, dyslipidemia, endothelial activation, and prothrombotic and antifibrinolytic effects[14]. CRP and other factors local released by leukocytes, contributes to early endothelial dysfunction and damage.

Immunological abnormalities such as auto-antibodies production may be involved in endothelial dysfunction and in the process of progression and rupture of the atherosclerotic plaque. Rheumatoid factor could be found in the atheroma as immunocomplex and is associated with impaired endothelial function and increased mortality[18].

Atherosclerotic vascular involvement and cardiac abnormalities including pericardial, myocardial, and endocardial involvement, were higher among anti citrullinated peptide antibodies (ACPA) positive RA patients[19]. Citrullinated proteins, including citrullinated fibrinogen, are present within atherosclerotic plaque, and co-localized with peptidylarginine deiminase type 4 (PAD-4). Moreover, ACPA serum levels correlates with subclinical atherosclerosis indices. These, and other observations, support the hypothesis that citrullinated epitopes within the atherosclerotic plaque may be targeted by RA-associated ACPAs, thus forming immune complexes capable of locally perpetuating plaque inflammation and progression[20].

Several studies demonstrated that endothelial dysfunction plays a central role in the pathogenesis of atherosclerosis, promotes early atherosclerotic changes and is predictive for the development of cardiovascular events[21,22]. Patients with RA have a greater prevalence of arterial atherosclerotic plaques than controls[23,24] and the presence of atherosclerotic plaques correlate with disease duration, radiological damage index and systemic inflammation[25].

Early detection of subclinical atherosclerosis in RA could be useful to prevent cardiovascular events, death and disability. Different non-invasive methods are available to detect atherosclerosis and to estimate risk of cardiovascular events. These tools include functional and morphological assessment of artery physiology.

FLOW MEDIATED DILATATION

The normal, healthy endothelium regulates vascular tone and structure and exerts anticoagulant, anti-platelet, and fibrinolitic properties. The maintenance of vascular tone is accomplished by the release of numerous dilator and constrictor substances. The major vasodilator substance released by the endothelium is nitric oxide (NO). Endothelial dysfunction occurs when NO bioavailability is

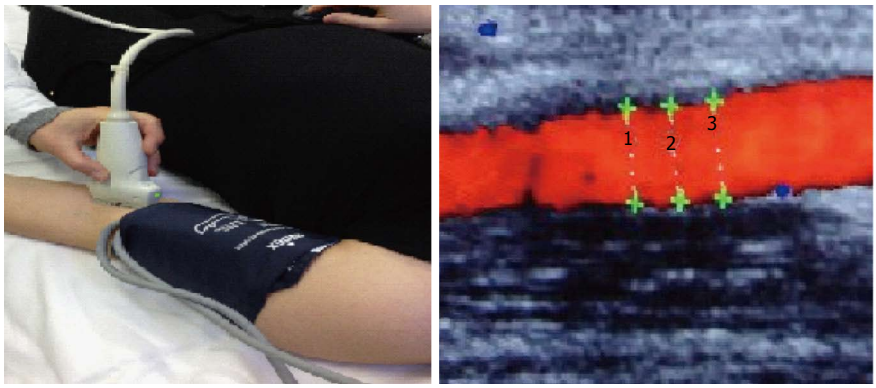

Figure 1 Flow mediated dilatation is based on the reactive phenomenon that occurs when arterial blood flow is restored after a period of transient arterial occlusion using a sphygmomanometer. This reactive hyperaemia is observable at ultrasound power Doppler mode monitor.

reduced[10,21,22,26,27].

Among different methods, the assessment of flow-mediated dilatation (FMD) is one of the most used to assess the endothelial function *in vivo*, with a non invasive approach[28]. FMD reflects the ability of brachial artery to dilate after reactive hyperaemia induced by shear stress. It depends on the endothelial production of agents with vasomotor action, specifically NO[29-31](Figure 1).

Traditional cardiovascular risk factors, such as smoking, obesity, abnormal glucose or lipid dismetabolism and hypertension, could alter endothelial function and have been related with impaired FMD. Moreover, impaired FMD predicts the risk of future cardiovascular events and it is a surrogate marker of general atherosclerosis[32-35].

Endothelial function could also be assessed with administration of sublingual nitroglycerin (NTG). NTG induces a vasodilatation that is endothelium-independent to production of local NO[36].

In RA patients, FMD is impaired, compared to controls, independent to the presence of classical atherosclerosis risk factors. RA patients showed similar FMD impairment than those with diabetes, supporting the theory that RA is an independent risk factor for atherosclerosis. Endothelial dysfunction in these patients seems to be related to disease activity (DAS28), disease duration, HLA-DRB1 shared epitope and inflammatory indices[37]. Furthermore, in RA patients disease activity, assessed by DAS28, ESR and CRP, predicts the magnitude of endothelial dysfunction[38]. FMD is impaired even in patients with early disease, suggesting that atherosclerotic process starts early[39]. Few studies demonstrate NTG-mediated vasodilatation impairment in RA patients. Hannawi *et al*[40] in a longitudinal study on 20 patients with early RA found that both FMD and NTG-mediated vasodilatation were significantly lower in patients in respect to control and negatively correlated with age and CRP.

INTIMA-MEDIA THICKNESS

Carotid atherosclerosis may be determined by the assessment of common carotid intima-media thickness (IMT) using high-resolution B-mode ultrasound technique (Figure 2). Increased IMT is associated to the onset of cardiovascular events and is strongly related to the presence of atherosclerosis risk factors, such as hypertension, hypercholesterolemia, smoke, diabetes and obesity[41-43]. Several studies reported increased IMT in patients with rheumatic disease, in particular, patients with systemic lupus erythematosus, psoriatic arthritis and ankylosing spondylitis show increased IMT in respect to control as demonstrated in some study[44,45]. Patients with RA showed increased IMT in respect to age and sex matched controls: a meta-analysis from 22 studies, in 2011, compared carotid IMT data of 1384 RA patients with 1147 control subjects. Seventeen of 22 studies reported a statistical significant higher IMT in RA patients compared with controls. Mean IMT in RA patients was 0.71 mm and in control subjects 0.62 mm even in subject without other cardiovascular risk factors[46,47]. In RA patients IMT correlates with disease activity, severity and disease duration, with CRP, erythrocyte sedimentation rate (ESR) and use of corticosteroids[25]. Furthermore, increased IMT and carotid plaque presence predict the risk of cardiovascular morbidity in RA patients, in particular, carotid artery IMT > 0.9 has a high predictive power for the development of cardiovascular events over a 5-years period follow-up[48,49].

ANKLE/BRACHIAL INDEX

The Ankle/Brachial Index (ABI) or Windsor's Index represents a simple, useful, reproducible, non-invasive method to detect asymptomatic peripheral artery disease (PAD). It expresses the ratio between the systolic blood pressure in posterior tibial artery measured at the ankle, and the systolic blood pressure measured in the brachial artery. It has been used for many years to assess the severity of peripheral artery disease and to detect the presence of asymptomatic, although hemodynamically relevant, stenosis[50,51].

ABI is an indicator of generalized atherosclerosis and can provide prognostic information about cardiovascular diseases. Moreover, patients with lower values of ABI are

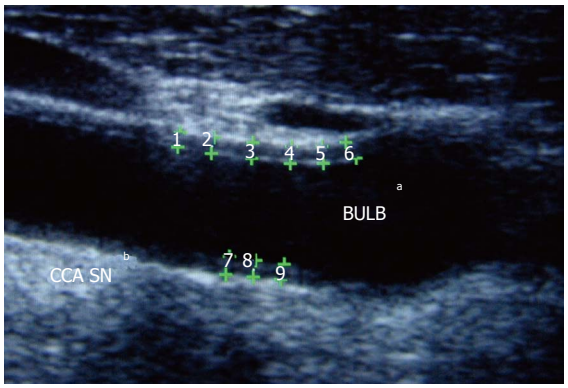

Figure 2 B-mode ultrasound measurement of carotid intima media thikness in patient with Rheumatoid Arthritis. [a]BULB: Carotid bulb; [b]CCA SN: Left common carotid arteria.

at higher risk of myocardial infarction or stroke. In RA patients, disease activity, disease duration and corticosteroid use are risk factors for PAD. Few studies evaluated the prevalence of peripheral artery disease in patients with rheumatic disease. Del Rincòn *et al*[52] studied 234 patients with RA and demonstrated an increased prevalence of impaired peripheral artery function. In this study there was high percentage of peripheral artery obstruction and incompressibility in RA patients in respect to controls[52].

CORONARY CALCIUM CONTENT

Coronary atherosclerosis is the major determiner of miocardial infarction, but could be directly detectable only through invasive exams such as angiography. Indirect information about coronary atherosclerosis could be obtained by measurement of calcium content. Coronary Calcium Content (CAC) measurement is considered as surrogate marker of atherosclerosis because of its high correlation with total atherosclerotic plaques demonstrated in angiographic, hystopathologic, and ultrasound studies. CAC is a marker of subclinical atherosclerosis of the coronary district and gives quantitative measurement of the calcified share of coronary atherosclerotic plaque. Moreover, it strongly predicts the risk of cardiovascular disease in general population[53].

Recent evidences suggest that measurement of CAC is predictive of myocardial infarction and cardiovascular disease at 5 years and the use of CAC can provide important informations, independent from the other traditional cardiac risk factors[53,54]. Different cross-sectional studies investigated the role of CAC detection in RA patients. In particular Giles *et al*[55] showed a higher prevalence and extent of CAC in RA patients compared with controls after adjustments for the main cardiovascular risk factors. Furthermore, patients with longstanding RA have more extensive subclinical atherosclerosis assessed by CAC compared to patients of the same age as a consequence of accelerated atherosclerosis[55]. Finally, in RA patients, higher CAC is significantly associated with serum TNF-alpha and IL-6 levels. This evidence-supports the role of inflammation in the promotion of atherosclerosis, and specifically of coronary calcification in RA.

CORONARY FLOW RESERVE

Coronary flow reserve (CFR) gives indirect information on the status of coronary district through the analysis of artery flow signals. Impairment of endothelial function and reduced CFR, which reflects coronary microvascular function, has been shown to be early manifestation of atherosclerosis and coronary artery disease. CFR is measured with non invasive trans-thoracic Doppler transducer used to identify patients with known or suspected cardiovascular diseases[56,57]. CFR is impaired in patients with connective tissue diseases and RA without clinical evidence of heart disease, as a result of impaired microcirculation, as demonstrated by reduced CFR in a cohort of 81 RA patients compared with healthy controls[58]. Moreover, in RA CFR correlated with disease duration and with left ventricular function[58,59].

PULSE WAVE ANALYSIS

Arterial stiffness is one of the events that occur in the natural process of aging, but it could also be related to pathological process as arteriosclerosis. Pulse Wave Analysis (PWA) is one of the most used and reproducible method to assess arterial stiffness. PWA consists of two fundamental components: pulse wave velocity (PWV) and augmentation index (AIx). PWV is an excellent indicator of arterial compliance of large vessels. Several studies demonstrated that hypertension, diabetes and smoke, reduce the compliance of artery wall. Furthermore, PWV is associated to coronary atherosclerosis and to an higher mortality. Significantly increase in PWV was observed also in inflammatory rheumatic diseases such as SLE and RA and correlates with impaired FMD and increased IMT[60-62]. Chronic and systemic inflammation could enhance arterial stiffness increasing the presence of fibroblasts cells at endothelial level, interfering with the processes that regulates arterial vasodilation and constriction. In RA patients arterial elasticity is also inversely related with inflammation indices[60]. PWA appears to be a more sensitive test of vascular dysfunction than FMD in RA and may be the preferred marker of vascular dysfunction in RA patients. Significantly increased PWV was observed in RA patients and PWV was correlated with impaired FMD and increased IMT. Instead, arterial elasticity is decreased and is inversely associated with measures of inflammation. In a recent study Provan *et al*[62] demonstrated the predictive value of CRP to increased arterial stiffness in 15 year follow up RA patients, confirming the role of inflammation on early atherosclerotic changes.

SERUM BIOMARKER OF SUBCLINICAL ATHEROSCLEROSIS

In addition to traditional risk factors in RA other possible biomarkers that could be associated with the develop-

ment of subclinical atherosclerosis were investigated. In particular, it has been suggested that serum biomarker could be useful to assess the presence of subclinical atherosclerosis or to estimate the risk to develop cardiovascular events. The levels of ox-LDL are associated with increased cardiovascular risk and were significantly more elevated in RA patients compared to controls. Moreover serum levels of NO in patients with RA are significantly lower than in controls and, also, correlated inversely with IMT[63].

Asymmetric-dimethylarginine (ADMA) is a molecule that inhibits endothelial NO synthase (eNOS). Elevated ADMA levels are an independent risk factor for endothelial dysfunction, and they have been associated with hypertension, diabetes, hypercholesterolemia, renal failure, and atherosclerosis in both experimental models and humans. Recent evidences demonstrated that ADMA levels are increased in RA patients in respect to control and its levels decreased after therapy[64].

Apeline is a recently described peptide that is known to be produced by several cell types. It causes endothelium-dependent vasorelaxation by triggering the release of NO. Apeline serum levels are significantly lower in RA patients[64]. Other potential biomarkers of subclinical atherosclerosis are anti-oxidant substances such as beta-carotene, vitamin E, D and C. Further studies are needed to define the role of these molecules in clinical practice.

CONCLUSION

Vascular function is abnormal in RA and the atherosclerotic process seems to be accelerated: increased arterial stiffness, reduced arterial elasticity, impaired endothelial response, increased IMT and coronary calcium content are related to presence of systemic inflammation and with increased risk of cardiovascular morbidity and mortality. The management of RA patients should be in line with the European League Against Rheumatism recommendations for the management of cardiovascular risk in patients with RA[65]: these recommendations provide adequate control of arthritis and periodic evaluations of the cardiovascular risk; in particular, treatment strategy to control cardiovascular risk factors should be based on the use of statins and ACE-inhibitors or angiotensin II blockers because of their potential anti-inflammatory effects[65]. Further studies are needed to understand the impact of traditional therapies and new biologic drugs on the development of subclinical atherosclerosis and cardiovascular risk prevention. Traditional DMARDs and anti-TNF therapy could potentially decrease cardiovascular risk and improve endothelial function through the impact on inflammation. To support this hypothesis, some studies showed improvement in endothelial function, assessed by FMD and no progression of carotid IMT, in RA patients treated with adalimumab and infliximab[66,67]. Effect of B-cells depletion therapy on subclinical atherosclerosis is still debated: some study reported no effects on arterial stiffness during 6 mo therapy with rituximab, while other evidences demonstrated beneficial effects on FMD and IMT[68,69]. In conclusion, patients and physicians should be aware of the potential cardiovascular risk of rheumatoid arthritis and take specific diagnostic and therapeutic measures to assess and reduce this risk.

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Protein kinase small molecule inhibitors for rheumatoid arthritis: Medicinal chemistry/clinical perspectives

Charles J Malemud, David E Blumenthal

Charles J Malemud, David E Blumenthal, The Arthritis Research Laboratory, Department of Medicine, Division of Rheumatic Diseases, Case Western Reserve University, Cleveland, OH 44106-5076, United States
Charles J Malemud, David E Blumenthal, Department of Anatomy, Case Western Reserve University, Cleveland, OH 44106-5076, United States
Charles J Malemud, David E Blumenthal, School of Medicine, Division of Rheumatology, Veteran's Administration Medical Center, Cleveland, OH 44106, United States
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Correspondence to: Charles J Malemud, PhD, Department of Medicine, Division of Rheumatic Diseases, The Arthritis Research Laboratory, Foley Medical Building, 2061 Cornell Road, Cleveland, OH 44106-5076,
United States. cjm4@cwru.edu
Telephone: +1-216-8447846 Fax: +1-216-8442288
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Abstract

Medicinal chemistry strategies have contributed to the development, experimental study of and clinical trials assessment of the first type of protein kinase small molecule inhibitor to target the Janus kinase/Signal Transducers and Activators of Transcription (JAK/STAT) signaling pathway. The orally administered small molecule inhibitor, tofacitinib, is the first drug to target the JAK/STAT pathway for entry into the armamentarium of the medical therapy of rheumatoid arthritis. The introduction of tofacitinib into general rheumatologic practice coupled with increasing understanding that additional cellular signal transduction pathways including the mitogen-activated protein kinase and phosphatidylinositide-3-kinase/Akt/mammalian target of rapamycin pathways as well as spleen tyrosine kinase also contribute to immune-mediated inflammatory in rheumatoid arthritis makes it likely that further development of orally administered protein kinase small molecule inhibitors for rheumatoid arthritis will occur in the near future.

Key words: Clinical trials; Protein kinase; Signal transduction; Small molecule inhibitor; Rheumatoid arthritis

Core tip: Signal transduction is a regulator of gene expression in cells. Janus kinase/Signal Transducers and Activators of Transcription (JAK/STAT) signaling is activated by pro-inflammatory cytokines which contributes to immune-mediated inflammation in rheumatoid arthritis. Medicinal chemistry was employed to develop JAK small molecule inhibitors for determining their clinical efficacy in active rheumatoid arthritis patients. Tofacitinib, a JAK small molecule inhibitor, is now generally used to treat moderate to severe rheumatoid arthritis patients who have not adequately responded to disease-modifying anti-rheumatic drugs or various biologic agents. The clinical efficacy of JAK small molecule inhibitors provides the impetus for future drug discovery targeted at other signal transduction pathways in rheumatoid arthritis.

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INTRODUCTION

Medical therapeutic intervention of rheumatoid arthritis

(RA) was dramatically altered with the introduction of biologic drugs with monoclonal antibody or fusion protein structures[1-5] into the armamentarium of disease-modifying anti-rheumatic drugs (DMARDs), which had previously included, non-steroidal anti-inflammatory drugs, immunosuppressive drugs, (*e.g.*, glucocorticoids, methotrexate, sulphasalazine), anti-malarial agents (*e.g.*, hydroxychloroquine), and modifiers of DNA synthesis (*e.g.*, leflunomide)[6-10] or various combinations of these DMARDs. Among the biological drugs chosen for development for RA were those whose mechanism of action was attributed to their capacity to neutralize the downstream effects of the elevated levels of the pro-inflammatory cytokines in RA sera and synovial fluid[11-15], tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and IL-6[16-18], among other interleukins[11-13] as well as possessing activity towards the inhibition of proliferation and dysfunctional RA T-cells and B-cells[19-23].

However, the general requirement that the biologic drugs need to be employed in RA therapy for long periods of time has caused problems inherent in their chronic use, including, but not limited to, the elevated relative risk for developing cancers and infections, inadequate drug responses and drug refractoriness and death as well as the potential for antibodies to be produced that are directed against the monoclonal antibodies or fusion proteins themselves[24-27] thus neutralizing their effectiveness. These crucial considerations have resulted in the contention that there needs to be continual identification of novel therapeutic targets coupled to drug development for intervention in RA and autoimmune diseases in general[28,29].

IDENTIFICATION OF PROTEIN KINASES AS POTENTIAL DRUG TARGETS FOR RA

The JAK/STAT pathway

A central theme for considering which component of RA pathology should be targeted for novel drug development first involves identifying a pathway(s) that is involved in the aberrant cell and humoral-mediated immune response and inflammation which regulate abnormal survival of T-, B-cells, macrophages and synoviocytes as well as the loss of chondrocyte viability and vitality, all of which are characteristic elements of RA progression[29]. In that regard, the Janus kinase/Signal Transducers and Activators of Transcription (JAK/STAT) signaling pathway perfectly fits this viewpoint because JAK/STAT signaling has been shown to regulate so many of the diverse cellular functions critical to RA pathogenesis and progression, including, cell survival and proliferation, immune cell-fate determination and apoptosis[26,28,30,31]. There are 4 members of the JAK family, namely, JAK1, JAK2, JAK3 and TYK2[32] and 7 STAT proteins, STAT1-4, STAT5A, STAT5 and STAT6[33].

The elevated gene expression of several pro-inflammatory cytokines, including interferon-γ (INF-γ), IL-2, IL-6, IL-7, IL-7 receptor, *IL-17*, *IL-15*, *IL-19*, *IL-21*, *IL-23* genes as well as other genes and transcription factors germane to RA pathology are all regulated by phosphorylated (*i.e.*, activated) STAT proteins[33-37]. In addition, there are several STAT-target genes relevant to cell differentiation, survival, apoptosis and cytokine signaling (*e.g.*, cyclin D1, c-Myc, Bcl-xL, Mcl-1, survivin, MKP-1, TNFRSF13b and SOCS-3), all of which play important roles in RA. For example, the complex interaction involving IL-7 and IL-7R appears to be critical for regulating the T-cell receptor-γ-locus *via* phosphorylated STAT5 and histone acetylase. Thus, the findings reported by Hartgring *et al*[38] that RA synovial fluid contained elevated levels of IL-7R made the *IL-7R* gene an even more attractive target for SMI drug development, perhaps through the inhibition of STAT5 activation.

Tofacitinib (CP-690,550)

The development and FDA approval of the first small molecule inhibitor (SMI) of a protein kinase, for use in the therapy of moderate-to-severe active RA in which methotrexate did not work well, arose from a series of sequential optimization protocols involving pyrrolopyrimidine based-JAK3 inhibitors[39], which eventually resulted in the drug CP-690,550, now called tofacitinib[40]. The efficacy of this drug for RA was established in numerous RA clinical trials[41,42] (see below) and tofacitinib has now entered general rheumatology practice.

Ruxolitinib (INCB018424)

Ruxolitinib/INCB018424 now referred to as ruxolitinib is a JAK1 and JAK2 SMI[43]. The results of studies conducted on normal volunteers[44] and RA patients[44] concluded that ruxolitinib was generally safe and well-tolerated and also exhibited acceptable oral bioavailability with dose-proportional systemic pharmacokinetics and pharmacodynamics with low oral dose clearance and a small volume of distribution. Additional results from that study showed that ruxolitinib inhibited the phosphorylation of STAT3 in whole blood that was correlated with the plasma levels of the drug. Additional clinical trials involving patients with mild-to-moderate psoriasis[43] or active RA[45] administered ruxolitinib have now been conducted. In the RA trial, Williams *et al*[45] showed that ruxolitinib achieved an American College of Rheumatology (ACR)-70 criteria in 33% of patients compared to 0% in the placebo arm. Pharmacokinetic analysis determined that ruxolitinib inhibited JAK1 and JAK2 and also reduced plasma levels of IL-6 and CD40, the latter a co-stimulatory protein found on antigen-presenting cells. Ruxolitinib was also a potent p-STAT3 SMI in *ex vivo* studies conducted on blood cells obtained from RA patients.

Pre-clinical studies and development of JAK SMIs

Clinical trials are presently being conducted with RA and psoriasis patients to determine the clinical efficacy of several JAK SMIs, including INCB020850 (specificity, JAK1

Table 1 Janus kinase small molecule inhibitors in development

SMI	JAK Specificity/other kinase inhibitory activity	Ref.
SAR302503 (Fedratinib)	JAK2	[46]
CEP701 (Lestaurtinib)	JAK2	[47]
SB1518 (Pacritinib)	JAK2/FLT3[1]	[48]
XL-019	JAK2	[48]
LY2784544	JAK2/V617F[2]	[49,50]
AZD1480	JAK2	[51]
NS-108	JAK2/Src[3]	[52]
BMS-911453	JAK2	[53]

[1]FLT3: Fms-like tyrosine kinase 3; a receptor-type tyrosine-protein kinase; [2]V617F: A point mutation in JAK2 (V617F) identified in the hematopoietic cells of patients with several chronic myeloproliferative disorders; [3]Src: V-src avian sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog; JAK: Janus kinase; SMI: Small molecule inhibitor.

= JAK2), INCB39110 (JAK1 > JAK2), LY3009104 (specificity, similar to INCB020850), PF-956980 (specificity, JAK3) and CYT387 (specificity, JAK1/JAK2; with activity towards TYK2 as well). Clinical studies in normal volunteers and patients with various malignancies are also being conducted with the ultimate goal of developing additional JAK SMIs for use in clinical therapy (Table 1).

According to the PubMed Central database at the time of this writing there are as yet no published Phase 3 RA or psoriasis clinical trials results for INCB020850, INCB39110, LY3009104 or PF-956980. However, Kyttaris[54] recently reviewed the status of the JAK3-selective SMI, VX-509, which showed "promising" results in a Phase 2b clinical trial. In that regard, Genovese *et al*[55] recently reported the results of a 12-24 wk placebo-controlled double-blind phase 2 clinical trial involving RA patients maintained on a stable dose of methotrexate. VX-509 administered orally at 100, 150 and 200 mg QD was employed. The subjects receiving VX-509 showed statistically significant ACR20, ACR50 and ACR70 responses *vs* placebo (*i.e.*, methotrexate) as well as a statistically significant improvement from baseline in the DAS-28-CRP, Health Assessment Questionnaire-D1 (HAQ-D1) and Clinical Disease Activity Index *vs* placebo. However, the adverse event rates were higher in the VX-509 arm, most notably the incidence of infection relative to the placebo.

In a recent preclinical evaluation comparing the effects of tofacitinib with INCB028059 on STAT protein activation, Migita *et al*[56] showed that both tofacitinib and INCB028050 suppressed activation of JAK1/JAK2/JAK3 as well as inhibiting phosphorylation of STAT1/STAT3/STAT5 while also reducing monocyte chemotactic protein-1 (MCP-1) and serum amyloid A1/2 (SAA1/2) levels by oncostatin-stimulated RA synovial fibroblasts. However, another JAK SMI, PF-956980, only inhibited the activation of STAT1/STAT5 and MCP-1, but not SAA1/2.

The efficacy of a JAK3-selective SMI in RA compared to several of the JAK1/JAK2 SMIs now in development for treatment of myeloproliferative diseases and malignancies (Table 1) may be a more desirable result because JAK3 is known to be less involved in hematopoietic cell development than is JAK2[57].

THE MAPK, PI3K/AKT/MTOR AND SYK PATHWAYS

MAPK and PI3K/Akt/mTOR

Signal transduction pathways other than JAK/STAT which are relevant to RA are the mitogen-activated protein kinase (MAPK) and phosphatidylinosotide-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) (PI3K/Akt/mTOR) pathways and intracellular signaling involving spleen tyrosine kinase (Syk)[58,59]. There is strong evidence for "cross-talk" between the JAK/STAT, MAPK and PI3K/Akt/mTOR pathways[26]. There are also many overlapping characteristics in the cellular events that promote the abnormal survival of cancer cells when compared to cells involved in the RA synovial joint which also involve MAPK and PI3K/Akt/mTOR signaling. Thus, it was not surprising that future drug development for RA has taken a page from those experimental interventions which particularly focus on inhibiting the proliferation of cancer cells. In that regard, insights gleaned from studies of MEK1/2, the upstream activator of extracellular signal-regulated kinase1/2 (ERK1/2) and mTOR activity[60] in mutant BRAF-metastatic melanoma[61,62] and other experimental models of malignancy may shed light on whether or not these molecules may be eventually applied to RA.

In that regard, the MEK1/2 SMI, AZD6244 (selumetinib) when used in combination with the mTORC1/mTORC2 SMI, AZD8055, showed significant anti-tumor activity in nude mouse xenograft models of human lung adenocarcinoma and colorectal carcinoma[60], whereas the MEK1/2 inhibitor, AZD6244, sensitized apoptosis-resistant NRAS-mutant lines of melanoma cells to undergo apoptosis. This was correlated with negative regulation of the Wnt/β-catenin signaling *via* ERK1/2 and increased levels of the downstream scaffolding protein, AXIN1[61]. Of note, a Phase 2 trial of selumetinib in patients with the BRAFV600E/K-mutated type of melanoma[62] resulted in tumor regression in 3 of 5 patients with BRAF-mutated low p-Akt activity. However, no response was observed in the AZD6244 treatment group with high p-Akt activity. These results provide a rationale for the dual targeting of MEK1/2 and p-Akt, especially in those melanoma patients with documented high p-Akt activity.

Although there was persuasive pre-clinical data supporting the targeting of p38 kinase-α in RA[63], the results from several clinical trials in which the efficacy of pamapimod was compared to methotrexate in RA patients was disappointing in favor of methotrexate. Thus it is unlikely that pamapimod will be further developed for treating RA[64-66] although the jury is still out, so to speak, regarding whether or not VX-702, another p38 kinase SMI should be further developed and assessed for clinical efficacy in RA patients[67].

SyK signaling

The clinical trial evidence is somewhat stronger, but not persuasive, for promoting the further development of the SyK inhibitor, fostamatinib (R-788)[68], although in 3 RA clinical trials with this drug, the ACR20 response rate ranged from only 35%-38%[69,70]. Moreover, in one of these clinical trials the ACR20 response in the fostamatinib (100 mg twice daily group) was 38%, compared to 35% in the placebo group after 3 mo and no significant differences were achieved in the ACR20, ACR50, or ACR70 response levels at that time.

Protein kinase C-θ

There is also increasing evidence for targeting protein kinase C-θ in RA[71]. This is because protein kinase C-θ is known to play an integral role in regulating T-cell viability and cytoskeletal reorganization by regulating the activities of Vav, PI3K and Rac1 (guanyl-nucleotide exchange factor)[72,73].

THE CLINICAL PERSPECTIVE

Data on the efficacy and safety of tofacitinib in RA was presented to the FDA in May 2012[74]. In November 2012, tofacitinib was approved for use in the US for the treatment of adults with moderately to severe active RA with an inadequate response to, or intolerance to methotrexate. Assessment of the efficacy in RA clinical trials has become fairly standardized[75] and the outcome measures used in the tofacitinib studies were similar to those used in previous clinical trials of biologic drugs for RA. The raw data included a measurement of the tender joint count and the swollen joint count by an examiner, the patient's assessment of pain on a visual analog scale, the patient's global assessment of disease activity on a visual analog scale, an examiner's global assessment of disease activity on a visual analog scale, the patient's assessment of physical function using the HAQ[76], blood testing to determine erythrocyte sedimentation rate (ESR) or CRP, and radiographs of the hands and feet[76]. In most RA studies the raw data is further "manipulated" to produce composite measures of drug efficacy. The ACR has defined the ACR20 response rate as a measure of efficacy in RA to be $\geqslant$ 20% improvement in tender joint count, $\geqslant$ 20% improvement in swollen joint count, and $\geqslant$ 20% improvement in 3 out of 5 of the following parameters: patient pain assessment, patient global assessment, physician global assessment, patient self-assessment of disability and blood acute phase reactant (ESR or CRP)[77]. In the Phase 3 tofacitinib clinical trials, approximately 25%-30% of study patients achieved an ACR20 efficacy when placebo was added to their prior therapy with methotrexate or to another oral immunosuppressant. This was a result that was similar to that previously reported in clinical trials with biologic therapies for RA[74]. In order to demonstrate efficacy that is less likely to be achieved by placebo alone, ACR50 and ACR70 data are also commonly reported, representing $\geqslant$ 50% and $\geqslant$ 70% improvement in the composite ACR score, respectively. Thus, the tender joint count of 28 joints, swollen joint count in 28 joints, serum ESR or CRP and the patient's global assessment of disease activity can be entered into a formula to generate a DAS28-4 score ranging from 0 to 10[78]. If the patient's global assessment of disease activity is omitted, the resulting score is a DAS28-3. A DAS score of $\leqslant$ 2.6 is considered to represent clinical remission, although such a DAS28 score does not necessarily represent a cessation of all joint inflammation. However, DAS28 efficacy measurements are potentially relevant to clinicians, since the DAS28 can be used to track efficacy in clinical practice and a DAS28 $\leqslant$ 2.6 is often the therapeutic goal in treat-to-target clinical trials. Radiographs are also assessed to determine joint space narrowing and the presence of periarticular erosions, which are used to calculate a radiographic score. The method of Sharp as modified by Van der Heijde is commonly employed[79]. This method generates a joint space narrowing score and an erosion score as secondary endpoints, which are combined to generate the primary endpoint, the total Sharp score[76]. Although the publication of this type of radiographic data has become standard over the past 15 years, there are some methodological flaws in this analysis. When efficacy of a new pharmaceutical is assessed, the study population usually adds the new drug to a stable dose of an oral immunosuppressant such as methotrexate. The efficacy data of this population is compared to a group randomized to receive a stable dose of oral immunosuppressant plus placebo. As a result, both groups of subjects receive medication with potential efficacy in RA, and the rise in the modified Sharpe/Van der Heijde score can be slow to rise, even in the placebo group. Therefore, to discern a meaningful difference between the new drug and placebo it may become necessary to choose study subjects with a high risk for the rapid accumulation of joint damage (for example, high serum levels of rheumatoid factor or anti-cyclic citrullinated peptide antibody), to continue to collect radiographic data for 1-2 years or more, or more often to enroll larger numbers of patients.

Ultrasound and Magnetic Resonance Imaging have been proposed as potential substitutes for radiography. However, issues of standardization, reproducibility, potential cost and correlation with other clinical outcome measures are still being worked out, but clinical trials employing these imaging techniques are beginning to appear in published reports.

The dose of tofacitinib used to treat RA in the US is 5 mg orally twice daily. The subjects enrolled in the 5 phase 3 clinical trials were those patients who had experienced an inadequate response to prior treatment with methotrexate, another oral immunosuppressant, or a TNF inhibitor[74]. Most of the study subjects were given either tofacitinib or placebo under a double-blind study design while continuing a stable dose of methotrexate or other oral immunosuppressant. In one of these studies, subjects on a stable dose of methotrexate were given subcutaneous injections (either adalimumab or placebo) plus a pill (placebo pill to recipients of adalimumab, placebo or tofacitinib to recipients of placebo injections). A small

number of subjects were enrolled in a 3 mo study of tofacitinib *vs* placebo without therapy with another immunosuppressant, but there were ethical concerns about randomizing patients with active RA to a study arm in which they were to receive no treatment. In most RA trials the new drug is compared to an active immunosuppressant commonly used in RA (usually methotrexate). The outcome data demonstrated statistically significant efficacy for tofacitinib 5 mg twice daily *vs* placebo as determined by the following outcome measures: ACR20, ACR50, ACR70, DAS-4 (ESR) $\leqslant$ 2.6, DAS-4 (ESR) improving $\geqslant$ 1.2, and HAQ-Disability Index. When compared to 199 subjects receiving adalimumab, 40 mg by subcutaneous injection every 14 d, plus methotrexate plus placebo pills, tofacitinib plus placebo injection plus methotrexate was not inferior using the following outcome measures: ACR20, ACR50, ACR70, DAS-4(ESR) $\leqslant$ 2.6, DAS-4(ESR) improving $\geqslant$ 1.2, HAQ-Disability Index. One of these 5 studies also provided radiographic outcome data. Only 20% of the subjects receiving a stable dose of methotrexate plus placebo demonstrated worsening of the radiographic score at 1 year. In the tofacitinib 5 mg twice daily plus methotrexate treatment group there was a trend toward decreased progression of the total Sharp score, but the difference did not meet statistical significance at either 6 or 12 mo.

Tofacitinib was the first JAK SMI submitted to the FDA for approval in the treatment of RA. As a result the safety assessment was broad in scope, with data collected on mortality, total adverse effects, serious adverse effects, infections, malignancies other than non-melanoma skin cancer, cardiovascular events, and bowel perforations, with monitoring of cell counts, creatinine, liver enzymes, creatinine phosphokinase, and lipid levels in the blood. Data was available for the blinded placebo controlled phase of the study and also the unblinded long-term extension clinical trial. Treatment with tofacitinib was associated with drug dose-dependent neutropenia and lymphopenia, a rise in total HDL and LDL cholesterol, but without associated cardiovascular events, and a rise in serum creatinine[74]. The increased LDL cholesterol improved after the addition of atorvastatin. Overall, the rates per 100 patient-years for all-cause mortality, serious infections, malignancy other than non-melanoma skin cancer, lymphoma, lung cancer, myocardial infarction and gastrointestinal perforation were similar to those reported in published clinical trials of biologic therapies for RA[80]. However, the rate of Herpes zoster infection was higher in the subjects treated with tofacitinib than the infection rates for Herpes zoster reported in prior clinical trials of biologic drugs for RA. After review of the clinical trial data, tofacitinib was considered to be sufficiently safe and effective to be approved for use in the US for moderate to severe active RA not responsive to methotrexate. Of note, post-FDA approval monitoring of the long term safety of tofacitinib is ongoing.

Published RA treatment trials of other small molecule inhibitors have employed a study design similar to those used to assess the safety and efficacy of tofacitinib. As stated above, a phase 2 clinical trial of fostamatinib in RA has now been concluded. Outcome criteria included ACR20, ACR50, ACR70, and DAS28 as measures of efficacy[81]. Imaging outcomes in that study were assessed by MRI. Patient-reported quality of life was assessed using the HAQ-Disability Index, multiple domains of the SF-36 questionnaire, and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire[82]. A 12 wk trial of pamapimod *vs* placebo added to a stable dose of methotrexate used ACR20, ACR50, ACR 70, DAS28, change in mean serum CRP, HAQ-DI, SF-36, and FACIT-F as efficacy outcome measures[83]. Clinical trials of other small molecule inhibitors currently under development are likely to have a similar study design.

CONCLUSION

The development of SMIs of the JAK/STAT (including the newly developed JAK3 SMI, VX-509)[84], MAPK, PI3K/Akt/mTOR and SyK signaling pathways has recently been the target of additional pre-clinical experimental arthritis studies and RA clinical trials assessment. The phase 3 clinical trial data for the JAK SMI, tofacitinib, illustrates the therapeutic potential of this class of SMI drug. For example, by comparison with the relative ease of storage and oral administration of these SMI drugs, the treatment of RA with biologic drugs such as the TNF blockade drugs, etanercept, adalimumab, golimumab, certolizumab, the T-cell co-stimulator inhibitor, abatacept, and the IL-6/IL-6R neutralizing monoclonal antibody, tocilizumab, requires that the medication be shipped by rapid delivery, stored at 2 ℃-8 ℃ and maintained in a cool storage temperature during travel. Administration of these drugs also requires mastery of the correct injection technique, and safe and proper disposal of hypodermic needles. Therefore, if the efficacy and safety of protein kinase SMIs proves to be comparable to the injectable types of biologic drugs, many RA patients may prefer the convenience of an oral medication. However, the relatively short half-life of tofacitinib means that twice daily dosing will be necessary to achieve optimal clinical efficacy. This can be an advantage to the RA patient if the patient develops an infection such that the treating clinician may wish to reverse the immunosuppressive effect of the drug. Thus, at present, treatment with tofacitinib is a therapeutic option for moderate-to-severe RA where disease progression cannot be controlled with methotrexate.

Although SMIs have been primarily targeted to inhibit the activity of JAKs, specific members of the MAPK pathway (*e.g.*, p38-α) and PI3K/Akt/mTOR signaling pathways were also shown to be relevant to the pathogenesis of immune-mediated inflammation associated with RA. Therefore, there are likely to be signaling components of the MAPK pathway, such as the upstream protein kinase, MEK1/2, whose activity is required for phosphorylation of ERK1/2 that may be targeted for further drug development[57]. In addition, since one tar-

get of STAT activation is it's potential to increase the expression of anti-inflammatory cytokines, such as, IL-4 and IL-10[37] and the signaling pathways these cytokines activate, it appears justified to consider developing SMIs that inhibit those protein kinases which can suppress the expression of anti-inflammatory cytokine genes.

However, as an example of the continuing SMI drug development for JAKs in RA, Baricitinib, (formerly known as LY3009104/INCB028050) an inhibitor of JAK1 and JAK2 is presently under investigation in clinical trials in RA with the results from an open extension of the phase 2b trial having been recently reported[85] with additional studies entering the recruitment phase[86]. In the open-extension phase 2b trial, among all patients, the proportions of patients achieving ACR20, ACR50, ACR70, clinical disease activity index (CDAI) Remission, simplified disease activity index (SDAI) Remission, DAS28CRP $\leqslant$ 3.2, DAS28CRP < 2.6, DAS28ESR $\leqslant$ 3.2, DAS28CRP < 2.6 or the ACR/European League Against Rheumatism (EULAR) Boolean remission at the start of the open label extension (week 24) were similar or increased at week 52.

The ultimate place of protein kinase SMIs in RA therapy is not yet known. It is likely to be determined by the following conditions; more patient-years of follow-up to better understand the long-term efficacy and safety of this drug class as well as head-to-head safety and efficacy comparisons with conventional and biologic DMARDs already in use including cost issues relative to other RA treatment options

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Efficacy and safety of tofacitinib for treatment of rheumatoid arthritis

Lisa M Lundquist, Sabrina W Cole, Martha L Sikes

Lisa M Lundquist, College of Health Professions, Mercer University, Atlanta, GA 30341, United States
Sabrina W Cole, School of Pharmacy, Wingate University, Wingate, NC 28174, United States
Martha L Sikes, College of Health Professions, Mercer University, Atlanta, GA 30341, United States
Author contributions: Lundquist LM, Cole SW and Sikes ML wrote and edited the manuscript.
Correspondence to: Lisa M Lundquist, PharmD, BCPS, College of Health Professions, Mercer University, 3001 Mercer University Drive, Atlanta, GA 30341, United States. lundquist_lm@mercer.edu
Telephone: +1-678-5476208 Fax: +1-678-5476231
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Abstract

Tofacitinib is the first in a new class of nonbiologic disease-modifying antirheumatic drugs (DMARDs), a targeted, synthetic DMARD, approved for the treatment of rheumatoid arthritis (RA) as monotherapy or in combination with methotrexate or other non-biologic DMARD. Tofacitinib, an orally administered Janus kinase (JAK) inhibitor, decreases T-cell activation, pro-inflammatory cytokine production, and cytokine signaling by inhibiting binding of type I cytokine receptors family and γ-chain cytokines to paired JAK1/JAK3 receptors. The net effect of tofacitinb's mechanism of action is decreased synovial inflammation and structural joint damage in RA patients. To date, six phase 3 trials have been conducted to evaluate the safety and efficacy of tofacitinib under the oral rheumatoid arthritis triaLs (ORAL) series. This review describes the pharmacology of the novel agent, tofacitinib, and details the safety and efficacy data of the ORAL trials.

Key words: Tofacitinib; Rheumatoid arthritis; Janus kinase inhibitor

Core tip: Tofacitinib, a Janus kinase inhibitor, is a targeted, synthetic, disease-modifying antirheumatic drug (DMARD) approved for the treatment of moderately to severely active rheumatoid arthritis in patients who have had an inadequate response to methotrexate. In numerous phase 2 and 3 trials, tofacitinib has proven to be safe and effective as monotherapy or in combination with methotrexate or other non-biologic DMARDs.

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INTRODUCTION

The 2012 American College of Rheumatology (ACR) guidelines on management of rheumatoid arthritis (RA) recommends the use of disease-modifying anti-rheumatic drugs (DMARDs) in early RA of less than six months duration as monotherapy for patients with low disease activity and combination therapy for moderate or high disease activity[1]. They also recommend the use of anti-tumor necrosis factor (TNF) alpha biologic DMARDs with or without methotrexate for early RA with high disease activity and poor prognostic factors. Approved biologic DMARDs include cytokine inhibitors of TNF alpha (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab), interleukin-6 (IL-6) receptor (tocilizumab), and interleukin-1 receptor (anakinra); cell depleting agent targeting of CD20 of B cells (rituximab); and costimulation blocker of cytotoxic T lymphocyte antigen 4 (abatacept). Limitations of biologic DMARDs, which require parenteral administration (intravenous or subcutaneous), has necessitated the development of orally effective treat-

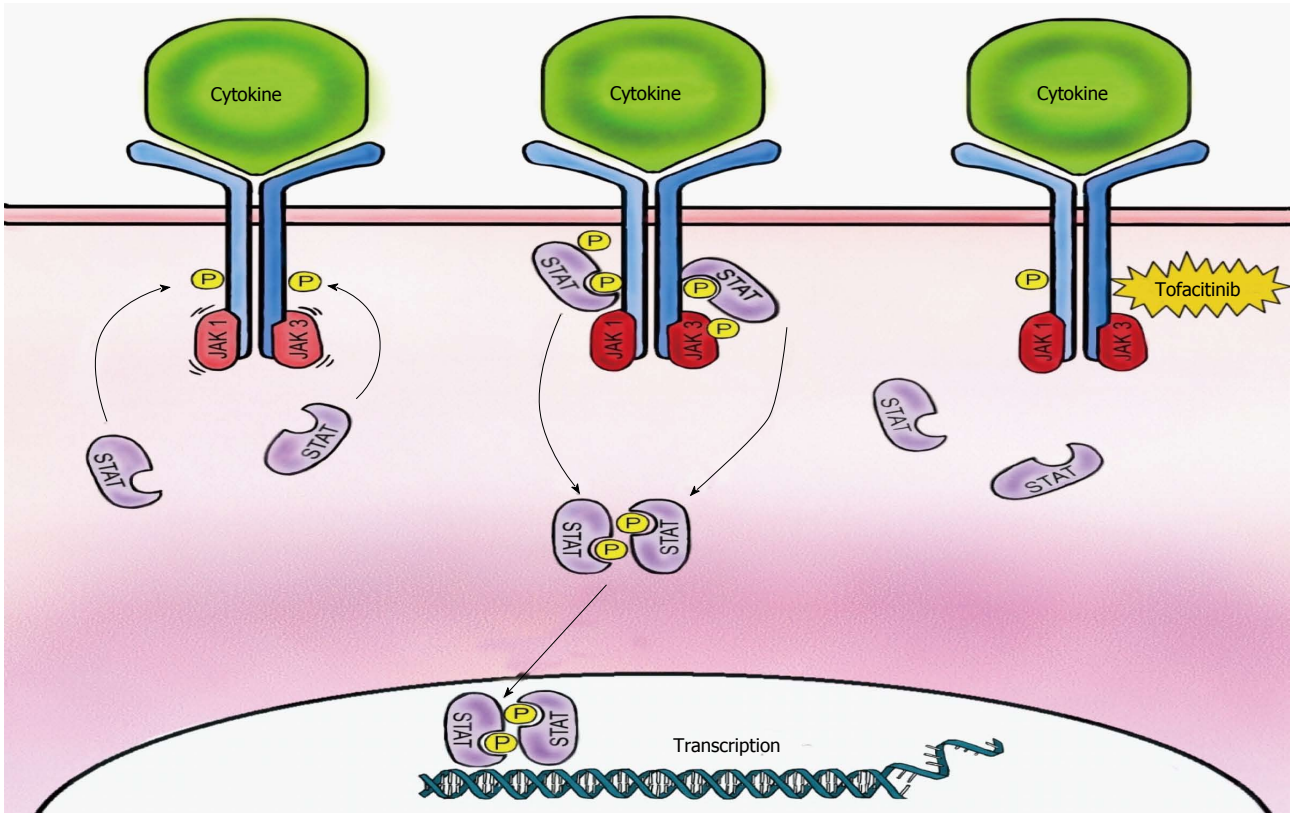

Figure 1 Mechanism of action of tofacitinib. JAK: Janus kinase; STAT: Signal transducer and activator of transcription.

ment options for RA. Although, the European Medicines Agency has twice refused the marketing authorization for tofacitinib based on major concerns of the overall safety profile, tofacitinib, a Janus kinase (JAK) inhibitor, is the first oral non-biologic DMARD approved by the United States Food and Drug Administration in more than a decade[2].

PHARMACOLOGY, MECHANISM OF ACTION, AND PHARMACOKINETICS

Cytokine signaling, pro-inflammatory cytokine production and immune cell activation are key functions of activated JAK in the perpetuation of autoimmune inflammatory disease[3]. The JAK family, JAK1, JAK 2, JAK 3 and Tyk2, are nonreceptor tyrosine kinases with a variety of intercellular domains, a pseudokinase domain, and SH2- and FERM domains[4]. Binding of cytokines to paired JAK receptors (JAK1/JAK3, JAK1/JAK2, JAK1/Tyk2, JAK2/JAK2) induces autophosphorylation, phosphorylation of tyrosine residues on the cytokine receptor, and phosphorylation with subsequent activation of various signal transducer and activator of transcription (STAT) molecules. This leads to increased JAK activity, further recruitment of cytokines, and changes in gene expression through JAK-STAT pathway. The synovium of RA patients has increased expression of the JAK-STAT pathway[3]. JAK1 and JAK2 play a role in growth, neurodevelopment, hematopoiesis, and host defense while JAK3 and Tyk2 are engaged in immune responses. Tofacitinib is a pan JAK inhibitor with potent inhibition of JAK3 and JAK1 and to a minor degree JAK2. JAK3 binds to the common IL-2Rγ chain of the type I cytokine receptor family (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21), which is crucial for T-cell activation. JAK1 binds with γ-chain cytokines (IL-6, IL-10, IL-13, IL-22, granulocyte colony-stimulating face, interferons). Inhibition of JAKs is responsible for decreased pro-inflammatory cytokines signaling *via* IL-2 and IL-4 inhibition, decreased IL-6 production by synovial fibroblasts, decreased receptor activator of nuclear factor-κB ligand production, decreased IL-8 production by $CD14^+$ monocytes, and decreased production of TNF-stimulated fibroblast-like synoviocytes. The net effect of tofacitinib is decreased synovial inflammation and structural joint damage in RA patients by limiting T cell and other leukocyte recruitment[3]. Other immune cells involved in RA pathogenesis express JAKs and may also be affected by tofacitinib inhibition. Figure 1 illustrates tofacitinib's mechanism of action.

Tofacitinib is well absorbed from the gastrointestinal tract following oral administration[2]. Peak plasma concentration (T_{max}) occurs within 0.5-1 h with an absolute oral bioavailability of 74%. Administration of tofacitinib with a high-fat meal resulted in a decrease in maximum plasma concentration (C_{max}) by 32% with no changes to the area under the plasma concentration time curve (AUC); therefore, tofacitinib was given without regard to meals during clinical trials. Steady state concentrations are achieved in 24-48 h with twice daily administration with minimal accumulation.

Tofacitinib is distributed between plasma and red blood cells equally with a half-life of approximately 3 h and is 40% bound to plasma proteins, mainly albumin[2]. Hepatic metabolism, *via* CYP3A4 (major) CYP2C19 (minor) accounts for 70% of tofacitinib clearance with the remaining 30% excreted in the urine. The activity of tofacitinib is related to the parent compound, with 8 metabolites retaining less than 10% of potency. No dosage adjustments are necessary for patients with mild hepatic impairment; however, tofacitinib should be reduced to 5 mg once daily in patients with moderate hepatic impairment or moderate to severe renal impairment. Safety and efficacy for patients with severe hepatic impairment, or positive Hepatitis B or Hepatitis C serology has not been established.

Tofacitinib is predominately metabolized *via* CYP3A4 and drug-drug interactions are of concern[2]. Results from a recent, small *in vitro* study utilizing midazolam, a highly sensitive CYP3A4 substrate used to evaluate CYP isoenzyme drug interactions, and *in vitro* data has established a relative lack of effect of tofacitinib on the CYP enzyme system[5]. However, the manufacturer recommends the dose of tofacitinib be reduced by 50% (*i.e.*, 5 mg once daily) when administered with potent CYP3A4 inhibitors (*e.g.,* ketoconazole) or drugs exhibiting both moderate CYP3A4 inhibition and potent CYP2C19 inhibition (*e.g.*, fluconazole)[2]. Concomitant administration of tofacitinib with potent CYP3A4 inducers (*e.g.*, rifampin) can significantly reduce AUC and clinical efficacy necessitating dosage adjustment, though specific recommendations are not provided by the manufacturer. Caution should be exercised during concomitant administration of tofacitinib with cyclosporine and tacrolimus, given the risk of severe infection due to added immunosuppression when co-administered.

EFFICACY STUDIES

Tofacitinib has demonstrated significant ACR20 response in phase 2 trials as monotherapy and with background therapy with methotrexate[6-10]. Six phase 3 trials have been conducted to evaluate the efficacy of tofacitinib under the oral rheumatoid arthritis triaLs (ORAL) series. To date, five trials were available as full publications[11-15] and one as a conference abstract[16]. Three primary efficacy outcome measures were central to the five fully published trials: (1) percentage of patients achieving an ACR20 response, which is defined as 20% reduction from baseline in tender and swollen joints and at least 20% improvement in three of the five ACR core set measures; (2) change from baseline in the Health Assessment questionnaire disability index (HAQ-DI), in which scores range from 0-3 and higher scores indicate greater disability; and (3) percentage of patients with a Disease Activity Score for 28 joint counts based on erythrocyte sedimentation rate (DAS28-4[ESR]) of less than 2.6 with score ranging from 0-9.4. A summary of the phase 3 trial details and results can be found in Tables 1 and 2, respectively.

ORAL Solo was a 6-mo, multicenter, multinational, randomized, double-blind, placebo-controlled trial[11]. Primary endpoints of this trial were percentage of patients with an ACR20 response, the change from baseline in physical function measured by HAQ-DI, and the percentage of patients with a DAS28-4(ESR) less than 2.6 at month 3. Secondary objectives included percentage of patients with ACR20, ACR50, and ACR70 response rates at all visits, the change in baseline at all visits in the HAQ-DI and DAS28-4(ESR), and the score at month 3 on the functional assessment of chronic illness therapy (FACIT) fatigue instrument. The use of nonsteroidal anti-inflammatory drugs and glucocorticoids ($\leqslant$ 10 mg of a prednisone equivalent) were permitted. A total of 555 patients completed the trial. All patients who received tofacitinib had statistically significant improvement in ACR20, ACR50, and ACR70 response criteria and HAQ-DI scores at month 3 ($P < 0.001$ for all comparisons). There were not significant benefits of tofacitinib seen in DAS28-4(ESR). The changes in the FACIT-fatigue score from baseline at month 3 were statistically significant compared with placebo ($P < 0.001$).

ORAL Step was a 6-mo, multicenter, multinational, randomized, double-blind, placebo-controlled trial[12]. Primary endpoints of this trial were percentage of patients with an ACR20 response, the change from baseline in physical function measured by HAQ-DI, and the percentage of patients achieving DAS28-4(ESR) less than 2.6 at month 3. Secondary objectives were the percentage of patients with ACR20, ACR50, and ACR70 response over time, changes from baseline in the HAQ-DI and DAS28-4(ESR) over time, pain (rated from 0-100), and fatigue measured by the FACIT. Stable doses of methotrexate 7.5 mg to 20 mg weekly for 6 wk prior to the start of the trial were required. The use of nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, or glucocorticoids ($\leqslant$ 10 mg of a prednisone equivalent) were permitted. A total of 399 patients completed the trial. At month 3, ACR 20, ACR50, ACR70 response rates were significant ($P < 0.01$ for all comparisons) and changes from baseline in HAQ-DI were significant ($P < 0.0001$) for tofacitinib compared to placebo. The proportion of patients with DAS28-4(ESR) less than 2.6 at month 3 were significant in tofacitinib 10 mg twice daily group compared to placebo. Improvements in arthritis pain and FACIT assessments were statistically significant for tofacitinib groups compared to placebo.

ORAL Standard was a 12-mo, multicenter, multinational, randomized, double-blind, placebo-controlled trial[13]. Primary endpoints of this trial were percentage of patients with an ACR20 response at month 6, the change from baseline in physical function measured by HAQ-DI at month 3, and the percentage of patients achieving DAS28-4(ESR) less than 2.6 at month 6. Secondary objectives were the percentage of patients with ACR20, ACR50, and ACR70 response over time and changes from baseline in the HAQ-DI and DAS28-4(ESR) over time. A total of 717 patients were included in the full analysis. Patients receiving active treatment achieved a significantly greater percentage of ACR20 response

Table 1 Summary of published phase 3 tofacitinib studies

Study	Duration	Participants	Demographics	Intervention	Primary outcome
ORAL solo	6 mo	Active RA patients with inadequate response to at least one DMARD (biologic or nonbiologic) receiving stable doses of antimalarial	*n* = 611 Age: 49.7-52.4 yr Female: 85.2%-88.2% Duration of RA: 7.7-8.6 Baseline HAQ-DI: 1.50-1.53 Baseline DAS-28: 6.65-6.71	Tofacitinib 5 mg *bid*; Tofacitinib 10 mg *bid*; placebo for 3 mo then Tofacitinib 5 mg *bid*; placebo for 3 mo then Tofacitinib 10 mg *bid*	ACR20 response at month 3; DAS 28-4 ESR < 2.6 at month 3; HAQ-DI at month 3 (change from baseline)
ORAL step	6 mo	Moderate to severe RA patients with inadequate response to TNF alpha inhibitors	*n* = 399 Age: 54.4-55.4 yr Female: 80.3%-86.36% Duration of RA: 11.3-13.0 yr Baseline HAQ-DI: 1.5-1.6 Baseline DAS-28: 6.4-6.5	Tofacitinib 5 mg *bid*; Tofacitinib 10 mg *bid*; placebo for 3 mo then Tofacitinib 5 mg *bid*; placebo for 3 mo then Tofacitinib 10 mg *bid*	ACR20 response at month 3; DAS 28-4 ESR < 2.6 at month 3; HAQ-DI at month 3 (change from baseline)
ORAL standard	12 mo	Active RA patients receiving stable doses of methotrexate	*n* = 717 Age: 51.9-55.5 yr Female: 75.0%-85.3% Duration of RA: 6.9-9.0 yr Baseline HAQ-DI: 1.4-1.5 Baseline DAS-28: 6.3-6.6	Tofacitinib 5 mg *bid*; Tofacitinib 10 mg *bid*; adalimumab 40 mg SC every 2 wk; placebo for 6 mo then Tofacitinib 5 mg *bid*; placebo for 6 mo then Tofacitinib 10 mg *bid*	ACR20 response at month 6; DAS 28-4 ESR < 2.6 at month 6; HAQ-DI at month 3 (change from baseline)
ORAL sync	12 mo	Active RA patients with inadequate response to one or more DMARD	*n* = 792 Age: 50.8-53.3 yr Female: 75.0%-83.8% Duration of RA: 8.1-10.2 yr Baseline HAQ-DI: 1.24-1.45 Baseline DAS-28: 6.14-6.44	Tofacitinib 5 mg *bid*; Tofacitinib 10 mg *bid*; Placebo	ACR20 response at month 6; DAS 28-4 ESR < 2.6 at month 6; HAQ-DI at month 3 (change from baseline)
ORAL scan	24 mo	Active RA patients receiving background methotrexate	*n* = 797 Age: 52.0-53.7 yr Female: 80.2%-91.1% Duration of RA: 8.8-9.5 yr Baseline HAQ-DI: 1.23-1.41 Baseline DAS-28: 6.25-6.34	Tofacitinib 5 mg *bid*; Tofacitinib 10 mg *bid*; placebo for 3 mo then Tofacitinib 5 mg *bid*; placebo for 3 mo then Tofacitinib 10 mg *bid*	ACR20 response at month 6; DAS 28-4 ESR < 2.6 at month 6; HAQ-DI at month 3 (change from baseline); SHS at month 6 (change from baseline)
ORAL start	24 mo	Methotrexate naïve patients with active RA	*n* = 952 Baseline TSS: 16.51-20.30	Tofacitinib 5 mg *bid*; Tofacitinib 10 mg *bid*; methotrexate 10 mg per week with 5 mg increments every 4 wk to 20 mg per week	Modified Total Sharp Score at month 6; ACR70 response at month 6

DMARD: Disease-modifying antirheumatic drug; TSS: Total sharp score; TNF: Tumor necrosis factor; SHS: Sharp/van der Heijde Score; HAQ-DI: Health Assessment Questionnaire Disability Index; DAS: Disease activity score.

compared to placebo at month 6 ($P < 0.001$ for all comparisons). Percentage of patients with DAS-28-4(ESR) less than 2.6 at month 6 and mean change from baseline in HAQ-DI score at month 6 were also statistically significant when compared to placebo. For secondary endpoints, greater ACR50 and ACR70 response and significant changes from baseline in DAS28-4(ESR) and HAQ-DI were seen over time ($P < 0.05$ for all comparisons).

ORAL Sync was a 12-mo, multicenter, multinational, randomized, double-blind, placebo-controlled trial[14]. Primary endpoints of this trial were percentage of patients with an ACR20 response, the change from baseline in physical function measured by HAQ-DI, and the percentage of patients with a DAS28-4(ESR)-defined remission at month 6. Secondary objectives were ACR20, ACR50, and ACR70 response rates, change from baseline HAQ-DI, DAS28-4(ESR) assessments, and FACIT-fatigue score over time. The use of oral corticosteroid therapy (≤ 10 mg of a prednisone equivalent) was permitted. DMARDs disallowed were biologics, cyclosporine, and azathioprine. A total of 792 patients were included in the primary analysis data set with methotrexate being the most frequently prescribe background DMARD (79%). For both tofacitinib groups compared to placebo at month 6, statistically significant differences were seen in ACR20 response rates, improvements from baseline in HAQ-DI and DAS-28 ($P < 0.005$ for all comparisons). For secondary endpoints, changes from baseline in HAQ-DI, DAS28-4(ESR) less than 2.6, and FACIT-fatigue for both tofacitinib groups compared with placebo were statistically significant. For tofacitinib 10 mg twice daily, ACR20, ACR50, and ACR70, significant response rates were observed by week 2. For tofacitinib 5 mg twice daily, significant response rates were observed by week 2 for ACR20 and ACR50, and by week 4 for ACR70.

ORAL Scan is a 24-mo, multicenter, multinational, randomized, double-blind, placebo-controlled trial[15]. Primary endpoints of this trial were percentage of patients with an ACR20 response at month 6, the change from baseline in physical function measured by HAQ-DI at month 3, percentage of patients achieving DAS-28-4 (ESR) less than 2.6 at month 6, and change from baseline in total modified Sharp/van der Heijde Score (SHS) at month 6. Stable doses of methotrexate were required. The use of nonsteroidal anti-inflammatory drugs and glucocorticoids (≤ 10 mg of a prednisone equivalent)

Table 2 Results summary for primary outcomes of phase 3 published trials

Primary outcomes	ORAL solo			ORAL step			ORAL standard			ORAL sync			ORAL scan		
	Placebo (n = 122)	Tofacitinib 5 mg *bid* (n = 243)	Tofacitinib 10 mg *bid* (n = 245)	Placebo (n = 132)	Tofacitinib 5 mg *bid* (n = 133)	Tofacitinib 10 mg *bid* (n = 134)	Placebo (n = 108)	Tofacitinib 5 mg *bid* (n = 204)	Tofacitinib 10 mg *bid* (n = 201)	Placebo (n = 159)	Tofacitinib 5 mg *bid* (n = 315)	Tofacitinib 10 mg *bid* (n = 318)	Placebo (n = 160)	Tofacitinib 5 mg *bid* (n = 321)	Tofacitinib 10 mg *bid* (n = 316)
ACR20 response (%)	26.7	59.8[d]	65.7[d]	24.4	41.7[b]	48.1[d]	28.3	51.5[d]	52.6[d]	30.8	52.1[d]	56.6[d]	25.3	51.5[d]	61.8[d]
Change from baseline HAQ-DI (LSM change)	-0.19	-0.50[d]	-0.57[d]	-0.18	-0.43[d]	-0.46[d]	-0.24	-0.55[a]	-0.61[a]	-0.16	-0.44[d]	-0.53[d]	-0.15	0.40[2]	-0.54[d]
DAS-28-4(ESR) less than 2.6 (%)	4.4	5.6[1]	8.7[1]	1.7	6.7[a]	8.8[a]	1.1	6.2[a]	12.5[a]	2.6	8.5[b]	12.5[d]	1.6	7.2[2]	16.0[d]

[b]$P < 0.01$; [a]$P < 0.05$; [d]$P < 0.001$ *vs* placebo trials. [1]Not significant; [2]Significance not declared for this co-primary endpoint. ORAL: Oral rheumatoid arthritis triaLs; HAQ-DI: Health assessment questionnaire disability index; DAS: Disease activity score.

were permitted. A total of 797 patients were randomized and treated. ACR20 response rates for both tofacitinib doses were significant compared to placebo ($P < 0.0001$ for both comparisons). Significant changes from baseline SHS scores ($P < 0.05$), HAQ-DI ($P < 0.0001$), and DAS28-4(ESR) ($P < 0.0001$) were seen with tofacitinib 10 mg twice daily; non-significant results with tofacitinib 5 mg twice daily.

ORAL Start is a 24-mo, multicenter, multinational, randomized, double-blind, placebo-controlled trial[16]. Primary endpoints of this trial were mean change from baseline in van der Heijde modified Total Sharp Score (mTSS) and percentage of patients with an ACR70 response at month 6. To date, complete methodology and results are unavailable as ORAL Start is published as a conference abstract. A total of 952 patients were randomized and treated. At month 6, mean changes from baseline in mTSS and percentage of patients achieving ACR70 were statistically significant.

SAFETY AND TOLERABILITY

Safety of tofacitinib was evaluated in six phase 3 clinical trials[11-16], four phase 2 trials[6-9], two phase 1 trials[17-18], and a study evaluating the impact on latent tuberculosis infection (LTBI) in a mouse model due to concerns with a risk of reactivation with treatments (*i.e.*, tumor necrosis factor alpha inhibitors) for chronic inflammatory disorders, including rheumatoid arthritis[19]. Several of the phase 2 and 3 trials have been reported in two meta-analyses to evaluate efficacy and safety of tofacitinib for treatment of rheumatoid arthritis[20-21]. In phase 1 studies, including a study with patients randomized to receive supratherapeutic doses of tofacitinib (*i.e.*, 100 mg), there were no serious adverse events reported[17-18]. Additionally, there were no discontinuations or dose reductions of study medication due to adverse events reported. All reported events were mild to moderate and resolved quickly, including two reports of anemia. Additional adverse events reported included headache, nausea, vomiting, dizziness, and disorientation. There were no clinically meaningful changes in laboratory values or ECG parameters.

Adverse events attributed to treatment with tofacitinib were similar in phase 2 trials with the most common events being headache, diarrhea, nausea, upper respiratory tract infections, and nasopharyngitis[6-9]. Patients receiving doses greater than the FDA-approved dose of 5 mg twice daily experienced the highest number of adverse events (*i.e.*, 10 mg twice daily, 15 mg twice daily, and 30 mg twice daily) in phase 2 trials with few treatment discontinuations reported[6,8,9]. In the trials reviewed, two deaths were reported in patients receiving tofacitinib[8,9]. One attributed to cerebrovascular accident in a patient receiving 15 mg twice daily and the other experiencing pneumonia that led to respiratory and cardiac failure with 3 mg twice daily dosing. Although infections were reported in patients receiving tofacitinib, the reports were mainly mild to moderate in severity[6-9]. Serious infections included nasopharyngitis, gastroenteritis, pharyngitis, pneumonia, and pneumococcal sepsis [8,9]. No opportunistic infections were reported in the phase 2 trials[6-9]. In one phase 2 trial, non-infectious serious adverse events were reported including foot deformity, osteoarthritis of the hip, femur fracture, cardiac failure, and acute dyspnea[7]. Each of these events resolved following discontinuation of the study drug with the exception of cardiac failure. Patients receiving tofacitinib also experienced decreased neutrophil counts, thrombocytopenia, decreased hemoglobin, and anemia[6-9]. Most adverse effects were reported to be mild to moderate not requiring discontinuation of the

Table 3 Summary of safety and tolerability data for tofacitinib from phase 3 clinical trials (month 0-3) *n* (%)

	ORAL solo			ORAL step			ORAL standard				ORAL sync			ORAL scan		
	Placebo (*n* = 122)	Tofacitinib 5 mg *bid* (*n* = 243)	Tofacitinib 10 mg *bid* (*n* = 245)	Placebo (*n* = 132)	Tofacitinib 5 mg *bid* (*n* = 133)	Tofacitinib 10 mg *bid* (*n* = 134)	Placebo (*n* = 108)	Tofacitinib 5 mg *bid* (*n* = 204)	Tofacitinib 10 mg *bid* (*n* = 201)	Adalimumab 40 mg once Q2W (*n* = 204)	Placebo (*n* = 159)	Tofacitinib 5 mg *bid* (*n* = 315)	Tofacitinib 10 mg *bid* (*n* = 318)	Placebo (*n* = 160)	Tofacitinib 5 mg *bid* (*n* = 321)	Tofacitinib 10 mg *bid* (*n* = 316)
Patients with AE,	67 (54.9)	124 (51)	139 (56.7)	75 (56.8)	71 (53.4)	76 (56.7)	51 (47.2)	106 (52)	94 (46.8)	105 (51.5)	97 (61)	166 (52.7)	173 (54.4)	73 (45.6)	157 (48.9)	171 (54.1)
Patients with SAE	6 (4.9)	1 (0.4)	5 (2)	6 (4.5)	2 (1.5)	2 (1.5)	2 (1.9)	12 (5.9)	10 (5)	5 (2.5)	6 (3.8)	9 (2.9)	8 (2.5)	5 (3.1)	12 (3.7)	10 (3.2)
Discontinuation due to AE	5 (4.1)	2 (0.8)	6 (2.4)	7 (5.3)	8 (6)	6 (4.5)	3 (2.8)	14 (6.9)	10 (5)	10 (4.9)	2 (1.3)	13 (4.1)	13 (4.1)	5 (3.1)	15 (4.7)	14 (4.4)

AE: Adverse events; SAE: Serious adverse events; Q2W: Every 2 wk; Oral Rheumatoid Arthritis triaLs (ORAL) Start was not included in the 3-month evaluation since data reported were for all events 0-12 mo.

Table 4 Summary of safety and tolerability data for tofacitinib from phase 3 clinical trials (final safety analysis) *n* (%)

	[1]ORAL solo				[1]ORAL step				[2]ORAL standard					[2]ORAL sync				[2]ORAL scan				[4]ORAL start		
	Tofacitinib 5 mg *bid* (after Placebo) (*n* = 61)	Tofacitinib 10 mg *bid* (after Placebo) (*n* = 61)	Tofacitinib 5 mg *bid* (*n* = 243)	Tofacitinib 10 mg *bid* (*n* = 245)	Tofacitinib 5 mg *bid* (after Placebo) (*n* = 66)	Tofacitinib 10 mg *bid* (after Placebo) (*n* = 66)	Tofacitinib 5 mg *bid* (*n* = 133)	Tofacitinib 10 mg *bid* (*n* = 134)	Tofacitinib 5 mg *bid* (after Placebo) (*n* = 56)	Tofacitinib 10 mg *bid* (after Placebo) (*n* = 52)	Tofacitinib 5 mg *bid* (*n* = 204)	Tofacitinib 10 mg *bid* (*n* = 201)	Adalimumab 40 mg once Q2W (*n* = 204)	Tofacitinib 5 mg *bid* (after Placebo) (*n* = 79)	Tofacitinib 10 mg *bid* (after Placebo) (*n* = 80)	Tofacitinib 5 mg *bid* (*n* = 315)	Tofacitinib 10 mg *bid* (*n* = 318)	Tofacitinib 5 mg *bid* (after Placebo) (*n* = 81)	Tofacitinib 10 mg *bid* (after Placebo) (*n* = 79)	Tofacitinib 5 mg *bid* (*n* = 321)	Tofacitinib 10 mg *bid* (*n* = 316)	Tofacitinib 5 mg *bid* (*n* = 371)	Tofacitinib 10 mg *bid* (*n* = 395)	MTX (*n* = 186)
Patients with AE	22 (36.1)	24 (39.3)	97 (39.9)	101 (41.2)	24 (36.4)	28 (42.4)	57 (42.9)	58 (43.3)	18 (32.1)	21 (40.4)	89 (43.6)	84 (41.8)	83 (40.7)	34 (43)	29 (36.3)	104 (33)	135 (42.5)	34 (42)	35 (44.3)	166 (51.7)	174 (55.1)	(70.1)[5]	(74.4)[5]	(69.9)[5]
Patients with SAE	1 (1.6)	0	5 (2.1)	6 (2.4)	3 (4.5)	2 (3)	5 (3.8)	6 (4.5)	1 (1.8)	4 (7.7)	10 (4.9)	6 (3)	7 (3.4)	2 (2.5)	0	7 (2.2)	9 (2.8)	1 (1.2)	4 (5.1)	13 (4)	9 (2.8)	(6.5)[5]	(6.1)[5]	(7.0)[5]
Discontinuation due to AE	0	0	1 (0.4)	3 (1.2)	1 (1.5)	2 (3)	4 (3)	7 (5.2)	0	2 (3.8)	6 (2.9)	3 (1.5)	4 (2)	0	1 (1.3)	1 (0.3)	9 (2.8)	2 (2.5)	2 (2.5)	9 (2.8)	7 (2.2)	13 (3.5)	17 (4.3)	11 (5.9)
Deaths	0	0	0	1 (0.4)	0	1 (1.5)	0	0	0	0	1 (0.5)	0	1 (0.5)	0	0	2 (0.6)	2 (0.6)	1 (1.2)	0	2 (0.6)	1 (0.3)	See note	See note	0
Patients with serious infection events	1 (1.6)	0	1 (0.4)	3 (1.2)	1 (1.5)	0	2 (1.5)	2 (1.5)	2 (3.6)	0	7 (3.4)	8 (4)	3 (1.5)	0	0	2 (0.6)	7 (2.2)	1 (1.2)	2 (2.5)	11 (3.4)	5 (1.6)	(31.8)[6]	(38.7)[6]	(27.4)[6]
Pulmonary Tuberculosis	0	0	0	0	0	0	0	0	0	0	0	2 (1)	0	0	0	0	2 (0.6)	0	0	0	0	0	0	0
[3]Opportunistic infections	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.3)	1 (0.3)	0	0	3 (0.9)	4 (1.3)	8 (2.2)	11 (2.8)	3 (1.6)
Malignancies	0	0	0	0	0	0	0	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	0	5 (1.6)	4 (1.3)	NR	NR	NR

AE: Adverse events; SAE: Serious adverse events; Q2W: Every 2 wk; NR: Not reported. [1]3-6 mo data point; [2]6-12 mo data point; [3]Excludes pulmonary tuberculosis; [4]0-12 mo data point; [5]data reported as total number of events; [6]All infections and infestations; serious infection events, pulmonary tuberculosis, opportunistic infections, and malignancies reported for all trial data.

study drug; however, several cases of severe anemia were reported leading to the temporary discontinuation of tofacitinib in one patient secondary to gastrointestinal bleeding. In addition to hematologic effects, increases in serum creatinine and lipid parameters [*i.e.*, total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL)] were observed. Most were not of clinical relevance; although, several reports of discontinuation were noted with increases in serum creatinine. Changes in blood pressure were minimal and not considered to be clinically relevant. Increased in transaminase concentrations, including aspartate aminotransferase and alanine aminotransferase were reported with treatment discontinuation in few patients. Most cases resolved spontaneously during treatment and did not require discontinuation of the study medication.

In six phase 3 clinical trials, the adverse events profile for tofacitinib was similar to that observed in phase 2 trials. Safety analyses were conducted at 3 and 6 mo for ORAL Solo and ORAL Step and at 3, 6, and 12 mo for ORAL Standard, ORAL Sync, and ORAL scan[11-15]. Safety information from ORAL Start is currently limited to abstract data and reported for the entire 12-mo period[16]. Table 3 summarizes the number of patients experiencing an adverse event, a serious adverse event, or discontinuation of the study medication due to an adverse event during the analysis period. Table 4 provides a summary of adverse events experienced by patients receiving study medication in the last analysis period for the respective trial. Deaths, serious infection events, reports of tuberculosis, other opportunistic infections, and malignancies are also provided. With concern for reactivation of LTBI in patients receiving immunologic agents, it is important to note that reports of tuberculosis infection in patients receiving tofacitinib were rare in phase 3 trials, with two cases reported in two trials, ORAL Standard and ORAL Sync. Additionally, malignancies reported with tofacitinib were rare and reported only in patients receiving tofacitinib in ORAL Scan.

Tofacitinib was associated with changes in laboratory tests, specifically lymphocytes, neutrophils, liver enzymes, lipid parameters, and serum creatinine[11-16]. Patients in the tofacitinib groups had decreases in lymphocyte and neutrophil counts. While patients with decreases in lymphocyte counts were more likely to experience an increased incidence of infections, there was no identifiable association between the decrease in neutrophil count and occurrence of serious infection in clinical trials. Similar to results from phase 2 trials, patients receiving tofacitinib experienced increases in liver enzymes greater than 3 times the upper limit of normal; however, normalization of liver enzymes was achieved with modification of study treatment (*e.g.*, dose reduction, interruption, discontinuation). Lipid parameters, including total cholesterol, LDL, and HDL, were also associated with dose-related elevations following initiation of tofacitinib therapy and remained stable throughout the study periods. Dose-related elevations were also observed with serum creatinine; the clinical significance remains unclear given the propensity for elevations to remain within the normal range. However, several trial discontinuations were attributed to elevations in serum creatinine. In addition to more serious events and laboratory changes, other adverse events reported during phase 3 trials included diarrhea, nasopharyngitis, upper respiratory infection, headache, and hypertension. Headache and diarrhea appear to be more common with tofacitinib treatment versus placebo.

Given the risk of reactivation of tuberculosis in patients with LTBI receiving other immunomodulating agents, such as tumor necrosis factor alpha inhibitors, Maiga and colleagues studied the impact of tofacitinib on LTBI in a mouse model[19]. Results indicated a reactivation of latent infection in the presence of tofacitinib due to an increase in bacterial replication and reduction in containment of the bacteria. The investigators concluded that tofacitinib should be prescribed with caution in patients with chronic inflammation and screening for LTBI is warranted prior to use. These results are consistent with reports of tuberculosis cases identified in the phase 3 trial by Kremer and colleagues[14].

CONCLUSION

ACR 2012 guidelines for treatment of rheumatoid arthritis with use of DMARDs and biologic agents do not specifically address the place in therapy for tofacitinib. However, European League Against Rheumatism (EULAR) recommendations suggest tofacitinib should be considered a targeted, synthetic DMARD for use after treatment failure of at least one biologic DMARD[22]. Safety and efficacy of tofacitinib have been demonstrated in six phase 3 trials[11-16]. Tofacitinib, a Janus kinase inhibitor, offers a novel mechanism of action in the treatment of rheumatoid arthritis and is administered orally, which may be a benefit for patients.

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WJO 5th Anniversary Special Issues (10): Rheumatoid arthritis

Arthrodesis of the wrist in rheumatoid arthritis

Klemens Trieb

Klemens Trieb, Department of Orthopaedics, Medical Director, Klinikum Wels, 4600, Austria
Author contributions: Trieb K designed and wrote the review.
Correspondence to: Klemens Trieb, Professor, Head of the Orthopaedic Department, Department of Orthopaedics, Medical Director, Grieskirchnerstr 42, Klinikum Wels, 4600, Austria. klemens.trieb@klinikum-wegr.at
Telephone: +43-72-4241592308 Fax: +43-72-424153938
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Abstract

In rheumatoid arthritis the small joints of the feet and hands are the first targets of the autoimmune process. In about one half of the patient the wrist is involved in the first stages of the disease (two years) increasing up to nearly 90 percent after a decade often including both sides. Osteoarthritis of the wrist is one of the most common conditions encountered by hand surgeons. One aim of all treatment options is to achieve the best possible hand function without pain. If conservative treatment fails, operative treatment is necessary. Choice of surgical treatment depends on the soft tissue and bone situation. Techniques can be differentiated by joint preservation or joint replacement. The first include radio-synoviorthesis, synovectomy and tendon repair, the latter resection-arthroplasty, total joint arthroplasty and arthrodesis. In this paper arthrodesis of the wrist as one treatment option is reviewed.

Key words: Arthritis; Rheumatoid; Wrist; Treatment; Surgical; Arthrodesis

Core tip: This paper discusses the pathophysiology of wrist destruction due to rheumatoid arthritis. A short overview of different treatment options is given with a special reflect on wrist arthrodesis, surgical techniques and outcomes are presented.

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INTRODUCTION

The natural course of joint arthritis

If once the inflammatory cascade is activated progressive autoimmune mediated joint destruction is the result. Joints are affected by immune cell mediated inflammation of the soft tissue which is progressive and with the time affects the bone, too. It starts with swelling and stiffness of small joints in the morning, postive blood tests and pain. The disease can be associated with rheumatic nodules in one fifth oft he patients in combination with postive rheuma factors. The disease is classified by American Rheumatoid Association, which enables dignostis and therapy and is based on a disease period of more than six weeks[1]. The course oft he disease can vary from patient to patient. Self limiting forms are possible, but if not joint destruction is the result. First targets oft he autoimmune system are the small joints of the feet and hands (Figure 1). In about one half of the patient the wrist is involved in the first stages oft he disease (two years) increasing up to nearly 90 percent after a decade often including both sides. Many social impairments such as long illness periods and loss of employment are the result in many cases[2-6].

RADIOLOGICAL CLASSIFICATIONS FOR RHEUMATOID ARTHRITIS

Due to arthritis and soft tissue inflammation pathological changes can be diagnosed and classified radiologically. The pathologies include bone and cartilage and result in periarticular sclerosis, metaphyseal osteoporosis and bone cystes, cartilage loss and consecutive joint space loss and instability. Different classifications are available, three of

Table 1 Radiographic classification of rheumatic changes according to Larsen

X-ray findings	Larsen scoring
No pathologic changes	0
Osteoporosic bone, soft tissue swelling	1
Narrowing of joint spaces, bony erosions	2
Increased erosions, bony destructions	3
Joint spaces diminished, significant bone destruction	4
Joint mutilation, ankylosis od the wrist	5

Table 2 The wrightington classification for wrist destruction in arthritis

Scoring	Radiographic signs	Therapeutic suggestion
1	Osteoporosis, cystic erosions	Synovial tissue resection
2	Instability of the carpus	Soft tissue procedures or limited arthrodesis
3	Bone destruction, subluxation	Arthroplasty or arthrodesis
4	Severe radial destruction	Arthrodesis

them are presented here. The Larsen classification describes five different stages of bone and cartilage changes (Table 1)[7]. The Wrightington classification is a combination radiological classification with regard to therapy describing four different groups (Table 2)[8]. Simmen *et al*[9] classified arthritic changes with respect to progression and is based on stability of bone and soft tissue.

The first type is the ankylosing, the second describes changes due to arthritic and arthritic destruction and the third type describes instability and disintegration, which needs bony stabilisation in the case of progression.

CLINICAL PRESENTATION

The autoimmune disease can affect all tissues, therefore a careful examination of the patient including all regions should be the first step of the orthopaedic evaluation. The patients history including the onset and expression of different typical symptoms such as swollen, painful, overwarmed, stiff, weak, red or numb changes are evaluated. The nature and character and location of the findings should be noted. The first examination should include the activity level of the patient, the social sourrounding and employment using one of the generally accepted scores for objective documentation of disease stage[10-12]. All medication, including corticosteroid application, immunosuppressive therapy and non-steroidal anti-inflammatory drugs and therapy history are documented. All other diseases should be kept in mind, this can be vascular impairment, diabetes mellitus and all inner organs. The so called "fifth extremity" of the patients, the cervical spine can be affected as often as other joints and can present instability, myelopathy due to compression can result in extremity pathology. In this is the case examination of nerve conduction velocity and electromyography are recommended before joint surgery. Clinical evaluation of the status of the upper and lower extremity include gait analysis, range of motion, test of grip strength. Vascular status or signs of vasculitis should be addressed before surgery to avoid wound complications.

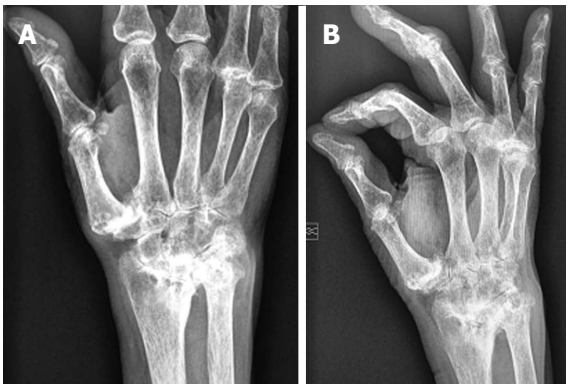

Figure 1 X-ray showing a rheumatoid hand, note axial deviation of the wrist and severe destruction. A: a.p.; B: lateral view.

SURGICAL TREATMENT

If the joint disease progressis for more than three months of medical treatment the rheumatologist should consult an orthopaedic surgeon. If conservative treatment, such as physiotherapy or ergotherapy fails, operative treatment is necessary. One aim of all treatment options is to achieve the best possible hand function without pain. One aim of all treatment options is to achieve the best possible hand function without pain[3,5,6]. Time point for surgery is sometimes discussed controversial, the same is for order of joints started with. This could be for an extremity from proximal to dista or the most affected joint first.

All different options for surgical treatment base on the situation of bone and soft tissue destruction. Basicly two approaches can be differentiated: joint preservation and joint replacement. If cartilage and ligaments are functional present a joint preserving technique should always be used. As a first approach synovectomy of the wrist is recommended and may be combined with soft tissue procedures. When the synovia is removed the target of the autoimmune reaction is removed and in the best case pain and swelling diminish and further joint destruction is prevented. If tendon rupture is associated with arthritis repair must be done in all cases. For extensor tendons different replacing methods exist: they include different transfers from one extensor tendon to another or free grafts. In the case of flexor tendon rupture of the thumb arthrodesis of the distal joint is recommended. Transfer or relocation of tendons are necessary to restore hand function and stability and therefore preventing further progression[3,13,14].

Due to hygienic reasons simultaneous surgery of both hands should be avoided. Surgery of the wrist and proximal or distal joints (for instance the elbow or finger joints) should be avoided because of the risk of extensive swelling and wound healing problems. The same is true for the lower extremity because of limited mobilisation

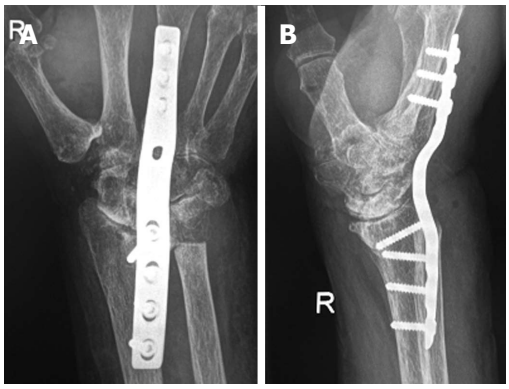

Figure 2 Postoperative X-ray after wrist arthrodesis of the hand seen in Figure 1. A: a.p.; B: Lateral view.

postoperatively. For this reason surgery of the lower extremity first is recommended[12].

WRIST ARTRODESIS IN RHEUMATOID ARTHRITIS

For patients with advanced arthritic changes, wrist fusion is a well-established, safe and reliable method. Several different operative techniques including intramedullary rods or plates for wrist fusion have been retrospectively analysed in long-term studies[15,16]. Osteosynthesis utilising a Rush pin was first described in 1965 by Clayton and was modified in 1971 by Mannerfelt[17,18]. Plate osteosynthesis was introduced by Mueller in 1961 and the original concept was modified in the 1980s with the development of dynamic compression plates which became widely used and have been shown to achieve good primary stability (Figure 2)[19,20].

The position of the fusion remains a matter of debate. In literature, there is a trend towards moderate extension and ulnar abduction. Nevertheless, some surgeons prefer the neutral position which maintains finger balance and allows for better pronation and supination, thus preserving sufficient muscular strength[15,17]. A recent study suggests no statistical difference for position of Mannerfelt arthrodesis in 34 wrists[21]. Another new study on follow up of 93 wrists with Mannerfelt arthrodesis describes this method as an alternative to plate arthrodesis with regard to its good results[22]. For bilateral fusions, it has been recommended to stabilise one side in some flexion and the other in some extension[23]. We compared two methods for arthrodesis, plate and pin fixation, and found comparable clinical outcome with regard to pain and fuction. Subjective satisfaction and strength of grip were higher in the plate group[24]. Despite regained strength and high patient satisfaction, some disadvantages of the fusion have to be considered and which were also observed in our study. Impaired precision mechanics, such as difficulties in performing personal hygiene functions, as well as handling coins and buttons, are the most frequently stated limitations of wrist fusion[24-26]. To overcome these limitations, alternative treatment strategies, including proximal row carpectomy and arthroplasty, have been developed. In conclusion, despite the advances in wrist arthroplasty, wrist fusion represents the method of choice in the treatment of the significant destructed wrist due to rheumatoid arthritis. One aim of this option is to re-establish wrist stability, permitting activities of daily life, to achieve painlessness, and ultimately to improve the quality of life. In selecting the fusion method, the surgeon should consider the need for possible additional surgeries, the quality of the local bone stock, as well as the grade of luxation of the wrist. A comparison of different fixation methods in four studies did not show any differences with regard to surgical technique. Prior to performing the procedure, the planned position of the fusion should be discussed with the patient to address the individual needs[23-30]. Reflecting the long experience and published results, arthrodesis of the wrist is still one of the golden treating standards.

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WJO 5th Anniversary Special Issues (10): Rheumatoid arthritis

Interleukins and interleukin receptors in rheumatoid arthritis: Research, diagnostics and clinical implications

Lili Magyari, Dalma Varszegi, Erzsebet Kovesdi, Patricia Sarlos, Bernadett Farago, Andras Javorhazy, Katalin Sumegi, Zsolt Banfai, Bela Melegh

Lili Magyari, Erzsebet Kovesdi, Katalin Sumegi, Zsolt Banfai, Bela Melegh, Department of Medical Genetics, University of Pecs, 7624 Pecs, Hungary
Lili Magyari, Erzsebet Kovesdi, Katalin Sumegi, Zsolt Banfai, Bela Melegh, Szentagothai Research Centre, 7624 Pecs, Hungary
Dalma Varszegi, Department of Dermatology, Venereology and Oncodermatology, University of Pecs, 7624 Pecs, Hungary
Patricia Sarlos, 1st Department of Internal Medicine, University of Pecs, 7623 Pecs, Hungary
Bernadett Farago, Institute of Human Physiology and Clinical Experimental Research, Semmelweis University, 1446 Budapest, Hungary
Andras Javorhazy, Department of Urology, University of Pecs, 7621 Pecs, Hungary
Author contributions: Magyari L, Varszegi D, Kovesdi E, Sarlos P, Farago B, Javorhazy A, Sumegi K, Banfai Z and Melegh B contributed equally to this work and wrote this review.
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Correspondence to: Bela Melegh, MD, PhD, DSc, Department of Medical Genetics, University of Pecs, Szigeti 12, Pecs 7624, Hungary. bela.melegh@aok.pte.hu
Telephone: +36-72-536427 Fax: +36-72-536427
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Abstract

Rheumatoid arthritis (RA) is an autoimmune disease, resulting in a chronic, systemic inflammatory disorder. It may affect many tissues and organs, but it primarily affects the flexible joints. In clinical practice patient care generates many questions about diagnosis, prognosis, and treatment. It is challenging for health care specialists to keep up to date with the medical literature. This review summarizes the pathogenesis, the polymorphisms of interleukin and interleukin genes and the standard available and possible future immunologic targets for RA treatment. The identification of disease-associated interleukin and interleukin receptor genes can provide precious insight into the genetic variations prior to disease onset in order to identify the pathways important for RA pathogenesis. The knowledge of the complex genetic background may prove useful for developing novel therapies and making personalized medicine based on the individual's genetics.

Key words: Rheumatoid arthritis; Interleukins; Polymorphisms; Immunologic targets; Therapy

Core tip: Rheumatoid arthritis (RA) is an autoimmune disease, resulting in a chronic, systemic inflammatory disorder. It may affect many tissues and organs, but mainly attacks the flexible joints. This review provides a comprehensive overview about the genetic background, especially with regard to inflammatory cytokines to understand the pathogenesis of the disease. Furthermore it summarizes the current therapy and the future therapeutic agents for RA.

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INTRODUCTION

Rheumatoid arthritis

Rheumatoid arthritis (RA) is one of the most common systemic autoimmune diseases which affects approximately 1% of the population[1-3], which can lead to signifi-

cant morbidity and mortality rates, and can shorten the lifespan by 10 years[4]. RA affects people all over the world, but it is more uncommon in Africa[5]. In contrast, its largest prevalence is registered among North-American Chippewa- and Pima-tribes[5]. Like in other autoimmune diseases females are more often affected than males.

RA is a severely disabling chronic inflammatory disease characterized by inflammation, persistent synovitis, progressive joint destruction, and systemic, extraarticular manifestations (*e.g.*, pericarditis, episcleritis/scleritis, secondary Sjögren syndrome, Felty syndrome, cervical myelopathy, neuropathy, interstitial lung disease, rheumatoid nodules, and vasculitis)[5,6]. Accelerated atherosclerosis is the leading cause of death among patients with RA. The incidence of lymphoma increases twofold in RA patients which is thought to be caused by the underlying severity of the inflammatory process, and not a consequence of the medical treatment[7].

Patients with RA typically present with pain, stiffness in multiple joints, swollen peripheric joints, regional osteoporosis, narrowing of the synovial space and fibrous ankylosis. The wrists, proximal interphalangeal joints, and metacarpophalangeal joints are most commonly affected, however, the clinical appearance can be heterogenous[5,6]. In 2010 the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) developed a new classification criteria, aiming to support diagnosis and facilitate the early introduction of effective RA therapy[8]. The 2010 criteria include tender and swollen joint count, acute phase reactants [C-reactive protein levels (CRP) and erythrocyte sedimentation rate (ESR)], anti-citrullinated protein antibodies (ACPA) or rheumatoid factor (RF), and symptom duration[8]. RF is not specific for RA and it may be present in patients with other diseases, such as hepatitis C and in also healthy older persons. However, patients seropositive for RF are characterized by rapid and more severe course of the disease, and it is frequently coupled with extraarticular manifestations. ACPA is more specific to RA (97.1%)[9]. It is produced against citrullinated proteins which derive from an RA-specific dysregulation of the humoral immune response[10,11]. Likewise RF, the presence of ACPA contributes to a more severe and extended type of RA[10]. The simultaneous presence of these two serological factors predestinates the onset of RA at a 28.9 times higher risk, compared to the population negative for both autoantibodies[10].

RA is an inflammatory arthritis that results from a systemic autoimmune response stimulated by an as yet unidentified antigen. It is commonly believed that the generation of autoantibodies through interactions of the innate immune system (antigen-presenting cells) with the adaptive immune system ($CD4^+$ T cells and B cells) is central to the pathogenesis[12]. Although the clear mechanisms of RA pathogenesis still remain to be defined, cytokines are considered to play an important role in the disease. The imbalance between pro- and anti-inflammatory cytokines promotes the induction of autoimmunity, inflammation and joint destruction. The synovial membrane in patients with RA is characterized by hyperplasia, proliferation, angiogenesis and an infiltrate of predominantly $CD4^+$ T helper (Th) cells. The pro-inflammatory cytokines, especially tumor necrosis factor alpha (TNF-α), and two interleukins (ILs), IL-1B and IL-6 are the key cytokines which drive inflammation and the destructive process[13]. However, it is likely that other cytokines such as IL-23, IL-17A and interferon gamma (IFN-γ) also play crucial roles in the pathogenesis of RA. IL-4 and IL-10, on the other hand, have been suggested to improve arthritis[14]. Joint damage results from the degradation of connective tissue by tissue-destroying matrix metalloproteinases (MMP) and the stimulation of osteoclastogenesis through the receptor activator of nuclear factor-kB ligand (RANKL). Activated $CD4^+$ T cells also stimulate B cells to produce immunoglobulins, including RF[15].

Similarly to other autoimmune disorders, RA is a disease of multifactorial etiology. The genetic predisposition is responsible for approximately 60% of the whole disease risk, while environmental factors, such as infections by microbial agents[16], smoking[17,18], obesity, or schizophrenia of first-degree relatives[19,20], and abnormalities of the autoimmune processes also play a role. The association with the human leukocyte antigen (HLA)-DRB1 locus was the first to be described to confer risk for RA (50% of the overall genetic predisposition)[21]. Linkage and genome-wide association studies identified over 30 validated additional genetic loci associated with RA, example HLA-DRB1, protein tyrosine phosphatase N22 (*PTPN22*), tumor necrosis factor alpha-induced protein 3 (*TNFAIP3*), TNF receptor-associated factor 1 (*TRAF1*), signal transducer and activator of transcription 4 (*STAT4*), chemokine (C-C motif) receptor 6 (*CCR6*), PX domain containing serine/threonine kinase (*PXK*)[22-24]. Further studies have revealed the importance of numerous other predisposing genes and their variants, including several pro-inflammatory and anti-inflammatory cytokine genes, especially interleukins (Figure 1).

RESEARCH

We conducted a systematic review of the literature of the last 10 years on the polymorphisms of interleukin and interleukin genes associated with RA, and also standard available and possible future therapeutic possibilities of RA. PubMed was searched for papers and abstracts published in English-language journals, using the following terms and/or text words alone and in combination "rheumatoid arthritis", "interleukins", "interleukin receptors", "polymorphisms" and "therapy". No restrictions were placed on race, ethnicity, or geographic area. Extraction from each study was conducted independently by all authors, and consensus was achieved for all data.

INTERLEUKIN AND INTERLEUKIN RECEPTOR GENE POLYMORPHISMS

ILs are a large group of cytokines which are especially

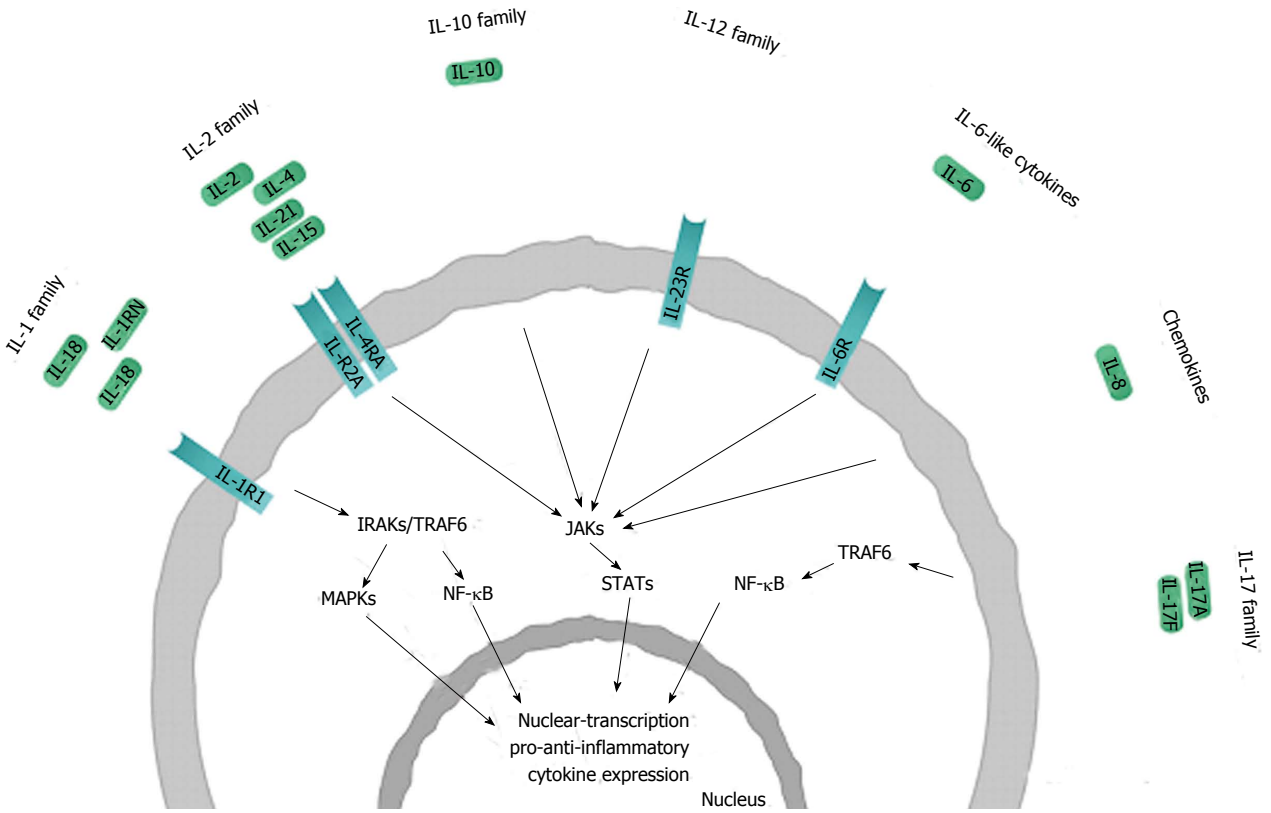

Figure 1 Schematic representation of the interleukin families and receptors involved in the pathogenesis of rheumatoid arthritis. Only those interleukins and interleukin (IL) receptors are shown where studies have demonstrated positive association between genes/SNPs and disease phenotype. Interleukins are assigned to each family based on sequence homology and receptor chain similarities or functional properties, considerable overlap between these families exists. Polymorphisms in genes encoding ILs and ILRs have been found to be involved in rheumatoid arthritis. Ligand binding initiates intracellular phosphorylation cascades that are mediated by kinases [i.e., interleukin 1 receptor associated kinase (IRAK); mitogen-activated protein kinase (MAPK); Janus kinase (JAK) and tumor necrosis factor (TNF) receptor associated factor, TRAF], resulting in signal transduction through certain transcription factors [including signal transducers and activators of transcription (STAT); nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)]. These transcription factors stimulate the expression of a number of pro-inflammatory and anti-inflammatory cytokine genes involved in the pathogenesis of rheumatoid arthritis.

important in stimulating immune responses, such as inflammation. Once an IL has been produced, it proceeds to its target cell and binds to it *via* a receptor molecule on the cell surface. This interaction triggers a cascade of signals within the target cell which finally alters the behaviour of the cell. Different types of ILs are known. The nomenclature is based on sequence homology and receptor chain similarities or functional nature (www.genenames.org/genefamilies/IL) (Table 1)[25]. Within the interleukin families several *IL* and *ILR* gene polymorphisms have been investigated that are associated with RA (Table 2).

The IL-1 family

Members of the IL-1 family (IL-1A, IL-1B, IL-1RN, IL-18, IL-33, IL-36A, IL-36B, IL-36G, IL-36RN, IL-37 and IL-38) have similar gene structures and induce a complex network of pro-inflammatory cytokines. IL-1 family has also expanded to 9 distinct genes including coreceptors, decoy receptors, binding proteins and inhibitory receptors[26].

IL-1: IL-1 is a key mediator of inflammation which has an effect on cell proliferation and differentiation. It mediates many inflammatory diseases by initiating and potentiating immune and inflammatory responses[25]. IL-1 is involved in several systemic autoinflammatory syndromes and in juvenile RA. It also plays a pathogenic role in inflammation and tissue destruction[27,28]. The most studied IL-1 proteins are IL-1α and IL-1β. *IL-1A* (OMIM 147760) encodes IL-1α which is cell-bound, and *IL-1B* (OMIM 147720) encodes IL-1β, a secreted cytokine. The IL-1 receptor antagonist (IL-1RN) (OMIM 147679) is an anti-inflammatory protein which binds to IL-1 receptor type 1 (IL-1R1, OMIM 147810) without transducing signal[29,30].

Two SNPs, the -511 C/T (rs16944) in *IL-1B* gene promoter and +3953 C/T (rs1143634) in the exon 5 of *IL-1B* are thought to influence *IL-1* expression[31,32]. Both loci may influence erosive damage in RA[33]. The rarer (-511) C-allele is associated with milder erosive disease in patients with a disease duration in excess of 20 years. In a Turkish cohort it was found that patients carrying the 2/2 (T/T) genotype of *IL-1B* +3953 gene are susceptible to RA. However, the 1/2 (C/T) genotype of *IL-1B* -511 has a protective role against RA[34]. In British Caucasian RA patients the *IL-1B* -1464 C/G (rs1143623) G allele showed the possibility to have protective effect in RA.

Table 1 Characteristics of cytokines in rheumatoid arthritis

Family	Cytokine	Cytogenetic location	Molecular weight	Receptor	Cell source
IL-1	*IL-1B* (*IL-1F2*)	2q14	17 kD	IL-1R1 IL-1R2	Macrophages, monocytes, lymphocytes, keratinocytes, microglia, megakaryocytes, neutrophils, fibroblasts and synovial lining cells
	IL-1RN (*IL-1F3*)	2q14.2	16.1-20 kD	IL-1R1 IL-1R2	Monocytes, macrophages, fibroblasts, neutrophils, epithelial cells and keratinocytes
	IL-18 (*IL-1F4*)	11q22.2-q22.3	22.3 kD	IL-18R1 IL-18RAP	Macrophages, Kupffer cells, keratinocytes, osteoblasts, astrocytes, and DCs
IL-2	*IL-2*	4q26-q27	15.5 kD	IL-2R	$CD4^+$, $CD8^+$ activated T cells, DCs, NK and NKT cells
	IL-2RA	10p15-p14	30.8 kD	IL-2R	Activated T and B cells, thymocytes, myeloid precursors and olygodendrocytes
	IL-4	5q23-q31	15 kD	IL-4R1 IL-4R2	Th2 cells, basophils, eosinophils, mast cells, NKT and γ/δ T cells
	IL-15	4q31	14-15 kD	IL-15R	Monocytes, activated $CD4^+$ T cells, keratinocytes, skeletal muscle cells
	IL-21	4q26-q27	15 kD	IL-21R	T and NKT cells
IL-10	*IL-10*	1q31-q32	18.6 kD	IL-10RA/IL-10RB	T and B cells, monocytes, macrophages and DCs
IL-12	*IL-23*	12q13.13	19 kD	IL-12RB1/IL-23R	Macrophages and activated DCs
IL-6-like cytokines	*IL-6*	7p21-p15	19-26 kD	IL-6R/IL-6ST	Endothelial cells, fibroblasts, monocytes/ macrophages
IL-17	*IL-17A*	6p12	35 kD	IL-17RA/IL-17RC	Th17, $CD8^+$ T cells, NK cells, NKT cells, γ/δ T cells and neutrophils
	IL-17F	6p12	44 kD	IL-17RA/IL-17RC	Th17, $CD8^+$ T cells, NK cells, NKT cells, γ/δ T ells and neutrophils
Chemokines	*IL-8*	4q13-q21	16 kD	IL-8RA/IL-8RB	Monocytes, macrophages, neutrophils, lymphocytes, endothelial cells, epithelial cells, fibroblasts, keratinocytes, chondrocytes, synovial cells, and hepatocytes

NK: Natural killer cells, NKT: Natural killer T cells, DCs: Dendritic cells; IL: Interleukin.

Meta-analysis revealed that *IL-1B* -511 SNP is associated with increased susceptibility to RA[35].

Variable number of tandem repeat (VNTR) + 2018 (rs419598) SNP of *IL-1RN* gene were investigated in Black South Africans where no significant differences were found in genotype and allele frequencies between RA group and healthy controls. Within the RA group, the *IL1RN*2* (two repeats of an 86bp tandem repeat) at the VNTR locus was independently associated with higher Larsen radiologic damage scores (LDS), corrected for disease duration. Furthermore the *IL1RN*2* and + 2018 C allele defined haplotype was associated with significantly higher LDS on average 15 points higher, compared to the base haplotype of *IL1RN**long (three or more repeats) and + 2018 T allele. The authors concluded that *IL1RN*2* is a marker of erosive joint damage in Black South Africans RA patients[36]. With respect to *IL1R1* loci, negative findings were reported in Indian, Swedish and Chinese RA patients[37-39]. In an Algerian population *IL-1B* (-511), *IL-1* (+3953), and *IL-1RN* VNTR polymorphisms were examined, where no significant differences were observed in the three polymorphisms in genotype, allele and haplotype frequencies between the RA group and the healthy controls. However, the TT genotype of *IL-1B*-511 is more frequent in the patients' cohort with positive ACPA compared with negative ACPA group. The *IL-1RN*1*/*IL-1B*-511T/*IL-1B* + 3953C haplotype was more frequent in the positive ACPA group. The association between *IL-1RN* allele 1 of VNTR, *IL-1B*-511 T allele and *IL-1B* + 3953 C allele seems to predispose to the synthesis of ACPA and therefore to the occurrence of ACPA positive RA[40].

Meta-analysis of 10 European, 7 Asian, and 1 Latin American RA population showed that the *IL-1B* + 3953 polymorphism was associated with the development of RA only in the Asian RA cohort[41]. Similarly to these results the genotype and allele distributions of *IL-1B* + 3953 showed significantly increased risks in a RA cohort from Northwest China compared to controls[42].

IL-18: The main function of IL-18 (OMIM 600953) is to promote the production of IFN-γ from T and natural killer (NK) cells, in particular the presence of IL12p70. IL-18 binds to its ligand binding chain, to the interleukin 18 receptor 1 (IL-18R1, OMIM 604494). It also recruits its co-receptor, the IL-18 receptor accessory protein (IL-18RAP, OMIM 604509). With these reactions IL-18 virtually initiates the activation of nuclear factor kappa-light-chain-enhancer of activated B cells/mitogen activated protein 8 (NF-κB/MAPK8)[43]. IL-18 is an important proinflammatory cytokine and plays a potential pathological role in RA[44]. It is highly expressed in sera, synovial fluids and synovial tissues of RA patients; furthermore, elevated IL-18 levels are correlated with RA disease activity, indicating an important role of IL-18 in the pathogenesis of RA[45].

Several studies examined the association of *IL-18* gene polymorphisms with RA, but these studies showed inconclusive and controversial results. In an Egyptian population the -607 C/A (rs1946518) and -137 G/C (rs187238) were analysed in the promoter region. The frequency of -137CC genotype was significantly lower in RA patients compared to controls. As *IL-18* -137CC and *IL-18* -607 were negatively associated with RA, they may not be risk factors for RA in the Egyptian patients[46].The same polymorphisms were analysed in a Chinese Han population. The genotype and allele frequency of -607 of the *IL-18* gene showed significant differences between

Table 2 The examined interleukin and interleukin receptor gene polymorphisms that are associated with rheumatoid arthritis

Gene	Polymorphism	Population	Ref.
IL-1B	*rs16944*	Algerian, British, Turkish	[34,35,40]
	rs1143623	British	[35]
	rs1143634	Algerian, Asian, Turkish	[34,40-42]
IL1-RN	*rs419598*	Black South Africans	[36]
IL-2/IL-21	*rs907715*	Australasian	[72]
	rs6822844	Australasian, Dutch	[65,72]
	rs17388568	Australasian	[72]
IL-2RA	*rs2104286*	Dutch	[64]
IL-4	*rs2243250*	Egyptian, Polish	[51,52]
IL-4R	*rs1801275*	African American, Egyptian	[54,55]
	rs1805010	African American, Egyptian	[54,55]
IL-6	*rs1800795*	Iranian, United Kingdom, Spain, Spanish, Turkish	[34,114,116, 117,122]
	rs1800796	Han Chinese, Taiwan, Turkish	[34,43,47,118]
IL-8	*rs112664*	Taiwan	[118]
	rs2227306	Caucasian	[137]
IL-10	*rs1800871*	Malaysian, Polish	[80,81]
	rs1800872	Chinese, Malaysian, Polish	[80-82]
	rs1800896	Malaysian, Polish	[80,81]
IL-15	*rs2322182*	North European	[59]
	rs4371699	North European	[59]
	rs6821171	North European	[59]
	rs7665842	North European	[59]
	rs7667746	North European	[59]
IL-17A	*rs1974226*	Japanese	[136]
	rs2275913	Norwegian	[135]
	rs3748067	Japanese	[136]
	rs3804513	Japanese	[136]
IL-17F	*rs763780*	Polish	[134]
	rs2397084	Polish	[134]
IL-18	*rs187238*	Chinese, Egyptian	[46,47]
	rs549908	Taiwan	[48]
	rs360718	Japanese	[49]
	rs360722	Japanese	[49]
	rs1946518	Chinese, Egyptian, Japanese	[46,47,49]
IL-23R	*rs1004819*	European, New Zealand, Spanish	[97,100,106]
	rs1343151	European, New Zealand, Spanish	[97,100,106]
	rs1495965	Spanish	[97]
	rs2201841	European, New Zealand, Hungarian	[96,97,100,106]
	rs7517847	European, New Zealand, Spanish	[97,100,106]
	rs7530511	Caucasian	[98]
	rs10889677	Hungarian	[96]
	rs11209026	European, Caucasian, New Zealand	[98,100,106]
	rs11209032	Spanish	[97]
	rs10489629	Europan, New Zealand, Spanish	[97,100,106]

RA patients and controls. There was no statistical significance in the distribution of genotype frequencies of -137. Significance was found in the data on statistical basis only on allele frequency levels[47]. The controls had significantly higher AA genotype frequency in the Chinese population at position-607 compared to RA patients. At position-137 no significant differences were observed in the distribution of either allelic or genotypic frequencies. Furthermore there was no association between the examined genotypes and the presence of rheumatoid factors. In the Chinese population only the AA genotype at position-607 is associated with a protective effect against development of RA. Meta-analysis was conducted on the associations between these promoter polymorphisms and RA in the Asian population. They found significant differences in genotype and allele frequencies only in the Chinese population which the previous study has also demonstrated[44].

Another polymorphism, the 105 A/C (rs549908) was analysed in a Chinese population living in Taiwan. There were significant differences in the genotype distribution of this polymorphism between patients and controls. The distribution of the AA homozygote in the RA patients was higher compared to the control group. The allele frequency also differed significantly between RA patients and controls[48].

In a Japanese study three haplotype tag SNP, rs1946518 A/C, rs360718 T/G, and rs360722 T/C, spanning from the 5'UTR region to intron 1 were genotyped using allelic discrimination with use of specific TaqMan probes, and three haplotypes (ATT, CTC and AGC). Among these polymorphisms, the T allele frequency of rs360722 which tags the ATT haplotype, was significantly lower in the RA cohort compared with the normal subjects. Having the TT genotype further increased the significance. The presence of the T allele and TT genotype at rs360722 reduces the susceptibility of Japanese people to RA[49].

The IL-2 family

The members of the IL-2 cytokine family are: IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21. This family includes a group of ILs which share a common receptor subunit, the "common γ chain". This acts in unison with a subtype specific α-chain to initiate the signaling cascade. These ILs act mainly as growth and proliferation factors for progenitors and mature cells, and they also have a role in lineage-specific cell differentiation[25].

IL-4: IL-4 (OMIM 147780) is a major stimulus of Th2-cell development which regulates allergic conditions and the protective immune response against helminthes and other extracellular parasites[50].

The -590 C/T (rs2243250) promoter polymorphism of the *IL-4* gene was tested in an Egyptian population with RA. In RA patients, the frequencies of TT genotype and T allele were significantly increased compared to controls. Subjects with TT genotype and carriers of T allele were significantly more likely to develop RA. In non-erosive RA patients, the frequencies of TT genotype were significantly increased compared to controls. CT and TT genotypes were significantly increased in erosive RA patients compared to control group. Carriers of T allele had significantly increased risk to develop erosive RA as compared to the control group. The frequencies of -590 CT and TT genotypes were significantly increased in erosive RA patients. RA patients carrying CT, TT genotypes were significantly more likely to have erosive arthropathy. In RA patients with positive anti-CPP, the frequencies

of CT and TT genotypes were significantly increased compared to anti-CCP group. Carriers of T allele were significantly more likely to have positive anti-CCP[51]. The same polymorphism was tested in a Polish RA population, where no significant differences were observed in the genotype and allele frequencies of controls *vs* RA patients[52]. Meta-analysis showed that the -590 C/T polymorphism is a risk factor for RA among Europeans[53].

Two functional polymorphisms in the *IL-4* receptor gene rs1801275 (Q551R) and rs1805010 (I50V) were analysed in African American RA patients. They found that patients positive for *HLA-DRB1* shared epitope (SE) and autoantibodies had a higher risk of developing rheumatoid nodules in the presence of rs1801275 AA and AG alleles, while patients positive for the *HLA-DRB1* SE and RF alone had a higher risk of developing rheumatoid nodules in presence of rs1801275 AA and AG alleles and rs1805010 AA allele[54]. These variants were examined in an Egyptian population as well. In RA patients, the IV genotype frequency was significantly increased compared to controls. Subjects with IV genotype were significantly more potential to have the disease. In patients with erosive RA, the VV genotype frequency was significantly increased compared to patients with non-erosive RA. Subjects with VV genotype were significantly more susceptible to erosive arthropathy. The QR genotype frequency was significantly decreased in patients with erosive RA compared to patients with non-erosive RA. Carriers of V allele and Q allele were significantly more potential to be RF-positive, respectively and consequently develop severe RA[55].

IL-15: IL-15 (OMIM 600554) is a T cell activating factor which has pleiotropic and physiological activities in both the innate and acquired immune responses[56]. It plays an essential role in the differentiation, survival and activation of NK cells[56]. These functions are mediated through IL -15 receptor (IL-15R)[57]. IL-15 exerts pro-inflammatory effect in several diseases like allergy, transplant rejection and autoimmune disorders. Abnormalities in IL-15 expression may be involved in the pathogenesis of inflammatory autoimmune disorders like RA[56]. IL-15 may be implicated in the perpetuation of synovial inflammation in RA by generating positive-feedback loop, in which IL-15 synthesis by activated synovial macrophages or fibroblasts could induce a continuous T-cell recruitment[58].

Five SNPs in *IL-15* gene (rs7667746, rs7665842, rs2322182, rs6821171 and rs4371699) were significantly associated with rate of joint destruction in North European RA patients[59]. Thirteen SNPs were screened within the IL-15 regulatory regions [promoter, 5' and 3' untranslated region (UTR) regions]. In addition, an association study of these SNPs was conducted in three independent case-control cohorts with Spanish Caucasian origin. The presence of the 13 selected *IL-15* SNPs was confirmed and no new genetic variants were found. The distribution of the *IL-15* selected SNPs in RA patients and controls showed no statistically significant difference in any studied populations. The haplotype analysis revealed that the three *IL-15* haplotype blocks were not associated with RA susceptibility or severity in the analysed cohorts. It was suggested that the *IL-15* gene polymorphisms may not play major role in RA genetic predisposition, and probably other molecules which are implicated in the IL-15 pathway might possibly be implicated in RA susceptibility[60]. These results are in accordance with two previous studies which analysed the contribution of *IL-15* gene to the genetics of immunity-related diseases. There was no significant association observed in two different Caucasian populations for a number of *IL-15* SNPs and allergic disorders[61].

IL-2/21: IL-2 (OMIM 147680) promotes proliferation and expansion of both antigen-specific clones of $CD4^+$ and $CD8^+$ T cells. The *IL-2* receptor (*CD25*) susceptibility locus has recently been reported to be associated with RA[62]. IL-21 is involved in cell-mediated and humoral responses. It has pleiotropic effect on a variety of immune and nonimmune cells. In RA, the synovial fluid and tissue have enhanced inflammatory responses to IL-21 and elevated IL-21 receptor expression[63]. In Dutch RA patients was found that the *IL-2RA* locus may predispose to less destructive course of RA. The minor C allele of *IL-2RA* (rs2104286) was associated with less progression of joint destruction. The *IL-2RA* (rs2104286) protective genotype was associated with lower circulating levels of soluble interleukin-2 receptor A (sIL2RA). Lower sIL2RA levels were associated with a lower rate of joint destruction[64]. The SNP rs6822844 for *IL-2/IL-21* was investigated for associations with the disease and for associations with autoantibody status in a Dutch RA cohort. *IL-2/IL-21* rs6822844 showed a clear trend toward association with RA[65].

The *KIAA1109-TENR-IL2-IL21* region has been associated with a wide variety of autoimmune diseases like type 1 diabetes (T1D)[66], ulcerative colitis[67], Crohn's disease[68], celiac disease, Graves' disease (GD)[66], systemic lupus erythematosus (SLE)[69], psoriatic arthritis[70], and juvenile idiopathic arthritis[71]. The rs6822844 within the *KIAA1109-TENR-IL2-IL21* gene cluster has been linked to RA. Other variants within this cluster, for example rs17388568 is not in linkage disequilibrium (LD), but rs907715 is in moderate LD with rs6822844. The rs17388568 has been described to be in association with a number of autoimmune phenotypes, including T1D. Australasian RA patients and controls of European Caucasian ancestry were genotyped for rs6822844, rs17388568 and rs907715. No statistically significant difference was observed in the Australasian sample set for rs6822844or rs17388568 or rs907715. In a meta-analysis there was a genome-wide level of significance supporting association of rs6822844 with RA. Meta-analysis of rs17388568 showed no significant association with RA, while the meta-analysis of rs907715 only a trend towards association, but this was not independent of the association at rs6822844. The analysis of the *KIAA1109-TENR-IL2-*

IL-21 gene cluster supported its association with RA and rs6822844 is the dominant association in this locus[72].

The IL-10 family

IL-10 cytokine family members (IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28 and IL-29) are mainly linked through their similar intron-exon structure[73].

IL-10: IL-10 (OMIM 124092) is an anti-inflammatory cytokine produced by B cells, T cells, NK cells, monocytes, macrophages, and dendritic cells (DCs). It inhibits both antigen presentation and subsequent release of pro-inflammatory cytokines, so it attenuates the activated immune system[74]. IL-10 has been shown to suppress the inflammatory cytokines IL-1, IL-6, IL-8, IL-12, TNF-α, hematopoietic growth factors and inhibit the synthesis of nitric oxide, gelatinase, and collagenase[75].

Three promoter polymorphisms of *IL-10* rs1800896, rs1800871 and rs1800872 have been studied in some populations with controversial results. The rs1800896 polymorphism is localized within a putative E-twenty six (Ets) transcription factor binding site, while rs1800871 is located within the putative positive regulatory region[76-78]. The rs1800872 is localized within the putative STAT3 binding site and negative regulatory region. These polymorphisms are in strong LD and appear in three potential haplotypes: GCC, ACC and ATA. The production of IL-10 depends on the genotypes. The ACC/ACC, ACC/ATA, and ATA/ATA are correlated with low, ACC/GCC and ATA/GCC with intermediate, whereas GCC/GCC with high IL-10 production[79]. In a Malaysian population the distribution of the *IL-10* genotypes did not differ significantly between RA patients and healthy controls. However, significant difference was found in the allele frequencies of rs1800896CT, rs1800871TT, rs1800872CA and AA between the RA patients and healthy subjects[80].

A Polish population study could not show association between *IL-10* genotypes and age at disease diagnosis, disease activity in a physician's global assessment, joint and extra-articular involvement. They found also no correlation between *IL-10* polymorphisms and disease activity parameters (ESR and CRP), number of swollen and tender joints, and duration of morning stiffness. The frequency of GCC, ACC, and ATA haplotypes in RA patients did not differ from that in the control group. These results suggest that *IL-10* promoter polymorphisms are not risk factors for RA activity[81].

In a Chinese population only rs1800872 was studied. The allele and genotype frequencies were significantly different between the RA patients and controls. In addition, significant differences of allelic and genotypic frequencies were also detected between the patients with or without anti-CCP. The CA genotype is the most frequently observed genotype in both patients and controls. However, the distributions of CC and AA genotype in patients and control were reverse. The AA genotype frequency was higher, whereas the CC genotype frequency was lower in patients than in controls. The A allele frequency showed increased level comparing the results to the controls. It showed decreased A allele frequency, but increased C allele frequency level[82].

In a meta-analysis related to rs1800896, 10 case–control studies were carried out with the result that G allele carriers (GG + GA) had 25% decreased risk of RA, compared to the homozygote AA. In the analysis of Europeans, significantly decreased risks were associated with G allele carriers. The results of this meta-analysis provided evidence for the association between rs1800896 polymorphism and the risk of RA[83].

The IL-12 family

The IL-12 family consists of IL-12, IL-23, IL-27, IL-30 and IL-35, which are important mediators of inflammatory disorders. The common part is the heterodimeric complex composed of two subunits, the expression of which is regulated independently and have very different biological activities[84].

IL-23: IL-23 (OMIM 605580) was first described as a member of the IL-6/IL-12 superfamily[85]. It is a heterodimeric cytokine composed of 2 subunits[86-90]. The α-subunit is homologous to type I cytokines and β-subunit is related to the extracellular domain of other hematopoietin receptor family members[91]. IL-23 is expressed by activated monocytes, macrophages, DCs, T cells, B cells and endothelial cells[85,92] which strongly correlate with the cellular responsiveness to IL-23. IL-23 binds to a heterodimeric receptor complex composed of IL12RB1 (OMIM 601604) and IL23R (OMIM 607562) subunits[93]. IL12RB1 is also part of the IL-12 receptor, while IL-23R is unique to the IL-23 receptor complex.

The genetic variants of *IL-23* and its receptor (*IL-23R*) were first examined in the context of inflammatory bowel diseases (IBDs) in non-Jewish subjects[94]. Previous studies using genetically deficient animals showed experimental evidence that a strong association exists not only between the carriage of certain *IL-23R* gene variants and IBDs, but the correlation also stands for collagen-induced arthritis as inactivation of the *IL-23R* gene resulting in disease resistance[95].

On the basis of these findings, the possible associations between the functional variants of the *IL-23R* gene and RA were studied in the Hungarian population, and it was reported that some allelic variants represent an elevated risk for the disease, particularly in the RF- and/or anti-CCP-seropositive subsets of patients[96]. An increased prevalence of the homozygous rs10889677 AA genotype of the exon-3'-UTR 2370 C/A variant and the homozygous rs2201841 CC genotypes of the intronic SNP could be observed not only in Crohn's disease, but also in the RA groups compared to the controls.

In a Spanish population the examinations were expanded with genotyping of rs1004819, rs7517847, rs10489629, rs1343151, rs11209032 and rs1495965 SNPs, but none of the examined allelic variants and genotypes showed an increased prevalence in RA patients, not even when patients were stratified according to their clinical and demographic features (gender, age at disease onset,

presence of shared epitope, RF, rheumatic nodules and extra-articular disease)[97].

These findings were supported by a large cohort genotyping of Caucasian subjects for rs7530511 and rs11209026 variants of the *IL-23R* gene, but none of these SNPs proved to contribute to the predisposition to RA[98]. A Spanish study proved that the minor allele of the rs7517847 variant is responsible for a slightly elevated risk to RA[99] which is in accordance with the former findings[98]. Also the exonic rs11209026 contributes to the onset of the disease as well. The same variant was reported to be significantly less frequent in RA patients compared to controls[94].

Analyses of six *IL-23R* SNPs (rs11209026, rs1004819, rs7517847, rs10489629, rs2201841 and rs1343151) were analysed in a New Zealand Caucasian set of RA patients and extended by the reanalysis of the Wellcome Trust Case Control Consortium[62] and the previously published Spanish data set[97]. Unfortunately, the results emphasized the lack of association of the exonic rs11209026 with RA, but provided evidence for a weak allelic association of the rs1343151 variant with the disease. The study also tested LD relationships between 11 *IL-23R* markers. Results showed that several SNPs which were reported to confer risk for RA (rs1343151 in the same paper, and rs10889677 and rs2201841 in the Hungarian cohort) seemed to be independent risk factors[96,100], while others, such as rs7530511 in the North America Rheumatoid Arthritis Consortium (NARAC) and the Swedish Epidemiological Investigation of Rheumatoid Arthritis EIRA genome wide scan[101] seemed to confer risk only due to their weak LD with the markers associated in the Hungarian cohort[96]. Additionally, the NARAC plus EIRA data did not support the predisposing nature of the rs1343151 genetic variant which contradicted the results of a New Zealand study and a meta-analysis performed by a Chinese medical research group, who were able to replicate the association in a data set consisting of four European Caucasian populations[102].

As several studies have examined the association between *IL-23R* polymorphisms and RA but the results were contradictory. There was a high need for a carefully designed meta-analysis which can clarify the issue. In 2012, two papers summarized the observations published before February 2012[103,104]. In a meta-analyis, all relevant original papers gathered from electronic databases were selected by strict inclusion criteria[104]. Six studies involving more than 5000 European patients and controls were assessed. The C allele of the rs10489629 and the G allele of the rs7517847 proved susceptibility to RA. Interestingly, these alleles are protective factors in ankylosing spondylitis, but the same genetic variants may not share a common mechanism in different autoimmune diseases[105].

A meta-analysis evaluated the possible role of four other *IL-23R* polymorphisms in the etiology of RA (rs10489629, rs11209026, rs1004819 and rs2201841). It revealed significant association between the A allele of the rs134151 variant and RA in European subjects, and also confirmed the results of the previous meta-analysis on the predisposing feature of the rs10489629. A allele in the overall population[106]. Interestingly, no association was found between the rs7517847 polymorphism and RA, although this variant is in moderate LD with rs1343151. None of the other SNPs in the focus of this meta-analysis (rs11209026, rs1004819, rs2201841) showed association with the disease. Although three, possibly predisposing *IL-23R* variants after the meta-analyses have been convincingly identified; the exact functional significance of these polymorphisms remains unclear.

The IL-6-like cytokines

Members of this family (IL-6, IL-11, IL-27 and IL-31) signal through receptors containing gp130 which are commonly referred to as the IL-6-like or gp130 utilizing cytokines family[107].

IL-6: IL-6 (OMIM 147620) is one of those pro-inflammatory cytokines which are involved in the pathogenesis of RA. It acts as a major mediator of the acute phase response[108]. IL-6 signals through a cell-surface type I cytokine receptor complex consisting of the ligand-binding IL-6R chain (OMIM 147880) and the shared signal-transducing component IL6ST (also called gp130; OMIM 600694)[109].

Conventional radiography is considered a well-established imaging technique for identifying progressive joint damage[110]. The *IL-6* gene polymorphism-174 G/C (rs1800795) have been associated with RA susceptibility and radiographic severity of bone-erosive damage[111-115]. Significant association was observed between *IL-6* -174 C allele and early disease onset of RA[116]. However no relationship was found between disease susceptibility and *IL-6* -174 C allele in a Spanish study[117]. Another SNP, the -572 G/C (rs1800796) of *IL-6* is associated with RA in a Chinese Han population[47] but with no association with RA in Taiwan[118]. Similarly to these studies no association was found between *IL-6* -174, -572, -597 genotype distributions and allele frequencies in Turkish RA patients[34].

Elevated levels of IL-6 and soluble IL-6R (sIL6R) were found both in the serum and also in synovial fluid of joints in Han Chinese patients with RA[119]. IL-6R can be released *in vivo* in sIL6R through differential mRNA splicing and proteolytic rupture controlled by a disintegrin and metalloprotease domain (ADAM17, also called tumor necrosis factor-α-converting enzyme, TACE). This process is influenced by the SNP rs8192284 resulting in an aspartic acid to alanine substitution (D358A) at the proteolytic cleavage site. Trans-signalling extends the IL-6 range of action to cells lacking constitutive IL-6R[120]. It plays a key role in the pathophysiology of RA[121], where synoviocytes and chondrocytes react to IL-6 through this pathway. In a Spanish RA study was found that rs8192284 polymorphism determines the sIL6R plasma level. Furthermore, increased sIL6R plasma levels and expression of spliced isoform generating sIL6R are genotype dependent.

Meta-analysis of different studies with different ethnicities found association between RA and *IL-6*-174

G/C polymorphism in the European population. An Asian study also revealed significant association between the same *IL-6* polymorphism and RA. Regarding to the *IL-6*-572 G/C polymorphism, the ethnicity-specific analysis in the Asian study revealed an association between RA and the *IL-6*-572 G/C. However no association was found between the *IL-6*-174 G/C polymorphism and RA in the Iranian study[122].

The IL-17 family

This recently discovered interleukin family contains six cytokines (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F). IL-17A was the first member and the others were discovered shortly after the first one by large-scale sequencing of the human genome[123-126]. Members of this family share the highest amino acid sequence homology and perform distinct biological functions[127].

IL-17: IL-17A (OMIM 603149) is a pro-inflammatory cytokine which was the first discovered member of this family in 1993[128]. It acts on a variety of cells involving the development of autoimmunity, inflammation, and tumors. IL-17A and IL-17F genes share the highest degree of homology of about 50%, while the others have only 16%-30% of identity at the primary sequence level[126,129-132]. IL-17F (OMIM 606496) is a novel pro-inflammatory cytokine which induces the expression of cytokines and chemokines. Furthermore, it may play a role in skeletal tissue destruction and inflammatory processes in RA. In arthritis, IL-17A and IL-17F induce significant cartilage matrix release, inhibit new cartilage matrix synthesis and directly regulate cartilage matrix turnover[130]. The IL-17 receptor (IL17R) family includes five members: IL-17RA (OMIM 605461), IL-17RB (OMIM 605458), IL-17RC (OMIM 610925), IL-17RD (OMIM 606807), and IL-17RE (OMIM 614995)[133].

The *IL-17F* gene polymorphisms 7488 A/G (rs763780) and 7383 A/G (rs2397084) were investigated in Polish RA patients. The examined polymorphisms were not correlated with susceptibility to RA, but the 7488A/G (His161Arg) variant was associated with parameters of disease activity (number of tender joints), Health Assessment Questionnaire (HAQ) score or Disease Activity Score (DAS-28)-CRP. The authors supposed that the 7383 A/G (Glu126Gly) polymorphism may be correlated with longer disease duration in patients with RA. Probably these two SNPs directly regulate the IL-17F expression. They hypothesized that polymorphisms in *IL-17* gene may cause redundant production of IL-1 and TNF-α which can mediate inflammatory pathology in many autoimmune diseases, including RA[134].

In Norwegian patients with RA, five *IL-17A* SNPs were analysed. They found a weak but significant RA correlation with the *IL-17A* promoter polymorphism rs2275913[135]. A Japanese study concerning early RA examined the association between age at RA onset, radiographic progression and three SNPs (rs3804513, rs3748067, rs1974226) in the *IL-17A* gene. They described a weak association between the intronic rs3804513 and joint destruction (Larsen score), but found no association with the risk of developing RA[136].

Chemokines

This group contains only two ILs, IL-8 and IL-16.

IL-8: In a Taiwan population the 2767 A/G (rs112664) polymorphism in the 3'-UTR of the *IL-8* gene were investigated and no significant differences were found in the genotype and allele frequencies between RA patients and controls. Clinical characteristics such as age at onset, RF positivity, joint erosion and extra-articular manifestations were compared among patients, and it was found that patients with *IL-8* 3'-UTR 2767AA genotype had a significantly younger age of onset of RA than patients without that genotype[118].

In caucasian RA patients and healthy controls the 781 C/T (2227306) SNP of *IL-8* gene was examined with the result that CC genotype is associated with the early onset of RA[137].

CLINICAL IMPLICATIONS, TREATMENTS

Till the 1950s, aspirin and non-steroid anti-inflammatory drugs (NSAIDs) were the mainstay of RA therapy. Oral, intramuscular or intra-articular corticosteroids are recommended for controlling pain and inflammation. Ideally, NSAIDs and corticosteroids are used only for short-term management of RA. The development of disease-modifying anti-rheumatic drugs (DMARDs) has revolutionized the long-term therapeutic approach of the chronic inflammatory rheumatic diseases, particularly in patients resistant to standard treatment.

In respect of the new nomenclature for DMARDs[138], the term conventional, synthetic DMARDs (csDMARDs) is used to subsume chemical agents such as methotrexate (MTX), sulfasalazine, leflunomide, hydroxychloroquine, minocycline (less commonly used: gold sodium, thiomalate, penicillamine, cyclophosphamide, cyclosporine, azathioprine); whereas tofacitinib, a new sDMARD specifically designed to target janus kinases (JAKs), will be designated as a targeted sDMARD (tsDMARD). Biologic agents (bDMARDs) include monoclonal antibodies (mAbs), soluble recombinant cytokine receptors and natural antagonists to block cytokines which promote the inflammatory cascade responsible for RA[139]. Biological originator (bo) DMARDs encompass the five currently available TNF-α inhibitors (infliximab, etanercept, adalimumab, certolizumab pegol and golimumab), the T cell costimulation inhibitor abatacept, the anti-B cell agent rituximab, and the IL6R-blocking monoclonal antibody tocilizumab, as well as the IL-1 inhibitor anakinra. While biosimilars (bs), such as bs-infliximab, approved newly in the United States and/or Europe, will be named bsDMARDs[140].

The last set of ACR recommendations for the treatment of RA were published in 2008[141] with an update in 2012 for the use of DMARDs[142]. The 2010 EULAR guideline was renewed in 2013[140]. Goals of RA therapy

include reaching a target of remission or low disease activity in every patient. The commonly used indices to depict clinical response to therapy in RA include the ACR response[143], HAQ score[144] and DAS[145]. DAS28 is derived by the number of swollen joints and tender joints using the 28-joint count, and measures the CRP and and the patient's own assessment on a visual analogue scale[145].

Therapy with DMARDs should be started as soon as the diagnosis of RA is made[140]. Methotrexate is recommended as the first-line treatment in patients with active RA, unless contraindicated or not tolerated[138,141]. Leflunomide may be used as an alternative to methotrexate, although gastrointestinal adverse effects are more common. Sulfasalazine or hydroxychloroquine is recommended as monotherapy in patients with low disease activity or without poor prognostic features (*e.g.*, seronegative, non-erosive RA)[141,146]. Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for up to 6 mo, but should be tapered as rapidly as clinically feasible. Combination therapy with two or more DMARDs is more effective than monotherapy; however, adverse effects may also be greater[15]. If RA is not well controlled with a csDMARD, a biologic DMARD should be initiated with MTX[140,141,146]. Current practice would be to start a TNFα inhibitor. If TNF inhibitors have failed, other biologic therapies can be considered (*e.g.*, abatacept, rituximab or tocilizumab). Simultaneous use of more than one biological therapy (*e.g.*, adalimumab with abatacept) is not recommended because of an unacceptable rate of adverse effects[141]. Tofacitinib, a new tsDMARD, may be considered after biological treatment has failed[138].

Although the precise etiology of RA still remains unknown, improved understanding of the pathogenesis of the disease DMARD treatment has undergone dramatic changes during the past decade. Biological DMARDs have the potential to inhibit the behaviour of cytokine, cellular activation, and inflammatory gene transcription by various means. Cardiovascular disease due to accelerated atherosclerosis is the major cause of excessive mortality in RA. Cytokine antagonists have shown a favourable response in endothelial cell dysfunction in these patients[147].

Because of the elevated levels of TNFα, IL-1 and IL-6 in the synovial fluid of patients with RA, these three cytokines have been targeted at the beginning of RA therapy. Numerous other biological therapies are in various stages of development. We now review the main biological drugs classifing according to the targeted mechanism of action.

Tumor necrosis factor inhibitors

TNFα is a pleiotropic, pro-inflammatory cytokine which plays a pivotal role in the origin and progression of RA. TNF is a 17-kD trimeric protein cytokine that is produced mainly by monocytes and macrophages. Newly synthesized TNFα is inserted into the cell membrane. Subsequently, the TNFα converting enzyme (TACE) cleaves this cell-bound TNFα to release it into circulation[148]. Both soluble (sTNF) and membrane TNF (mTNF) are biologically active when interacting with either of two distinct receptors, TNF receptor 1 (TNFR1, p55) and TNFR2 (p75), expressed on a wide variety of target cells[149]. TNF receptor signalling occurs through two pathways: one arm has death-domain proteins which lead to apoptosis, the second and dominant signalling pathway goes through a series of kinases, leading to the activation of nuclear-factor kappa B (NF-κB).

The mechanism of action of TNF-α antagonists is based on the neutralization of both sTNF and mTNF and has a more global effect on inflammation than the blockade of other cytokines. The interruption of the signal pathways mediated by TNF has numerous consequences, reflecting the pleiotropic effect of the cytokine: apoptosis, inhibition of pro-inflammatory cytokine and chemokine release, but also of chondrocyte, osteoclast, and endothelial cell activation, reduction of leukocyte accumulation and angiogenesis, increase of T reg cell number.

Currently, 5-TNF inhibitors are approved for use by the United States Food and Drug Administration. Infliximab (Remicade®) is a chimeric (75% human + 25% mouse) monoclonal full-length, bivalent IgG1 mAb[150]. Certolizumab Pegol (Cimzia®) is a humanized protein containing amino acid sequences derived from a mouse anti-TNF mAb and inserted into human domains; adalimumab (Humira®) and golimumab (Simponi®) are fully human mAbs[151]. Etanercept (Enbrel®) is a dimeric fusion protein consisting of soluble p75-TNFR2 and the Fc portion of human IgG1. The primary action of etanercept is to bind and inactivate soluble and cell-bound TNF-α and lymphotoxin-α.

Another way to block TNF-α in biological fluids is to inhibit TACE, up to 95% reduction of the TNF production is attainable. TACE inhibitors are under development, but, even after more than a decade no single TACE inhibitor has passed the phase 2 clinical trials[152].

IL-1 antagonism

IL-1 is implicated in the pathogenesis of RA, its level correlates with RA disease activity[153]. IL-1 type 2 receptor (IL-1R2) (OMIM 147811) is a decoy receptor which binds to circulating IL-1[154] and is not involved in signal transduction. An antagonist of these receptors has also been identified (IL1RN) which neutralizes the effects of IL-1, consequently, IL1RN acts as a physiological inhibitor of IL-1. Complete inhibition of IL-1 requires 10-fold to 100-fold molar excess of IL1RN over IL-1. The balance between IL-1 and IL1RN is important in maintaining the normal physiology of the joints and homeostasis of the immune system.

Anakinra (Kinaret®) is a recombinant form of the naturally occurring IL1RN[155], approved in 2001 for the treatment of patients affected by RA. It should also be mentioned that anakinra, while effective in individual patients with RA, did not show a high level of clinical efficacy in clinical trials[156] and therefore has not been recommended as a major biological agent for use in RA[140].

Many IL-1 inhibiting agents are being developed and tested. These include a recombinant form IL-1R2, rilonacept, also known as IL1Trap (recombinant molecule consisting of IL1R1 and IL1RAP fused to human IgG1 Fc portion which acts as a soluble decoy receptor, trapping both IL-1A and IL-1B[155]). Canakinumab, a human anti-IL-1B mAb (currently investigated in phase 3 studies[157]), and an inhibitor of IL-1 converting enzyme[154,158].

IL-6 antagonism

Evidence has indicated that blocking the effects of IL-6 in RA is effective and safe, especially with the IL-6R inhibitor, tocilizumab[159]. Tocilizumab (Actemra®) is a humanized mAb of IgG1 class against IL-6R which prevents the formation of the IL-6/IL-6R complex and the activation of signal transduction cascade through JAKs and STATs. Over the next few years, new biological agents targeting the IL-6 receptor (sarilumab) or IL-6R (clazakizumab, sirukumab) may become available[160].

Co-stimulation signal blockade

There are several sets of T cell co-stimulatory molecules like CD40-CD40 ligand (CD40L) and CD28-CTLA4-B7. Blockade of some of these are under various stages of development[139]. Abatacept (Orencia®) is a biologic agent which blocks T cell activation through the inhibition of CD28-B7 mediated costimulation of the T cell. It has been approved for the treatment of RA[161]. Structurally, abatacept is a recombinant dimeric fusion protein consisting of the extracellular domain of CTLA-4 fused with the modified Fc portion of a human IgG1. Blocking anti-CD40 ligand antibody and anti-CD11a monoclonal antibody (efalizumab) could be also beneficial for the treatment of RA.

B-cell-depleting therapy

B cells behave as antigen presenting cells, stimulating the activation and proliferation of T cells. In addition, the synovium of patients with RA contains a large number of plasma cells producing RF. The easiest method to obtain a reduction in the number of B cells is to use mAbs directed against surface markers such as CD19, CD20, and CD22.

Rituximab (Rituxan®) is a chimeric mouse/human mAb which selectively depletes B cells bearing the CD20 surface marker. Widely used in the treatment of B-cell lymphomas, it has been shown to be surprisingly effective in RA. The rituximab/MTX combination represents a potential therapeutic option for moderate/severe RA patients, resistant or intolerant to at least one TNF antagonist[140]. Epratuzumab is a humanized mAb formed by an IgG1 directed against CD22.

Tumor necrosis family proteins (*e.g.*, death receptors, anti-B lymphocyte stimulator antibodies) are the molecules of the immune system which take part in the negative feedback regulation to eliminate autoimmune cells. Excessive levels of the TNF family ligand B-lymphocyte stimulator (BLyS) have been demonstrated in RA synovial fluid. Approaches targeting the BLyS and other systems (like APRIL) to selectively eliminate the activated autoimmune lymphocytes in RA are under development[162]. Belimumab is a human recombinant IgG mAb which acts by binding BLyS protein and prevents the interaction with the B cell activating factor receptor.

Atacicept is a recombinant fusion protein comprising the extracellular domain of the TACI (Transmembrane Activator and CAML Interactor) receptor joined to a human IgG1 Fc domain. Atacicept also inhibits the survival of long-lived plasmacells directly involved in the pathogenesis of RA and SLE.

Kinase inhibitors

In the case of RA, kinases play a central role in the aberrant immune system activation and hence have been targeted using small molecule inhibitors. Mitogen-activated phosphokinase p38 (MAPK), spleen tyrosine kinase (Syk), and JAKs have been studied extensively in clinical trials in RA[163]. Several p38 MAPK inhibitors proved inefficient in treating rheumatoid arthritis.

The Syk inhibitor, fostamatinib, proved superior to placebo in Phase 2 trials and is currently under phase 3 investigation. Tofacitinib (Xeljanz®), a JAK1/3 inhibitor, was approved for the treatment of RA in the United States, Japan and Russia in April 2013[164]. This new tsDMARD may be considered for use after biological treatment has failed[138]. Ruxolitinib and baricitinib (JAK1/2 inhibitors) and pan-JAK inhibitors (JAKinibs) have also been studied in RA where preliminary results were promising in terms of efficacy and safety in a Phase 2a trial.

Upcoming therapies

IL-1 superfamily: IL-18 could be an interesting target in the treatment of RA and one opportunity for antibody-based biological therapies in RA. Blocking of IL-18 by the administration of a recombinant IL-18 binding protein (IL18BP, OMIM 604113) which has the ability to prevent binding of IL-18 to its receptor, or anti-IL-18 in mice with collagen-induced arthritis resulted in a clear reduction of the disease severity compared with placebo-treated mice[165].

IL-33 (OMIM 608678), a newly identified IL-1 family member cytokine, is a chemoattractant for Th2 cells and facilitates the production of Th2 cytokines. IL-33 binds to its receptor consisting of the orphan receptor ST2 (IL1RL1, OMIM 601203) and IL-1 receptor accessory protein (IL1RAP). The soluble ST2 (sST) acts as a decoy receptor of IL-33 and is a natural inhibitor of IL-33. Increased serum and synovial fluid levels of sST2 in RA patients reflect an active inflammatory state[166,167]. Furthermore, the inhibition of IL-33 receptor signaling with anti-ST2 antibodies or sST2-Fc fusion protein resulted in reduced severity of collagen-induced arthritis[166,168].

IL-2 superfamily: The role of IL-2 in the immunopathogenesis of RA is debated. IL-2 is hardly detectable in the synovial fluid, and only a low percentage of the intra-articular T cells express T cell activation markers (Tac antigen)[169]. IL2-directed therapy may have beneficial effects

in RA patients[170]. The humanized monoclonal antibody daclizumab (Zenapax®) against the α-chain of the IL-2R (CD25) caused significant reduction of joint-inflammation and joint-erosion in collagen-induced arthritis in rhesus monkeys[171]. Antagonistic IL2RA mAbs (anti-Tac/daclizumab, basiliximab) are effective in preventing rejections of organ transplants.

IL-15 is a pro-inflammatory, innate response cytokine. In patients with RA, innate response cytokine IL-15 is expressed in the synovial tissue and the serum levels of IL-15 have been reported to correlate with disease severity[172]. Anti-IL15 monoclonal antibodies are being examined for their anti-arthritic activity. Baslund and colleagues conducted a phase 1/2 clinical trial of a human IgG1 anti-IL15 monoclonal antibody, HuMax-IL15. This antibody could neutralize various biological effects of IL-15 in synovial tissue *in vitro*, and it caused significant improvement in disease activity at 12 wk after treatment initiation[56,173,174]. Clinical trials are underway evaluating the safety and efficacy of monoclonal antibody IL-15 (HuMax-IL15) and CD2 receptor (Alefacept).

IL-21 contributes to joint inflammation and synovial cellular infiltration in RA, as expected for a Th17-related cytokine[25,175]. Increased level of IL-21 has been reported in RA sera, and the concentration of IL-21 in serum and synovial fluid was higher in RA than osteoarthritis[175]. Treatment with IL21RFc chimeric protein in animal models of RA resulted in significantly reduced disease severity[176-178].

The IL-12 family: IL-12 and IL-23 bind to the IL12RB1 of T cells and NK cells via their shared p40 subunit. Evidence shows that IL-23 plays a key role in the development of pathogenic Th17 cells producing IL-17, which further induces the production of several pro-inflammatory cytokines, such as TNFα and IL-6, chemokines, which cause the aggravation of synovial inflammation and osteoclast differentiation leading to joint destruction in patients with RA[179,180]. In addition, the serum level of IL-23 in patients with RA correlates with the number of swollen joints, the DAS28 joints. Studies have shown that IL-23 induces receptor activator of RANKL expression on $CD4^+$ T cells and promotes osteoclastogenesis in an autoimmune arthritis[181]. Thus anti-IL23 therapy could be a therapeutic target not only of inflammation but also bone erosion in RA. The level of interest in this target can be seen from the fact that 15 different IL23R antagonists are now reported to be in clinical or pre-clinical development[182] .

Recent clinical studies associated with IL-23 inhibition in arthritis include the use of apilimod mesylate, an orally administered inhibitor of IL-12/IL-23 in RA[183]. Ustekinumab and briakinumab, fully human mAbs directed against the p40, are currently in phase 2 trials. However, due to the common p40 subunit and IL12RB1 chain, the major drawback of anti-IL23 treatment may be the simultaneous inhibition of IL-12 and a possible shutdown of the immune system. Nevertheless, it would be much more useful to design drugs that target the IL23p19 or IL23RA itself, thus inhibiting IL-23 without modifying the effects of IL-12 (*e.g.*, MP-196, FM-303, IL-23 Adnectin)[182].

The IL-17 family: Increased levels of IL-17A have been found in sera, synovial fluid, and in the T cell-rich area of the synovium in patients with RA[184,185] and these levels are predictive of a more severe joint damage progression[186]. Besides the enhancement of inflammation commonly observed in arthritis, IL-17A also mediates bone and cartilage destruction through the stimulation of fibroblast-like synoviocytes to produce pro-inflammatory cytokines, IL-6 and IL-8, as well as matrix-degrading enzymes, matrix metalloproteinases. In addition, IL-17 upregulates the receptor activator of RANK on osteoclast precursors causing increased sensitivity to RANK signaling.

Treatment of RA patients with a humanized anti–IL-17 antibody (LY2439821) given intravenously is shown to improve the signs and symptoms of the disease[187]. In another study on RA, treatment with AIN457 (anti-IL17) induced clinically relevant responses, although of variable magnitude[188]. The IL-17 blockers secukinumab (anti-IL-17A), ixekizumab (anti-IL17A), and brodalumab (anti-IL17RA) have shown efficacy in phase 2 trials in RA. The results of the ongoing phase 3 trials should help to shed light on whether IL-17A is truly a viable therapeutic target in RA. The effect of blocking other IL-17 family members including IL-17F has yet to be evaluated in human diseases.

Agents blocking the chemokines and adhesion molecules: Agents blocking the chemokines and adhesion molecules are also under trial. These include antibodies to IL-18[165], humanized anti-integrin avb3 monoclonal antibody (MEDI-522) and anti-VCAM antibodies. Suppression of new wessel formation could also be an interesting target in the future treatment of RA.

Anti-inflammatory cytokines in RA: IL-10 and IL-4 are cytokines with counter-regulatory mechanism that down-regulates pro-inflammatory responses. Some anti-inflammatory effects are also naturally provided by the presence of IL-1RN, IL-1R2 decoy receptor and soluble TNF receptor. In vitro, IL-10 and IL-4 inhibit the production of inflammatory cytokines including IL-1, IL-6 and TNF-α RA[189,190], furthermore IL-10 has been shown to reverse the cartilage degradation seen in RA[189]. *In vivo*, however, they are inherently weak and proved inadequate.

IL-27 (OMIM 605816) is an IL-12 superfamily cytokine that plays a role in the immune effector responses in autoimmune diseases, including arthritis. The role of IL-27 as a pro-versus an anti-inflammatory cytokine has not yet been fully resolved. In collagen-induced arthritis, treatment of mice with IL-27 reduced the severity of arthritis, as well as the levels of IL-6, IL-17[87]. Another mechanism of IL-27-mediated protection against arthritis involves the inhibition of osteoclastogenesis[191].

It has recently been shown that human Tregs express

IL-35 and require this cytokine for their optimal suppressive effect[192]. These findings reinforce a potential mechanism (*e.g.*, suppression of Th17 response) that Tregs can be used to control pathogenic T cell responses in RA. Treatment of mice with IL-35 reduced disease severity which was associated with reduction in IL-17, IFN-γ, and an increase in IL-10 production[193].

Small molecular inhibitors of intracellular signalling: Small molecular inhibitors of intracellular signalling (*e.g.*, NF-κB and associated activator molecules) are in focus of numerous clinical and preclinical research and have shown promising results in animal models[194,195].

RANKL inhibition: Denosumab, a human anti-RANKL mAb is approved in the United States for the treatment of postmenopausal osteoporosis but is not currently indicated for the treatment of RA (phase 2).

CONCLUSION

RA is the most common chronic inflammatory disease of the joints and is characterized by a complex genetic architecture. In our review, we discussed the pathogenesis, the polymorphisms of IL and *IL* genes and also the standard available and possible future immunologic targets for RA treatment. The identification of disease-associated interleukin and interleukin receptor genes could provide precious insight into the genetic variations prior to disease onset in order to identify the pathways important for RA pathogenesis. From the discussed interleukins the IL-1, the IL-6, and the IL-23 were the most investigated.

IL-1 is very important, because it mediates many inflammatory diseases by initiating and potentiating immune and inflammatory responses. Several studies have dealed with the association of *IL-1* gene polymorphisms with RA. The IL-1 expression is influenced by two variants of the *IL-1B* (-511 T/C and +3953 C/T). Carrying the TT genotype of *IL-1B* +3953 gene is susceptible to RA in a Turkish cohort, while the CT genotype of *IL-1B* -511 has a protective role against RA. In a British Caucasian RA patients the G allele of *IL-1B* -1464 C/G was found to possibly have protective effect in RA. In the Asian populations +3953 C/T SNP of the *IL-1B* polymorphism was associated with the development of RA.
IL-6 is the main pro-inflammatory cytokine which is involved in the pathogenesis of RA. Several SNPs of the *IL-6* gene were investigated (promoter polymorphisms: -174, 572, -597, exonic polymorphisms: 869), but with controversial results. In a Spanish, Turkish and Iranian cohort the *IL-6*-174 G/C is not a risk factor for RA, but meta-analyses with different ethnicities showed an association between RA and these SNP in other European population. An Asian study also revealed a significant association between the same SNP and RA. The -572 G/C SNP is associated with RA in a Han Chinese population, while no correlation could be detected in a Taiwan population. Ethnicity-specific analysis in an Asian study revealed an association between RA and *IL-6* -572 G/C polymorphism.

IL-23 is the most extensively studied cytokine. IL-23 is very important in innate and adaptive immunity. The *IL-23R* gene was identified first as a CD susceptibility gene in North American non-Jewish subjects but the studied were extended to RA. Association between independent functional SNPs in the gene and its neighboring region and RA were investigated (rs10889677, rs11209032, rs1495965, rs2201841, rs1004819, rs11209026, rs7517847, rs10489629, rs1343151) in numerous studies. Several SNPs are susceptible, others are protective to the disease but the predisposition was population dependent.

In the lack of knowing genetic variants that influences the development of RA and in default of adequate therapy, the patient's way of life continuously declines, even permanent disability might arise. However, conventional DMARD therapy of RA has several limitations like slow onset of action and induction of partial remission. By targeting molecules that are directly involved in pathogenesis pathways, blocking biologic activity of pro-inflammatory cytokines and their receptors may be more specific, more efficacious, and less toxic in the short-term than current treatment modalities. Because biologics are relatively new, evidence is insufficient to determine their long-term benefits and risks, including the risk of lymphoma and malignancies.

Evidence suggests that although biologics are relative expensive, they remain cost-effective because of the major clinical benefits that patients may experience. Currently, data is available for one biosimilar product (infliximab) which shows similar efficiancy and safety profiles to the original biological agent. It has been estimated that the price for biosimilar products will be 65%-85% of their originators. Nevertheless, combinations of biological agents targeting different disease processes may allow more promising results in future. The knowledge of the complex genetic background may prove to be greatly useful for developing novel therapies and producing personalized medicine based on the individual's genetics.

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Rheumatoid arthritis susceptibility genes: An overview

Izabela Korczowska

Izabela Korczowska, Department of Rheumatology and Clinical Immunology, University of Medical Sciences in Poznan, 61-701 Poznan, Poland
Author contributions: Korczowska I solely contributed to this paper.
Correspondence to: Dr. Izabela Korczowska, Department of Rheumatology and Clinical Immunology, University of Medical Sciences in Poznan, Fredry 10, 61-701 Poznan, Poland. ikorcz@post.pl
Telephone: +48-61-8547210 Fax: +48-61-8547212
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Abstract

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease sustained by genetic factors. Various aspects of the genetic contribution to the pathogenetics and outcome of RA are still unknown. Several genes have been indicated so far in the pathogenesis of RA. Apart from human leukocyte antigen, large genome wide association studies have identified many loci involved in RA pathogenesis. These genes include protein tyrosine phosphatase, nonreceptor type 22, Peptidyl Arginine Deiminase type Ⅳ, signal transducer and activator of transcription 4, cytotoxic T-lymphocyte-associated protein 4, tumor necrosis factor-receptor associated factor 1/complement component 5, tumor necrosis factor and others. It is important to determine whether a combination of RA risk alleles are able to identify patients who will develop certain clinical outcomes, such myocardium infarction, severe infection or lymphoma, as well as to identify patients who will respond to biological medication therapy.

Key words: Rheumatoid arthritis; Gene; Polymorphism; Human leukocyte antigen; Genome wide association study

Core tip: This is a comprehensive review concerning genetic factors in rheumatoid arthritis.

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INTRODUCTION

Rheumatoid arthritis (RA) is the most common autoimmune disease, afflicting around 0.5%-2% of the human population, especially females, but the precise etiology is still unknown. RA is characterized by chronic, systemic inflammation that may affect many tissues, principally synovial tissue, leading to joint destruction, functional disability and sometimes death[1]. Environmental and genetic factors are responsible for susceptibility and the phenotype. Environmental factors include geography, climate, endemic microbes and lifestyle, such as smoking and diet[2,3]. Native Americans show a relatively higher incidence than African or Asian populations. Familial clustering is important, with the prevalence of RA ranging from 2% to 12% in first degree relatives of patients, 5%-10% in same sex dizygotic twins and almost 12%-30% in monozygotic twins[3,4].

The human leukocyte antigen (HLA) region in the human genome is the most heterogeneous and many diseases are known to be associated with this region. The first risk alleles for RA were identified within 36Mb, the major histocompatibility complex (MHC) region[3]. Several studies beginning in the 1980s explained the strong association of the HLA-DRB1 alleles with RA. The associated alleles encode five amino acids at position 70-74 of the HLA-DRβ1 chain, which is known as a shared epitope (SE). It was established that the HLA-DRB1*01, HLA-DRB1*04 and HLADRB1*10 alleles containing the SE were associated with susceptibility to RA and amino acid sequences QKRAA, QQRAA and KKRAA were known SEs conferring susceptibility, while DERAA sequences were for protective effects[5,6]. Caucasian RA patients have

Table 1 The most relevant alleles associated with susceptibility in rheumatoid arthritis according to genome wide association studies

Gene candidate	Locus	SNP	OR
HLA-DRB1			
PTPN22	1	Rs2476601	1.23-1.75
PADI4	1	Rs 2240340a	1.4
STAT4 T/C	2	Rs1188934	1.22 (0.98-1.53)
FCGR2A	1	Rs12746613	1.1
CTLA4	2	Rs3087243	0.75-1.136
CCL21	9	Rs2812378	1.1
TRAF1	9	Rs3761847	1.1 (0.97-1.32)
IRF5	7	Rs10488631	1.16 (0.72-1.87)
CCR6	6	Rs3093023	0.79 (0.64-0.98)
CD40	20	Rs4810485	0.91-1.02
IL2RA	10	Rs2104286	0.92

RA: Rheumatoid arthritis; HLA: Human leukocyte antigen; IL: Interleukin; PTPN22: Protein tyrosine phosphatase, nonreceptor type 22; TRAF1: Tumor necrosis factor receptor associated factor 1.

been tested for ACPA antibodies, RF and HLA-DR genotype, and the results showed a correlation between the presence of RF and ACPA antibodies within the HLA-DRB1 SE[3,7]. Moreover, current smoking habits and SE, especially homozygous SE, have a strong interaction[3,8]. SE is a risk factor for the development of an extra-articular manifestation and so for more severe, destructive RA. However, the non-SE alleles DRB1*1301, *1302 and *1304 seem to be linked to the DERAA motif[9-11]. The study in Hungarian RA patients recommended that HLA-DRB *1301 allele may protect against ACPA positive or ACPA negative RA[9,12-15]. Also, enhanced production of ACPA has been connected with HLA-DRB1*15 positively in RA[9,16-18]. In a Korean population, heterozygous for HLADRB1 0404 or 0901 have up to a 60-fold increased risk of developing susceptibility to RA[19].

A new taxonomy system for the risk of developing RA has been proposed[9,11]. This new classification depends on whether the RAA (motif which represents susceptibility risk of RA) sequence occupies position 71-74 of HLA-DRB1 but is modulated by amino acids at positions 70; glutamine (Q) and arginine (R) represent a higher risk than aspartic acid (D). Lysine (K) confers the highest risk, arginine (R) intermediate risk and the lowest risk is for alanine (A) and glutamic acid (E) in position 71. According to this new classification, SE alleles are divided into S1, S2, S3P and S3D groups and allele X which denotes all non-RAA motifs. The presence of S2 and S3P alleles are a positive association with RA and also correlated with ACPA production, while S1, S3D and X were found to be low risk alleles[9,11,20].

Genome wide association studies (GWAS), large scale cohorts and Wellcome Trust Case Control Consortium databases have allowed the simultaneous evaluation of thousands of genes[9,21-23] and drawn attention to association with RA susceptibility, determining the phenotype of the disease, and response to therapy. Additional variants in the MHC contribute to the heritability of RA independently of the HLA-DRB1, leading to more consequent results of genetic associations. Alleles associated with the susceptibility with RA according to the GWAS study are shown in Table 1. Loci outside the MHC have been associated in a RA population in approximately 4% to the phenotypic variance of RA risk. One of them is peptidyl arginine deiminase, type Ⅳ (PADI4) encoding peptidylarginine deiminase type Ⅳ.

PADI4

One of the isoenzymes carrying the post-translational conversion of arginine residues to citrulline is known as the type 4 peptidylarginine deiminase type Ⅳ. PADI4 enzyme may be connected to the production of ACPA. PADI4 is present in bone marrow and peripheral blood leukocytes and is one of the four isoforms of PADI enzyme in humans encoded by the *PADI4* gene[3,24]. *PADI4* gene maps on 1p36 locus have been associated with European and Japanese RA populations. A meta-analysis done by Lee *et al*[25] showed that in Asian patients, all 5 researched polymorphisms (PADI4_89, PADI4_90, PADI4_93, PADI4_94 and PADI4_104) were significantly associated with RA, while in Europeans only PADI4_94 was associated with RA risk, much less than in Asian patients[26,27]. The function of this gene in the European RA population is still questionable as the results of large studies from Spain, France and the UK found no association with RA[3,28,29].

Within the genes investigated for susceptibility to RA, protein tyrosine phosphatase type 22 (PTN22) is one of the most strongly associated.

Protein tyrosine phosphatase, nonreceptor type 22

Protein tyrosine phosphatase, nonreceptor type 22 (PTPN22) encodes the intracellular tyrosine phosphatase LYP, known as a powerful inhibitor of T-cell activation. The gene encoding PTPN22 shows the second strongest (just after HLA-DRB1) association with RA. The gene was first associated with type 1 diabetes, systemic sclerosis, Graves disease and lupus erythematosus. Then it was associated with RA in a Caucasian population; rs2476601, C1885T polymorphism leading to an amino acid modification from Arg to Trp at amino acid position 620. This polymorphism resides in a rather large haplotype block encompassing the entire PTPN22 gene[3,30-32]. This SNP has been associated with RF, ACPA positive and SE. ACPA status powerfully supports the early diagnosis of RA. It is worth mentioning that in contrast to SE, C1885T polymorphism may not be associated with smoking[9,33-35]. The important fact is that this polymorphism is not associated with RA in Asian populations, maybe only with Asiatic Indians with RA positive[36].

Signal transducer and activator of transcription 4

The signal transducer and activator of transcription 4 (STAT4) is a transcription factor that intercedes the intracellular signal activation by cytokines such IL-12, IL-23 and IL-27 and type I interferons. STAT4 can be induced

upon activation and maturation of monocytes as well as immature dendritic cells. STAT is also overexpressed in RA synovium. Lee *et al*[37] and Amos *et al*[38] detected linkage at chromosome 2q33 in RA and then revealed that the polymorphism located at 2q33 STAT4 gene is the marker responsible for the linkage signal in 2q33. It has been found that STAT4 rs7574865 polymorphism is associated with European, Asian and Latin American RA patients[37,39-43]. Comparison between ACPA positive and negative patients showed no significant differences[37]. It seems that the intronic variant rs11893432 C/G of *STAT4* gene could also predispose to RA[26,44].

Cytotoxic T lymphocyte-associated antigen 4

Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) is expressed on T cells, is a member of the immunoglobulin superfamily and performs a critical role in the inhibition of T-cell activation and peripheral tolerance. Three polymorphisms have been described in the *CTLA-4* gene: first, microsatellite at position 642 of the 3' untranslated region of exon 4; second, the polymorphism 49G/A in exon 1 causes a threonine to the alanine substitution of amino acid 17; and the third, -318 of the promoter sequence C/T transition[45]. The CT60 allele has been associated with autoimmune diseases. In the end, CTLA-4 export to the membrane reduces and decreases the inhibitory function of CTLA-4. CTLA4 increased the development of ACPA positive RA in contrast to RA patients with ACPA negative. The meta-analysis showed a positive connection of 49A/G polymorphism susceptibility with RA in Asians, but only 1 in Asians and Europeans[3,46-48]. However, the exact role of this gene in RA is quite modest and still must be clarified.

TRAF1-C5

Two biological candidate genes, TNF receptor associated factor 1 (TRAF1) and complement component 5 (C5), were described by GWAS. TRAF1 is a member of the TNF receptor associated factor family, which are a class of proteins that link TNF receptor family members associated with signaling pathways that play a function in apoptosis, cell proliferation and differentiation, activation and inhibition cytokines and bone remodeling. The most strongly associated SNPs are rs3761847 and rs10818488 in the genome. It seems that the maximal genetic signal is located between the TRAF1 and C5 gene[39,49].

TNF

TNF alpha is a pleiotropic inflammatory cytokine. TNF-308A/G (rs1800629) polymorphism is associated with RA in the Latin American population[26,50] but not in any other ethnic group. Also, the TNF promoter polymorphism -609G/T and -238A/G are not associated with RA[45]. TNF-308A/G polymorphism was associated with radiological damage in a RA patient. Khanna *et al*[51] showed that patients with -308 TNF alpha AA+AG genotypes had considerably higher rates of progression in erosion scores and Sharp scores equal to the GG genotype patients. In contrast, Lacki *et al*[52] suggest that TNF-308 polymorphism cannot serve as an indicator of the disease course in RA patients.

INTERLEUKIN

Interleukins are a large part of cytokines which promote the development and differentiation of lymphocytes T, B and hematopoietic cells. In RA patients, SNPs of cytokines have been investigated regarding an association with erosive damage. One of them is IL-1. Polymorphism -511A/G (rs16944) in promoter IL-1b was positively associated with RA. +3954T allele was associated with more severe structural damage (mainly with Larsen's score in wrist joints)[3,53,54]. IL-6 is a multifunctional cytokine implied in the inflammatory and immune response. Some studies reported that -174G/C (rs1800795) allele was associated with radiological damage in RA patients who were ACPA and RF positive[55]. The presence of two functional polymorphisms in the promoter region of IL-6, the -174G/C and -572G/C, suggests a strong susceptibility for European RA patients compared to Asians. These two polymorphisms (rs1800795 and rs1800795) may also influence the risk of osteoporosis. Another multifunctional cytokine is IL-10, produced by monocytes and lymphocytes, a protein that inhibits the synthesis of a number of cytokines and has a range of anti-inflammatory and immunoregulatory properties. Three polymorphisms placed in the promoter IL-10 were studied, including -1082G/A (rs 1800896), -892C/T (rs1800871) and -592C/A (rs1800872). The results are controversial as one showed that -1082G/A polymorphism is not associated with RA of either European or Asian populations and the other showed a positive association with RA, indicating that the carriers of the G allele could have a decreased liability of RA[26,56]. Some studies reported that the homozygosity of -592C/A was associated with higher Larsen scores in RA patients with ACPA and RF negative[55]. Polymorphisms of the *IL-2* and *IL-21* genes (region 4q27) have been implicated in several autoimmune diseases, including RA. One of them is intronic change A/G rs13151961[57]. Next studied were polymorphisms in RA susceptibility which may modulate gene expression of IL-2 or IL-21 located in the noncoding region, upstream of IL-21 and downstream of IL-2 is the G/T rs6822844. In a study on European Caucasian and South American populations, significant association with RA was shown[26,58,59].

With the use of GWAS, genetic studies can examine many common genetic variants across the entire human genome. There are a lot of other gene and chromosome loci revalidated as RA susceptible regions, such as CD226, CD40, CDK6, MBP, BLK, REL and more[60].

In conclusion, rheumatoid arthritis has a strong genetic influence mediated by alleles. Human genetics should be able to determine the value of RA risk alleles by providing clinical predictions. One of the most direct clinical applications is to use human genetics to lead the development of treatment for RA. It will be crucial to determine whether a combination of RA risk alleles are

able to identify patients who develop certain clinical outcomes, such as myocardium infarction, severe infection or lymphoma, as well as to identify the patients who will respond to biological medication therapy.

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WJO 5th Anniversary Special Issues (2): Ankle

Power Doppler ultrasonographic assessment of the ankle in patients with inflammatory rheumatic diseases

Takeshi Suzuki

Takeshi Suzuki, Division of Rheumatology, Mitsui Memorial Hospital, Tokyo 101-8643, Japan
Author contributions: Suzuki T was involved in the conception of this topic highlight article, the literature review process, the acquisition of ultrasound images and preparing the manuscript.
Correspondence to: Takeshi Suzuki, MD, Division of Rheumatology, Mitsui Memorial Hospital, 1 Kandaizumi-cho, Chiyoda-ku, Tokyo 101-8643, Japan. suzuki-rheum@mitsuihosp.or.jp
Telephone: +81-3-38629111 Fax: +81-3-56879765
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Abstract

Ankle involvement is frequent in patients with inflammatory rheumatic diseases, but accurate evaluation by physical examination is often difficult because of the complex anatomical structures of the ankle. Over the last decade, ultrasound (US) has become a practical imaging tool for the assessment of articular and periarticular pathologies, including joint synovitis, tenosynovitis, and enthesitis in rheumatic diseases. Progress in power Doppler (PD) technology has enabled evaluation of the strength of ongoing inflammation. PDUS is very useful for identifying the location and kind of pathologies in rheumatic ankles as well as for distinguishing between inflammatory processes and degenerative changes or between active inflammation and residual damage. The aim of this paper is to illustrate the US assessment of ankle lesions in patients with inflammatory rheumatic diseases, including rheumatoid arthritis, spondyloarthritis, and systemic lupus erythematosus, focusing on the utility of PDUS.

Key words: Ankle; Power Doppler; Ultrasound; Rheumatoid arthritis; Psoriatic arthritis; Spondyloarthritis; Tenosynovitis; Enthesitis

Core tip: Over the last decade, ultrasound (US) has become a practical imaging tool for the assessment of articular and periarticular pathologies in rheumatic diseases. Progress in power Doppler (PD) technology has enabled evaluation of the strength of ongoing inflammation. PDUS is useful not only for identifying the pathologies in rheumatic ankles, but also for distinguishing between inflammatory processes and degenerative changes or between active inflammation and residual damage. The aim of this paper is to illustrate the US assessment of ankle lesions in patients with inflammatory rheumatic diseases, including rheumatoid arthritis and spondyloarthritis, focusing on the utility of PDUS.

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INTRODUCTION

Many kinds of systemic arthritic diseases affect the ankle. Among them, there are also diseases for which ankle involvement is a hallmark. As the ankle is one of the major weight-bearing joints, it is prone to being affected by injury and/or by degenerative disorders. In the ankles of patients with inflammatory rheumatic diseases, this extrinsic damage commonly coexists, and it is not always easy to distinguish between them.

Anatomical structures in the ankle lie close together and are sometimes overlying, making differentiation between adjacent structures problematic[1]. Inflamed synovia are relatively small in size and located relatively deep beneath the skin. Obesity, peripheral edema, and predisposing degenerative conditions such as osteophytes, especially in elderly patients, also impede the detection of

Table 1 The Outcome measures in rheumatology clinical trials definitions of ultrasound pathological findings

RA bone erosion	An intra-articular discontinuity of the bone surface that is visible in two perpendicular planes
Synovial fluid	Abnormal hypoechoic or anechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intra-articular material that is displaceable and compressible, but does not exhibit a Doppler signal
Synovial hypertrophy	Abnormal hypoechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intra-articular tissue that is nondisplaceable and poorly compressible and which may exhibit a Doppler signal
Tenosynovitis	Hypoechoic or anechoic thickened tissue with or with- out fluid within the tendon sheath, which is seen in two perpendicular planes and which may exhibit a Doppler signal
Enthesopathy	Abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment (may occasionally contain hyperechoic foci consistent with calcification), seen in two perpendicular planes that may exhibit a Doppler signal and/or bony changes, including enthesophytes, erosions, or irregularity

RA: Rheumatoid arthritis.

synovitis.

In this context, a diagnostic imaging technique is important for the evaluation of ankle lesions. However, plain radiography has limited value for the detection of soft tissue changes, and it lacks tissue specificity. Although magnetic resonance (MR) imaging is a high resolution imaging method that can disclose both bone and soft tissue abnormalities, it involves problems such as MR-incompatible metallic implants, patient claustrophobia, accessibility issues, and high cost, all of which prevent it from being widely used for the examination of ankles in rheumatic diseases.

In contrast, ultrasound (US) is a versatile, accurate, safe, and relatively cheap modality that is increasingly used in daily rheumatologic practice. It offers multiplanar evaluation and allows parallel dynamic assessment of multiple target structures, including joints, tendons, ligaments, and bony cortex[2].

In addition to the advantages of grey-scale ultrasound (GSUS), power Doppler (PD) technology has allowed the visualization of the hyperemia of soft tissues in inflammatory articular diseases[3]. A comparison of PDUS findings with histopathologic findings of synovial membrane vascularity in rheumatoid arthritis (RA) patients who have undergone knee arthroplasty has shown that PD signals represent abnormal hypervascularity in RA synovial tissue[4]. Many reports indicate that the intensity of PD signals in the synovium correlates with the intensity of articular and tenosynovial inflammation in RA patients[5,6]. Moreover, PD techniques seem to help differentiate inflammatory enthesis diseases[7].

The aim of this paper is to illustrate the US assessment of ankle lesions in patients with inflammatory rheumatic diseases, focusing on the utility of PDUS.

US SCANNING TECHNIQUE FOR THE ANKLE REGION

The important pathologies addressed here are synovial inflammations, including articular synovitis and tenosynovitis, and enthesitis of tendon insertion, including subtendinous bursitis. Structural damage such as bone erosion and tendon degeneration are addressed collaterally and ligament lesions are not mentioned here.

The Outcome Measures in Rheumatology Clinical Trials (OMERACT) US definitions for the most common pathological findings occurring in inflammatory rheumatic diseases are presented in Table 1[8]. For detailed information regarding the US machine settings and fundamental scanning techniques, please refer to the relevant published papers[9].

Data regarding the positioning of the patient and anatomical structures to be scanned in the ankle region are presented in Table 2[10]. An encompassing scanning technique makes it possible for the examiners not to overlook pathologies, regardless of whether they were symptomatic or asymptomatic[11,12]. Utilizing these techniques, we have shown the frequencies of various pathologies in symptomatic ankles with either early or established RA in a previous study (Table 3)[13]. This study revealed that ankle tenosynovitis is observed more frequently than ankle synovitis among early RA patients.

US EVALUATION OF PATHOLOGIES IN ANKLES WITH RHEUMATIC DISEASES

The major inflammatory rheumatic diseases addressed in this paper are RA, psoriatic arthritis (PsA), reactive arthritis (ReA), undifferentiated spondyloarthritis (uSpA), and systemic lupus erythematosus (SLE). US assessment of crystal-associated diseases and degenerative disorders related to aging or trauma will be addressed elsewhere. Multiplanar scanning using both GSUS and PDUS should be carried out. Synovial fluid detected by GSUS and/or hyperemia detected in or adjacent to the synovial membrane by PDUS represents synovitis[14]. Although the degree of hyperemia is indicative of the extent of inflammation, hyperemia itself is not specific to a certain disease[15].

Synovial hypertrophy detected by GSUS represents cellular infiltration into synovial tissues with or without synovial cell proliferation. Fine and slow blood flow detected in thickened synovium by PDUS represents proliferative synovitis associated with vascularization, which is a hallmark of the active synovitis observed in RA, PsA, and sometimes SLE[16].

The respective features of the pathologies in inflammatory rheumatic disease depicted in each anatomical

Table 2 Patient positions for ultrasound examination of ankle structures

Supine, with flexed knee, foot on the examination bed
Tibiotalar joint: anterior recess
Talonavicular joint
Subtalar joint: lateral and medial recess
Tendon compartments
Anterior:
Tibialis anterior tendon
Extensor hallucis longus tendon
Extensor digitorum longus tendon
Lateral:
Peroneus brevis tendon
Peroneus longus tendon
Medial (frog position):
Tibialis posterior tendon
Flexor digitorum longus tendon
Flexor hallucis longus tendon
Prone, with the foot hanging over the examination bed
Achilles tendon
Superficial and retrocalcaneal bursae
Subtalar joint: posterior recess

Table 3 The frequencies of various pathologies in the symptomatic ankles with either early or established rheumatoid arthritis

	Early RA	Established RA	Overall
Number of ankles	62	38	100
Joint synovitis			
Talocrural joint synovitis	32.2%	39.5%	35.0%
Subtalar joint synovitis	30.7%	36.8%	33.0%
Talonavicular joint synovitis	27.4%	26.3%	27.0%
Overall	48.4%	68.4%	56.0%
Tenosynovitis			
Ankle flexors (TP, FDL, FHL)	54.8%	31.6%	46.0%
Peroneal tendons (PB, PL)	33.9%	21.1%	29.0%
Ankle extensors (TA, EHL, EDL)	12.9%	5.3%	10.0%
Overall	69.4%	47.4%	61.0%
Achilles tendon involvement			
Retrocalcaneal bursitis	35.5%	13.2%	27.0%
AT enthesitis	19.4%	26.3%	22.0%
AT tendonitis	12.9%	13.2%	13.0%
AT paratenonitis	8.1%	2.6%	6.0%
Overall	38.7%	39.5%	39.0%

TP: Tibialis posterior; FDL: Flexor digitorum longus; FHL: Flexor hallucis longus; PB: Peroneus brevis; PL: Peroneus longus; TA: Tibialis anterior; EDL: Extensor digitorum longus; EHL: Extensor hallucis longus; AT: Achilles tendon; RA: Rheumatoid arthritis.

structure are addressed below.

Tibiotalar joint (talocrural joint)

To visualize the anterior recess of the tibiotalar joint, place the transducer in the sagittal plane distal to the tibia. In the normal joint, a hyperechoic anterior fat pad can be seen to fill the space between the tibia and the talus anteriorly with a layer of anechoic hyaline cartilage on the surface of the talar dome[17].

A small simple effusion in mild acute synovitis of the tibiotalar joint in a patient with reactive arthritis is depicted as an anechoic area (Figure 1). Severe proliferative

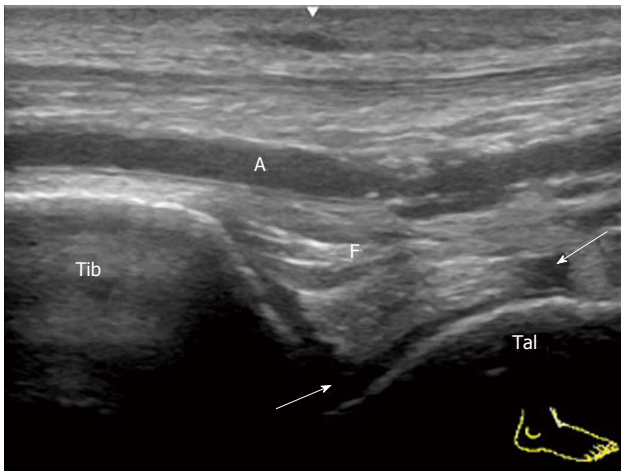

Figure 1 Mild tibiotalar joint synovitis in reactive arthritis. Sagittal grey-scale sonogram of the anterior recess of the tibiotalar joint shows localized anechoic synovial effusion (arrow). Tib: Tibia; Tal: Talus; F: Fat pad; A: Dorsalis pedis artery.

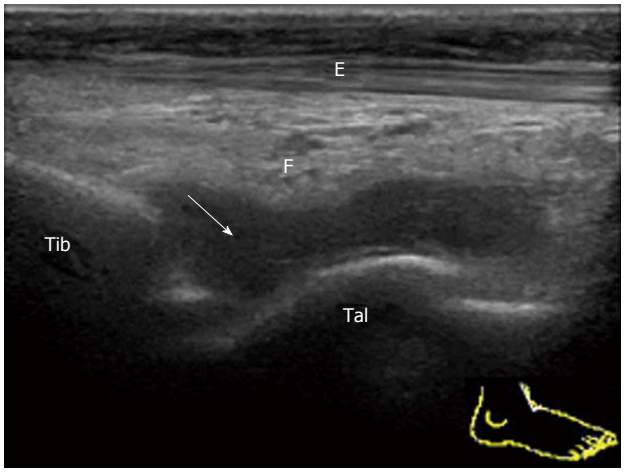

Figure 2 Severe tibiotalar joint synovitis in rheumatoid arthritis. Sagittal grey-scale sonogram of the anterior recess of the tibiotalar joint shows that a normal hyperechoic anterior fat pad (F) is displaced anteriorly by hypoechoic synovium (arrow). Tib: Tibia; Tal: Talus; F: Fat pad; E: Extensor hallucis longus.

synovitis of the tibiotalar joint in rheumatoid arthritis is depicted as a hypoechoic area over the talar dome (Figure 2). Large effusion and/or proliferative synovium lead to the displacement of the fat pad covering the talus neck and creating capsule distension.

Complex joint fluid can be seen as a hypoechoic area. To distinguish synovium from complex joint fluid, blood flow detected by PD sonography is helpful[18]. However, PD sensitivity is relatively low at the median part of the anterior recess because the synovium is located deep beneath the tendons and the fat body. Strong blood flow in the dorsalis pedis artery also hinders the identification of the fine synovial vessels. In order to increase the sensitivity of the PD detection, scanning both lateral and medial sides of the anterior recess must be performed (Figure 3).

Posterior subtalar joint

The subtalar or talocalcaneal joint is composed of three

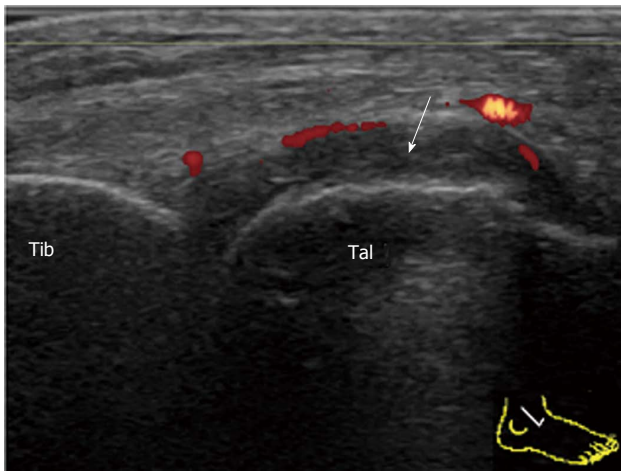

Figure 3 Synovial proliferation in rheumatoid arthritis. Sagittal power Doppler sonogram of the lateral side of the anterior recess of the tibiotalar joint shows synovial thickening (arrow) with peripheral vascularization. Tib: Tibia; Tal: Talus.

facets: a broad posterior facet representing the primary articulating surface, a medially located middle facet in which the sustentaculum tali articulates with the medial process of the talus, and an anterior facet. There are limited sonographic windows for imaging the subtalar joint (STJ), and the posterior subtalar joint (PSTJ) is usually the target. Synovitis of the PSTJ is best evaluated by scanning its posterior recess. The joint space of the PSTJ is easy to determine in the sagittal view crossing the posterior talar process. In order to fully visualize the posterior recess, which tends to distend laterally, the transducer should be placed just lateral to the Achilles tendon in an anatomic parasagittal plane by medially angling the transducer face (Figure 4). Because synovium is depicted as relatively shallow through this posterolateral window, better detection of the PD signal and a safer route for aspiration are provided[19].

The medial facet of the PSTJ can be partly observed in the coronal view crossing the medial malleolus. In the normal joint, the joint space between the talus and the sustentaculum tali can be depicted beneath the tibiocalcaneal ligament. In the case of synovitis, effusion and/or proliferated synovium stretch cranially along the tibiocalcaneal ligament (Figure 5).

Talonavicular joint

The talonavicular joint (TNJ) is best evaluated by the longitudinal dorsal view of the joint. In the case of TNJ synovitis in RA patients, proliferated synovium bulges out of the joint space dorsally and the PD signal can be easily detected (Figure 6).

It has been reported that TNJ synovitis is frequently detected by US in both symptomatic and asymptomatic ankles in RA patients[13]. Similarly, proliferative synovitis of the TNJ can arise in PsA patients (Figure 7).

It has also been reported that TNJ synovitis is often detected by US in the ankles of healthy control subjects[20]. The ankle is one of the sites of predilection for osteoarthritis. In long-standing RA patients, degenerative changes in the TNJ are frequently encountered (Figure 8). PDUS can add to the information regarding the activity of ongoing inflammation in the joint.

Extensor tendons

The three tendons in the anterior aspect of the ankle from medial to lateral are the tibialis anterior (TA), extensor hallucis longus (EHL), and extensor digitorum longus (EDL)[17]. These extensor tendons pass beneath retinacula and have sheaths to protect them. The main pathology that occurs in inflammatory rheumatic diseases in this area is tenosynovitis. Tenosynovitis of the EDL is most frequently observed, followed by that of the TA. Tenosynovitis of the EHL seems to be less frequent while the myotendinous junction should not be confounded with dilated tenosynovium. These extensor tendons tend to present with serous tenosynovitis rather than proliferative tenosynovitis, unlike the medial flexors and lateral peroneal tendons, which frequently present with proliferative tenosynovitis (Figure 9)[21].

Medial flexors

By transverse scanning of the medial ankle tendons, the tibialis posterior (TP) tendon, flexor digitorum longus (FDL) tendon, and flexor hallucis longus (FHL) tendon can be visualized from the anterior to the posterior side[22].

As the TP and FDL hook around the medial malleolus and the FHL runs in a groove along the calcaneus, all tendons have individual sheaths. Tenosynovitis frequently occurs in this area in inflammatory rheumatic diseases. Tenosynovitis of TP is most frequently observed, and is sometimes accompanied by FDL tenosynovitis (Figure 10). Pathology usually occurs at or distal to the medial malleolus. Fluid collection within the synovial sheath is predominantly observed near the distal end of the sheath, while small effusion often exists at the same site in the ankles of healthy subjects. Proliferative tenosynovitis of TP is frequently observed in RA patients[21]. Thickening and hyperemia of the sheath with or without fluid in it are the typical features. It has been reported that tenosynovitis is observed more frequently than joint synovitis in symptomatic ankles with early RA[13].

The second site of pathology on the TP is where it inserts into the navicular bone. A longitudinal scan is more informative in proximity to its insertion. An important active inflammatory pathology in rheumatic diseases at tendon insertion is enthesitis. Enthesitis frequently occurs in patients with SpA (Figure 11A). The distal end of a normal TP tendon splays at the insertion and may appear hypoechoic due to anisotropy. Therefore, the presence of intratendinous hyperemia permits a more confident diagnosis of enthesitis.

Although enthesitis is the hallmark of PsA, ankle tenosynovitis is also often observed in PsA patients. In some cases, the implication of enthesitis in a functional enthesis formed by fibrocartilage on the surface of bone

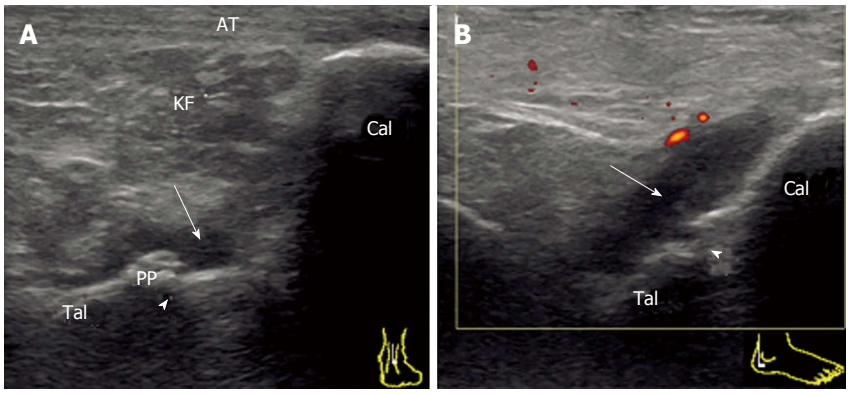

Figure 4 Synovitis of the posterior subtalar joint in rheumatoid arthritis. A: Sagittal grey-scale sonogram crossing the posterior talar process shows the edge of the distended posterior recess (arrow) of the PSTJ. B: Posterolateral view of the power Doppler sonogram fully depicting the distended posterior recess (arrow) of the PSTJ. Note the close relation of this recess with the superior margin of the calcaneus (Cal). Tib: Tibia; Tal: Talus; KF: Kager's fat pad; AT: Achilles tendon, arrowhead (joint space); PSTJ: Posterior subtalar joint; PP: Posterior talar process.

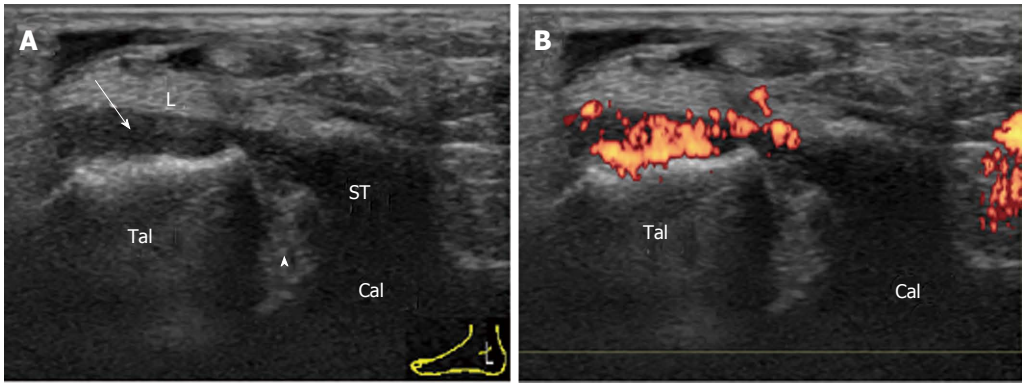

Figure 5 Synovitis of the posterior subtalar joint in rheumatoid arthritis. Coronal grey-scale (A) and power Doppler (B) sonogram of the medial facet (arrowhead) of the PSTJ. PD-signal-positive proliferated synovium (arrow) of the PSTJ stretches cranially along the tibiocalcaneal ligament (L). Tal: Talus; Cal: Calcaneus; ST: Sustentaculum tali; PSTJ: Posterior subtalar joint.

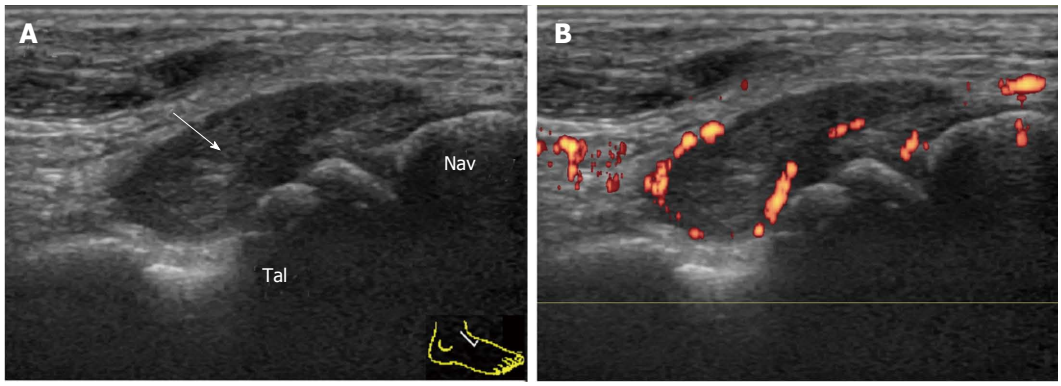

Figure 6 Synovitis of the talonavicular joint in rheumatoid arthritis. Longitudinal grey-scale (A) and power Doppler (B) sonogram of the dorsal aspect of the TNJ shows marked synovial thickening (arrow) with peripheral vascularization. Tal: Talus; Nav: Navicular; TNJ: Talonavicular joint.

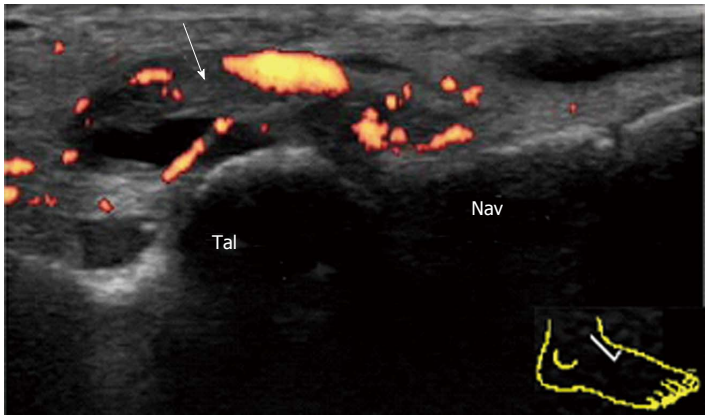

Figure 7 Synovitis of the talonavicular joint in psoriatic arthritis. Longitudinal power Doppler sonogram of the dorsal aspect of the TNJ shows synovial effusion and marked synovial thickening (arrow) with peripheral vascularization. TNJ: Talonavicular joint; Tal: Talus; Nav: navicular.

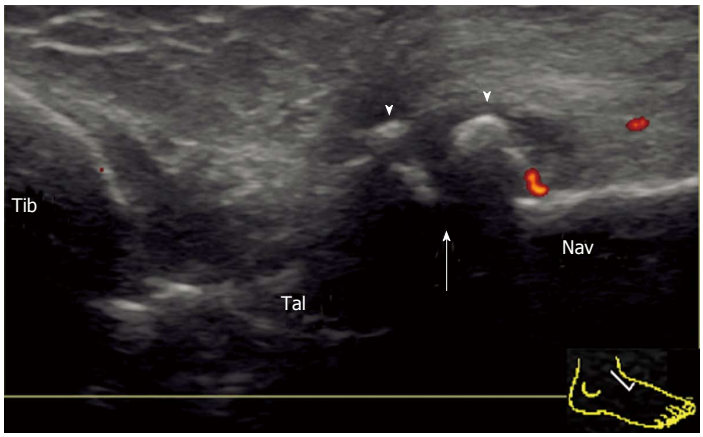

Figure 8 Deformity of the talonavicular joint in rheumatoid arthritis. Longitudinal power Doppler sonogram of the dorsal aspect of the TNJ shows joint space narrowing (arrow) and osteophyte formation (arrowhead) with minimum flow signal adjacent to an osteophyte. TNJ: Talonavicular joint; Tib: Tibia; Tal: Talus; Nav: Navicular.

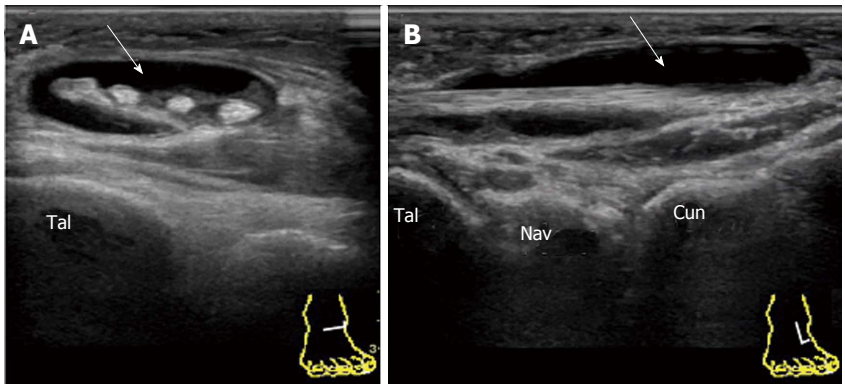

Figure 9 Serous tenosynovitis of the extensor digitorum longus in rheumatoid arthritis. Transverse (A) and longitudinal (B) grey-scale sonogram of the dorsal aspect of the EDL shows marked expansion of the tendon sheath with anechoic synovial effusion (arrow). Tal: Talus; Nav: Navicular; Cun: Cuneiform; EDL: Extensor digitorum longus.

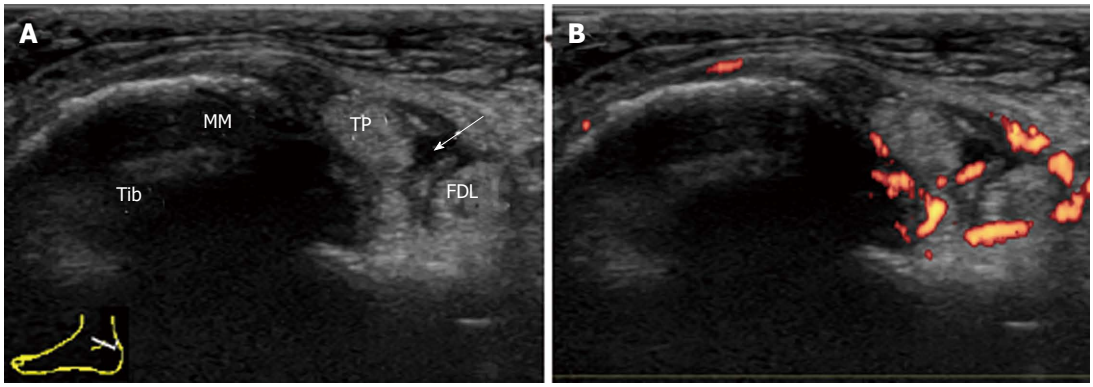

Figure 10 Proliferative tenosynovitis of the tibialis posterior in rheumatoid arthritis. A: Transverse grey-scale sonogram through the medial ankle at the level of the medial malleolus (MM). Hypoechoicthickened tenosynovium of the TP with anechoic effusion (arrow) within the sheath is depicted; B: Power Doppler sonogram shows hyperemia of the tenosynovium surrounding the TP and the FDL. Tib: Tibia; TP: Tibialis posterior; MM: Medial malleolus; FDL: Flexor digitorum longus.

and tendon is suggested (Figure 11B)[23].

Periarticular involvement is an important characteristic of musculoskeletal manifestation in SLE patients[24]. In particular, tendinopathies including tendonitis, tenosynovitis and tendon rupture are thought to be common. Although there have only been a few reports about the sonographic feature of tenosynovitis only in hands or wrists with SLE, ankle tendinopathies do not seem to be rare (Figure 12). The appearance of tenosynovitis or enthesitis, however, seems to be unspecific.

Peroneal tendons

The lateral ankle tendons are the peroneus longus and brevis. They hook behind the retromalleolar sulcus of the fibula and are stabilized by the superior peroneal retinaculum. At the level of the lateral malleolus, the peroneus longus and brevis share a common sheath. Distal to the lateral malleolus, the peroneals diverge[22].

Pathology usually occurs at or distal to the lateral malleolus (Figure 13). Tenosynovitis of peroneus longus and brevis can occur either independently or concurrently. Proliferative tenosynovitis of peroneal tendons and TP is frequently observed in RA patients[21]. Thickening and hyperemia of the sheath with or without fluid in it are sonographic findings suggestive of active inflammation.

In addition to TP, enthesitis of PB at its insertion into

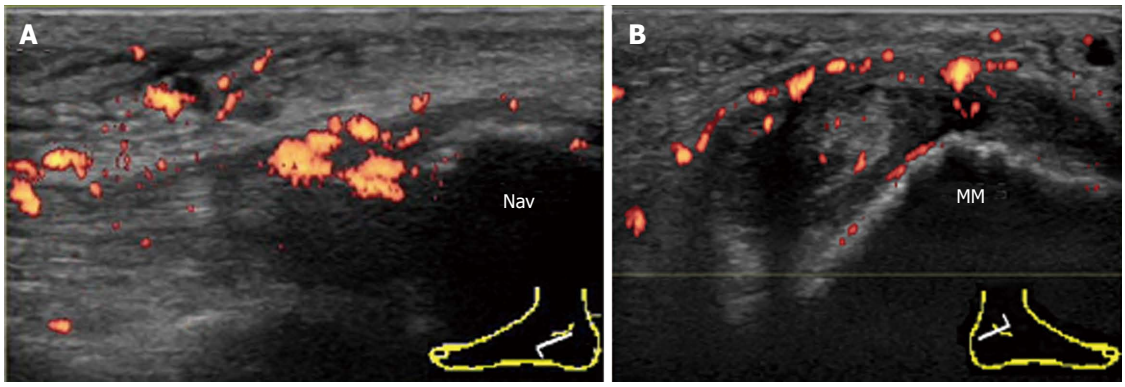

Figure 11 Involvement of the tibialis posterior tendon in psoriatic arthritis. A: Enthesitis of the TP at the navicular insertion in psoriatic arthritis. Longitudinal power Doppler sonogram of TP shows intratendinous hypoechoic change and loss of the fibrillar echoes with hyperemia adjacent to the insertion into thenavicular bone. Cortical irregularities of the navicular bone at the insertion are also depicted; B: Tenosynovitis of the contralateral TP in the same patient. Transverse power Doppler sonogram at the level of the tip of the medial malleolus shows thickening and hyperemia of both the tendon sheath and the flexor retinaculum. Cortical irregularities of the medial malleolus are also depicted. Nav: Navicular bone; MM: Medial malleolus; TP: Tibialis posterior.

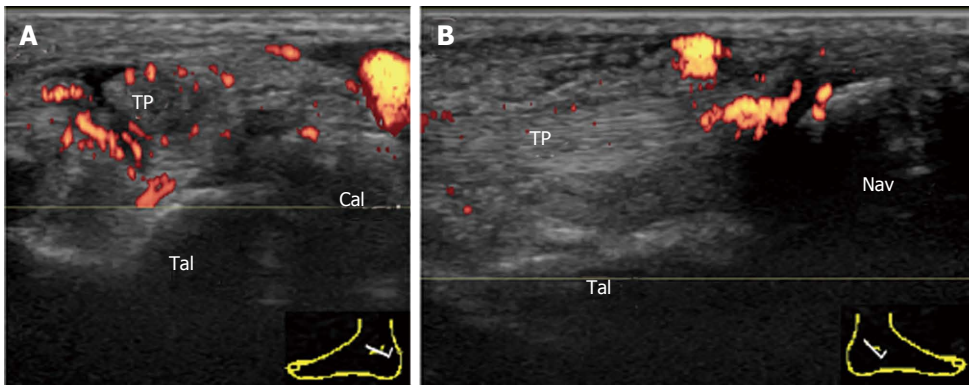

Figure 12 Involvement of the tibialis posterior tendon in systemic lupuserythematosus. A: Tenosynovitis of the TP in systemic lupus erythematosus. Transverse power Doppler sonogram over the inframalleolar area shows thickening and hyperemia of the tendon sheath with small synovial effusion; B: Enthesitis of the contralateral TP in the same patient. Longitudinal power Doppler sonogram of the TP shows intratendinous hyperemia adjacent to the insertion into the navicular bone. Tal: Talus; Cal: Calcaneus; TP: Tibialis posterior; Nav: Navicular bone.

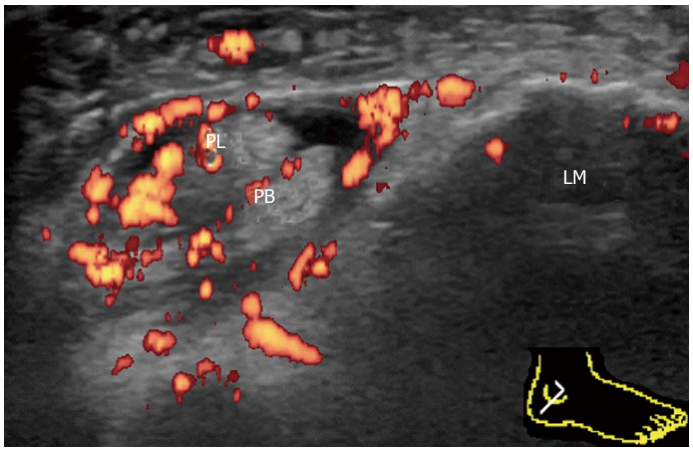

Figure 13 Proliferative tenosynovitis of the peroneus longus and brevis in rheumatoid arthritis. Transverse power Doppler sonogram through the lateral ankle at the level of the lateral malleolus shows thickening and marked hyperemia of the tenosynovium surrounding the peroneus longus and peroneus brevis. PL: Peroneus longus; PB: Peroneus brevis; LM: Lateral malleolus.

the base of the fifth metatarsal is frequently observed in PsA patients (Figure 14A). Tenosynovitis of peroneal tendons is also commonly observed in PsA patients (Figure 14B).

Achilles tendon

The Achilles tendon is a typical tendon with a linear fibrillar pattern. It inserts into a relatively small footprint on the posterosuperior aspect of the calcaneus. Between the calcaneus and the Achilles tendon there is a retrocalcaneal bursa. A normal bursa is thin walled and contains only minimal fluid[25].

Achilles tendon enthesopathy is a common finding in SpA, and can be present in both symptomatic and as-

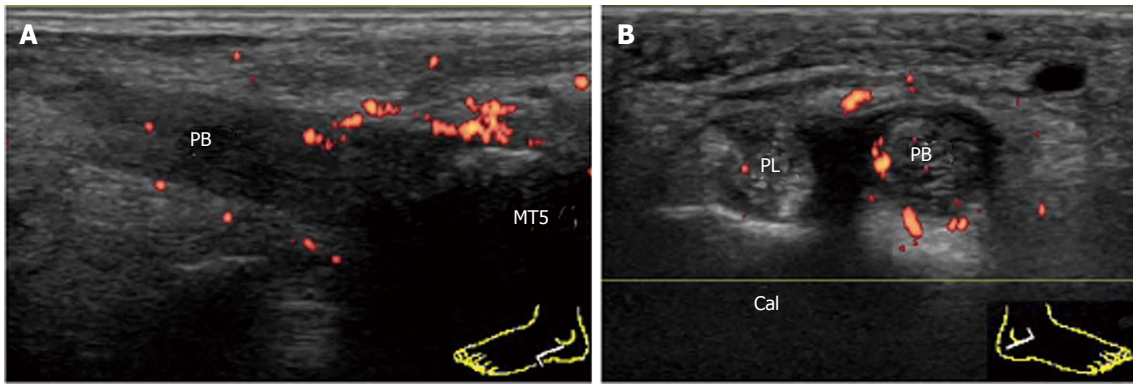

Figure 14 Involvement of peroneal brevis tendon in psoriatic arthritis. A: Enthesitis of the PB in psoriatic arthritis. Longitudinal power Doppler sonogram of the PB shows intratendinous hypoechoic change and loss of the fibrillar echoes with hyperemia adjacent to the insertion into the base of MT5. Cortical irregularities of the bone at the insertion are also depicted; B: Tenosynovitis of the contralateral PB in the same patient. Transverse power Doppler sonogram at the level of the peroneal tubercle of the Cal shows thickening and hyperemia of the PB tendon sheath. PL: Peroneus longus; PB: Peroneus brevis; MT5: The fifth metatarsal bone; Cal: Calcaneus.

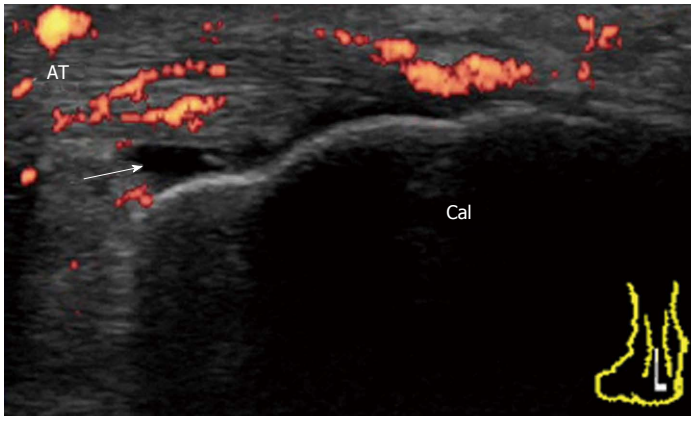

Figure 15 Achilles tendon enthesitis in reactive arthritis. Longitudinal power Doppler sonogram of the AT shows enthesial and intratendinous hyperemia and a small amount of fluid in retrocalcaneal bursa (arrow) with minimal cortical irregularities and tendinosis. Cal: Calcaneus; AT: Achilles tendon.

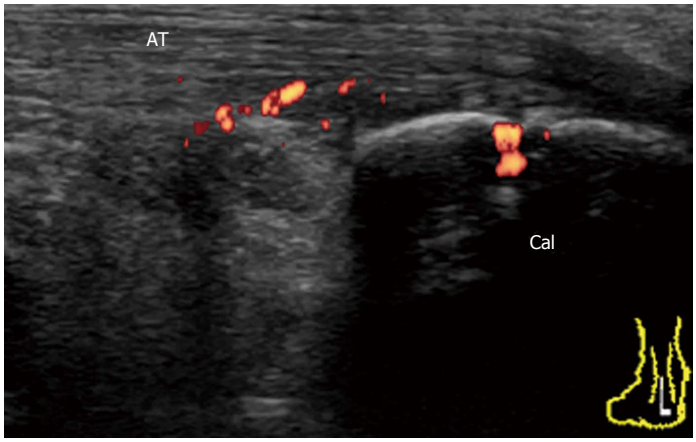

Figure 16 Achilles tendon enthesitis in early undifferentiated spondyloarthritis. Longitudinal power Doppler sonogram of the AT shows abnormal vascularization at the enthesis insertion into the calcaneal bone with minimal tendinosis. Cal: Calcaneus; AT: Achilles tendon.

ymptomatic patients[7]. In the OMERACT definition (Table 1), acute and chronic inflammatory aspects in gray-scale US (*i.e.,* loss of normal echo structure, increased thickness, or focal calcific deposits) and Doppler US are combined with findings of structural damage (*i.e.*, enthesophytes and bony erosions). This combination may be helpful for diagnostic purposes (*i.e.*, presence or absence of enthesis involvement) but probably not for responsiveness or for the differential diagnosis of inflammatory diseases (*i.e.*, SpA or RA versus mechanical or metabolic entheseal involvement). Enthesitis rather than enthesopathy is important to evaluate in inflammatory rheumatic diseases. For defining enthesitis, a Doppler signal should be detected at the cortical enthesis insertion and should be differentiated from a reflecting surface artifact or nutrition vessel signal[7]. A Doppler signal may be detected even in the absence of either bone changes (cortical irregularities, erosions, or enthesophytes) or tendon degeneration (tendinosis, tendon erosions and tears). For example, ReA patients with subacute enthesitis together with enthesial and intraten-

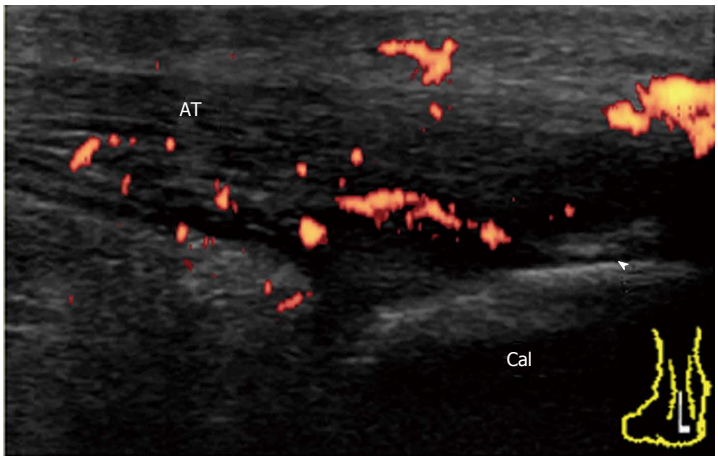

Figure 17 Achilles tendon enthesitis in chronic active psoriatic arthritis. Longitudinal power Doppler sonogram of AT shows increased thickness, hypoechogenicity, and loss of fibrillar pattern of AT with intratendinous hyperemia adjacent to the enthesis insertion into the calcaneal bone. Calcification (arrowhead) is also depicted. Cal: Calcaneus; AT: Achilles tendon.

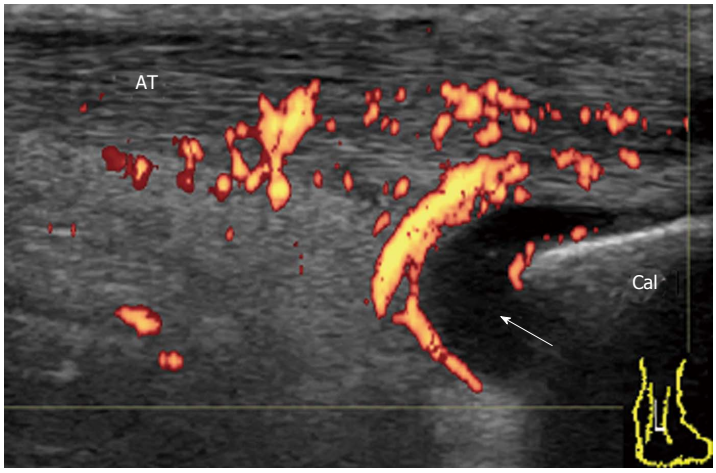

Figure 18 Retrocalcaneal bursitis in rheumatoid arthritis. Longitudinal power Doppler sonogram of the AT shows distended retrocalcaneal bursa (arrow) associated with peribursal hyperemia. Increased thickness of the AT with intratendinous hyperemia adjacent to the bursa is also depicted. Cal: Calcaneus; AT: Achilles tendon.

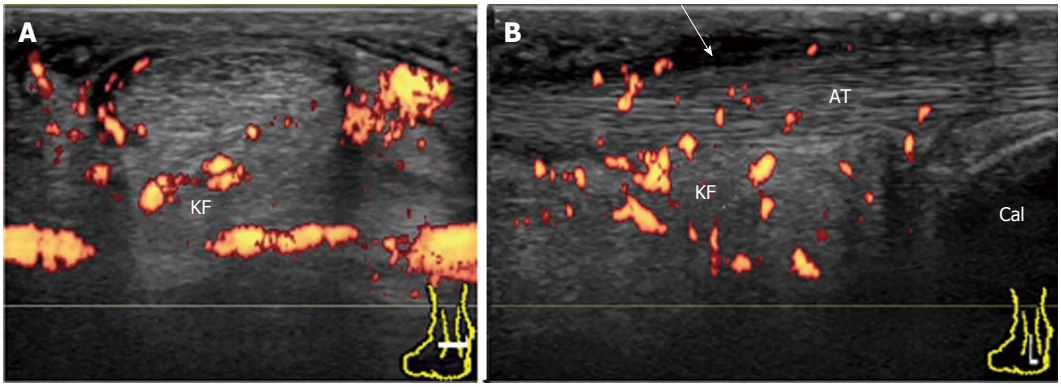

Figure 19 Achilles paratenonitis in early rheumatoid arthritis. Transverse (A) and longitudinal (B) power Doppler sonogram of the AT shows thickened, hypoechoic, and hyperemic paratenon (arrow) at the level of the KF with minimal tendinopathy. Hyperemia in the KF is also depicted. AT: Achilles tendon; KF: Kager's fat pad; Cal: Calcaneus.

dinous hyperemia and a small amount of fluid in retrocalcaneal bursa with minimal structural damage (Figure 15).

It has been suggested that inflammation at the bursal part of the fibrocartilage is important for the pathogenesis of enthesitis in SpA patients[26]. Bone erosion that is cranially adjacent to the insertion is characteristic of enthesitis in SpA. In early undifferentiated SpA patients, a Doppler signal at the enthesis insertion that is associated with cortical erosion can be observed with minimal tendinosis (Figure 16). In chronic active enthesitis, increased thickness, hypoechogenicity, and loss of fibrillar pattern of the Achilles tendon are associated with abnormal vascularization at the enthesis insertion with bone changes (Figure 17). Enthesitis is also often observed among RA patients. It has been suggested that retrocalcaneal bursa is primarily involved in the rheumatoid enthesitis symptom (Figure 18)[7].

The Achilles tendon does not have a tendon sheath. Instead, it has a U-shaped paratenon wrapping around the tendon from its dorsal aspect, which is normally barely visible. Achilles paratenonitis is inflammation in the paratenon and can occur in isolation or in association

with tendinopathy. The paratenon becomes thickened, hypoechoic and hyperemic in the case of paratenonitis (Figure 19). Achilles paratenonitis is sometimes observed among RA patients, especially in the early stage of disease[13].

CONCLUSION

US is useful for identifying the location and kind of pathologies in rheumatic ankles. Furthermore, PDUS is useful for distinguishing between inflammatory processes and degenerative changes or between active inflammation and residual damage. PDUS is of vital use in the assessment of ankles in patients with inflammatory rheumatic diseases in daily practice.

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Thromboembolic disease in patients with rheumatoid arthritis undergoing joint arthroplasty: Update on prophylaxes

Antonella Mameli, Francesco Marongiu

Antonella Mameli, Internal Medicine and Haemocoagulopathies Division, AOU of Monserrato (Ca), 09042 Monserrato, Italy
Francesco Marongiu, Internal Medicine and Haemocoagulopathies Division, University of Cagliari, 09123 Cagliari, Italy
Author contributions: Mameli A and Marongiu F contributed equally to this work.
Correspondence to: Antonella Mameli, MD, Internal Medicine and Haemocoagulopathies Division, AOU of Monserrato (Ca), SS 554, 09042 Monserrato, Italy. amameli@medicina.unica.it
Telephone: +39-070-6754188 Fax: +39-070-51096201
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Abstract

The risk of venous thromboembolism (VTE) in rheumatoid arthritis (RA) and the higher incidence of RA patients undergoing major orthopedic surgery is well recognized. The objective of the present study is to describe the incidence of VTE and discuss the correct prophylaxis in RA patients undergoing knee or hip replacement. A systematic review of studies on thromboprophylaxis in RA patients undergoing major orthopedic surgery was performed. Detailed information was extracted to calculate the rate of VTE in RA orthopedic patients and analyze the thromboprophylaxis performed and bleeding complications. Eight articles were eligible for full review. No difference in the overall rate of VTE was observed between RA patients and controls. No significant differences were found in RA patients in terms of bleeding complications. The data on the optimal prophylaxis to be used in RA patients were insufficient to recommend any of the several options available. In the absence of dedicated guidelines for the care of RA patients undergoing orthopedic surgery, management must be individualized to obtain favorable patient outcome, weighing up all the factors that might put the patient at risk for higher bleeding and thrombotic events.

Key words: Thromboprophylaxis; Rheumatoid arthritis; Orthopaedic surgery; Total hip arthroplasty; Total knee arthroplasty

Core tip: The purpose of this review is to quantify the incidence of venous thromboembolism (VTE) in patients with rheumatoid arthritis (RA) undergoing major orthopedic surgery and to discuss the current management of VTE prophylaxis in RA patients undergoing major joint arthroplasty and establish whether these patients are at higher risk for VTE than the general population.

Original sources: Mameli A, Marongiu F. Thromboembolic disease in patients with rheumatoid arthritis undergoing joint arthroplasty: Update on prophylaxes. *World J Orthop* 2014; 5(5): 645-652 Available from: URL: http://www.wjgnet.com/2218-5836/full/v5/i5/645.htm DOI: http://dx.doi.org/10.5312/wjo.v5.i5.645

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder that can affect many tissues and organs. It principally attacks synovial joints, resulting in a painful condition and even in disability if inadequately treated. At present, surgical correction in patients with RA is a highly successful solution for those suffering from advanced joint destruction. However, it should be taken into account that venous thromboembolism may be a possible complication after total hip arthroplasty (THA) and total

knee arthroplasty (TKA) since orthopedic surgery carries *per se* a high risk for this thrombotic condition[1]. The link between chronic systemic inflammatory disease, such as RA and thrombotic disease has been documented: it may be the final effect of a hypercoagulability state concomitantly to a reduced fibrinolysis[2]. It is thought that hypercoagulability is induced by active systemic inflammation and production of cytokines such as TNF-α and interleukin-1, that can lead to endothelial dysfunction, down regulation of Protein C, a natural anticoagulant, and then to an inhibition of fibrinolysis[2,3]. Acute hospitalizations, drugs, surgical procedures, physical inactivity and other co-morbidities may represent further risk factors for VTE in RA patients[4].

On the basis of the nine American College of Chest Physicians (ACCP) guidelines on VTE prevention, prophylaxis may be extended to more than 30 d, particularly after THA. The recommended thrombo-prophylactic regimens include low-molecular-weight heparin, fondaparinux, dabigatran, apixaban, rivaroxaban (total hip arthroplasty or total knee arthroplasty but not hip fracture surgery), low-dose unfractionated heparin, adjusted-dose vitamin K antagonist, aspirin (all Grade 1B), or an intermittent pneumatic compression device (IPCD) (Grade 1C) for a minimum of 10 to 14 d[1].

These guidelines are based on investigations in which predominantly osteoarthritis (OA) patients were studied. Paradoxically, although the thromboembolic risk in RA patients is recognized to be high, contradictory results emerge from the few studies performed on RA patients undergoing orthopedic surgery.

The aim of this review is to understand better the incidence of thromboembolic diseases in RA patients undergoing major orthopedic surgery. Furthermore, the authors' aim is to discuss the current management of VTE prophylaxis in RA patients undergoing major joint arthroplasty and establish whether RA patients undergoing orthopedic surgery are at higher risk than the general population for VTE.

RESEARCH

A systematic PubMed search was conducted to identify all articles between January 1970 and 15 November 2013 that analyzed the thromboprophilaxis in RA patients undergoing major orthopedic surgery. The Key words used in the search were: "Arthroplasty" OR "knee surgery," OR "Hip surgery" OR "Venous thromboembolism" OR "Prophylaxis of venous thromboembolism". The search results were combined with "Rheumatoid arthritis" using the Boolean search operator AND.

The authors carried out an initial screening of all titles and abstracts retrieved from the search. Articles were eligible for full text assessment if they reported original data on RA patients that had undergone THA and TKA, and reported information on the thromboprophylaxis performed, the rate of VTE and bleeding complications.

Studies pertaining anticoagulation, DVT, pulmonary embolism (PE) or thromboembolic diseases in RA patients having major orthopedic surgery were included. Articles were excluded if they were not in English. Case reports were also excluded. To ensure that the research was thorough, the reference lists of each article were also reviewed for other potentially eligible studies. Data were extracted from each article using a self-composed form to extract the following: (1) number of RA patients; (2) type of surgical procedure; (3) method of prophylaxis; (4) method of surveillance used; (5) the incidence of DVT; (6) the incidence of PE; and (7) incidence of bleeding complications. A meta-analysis was carried out entering only those studies that provided the event rate both in patients with RA and controls. For this purpose MEDCALC software (version 10.0.1.0) was used computing both fixed and random model. Pooled results are reported as odds ratio (OR) and 95%CI. A probability value of 0.05 or less was considered statistically significant. Statistical heterogeneity was evaluated using the I^2 statistic which assess the appropriateness of pooling the individual study results. The I^2 value provides the estimate of the amount of variance across studies due to heterogeneity rather than chance.

STUDY IDENTIFICATION AND SELECTION

A total of 1178 titles were found through the electronic search on PubMed. After deleting duplicates and screening titles and abstracts, 1120 articles were excluded leaving 58 articles for full-paper review. Review of references revealed 2 further articles. After a detailed full-paper review, another 52 were excluded. A total of 8 articles[5-12] satisfied most of the inclusion criteria for data extraction after full review (Figure 1): Seven observational cohort studies, and 1 randomized clinical trial. Of the 8 studies, 7 were retrospective, 1 was prospective.

STUDY CHARACTERISTICS

Characteristics and extracted data of the studies are summarized in Table 1. A total of 8886 RA patients were included in our review. The agents for prophylaxis were: Nadroparine[5], low doses of unfractionated heparin[6], Aspirin[7], Acenocumarol[8] and mechanical prophylaxes[10].

As can be observed in table 1, only 3 studies satisfied all the inclusion criteria[5,6,8]. In the other studies there were several bias: the prophylaxis utilized was not reported in 3 studies, the duration of prophylaxis was not indicated in 3, the method of surveillance for the diagnosis of VTE was not reported in 3, and the incidence of bleeding complications was not reported in 4 studies.

Rate of VTE

A total of 4 studies which reported the incidence of VTE in RA patients and controls (mainly patients with Osteoarthrosis) undergoing orthopedic surgery were identified[6,7,9,10] and included in the meta-analysis. Three studies were excluded from the meta-analysis since the

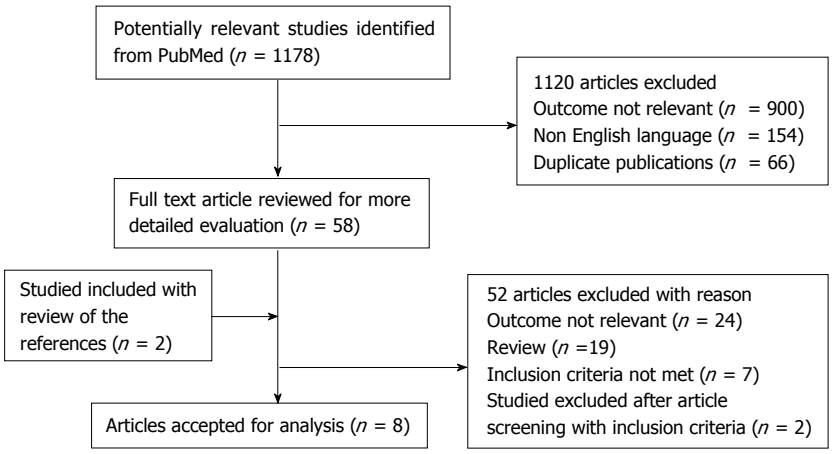

Figure 1 Flow diagram of study selection and information through different phases of the systematic review.

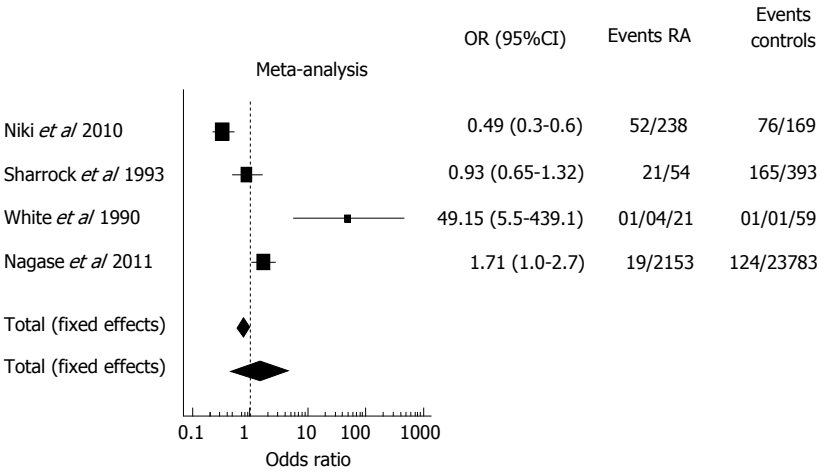

Figure 2 Forrest plots of the rate of venous thromboembolism in rheumatoid arthritis patients and controls underwent major orthopaedics surgery, according to a random and fixed-effects model.

rate of VTE in RA patients was not reported. Another study was excluded because the incidence of VTE in both the RA group and controls was expressed only as Odds Ratio. The final results of the meta-analysis are shown in Figure 2: the OR calculated with both the fixed and the random effect models shows no difference between AR patients and controls in terms of VTE rates. The random effect analysis shows a wider variance between the studies as expected. This data is confirmed by the great heterogeneity found among the studies (I^2 = 92.1). Consequent forest plot is also shown to depict the overall rate of the frequency of VTE in RA and controls undergoing orthopedic surgery.

Bleeding complications

Since bleeding events that occurred both in the AR group and controls were reported in only two studies it was decided not to perform meta-analysis. Niki *et al*[6] reported similar figures of bleeding in both groups: 1/238 (0.42 %) in AR patients and 2/169 (1.1 %) (P = 0.57) in the controls while in the study of White *et al*[9] bleeding events were 30/721 (4.2 %) in RA patients and 345/8859 (3.9 %) (P = 0.68) in controls (OA patients). van Heereveld *et al*[5] reported a bleeding event in 20/151 (13.2 %) AR patients, Swierstra *et al*[8] reported 2 bleeding episodes in 14 patients with AR but secondary to anti-vitamin K overdose. In the other studies no data on bleeding were reported.

DISCUSSION

On the basis of the results obtained from this review we tried to answer some questions with the aim to confer a practical approach to this topic.

Do patients with RA that undergo major orthopedic surgery encounter a higher incidence of DVT than other patient groups?

Historically the rate of DVT or PE after major orthopedic surgery was estimated to be 40% to 84% in patients undergoing total knee arthroplasty (TKA)[13,14] and in 45% to 57% of those undergoing total hip arthroplasty (THA) in the absence of thromboprophylaxis. Proximal DVT in the absence of thromboprophylaxis has been reported to occur in 9% to 20% of TKA patients and in 23% to 36% of THA patients[12,15,16]. Currently with modern techniques and post-operative care, the estimated risk of developing a symptomatic VTE without prophylaxis is approximately 4.3%[1]. As for RA patients who underwent major orthopedic surgery, Abernethy and Kelly report a rate of DVT and PE r of 70% and 50% respectively in the absence of prophylaxis[17,18]. The meta-analysis we have carried out involved only 4 studies for which the rate of VTE both in RA patients and controls were avail-

Table 1 Summary of the 8 articles selected for inclusion in systematic review

Ref.	Study design	Operation	RA patients	Methods of prophylaxis	Duration of prophylaxis	Methods of surveillance	VTE	EP	Bleeding complications
van Heereveld *et al*[5]	Retrospective open study of all medical record of patients with RA who underwent a Hip or Knee replacement from Jan 1987 to April 1995	THA and TKA	103 patients with RA who underwent 151 surgical procedure 55 (TKRH) 96 (THR)	Subcutaneous SH 5000 UI twice a day, starting two-six ours before surgery and was given twice a day, or nadroparin 7500 IC-U (10.000-20.00 IC U for obese patients) once a day. NSAIDs in 85% daily and continued after hospital discharge	For a minimun of 7 d and discontinued as soon as patient was adequately mobilized	Sonography, phlebography and V/Q scanning only in patients with clinical suspicion of VTE or PE The patients were seen every three months. the total of follow up was one year	1	0	20/151 (13%) Fifteen haematoma necessitating blood transfusion in six cases In one instance a surgical decompression was made. In none of bleeding episodes were signs of haemodynamic instability
Niki *et al*[6]	Prospective study of 333 patients who underwent primary TKA between October 2003 and June 2007 with diagnosis of RA and OA	TKA	199 (238 KNEES)	LOW dose unfractionated heparin (5000 U) for when patients had history of DVT or D-Dimer levels > 10 g/mL)	From second to eight day post-discharge	Sonography (pre-operatively and on POD 7), d-dimer on POD 0, 1 and 7	51	1	1
Sharrock *et al*[7]	Retrospective review of 571 primary TKA in epidural anesthesia between July 1986 to June 1990	TKA	54 RA	Aspirin (650 mg) and elastic streaking	5 d	Venography at forty and fifty post operative day	21 (39%)	Not reported	Not reported
Swiestra *et al*[8]	Retrospective randomized study of 101 consecutive patients admitted for primary THA	THA	14 RA	Acenocumarol started four or one day preoperatively aiming a thrombotest of 25% during the operation (1.5-1.6 INR)	Discontinuation of anticoagulation after negative venogram	Venography with 99mtc labeled macroaggregates of albumin, performed about 10 d after the operation for identifying proximal DVT	23/101	1 patient post-discharge	2 bleeding complication associated to excessively prolonged protrombine time
White *et al*[9]	Retrospective analysis of in hospitality mortality and morbidity of 721 RA *vs* 8859 OA patients who underwent a non emergent THR from 1984 to 1985	THA	721 RA	Not reported	Not reported	Not reported	0.3 % of VTE *vs* 1.2% in OA patients		4.20%
Nagase *et al*[10]	Retrospective analysis of 27542 patients who underwent THA or TKA in 723 japan hospital between 2007 and 2008	THA/ TKA	2153 RA	Mechanical prophylaxis or mechanical prophylaxis and fondaparinux	Not reported	Not reported	19 (0.89%)		Not reported

Soohoo *et al*[11]	reviewed discharge data from 138399 patients undergoing primary THA in California from 1995 to 2005	THA	5565 RA	Not reported	Not reported	Not reported	OR = 1.46 (95%CI: 0.82-1.61; *P* = 0.2)	Not reported
Hull *et al*[12]	A randomized trial was performed in 310 consecutive patients undergoing total hip replacement between 1978 and 1986	THA	77 RA	Sequential calf and thigh intermittent compression was begun postoperatively in the recovery room compared with none prophylaxis	Intermittent compression was continued until the patient was discharged from the hospital or for 14 d, at which time most patients were fully ambulant	Leg scanning was performed on the first day after surgery and then daily for 14 d	None prophylaxis: 77/158 Intermittent leg pneumatic compression: 36/152	Not reported

VTE: Venous thromboembolism; RA: Rheumatoid arthritis; THA: Total hip arthroplasty; TKA: Total knee arthroplasty; POD: Postoperative days; OA: Osteoarthritis.

able. Results show no differences between these group of patients. However, a limitation of these results is the important heterogeneity among the studies documented by the very high value of I^2. On the basis of these results it is difficult to conclude that RA patients are different from other groups of patients in terms of thromboembolic risk. We therefore believe that RA patients should be given the same prophylactic approach recommended for orthopedic surgery. Another limitation of the meta-analysis we performed is the extremely different antithrombotic prophylaxis used in the 4 considered studies.

If other studies not included in the meta-analysis are considered, an indirect confirmation comes from Soohoo *et al*[11] who reviewed discharge data from 138399 patients undergoing primary THA in California from 1995 to 2005. Diagnosis of Rheumatoid arthritis was associated to an increase of complications at 90-d after surgery considered as a whole (mortality, infection, dislocation, revision, perioperative fracture, neurologic injury, and thromboembolic disease) compared with patients without RA (OR = 1.53, 95%CI: 1.23-1.91, $P < 0.001$). In particular, the risk is particularly increased for mortality at 90 d (OR = 1.88, 95%CI: 1.17-3.03, $P = 0.01$) but not for thromboembolism [OR = 1.46 (0.82-2.61, $P = 0.20$)[11].

Another study, not included in the meta-analysis because it dealt retrospectively only with RA patients, was that of van Heereveld *et al*[5] who found only one patient, in 151 surgical procedures, who developed symptoms of post-discharge VTE, despite the short duration of heparin administration (7 d). Interestingly, 85% of the RA patients used NSAIDs daily and thus they may have been protected, at least partially, from venous thromboembolism because of the anti-platelet activity of these drugs. However, this possible favorable effect was offset by a relatively high rate of bleeding complications (13%). In summary, the data show that in the presence of a prophylaxis the incidence of VTE in patients with RA is not only greater than other groups of comparison, but even lower in some studies.

Is there a most effective method of VTE prophylaxis after major orthopedic surgery in RA patients?

To our knowledge the data about the best prophylaxis to be used in RA patients are insufficient to conclude in favor of any of the several options available. Significantly, different rates of DVT following TKA were observed in different preoperative strategies. Maneuvers to reduce accumulation of blood in the deep vein of the limb during surgery or to dislodge adherent clot may be useful strategies to minimize deep vein thrombosis following TKA. Elevation of the leg after surgery and early ambulation may also contribute to lower deep vein thrombosis rates[5]. In 2012, the ACCP recommends the use of several drugs for antithrombotic prophylaxis in patients who undergo THA or TKA. These drugs range from heparins (unfractioned, LMWH and fondaparinux) to aspirin. VKA and the new oral anticoagulants (dabigatran, rivaroxaban nd apixaban) are also considered. However this recommendation is referred to any anti-thrombotic drug in comparison to no anti-thrombotic prophylaxis. In a further recommendation, the ACCP suggests the use of LMWH, irrespective of the concomitant use of any pneumatic compression device (IPCD), in preference to the other drugs listed above. This choice could be explained by several factors (1) the favorable effect of aspirin is mild and is counterbalanced by the hemorrhagic risk conferred by this drug. Surprisingly we have read the recommendations of ACCP also on the use of aspirin in the thromboembolism prophylaxis after THA and TKA. It worth noting, however, that it was intended that the use of aspirin is to be considered better than nothing so that it is not certainly the drug of choice in that orthopedic setting[1]; (2) the difficulty in the peri-operative management of AVK; and (3) the similar efficacy of the new oral anticoagulants (NOAC) in comparison to LMWH, their longer half-life and the lack of post-marketing stud-

ies. In particular, NOAC (dabigatran, rivaroxaban and apixaban) show an increased risk for major bleeding[19] and a poor adherence[20]. Moreover, there is no data about both the safety and the efficacy of these drugs in patients with RA since the inclusion criteria of the clinical trials comparing NOAC with LMWH did not reflect the typical patient with RA who undergone major orthopedic surgery, that is a subject with several co-morbidities and that frequently use NSAID. Another point of concern may be the number of possible drug-interactions due to the metabolism of NOAC by the cytochrome P450 CYP 3A4 (rivaroxaban and apixaban) and the p-glycoprotein system (dabigatran, rivaroxaban and apixaban)[21]. These aspects may be not negligible when considering the Disease Modifying Antirheumatic Drugs (DMARDs) commonly utilized in the management of RA.

When should prophylaxis in RA patients be started?

The historical data suggest that both pre and post-operative initiation of thromboprophylaxis are similar in terms of safety and efficacy. Meta-analysis or systematic review comparing pre- and post-operative initiation of therapy have found no consistent difference in efficacy and safety (bleeding rates) between the two strategies[22,23,24]. In many European countries LMWH is considered the standard therapy for prophylaxis following THA or TKA and is initiated pre-operatively to maximize its efficacy[24]. Preoperative thrombo-prophylaxis is initiated on the assumption that the surgery *per se* and the accompanying immobility are the main causes of thrombosis[22,25]. However, as most thrombi develop post-operatively, starting anticoagulant therapy following surgery could also prevent VTE[26].

Since RA is a medical condition with increased risk of venous thrombotic events, the use of prophylaxis with heparin to prevent venous thrombosis should be administered even several days before surgery if the patient is bed ridden. In other words, if a patient with RA is immobilized and has been scheduled for surgery antithrombotic, prophylaxis should be started regardless of the waiting time for surgery. Immobilization *per se* may be related *per se* to disease activity and inflammation which in turn may induce a hypercoagulable state[27].

DURATION OF PROPHYLAXIS

Most VTE events occur after hospital discharge. Consequently, extended thromboprophylaxis after discharge should be considered and is particularly important after major surgery. The peak of DVT incidence is observed around the fifth postoperative day[28]. After the first postoperative week a second coagulation process occurs, as demonstrated by an increase of thrombin-antithrombin Ⅲ complexes and D-dimer, markers of coagulation activation, which may persist for up to six weeks or longer[29]. This might be attributable to a relative immobilization of the patient after discharge.

In summary, RA patients should undergo physical therapy since physical activity is necessary to prevent disabilities and restore functions, decrease pain and joint inflammation and increase ROM and strength. The early mobilization is the primary objective for the physician in order to assess the duration of prophylaxis Anti-thrombotic prophylaxis should be last at least 5 wk as recommended by the ACCP but in RA patients a longer period of anti-thrombotic prophylaxis should be considered depending on recovery of mobility.

RISK OF BLEEDING DURING POST-DISCHARGE PROPHYLAXIS IN RA PATIENTS

A delicate balance exists between VTE prophylaxis and systemic and surgical site of bleeding, which can lead to surgical wound complications including infection, haematoma and gastrointestinal bleeding. Many orthopedic surgeons fear the risk of bleeding associated with the introduction of anticoagulant prophylaxis for VTE prevention. Bleeding may occur earlier than VTE, and seriously compromise the result of surgery, or later as a complication of prophylaxis. A meta-analysis of 9 trials of extended duration (up 42 d) of VTE prophylaxes with LMWH after TKA or THA showed that there was no significant increase in major bleeding episodes despite the marked reductions in symptomatic VTE[30]. Only a small (1.2%) increase in minor bleeding was observed compared with patients receiving post-discharge placebo. In summary, in the single RA patient it is important to balance the bleeding risk against that of thromboembolism whilst keeping in mind that the latter represents a priority to be managed.

CONCLUSION

RA patients who undergo major orthopedic surgery for joint destruction typically have severe disease. In these patients medical therapy has generally failed. In the absence of dedicated guidelines for the care of patients with RA undergoing orthopedic surgery, management must be individualized to obtain favorable patient outcome, weighing up all the factors that place the patient at the same time at a higher bleeding and thrombotic risk.

Ideally, preoperative evaluation by an orthopedic surgeon should start several weeks before elective surgery for an optimal management of thrombotic and bleeding risk of RA patients.

RA patients may be at increased risk of VTE due to active inflammatory disease, specific joint problems and the surgical procedures themselves. The presence of comorbidities, as impaired renal function, cardiovascular and liver diseases and some drugs, especially NSAIDs should be carefully examined prior to starting thromboprophylaxis. Finally, RA patients should be treated as the other candidates for orthopedic surgery but special care should be paid to their comorbidities before and after surgery. Dedicated clinical trials should be planned to respond to the several still unanswered questions we have

tried to discuss here.

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WJO 5th Anniversary Special Issues (10): Rheumatoid arthritis

Inhibition of rheumatoid arthritis by blocking connective tissue growth factor

Kazuhisa Nozawa, Maki Fujishiro, Yoshinari Takasaki, Iwao Sekigawa

Kazuhisa Nozawa, Yoshinari Takasaki, Department of Rheumatology, School of Medicine, Juntendo University, Tokyo 113-8421, Japan
Maki Fujishiro, Iwao Sekigawa, Institute for Environment and Gender Specific Medicine, Juntendo University Graduate School of Medicine, Chiba 261-7114, Japan
Iwao Sekigawa, Department of Internal Medicine and Rheumatology, Juntendo University Urayasu Hospital, Chiba 261-7114, Japan
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Correspondence to: Kazuhisa Nozawa, MD, PhD, Department of Rheumatology, School of Medicine, Juntendo University 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. k-nozawa@juntendo.ac.jp
Telephone: +81-3-58021067 Fax: +81-3-58004893
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Abstract

The pathogenesis of rheumatoid arthritis (RA) remains to be completely elucidated so far; however, it is known that proinflammatory cytokines play a pivotal role in the induction of RA. Tumor necrosis factor (TNF-α), in particular, is considered to play a central role in bone destruction by mediating the abnormal activation of osteoclasts or the production of proteolytic enzymes through direct or indirect mechanisms. The use of TNF-α blocking agents has a significant impact on RA therapy. Anti-TNF-α blocking agents such as infliximab are very effective for treatment of RA, especially for the prevention of articular destruction. We have previously shown that several proteins exhibited extensive changes in their expression after amelioration of RA with infliximab treatment. Among the proteins, connective tissue growth factor (CTGF) has a significant role for the development of RA. Herein, we review the function of CTGF in the pathogenesis of RA and discuss the possibility of a novel treatment for RA. We propose that CTGF is a potentially novel effector molecule in the pathogenesis of RA. Blocking the CTGF pathways by biological agents may have great beneficial effect in patients with RA.

Key words: Connective tissue growth facto; Rheumatoid arthritis; Osteoclasts; Condrocytes; Tumor necrosis factor-α

Core tip: Connective tissue growth factor (CTGF) plays an important role in the pathogenesis of rheumatoid arthritis (RA). We propose that CTGF is a potentially novel effector molecule in the pathogenesis of RA. Blocking the CTGF pathways by biological agents may have great beneficial effect in patients with RA.

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INTRODUCTION

Rheumatoid arthritis (RA) causes chronic inflammation and consequently destruction of the articular tissue. Although the pathogenesis of RA are not fully understood, proinflammatory cytokines such as tumor necrosis factor (TNF)-α have been proposed as important factors in the pathogenesis of RA[1-4]. TNF-α is multiple functional cytokine. In addition to inflammatory process, TNF-α concerns various physiological phenomena in RA[5,6]. Moreover, accumulating reports suggest that TNF-α

Table 1 Proteins with greater changes after infliximab treatment[1]

	Molecular weight	pI	Accession#
Peptidylprolyl isomerase B precursor	23728	9.42	NP_000933
Caldesmon 1 isoform 1	93175	5.62	NP_149129
Family with sequence similarity 62 (C2 domain containing), member A	122780	5.57	NP_056107
Amylase, alpha 2A; pancreatic precursor	57670	6.60	NP_000690
Filamin 1 (actin-binding protein-280)	280586	5.73	NP_001447
Vasodilator-stimulated phosphoprotein isoform 1	39805	9.05	NP_003361
Cycteine and glycine-rich protein 1	20554	8.90	NP_004069
Myoglobin	17173	7.14	NP_005359
Transgelin 2	22377	8.41	NP_003555
Microtubule-associated protein, RP/EB family, member 1	29980	5.02	NP_036457
NCK adaptor protein isoform A	42889	6.49	NP_003572
Tropomudulin 3 (ubiquitous)	39570	5.08	NP_055362
Connective tissue growth factor	38043	8.36	NP_001892
Latent transforming growth factor beta binding protein 1 isoform	186716	5.63	NP_996826
Regenerating islet-derived 1 alpha precursor	18719	5.65	NP_002900
Peptidylprolyl isomerase A isofoem 1	18001	7.68	NP_066953
Coronin, actin binding protein, 1C	53215	6.65	NP_055140
Triggering receptor expressed on myeloid cells-like 1	32658	5.70	NP_835468
Heparin sulfate proteoglycan 2	468528	6.06	NP_005520
Peptidoglycan recognition protein 1	21717	8.92	NP_005082
Superoxidase dismutase 1, soluble	15926	5.70	NP_000445

promotes bone destruction in RA, as excess TNF-α cause the abnormal osteoclaststic activation by direct or indirect interaction[2,3]. Our previous study used a novel approach of proteomic research and showed a significant profile change of serum protein biomarkers (approximately 20 proteins) in patients with RA treated using infliximab[1]. Among the proteins listed in our previous study, we found that connective tissue growth factor (CTGF) played an important role for the amelioration of RA[7-9] patients in infliximab treatment (Table 1). Based on this finding, we undertook subsequent studies to analyze the contribution of CTGF in the pathogenesis of RA and found that it plays an important role[8-10]. Herein, we review the function of CTGF in the pathogenesis of RA based on these findings. In RA, aberrant CTGF regulation may induce aberrant osteoclastogenesis and cause disturbance in cartilage homeostasis, subsequently resulting in articular tissue destruction. Blocking the CTGF pathways may be a novel effective strategy in the treatment of RA.

CONNECTIVE TISSUE GROWTH FACTOR

CTGF was originally identified in human umbilical endothelial cell supernatants that exhibit platelet-derivedgrowth factor (PDGF)-like chemotactic and mitogenic activities toward mesenchymal cells; the cDNA was isolated from a human vein endothelial cells (HUVECs) cDNA expression library using anti-PDGF and it encoded a 349-amino acid protein[11]. CTGF belongs to the CCN protein family and is believed to be a downstream molecule of transforming growth factor (TGF)-β pathway[12]. Although several candidate specific CTGF receptors have been currently proposed, they have not yet been completely identified to date. CTGF is associated with several biological functions such as fibrosis, tumorigenesis, angiogenesis, and endochondral ossification[13]. CTGF in articular tissue, consisting different types of cells, is produced by chondrocytes and maintains cartilage tissue homeostasis *via* the autocrine process. Furthermore, incomplete knock-down of the CTGF gene dramatically inhibits osteoclast-like cell formation in mice, even though the complete knock-down mice exhibit embryonic lethality[14].

CONTRIBUTION OF CTGF TO THE PROGRESSION OF RA

In vivo transfection with an adenovirus expression vector that encodes CTGF into mouse knee joints has been shown to cause cartilage damage due to an increase in mRNA coding for proteolytic enzymes such as matrix metalloproteinase (MMP)-3[15]. Manns *et al*[16] reported the up-regulation of CTGF in an experimental animal model of RA; treatment with a thrombospondin-1-derived peptide ameliorate the development of arthritis concomitant with the down-regulation of CTGF. These reports have indicated that CTGF has a significant role in the pathogenesis of RA. In addition, we observed the following interesting findings in our previous studies: (1) CTGF was overproduced by synovial fibroblasts in patients with RA (Figure 1); (2) the production of CTGF was regulated by TNF-α. CTGF production was up-regulated in synovial fibroblasts and down-regulated in chondrocytes (Figure 2); and (3) CTGF in combination with MCSF/RANKL promoted osteoclastogenesis (Figure 3)[8]. In the results of our study, we observed that TNF-α induced CTGF production by synovial cells. In contrast, TNF-α inhibited CTGF production by chondrocytes. TNF receptors have shown to transduce and amplify receptor activation resulting different cellular fates such as NF-κB activation or apoptosis. Although precise intracellular mechanisms

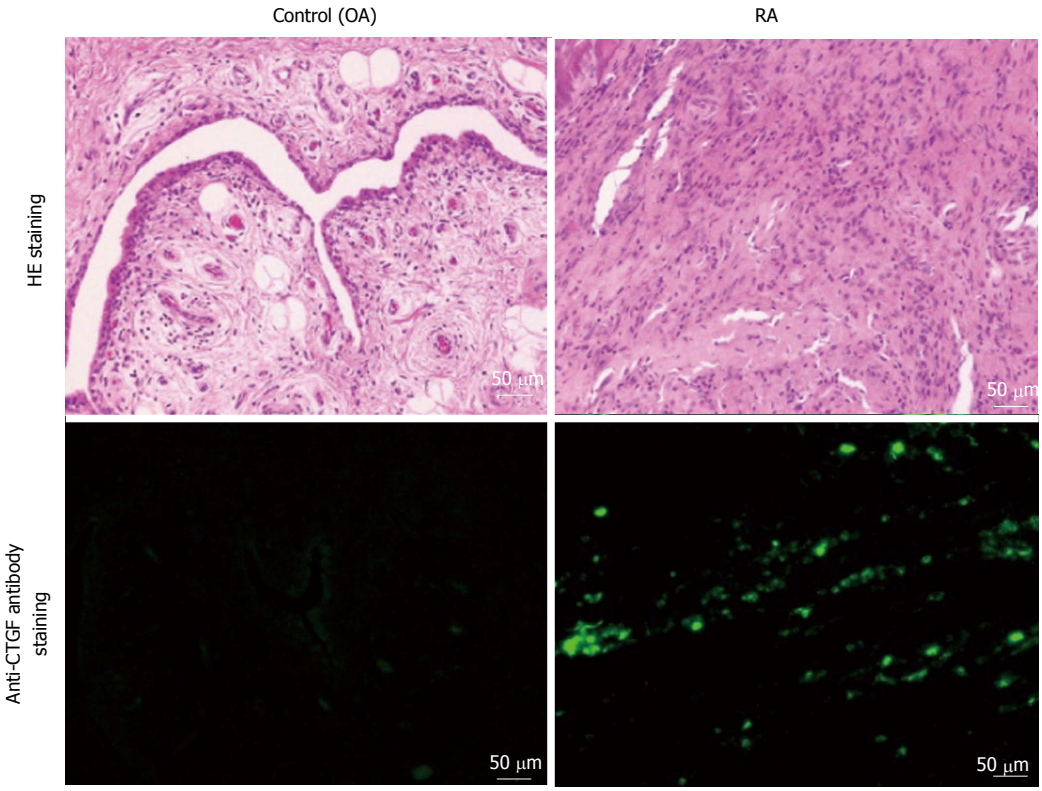

Figure 1 Connective tissue growth factor expression was increased at synovial tissue in rheumatoid arthritis. Representative results of hematoxylin and eosin (HE) staining, immunofluorescence anti-connective tissue growth factor (CTGF) antibody staining, and anti-F4/80 antibody staining are shown using surgical samples from patients with rheumatoid arthritis (RA) and osteoarthritis (OA). The observed CTGF expression was stronger in the samples of patients with RA than in the samples of patients with OA.

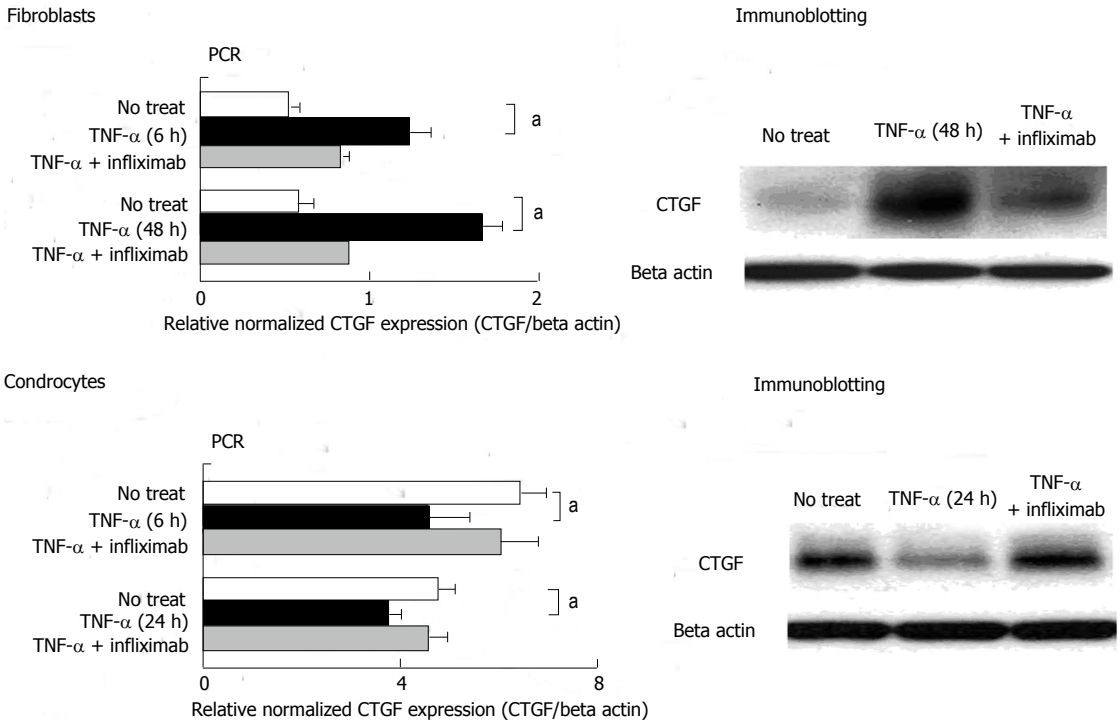

Figure 2 Tumor necrosis factor-α positively regulated connective tissue growth factor production in synovial fibroblasts and negatively regulated connective tissue growth factor production in chondrocytes. Connective tissue growth factor (CTGF) production from the human synovial fibroblasts cell line (MH7A) and the human chondrocytes cell line (OUMS-27) stimulated with/without tumor necrosis factor (TNF)-α were evaluated by immunoblotting and quantitative real time polymerase chain reaction (PCR). TNF-α promoted CTGF production by synovial fibroblasts and inhibited the production by chondrocytes. Statistical analysis (paired *t* test) was performed, and $^{a}P < 0.05$ were considered to be statistically significant. $^{a}P < 0.05$, TNF-α *vs* no treat.

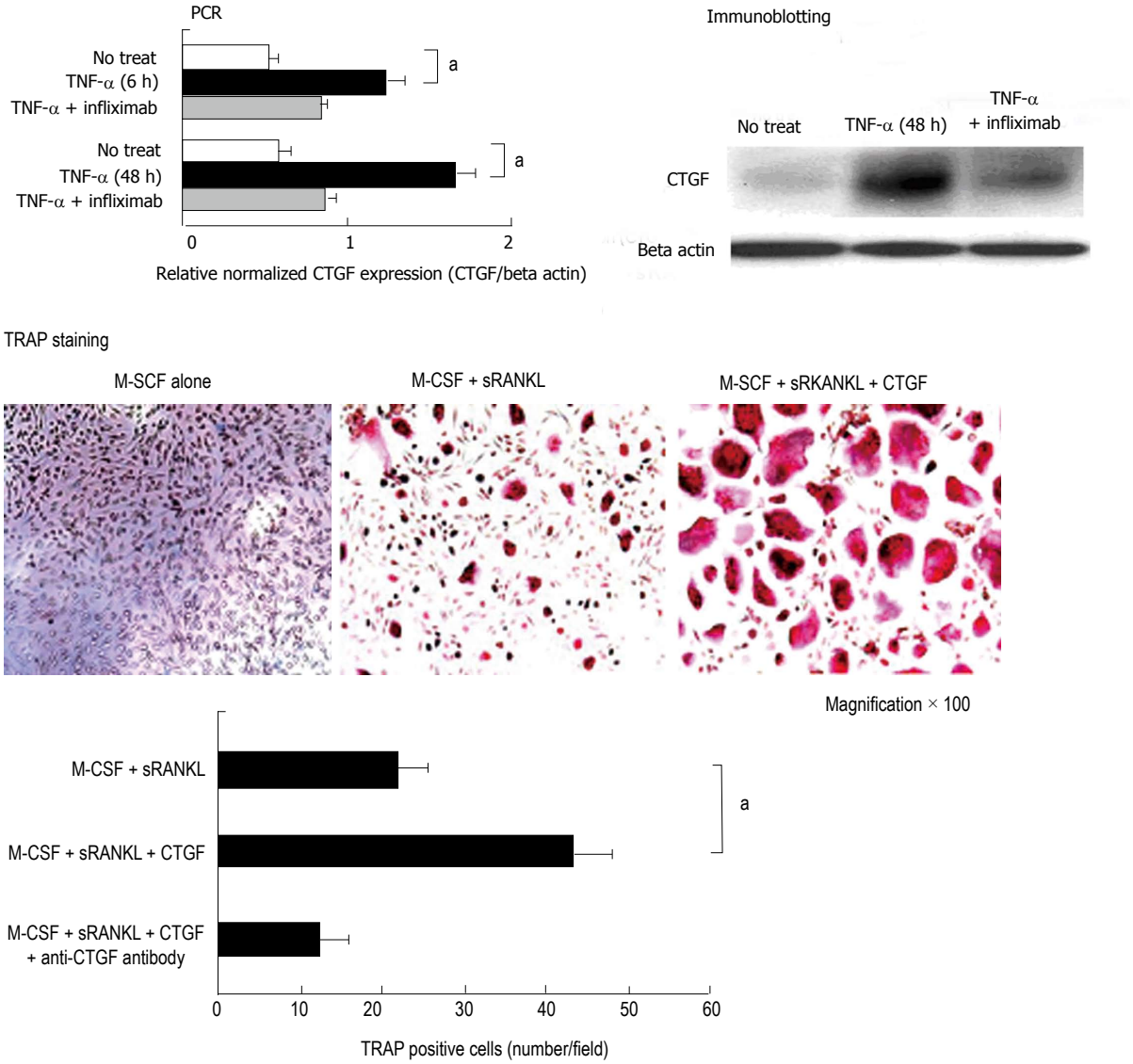

Figure 3 Connective tissue growth factor enhanced macrophage-colony stimulating factor/ receptor activator of nuclear factor kappa-B ligand mediated osteoclastgenesis. Figure 3 Shows images of tartrate-resistant acidic phosphatase (TRAP) staining and the number of TRAP positive cells. For the evaluation of osteoclastogenesis, $CD14^+$ were purified from peripheral blood mononuclear cells of healthy volunteers to obtain osteoclastic progenitor cells. Osteoclasts were induced with macrophage-colony stimulating factor (M-CSF) and soluble receptor activator of nuclear factor kappa-B ligand (sRANKL) and the osteoclastgenesis was evaluated by TRAP staining. The TRAP positive cells were defined as osteoclasts. Connective tissue growth factor (CTGF) alone could not help in the differentiation of osteoclasts (data not shown). M-CSF/RANKL-mediated osteoclastogenesis was enhanced, which was detected by the production of CTGF by larger and higher number of osteoclasts; this enhancing effect was abolished by anti-CTGF antibody. The bars in Figure 2 indicate the standard deviation. Statistical analysis (paired *t* test) was performed, and *P* values < 0.05 were considered to be statistically significant. [a]*P* < 0.05, M-CSF + sRANKL + CTGF *vs* M-CSF + sRANKL.

has not elucidated, previous studies have indicated that TNF-α increased or inhibited CTGF production depend on cell types. For example, TNF-α positively regulated CTGF production in mesangial cells[17]. On the other hand, TNF-α negatively regulated CTGF production in human lung endothelial cells[18].

CTGF has been suggested to contribute to the homeostasis of cartilaginous tissue by autocrine process[14]. CTGF also may positively regulate proliferation of osteoblasts[14], Therefore, CTGF may function as positive regulator functions for proliferation of chondrocytes and osteoblasts, consequently remaining the physiological articular tissue homeostasis. The disturbance of homeostasis due to impairment of CTGF production from chondrocytes possibly result in cartilage tissue damage in RA. However, our data indicated that TNF-α was able to stimulate CTGF production in synovial fibroblasts. The excessive CTGF produced by synovial fibroblasts logically may function as protective factor for cartilage destruction in RA, because CTGF plays an important role for chondrogenesis. On the other hand, TNF-α has shown to induce catalytic enzymes production such as MMPs which cause cartilage destruction in synovial fibroblasts. Moreover, our data also indicated that TNF-α oppositely inhibited CTGF production in condrocytes. In RA, TNF-α possibly functions as positive regulator for cartilage destruction through catalytic enzymes production or the inhibition of CTGF production in condrocytes more efficiently rather than functions as negative regulator for cartilage destruction through increased CTGF produc-

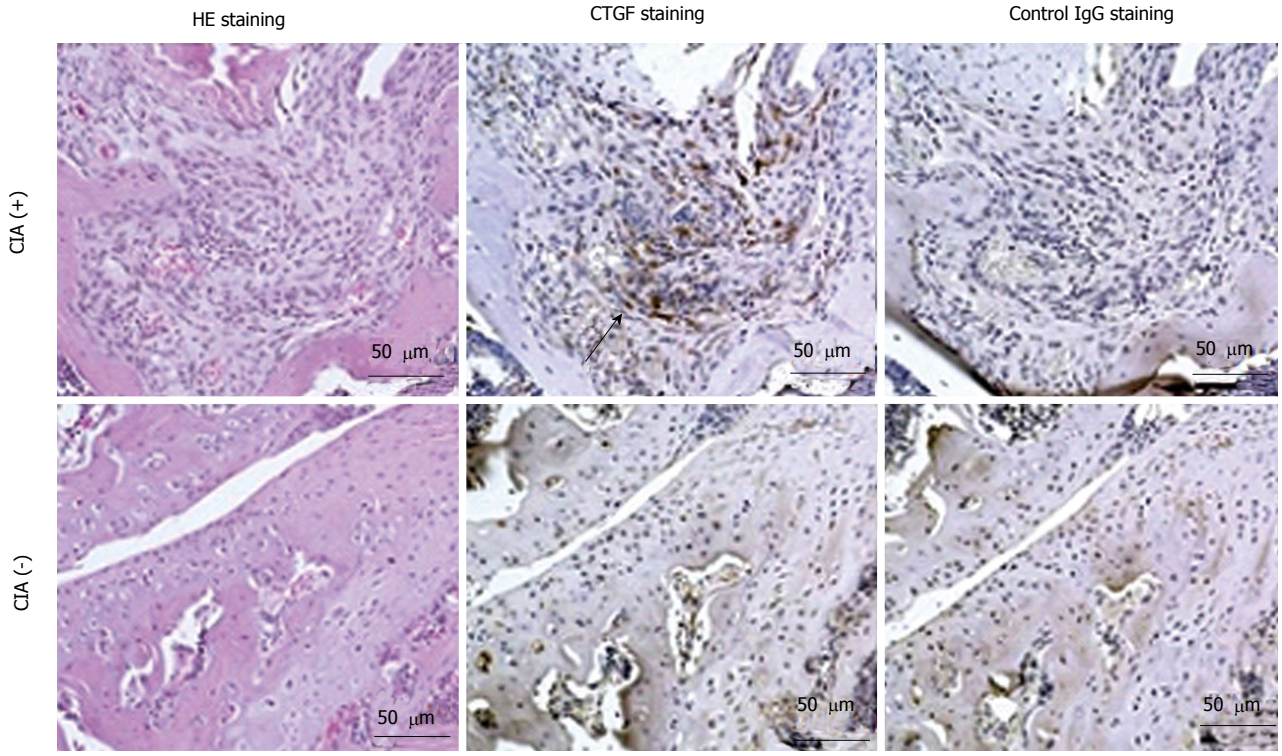

Figure 4 Increased *in vivo* expression of connective tissue growth factor at the articular tissue in collagen-induced arthritis mice. The collagen-induced arthritis (CIA) mice were sacrificed at 8 wk after immunization for immunohistochemical analysis. The immunohistochemical staining showed massive connective tissue growth factor (CTGF) expression in the articular tissue samples from CIA mice (indicated by arrow) using anti-CTGF antibody or control goat immunoglobulin G antibody. Serial sections of the articular tissue samples were also counterstained with hematoxylin/eosin (HE) for detection of the arthritis.

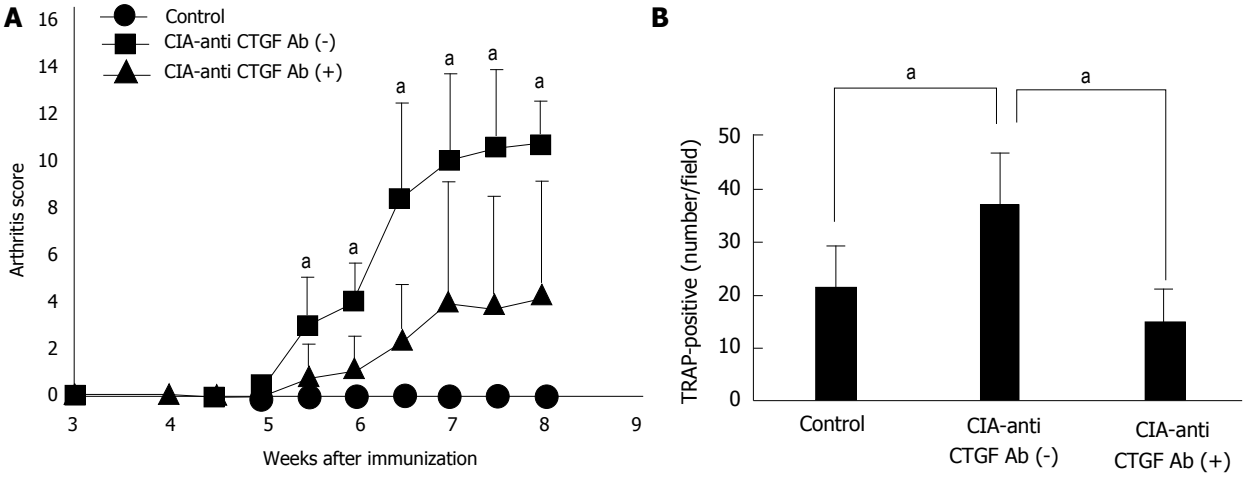

Figure 5 Blocking connective tissue growth factor prevented the development of arthritis in collagen-induced arthritis mice. Mice with collagen-induced arthritis (CIA) were randomly selected and were intraperitoneally administered every week with anti-connective tissue growth factor (CTGF) monoclonal antibodies (mAbs) (white triangle; CIA-anti-CTGF Ab+) or control purified immunoglobulin (white square; CIA-anti-CTGF Ab−) from 1 wk before immunization to 6 weeks after immunization. Each group comprised 12 mice. The mice were monitored for arthritis every week and scored in a blinded manner (A). Blocking CTGF could efficiently prevent the development of CIA in mice. Bars in Figure 3 indicate the standard deviation. Statistical analysis (anti-CTGF Ab$^+$ *vs* anti-CTGF Ab−) was performed, and *P* values < 0.05 were considered to be statistically significant. ^{a}*P* < 0.05, CIA anti-CTGF Ab *vs* Control. For evaluation of osteoclastogenesis, CD14$^+$ osteoclastic progenitor cells were purified from splenocytes at 8 wk after immunization and osteoclasts were then induced with macrophage-colony stimulating factor (M-CSF) and soluble receptor activator of nuclear factor kappa-B ligand (sRANKL). Osteoclastogenesis was suppressed in mice with CIA treated using anti-CTGF mAb (B) compared to the non-treated mice. The bars in Figure 3 indicate the standard deviation. Statistical analysis was performed, and *P* values < 0.05 were considered to be statistically significant. ^{a}*P* < 0.05, CIA anti-CTGF Ab (-) *vs* Control; CIA anti-CTGF Ab (-) *vs* CIA anti-CTGF Ab (+).

tion in synovial fibroblasts. Taken together, excessive CTGF production by synovial fibroblasts regulated by TNF-α promotes aberrant activation of osteoclasts and disturbs the homeostasis of cartilage tissue, ultimately resulting in articular distraction.

Next, we performed an *in vivo* study to clarify the

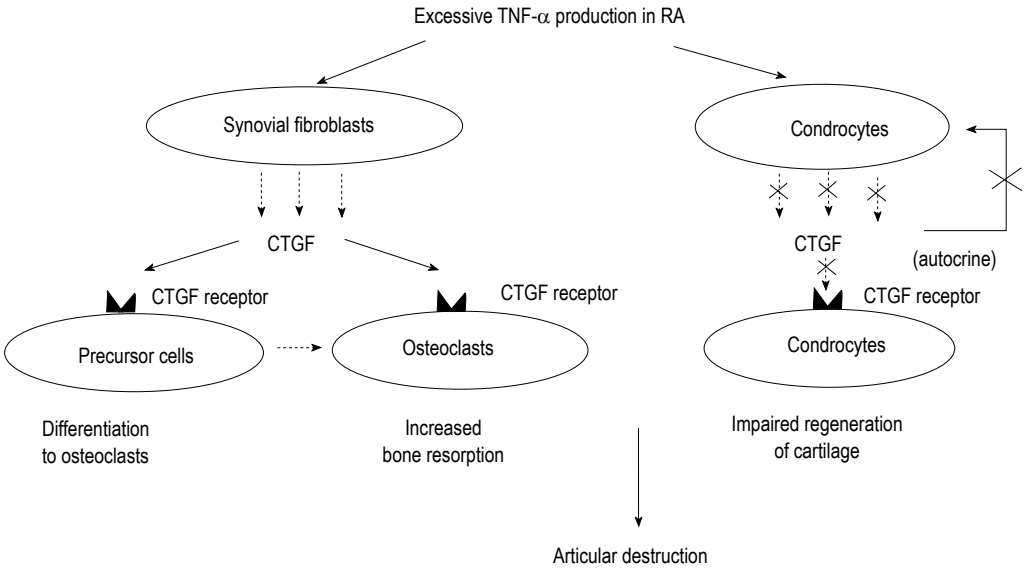

Figure 6 Hypothesis of the role of connective tissue growth factor in the pathogenesis of rheumatoid arthritis. Hypothesis of the possible role of connective tissue growth factor (CTGF) in the pathogenesis of rheumatoid arthritis (RA). TNF: Tumor necrosis factor.

pathological roles of CTGF in the arthritis development using a murine collagen-induced arthritis (CIA) model. A DBA/1J mice were immunized with a combination of type Ⅱ collagen and complete Freund adjuvant (CFA) for induction of CIA. We confirmed *in vivo* CTGF expression was increased at the articular tissue in CIA mice as well as human patients with RA (Figure 4). Moreover, we evaluated the efficacy of the neutralizing anti-CTGF monoclonal antibody (mAb) in the prevention of CIA development in mice. We found that the neutralizing anti-CTGF mAb significantly ameliorated CIA in the treated mice (Figure 5A). In addition, aberrant osteoclastogenesis observed in the mice with CIA was reduced by anti-CTGF mAb treatment (Figure 5B). Our consecutive studies showed that blocking the production of CTGF prevented the progression of RA. Therefore, CTGF may be a new therapeutic target for the treatment of RA.

CONCLUSION

We confirmed that CTGF is a novel effecter molecule in the pathogenesis of RA. A schematic hypothesis of its role is presented in Figure 6. CTGF is a multiple functional cytokines and possess a several biological functions depend on the target cells. Although many candidate molecules on the cell surface have been suggested as specific CTGF receptors such as integrins, they have not been completely identified to date. Biological functions of CTGF may differ depend on its receptor as well as cell types. Although the mechanism of action and the importance of CTGF in contribution to the RA development are unclear, we showed that blocking the CTGF pathway could ameliorate CIA especially through the reduction of aberrant osteoclastogenesis. These data imply the possible mechanism underlying the efficacy of anti-CTGF antibody in the treatment with RA. Our study indicated that CTGF is important factor in the development of RA. These results may shed light on the new therapeutic strategies for RA. Further precise studies that will provide clues to assist in the development of new treatment for RA as well as a deeper understanding of its etiology are required.

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