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EDITORIAL

Exercise awareness and barriers after spinal cord injury

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Abstract

Exercise is an essential element in managing several of the non-communicable diseases after spinal cord injury (SCI). Awareness of the importance of prescribing a customized exercise program that meets the goals of persons with SCI should be highly considered in the rehabilitation community. The barriers of implementing specific exercise program as well as the factors that may mask the outcomes of regular exercise regimen need to be continuously addressed as a part of patients' rehabilitation care. The focus of this editorial is to encourage the medical community to consider routine physical activity as one of the necessary vital signs that needs to be routinely checked in patients with SCI. Providing education tips, nutritional counseling and engaging in recreational programs may provide motivational route to the community of SCI. This may result in reinforcing active lifestyle in survivors with SCI as well as to reduce the impact of chronic life threatening medical disorders.

Key words: Spinal cord injury; Rehabilitation; Exercise awareness; Barriers to exercise; Medical community

Core tip: Exercise is an essential component in managing persons with spinal cord injury (SCI). Knowledge of the barriers that encounters prescribing exercise routine is essential to ensure successful engagement in active lifestyle after SCI. Interdisciplinary approach may be the key of addressing some of these barriers after SCI.

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INTRODUCTION

Spinal cord injury (SCI) is a devastating medical problem that may result from direct or indirect insult to the cord. The trauma may result from motor vehicle accidents, military or civilian gunshot wounds, wounded warriors in the combat fields or sports related injuries or non-traumatic causes such as infectious, inflammatory or tumor-related causes. It is estimated that there are more than 250000 survivors with SCI in the United States[1]. The clinical care burdens of chronic SCI are extensive and can lead long-term disability with serious social and economic consequences.

Skeletal muscle atrophy and decline in lean mass are key features after SCI. Within few weeks post-SCI, there is more than 40% loss in skeletal muscle size in lower extremity[2,3]. The process of continuous loss in muscle mass is magnified as the aging process continues; "baby boomers" with SCI may have profound muscle atrophy. The rapid loss in muscle mass following SCI leads to serious metabolic consequences similar to extensive decline in basal metabolic rate (BMR), insulin resistance and impaired glucose tolerance. The evidence suggests that

there is up to 22%-40% decline in BMR in person with SCI based on their level of injury and about 50%-75% suffers from impaired glucose tolerance or type Ⅱ diabetes mellitus[4-6]. The disruption in energy balance process predisposes these individuals to become a fat building machine. Body composition assessment studies reveal intriguing evidence that body mass individuals with chronic SCI composes of more than 30% fat mass, despite their normal and healthy body mass index[3,7]. The process is further complicated with a decline in routine daily physical activity[8].

The stacking of fat mass in non-fat sites leads to accumulation of depot of ectopic adipose tissue similar to muscle (intramuscular fat) or perineum (visceral fat)[9,10]. Ectopic adipose tissue accumulation has serious health consequences on insulin signaling, glucose tolerance and may lead to disruption in lipid metabolism. The mechanistic links by which ectopic adipose tissue disrupts several of the key metabolic functions have yet to be determined. It is important to recognize that the prevalence of cardiovascular diseases, type 2 diabetes mellitus and amputation exceeds 200%, 50% and 30% in persons with SCI[6,10,11]. The prevalence of these medical conditions escalates with aging. This leads to life threatening conditions, extensive economic burden, poor quality of life and shorten life span among those with SCI.

SCI leads to extreme physical inactivity. Sitting time has been identified as an independent health risk factor that may lead to all cause mortality. Reduction in the level of physical activity after SCI is a life a threatening condition and it is complicated by the prolonged sitting time in their wheelchairs. Recreational activities as well as rehabilitation strategies that help reverse this pattern of physical inactivity and prolonged lifetime sitting are highly recommended after SCI. The primary focus of the current editorial is to shed the light about the most common exercise strategies available to the SCI community and the main barriers which prevent implantation of these strategies. Previous publications have identified some of the challenges that involve conducting exercise research trials after SCI[12,13]. The editorial offers few recommendations based on the current exercise research studies on how to address these barriers.

EXERCISE AWARENESS AFTER SCI

Exercise is a cornerstone that can ameliorate several of the aforementioned medical conditions after SCI. The American College of Sports Medicine (ACSM) refers to exercise as a type of physical activity consisting of planned, structured, and repetitive bodily movement done to improve and/or maintain one or more components of physical fitness. This can be accomplished for variety of purposes including musculoskeletal strengthening, cardiovascular performance and weight reduction and weight maintenance. Exercise after SCI can be either target towards fitness (cardiovascular or muscular), compensatory (using assistive device) and restorative (functional electrical stimulation and locomotor training). According to current guidelines, adults with SCI should engage in at least 20 min of aerobic exercise training twice weekly prescribed at moderate-vigorous intensity or 3 sets of 8-10 repetitions of resistance training to the major muscle groups[14].

Cardiovascular or muscular fitness programs encourage individuals with SCI to engage their innervated upper extremity musculature in either aerobic type training using arm-crank ergometer or circuit-resistance type training to build major muscle groups above the level of injury. There is established evidence that twice to three times weekly for 30-60 min may be sufficient to achieve desirable cardiovascular and muscular fitness gains[14]. In our facility, engagement of persons with paraplegia or tetraplegia in upper extremity circuit resistance training once weekly for 45-60 min resulted in a modest gain in muscular strength as measured by the number of plates lifted per session (clinical observation). Engagement in upper extremity training results in improvement in glucose/lipid profile; however, it is unclear if these rehabilitation interventions may lead to improvement in whole and regional body composition after SCI.

Functional electrical stimulation (FES) or neuromuscular electrical stimulation (NMES) training of the paralyzed lower extremity muscles have been targeted to offset for the rapid process of skeletal muscle atrophy, regional adiposity and improve metabolic profile. Long-term training with FES or NMES has also led to improvement in bone health parameters after SCI. Early engagement in NMES training immediately after SCI can offset for the negative effects on skeletal muscle size and prevent the development of other medical complications similar to pressure ulcer. Recent research work noted the significance of loading the paralyzed skeletal muscles to improve musculoskeletal, metabolic and cardiovascular features in persons with SCI[15]. One interesting area for potential future study is the interaction between exercise and medical supplements to boost the outcomes of exercise. Similar to administration of Testosterone supplements which are likely to overcome the diminished anabolic profile and provide appropriate homeostatic environment for improving body composition by increasing lean mass and decreasing fat mass accumulation after SCI. Research in our laboratory is currently ongoing to investigate this interaction on body composition and metabolic profiles.

The compensatory strategy has been commonly used to exercise the paralyzed the lower extremity muscle as well as to provide loading to attenuate negative effects on musculoskeletal health after SCI. The knee, ankle, foot orthosis (KAFO) brace as well as reciprocal gait othrosis have been utilized by persons with SCI to allow them to walk with bilateral crutches or walker[16]. However within few months, individuals with SCI are likely to give them up because of their bulkiness, difficulty to doff/don and reliance on caregivers to ambulate with these units. Advancement in electronics allows the availability of new

generation of functional neuromuscular units that may compensate for functional deficits after SCI. The Bioness unit (L300) allows stimulating of the ankle dorsiflexors to compensate for drop foot at heel strike of the gait cycle. These units although proven effective in improving gait cycle after SCI, however, they are not easily accessible because of their costs, the need of a qualified staff to train their patients and the need of a long-term training for patients to efficiently utilize them.

Manual and power wheelchairs may offer the possibility to stand up to ameliorate several of the negative effects of sitting and experiencing health benefits of loading the lower extremities. Exoskeletons or robotic suits offer a scientific breakthrough in walking rehabilitation after SCI. The efficacy of exoskeleton is yet to be established before it can be recommended for rehabilitation and exercise after SCI. Exoskeletons can be used in conjunction with a walker and can progress to be used with bilateral crutches. However, the cost of these units may preclude their practical use in rehabilitation settings.

Restorative type exercise has focused on providing afferent feedback to evoke spinal reflexes to regain motor recovery in the paralyzed muscles below the level of injury[17-19]. The introduction of central pattern generator theory allows many researchers to utilize locomotor training in conjunction with other therapeutic modalities similar to electrical stimulation, magnetic stimulation and sensory transcutaneous electrical stimulation to encourage motor recovery. A recent breakthrough showed that epidural stimulation allows recovery of walking in persons with motor complete SCI[20]. It should also be noted that locomotor training is not only about walking, but offers other metabolic and cardiovascular benefits after SCI[18]. It is essential to maintain the integrity of musculoskeletal system below the level of injury to maximize the benefits of utilizing restorative interventions. The atrophic adaptations and weakening of bone after SCI may potentially limit the outcomes of these promising restorative trials. Finally, published evidence suggests that individuals with SCI who are participating in a regular wellness program or engaged in a regular physical activity routine are less likely to develop several of the aforementioned medical conditions[19].

EXERCISE BARRIERS

We have to be aware of the barriers that interfere with long term commitments to persons with SCI. These barriers may include lack of access to exercise facility, lack of accessible public transportation, lack of background knowledge on dealing with persons with SCI, failure to provide the appropriate exercise routine based on the person's neurologic level and spared muscle function. For example, prescribing an exercise routine for a person with C6 SCI will be completely different than one for a person with T6 SCI. Clinicians should be aware of these factors to appropriately customize exercise programs which allow long-term engagement and prevent drop-out.

Spinal cord injury medicine requires special training and expertise to understand the consequences on physical, mental and psychological health in this population. Several programs in United States and other countries offer clinical program to train health care specialists to understand the major physiological and pathological adaptations after SCI. Prescribing exercise programs to improve cardiorespiratory fitness, muscular strength, and changes in body composition requires extensive training to understand medical issues that may arise similar to autonomic dysreflexia, pressure ulcers, urinary tract infection, heterotrophic ossifications, osteoporosis. Protecting participants with SCI who engage in specialized exercise programs is vital to ensure their safety. Exercise facilities should be equipped with ceiling or portable lifts to ensure safe transfer especially for those with high level of SCI.

The lack of appropriate guidelines on how to evaluate the effectiveness of specific exercise intervention in the SCI community is a considered a major hurdle for this population. Many clinicians/researches are still utilizing body mass index (BMI) to evaluate the effectiveness of specific exercise protocols on weight management and body composition changes after SCI; although it is well established that the World Health Organization (WHO) BMI criteria cannot be adopted to this population because it underestimates the percentage fat mass after SCI. A clinical tool similar to waist/abdominal circumference needs to be validated to accurately evaluate the longitudinal changes in response to diet/exercise. At Miami project, Kressler *et al*[21] validated a tool to evaluate the effectiveness of gauging exercise intensity compared to utilizing VO_2 peak that requires specific equipment or heart rate that may be limited by the level of injury. The study showed that Borg-rate of perceived exertion (RPE) scale can be used effectively to determine the intensity of the exercise intervention necessary to elicit the highest fat oxidation that is equivalent to approximately 50% of total energy expenditure[21]. Another study utilized thigh circumference to determine the effects of different FES cadence on thigh muscle size after 6 wk of training[22]. These studies are essential to bridge the gap between research and clinical community to provide simple tools to evaluate the effectiveness of exercise interventions after SCI.

Another important aspect is to identify the primary goal(s) for which the exercise program is being designed. Establishing the goal requires an interdisciplinary team of professionals to determine the appropriateness of these goals based on the person's level of injury, medical and psychological status and duration post-SCI. Several medical centers have adopted strategies such as locomotor training to restore motor function and facilitate recovery of walking following SCI[17,18]. This goal requires daily intervention and frequent repetitions to reeducate the injured nervous system on the possibility of restoring walking. However, it is impractical to adopt the same exercise regimen to improve body composition or to restore muscle mass. A typical exercise physiology phenomenon is

that protein accretion is a cycle of protein synthesis and protein breakdown and providing a reasonable resting interval between exercise sessions facilitates the process of restoring or building muscle mass. Therefore, identifying appropriate goals is a key element that ensures successful rehabilitation intervention.

Exercise adherence is another common barrier that can be overcome by reducing the frequency of exercise to twice or thrice weekly workouts. Previous evidence suggests that twice weekly for 12 wk is adequate to increase muscle mass and reduce accumulation of ectopic adipose tissue as well as improving metabolic profile[15]. A very important shift in the rehabilitation paradigm is the translation of clinical based laboratory studies or hospital based training protocols to home based environment. This can be easily monitored *via* advances in video conference communication taking advantages of the high speed internet. This allows safe monitoring and overcoming the hurdles of commuting to the rehabilitation centers. We have recently reported that exercise adherence was above 60% when exercise program using FES was administered as a home based routine twice or three times a week[23]. Therefore, future clinical trials need to have translation plans that allow clinicians, caregivers and patients easy access to rehabilitation strategies without reliance on bulky or expensive equipments to exercise.

Awareness of the environmental and community barriers that may limit engagement in a long-term physical activity needs to be identified. Public transportation with reasonable wheelchair lifts, accessible doors and curbs need to be considered as a public health policy especially in the developing countries. Promoting exercise facilities that encourage individuals with SCI to engage in community programs are highly desirable. Improvement in the outcomes of exercise interventions can be translated into improvement in activities of daily living (*e.g.*, transfer, grasping, *etc.*). Moreover, the outcomes of any exercise program can be further complicated by several factors including dietary intake, smoking, mental health and family support. For example, excessive caloric intake can mask any metabolic benefits that may result from engaging in daily active routine. There is established evidence that persons with SCI are likely to consume high fat diet and they are low on daily protein intake[24]. This observation is likely to disrupt several metabolic signaling and interferes with exercise protocols aiming to restore muscle mass. Therefore, dietary counseling is an essential component to the success of any exercise regimen. Several of the established SCI programs offer smoking cessation programs as well as recreation programs in the community to provide continuous motivation to survivors with SCI to engage in active life style as well as to reduce the factors that may lead life threatening medical conditions.

CONCLUSION

The medical community engaging in caring and rehabilitation of persons with SCI needs to consider adding routine physical activity as one of the necessary vital signs. Moreover, continuous medical education needs to be provided to medical, physical therapy and occupational therapy students and clinicians about the necessity of identifying the suitable exercise regimen to their patients as well as to provide awareness of the factors which are essential to optimize the outcomes of any exercise interventions after SCI. Awareness in medical community about different exercise strategies as well as with the barriers of prescribing exercise protocols is a key to ensure successful outcomes for persons with SCI. A custom based exercise program that can balance both the goals and identify potential limitations for adherence may consider a gold-standard strategy that ensures engagement after SCI. Goals sharing and planning with SCI participants are crucial elements in designing a custom based exercise program that ensures long-term exercise commitment. Providing an appropriate long term exercise programs for persons with SCI which incorporates lifestyle and dietary modifications may enhance health, function and quality of life in this population.

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EDITORIAL

Anterior knee pain after a total knee arthroplasty: What can cause this pain?

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Core tip: Total knee arthroplasty (TKA) has been shown to be a successful procedure for treating patients with osteoarthritis, and yet approximately 5%-10% of patients experience anterior knee pain (AKP). To prevent AKP after TKA it is important to first identify the different anatomical structures that can cause this pain. Greater attention to and understanding of AKP should lead to significant pain relief and greater overall patient satisfaction after TKA. This article is a review of what pain is, how nerve signalling works and what is thought to cause AKP after a TKA.

Abstract

Total Knee Arthroplasty has been shown to be a successful procedure for treating patients with osteoarthritis, and yet approximately 5%-10% of patients experience residual pain, especially in the anterior part of the knee. Many theories have been proposed to explain the etiology of this anterior knee pain (AKP) but, despite improvements having been made, AKP remains a problem. AKP can be described as retropatellar or peripatellar pain, which limits patients in their everyday lives. Patients suffering from AKP experience difficulty in standing up from a chair, walking up and down stairs and riding a bicycle. The question asked was: "How can a 'perfectly' placed total knee arthroplasty (TKA) still be painful: what can cause this pain?". To prevent AKP after TKA it is important to first identify the different anatomical structures that can cause this pain. Greater attention to and understanding of AKP should lead to significant pain relief and greater overall patient satisfaction after TKA. This article is a review of what pain is, how nerve signalling works and what is thought to cause Anterior Knee Pain after a Total Knee Arthroplasty.

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INTRODUCTION

One of the remaining challenges in the field of total knee arthroplasty (TKA) is the elimination of anterior knee pain (AKP). TKA itself has been shown to be a successful procedure for treating patients with osteoarthritis[1], and yet a significant proportion of the patients still experience AKP after surgery. The symptoms of AKP after TKA can be described as retropatellar or peripatellar pain limiting patients in their everyday lives[2]. Patients suffering from AKP experience difficulty in standing up from a chair, walking up and down stairs, and riding a bicycle.

In the early TKA designs the primary goal was resurfacing the medial and lateral compartments and little attention was paid to the patellofemoral joint (PFJ)[3]. In these designs a 40% to 58% rate of patellofemoral pain was identified[4]. Insall *et al*[5] in 1976 hypothesized that the

residual pain was most frequently attributed to the patellar compartment. During the early years of TKA residual AKP was often treated with either a patellectomy and/or soft tissue realignment[5]. It would therefore, seem more appropriate to refer to AKP rather than patellofemoral pain as the general term for pain in the anterior part of knee. The continuing high incidence of postoperative AKP led to the changes in the shape of the patellofemoral part of the TKA, such as modifying the femoral trochlea and placing a patella component[3,5].

The first step in understanding AKP after TKA is to look at a healthy functioning knee. According to the theory of Dye, "the healthy knee can be viewed as a biologic transmission with a complex assemblage of living asymmetrical moving parts whose purpose is to accept, transfer, and ultimately dissipate often high loads generated at the ends of the long mechanical lever arms of the femur, tibia, patella, and fibula"[6]. Furthermore, Dye' s refers to each knee having a unique "envelope of function"; a potential range of activity in which it maintains a homeostasis of all surrounding tissues[6]. The potential range of activity is different for individual knees, whether healthy, arthritic or with a knee arthroplasty. An arthritic knee can be viewed as a transmission with worn bearings, and thus with a limited capacity to accept and transfer loads. In other words, arthritis causes the potential range of activity to become limited, causing pain and restrictions in daily activities such as walking and cycling, and sometimes even pain when at rest.

The fundamental aim of knee arthroplasty or joint replacement surgery is to restore, as far as possible, a normal functioning, pain free knee. Applying Dye's theory to a TKA patient gives an interesting perspective. A TKA knee can then be viewed as a knee functioning with a combined biologic and artificial transmission with a limited potential range of activity. The limitation is in part due to the use of artificial products containing metals and polyethylene, which are harder and less flexible than the original cartilage and therefore make it unlikely that the knee will return fully to its pre-injury/pre-arthritis state. A pain free knee with a good function can be described in Dye's terms as functioning in a zone of homeostasis of all knee tissues. The knee that is structurally overloaded, and thus functioning in a zone of abnormal loading (supraphysiological) of knee tissues is clearly no longer functioning in the zone of homeostasis[6]. If this abnormal loading of the knee continues for long periods of time, a TKA can ultimately fail (*i.e.,* it enters the zone of structural failure)[6].

Although numerous design improvements have reduced the incidence of AKP, nevertheless approximately 5%-10% of patients still experience Anterior Knee Pain (AKP)(ranging from 0.4%-49.0%)[1-4,7-24]. Many theories have been proposed to explain the etiology of AKP[1-4,7-25]. In sports medicine it has been observed that some patients can have severe patellofemoral pain while their articular cartilage appears normal, and that patients with severe patellofemoral cartilage damage can be pain free[26]. Even though significant knowledge exists about AKP after TKA, its etiology and pathogenesis are still not fully understood. In this review the most important factors related to the development of AKP after TKA are therefore analysed, starting with how this pain signalling works and what anatomical structures can cause this pain to occur after TKA.

PATHOPHYSIOLOGY AND ETIOLOGY OF PAIN

Pain is a normal manifestation of everyday life and serves as a protective mechanism for the body, causing the individual to react to try to eliminate the pain stimulus[2,27]. However, excessive pain after a TKA can diminish or hinder quality of life[12,21,22,27]. This form of pain typically originates in the peripheral nervous system (PNS)[27].

The PNS consists of all the nerves outside of the brain and the spinal cord[27,28]. It is made up of bundles of axons which are enclosed by connective tissue to maintain the continuity, nourish and protect the axon[28]. Each axon in the PNS can be surrounded by a myelin sheath, called a Schwann cell sheath, and these two together form a nerve fibre[28]. An axon can be myelinated once it reaches a thickness of one or two micro metre[28]. The difference between a myelinated and non-myelinated nerve fibre is the conduction velocity (myelinated is faster)[28]. Nerve fibres can therefore be classified into different types depending on their diameter and conducting velocity[28].

When nerve fibres transmit information from sensory receptors to the central nervous system (CNS) they are called afferent nerves[28]. Afferent nerves are triggered by specialized neural structures called sensory receptors[28]. These receptors are sensitive to a specific form of physical energy[28]. In the joint these are called joint receptors or mechanoreceptors and can be divided into four basic categories: Ruffini endings (stretch), Pacinian corpuscles (pressure and pain), Golgi tendon organ-like endings and Free Nerve Endings (FNE)[2,28]. Pain occurs when tissues are being compressed, damaged or irritated[2]. The perception of pain appears to be activated by pain-specific sensory receptors called nociceptors in a process called nociception[29]. FNE, especially type Ⅳ FNEs detect touch, pressure, pain, heat and cold[2].

These FNEs primarily form the basis of the nociceptive system by sending signals to the spinal cord and CNS on pain and inflammation[2,29]. Under normal circumstances FNEs remain inactive, but they become active when subjected to abnormal mechanical deformation, thermal stimuli or special chemical agents[2,29]. Pain signals are transmitted to the CNS by a fast or a slow pathway[2]. Fast pain can be triggered by mechanical and thermal stimuli, but slow pain can be caused by mechanical and thermal stimuli and by chemical agents[2]. Fast pain is transmitted through A fibres (also called A delta fibres, they are myelinated) at velocities estimated to be between 6 m and 100 m per second[2,28]. This is often experienced

as a sharp, acute or electric pain[2]. The slow pain is transmitted through C fibres (unmyelinated) with velocities between 0.5 m and 2 m per second and is often described as burning, aching or chronic pain[2,28]. This type of pain is normally present with tissue destruction[2]. Slow pain can occur in the skin and deep tissues whereas fast pain is not felt in the deeper structures[2].

Chemical substances, as mentioned, play an important role in stimulating the slow type of pain[2]. Chemicals that excite pain include histamine (also causes itching), serotonin and bradykinin[2,29]. Bradykinin acts *via* G-protein-linked receptors to produce a range of proinflammatory effects including vasodilatation and edema[2,29]. Prostaglandins and Substance P (SP) enhance the sensitivity of nociceptors but do not directly excite them[2,29]. SP can function as a vasodilator and therefore can produce inflammation[2]. SP is a neuropeptide that can function as a neurotransmitter and is detected and isolated in the lateral retinaculum, the infrapatellar fat pad, synovial membrane, periosteum and subchondral bone of patellae affected with degenerative disease[2,30]. Nerve fibres immunoreactive for SP are not observed in the intact articular cartilage and are present in degenerative erosion of the patella[2]. Examination of subchondral bone, however, shows the presence of SP positive nerve fibres in a degenerative joint.

The problem with pain receptors is that, unlike smell or taste for example, they adapt very little and sometimes not at all[2]. The continuous excitation of nociceptors, therefore, tends to lead to a chronic aching pain[2]. This increase in sensitivity of the nociceptors is called hyperalgesia[2].

Having looked at how nerves transmit pain, the next step is to focus on which nerves are responsible for different parts of the knee joint. The innervation of the knee joint follows Hilton's law, meaning that all of the motor efferent nerves carry afferent branches from the knee capsule[31,32]. The innervation of the knee joint can be divided into two groups; a posterior and an anterior group[31,32]. The posterior group is made up of branches of the tibial nerve and a terminal branch of the obturator nerve. If necessary, signals from the posterior capsule and cruciate ligaments are transmitted to the CNS[31,32]. The anterior group consists of branches of the femoral, common peroneal and saphenous nerves[31,32]. The femoral nerve divides into the vastus muscles and the anterior medial joint capsule. The saphenous nerve innervates the anterior medial capsule and some sensory branches to the patellar tendon[31,32]. The medial side of the patella is innervated by the nerves of the vastus medialus muscle[2]. The lateral part of the knee is innervated by the nerves of the biceps femoris muscle and the vastus lateralis muscle[2].

The knee is a hinge type of joint and in the Total Knee Arthroplasty (TKA) is made up of the articulations between the femoral and tibial components and between the patella and the patellar surface of the femur, the patellofemoral joint (PFJ). The femur component (metal alloy) articulates with a Polyethylene surface either on a tibial base plate (metal alloy) or a total Polyethylene tibial component. A hinge joint mainly allows for motion in one plane and only slight side to side motion is possible. The femur and tibia are connected together by strong collateral ligaments and depending on the arthroplasty used, sometimes a posterior cruciate ligament.

The complexity of patellofemoral joint and the high number of pain transmitters are of relevance to the issue of whether or not to resurface the patella, which is an area of ongoing controversy in the field of TKA[1,3,4,7,14,17,24,33,34]. If the patella is resurfaced, the articular cartilage is removed and substituted with a polyethylene component. Alternatively, if needed, the patella can be reshaped (denervation, a partial resection of the lateral facet, removal of osteophytes or a combination of the above mentioned). The complexity of the PFJ means it is not only the articulation of the patella on the femoral groove of the femur component (metal alloy). Several muscle as well as ligament forces act on the patella to provide stability and a proper patellar tracking. The patella allows for multidirectional movement, especially cranial and caudal, but it also tilts and even rotates. There are, therefore, numerous points of contact between the undersurface of the patella and the femur component. The PFJ also depends on the synovial plica, infrapatellar fat pad, tendons, retinacula and the capsule[2,26]. The PFJ appears to be very sensitive to pain due to the high number of FNEs in different structures[2]. The highest numbers are found in the quadriceps muscles, with significant numbers also in the retinacula, patellar tendon and synovium[2,26]. Intact hyaline cartilage is completely free of nerve fibres[2,30]. Therefore intact aneural cartilage cannot be a source of pain[2,26]. Dye had an arthroscopic palpation of his patellar cartilage lesion done on his own knee. The operation was performed without intraarticular analgesia. Dye reported experiencing no pain when the patellar cartilage lesion was palpated[26]. However, he did experience severe pain when the synovial plica, infrapatellar fat pad, tendons, retinacula and the capsule were palpated[26].

REGENERATION OF NERVES

After looking at how pain signalling works, the interesting next question for clinicians is: how can these findings be translated into practical daily patient care? With the skin incision in a TKA, nerves are surgically cut, and axons are injured or damaged[35]. The neurons can regenerate a new axon in a process called chromatolysis[35]. The process starts with exudation, cell proliferation and then collagen synthesis[28]. First the gap is filled with blood corpuscles and macrophages and a fibrin clot is formed[28]. This results into an ingrowth of capillaries and fibroblasts. This ingrowth only develops in the proximal stump of the damaged axon by forming sprouts, as the distal part of the axon dies[27,35]. These sprouts grow along the path of the original nerve, if this route is still available[35]. In the distal stump the Schwann cells of the nerves not only

survive the wallerian degeneration, but also proliferate and form rows along the course previously taken by the axons[35]. These Schwann cells form nerve growth factor, which attracts the nerve fibres to grow back across the surgical cut[27]. The rate of regeneration is slow and is approximately 1 mm per day in the knee[28,35]. When peripheral nerve regeneration gets blocked in the scar tissue, a neuroma can be formed[27,28].

Another way pain might be transmitted is when nerves around the knee are compressed. The nerve, a soft structure, can be compressed between bone, ligaments or due to swelling (hematoma)[27], but also by a knee arthroplasty or the scar tissue that is formed after a TKA. Dellon describes how, when a nerve is compressed, blood flow to the nerve is reduced[27]. When a nerve does not get enough oxygen, it stops conducting normal signals to the CNS[27]. This can be felt as a "buzzing" or "tingling" feeling[27].

CLINICAL IMPLICATIONS

Assuming that the incapacitating AKP is caused by the activation of FNE, the main interest of this study is to know how they become active and whether this is due to an abnormal mechanical deformation, thermal stimuli or special chemical agent[2,29]. It is known that the structures in and around the PFJ are very sensitive to pain, being full of nociceptors[2,29]. The synovium, lateral retinaculum, infrapatellar fat pad, periosteum and subchondral bone of patellae affected with degenerative disease are all richly supplied with type IVa FNEs and fibres containing Substance P[2].

A key aim of this study was to identify literature evaluating the different determinants of AKP after a TKA was found[2,8,9,12,13,15,18,22,23,25-27,30,34,36-41]. The articles reviewed confirm this study's hypothesis that anything that alters the patellofemoral joint (PFJ) mechanics can activate these FNEs and thus induce AKP after TKA[22]. It can further be hypothesised that the nociceptive system can be activated by several factors, either alone or in combination: Hoffa impingement, peripatellar synovitis, increased osseous pressure and mechanical changes that alter the PFJ in an abnormal way.

The influence of preoperative AKP does not seem to be predictive in relation to postoperative AKP[8,12,22,24,42]. However, the influence of preoperative AKP does seem to be predictive in relation to postoperative AKP[8,12,22,24,42]. Some researchers investigated the influence of walking on AKP after TKA. A higher knee extension moment in the early midstance phase of walking causes higher forces on the PFJ and consequently a higher frequency and severity of AKP after TKA[42]. Interestingly, the patients that modify and decrease the PFJ loading had less or no AKP[42]. Muscle balance also has an influence on AKP, for instance the preoperative weakness of the vastus medialis muscle was seen to lead to increased activation of the vastus lateralis, and the ensuing lateral maltracking of the patella can lead to AKP after TKA[25,43]. Weakness of the hip adductors was also seen to lead to a dynamic valgus and thus to lateral patella maltracking, which therefore makes it a contributor to AKP after TKA[25].

Moving on to focus on the influence of the knee design, Mahoney *et al*[44] suggested that the design of the specific TKA can have an influence on PFJ loading. They studied which designs were able to change the posterior flexion extension axis, thereby lengthening the extensor mechanism moment arm, which could decrease the quadriceps' muscle force and reduce the PFJ forces[44]. The importance of trochlear design was emphasised by Popovic, who found a high number of patients experiencing pain due to an inappropriate trochlear design[40]. Some other researchers have suggested that the posterior stabilized knees have less AKP compared to the cruciate retaining designs, but a recent meta-analysis could not prove this difference (6% AKP in both groups)[45]. Breugem *et al*[12,13] performed two studies that specifically evaluated whether the mobile bearing knee could reduce AKP compared to the fixed bearing knee. In the short-term follow-up study less AKP in the mobile bearing knees compared to the fixed knees[12] was observed, which seemed to suggest that the mobile bearing knee did have an influence on AKP[12]. Kim *et al*[46] reported less pain in the mobile bearing group compared to a fixed bearing group at a mean follow-up of 2.6 years. Wohlrab *et al*[47] found a difference in pain scores at 3 mo favouring the mobile bearing, but found no difference after three and five years. In the 6 to 10 year (median 7.9 years) follow-up study the mobile bearing knees did not sustain the difference in AKP that had been found in the short-term study[12,13]. These results are comparable to the findings of other systematic reviews and/or meta-analysis, most of which have not shown an advantage of using a mobile bearing[22,36,48-51]. Based on these results combined with a recent meta-analysis showing less AKP in the mobile bearing TKA, it seems that the debate can be reopened as to whether the mobile bearing TKA is part of the solution to AKP[52]. Aglietti *et al*[36] suggested that the performance of a mobile bearing knee might decline over time. Yet, even if this difference is only relevant in the short term, it would still seem advantageous to use a mobile bearing TKA for the benefit of patients that experience less pain in this period. The reason why the mobile bearing TKA seems to make a difference in AKP, could be due to the femur component being highly congruent to the PE bearing this in combination with the self alignment ability of the PE bearing and the fixed tibial base plate, in a knee that is well balanced in flexion and extension thus unloading the PFJ.

The influence of placement of the TKA is another issue. The PFJ loading is influenced both by changes in the joint line height and by selecting a femoral component that is too large[39,53]. Tibia-femoral instability, due to inappropriate placement or other causes, leads to increased pressure on the PFJ, especially in flexion[54]. However, perhaps the most important aspect of placement is the influence of malrotation after TKA[8,9,18,34,55-57]. Berger *et*

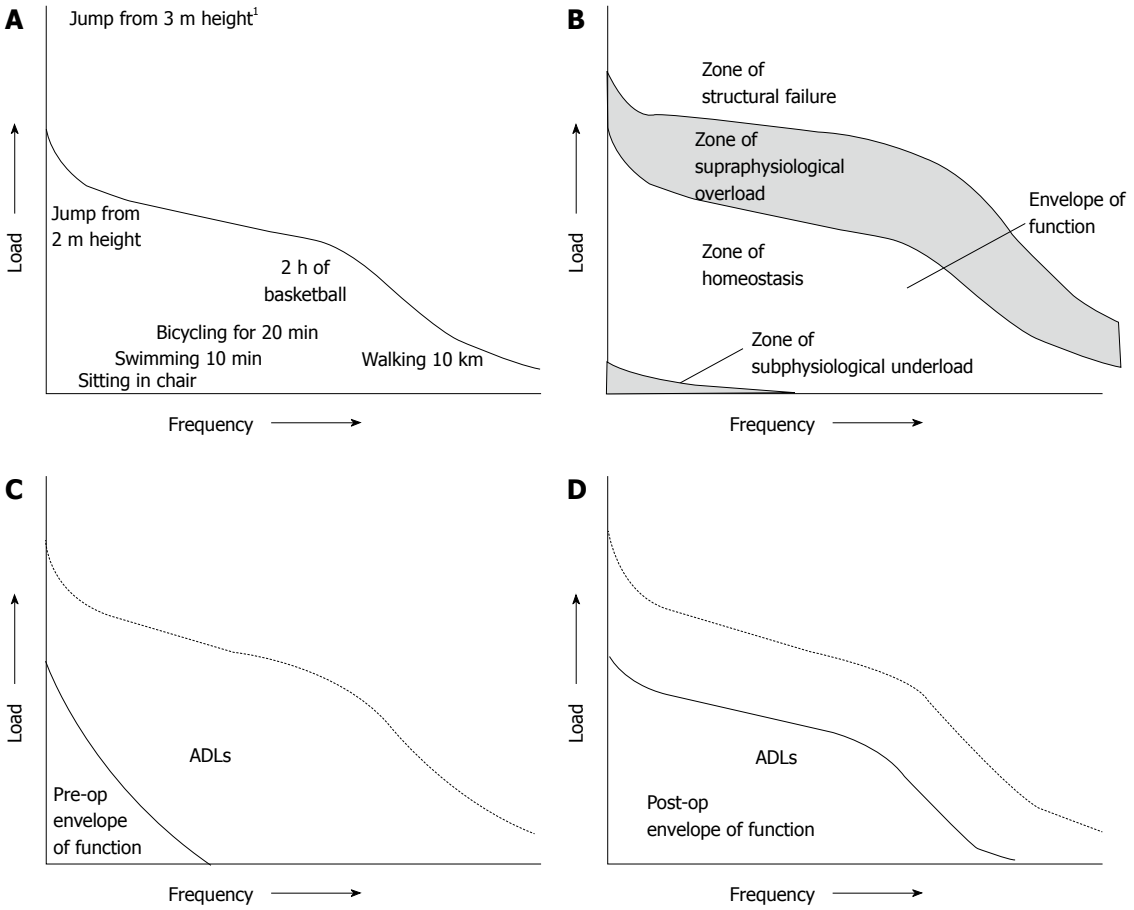

Figure 1 Applying Dye's theory to patients with Anterior Knee Pain after total knee arthroplasty provides useful insights. A: The potential range of activity or envelope of function for a specific joint: all activities fall within the zone of homeostasis except the jump from 3 m height[1]; B: The different zones of loading across the knee joint. The first zone is the zone of subphysiological underloading, the second is the preferred zone of tissue homeostasis, the third is the zone of supraphysiological overloading and the fourth is the zone of structural failure; C: Arthritis causes the potential range of activity (envelope of function) to become limited, causing pain and restrictions in daily activities such as walking and cycling. The dotted line is the original zone of homeostasis for this specific knee; D: The postoperative situation where total knee arthroplasty placement increases the potential range of activity but does not return it to the original range of activity. (Reprinted with permission from Dye *et al*[6]).

al[9] reported that combined component internal rotation is associated with lateral tracking followed by patellar tilting and potential patellar subluxation. Dislocation and component failure were reported when severe malrotation was present[9]. Barrack *et al*[8] studied the influence of malrotation on AKP and found a combined internal rotation had a relative risk of AKP which was five times higher than cases without combined component internal rotation. It is thought that a femoral component placed in internal rotation shifts and tilts the patella medially and this can have a negative influence on the PFJ[8,9,18,55]. This could be an important reason to explain why secondary resurfacing of the patella does not always solve AKP after TKA[34,58].

Without doubt the most studied aspect of AKP has been the influence of the patella, especially in relation to resurfacing[3,7,14,24,33,34,58-61]. Many studies have focused on patella resurfacing, some demonstrating no difference[4,14,22], some showing better results after resurfacing[1,3,17,24,33], and others advising against resurfacing[7,58,62]. It is known that simply resurfacing the patella is not a universal solution for AKP, although it may solve the problem in selected cases[3,4,7,14,16,58]. A meta analysis of 7 high quality studies showed no advantage for resurfacing the patella with regard to AKP[61]. Interesting publications from the Oxford group show that full thickness cartilage damage of the PFJ is not a contraindication for the placement of the medial Oxford mobile bearing knee arthroplasty, since this does not seem to influence the outcome or the revision rate[63,64]. It is still not clear why in a mobile bearing uni compartmental knee, PFJ arthritis does not seem to play an important role, whereas in a TKA it is a recurring debate. Maybe the influence of the intact anterior cruciate ligament (propriocepsis) is part of the AKP solution. Future research will hopefully provide new insights to these questions.

Finally, although soft tissue irritation is often related to malalignment, the mechanical cause cannot always be defined. Therefore, it may be that soft tissue problems play a significant role in AKP after TKA. Synovial impingement after TKA can play an important role in postoperative pain[65]. Two studies evaluated the influence of denervation of the patella and Van Jonbergen found a difference in favour of circumpatellar electrocautery

denervation[23]. One study found a lower prevalence of AKP due to the resection of Hoffa's fat pad[66]. Other factors contributing to AKP have been proposed; wear[21], referred pain[21,22], patella height[24,39], patellar thickness[67,68] and patella baja (pseudonaja), but these studies could not demonstrate a correlation with AKP after TKA. This is often more a lack of power than proof.

Applying Dye's theory to patients with AKP after TKA provides useful insights (Figure 1). The zone of homeostasis can then be seen as a zone without AKP. The zone of supraphysiological "overload" can be seen as the zone for abnormal loading of the PFJ and therefore a cause of AKP after TKA[6]. A good example of this is the relationship between malrotation and the severity of experienced AKP[8]. If the components of the TKA are malrotated, the knee tissues are overloaded and thus clearly functioning in a zone of abnormal loading rather than in the zone of homeostasis[6]. If this abnormal loading of the knee continues for long periods of time, a TKA can ultimately fail (*i.e.,* it enters the zone of structural failure)[6]. As mentioned by Berger *et al*[9], slightly combined component internal rotation is associated with lateral tracking of the patella followed by tilting and potential patellar subluxation and the knee is thus functioning in the zone of abnormal loading, which could lead to AKP after TKA. Dislocation and component failure were reported when severe malrotation of the components was present and thus the knee was functioning in the zone of structural failure[9].

If AKP is present after TKA placement, it is interesting to find out if it is possible to bring the knee back into a zone of homeostasis, and if this can influence the AKP. This can sometimes be achieved by conservative measures, for example in the study by Smith *et al*[42], where patients that were able to learn how to walk in a different way could reduce or even had no AKP, compared to patients who could not learn how. Other corrective measures include muscle-training (the quadriceps/hamstrings but also the hip and trunk muscles, therefore avoiding a dynamic valgus[25,43]), medication (painkillers), taping of the patella, using inlays or avoiding certain activities. If structural mechanical causes are present, revision surgery may be indicated, but caution is advised within the first 12 mo. This review will not focus on operative treatment options, as these are areas for separate review.

CONCLUSION

It can be concluded that anterior knee pain after TKA can be seen as the presenting symptom of a multifactorial problem. It is known that the nociceptive system is being activated by abnormal mechanical deformation, thermal stimuli or special chemical agents. The pain is caused by soft tissues (*i.e.,* retinaculum, infrapatellar fat pad and the synovial membrane) being overloaded and/or due to impingement; for example due to malrotation of the components, overstuffing of PFJ, instability of the PFJ or a combination. Simply changing to a mobile bearing, releasing the retinacula or resurfacing the patella does not seem to be a universal solution. A perfect placement of a well-designed TKA can minimize AKP, however it cannot be concluded that it will prevent AKP, due to the large number of different factors playing a role in the origin of AKP. It is suggested that clinicians determine the specific envelope of function or zone of tissue homeostasis for TKA patients. Future research should focus on making further progress towards understanding the complex interaction of factors causing AKP in order to find a solution to prevent and eliminate it. The recommendation of this study is that the main focus should be on determining the correct placement and maybe incorporating the ACL (if present) in TKA placement.

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TOPIC HIGHLIGHT

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Cartilage repair techniques of the talus: An update

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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

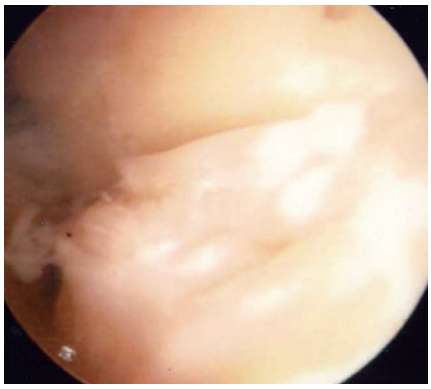

Figure 1 Arthroscopic view of an osteochondral lesion of the lateral shoulder of the talus.

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-

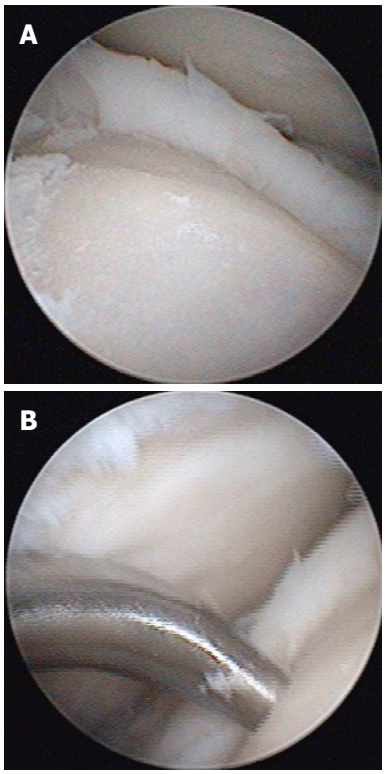

Figure 2 Chondral defect grade Ⅳ (A) of the lateral aspect of the talus, breaching the subchondral plate with an awl (B).

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].

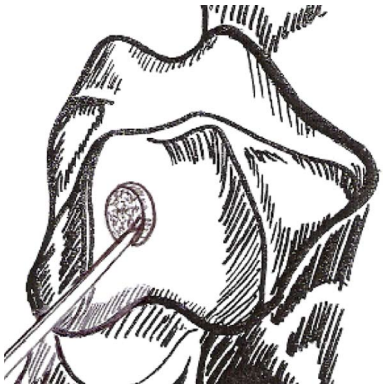

Figure 3 Schematic drawing: It is necessary to obtain a vertical and stable border of healthy cartilage after debridement of the cartilage defect.

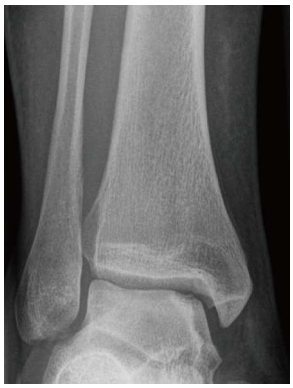

Figure 4 A.-P. radiograph of the ankle showing an osteochondral defect of the medial shoulder of the talus.

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

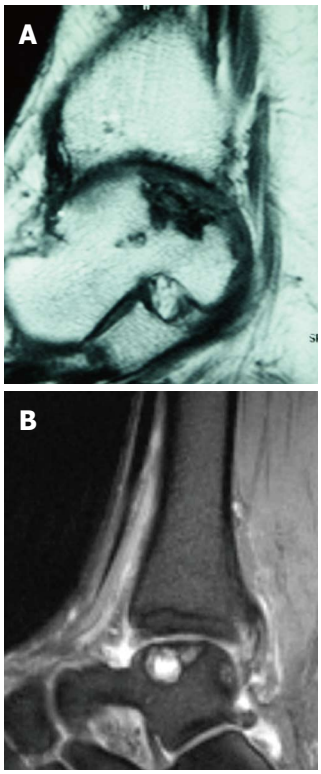

Figure 5 Sagittal T1 and T2-weighted magnetic resonance imaging scan. A: Sagittal T1-weighted magnetic resonance imaging scan demonstrating deep osteochondral defect of the posterior aspect of the talus; B: Sagittal T2-weighted magnetic resonance imaging scan showing the several cystic lesions of the 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.

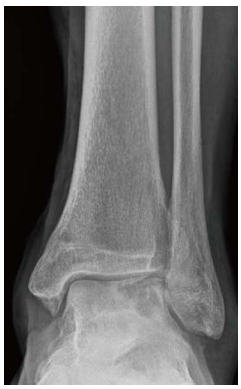

Figure 6 A.-P. radiograph of the ankle demonstrating a distinctive cystic lesion due to an osteochondral defect of the lateral shoulder of the talus.

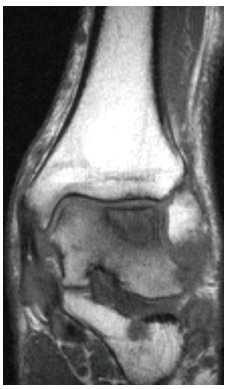

Figure 7 Sagittal T1-weighted magnetic resonance imaging scan demonstrating an osteochondral defect of the wholelateral aspect of the talus and a consecutive talar edema.

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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TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (4): Hip

Dual mobility cups in total hip arthroplasty

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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-

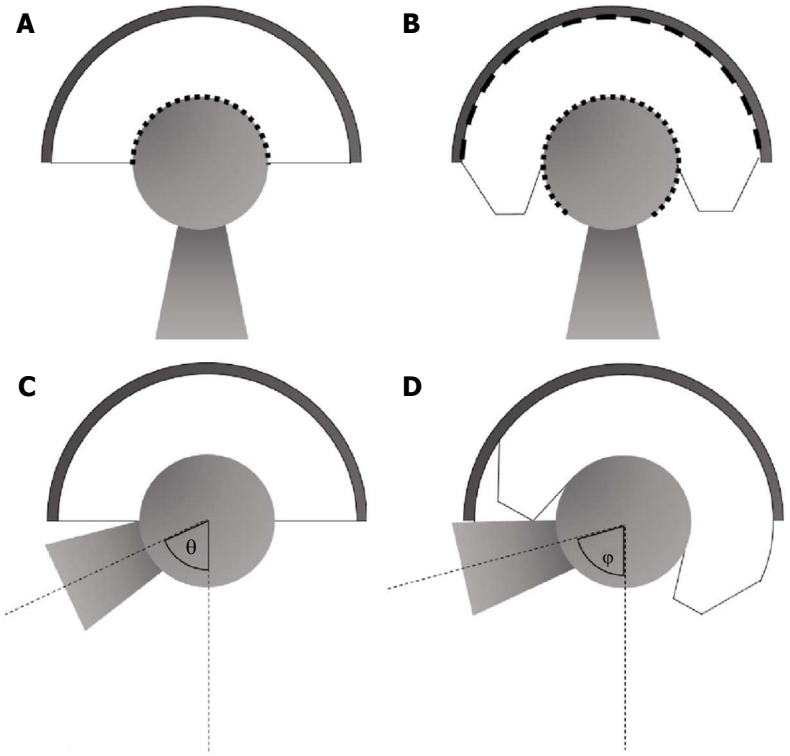

Figure 1 Standard cup *vs* dual mobility cup. Standard metal-on-polyethylene implants (A) include one articulation between the femoral head and the acetabular liner (dashed line). A dual mobility cup (B) consists of two distinct articulations, one between the femoral head and the liner, and another one 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

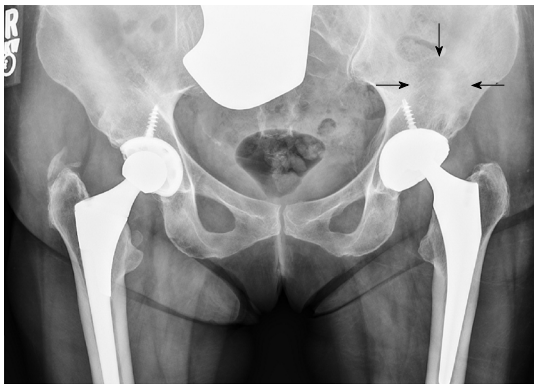

Figure 2 Bubble sign. AP pelvis radiograph of a patient with acute onset of left hip pain and limp. On the left, eccentric position of the femoral head within the dual mobility cup can be noted. Careful scrutiny reveals a circular radiolucent area superior to the acetabular component (arrows), which 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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TOPIC HIGHLIGHT

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New oral pharmacotherapeutic agents for venous thromboprophylaxis after total hip arthroplasty

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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.

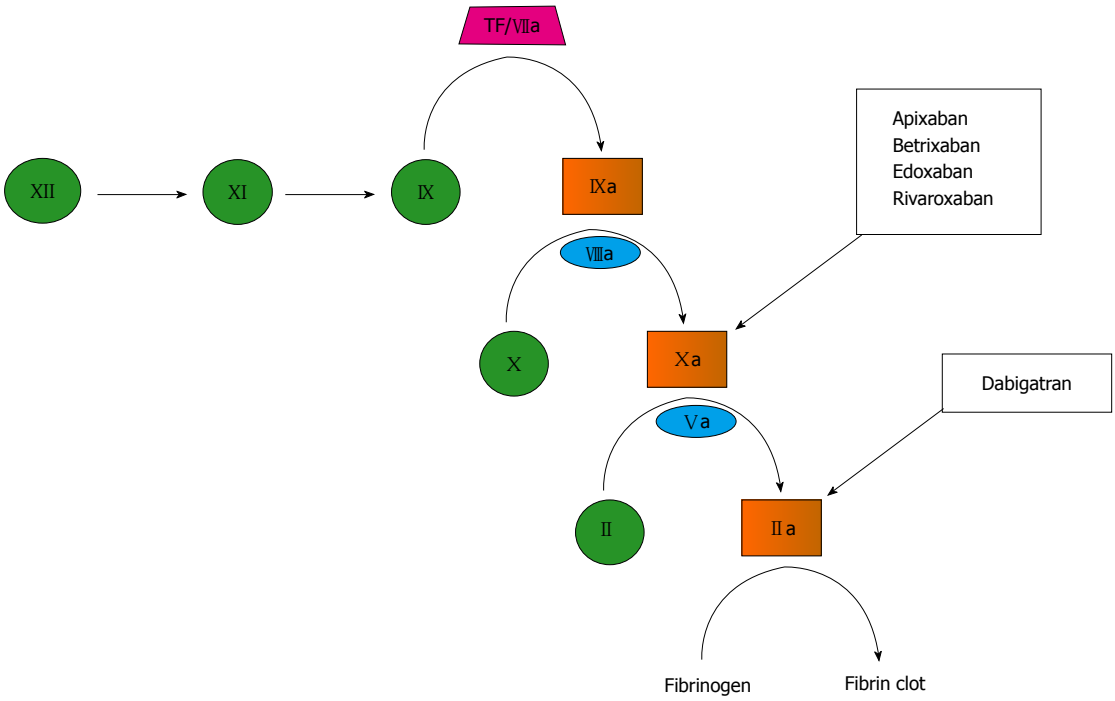

Figure 1 Coagulation cascade and site of target specific oral anticoagulants action.

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*c*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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TOPIC HIGHLIGHT

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Management of femoral neck fractures in the young patient: A critical analysis review

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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 fracture in the young adults. Additionally, it offers recommendations to guide the orthopedic surgeon in the management of femoral neck fracture 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 the young patient with a femoral neck fracture 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 of 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

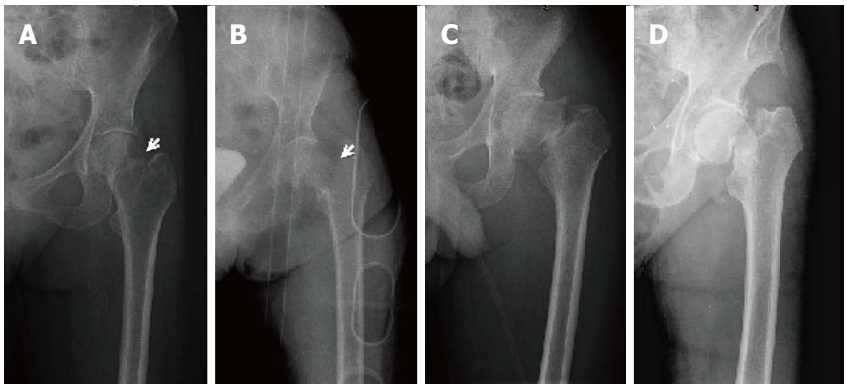

Figure 1 Garden classification. A: Incomplete fracture of the femoral neck with valgus impacon. Note the radiopaque overlap of the femoral neck and head; B: Displaced complete fracture of the femoral neck; C: Less than 50% displacement of a complete fracture of the femoral neck; D: Complete fracture 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 fracture (Garden Ⅰ-Ⅱ), Raatmakers *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 outcomes 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 fracture 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 trial 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 fracture 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 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

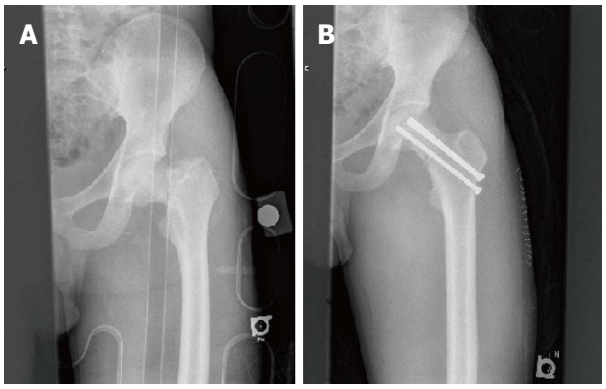

Figure 2 Cannulated screw fixation. A: Anterior posterior view; B: Anterior posterior view with cannulated screw.

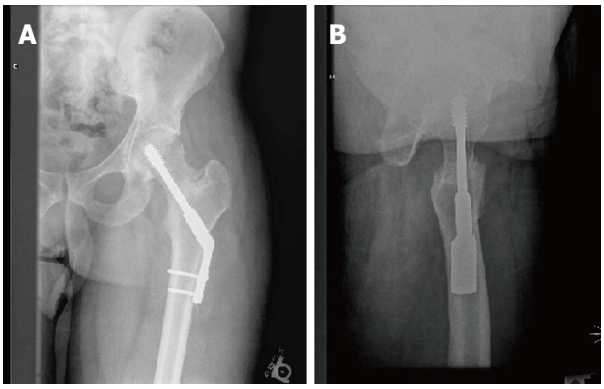

Figure 3 Dynamic hip screw fixation. A: Anterior posterior view with 2 holes 135° dynamic hip screw; B: Lateral view of 2 holes 135° dynamic hip screw.

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 outcomes 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 fracture. 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

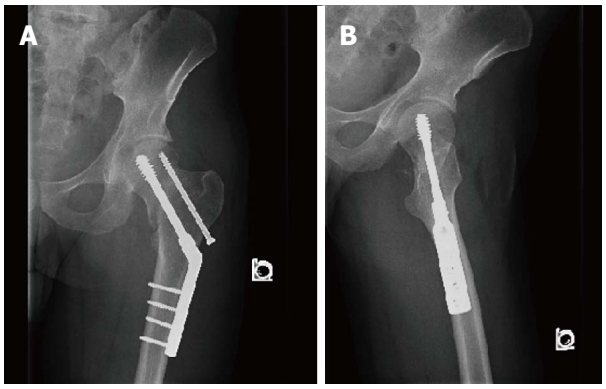

Figure 4 Dynamic hip screw with derotation screw. A: Anterior posterior view pre-operative of 4 holes 145° dynamic hip screw; B: Lateral view pre-operative of 4 holes 145° dynamic hip screw.

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 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

decompression fails[111]. It is 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 the femoral head and preservation the hip joint is preferable. This can be achieved by either improving the mechanical environment to favor healing by attempting valgus-producing osteotomies or 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] has 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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TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (4): Hip

Can periprosthetic hip joint infections be successfully managed by debridement and prosthesis retention?

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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.

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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].

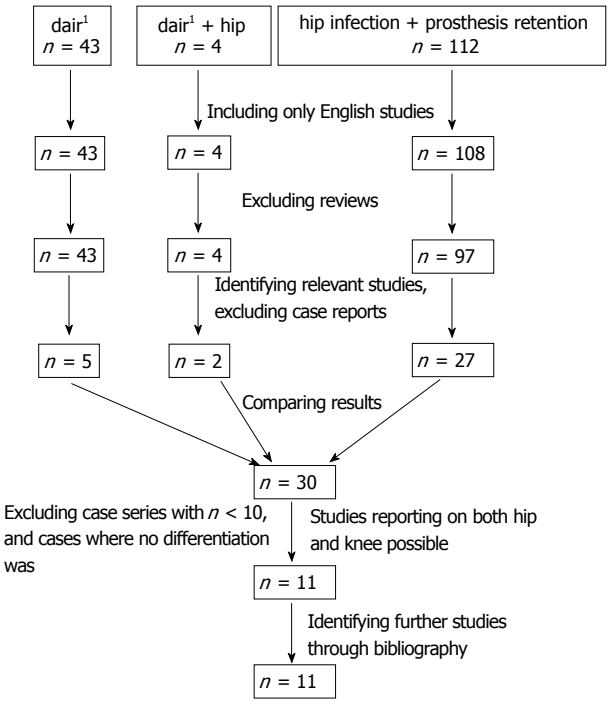

Figure 1 Flow chart diagram showing the single steps of literature search for identification of relevant studies. [1]dair: Debridement, antibiotics, irrigation, and retention.

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.

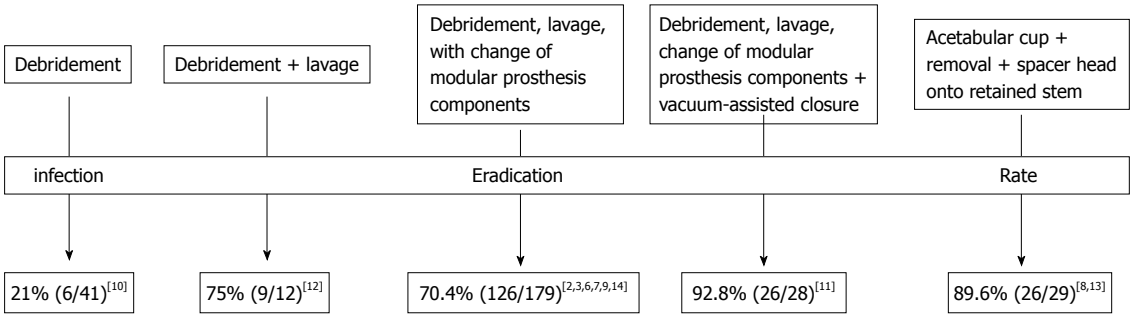

Figure 2 Overview of treatment procedures for management of periprosthetic hip joint infections.

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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TOPIC HIGHLIGHT

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Perioperative pain control after total knee arthroplasty: An evidence based review of the role of peripheral nerve blocks

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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 adducctor 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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TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (5): Knee

Treatment of meniscal tears: An evidence based approach

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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.

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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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

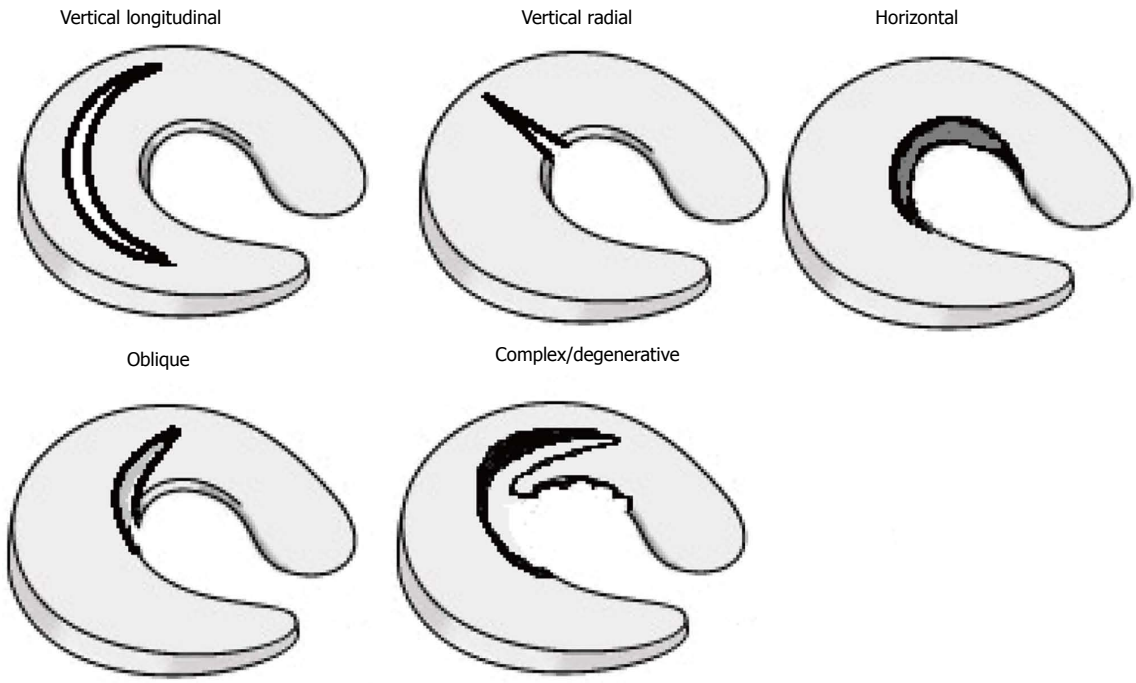

Figure 1 Meniscal tear patterns.

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-

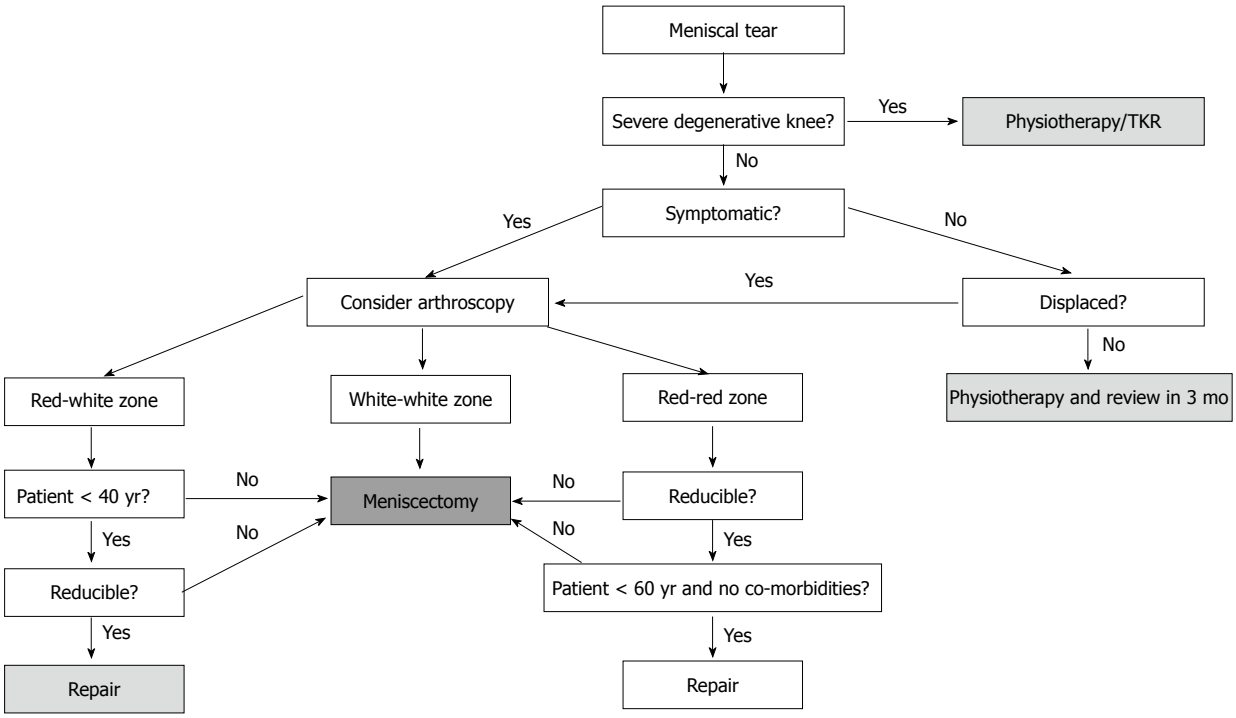

Figure 2 Meniscal tear management tree.

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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TOPIC HIGHLIGHT

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

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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.

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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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TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (6): Osteoporosis

Bone anabolics in osteoporosis: Actuality and perspectives

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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

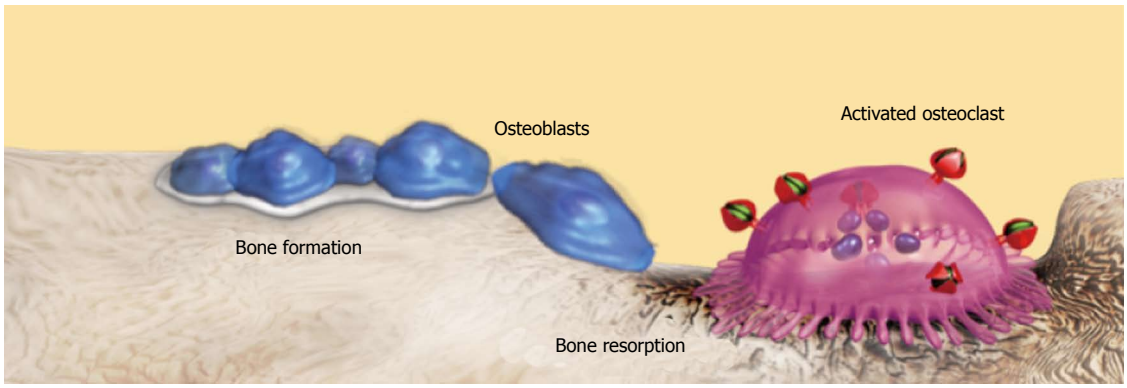

Figure 1 Osteoblasts and osteoclasts are close related in determining bone formation and bone resorption (bone turnover) that maintain the quantitative and qualitative characteristics of bone.

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,

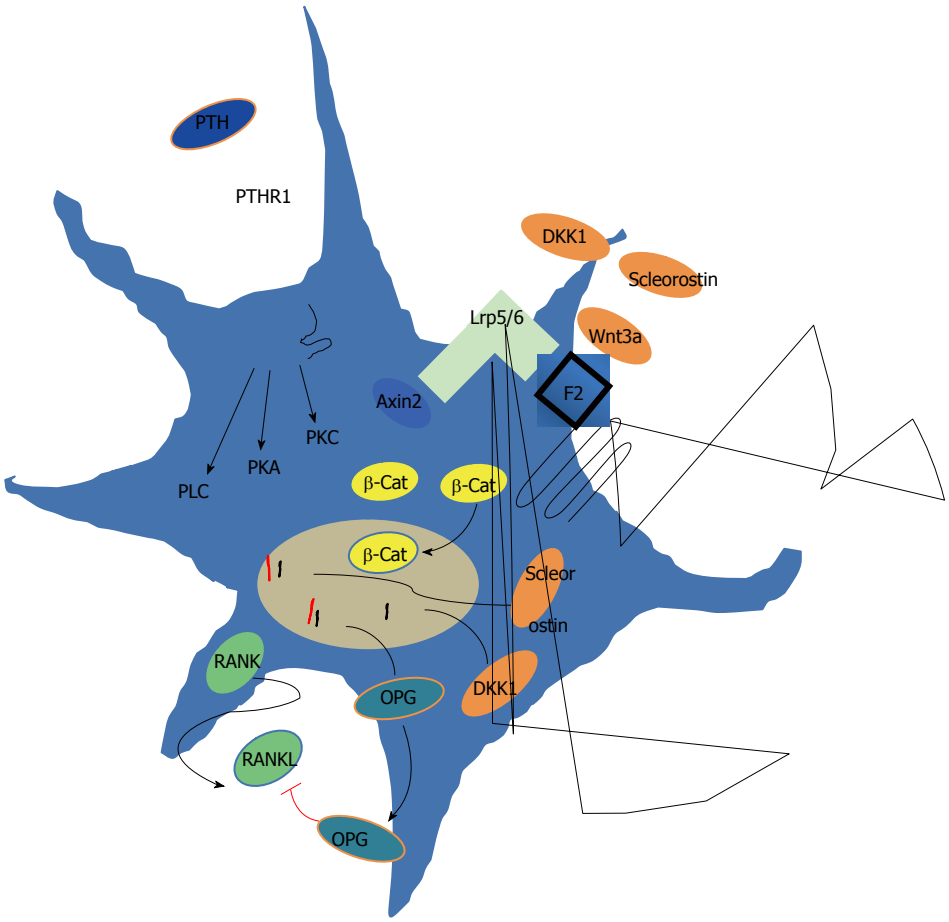

Figure 2 Signaling and cross talk of the parathyroid hormone and Wnt signaling pathways in the late osteoblast (osteocyte). Parathyroid hormone (PTH) binds to its seven-transmembrane-spanning receptor and activates phosphatidyl inositol-specific phospholipase C (PLC), cAMP-dependent protein kinase A (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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TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (7): Shoulder

Reverse polarity shoulder replacement: Current concepts and review of literature

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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

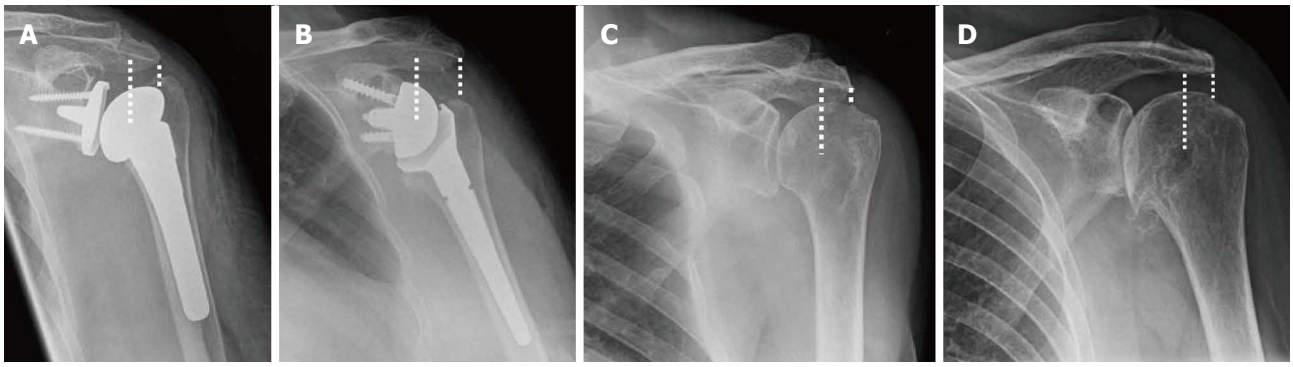

Figure 1 Shoulder replacement, shoulder with native glenohumeral joint and osteoarthritis. A: Following total shoulder replacement; B: Following reverse shoulder replacement. The interval between the two plumb lines is wider than in Figures 1A, C and D, indicating medialisation of the center of shoulder 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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TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (8): Spine

Scoring system for prediction of metastatic spine tumor prognosis

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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.

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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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TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (9): Myeloma

Imaging of multiple myeloma: Current concepts

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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].

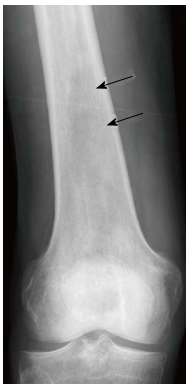

Figure 1 X-ray of an osseous myeloma lesion. Conventional X-ray of the right femoral bone showing an osteolytic lesion (arrows) representing an osseous myeloma manifestation.

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

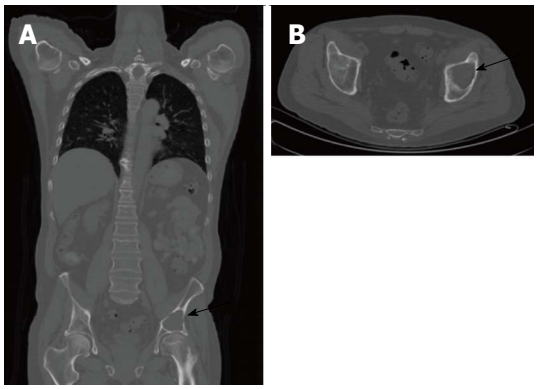

Figure 2 Computed tomography of an osseous myeloma lesion. Computed tomography in coronal (A) and transversal views (B) showing an osteolytic lesion in the left iliac bone (arrows) representing an osseous myeloma manifestation.

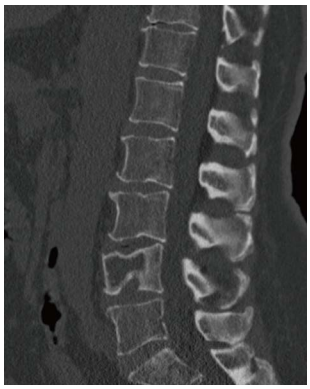

Figure 3 Computed tomography of an osseous myeloma lesion. Computed tomography in sagittal view showing an osteolytic lesion in L4 with associated pathologic fracture.

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

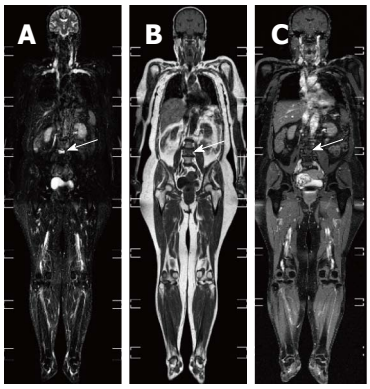

Figure 4 Whole-body magnetic resonance imaging of an osseous myeloma lesion. Whole-body magnetic resonance imaging: short-tau-inversion-recovery sequence (A), T1-weighted image (B) and T1-weighted image with fat suppression after contrast administration (C) showing an osseous lesion in L4 (arrows) representing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

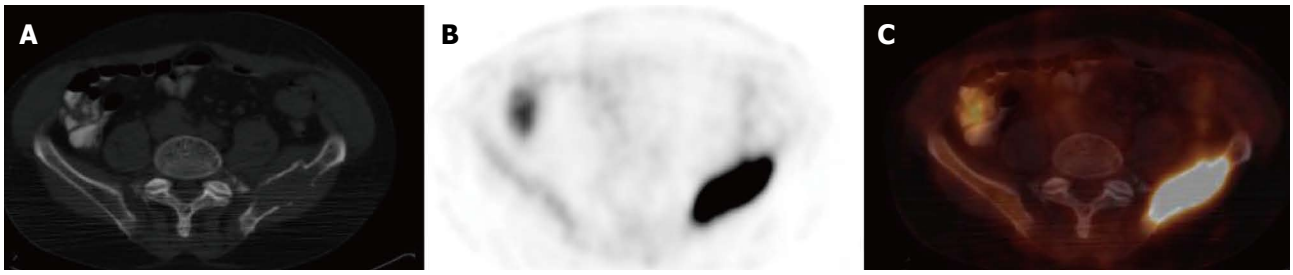

Figure 5 Positron emission tomography/computed tomography of an osseous myeloma lesion. Transversal computed tomography (CT) (A), ^{18}F-fluorodeoxyglucose positron emission tomography (PET) (B) and fused PET/CT (C) showing an osteolytic lesion in the left iliac bone with cortical destruction representing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

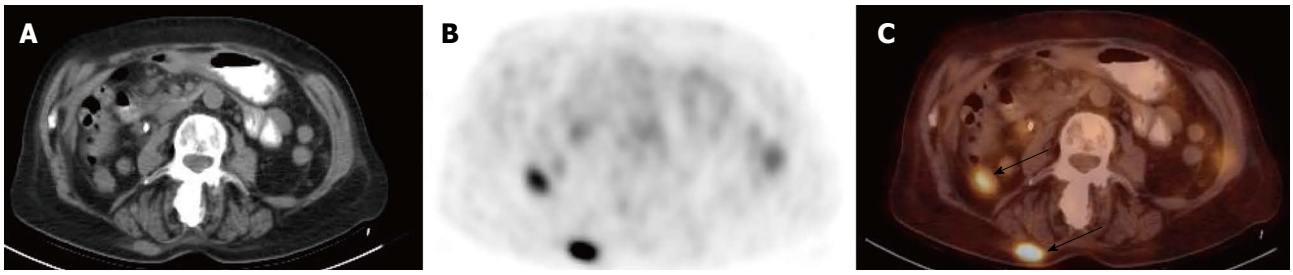

Figure 6 Positron emission tomography/computed tomography of extraosseous myeloma lesions. Transversal computed tomography (CT) (A), ^{18}F-fluorodeoxyglucose positron emission tomography (PET) (B) and fused PET/CT (C) showing extraosseous myeloma manifestations (arrows).

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-

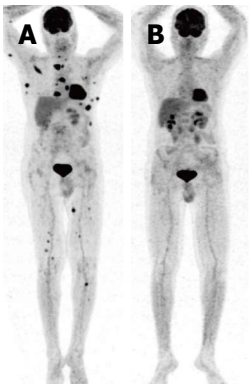

Figure 7 Positron emission tomography for therapy monitoring. Whole-body maximum-intensity-projection positron emission tomography (PET) images before and after stem cell transplantation showing extensive osseous and extraosseous myeloma manifestations before therapy (A) and complete resolution on PET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

WJO 5th Anniversary Special Issues (10): Rheumatoid arthritis

Perioperative management of the patient with rheumatoid arthritis

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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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TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (10): Rheumatoid arthritis

Advances in the treatment of cervical rheumatoid: Less surgery and less morbidity

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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

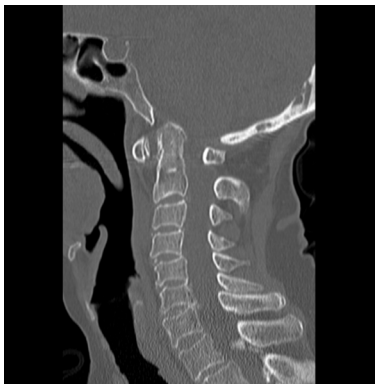

Figure 1 Sagittal computed tomography of the cervical spine of an 82-year-old female with rheumatoid arthritis and neck pain with cranial settling.

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].

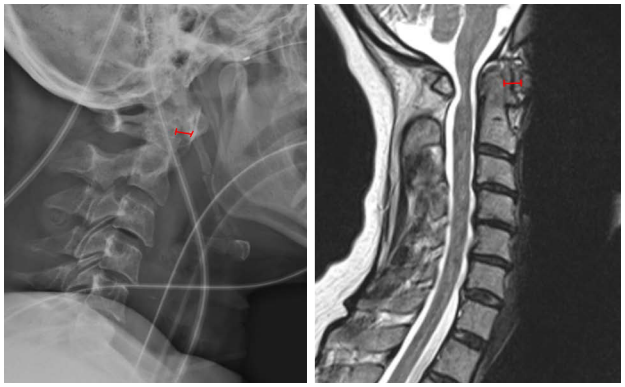

Figure 2 Lateral X-ray (left) and sagittal magnetic resonance imaging (right) of a 52-year-old with atlantoaxial subluxation. Left: Lateral X-ray; Right: Sagittal Magnetic resonance imaging. The anterior atlantodental interval is shown (red line).

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

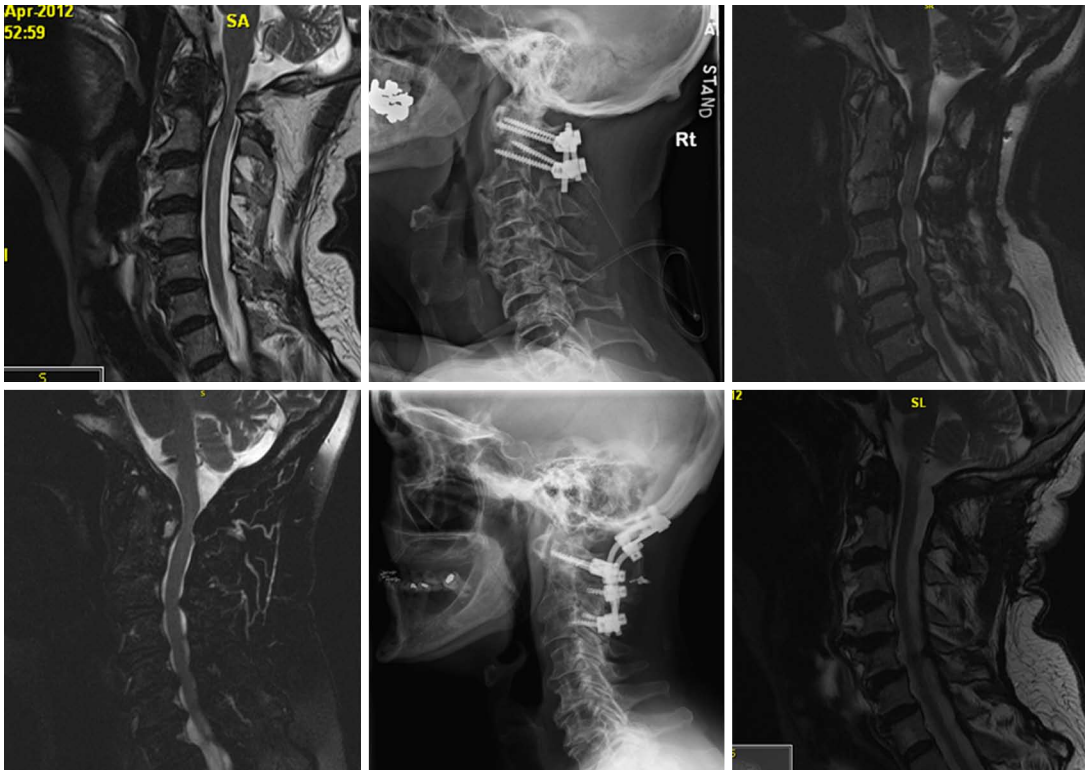

Figure 3 Resolving rheumatoid pannus after occipital cervical (top) and C1-2 fusion (bottom). Left: Preoperative magnetic resonance imagings; Middle: Postoperative lateral X-ray; Right: Postoperative magnetic resonance imagings.

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-

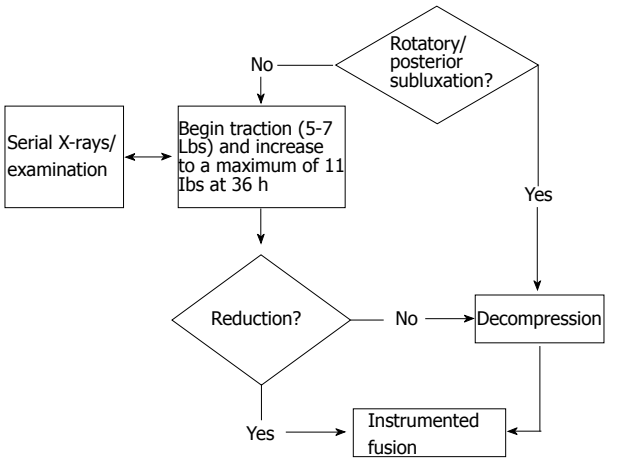

Figure 4 Preoperative traction and surgical approach to cervical rheumatoid.

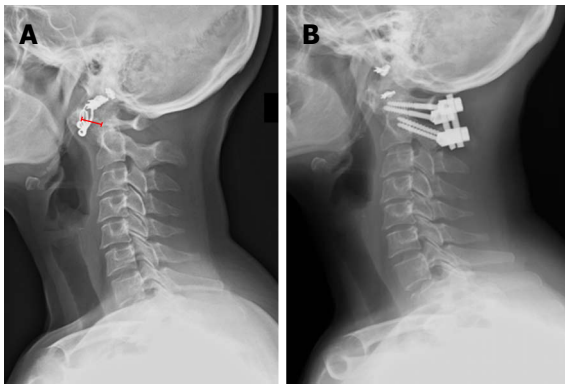

Figure 5 Lateral X-ray images of the spine before (A) and after (B) surgical intervention. The anterior atlantodental interval is shown (red line).

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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TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (10): Rheumatoid arthritis

Inflammation, lipid metabolism and cardiovascular risk in rheumatoid arthritis: A qualitative relationship?

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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

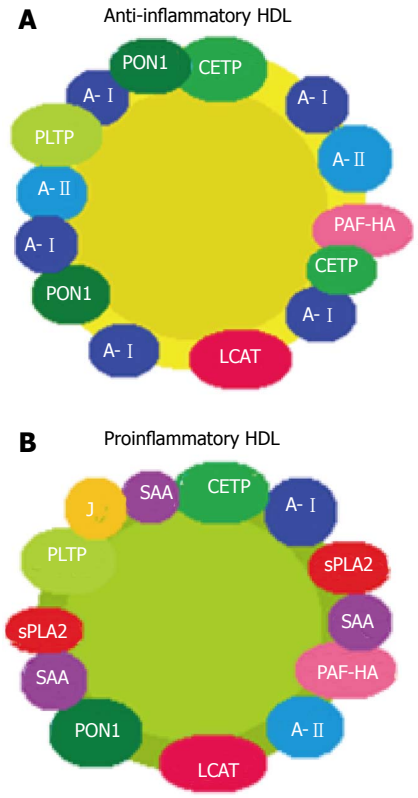

Figure 1 Structural change from normal protective anti-inflammatory high-density lipoproteins (A) to proinflammatory high-density lipoproteins (B) in the context of inflammation. A- Ⅰ: Apolipoprotein A Ⅰ; A- Ⅱ: Apolipoprotein A Ⅱ; J: Apolipoprotein J; PON1: Paraoxonase 1; PLTP: Phospholipid transfer 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

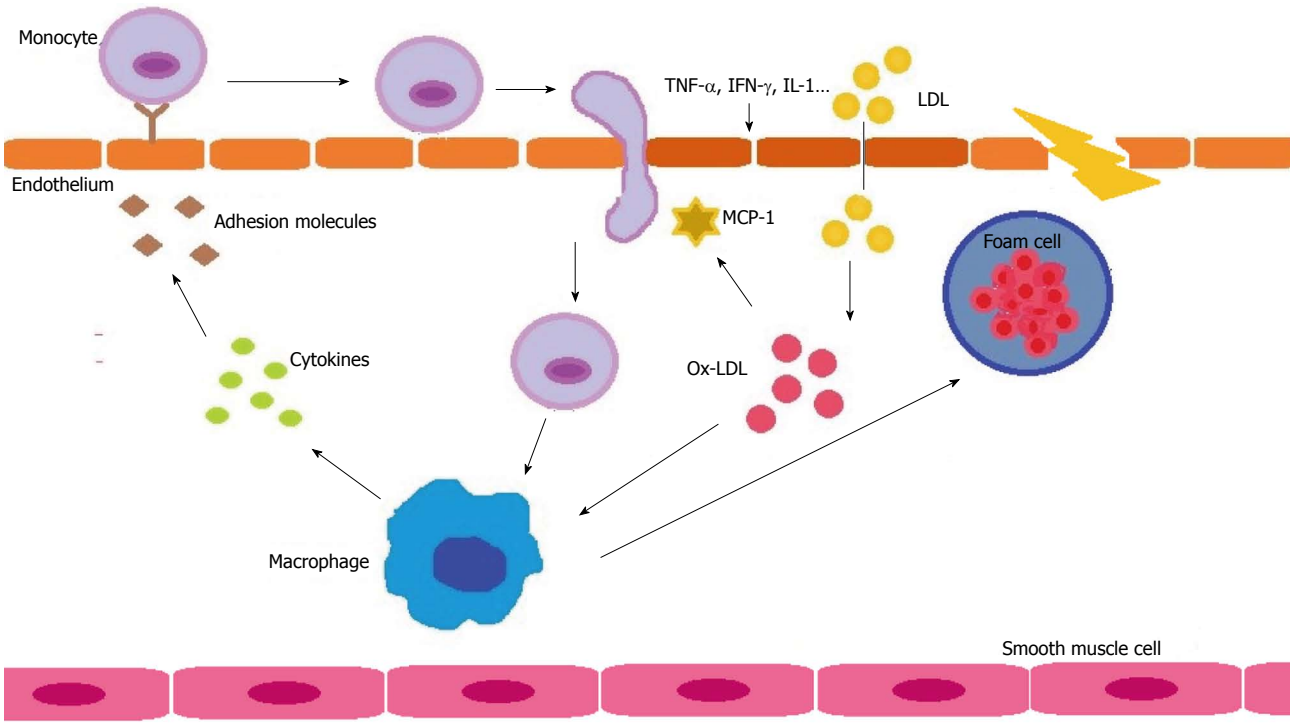

Figure 2 Oxidation of low-density lipoprotein in the context of inflammation to produce atherosclerosis (see text). Ox-LDL: Oxidation of low-density lipoprotein; MCP-1: Monocyte chemotactic protein-1; TNF-α: Tumor necrosis factor α; IFN-γ: Interferon γ; IL-1: Interleukin-1.

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

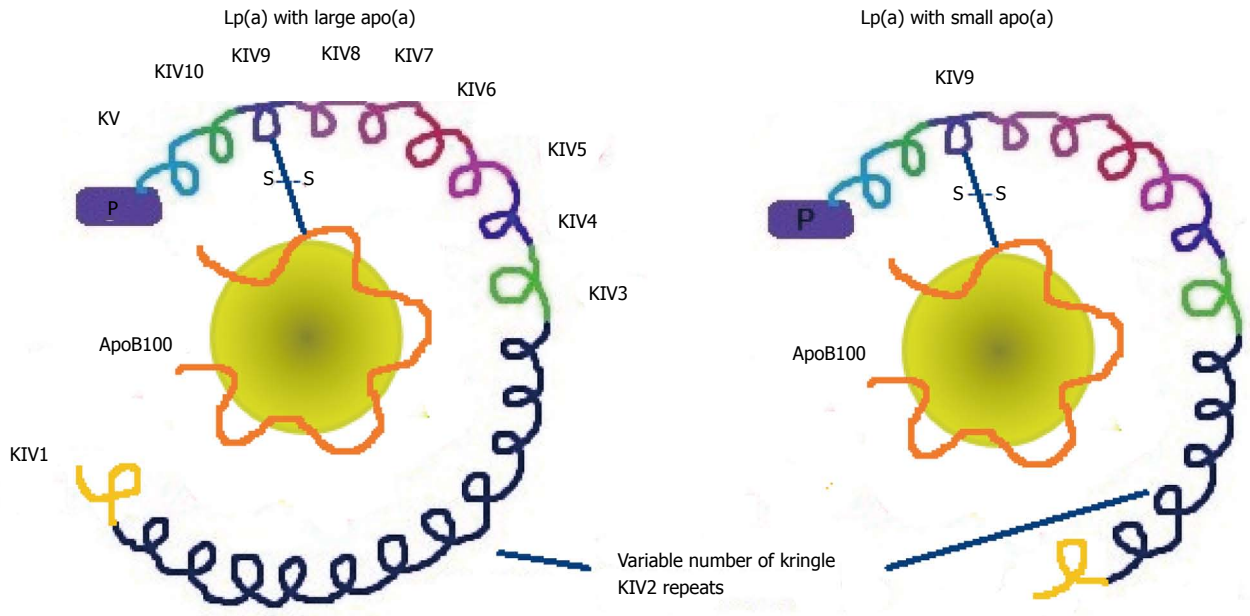

Figure 3 Outline of the different lipoprotein (a) sizes depending on apolipoprotein (a) size, which in turn depends on the number of copies of one of the domains of the protein, the Kringle Ⅳ type 2. Apo(a) is formed by 10 different types of plasminogen Kringle Ⅳ-like repeats and also contains other 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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TOPIC HIGHLIGHT

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Rheumatoid arthritis: Nuclear medicine state-of-the-art imaging

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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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TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (10): Rheumatoid arthritis

Adipokines: Biomarkers for osteoarthritis?

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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-day 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

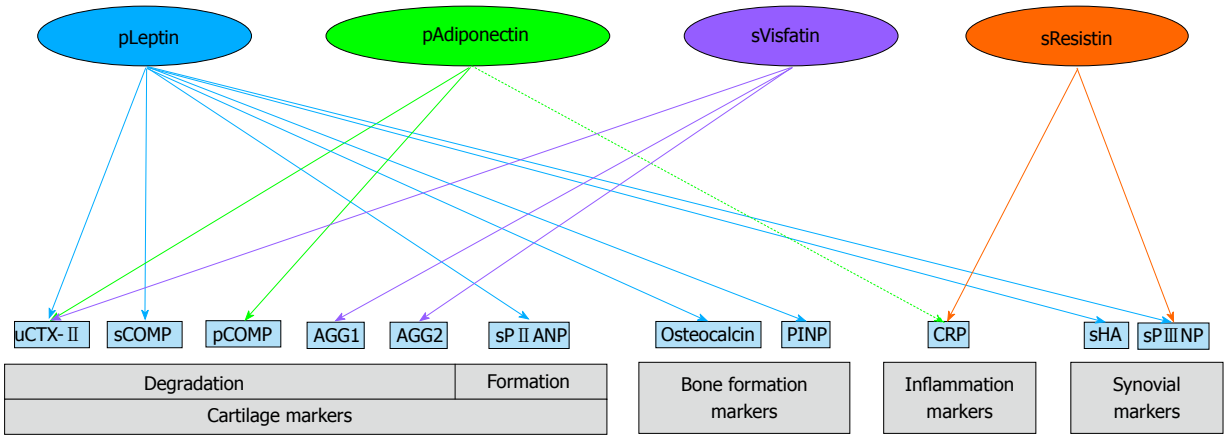

Figure 1 Association between adipokines and other osteoarthritis biomarkers. Solid lines represent positive association; dashed lines represent negative association. AGG: Aggrecan; PINP: N-terminal type Ⅰ procollagen propeptide; COMP: Cartilage oligomeric matrix protein; CRP: C-reactive protein; CTX-Ⅱ: 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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REVIEW

Beyond the joint: Subclinical atherosclerosis in rheumatoid arthritis

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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

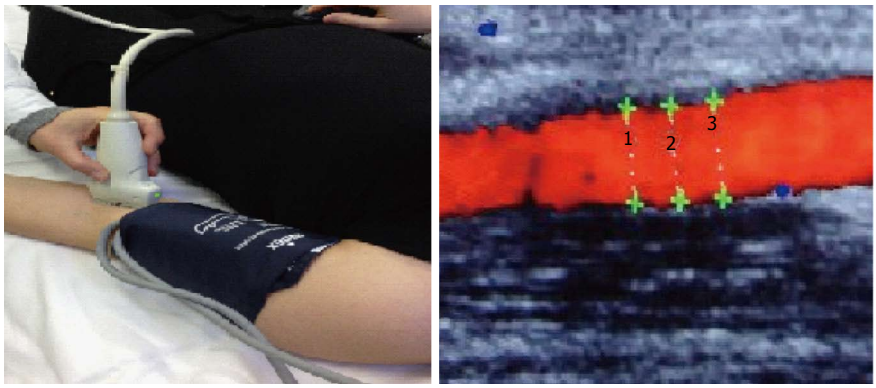

Figure 1 Flow mediated dilatation is based on the reactive phenomenon that occurs when arterial blood flow is restored after a period of transient arterial occlusion using a sphygmomanometer. This reactive hyperaemia is observable at ultrasound power Doppler mode monitor.

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

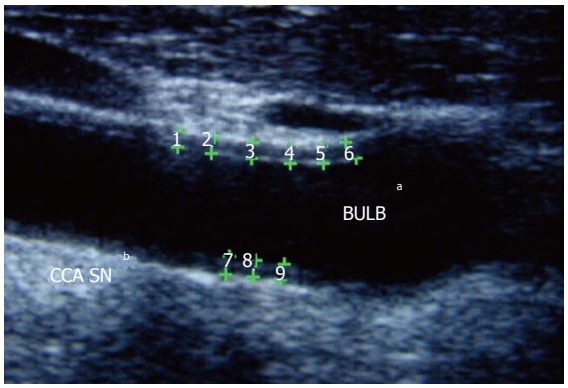

Figure 2 B-mode ultrasound measurement of carotid intima media thikness in patient with Rheumatoid Arthritis. [a]BULB: Carotid bulb; [b]CCA SN: Left common carotid arteria.

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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REVIEW

Perioperative outcomes and type of anesthesia in hip surgical patients: An evidence based review

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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 collec-

tion. 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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REVIEW

Superior labrum anterior to posterior lesions of the shoulder: Diagnosis and arthroscopic management

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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.

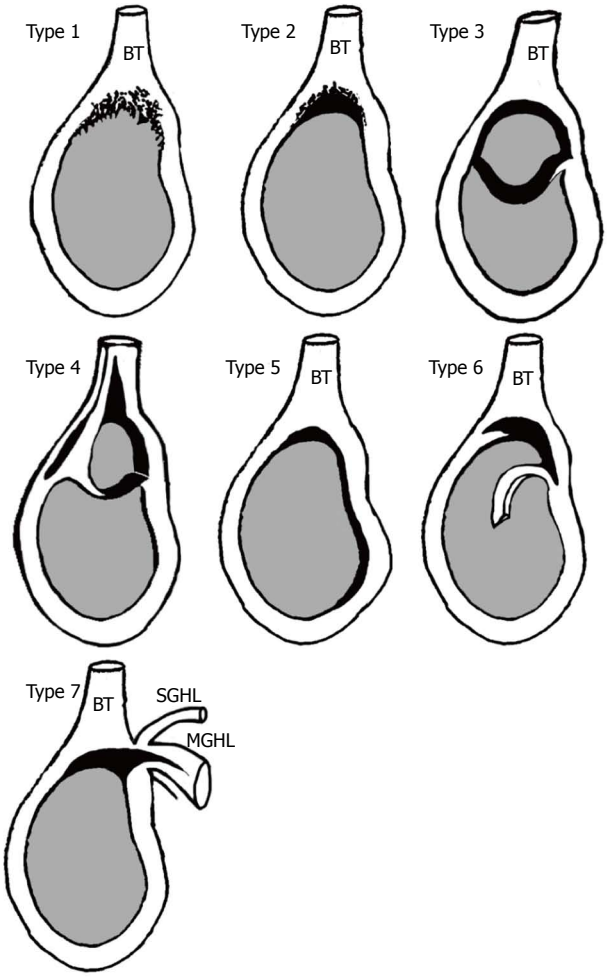

Figure 1 Superior labrum anterior to posterior tear classification. Type 1: Degenerative fraying of the superior labrum, biceps anchor is intact; Type 2: Superior labrum and biceps tendon detachment from glenoid rim; Type 3: Bucket-handle tear of labrum with intact biceps anchor; Type 4: Bucket-handle 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].

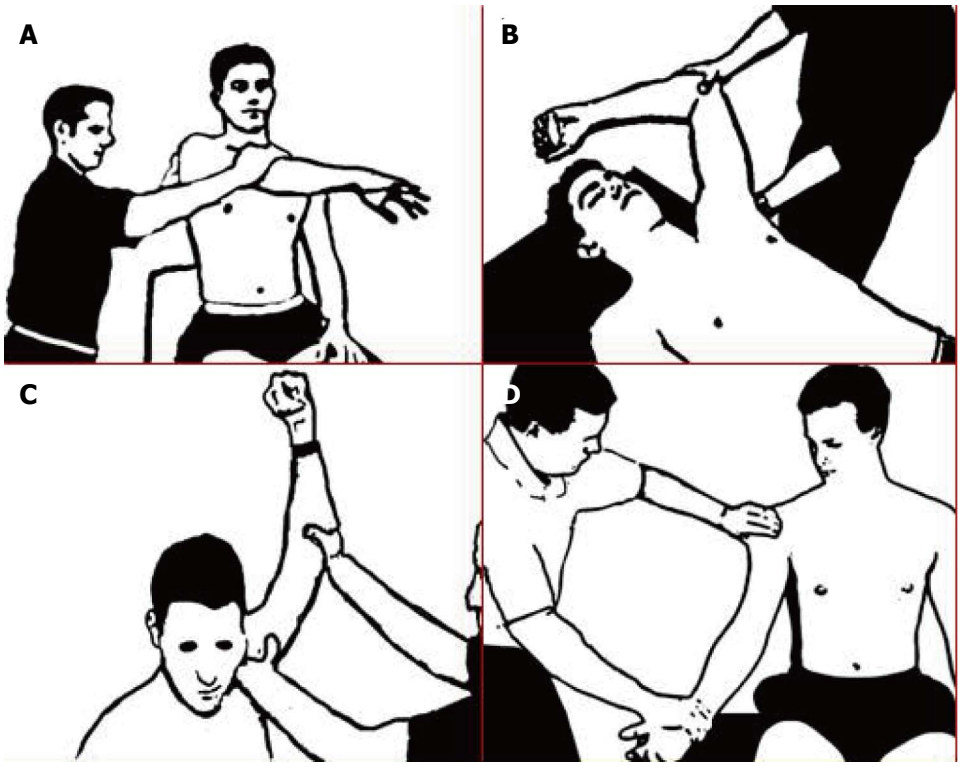

Figure 2 Physical examination tests described to detect a superior labrum anterior to posterior injury. A: O'Briens's test. When the patient sitting with 90° of shoulder flexion and 10° of horizontal adduction, completely internally rotates the shoulder and pronates at the elbow. The physician applies 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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REVIEW

Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis

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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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REVIEW

Identification and preoperative optimization of risk factors to prevent periprosthetic joint infection

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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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RETROSPECTIVE STUDY

Primary total elbow arthroplasty in complex fractures of the distal humerus

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Abstract

AIM: To evaluate short- to medium term outcome of total elbow arthroplasty (TEA) in complex fractures of the distal humerus.

METHODS: A consecutive series of 24 complex distal humerus fractures operated with TEA in the period 2006-2012 was evaluated with the Mayo Elbow Performance score (MEPS), plain radiographs, complications and overall satisfaction. The indications for surgery were 1: AO type B3 or C3 or Sheffield type 3 fracture and age above 65 or 2: fracture and severe rheumatoid arthritis. Mean follow-up time was 21 mo.

RESULTS: Twenty patients were followed up. Four patients, of which 3 had died, were lost to follow up. According to the AO classification there were 17 C3, 1 B2 and 2 A2 fractures. Mean follow-up was 21 months (range 4-54). Mean MEPS was 94 (range 65-100). Mean flexion was 114 degrees (range 80-140). According to MEPS there were 15 excellent, 4 good and 1 fair result. Patient satisfaction: 8 excellent, 10 good, 2 fair and 1 poor. There were two revisions due to infection treated successfully with revision and three months of antibiotics. In two patients the locking split had loosened. One was referred to re-insertion and one chose yearly controls. Two patients had persistent dysaesthesia of their 5th finger, but were able to discriminate between sharp and blunt.

CONCLUSION: Our study suggests that TEA in complex fractures of the distal humerus in elderly patients can result in acceptable short- to medium term outcome.

Key words: Elbow arthroplasty; Distal humeral fracture; Elbow prosthesis; Elbow replacement; Humeral fractures

Core tip: The number of distal humerus fractures in the elderly has increased in the last decades. The results after open reduction internal fixation in elderly with complex fractures of the distal humerus are highly variable with many failures and often poor outcome. We retrospectively reviewed a consecutive series of patients treated with total elbow arthroplasty (TEA) for complex fractures of the distal humerus. Our aim was to report short- to medium-term outcome. According to the Mayo Elbow Performance Score there were 15 patients with excellent results, 4 good, 1 fair and none poor. Our study suggests that TEA on fractures of the distal humerus in elderly patients can result in acceptable short- to medium-term outcome.

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INTRODUCTION

The number of distal humerus fractures in the elderly has

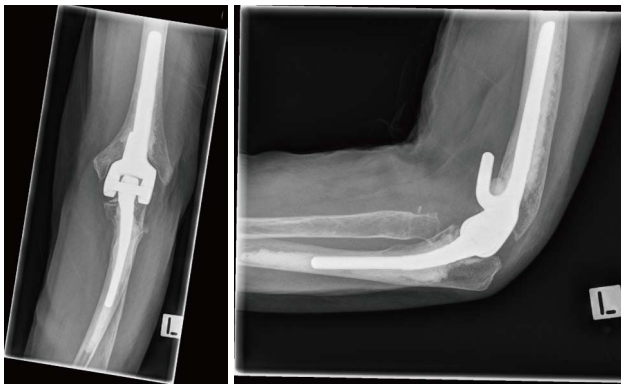

Figure 1 Post-operative X-ray.

increased in the last decades**.** Palvanen *et al*[1] reported that in Finnish women the annual rate of osteoporotic fractures of the distal humerus increased from 11 per 100000 in 1970 to 30 per 100000 in 1995 with a 9-fold increase in women aged > 80 years. In elderly patients with poor bone quality the fractures are often complicated by multiple fragments and articular involvement which can lead to pain, joint stiffness and impaired elbow function. The results after open reduction internal fixation (ORIF) in elderly with complex fractures of the distal humerus are highly variable with many failures and often poor outcome[2-9].

Studies have reported good results of primary total elbow arthroplasty (TEA) in the treatment of complex distal humerus fractures in the elderly[10-20]. Data from these studies shows that out of 194 operated elbows 10 (5.2%) received component revision. Ten (5.2%) were treated for varying degrees of infection. Sixteen (8.2%) had varying degree of ulnar nerve symptoms. The mean Mayo Elbow Performance Score (MEPS) was 91.

To our knowledge only 2 studies compare ORIF with TEA in treatment of distal humerus fractures. Frankle *et al*´s[16] retrospective review compares 12 ORIF´s with 12 TEA´s in patients older than 65. They found that 25% of the ORIF group was converted to TEA due to fixation failure. According to the MEPS 67% scored excellent or good in the ORIF group whereas 100% in the TEA Group scored excellent or good[16]. McKee *et al*´s[20] prospective, randomized trial compares 20 patients in each group ORIF/TEA with a mean age of 78. They found that 25% of the ORIF was intra-operatively converted to TEA. According to MEPS 53% of the ORIF group scored excellent or good whereas 100% in the TEA group scored excellent or good[20].

We retrospectively reviewed a consecutive series of patients treated with TEA for complex fractures of the distal humerus. Our aim was to report short- to medium-term outcome after total elbow arthroplasty on complex fractures of the distal humerus.

MATERIALS AND METHODS

Between January 2006 and October 2012, we treated 24 patients with primary total elbow arthroplasty for complex fracture of the distal humerus using the Coonrad-Morrey semi-constrained prosthesis. Twenty out of 24 patients were retrospectively reviewed. Three patients had died and one we were not able to reach: The indications for surgery were 1: AO type B3 or C3 or Sheffield type 3 fracture and age above 65 or 2: fracture and severe rheumatoid arthritis. Two patients were younger than 65. They were both planned to have ORIF but were intra-operatively converted to arthroplasty because of inability to reach an acceptable reduction and fixation of the multiple fragments of the fracture. 17 patients had a type C3 fracture according to AO classification[21], 2 had type A2 fracture and 1 had a B3 fracture. According to the Sheffield classification[22] 18 had a type 3 fracture, 2 had a type 1 fracture. Two patients also suffered an ipsilateral olecranon fracture. Mean age was 77 (range, 55-95). Fifteen fractures involved the dominant extremity and five the non-dominant extremity. The mean interval between injury and operation was 9.1 d (range 1-22) and the mean postoperative stay was 1.8 d (range 1-4). Mean follow-up time was 21 months (range 4-52).

Nineteen patients were clinically examined and interviewed by the first author. 1 patient was interviewed by phone and did not have clinical function measured or radiographs taken. Clinical function was reviewed using the Mayo Elbow Performance Score[23]. Furthermore patients were asked to rate their overall satisfaction on a four-part ranking scale: "poor", "fair", "good" or "excellent". The range of motion was measured using a hand-held goniometer[24]. Stability of the joint was determined based on history and physical examination. Radiographs were taken within few days of the clinical examination. They were evaluated to determine radiolucent lines. Primary radiographs and in some cases CT-scans were reviewed to classify the fractures

Technical details

The Coonrad-Morrey semi-constrained total elbow prosthesis was used in all cases[25] (Figure 1). The patients were placed in a lateral supine position. A tourniquet was used. A midline skin incision was made and the ulnar nerve identified and protected throughout the procedure. The triceps was split by a reversed Y-shaped incision. The radial head was excised to the level of the annular ligament. The distal humerus was then resected and the humeral and ulnar medullary canals were reamed. Trial components were inserted and range of motion was checked. Then the canals were cemented and the prosthesis inserted and assembled. The triceps were sutured and the skin closed in layers. An extension splint was used for two weeks to allow wound healing. Physiotherapy was begun at day 14 d postoperative.

In one case the patient prior had an ipsilateral olecranon fracture, treated with two Kirschner wires and cerclage. The osteosynthesis material was left *in situ* during the implantation of the TEA. In another case the patient at the trauma sustained an ipsilateral olecranon fracture and intercondylar distal humerus fracture. In this case the

Table 1 The Mayo Elbow Performance Score

	Points	No. of elbows	Mean score points
Pain (maximum 45 points)			
None	45	15	
Mild	30	4	
Moderate	15	1	
Severe	0		41
Range of movement, degrees (maximum 20 points)			
Arc > 100	20	17	
Arc 50 to 100	15	3	
Arc < 50	5		19
Stability (maximum 10 points)			
Stable	10	20	
Moderate unstable	5		
Grossly unstable	0		10
Function (maximum 25 points)			
Comb hair	5	19	
Feed oneself	5	20	
Personal hygiene	5	19	
Put on shirt	5	20	
Put on shoes	5	20	25
Mean total (maximum 100)			94

Table 2 Data sheet

Age	Gender	Affected side (Dominant extr.)	Classification (AO)	Associated diagnosis	Days at hospital after surgery	Complications	Arc of flexion (sum - degrees)	Rotation (Degrees)	MEPS
79	F	R (R)	B3		1	Ulnar palsy	110	180	100
66	F	R (R)	C3		1	Ulnar palsy	135	180	100
95	F	L (R)	C3		1		105	180	100
63	F	R (R)	C3		1		100	100	65
74	F	R (R)	C3	Olecranon fracture	1		80	170	90
83	M	R (R)	C3		2		105	110	85
75	F	R (R)	C3		3		110	180	85
74	F	R (R)	C3		1	Infection	105	180	100
89	F	R (R)	C3		2		135	180	85
89	F	R (R)	C3	Olecranon fracture	2		140	165	100
81	F	L (R)	C3		4		125	180	100
55	M	R (R)	C3		4		120	170	100
81	F	R (R)	C3		1	Infection	130	160	85
67	F	R (R)	A2	Rheumatoid arthritis	1		105	115	100
73	F	L (R)	C3		1	Loose locking pin	80	160	95
89	F	L (R)	C3		2		110	180	100
76	F	R (R)	A2	Rheumatoid arthritis	1	Ulnar palsy	120	170	100
56	F	R (R)	C3		2	Loose locking pin	90	180	95
88	F	R (R)	C3		1		130	180	100
88	F	L (R)	C3		4		135	180	100

TEA was implanted through the olecranon fracture with preservation of the triceps tendon, followed by osteosynthesis of the olecranon fracture, using two Kirschner wires and cerclage. The cerclage but not the Kirschner wires were later removed.

RESULTS

The average MEPS was 94 (range 65-100) (Table 1). According to the MEPS there were 15 patients with excellent results, 4 good and 1 fair. Fifteen patients had no pain, 4 had mild pain and only 1 had moderate pain. Mean arc of flexion was 114 (80-140) degrees. Mean forearm rotation was 165 (range 110-180) degrees. Two patients were revised because of deep infection. The infected patients were after the revision treated with oral antibiotics for respectively two and three months and were respectively one and two months hereafter found

without clinical or biochemical signs of infection. In two cases the 2-piece locking pin had loosened. One patient was re-operated with insertion of a new locking pin, the other patient is followed at yearly controls. Two patients reported dysaesthesia of their 4th and 5th finger, but were both able to discriminate between sharp and blunt impact. In total 6 complications were observed (Table 2). The patients reported their results as: 8 excellent, 10 good, 2 fair and none poor.

DISCUSSION

Comminuted distal humerus fractures in elderly are difficult to treat. The standard treatment for younger patients is ORIF. In the elderly, however, this treatment often results in less good results. John *et al*[4] had 20% fair and poor results in their series of 49 elderly patients with distal humerus fractures treated with ORIF. Kocher *et al*[6] had 25% fair and poor results in their retrospective review of 33 cases. Korner *et al*[7] had 42% fair and poor results in their retrospective review of 45 patients. An older review by Helfet *et al*[2] reported less good results in 25% in a compilation of 9 studies made from 1985 to 1990. Current studies on TEA in distal humerus fracture mainly consist of small case series[10-15,17-19], a retrospective case-control study[16], and a randomized trial[20]. Our study shows comparable results with 95% good or excellent results.

The Coonrad-Morrey semi-constrained elbow prosthesis has been reported to be an effective treatment for patients with rheumatoid arthritis (RA). Gill *et al*[26] found 86% good or excellent result with the Coonrad-Morrey prosthesis at 10-15 years follow-up on 41 RA patients. The rate of survival of the prosthesis was 92.4%. Park *et al*[27] had an 8 years survival rate of 100% in 35 RA patients. Plaschke *et al*[28] showed that TEA revision can give a good outcome. At 4.4 years follow up 20 patients scored mean 79 according to MEPS. The mean age of the TEA´s was 9.5 years before revision[28].

Wang *et al*[29] concludes in a Cochrane review from 2013 that the quality of the available evidence is limited and more studies are needed to determine the most appropriate surgical intervention for AO Type C distal humerus fractures in adults.

We acknowledge that this is a relatively short term retrospective study with no control group. Randomized studies are needed to assess the outcome after interventions for complex fractures of the distal humerus

In conclusion, our study suggests that TEA on fractures of the distal humerus in elderly patients can result in acceptable short- to medium-term outcome. However, the optimal treatment for complex fractures of the distal humerus has yet to be determined.

COMMENTS

Background

Osteoporotic fractures of the distal humerus have increased within the last 40 years. The results of osteosynthesis on distal humerus fractures in elderly are variable and studies show up to 42% less-then-good results according to Mayo Elbow Performance score. Total elbow arthroplasty (TEA) has gained popularity in the treatment of complicated distal humerus fractures in elderly.

Research frontiers

TEA is a relatively new treatment option for distal humeral fractures. In this study the authors report acceptable short- to medium-term results.

Innovations and breakthroughs

Studies have reported good results of primary TEA in the treatment of complex distal humerus fractures in the elderly. Data from these studies shows that out of 194 operated elbows 10 (5.2%) received component revision. Ten (5.2%) were treated for varying degrees of infection. Sixteen (8.2%) had varying degree of ulnar nerve symptoms. This study shows comparable results in a Scandinavian context with average Mayo Elbow Performance Score of 94.

Applications

This study suggests that TEA on fractures of the distal humerus in elderly patients can result in acceptable short- to medium-term outcome. However, the optimal treatment for complex fractures of the distal humerus has yet to be determined.

Terminology

The Mayo Elbow Performance Score is used in most studies where the results of operative intervention in distal humerus fracture are reported. The total score reflects pain, range of movement, stability and function.

Peer review

This is a well written case series with appropriate documentation and referencing for the problem discussed. As noted, this is a complex problem with a relatively high rate of complications.

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RETROSPECTIVE STUDY

Partial anterior cruciate ligament tears treated with intraligamentary plasma rich in growth factors

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Abstract

AIM: To evaluate the effect of the application of plasma rich in growth factors (PRGF)-Endoret to the remaining intact bundle in partial anterior cruciate ligament (ACL) tears.

METHODS: A retrospective review of the rate of return to play in football players treated with the application of PRGF-Endoret in the remaining intact bundle in partial ACL injuries that underwent surgery for knee instability. Patients with knee instability requiring revision surgery for remnant ACL were selected. PRGF was applied in the wider part of posterolateral bundle and the time it took patients to return to their full sporting activities at the same level before the injury was evaluated.

RESULTS: A total of 19 patients were reviewed. Three had a Tegner activity level of 10 and the remaining 16 level 9. The time between the injury and the time of surgery was 5.78 wk (SD 1.57). In total, 81.75% (16/19) returned to the same pre-injury level of sport activity (Tegner 9-10). 17 males and 2 females were treated. The rate of associated injury was 68.42% meniscal lesions and 26.31% cartilage lesions. The KT-1000 values were normalized in all operated cases. One patient was not able to return to sport due to the extent of their cartilage lesions. The 15 patients with Tegner activity level 9 returned to play at an average of 16.20 wk (SD 1.44) while the 3 patients with Tegner activity level 10 did so in 12.33 wk (SD 1.11).

CONCLUSION: With one remaining intact bundle the application of PRGF-Endoret in instability cases due to partial ACL tear showed high return to sport rates at pre- injury level in professional football players.

Key words: Anterior cruciate ligament; Plasma rich in growth factors; Platelet-rich plasma; Partial tears anterior cruciate ligament; Platelet-rich plasma

Core tip: The treatment with plasma rich in growth factors during an arthroscopy in cases of partial tears of ACL in soccer players could provide a restoration of function of the knee and return to play rates to pre injury levels in less than 4 mo.

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INTRODUCTION

Anterior cruciate ligament (ACL) tears are common in

Table 1 Inclusion and exclusion criteria for the review

Inclusion criteria	Exclusion criteria
Acute ruptures of the anterior cruciate ligament	Patients who were not active before the ACL injury
Active players competing in national and international teams (Tegner 9-10)	Patients with Tegner < 9
Clinic knee instability	Patients without evidence of instability (pivot shift more than 5 mm difference)
Magnetic resonance imaging of anterior cruciate ligament rupture	Ligaments with both bundles intact
Positive drawer	Ligaments with injury to both bundles or where the remaining bundle was clearly insufficient
One of the bundles intact	Infectious diseases, tumors, collagen, soft tissue or blood
First surgical procedure on evaluated knee	
Informed consent of the treatment	

ACL: Anterior cruciate ligament.

athletes and are often related to a non-contact pivoting injury mechanism in a deceleration maneuver[1,2]. The annual incidence in the United States is about 200000 cases with about 100000 treated with arthroscopic surgical procedures[3]. The symptoms have been described as a "pop" sensation and the development of an acute or subacute effusion. The clinical instability that often accompanies this injury limits sport activity especially contact-sports[1].

Partial tears that predominantly affect one of the two major ACL bundles can also provoke conditions of pain and instability that pose a great challenge with respect to treatment, as treatment involves the preservation of the bundle that is found to be intact and its reinforcement with the objective of overcoming the symptoms that brought the patient to the operating room to begin with and return them to their sporting activity[2].

The use of plasma rich in growth factors has proven useful in improving ligament maturation and specifically anterior cruciate ligament in vitro, in animals and in humans[4-6].

The current study is a series of federated football players with a Tegner activity level of 9 and 10, who had suffered partial ACL injuries and underwent arthroscopic surgery for pain and instability and received PRGF-Endoret in the remaining intact bundle, assessing re-rupture and return to sport rates with such treatment.

MATERIALS AND METHODS

A series of football players treated at the Mutualitat de Futbolistas Españoles, Barcelona Delegation, that underwent surgery for ACL injury during the 2009-2010 season were included in the study. The inclusion and exclusion criteria are described in Table 1.

A thorough check of patient medical history was performed on all patients and the time of injury was determined, as well as the moment at which they were unable to continue playing football, along with a physical examination including anterior drawer and pivot shift maneuvers. MRI was performed to confirm the ACL injury. The arthroscopic surgical procedure was performed by the same surgical team reviewing the intercondylar space and evaluating the integrity of the ACL bundles.

PRGF-Endoret was applied using the technique described by Anitua[7] (PRGF-Endoret) with a spine needle in both the proximal origin of the bundle and in the middle portion thereof in an amount of about 4 cc. At the end of the surgery when the articulation had been emptied and all surgical instruments had been removed another injection of PRGF-Endoret was administered (6 cc) in the articular space.

The knee was immobilized with a knee splint and maintained for 4 wk, with partial support from the affected limb and walking supported by 2 crutches. Upon completing this phase, the splint was removed permanently and progressive rehabilitation and physiotherapy was initiated with quadriceps strengthening exercises. At 6 wk post-op static bicycle exercises were initiated, at 8 wk elliptical trainer and at 12 wk running. The return to play was aimed at 16 wk post-op.

All patients underwent clinical follow up, MRI at 6 mo, anterior drawer, pivot shift and the time to return to play recorded.

RESULTS

19 patients were reviewed aged between 20 and 32 years with a mean age of 25.52 years (SD 3.18). 17 men and 2 women, affecting 11 right and 8 left knees. Three cases were Tegner level 10 and the other 16 Tegner 9 (Table 2).

The time between the injury and the time of surgery was 5.78 wk (SD 1.57). No notable complications in any patients in the series, no obvious bleeding or infections.

All patients followed the protocols established for inclusion in this study. All patients were informed that they would be subjected to a diagnostic arthroscopy to assess the remnant ACL and in case of failure of both bundles, a reconstruction of the anterior cruciate with ipsilateral autologous graft from the central third of the patella ligament was performed.

The 19 cases presented complete rupture of the anteromedial bundle with an intact posterolateral bundle. In all cases the tension of the remnant bundle was tested by a senior surgeon with over 30 years' experience in ligamentoplasty. If the remaining bundle failed the test, reconstruction was performed using autologous patellar

Table 2 Epidemiological data

No.	Age	Tegner	RTP wk	KT-1000 pre	KT-1000 post	TTS wk
1	24	9	15	3	1	7
2	23	9	16	3	0	6
3	27	9	15	2	0	7
4	29	9	17	2	0	8
5	21	9	14	4	1	6
6	22	9	15	3	0	7
7	28	10	12	3	0	2
8	32	9	-	5	2	5
9	31	9	15	4	1	6
10	25	10	11	3	0	1
11	20	9	14	4	1	6
12	23	10	14	3	0	1
13	21	9	15	3	0	7
14	27	9	17	4	1	8
15	29	9	18	3	0	5
16	24	9	17	2	0	8
17	27	9	19	2	0	7
18	30	9	20	3	1	7
19	22	9	16	2	1	6

RTP: Return to play; TTS: Time to surgery; KT-1000: Difference between both knees.

graft. In the 19 cases examined remnant bundles were determined as intact with sufficient tension and PRGF was applied as previously described.

During surgery, associated injuries were observed in 68.42% of the cases (21.04% medial meniscus, 36.84% lateral meniscus, and 10.52% bilateral) with cartilage injuries in 26.31% all of which in the medial femoral condyle cartilage.

Of the 19 cases, the 3 patients with Tegner activity level 10 returned to play at pre-injury level. Of the remaining 16 patients with Tegner activity level 9, three (18.75 %) cases were not able to return to the same level of competition. Of these, one re-ruptured his ACL at 7 mo after surgery upon resuming normal training at competition level, another re-ruptured the ACL at 22 mo post-surgery competing at pre-injury level and the third presented meniscal and cartilage lesions that prevented him from reaching his pre-injury level of fitness due to the discomfort and pain these injuries provoke (although without evident instability).

The 15 patients with Tegner activity level 9 returned to play at an average of 16.20 wk (SD 1.44) while the 3 patients with Tegner activity level 10 did so in 12.33 wk (SD 1.11). Apart from the 3 cases described above and two players who voluntarily left their sport for personal reasons, at 2 years follow up there were no new signs of instability in all players, all of them able to reach and maintain their pre-injury level of competition.

MRI study was performed in all cases, observing the remnant anterior cruciate ligament bundle with complete ligamentization at 1 year post-surgery and good anatomical arrangement.

DISCUSSION

The application of PRGF-Endoret in the remnant ACL allowed for an early return to play in partial ACL injuries in Federated and Professional Footballers.

The ACL has been described basically as having two functional bundles[8-10], the anteromedial bundle (AM) and posterolateral (PL). From a biomechanical point of view the AM resists anterior drawer displacement of between 60° and 90° while the PL does the same near full knee extension[9].

Partial ACL tears compromise one of the two bundles. In previous works it has been pointed out how ruptures to one of the two bundles are produced[11] also linking the relationship between the ACL and rotational stability. While Furman published in 1976 that the ACL provided stability in anterior translation mechanisms[12], more recent studies insist that rotational instability is closely related to the PL bundle[13] and this situation translates into maneuvers like the positive pivot shift. This same situation occurs in ACL reconstructions with femoral tunnel positioned excessively vertical (11- to 1-o' clock) when the anterior displacement maneuvers can be negative (anterior drawer, Lachman test) while the pivot shift is positive[10].

Different authors have published figures on the occurrence of partial ACL lesions to be between 10% and 38%[8,14,15], although the figures for partial ACL lesions symptomatic in surgeries are situated between 5% and 14% of the total for ACL lesions[11,16-19].

The natural history of ACL total rupture has been described previously and is estimated at causing a risk of instability in 15% to 66 % of patients and 15% to 86% risk of meniscal tear[20]. The natural history of knees with partial ACL tear has not been described sufficiently, although the review by Pujol *et al*[18], which was based on previously published studies and collecting more than 400 patients, concluded that partial ACL tear offers good functional results short to medium term, especially when limiting patients' physical activities[18]. Since these patients have residual pain especially when exerting themselves, even without a subjective feeling of instability, a surgical approach is recommended[18]. The proportion of patients who return to play at pre- injury level without undergoing surgery is estimated to be between 30% and 44% of patients with follow-up of 18 mo to 5 years[21,22].

Some authors have also described the proportion of partial ACL tears that become complete ruptures to be between 38 and 50%, possibly related to necrosis at the injury site after vascular injury to the remnant ACL[14,23,24].

These data have inspired various specialists to find alternative surgical solutions. In many cases total reconstruction is opted for[25] sacrificing the remnant intact ACL bundle and performing a standard ligamentoplasty with Bone-Tendon-Bone or hamstrings.

Cases that opted for retensioning of the tissue with Electrothermal shrinkage[26]. have not proven to be successful.

This has led different authors to consider the reconstruction of one of the two bundles, typically the AM, in the presence of the integrity of the other bundle[10,11].

The use of biological therapies has seen an increase in

recent years, especially the use of plasma rich in growth factors (PRGF). The application of PRGF in various tissues, especially the ACL, has been the focus of several studies, which have not only shown structurally improved tissues but also enhanced ACL graft healing[5,6], or even in the autologous central third patellar tendon harvest site[27-30]. The role of PRGF has been linked to the regeneration processes such as angiogenesis, cell activation and differentiation and stem cells[31,32]. Several studies have shown improvement to processes such as neovascularization and angiogenesis in tendon and ligament tissue with increased tenocytes[33-40], increased tissue strength in animals[29,30,41-46] and human studies with early return to competition level sport and early maturation of ligaments and tendons, and a reduction in pain[27,28,47-49]. It is important to point out that findings from both clinical studies and tissue studies coincide on the importance of the role of platelet-rich plasma (PRP) in the early phase of repair, and this is precisely where to look for differences in the control groups[50-53].

The main limitation of the current study is the lack of similar studies to this one and therefore lack of comparisons with other series. Another significant limitation is the lack of a control group that would have received physiological saline solution in the remnant ACL bundle to assess changes after a simple stimulus puncture. This lack of control group impedes the quantification of the impact of surgery simply for the influence of surgery on the knee without even considering the role of PRGF. In the design of this review no functional assessments were performed and no scores were taken, which could have improved the quality of this study.

Possible studies that could follow this one should definitely include the design of a clinical trial with a control group to assess the natural history of partial ACL ruptures, and a functional assessment, although early functional tests in the first mo are recommended as this is when changes in the groups receiving PRGF are to be expected as it accelerates the healing and tissue regeneration processes.

One remaining intact bundle and the application of PRGF-Endoret in instability cases due to partial ACL tear in professional football players with Tegner activity levels 9 and 10, provides sufficient stability for the return to play at pre- injury level.

COMMENTS

Background

Partial anterior cruciate ligament (ACL) tears are a therapeutic challenge. Biological treatments have shown an acceleration of the processes of regeneration and repair. The use of biologic therapies to repair instabilities due to partial tears may be an alternative to surgical augmentation plasty.

Research frontiers

The use of plasma rich in growth factors (PRGF) can be an effective treatment for partial ACL tears during revision arthroscopy avoiding the necessity for reconstruction of the injured fascicle.

Innovations and breakthroughs

The use of PRGF has been reported in the regeneration of cartilage and ligaments. It has been shown to accelerate the phases of plasty maturation and/or ligamentization. There is no prior publication similar to this, offering a new therapeutic possibility for this problem.

Applications

It is clear that this is a preliminary study and may give rise to a clinical trial to evaluate the impact of using PRGF in partial ACL tears.

Terminology

PRGF is plasma rich in growth factors, one of the ways of obtaining platelet-rich plasma. PRGF's role in accelerating the regeneration of tissues has been demonstrated, including ligaments and tendons.

Peer review

The fact that patient's return to play at pre-injury level was assessed gives us a clear indication of the degree of improvement in these patients from a clinical point of view. Their full return to sport at pre-injury level is objective data on their improvement.

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RETROSPECTIVE STUDY

Treatment of distal femur fractures in a regional Australian hospital

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Abstract

AIM: To review our outcomes and compare the results of the Less Invasive Stabilization System (LISS) to other implants for distal femur fracture management at a regional Australian hospital.

METHODS: The LISS is a novel implant for the management of distal femur fractures. It is, however, technically demanding and treatment results have not yet been assessed outside tertiary centres. Twenty-seven patients with 28 distal femur fractures who had been managed surgically at the Mackay Base Hospital from January 2004 to December 2010 were retrospectively enrolled and assessed clinically and radiologically. Outcomes were union, pain, Lysholm score, knee range of motion, and complication rates.

RESULTS: Twenty fractures were managed with the LISS and eight fractures were managed with alternative implants. Analysis of the surgical techniques revealed that 11 fractures managed with the LISS were performed according to the recommended principles (LISS-R) and 9 were not (LISS-N). Union occurred in 67.9% of fractures overall: 9/11 (82%) in the LISS-R group *vs* 5/9 (56%) in the LISS-N group and 5/8 (62.5%) in the alternative implant group. There was no statistically significant difference between pain, Lysholm score, and complication rates between the groups. However, there was a trend towards the LISS-R group having superior outcomes which were clinically significant. There was a statistically significant greater range of median knee flexion in the LISS-R group with compared to the LISS-N group (P = 0.0143) and compared with the alternative implant group (P = 0.0454).

CONCLUSION: The trends towards the benefits of the LISS procedure when correctly applied would suggest that not only should the LISS procedure be performed for distal femur fractures, but the correct principle of insertion is important in improving the patient's outcome.

Key words: Distal femur fracture; Less Invasive Stabilization System; Locking plates; Retrospective; Operative technique

Core tip: We recommend that orthopaedic surgeons have a good understanding of the Less Invasive Stabilization System (LISS) principles, and endeavour to follow these principles when using the LISS to treat distal femur fractures. Improved outcomes with the LISS may be achieved by providing more in-service training and courses on the use of this system for orthopaedic surgeons.

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Table 1 Biomechanic principles and recommended insertion technique of the Less Invasive Stabilisation System[10,11]

The approach to the distal femur should be minimally invasive, through either a lateral or antero-lateral incision
Stable fixation of the joint fragments is done under direct visualisation
The metaphyseal part of the fracture is reduced in a closed manner under image intensifier guidance. Direct Handling of the fracture is avoided, and the fracture must be reduced before application of the LISS
The LISS implant is inserted sub-muscularly under image intensifier guidance and is positioned alongside the femur.
The LISS is fixed distally and proximally to the femur with locking screws. The screw ratio for the diaphyseal part should be 0.4, meaning that in a 10 hole plate the maximum number of screws should be 4. The diaphyseal screws should have bicortical fixation.
The plate used should have a minimum length of nine holes
Primary bone grafting of the fracture site is not necessary.

LISS: Less Invasive Stabilization System.

INTRODUCTION

Distal femur fractures are defined as fractures that affect the lower nine to fifteen centimetres of the femur, down to the articular surface of the knee[1-3]. These fractures account for approximately 4% to 6% of all fractures affecting the femur[4]. A study by Martinet *et al*[5] found that distal femur fractures have a bimodal age distribution. The younger age group comprises mostly males in their second to third decade of life who typically sustain their injuries *via* high energy mechanisms such as motor vehicle accidents. The older age group mostly comprises females in their sixth decade of life onwards, who typically sustain their injury *via* low energy mechanisms of injury from osteoporosis[6,7]. Because of its biomechanical specifics, the treatment of distal femur fractures has historically been associated with a high incidence of complications, including non-union or delayed union, malalignment of the femur, infections of the bone and soft tissues, chronic pain and decreased range of motion and function of the knee joint[8-10]. The evolution of the minimally invasive plate osteosynthesis (MIPO) concept, however, has significantly changed the approach to distal femur fracture management[10-13]. The MIPO technique avoids extensive open surgical procedures in order to reduce damage to the blood supply of the bone and surrounding tissues, thus, in theory, facilitating better healing[14,15]. The Less Invasive Stabilization System (LISS) is a novel implant which has been developed to conform to the MIPO concept[16,17]. The LISS incorporates many new features that potentially make it favourable for the management of distal femur fractures[18-20] (Table 1). Despite the proposed benefits of the LISS, a number of limitations have been identified, the most important being the LISS is technically demanding[18]. Many studies have concluded that significant surgical experience is a prerequisite for optimal outcomes when using the LISS implant, however there is limited information on outcomes from using the LISS in the generalist orthopaedic setting[9,18,21,22].

The aim of this study was to compare the results of the LISS with other implants for distal femur fracture management at a regional hospital where orthopaedic surgeons are not sub- specialised in lower limb conditions. The outcome measures were union, pain, Lysholm score, range of knee motion, and complication rates. The study setting was a regional hospital which services a population of approximately 160000 people, and receives an average of eight to ten distal femur fractures annually.

MATERIALS AND METHODS

A retrospective, single centre study was designed to identify and evaluate the method of distal femur fracture management. Potential study participants were identified by a search of Mackay Base Hospital's electronic clinical database from January 2004 to December 2010. Additionally, a manual search of the electronic surgical records for all orthopaedic surgeries performed at the hospital during this time was undertaken to identify any potential participants missed by the initial primary search.

Participants were included if they had a distal femur fracture and were age > 18 years, able to mobilise independently prior to fracture, and the fracture was managed surgically. Eligible participants were invited to attend an assessment at the orthopaedic outpatient clinic. The assessment involved four components: (1) Lower limbs were examined for fracture site deformity, prominence of the implant, knee range of motion, and pain in the knee and over the implant; (2) A Lysholm questionnaire was completed to determine the level of knee function; (3) Pain was assessed using a Visual Analogue Scale; and (4) Radiographs were taken (standard anterior-posterior and lateral projections of the affected distal femur, and standing long leg radiographs of both legs) to assess the leg length and axis.

Ethical approval was obtained through Queensland health ethics committee. Statistical Analysis was performed using SAS 9.1 (SAS Institute, Cary, NC) and R 2.12.0. Data was categorized based on surgical management: LISS or alternative implants which include distal femoral nail (DFN), dynamic condylar screw (DCS), and angled blade plate (ABP). The LISS group was further sub-classified based on whether the recommended principles of insertion were used (LISS-R) or not (LISS-N). Continuous variables are reported as means, and standard deviations with group comparisons were analysed by variance. Discrete variables are reported as numbers and percentages, with group comparisons analysed by Pearson's chi-square or Fisher's exact test. All statistical tests were evaluated at the 5% level of significance.

Table 2 Comparison of surgical, acute care, rehabilitation and follow-up between implant treatment groups

	Surgical implant				*P*-value		
	LISS (*n* = 19)	LISS-R (*n* = 11)	LISS-N (*n* = 8)	Alternative (*n* = 8)	LISS *vs* alternative	LISS-R *vs* LISS-N	LISS-R *vs* LISS-N *vs* alternative
Surgery within first 48 h	11 (58%)	6 (55%)	5 (63%)	6 (75%)	0.6655	1.0000	0.8773
Operation blood loss (mL)	521.1 (296.4)	490.9 (328.5)	562.5 (261.5)	806.3 (925.2)	0.2304	0.6173	0.4761
Operation time (min)	118.4 (24.6)	121.0 (30.0)	114.8 (16.7)	158.5 (42.8)	0.0048	0.5988	0.0187
Length of acute hospital stay (d)	11.7 (6.9)	9.4 (4.6)	14.9 (8.5)	8.9 (6.6)	0.3378	0.0859	0.1357
No rehabilitation	11 (58%)	4 (36%)	7 (88%)	7 (88%)	0.2011	0.0587	0.0308
Rehabilitation less than 14 d	4 (21%)	4 (36%)	0 (0%)	0 (0%)	0.2855[1]	0.1032[1]	0.0268[1]

[1]Less than 2 observations in a group makes this *P*-value unreliable. LISS: Less Invasive Stabilization System.

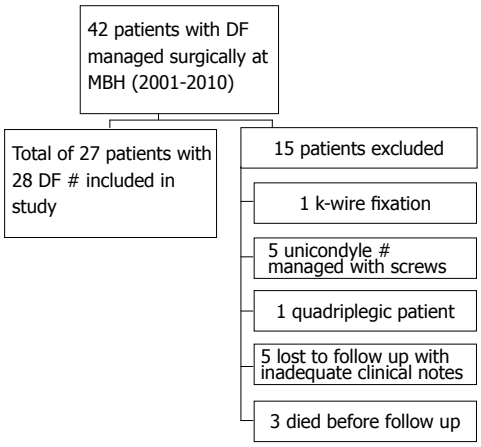

Figure 1 Flowchart of patients with distal femur fractures managed surgically during the study review period.

RESULTS

From January 2004 to December 2010, 42 adult patients were managed surgically for distal femur fractures, 32 of which were eligible for this study. Of the 32 eligible participants identified, 27 participants (8 male, 19 female) with 28 distal femur fractures attended an orthopaedic outpatient clinic for further assessment (Figure 1). The participants' mean age was 64.7 years (range 18 to 94 years) with the mean age of female participants being 72.3 years (range 32 to 94) compared to 46.6 years (range 18 to 81) for males. The mean duration of follow-up for study participants was 30 mo (6 to 74 mo).

Twenty of the 28 fractures (71.4%) were managed with the LISS, while eight (28.6%) were managed with alternative implants: four with Distal Femoral Screw (DFN), three with Dynamic Condylar Screw (DCS), and one with an angular blade plate (ABP). A review of the operative notes revealed that 11/20 (55%) of the LISS procedures had been conducted according to recommend procedures for insertion (LISS-R group). However, 9/20 (45%) of fractures managed with the LISS were not operated on according to the recommended principles, using atypical techniques or implant constructs (Figure 2). There were no significant differences between the three treatment groups (LISS-R, LISS-N and alternative implants) with regard to patient demographics and co-morbidities or periprosthetic factors (Table 2). However, patients in the LISS group had significantly shorter operation times compared to the alternative implant group ($P = 0.0048$) however, there was no difference in blood loss ($P = 0.2304$). In regard to rehabilitation post-op, the LISS-R group required less rehabilitation time than both the LISS-N and alternative implant groups ($P = 0.0308$).

Overall, 67.9% of fractures proceeded to complete union within six months postoperatively: 14/20 (70%) managed with the LISS compared to 5/8 (62.5%) treated with alternative implants ($P = 1.0000$). In the LISS-R group 9/11 (82%) achieved complete union versus 5/9 (56%) in the LISS-N group, which was clinically, but not statistically, significant ($P = 0.3359$).

Pain on a constant or daily basis was reported in 10/27 (47.4%) of fractures treated with the LISS, and 5/8 (62.5%) of fractures treated with alternative implants. Pain was less common in the LISS-R treatment group than LISS-N patients, affecting 3/11 (27.3%) and 6/8 (75.0%) respectively ($P = 0.0698$), which tended towards significance.

There was no difference in the Lysholm scores between the LISS and alternative implant groups ($P = 0.9108$).

Knee range of motion (ROM) was categorised into flexion and extension. There was a statistically significant difference in the median knee flexion in the LISS-R group with 102.0 degrees compared to the LISS-N group with 90.0 degrees ($P = 0.0143$) which remains statistically significant when compared across all implant groups ($P = 0.0454$) All other primary outcomes did not reach statistical significance (Table 3). There was no statistically significant difference across the different implant groups regarding knee extension (Table 3).

There were no statistically significant differences in the rate of complications between any of the treatment groups (Table 4). There were 5/20 (25.0%) cases of malunion in the LISS group: 2/11 (18.2%) in the LISS-R group and 3/9 (33.3%) in the LISS N group compared with 4/8 (50.0%) in the alternate implant group. This was clinically but statistically significant. There were 4/20 (20.0%) cases of implant failure in the LISS group: 1/11(9.1%) in the LISS-R group and 3/9 (33.3%) in the LISS-N group compared with 1/8 (12.5%) in the alternative implant group. Again this was of clinical, but not

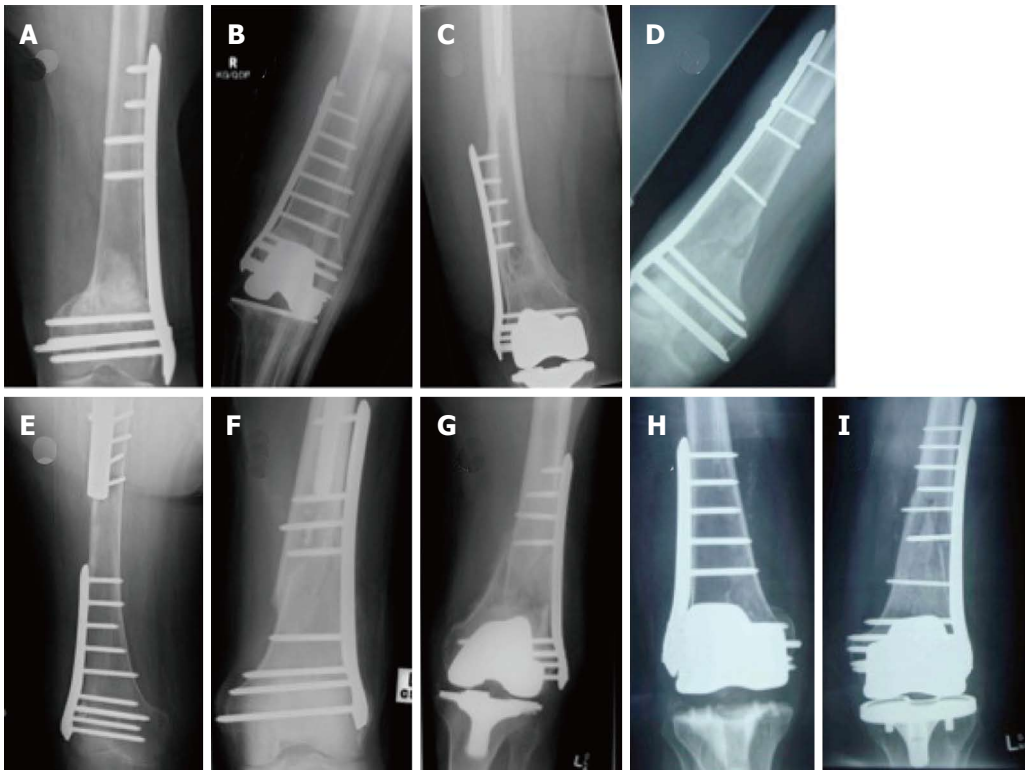

Figure 2 Fractures treated using the Less Invasive Stabilization System not according to recommended principles (Less Invasive Stabilization System-N group). A: Short implant with distal screws being too long, thus irritating the medial soft tissues; B: Short implant fixed with too many proximal screws; C: open procedure, short implant with too many proximal screws, unicortical proximal; D: non-locking proximal screws used; E: short implant fixed with too many proximal screws; F: open procedure, too few distal screws used; G: short implant; H: short implant fixed with too many proximal screws; and I: appropriate length implant with too many proximal screws.

statistical, significance.

DISCUSSION

Our study shows that when comparing outcomes of fracture union, pain, Lysholm scores, knee ROM, and complication rates, there is no difference between the entire LISS procedure group and the alternative implants group. However, a number of LISS procedures included in this series were performed in a manner contrary to recommended LISS principles. Trends in the results showed better outcomes for patients that were managed with the LISS according to the recommended principles (LISS-R), compared to fractures treated with atypical LISS techniques (LISS-N) or with alternative implants. Difference in median knee flexion was our only significant outcome measure across the implant groups with better outcomes in the LISS-R group. Despite reaching statistical significant, the difference was not considered to be of clinical relevance. On the other hand, the superior outcomes of the LISS-R group compared with the LISS-N groups with regard to union, malunion and implant failure were considered to be clinically significant although the study was not adequately powered to show statistical significance.

Overall, the results of the LISS procedure in our study was worse than in the literature[18,23,24] (Our study has a fracture union rate at 6 mo of 70% which is significantly lower than the literature found - a rate of 85%[23]. However, when examining the LISS-R group only, the union rate at 6 mo become 82% which is much closer to the literature rate.

This was not the case for the Lysholm score where the literature six months after surgery had a score of 80.5 (40-100)[18] where our LISS group had a Lysholm score 57.0 (12 to 100) which was not much improved looking only at the LISS-R group 67.0 (12-100).

A similar trend was seen with the median knee flexion. The median knee flexion of 96 (70 to 136) degrees for the LISS group is lower than the corresponding results in many other studies, such as in the paper by Schandelmaier *et al*[18] with median knee flexion of 104 (20 to 140). Again, when examining only the LISS-R group, the median knee flexion becomes much closer to the literature result at 102 (90 to 136).

In total, nine of the 20 (45%) fractures fixated with LISS in this study series were managed using a technique which differed from the recommended procedure. Of these, only one had a documented explanation for the deviation from the standard LISS procedure, which was conversion to an open procedure after the closed technique had failed. The most common reasons for divergence from the recommended LISS procedure were the use of short implants and the use of unicortical proximal locking screws for fixation of the LISS in osteoporotic bone. Wong *et al*[25] reported a 20% failure rate in their

Table 3 Comparison of primary end points for the implant treatment groups

	Surgical implant				*P*-value		
	LISS (*n* = 20)	LISS-R (*n* = 11)	LISS-N (*n* = 9)	Alternative (*n* = 8)	LISS *vs* alternative	LISS-R *vs* LISS-N	LISS-R *vs* LISS-N *vs* alternative
Median Knee Extension (degrees)	0.5 (12.5)	6.0 (5.7)	0.0 (18.2)	2.5 (9.8)	0.8257	0.9134	0.9698
Median knee flexion (degrees)	96.0 (19.6)	102.0 (13.7)	90.0 (20.2)	90.0 (18.5)	0.8634	0.0143	0.0454
Median lysholm score	57.0 (29.4)	67.0 (30.4)	42.0 (21.9)	56.5 (11.0)	0.9108	0.1809	0.3075
Excellent (> 90)	2 (10%)	2 (18%)	0	0	1.0000[1]	0.4789[1]	0.3148[1]
Good (84-90)	0	0	0	0	NA	NA	NA
Fair (65-83)	2 (10%)	2 (18%)	0	1 (13%)	1.0000[1]	0.4789[1]	0.6071[1]
Poor (< 65)	8 (40%)	4 (36%)	4 (44%)	3 (38%)	1.0000	1.0000	1.0000
Union after 6 mo	14 (70%)	9 (82%)	5 (56%)	5 (63%)	1.0000	0.3359	0.4670

[1]Less than 2 observations in a group makes this *P*-value unreliable. LISS: Less Invasive Stabilization System.

Table 4 Comparison of complication rates for the implant treatment groups *n*(%)

	Surgical Implant				*P*-value		
	LISS (*n* = 20)	LISS-R (*n* = 11)	LISS-N (*n* = 9)	Alternative (*n* = 8)	LISS *vs* alternative	LISS-R *vs* LISS-N	LISS-R *vs* LISS-N *vs* alternative
Complications of healing							
Non-union	6 (30)	2 (18)	4 (44)	2 (25)	1.0000	0.3359	0.5065
Delayed union	0	0	0	1 (13)	0.2857[1]	n/a	0.2857[1]
Varus/valgus malalignment	5 (25)	2 (18)	3 (33)	4 (50)	0.3715	0.6169	0.3627
Recurvation	2 (10)	2 (18)	0	0	1.0000[1]	0.4789[1]	0.3148[1]
Limb shortening	3 (15)	1 (9)	2 (22)	1 (13)	1.0000[1]	0.5658[1]	0.8066[1]
Superficial infection	2 (10)	2 (18)	0	0	1.0000[1]	0.4789[1]	0.3148[1]
Implant related complications							
Implant malpositioning	2 (10)	1 (9)	1 (11)	n/a[2]	n/a	1.0000[1]	n/a
Proximal screw pullout	1 (5)	0	1 (11)	n/a[2]	n/a	0.4500[1]	n/a
Implant failure	4 (20)	1 (9)	3 (33)	1 (13)	1.0000[1]	0.2848[1]	0.4641[1]

[1]Less than 2 observations in a group makes this P-value unreliable; [2]These complications are LISS specific. LISS: Less Invasive Stabilization System.

study population which they attributed to using short plates and mono-cortical screws. Other authors made similar observations[19,26]. Kregor *et al*[19] hypothesized that this was caused by the inability of the plate to adequately bridge the fracture and create a construct with enough rigidity and flexibility to allow secondary fracture healing by callus formation. In our population the rate of proximal screw pull-out was 11% (1/9) in the LISS-N with none in the LISS-R group; the most common reason for failure was using an implant that was too short. There were no statistically significant differences in the rate of complications between any of the treatment groups.

An interesting observation was the significant difference in the rehabilitation time required prior to discharge from hospital. The majority of the patients admitted to the rehabilitation ward were in the LISS-R group (78%). Despite the LISS-R group having the most patients, they required the least amount of rehabilitation time, with 57% requiring less than 14 d ($P = 0.0308$). All the rehabilitation attendees were females older than 55 years with more co-morbidities than the no-rehabilitation patients, including 78% with osteoporosis, 67% with previous TKR, and 22% with diabetes. Following the categorization of distal femur fractures suggested by Martinet *et al*[5], rehabilitation patients tended to be from the older age group who typically sustained their injury via low energy mechanisms.

To the best of our knowledge, this is the first study to evaluate the use of the LISS implant system in a regional hospital, where surgeon experience with this system and distal femur fracture management in general is limited. Furthermore, it is the first study to identify a distinct series of distal femur fractures that have been treated with the LISS system using a non-recommended technique, and to compare these to other fractures which have been managed according to the recommended principles of this system. Despite small numbers, we think this study successfully explains that good outcomes with the LISS in distal femur fractures are dependent on its correct application. This relies on a comprehensive understanding of the LISS principles by the surgeon and a high level of exposure to, and experience with, the use of the LISS for the treatment of these fractures.

It must be acknowledged that there are several limitations in analysing and generalising our study. The study involved a small number of participants enrolled at a single centre which is a small regional hospital. Numbers do not allow meaningful statistical analysis of several of the outcomes, and in some cases we can provide only a description of our findings. However, our results do

show some interesting trends which can inform clinical practice. We feel that the results of this preliminary study can be used to inform future research.

Although most results were not statistically significant, there was a trend towards the correctly inserted LISS-R group having superior outcomes to both the incorrectly inserted LISS-N group as well as the alternative implants. This trend would suggest that not only should the LISS procedure be performed for distal femur fractures, but the correct principle of insertion is important in improving the patients' outcome.

On the basis of these trends, it is recommended that orthopaedic surgeons have a good understanding of the LISS principles, and endeavour to follow these principles when using the LISS to treat distal femur fractures. Improved outcomes with the LISS may be achieved by providing more in-service training and courses on the use of this system for orthopaedic surgeons.

COMMENTS

Background

The Less Invasive Stabilization System (LISS) is a novel implant for the management of distal femur fractures. It is, however, technically demanding and treatment results have not yet been assessed outside tertiary centres.

Research frontiers

LISS was introduced in 2000. Early research has shown improved outcomes and reduced complications in comparison with previous conventional implants.

Innovations and breakthroughs

Although most results were not statistically significant, we showed a clinically significant trend towards the correctly inserted LISS-R group having superior outcomes to both the incorrectly inserted LISS-N group as well as the alternative implants. This trend would suggest that not only should the LISS procedure be performed for distal femur fractures, but the correct principle of insertion is important in improving the patients' outcome.

Applications

It is important that LISS is inserted correctly in order to result in better outcomes that alternative implants. Improved outcomes may be achieved by providing more in-service training for orthopaedics surgeons.

Peer review

Adequate surgeon training for LISS procedures should be emphasized irrespective of clinical experience of the surgeon.

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PROSPECTIVE STUDY

Ten years of hip fractures in Italy: For the first time a decreasing trend in elderly women

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Abstract

AIM: To evaluate the hospitalization rate of femoral neck fractures in the elderly Italian population over ten years.

METHODS: We analyzed national hospitalizations records collected at central level by the Ministry of Health from 2000 to 2009. Age- and sex-specific rates of fractures occurred at femoral neck in people $\geqslant$ 65 years old. We performed a sub-analysis over a three-year period (2007-2009), presenting data per five-year age groups, in order to evaluate the incidence of the hip fracture in the oldest population.

RESULTS: We estimated a total of 839008 hospitalizations due to femoral neck fractures between 2000 and 2009 in people $\geqslant$ 65, with an overall increase of 29.8% over 10 years. The incidence per 10000 inhabitants remarkably increased in people $\geqslant$ 75, passing from 158.5 to 166.8 (+5.2%) and from 72.6 to 77.5 (+6.8%) over the ten-year period in women and men, respectively. The oldest age group (people > 85 years old) accounted for more than 42% of total hospital admissions in 2009 (n = 39000), despite representing only 2.5% of the Italian population. Particularly, women aged > 85 accounted for 30.8% of total fractures, although they represented just 1.8% of the general population. The results of this analysis indicate that the incidence of hip fractures progressively increased from 2000 to 2009, but a reduction can be observed for the first time in women $\leqslant$ 75 (-7.9% between 2004 and 2009).

CONCLUSION: Incidence of hip fractures in Italy are continuously increasing, although women aged 65-74 years old started showing a decreasing trend.

Key words: Femoral fractures; Hip fragility fractures; Osteoporosis; Hospitalizations; Incidence

Core tip: We evaluated hospitalization rate of femoral neck fractures in the elderly Italian population over ten year-period (from 2000 to 2009). Our data confirm the dramatic social impact of hip fractures in the elderly, although the perception of their clinical and social relevance is still limited in public and medical profession. Despite this for the first time a reduction in the number of hospitalizations for women aged 65-74 resulted.

Piscitelli P, Feola M, Rao C, Celi M, Gasbarra E, Neglia C, Quarta G, Liuni FM, Parri S, Iolascon G, Brandi ML, Distante A, Tarantino U. Ten years of hip fractures in Italy: For the first time a decreasing trend in elderly women. *World J Orthop* 2014; 5(3): 386-391 Available from: URL: http://www.wjgnet.com/2218-5836/full/v5/i3/386.htm DOI: http://dx.doi.org/10.5312/wjo.v5.i3.386

INTRODUCTION

Life expectancy of the Italian population has constantly increased during the last 50 years, so that Italy is currently the Country with the highest percentage of elderly people in the general population in the world, thus representing an interesting case study for all industrialized countries[1]. People aged ⩾ 85 years old are estimated to exceed 12% of the entire population by the year 2050[1]. In this perspective, chronic and degenerative diseases - including osteoporosis and fragility fractures - will represent a dramatic challenge for health professionals and decision makers. Actually, the World Health Organization considers osteoporosis to be second only to cardiovascular diseases as a critical health problem[1]. In our previous study, we have shown that incidence and costs of hip fractures in Italy are already comparable to those of acute myocardial infarctions, with costs per patient having been computed at € 13.500 per patient[2], thus confirming the very high burden of these fractures in terms of expenditures[3].

Hip fractures, the most catastrophic complication of osteoporosis, result in significant 1-month and 1-year mortality (5% and 20%, respectively)[4]. Furthermore, 30% of patients are estimated to become permanently disabled, while 40% of them loose the ability to walk independently, and 80% are unable to perform independently activities of daily living after the fracture has occurred[4].

The correct perception of the epidemiological picture of fragility fractures and their impact on the population over 65 of age is essential. Actually, information about fracture incidence allow institutions to understand the importance of planning large-scale prevention initiatives and to identify the target population who need to be treated.

In our previous researches, we have already provided some pictures about the burden of hip fractures in Italy between the years 2000 and 2005[5-8]. More recently, a study carried out by Kanis *et al*[9] has classified Italy in the group of nations with the highest incidence of hip fractures, with rates per 100000 being > 300 for women and > 150 for men, respectively. However, in some countries a decreasing trend in the number of hip fractures in elderly people has been observed[10]. This study aimed to estimate the yearly number of femoral neck fractures that occurred in the elderly Italian population from 2000 to 2009, based on such official information source as hospitalization records.

MATERIALS AND METHODS

Information concerning all hospitalizations occurring in Italian public and private care settings are registered in hospital discharge records, which are collected at the Italian Ministry of Health (National Hospitalization Database, SDO). This information is anonymous and includes the patient's age, sex and diagnosis. The present manuscript focuses on the number of hospitalizations due to femoral neck fractures in Italy from year 2000 to 2009. We assumed that almost all hip fractures occurred in the elderly resulted in hospital admissions, as confirmed by a previous study on this specific topic[11]. Population data was obtained from the National Institute for Statistics (ISTAT) for each year[1]. Hip fractures were defined by the following ICD-9CM major diagnosis codes: 820.0 (femoral neck fractures), 820.2 (per-trochanteric femoral fractures), and 820.8 (other femoral neck fracture). We excluded all hospitalization assigned to major diagnosis code 820.1 or 820.3 (open femoral neck fractures) or 821 (all the extensions; diaphyseal and distal femoral fractures) because they were considered likely to be fractures due to high energy trauma. Thus, we have limited our current analysis to femoral neck fractures. Data was stratified by gender and into two age groups (65-74 and ⩾ 75 years) and was processed using Stata (StataCorp, College Station, United States) and Excel (Microsoft, Redmond, United States) softwares. We performed descriptive statistical analyses of the incidence in each gender and age subgroup across the ten examined years. The incidence of hospitalization due to hip fractures per 10.000 inhabitants has also been computed. We also performed a sub-analysis over the more recent three-year period (2007-2009), that is the only year with data available per five-year age groups (65-69, 70-74, 75-79, 80-84, and ⩾ 85 years old), in order to specifically evaluate the incidence of hip fragility fractures in the oldest people.

RESULTS

We recorded a total of 839008 hospitalizations due to femoral neck fractures in people ⩾ 65 years old between 2000 and 2009. Hospitalizations showed an overall increase of 29.8% over the ten-year period (Figure 1). As reported in Figure 1, hospitalizations due to hip fractures were 71762 in year 2000 (15686 men and 56076 women); 76410 in year 2001 (16456 men and 59954 women);

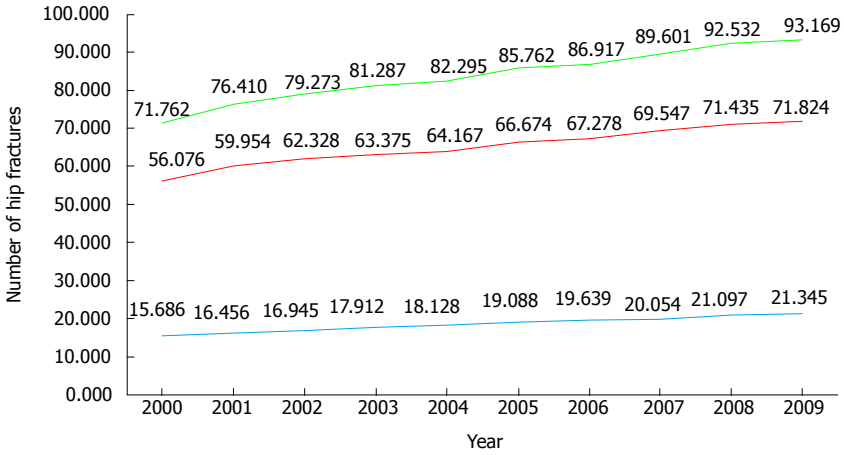

Figure 1 Total number of hip fractures. Number of hospitalizations following hip fractures in Italy in women (red line), men (blue line) and all patients (green line) ⩾ 65 years old, years 2000-2009 (Italian National Hospitalizations Records).

79273 (16945 men and 62328 women) in year 2002; 81,287 (17912 men and 63375 women) in year 2003; 82295 (18128 men and 64167 women) in 2004; 85762 in 2005 (19088 men and 66674 women); 86917 (19639 men and 67278 women) in 2006; 89601 (20054 men and 69547 women) in 2007; 92532 (21097 men and 71435 women) in 2008; 93169 (21345 men and 71824 women) in 2009.

Incidence per 10000 of hip fractures was 696 in year 2000 (36.3 in men and 92.3 in women); 72.8 in year 2001 (38.1 in men and 97.0 in women); 74.4 (38.6 in men and 99.4 in women) in year 2002; 74.9 (40.0 in men and 99.5 in women) in year 2003;74.5 (39.6 in men and 99.2 in women) in 2004; 75.9 in 2005 (40.6 in men and 101.0 in women); 75.4 (40.8 in men and 100.1 in women) in 2006; 76.6 (41.0 in men and 102.2 in women) in 2007; 78.1 (42.5 in men and 103.9 in women) in 2008; 77.8 (42.4 in men and 103.5 in women) in 2009.

The incidence of hip fracture shows an increase of 14.5% in men and of 12.1% in women over the ten-year period. When looking at the oldest age group, we recorded an increase in the incidence per 10000 inhabitants in people over 75, which passed from 158.5 to 166.8 (+5.2%) and from 72.6 to 77.5 (+6.8%) in women and in men, respectively.

In the analysis per 5-year age groups (Figure 2), we reported a total of 275302 femoral neck fractures in people over 65 during the last three years (2007-2009). In patients aged ⩾ 85 years old, hip fracture progressively increased over the three-year period, passing from 35472 (39.6% of total) in 2007 to 37899 (41% of total) in 2008 and 39244 (42.1% of total) in 2009 (Figure 2). In this latter year, people ⩾ 85 years old represented more than 40% of total hospitalizations due to femoral neck fractures although they accounted for 2.5% of the overall Italian population. Particularly, women aged 85 and over accounted for 30.8% of total hospitalizations, despite representing only 1.8% of the population.

Finally, it is interesting to point out that - for the first time in the recent Italian medical history - the incidence of hip fractures in women under 75 years of age has increased from 2000 to 2004 by a 5.9% rate, but it has subsequently decreased by a 7.9% between 2004 and 2009, thus showing a clear inversion in its temporal trend (Figure 3).

DISCUSSION

Our study confirms the increasing trend of incidence of femoral neck fractures in the elderly Italian population during the last decade, but first good news has emerged for the first time. Having found a reduction in the incidence in women aged 65-74 years old is a remarkable issue, although they represent a minor proportion (about 10%) of hip fractures occurred in the elderly. When looking at this finding, it must also be kept in mind that some differences are expected between the Italian regions. Actually, our preliminary ongoing analyses of the Tuscany region healthcare system database shows that the decrease in the incidence of hip fractures in older women also involves those aged 75-84 years old (data not presented).

Compared with our previous research[5-8], we have limited the study to those fractures that occurred in femoral neck among people aged over 65 years old, thus excluding all other hip segments usually interested in cases of high energy trauma. This methodology has allowed us to catch only hip fractures which were likely to be a consequence of osteoporosis (fragility fractures). Actually, in older subjects there is an alteration of bone architecture with decreased bone strength, leading to an increased fracture risk[1]. These fractures are often due to falls that occur especially in a domestic environment, because of a low-energy trauma in people with an increased risk of falling. Several causes are known to contribute to that, including sarcopenia, a depletion of muscle fibers (occurring especially at the proximal segment of the hip) caused by low levels of vitamin D[1]. However, the issue of updating the definition of fragility fracture focusing not only on trauma energy but also on patient conditions

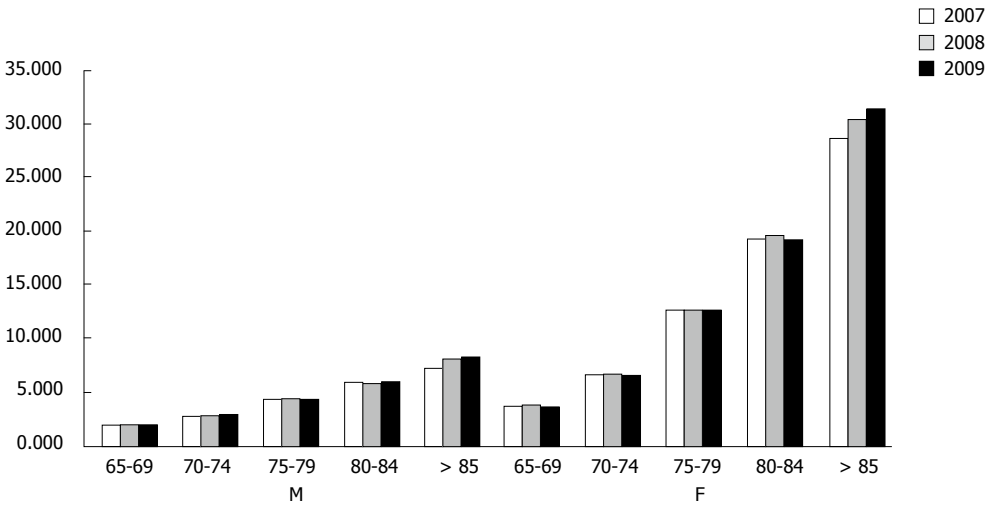

Figure 2 Number of hip fractures per age group. Hospitalizations following hip fractures in Italy in patients ⩾ 65 years old, presented by five-year age groups and sex between 2007 and 2009 (Italian National Hospitalizations Records).

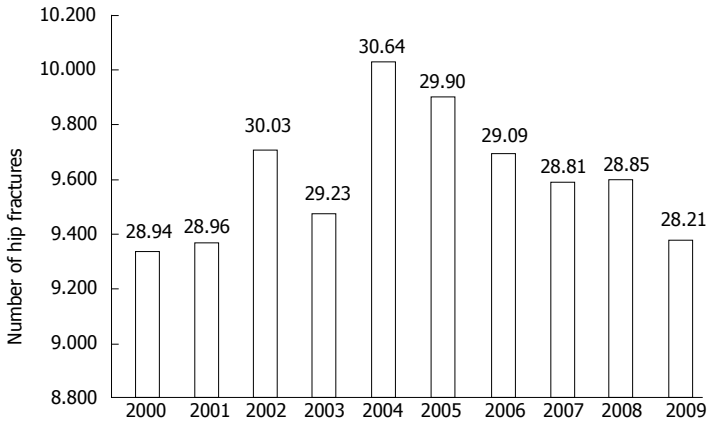

Figure 3 Trend of hip fractures. Decreasing trend in number of hospitalizations following hip fractures and in their incidence per 10000 in women 65-74 years old, years 2000-2009 (Italian National Hospitalizations Records).

should be addressed by the scientific community.

In 2009, the Italian National Healthcare System has paid for more than 93000 hospitalizations, with a constant increase of incidence over the last ten years, as expected according to the progressive aging of the Italian population. Looking at this picture might be useful for all the other industrialized countries who are supposed to cope with similar problems within the next decades. The incidence of hip fractures is particularly growing in people over 75 (especially among women), the age group in which both the prevalence of osteoporosis and the risk of falls are known to be higher[1,4]. When looking at the different age groups, the risk of being hospitalized because of hip fracture was higher in women (more than twice, particularly in the age group > 75 years old). These findings confirm the crucial role of osteoporosis, which is the most frequent underlying cause of hip fractures in the elderly[1]. Actually, almost 83% of hip fractures were found to have been experienced by patients 75 years of age or older, in accordance with the higher prevalence of osteoporosis in this age group[4]. Our findings seem to be consistent with International Osteoporosis Foundation estimations concerning the overall incidence and costs of hip fractures in Italy and provide detailed information regarding hospitalizations occurring in the elderly age groups[12]. Furthermore, these results are consistent with the analyses we had already performed[5-8] and with data from other European or non- European countries, where an increasing trend of hip fractures incidence and costs was shown[13-19]. These differences can be explained by considering the higher incidence of hip fractures among the oldest age groups in those countries where effective preventive strategies have not yet been fully implemented, especially for nursing home residents, whose risk of fractures is two- or three fold higher than community dwelling elderly people[20].

Our results confirm the dramatic social impact of hip fractures in the elderly, although the perception of their clinical and social relevance is still limited in the public and in the medical profession. In order to demonstrate this, we have to consider that only 12% of patients with a femoral fracture (which have an increased risk of another

fracture both in the femur and in another skeletal site) receive anti-fracture drug therapy and that the gap between expenditure on pharmaceuticals sustained for drugs to prevent the risk of fracture and active on the prevention of cardiovascular disease remains very high (about 1%-4% *vs* 32% of the national pharmaceutical spending). Our data claim for preventive interventions aimed to primary prevention of osteoporosis and to reduce the incidence of hip fractures above all, as their consequences have a considerable impact on the elderly and their families in terms of reduced levels of health, loss of productivity and quality of life.

In a conclusion, the improvement of standards of care led to a lengthening of life with an increase in the number of people over 75 in Italy. In older subjects there is an alteration of bone architecture with decreased bone strength, leading to an increased fracture risk. These fractures are often due to falls that occur especially in a domestic environment, because of a low-energy trauma, in people with an increased risk of falling. There are several causes that lead to a similar picture, including in particular sarcopenia; the depletion of muscle fibers, especially at proximal level, is caused by low levels of vitamin D. In these subjects comorbidities further aggravate the bone quality, worsening the outcome of the fracture.

Behind every femoral fracture, there is a dramatic picture that requires special attention from physicians and institutions, whereas our results over the last 10 years show that the number of hip fractures increased by about 30%. As the number of people over 65 in Italy - as well as in all industrialized countries - will continue to increase, this picture could become even worse, with a remarkable burden on people and on the healthcare system, unless specific preventive strategies will be adopted.

A good knowledge of the real number of fractures is necessary to set health prevention programs aimed at reducing the incidence of falls and following fractures. A proper allocation of resources will allow to prescribe in subjects with low BMD adequate anti-osteoporotic therapy, reducing the fracture risk. It should be useful to extend this study considering other variables that have not been addressed in this work, as the geographical and seasonal distribution of fractures, to better identify not only intrinsic factors that determine the fracture but also other elements that could increase fracture risk.

This work confirms that the incidence of femoral neck fractures in Italy have increased over a ten-year period. On the other hand, the reduction that we have observed for the first time in the number of hospitalizations, at least for women aged 65-74, might already be an effect of the awareness about the treatment of osteoporosis which has been increasing since the beginning of the millennium.

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COMMENTS

Background

Chronic and degenerative diseases - including osteoporosis and fragility fractures - will represent a dramatic challenge for health professionals and decision makers. The World Health Organization considers osteoporosis to be second only to cardiovascular diseases as a critical health problem.

Innovations and breakthroughs

Authors' data confirm the dramatic social impact of hip fractures in the elderly, although the perception of their clinical and social relevance is still limited in public and medical profession.

Applications

The reduction that have observed for the first time in the number of hospitalizations, at least for women aged 65-74, might already be an effect of the awareness about the treatment of osteoporosis which has been increasing since the beginning of the millennium.

Peer review

The manuscript gives information about a reduced incidence of hip fractures in the younger elderly population, but emphasizes an increased incidence in the very old population. The topic has high importance because the number of hip fractures has doubled in the last 30-40 years in many countries.

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SYSTEMATIC REVIEWS

Top 20 cited *Spine Journal* articles, 1990-2009

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Abstract

AIM: To determine the most cited articles and most published authors in *Spine Journal* from 1990-2009.

METHODS: *Spine Journal*, established in 1976, is affiliated with 12 spine societies and a leader in spine research articles. Citation analysis is a method to determine the impact of a journal and its articles on academia and clinical practice. Using the Institute for Scientific Information Web of Knowledge, we determined the most cited articles in *Spine Journal* between1990-2009. The characteristics and type of article were recorded. Next, we evaluated the most published authors during the same time period and calculated the number of citations for each author. The number of first authorships for each of these authors was also determined along with the number of citations for those articles.

RESULTS: The top 20 cited articles range from 491 to 267 total citations. The top 20 published authors had between 41 and 135 articles. Seventeen of the top 20 articles were clinical studies. The range of citations per lead authorship ratio was 36 to 724 with one author having no lead authorships. Low back pain was the most common theme encountered in the top cited articles. The first-ranked article was not a spine-specific topic rather it was regarding general physical and mental health status survey update review.

CONCLUSION: *Spine Journal* and its authors have a clear impact on the scientific community based on this review of the top articles and authors in the last 20 years.

Key words: Citation analysis; Back pain; *Spine Journal*

Core tip: *Spine Journal*, established in 1976, is affiliated with 12 spine societies and a leader in spine research articles. Citation analysis is a method to determine the impact of a journal and its articles on academia and clinical practice. Using the Institute for Scientific Information Web of Knowledge, we determined the most cited articles in *Spine Journal* between 1990-2009. The characteristics and type of article were recorded. Next, we evaluated the most published authors during the same time period and calculated the number of citations for each author. The top 20 cited articles range from 491 to 267 total citations. The top 20 published authors had between 41 and 135 articles. Seventeen of the top 20 articles were clinical studies. The range of citations per lead authorship ratio was 36 to 724 with one author having no lead authorships. The most popular topics included low back pain. Interestingly, the first-ranked article was not a spine-specific topic rather it was regarding general physical and mental health status survey update review.

Elgafy HK, Miller JD, Hashmi S, Ericksen S. Top 20 cited *Spine Journal* articles, 1990-2009. *World J Orthop* 2014; 5(3): 392-397 Available from: URL: http://www.wjgnet.com/2218-5836/full/v5/i3/392.htm DOI: http://dx.doi.org/10.5312/wjo.v5.i3.392

INTRODUCTION

Modern medicine has been evolving at an increasingly rapid rate for the past 40 years. Advancements in spine

surgery are no exception to this trend. *Spine Journal* released its first issue in March 1976, and for nearly 35 years has been the premiere journal dedicated to the medical management and surgical practice of the spine. At present, *Spine* is affiliated with 12 international spine societies including Cervical Spine Research Society and Scoliosis Research Society.

With the current expansion of information and research in the field of spine surgery, it has become important to measure the academic significance of journals and research articles. The use of citation analysis is another method in the evaluation of academic influence. Citation analysis has been used to assess the contributions of multiple journals[1-22]. One method of analysis is the use of impact factor (IF) in the assessment of the academic importance of a journal. In 1972, Dr. Eugene Garfield introduced IF in order to serve as a means of rating journal quality. IF is defined as the total number of citations of all articles within a journal within a specific time period divided by the total number of publications within the journal in the same period. In 1981, the first calculated IF for Spine was 0.894, whereas in 2007 the IF was reported 2.499[6,7].

Another approach in evaluating citation-based significance is the use of the Institute for Scientific Information (ISI). ISI database has managed journal publications and citations since 1945. This is a collection of all types of information as well as citations that are related to this and all other academic medical fields. The most current journal citation database under the ISI consists of the Science Citation Index (SCI). The SCI collects citation statistics from more than 6650 journals encompassing over 150 diverse disciplines.

The purpose of this study was to determine the most influential authors and articles contributing to spine research. SCI was searched for the 20 most cited articles and authors in the *Spine Journal* during the last 20 years of publication.

MATERIALS AND METHODS

On December 19, 2010, ISI Web of Knowledge was accessed to search the top cited articles in the *Spine Journal* from the last two decades[8]. First we narrowed the search to only entries in *Spine*. Then we ensured only articles were included, omitting editorials, letters and case reports. We further narrowed the search to include articles published between 1990 and 2009. Each of the top 20 articles was reviewed and basic information was recorded including type of article (basic science or clinical), subtype (biomechanics, animal study, randomized control trial, cohort study, case series or review article), level of evidence if clinical type, and anatomical part of the *Spine* studied.

Next, on the same day, we gathered data for the top published authors in *Spine* from 1991-2009. We accessed ISI Web of Knowledge to compile the data. Again omitting editorials and letters, we narrowed our search to the specific years and sorted the results based on number of publications per author. The top 20 authors and their articles were reviewed. The total number of citations for each author was calculated. We also collected data based on number of first-authorships per top published author. Further, the number of citations for these papers was also calculated. Finally, a ratio of number of citations divided by number of first-authorship was calculated for each author.

RESULTS

Based on information gathered in December 2010, the top 20 cited articles from 1990 to 2009 are listed by numerical rank in Table 1. The number of citations per article ranged from 491 to 267. There was a tie for the 18th spot. Although the range between the first and the twentieth ranked paper was 224, there were no drastic drops between any consecutive ranks. The average decrease in the number of citations between consecutive articles is 10.52, with a range of 44 (between third and fourth ranked articles) and 1 (between 18th and 20th ranked articles). The overall range of citations may seem large at 224, however the highest data point was only cited less than twice as often as the lowest.

The study characteristics of each article of the top 20 are summarized in Table 2. Included in this table is the article type, sub-type, level of evidence, and anatomical or diagnostic field of spine studied if applicable. Of the top 20, 17 articles involve clinical research and three are basic science articles. The clinical research articles included six review articles, three prospective cohort studies, three randomized-control trials, three case series, two cross-sectional studies, and one biomechanical study. It is worth noting; of the top three spots, two papers are review articles. The basic science studies included one biomechanical, one animal study, and one review article.

Various subjects are covered among these top 20 papers. The most common theme involved back pain; five papers discussed low back pain and one paper discussed neck pain. Three articles involved the topic of osteoporotic compression fractures, making this the second most common subject in the top articles. Of the top 10 articles, two involve low back pain, the most common theme, while two other articles in the top 10 involve general health status.

The top-cited 20 authors of *Spine* between 1990-2009, number of total articles published, total citations, lead authorships, lead authorship citations, and ratio of total citations divided by lead authorships are listed in Table 3. There are two authors that have more than 100 publications. The range of publications is 41 to 135. Three authors tied for 19th position with 41 publications each, making the list a total of 21 authors. Three authors currently work in Japan, one in China, one in Sweden and the remaining 16 authors work in the United States. The original rank of these authors is in order of most articles published. After calculation of the ratio, number of

Table 1 Top 20 cited papers in the spine journal, 1990-2009

Rank	Ref.	Title	Number of citations
1	Ware *et al*[23]	SF-36 health survey update	491
2	Bigos *et al*[24]	A prospective study of work perceptions and psychological factors affecting the report of back injury	460
3	Deyo *et al*[25]	Outcome measures for low back pain research - A proposal for standardized use	432
4	Hodges *et al*[28]	Inefficient muscular stabilization of the lumbar spine associated with low back pain - A motor control evaluation of transversus abdominis	388
5	Banwart *et al*[29]	Iliac crest bone-graft harvest donor site morbidity- A statistical evaluation	384
6	Zdeblick *et al*[30]	A prospective, randomized study of lumbar fusion – preliminary results	376
7	Beaton *et al*[31]	Guidelines for the process of cross-cultural adaptation of self-report measures	364
8	Buckwalter *et al*[32]	Spine update- Aging and degeneration of the human intervertebral disc	358
9	Spitzer *et al*[33]	Scientific monograph of the Quebec task-force on whiplash-associated disorders-Redefining whiplash and its management	348
10	Garfin *et al*[34]	New technologies in spine - Kyphoplasty and vertebrosplasty for the treatment of painful osteoporotic compression fractures	335
11	Lieberman *et al*[35]	Initial outcome and efficacy of "kyphoplasty" in the treatment of painful osteoporotic vertebral compression fractures	330
12	Barr *et al*[36]	Percutaneous vertebroplasty for pain relief and spinal stabilization	328
13	Patrick *et al*[37]	Assessing health-related quality-of-life in patients with sciatica	311
14	O'Sullivan *et al*[38]	Evaluation of specific stabilizing exercise in the treatment of chronic low back pain with radiologic diagnosis of spondylolysis or spondylolisthesis	299
15	Marras *et al*[39]	The role of dynamic 3-dimensial trunk motion in occupationally-related low back disorders- The effects of workplace factors, trunk position, and trunk motion characteristics on risk of injury	289
16	Klenerman *et al*[27]	The prediction of chronicity in patients with an acute attack of low-back pain in a general-practice setting	287
17	Olmarker *et al*[40]	Autologous nucleus pulposus induces neurophysiologic and histologic changes in porcine cauda-equina nerve roots	282
18	Fritzell *et al*[41]	2001 Volvo Award winner in clinical studies: Lumbar fusion versus nonsurgical treatment for chronic low back pain - A multicenter randomized controlled trial from the Swedish Lumbar Spine Study Group	268
18	Thompson *et al*[42]	Preliminary evaluation of a scheme for grading the gross morphology of the human intervertebral disk	268
20	Bovim *et al*[43]	Neck pain in the general population	267

citations to first authorship, a new rank was distributed amongst the authors. This rank can be found in the last column of Table 3.

DISCUSSION

Scholastic importance and academic weight given to a journal article is often measured by the amount of citations received. Commonly, throughout specialized areas of medicine, the number of citations given to an article correlates to the influence it has in medical literature. However, the received citations can also be used to investigate the internal growth of a journal. As the number of citations correlates with academic impact, it also directly contributes to the increase in IF of a journal. As a tool to delineate the articles and subjects that have contributed growth in spine surgery, it was the goal of this study to determine the top 20 articles of *Spine* between 1990-2009.

The first ranked article had 491 citations, while the 20th ranking article had 267 citations recorded. The range is modestly established as 224, while the average difference between consecutive ranking articles in the top 20 is 10.5. The difference between the first-ranked article (491) and second-ranked article (460) is 31 citations. However, the difference between the tied 18th and 20th ranked articles is 1 citation. The 20 top-cited articles in the *Journal of Orthopaedic Trauma* (*J Orthop Trauma*) include two "citation classics" surpassing the 100 citation level[22]. The range of citations in the top 20 articles was 566 to 64 citations. In the "Leading 20 at 20" study the top-ranked article has 566 citations, with the second-ranked article having 150, with a difference of 416. While this is significantly higher difference than the top two articles in *Spine*, the 19th and 20th ranked articles in *J Orthop Trauma* also differed by 1 citation. The top 20 articles in the *Journal of Pediatric Orthopaedics* had a range of 231 to 51 citations, including four articles with over 100 articles[10]. This suggests the popularity of many different articles within *Spine* over nearly two decades, no one article being completely controlling in the increasing academic impact of *Spine*.

A large number of the top 20 articles were clinical articles, rather than basic science articles. The 17 clinical articles included five review articles, while the remaining articles were equally divided with three prospective cohort studies, case-series, and cross-sectional studies. Overall, 20% (5) of the top 20 articles were review articles. A similar rate of 15%-20% review articles has been noted in other studies in top-cited literature[10,20]. Two of the top three ranked articles were clinical review articles, suggesting the importance of literature review as a role of *Spine*. Yet, 14 of the top 20 articles are original articles with four Level 1 articles. This differs from other top-cited article studies, including the Lefaivre *et al*[22] report of the top 20 articles in the *J Orthop Trauma* in which there was one Level 1 article.

Interestingly, the first-ranked article was not a spine-specific topic rather it was regarding general physical and mental health status survey update review[23]. The SF-36 survey has been used in both general population, as well

Table 2 Study characteristics of the top 20 cited papers in the spine journal, 1990-2009

Rank	Ref.	Type	Subtype/level of evidence	Subject
1	Ware *et al*[23]	Clinical	Review/level 4	General health
2	Bigos *et al*[24]	Clinical	Prospective cohort/level 1	Back injury
3	Deyo *et al*[25]	Clinical	Review/level 3	Low back pain
4	Hodges *et al*[28]	Clinical	Prospective cohort/level 3	Low back pain
5	Banwart *et al*[29]	Clinical	Case series/level 4	Iliac crest bone graft harvest
6	Zdeblick *et al*[30]	Clinical	Randomized control trial/level 2	Lumbar/lumbosacral fusion
7	Beaton *et al*[31]	Clinical	Review/level 4	General health
8	Buckwalter *et al*[32]	Basic Science	Review	Intervertebral disk
9	Spitzer *et al*[33]	Clinical	Review/level 4	Whiplash disorders
10	Garfin *et al*[34]	Clinical	Review/level 2	Osteoporotic compression fractures
11	Lieberman *et al*[35]	Clinical	Case series/level 4	Osteoporotic compression fractures
12	Barr *et al*[36]	Clinical	Case series/level 4	Osteoporotic compression fractures/spinal tumor
13	Patrick *et al*[37]	Clinical	Prospective cohort/level 1	Low back pain
14	O'Sullivan *et al*[38]	Clinical	Randomized control trial/level 1	Spondylolysis/spondylolisthesis.
15	Marras *et al*[39]	Clinical	Cross-sectional	Occupationally-related low back pain
16	Klenerman *et al*[27]	Clinical	Cross-sectional	Chronicity of low back pain
17	Olmarker *et al*[40]	Basic Science	Animal study	Nucleus pulposus induced histological/morphological changes
18	Fritzell *et al*[41]	Clinical	Randomized control trial/level 1	Lumbar fusion
18	Thompson *et al*[42]	Basic Science	Biomechanics	Intervertebral disk morphology
20	Bovim *et al*[43]	Clinical	Cross-sectional	Neck pain

Table 3 The top-cited 20 authors in the spine journal, 1990-2009

Rank	Author	Current institution	Articles published	Total citations	Lead authorships	Lead author citations	Ratio
1	Lenke LG	Washington University; United States	135	2833	8	205	354.1
2	Bridwell KH	Washington University; United States	117	2553	13	371	196.4
3	Vaccaro AR	Thomas Jefferson University; United States	88	1701	20	517	85.1
4	Takahashi K	Chiba University; Japan	72	1021	9	132	113.4
5	An HS	Rush University; United States	67	1506	9	252	167.3
6	Panjabi MM	Yale University; United States	64	3034	22	989	137.9
7	Weinstein JN	Dartmouth University; United States	64	2315	6	142	385.8
8	Deyo RA	University of Washington; United States	63	4152	8	1047	519
9	Albert TJ	Thomas Jefferson University; United States	61	1307	6	191	217.8
10	Ebraheim NA	University of Toledo; United States	57	1053	27	539	39
11	Kikuchi S	Fukushima Medical University; Japan	56	1212	4	64	303
12	Moriya H	Chiba University; Japan	52	907	0	0	n/a
13	McAfee PC	St. Joseph Medical Center; United States	48	1762	10	377	176.2
14	Newton PO	Rady Children's Hospital; United States	45	468	13	251	36
15	Andersson GBJ	Rush University; United States	45	1448	2	42	724
16	Luk KDK	University of Hong Kong; China	44	568	10	137	56.8
17	Boden SD	Emory University; United States	43	2215	14	1349	158.2
18	Olmarker K	University of Gothenburg; Sweden	43	1512	12	767	126
19	Kim YJ	Columbia University; United States	41	751	17	466	44.2
20	Garfin SR	University of California, San Diego; United States	41	1239	5	448	247.8
21	Bradford DS	University of California, San Francisco; United States	41	1288	3	102	429.3

as clinical trials. Ware stated in the review article the broad use of the SF-36 health survey was attributed to its brevity and comprehensiveness. As this review article was not limited to spine-related disorders and treatment, its clinical applicability may have been greater than the other articles. Surprisingly the number of citations of this article was comparable to the leading articles.

A variety of subjects were investigated in the top 20 articles in *Spine*. The most popular topics included low back pain, back injury, osteoporotic compression fractures and lumbar fusion. The second most cited article investigated perceptions and factors in reporting back injury[24]. This study sought to identify risk factors for reporting back pain at work. The third ranked article considered recommendations in the use of standardized measures in clinical outcomes research in patients with back pain[25]. Of the top three articles, two are concerned with outcome measurement and analysis.

Low back pain was the most common theme encountered in the top cited articles. A study by Deyo *et al*[26] in 2002 found that low back pain lasting at least a whole day in the past 3 mo was reported by 26.4% and neck pain was reported by 13.8% of a total 31044 adult respondents. Also it was concluded that physician visits for low back pain have changed little since the 1990s. Given the high prevalence of low back pain, it was expected to be a

reoccurring subject in the top cited articles. Some articles investigated predictive factors, while others studied novel techniques in the treatment of low back pain. Klenerman *et al*[27], investigated the factors predictive of the progression of acute to chronic low back pain. This shows focus on preventative measures with regard to low back pain.

Of the top 20 cited articles, six articles researched topics related to surgical management and outcomes of spine disorders. These topics included iliac crest bone graft harvest, comparison of kyphoplasty and vertebrosplasty, outcome and efficacy of kyphoplasty, percutaneous vertebroplasty, and lumbar fusion. On the other hand, Lefaivre's study of the top 20 cited articles in *J Orthop Trauma* found 15 articles involving the subject of surgical treatment[22]. The number of non-surgical studies highly cited in *Spine* indicates a multimodal nature of spine care.

The most published authors between the 1990-2009, shown in Table 3, have had significant impact in the field of spine surgery. However, it is interesting to note that only two authors with articles in the top 20 cited articles are included in the list of top 21 total citations from 1990-2009. The disconnect between these two data sets brings to light the tremendous contributions of authors *vs* the contributions of single articles in *Spine*. The top cited author between 1990-2009 had 4152 total citations, more than eight times the number of the total citations received by the first ranked article in *Spine* during this era. RA Deyo received a total of 4152 citations in this nearly two-decade period, and also had the third-ranked top-cited article in *Spine*. The other author included in both lists was SR Garfin, he received 335 citations for the tenth ranked article in *Spine,* and received a total 1239 citations for 41 articles published from 1990-2009. LG Lenke was first-ranked according to total number of articles published. The ratio of total number of articles published to lead authorships, or citations per first authorship, relays the relative citation impact. The first-ranked author by relative impact factor was GBJ Andersson with a ratio of 724. The lowest ratio of the top 21 authors by total publications was 36, with one author having no lead authorships thus a null ratio.

There are several limitations to this study. Articles with citations by the author themselves, textbook citations of articles, and citations in journals in which authors prefer to cite their own research were not included in the number of total citations. Further, the measurement of academic importance cannot be determined using only citation analysis. The total number of citations cannot reflect necessarily on the overall quality of research presented. Another bias within this study is that of lead authorship. First authors tend to be more senior faculty, and at times may not duly reflect the main influence or source of the research. In addition, the most influential author of a paper may not be the lead author. Time is another bias in this study, as more recent articles have less opportunity to gain citations. Most importantly, the trends observed in this study only describe *Spine* in a snapshot in time, and cannot reflect the trends and changes in spine surgery as a field.

In conclusion, *Spine Journal* and its authors have a clear impact on the scientific community based on this review of the top articles and authors in the last 20 years. Out of the 21 most cited authors, 16 work in the United States, 3 work in Japan, one in China, one in Sweden. A variety of subjects were investigated in the top 20 articles in *Spine*. The most popular topics included low back pain, back injury, osteoporotic compression fractures and lumbar fusion. Interestingly, the first-ranked article was not a spine-specific topic rather it was regarding general physical and mental health status survey update review.

COMMENTS

Background

Modern medicine has been evolving at an increasingly rapid rate for the past 40 years. Advancements in spine surgery are no exception to this trend. With the current expansion of information and research in the field of spine surgery, it has become important to measure the academic significance of journals and research articles.

Research frontiers

Spine is affiliated with 12 international spine societies including Cervical Spine Research Society and Scoliosis Research Society.

Innovations and breakthroughs

Using the Institute for Scientific Information Web of Knowledge, the authors determined the most cited articles in *Spine Journal* between 1990-2009. The characteristics and type of article were recorded. Next, the authors evaluated the most published authors during the same time period and calculated the number of citations for each author. The number of first authorships for each of these authors was also determined along with the number of citations for those articles.

Applications

Spine Journal and its authors have a clear impact on the scientific community based on this review of the top articles and authors in the last 20 years.

Peer review

Interesting topic and well-organized paper, should be accepted.

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CASE REPORT

Delayed presentation of a loose body in undisplaced paediatric talar neck fracture

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Author contributions: Patel V contributed to main body of report; Bloch B contributed to discussion section; Johnson N contributed to literature search; Mangwani J is senior author, supervisor and technical advisor of the paper.

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Abstract

Fractures of the talus are rare in children. A high index of suspicion is needed to avoid missing such an injury, which is not an uncommon occurrence especially with undisplaced fractures. We present an unusual case of an undisplaced talar neck fracture in a five-year-old child leading to a delayed presentation of a symptomatic osteochondral loose body in the ankle joint. To our knowledge there are no reports in the literature of osteochondral loose bodies occurring in conjunction with an associated undisplaced talar neck fracture in either children or adults. The loose body was removed using anterior ankle arthroscopy. The child had an uneventful post operative recovery and regained full range of movement and function of his ankle joint and was discharged at one year follow-up. We aim to highlight the need to have a low threshold to further evaluate symptomatic children after fracture healing of an undisplaced talar neck fracture for a possible associated loose body in the ankle joint.

Key words: Talus; Fracture; Loose body; Ankle arthroscopy; Children

Core tip: Undisplaced talar neck fractures in children rarely present with an associated osteochondral loose body. If a child remains symptomatic after fracture healing we would advocate further evaluation with magnetic resonance imaging (MRI) scan to exclude an associated loose body. If a loose body or an osteochondral lesion is identified on MRI scan it can be safely treated with anterior ankle arthroscopy.

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INTRODUCTION

Fractures of the talus are rare in children. Skeletally immature bone is less brittle with higher elastic resistance than adult bone. The paediatric talus can therefore sustain higher forces before fractures occur[1].

The mechanism of injury is generally as a result of axial loading of the talus against the anterior tibia with the foot in dorsiflexion and usually follows high-energy trauma such as falls from height and road traffic collisions. However recently supination has also been considered as a mechanism of injury which due to impingement of the talus against the medial malleolus[2]. History and clinical examination in children can be challenging and plain radiographs may not necessarily demonstrate

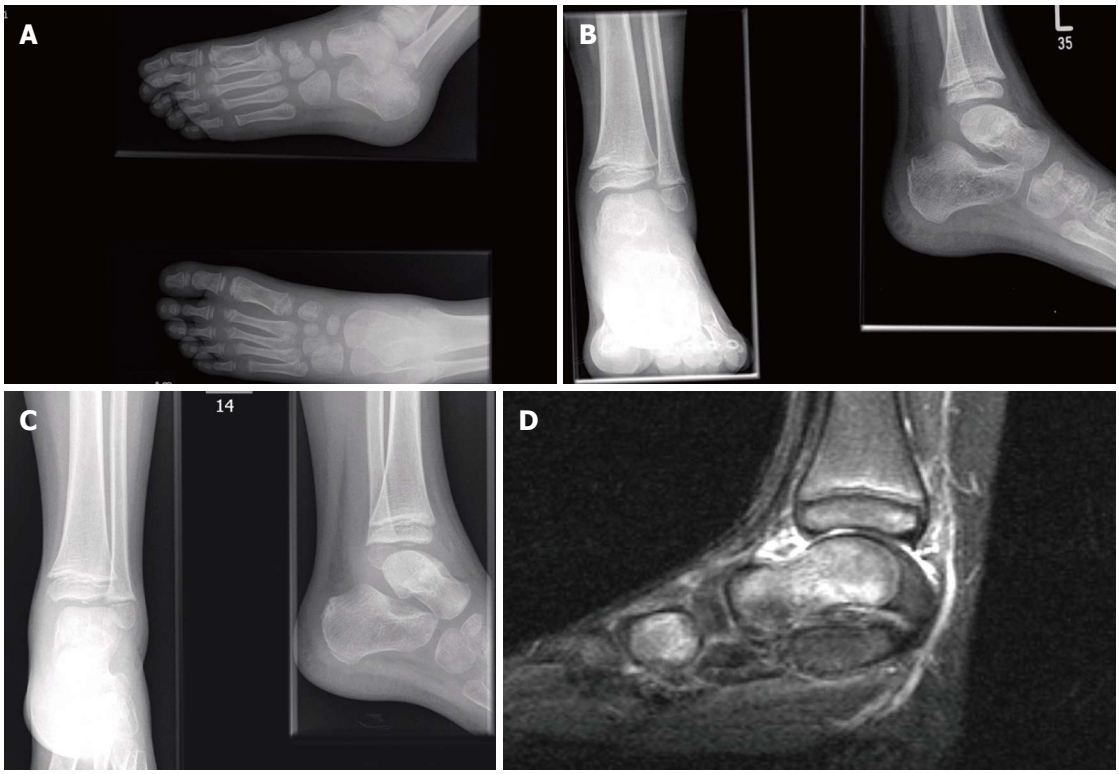

Figure 1 The magnetic resonance imaging scan for delayed presentation of a loose body in undisplaced paediatric talar neck fracture. A: Initial foot and ankle radiographs taken post injury in the United Kingdom showing an undisplaced talar neck fracture; B: Radiographs taken at four weeks following immobilisation in plaster showing a healed fracture; C: Repeat radiographs taken three weeks following discharge from clinic as patient returned symptomatic. A clear loose body in ankle joint is present; D: Pre-operative magnetic resonance imaging scan of ankle demonstrates a 5.5 mm loose body antero-superiorly to the left talar dome and an osteochondral defect (OCD) of the distal talar dome.

an obvious fracture or associated osteochondral defect (OCD)[3]. Time constraints, limited resources or failure to appreciate the nature of the injury can lead to failure of establishing correct diagnosis and follow up.

CASE REPORT

A five-year boy sustained an injury to his left ankle after jumping off a bunk bed whilst on holiday abroad. He was seen at the local hospital and his parents were told that the child had sustained a simple soft tissue injury following a normal plain radiograph of his ankle.

Upon his return to the United Kingdom he was brought to the local Emergency Department (ED) two days following his injury as he was still reluctant to bear weight through his left ankle and complained of increasing pain and swelling.

Radiographs revealed an undisplaced fracture of the talar neck (Figure 1A). The child was managed conservatively in a below knee cast and kept non-weight bearing for four weeks.

After four weeks his plaster was removed and clinical examination was satisfactory. Repeat radiographs taken showed a healing talar neck fracture (Figure 1B).

Three weeks later the child returned to the ED struggling with bearing weight after a trivial injury to his left ankle caused by jumping from a standing height. Although there was no obvious swelling around the ankle there was specific tenderness over the anterior aspect of the ankle joint. Radiographs were suggestive of an osteochondral loose body in the joint space between the tibia and talus (Figure 1C).

An magnetic resonance imaging (MRI) scan confirmed a 5.5 mm loose body antero-superiorly to the left talar dome and an OCD of the distal talar dome with a healed talar neck fracture (Figure 1D).

Following discussion with the child's parents we elected to perform an arthroscopic removal of the osteochondral loose body. Arthroscopy was performed using a 2.7 mm wrist arthroscope. Intra-operatively a fibrocartilage cap was found covering the OCD on the talar dome and therefore there was no need to perform microfracture.

One month after the procedure the child was pain free with no tenderness on palpation of the ankle joint. At final follow up one year after injury the child remained asymptomatic and radiographs revealed no progression of the osteochondral lesion or evidence of avascular necrosis (AVN).

DISCUSSION

The reported rate of avascular necrosis in children with non-displaced talus fractures is 16%. This is considerably

higher than the reported rate in adults[4]. This suggests that the immature talus may be more prone to AVN. Rammelt *et al*[4] reported nearly half of all cases of AVN following an undisplaced talus fracture in a child occurred when the fracture had been initially missed.

The incidence of AVN following Hawkins Type Ⅲ fractures of the talar neck (talar neck fracture with dislocations involving the subtalar and ankle joints) may approach 100%, particularly if diagnosis and reduction are delayed[5-7].

Most type I fractures can be treated closed unless there is loss of reduction. Hawkins' original work in patients with a mean age of 30.4 years (8-63 years range) reported a less than 10 % association of AVN with type I fractures[8].

In this case there was an osteochondral loose body associated with an undisplaced talar neck fracture which had a delayed presentation. To our knowledge there are no reports in the literature of osteochondral loose bodies occurring in conjunction with an associated undisplaced talar neck fracture in either children or adults.

Isolated osteochondral lesions of the talar dome are a rare entity in children. The aetiology is thought to be due to either ischaemia or trauma, with the latter considered the most important. Berndt and Herty in 1959 were able to reproduce medial and lateral osteochondral defects in cadavers. Lateral OCDs were produced by a strong inversion force to a dorsi-flexed foot and medial OCDs were produced by a strong inversion force to a plantar-flexed foot with lateral rotation of the tibia[9].

Conservative management remains the mainstay of treatment of traumatic OCDs in children. Wester *et al*[10] reported a series of 13 cases which were followed up after 24 years. Eight cases had normal follow up CT scans and clinical findings. Two cases had a loose body in the ankle joint of which one had remained symptomatic since the time of injury although it was noted that the primary OCD had healed[10].

The role of ankle arthroscopy in the management of chronic and post-traumatic ankle disorders in adults is well established. Uglow and colleagues[11] reported outcomes in children following arthroscopy being comparable to adult series for the management of OCDs and anterolateral soft tissue impingement. In particular they highlighted the poor correlation between findings on MRI and intraoperative findings on arthroscopy especially in relation to small OCDs and impingements lesions.

This case highlights the need for high index of suspicion required to diagnose an undisplaced talar neck fracture in a child. If there are ongoing symptoms after fracture healing one should look for presence of an osteochondral loose body. Removal of osteochondral loose body using arthroscopic technique is safe and effective procedure.

COMMENTS

Case characteristics

Five-year-old child presenting with a symptomatic painful ankle which following a healed undisplaced talar neck fracture.

Clinical diagnosis

Painful ankle with difficulty weight bearing.

Differential diagnosis

Ligamentous injury, osteochondral defect, non-union and loose body.

Laboratory diagnosis

Normal serum Haematology and biochemistry.

Imaging diagnosis

An magnetic resonance imaging (MRI) scan confirmed a 5.5 mm loose body antero-superiorly to the left talar dome and an osteochondral defect of the distal talar dome with a healed talar neck fracture.

Pathological diagnosis

Delayed presentation of a symptomatic osteochondral loose body in the ankle joint associated with a healed undisplaced talar neck fracture

Treatment

Arthroscopic removal of the osteochondral loose body used a 2.7 mm wrist arthroscope.

Related reports

To the authors knowledge there are no reports in the literature of osteochondral loose bodies occurring in conjunction with an associated undisplaced talar neck fracture in either children or adults.

Experiences and lessons

Undisplaced talar neck fractures in children rarely present with an associated osteochondral loose body. If a child remains symptomatic after fracture healing the authors would advocate further evaluation with an MRI scan to exclude an associated loose body.

Peer review

This manuscript is suitable to be published.

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pres-

sure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23243641.

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Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

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