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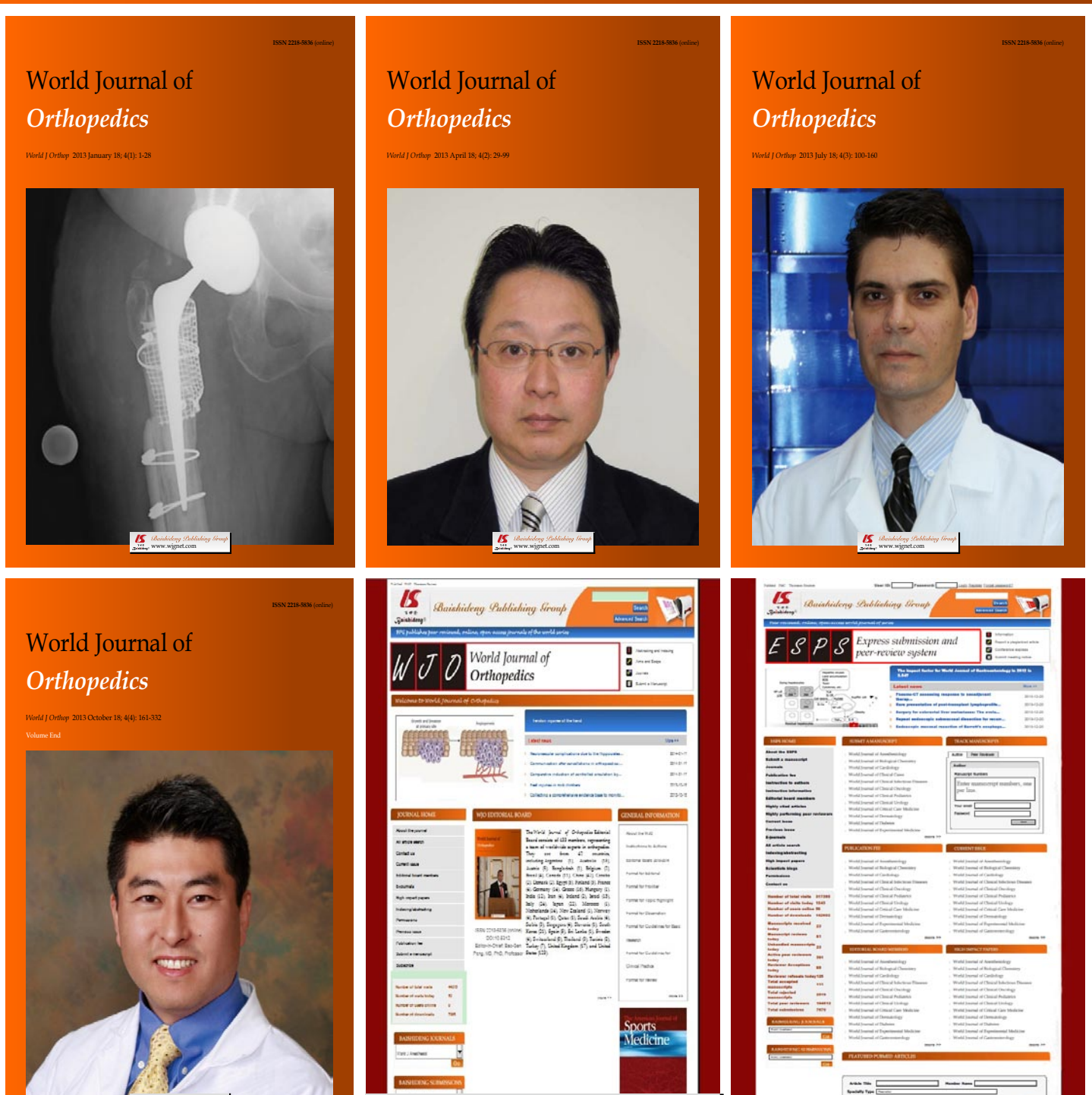

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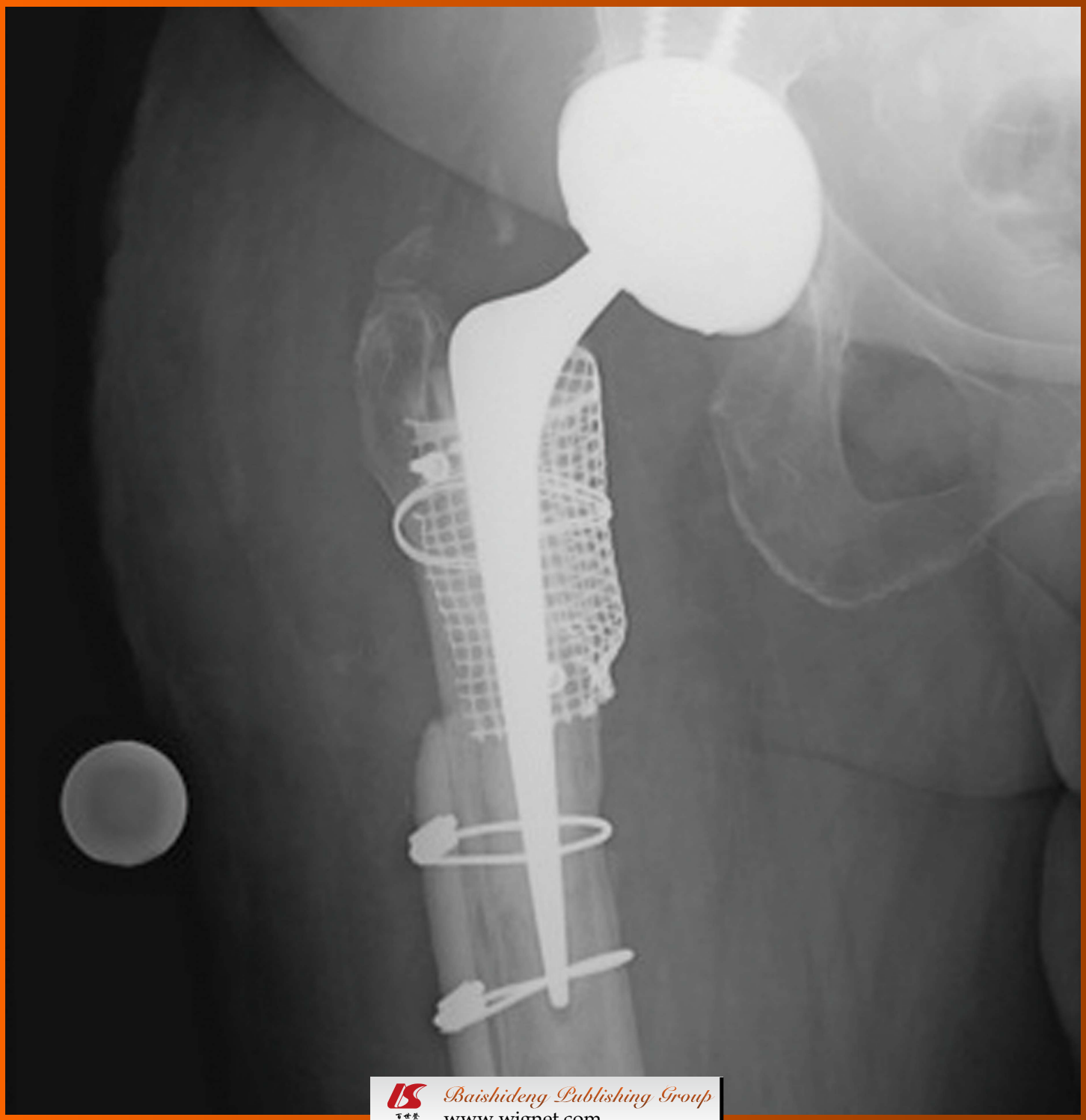

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EDITORIAL

Regulation of bone destruction in rheumatoid arthritis through RANKL-RANK pathways

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Abstract

Recent studies have demonstrated that osteoclasts, the primary cells responsible for bone resorption, are mainly involved in bone and joint destruction in rheumatoid arthritis (RA) patients. Recent progress in bone cell biology has revealed the molecular mechanism of osteoclast differentiation and bone resorption by mature osteoclasts. We highlight here the potential role of the receptor activator of nuclear factor κB ligand (RANKL)-RANK pathways in bone destruction in RA and review recent clinical trials treating RA by targeting RANKL.

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Key words: Rheumatoid arthritis; Osteoclast; Receptor activator of nuclear factor κB ligand; Bisphosphonate; Denosumab

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by remarkable synovial hyperplasia followed by the massive joint destruction[1,2]. Investigation into the pathogenesis of joint destruction in RA has revealed the transformed phenotype of rheumatoid synovial cells[3]. Proliferating inflammatory synovial cells lead to pannus formation that invades articular cartilage and bone[4]. Radiographic studies demonstrate that bone erosion in RA begins early in the disease, and progresses throughout its course[5,6]. Bone erosion results in severe deformity of the affected joints and impairs the normal activity of patients. Therefore, inhibiting bone destruction is one of the most challenging goals in the treatment of RA. Because the exact etiology of RA remains unknown, most treatments of RA have targeted symptoms of the disease. Non-steroidal anti-inflammatory drugs have been used to reduce the painful symptoms of the disease, but they have little effect on stopping the progression of joint destruction. Some disease-modifying anti-rheumatic drugs such as methotrexate are known to suppress joint destruction in RA[7,8]. In addition, recent clinical studies have demonstrated that various biological agents such as antibodies against inflammatory cytokines (e.g., infliximab, adalimumab and tocilizumab) or CTLA4-Ig (abatacept) not only suppress joint symptoms in RA patients but also markedly ameliorate joint destruction[9-12]. However, the bone-protective function of these drugs is still limited, and they are accompanied by severe side effects, such as infection, since they suppress a patient's immunological reaction[13].

There is accumulating evidence that osteoclasts, primary cells responsible for bone resorption, are involved in bone destruction in RA, and recent progress in molecular biology and biochemistry has revealed the molecular mechanism of osteoclast differentiation and bone resorption. In this chapter, I would like to focus on the role of osteoclasts in bone and joint destruction in RA, the mechanism of osteoclast generation in inflammatory joint, and propose that osteoclasts can be potential targets in RA therapy.

INVOLVEMENT OF OSTEOCLASTS IN BONE DESTRUCTION IN RA

RA is characterized by proliferative pannus formation leading to erosive bone destruction originating from the interface of cartilage and bone (the bare area). Synovial tissues of RA joints produce various inflammatory cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), which are believed to play important roles in joint destruction. The cellular mechanism of bone and cartilage destruction in RA still remains unclear, but recent studies have revealed the essential role of osteoclasts (Figure 1). Bromley *et al*[14] observed a number of acid phosphatase-positive multinucleated cells (chondroclasts and osteoclasts) in the erosive areas of RA joints obtained at the time of joint replacements. In collagen-induced arthritis, multinucleated giant cells were observed at the bone-pannus junctions of arthritic joints, and cells isolated from the lesions were able to differentiate into mature osteoclasts. Gravallese *et al*[15] also found multinucleated cells present on subchondral bone surface and in the areas of direct invasion of pannus into subchondral bone. Their important discovery was that those multinucleated cells were positive for unique markers of osteoclasts such as tartrate-resistant acid phosphatase (TRAP), cathepsin K, and calcitonin receptors, satisfying the major criteria of mature osteoclasts. Interestingly, some multinucleated cells and mononuclear cells apart from the bone surface were TRAP-positive. These findings suggest the possible role of synovial tissues for osteoclastogenesis in RA. To reveal the osteoclastogenic potential of RA synovial tissues, synovial cells from RA synovia were cultured in the presence of osteotropic factors such as 1β,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$] and macrophage colony-stimulating factor (M-CSF)[16]. After 3 wk of culture, we observed many multinucleated giant cells, which were TRAP-positive, possessed abundant calcitonin receptors, and made resorption pits on dentine slices. We also demonstrated that peripheral monocytes can differentiate into osteoclast-like cells when co-cultured with synovial fibroblasts obtained from RA synovial tissues in the presence of 1,25$(OH)_2D_3$ and M-CSF. Similar results were reported by Fujikawa *et al*[17]. They found that synovial macrophages isolated from RA synovial tissues can differentiate into osteoclast-like cells when co-cultured with UMR 106 rat osteoblast-like cells. These results suggest that RA synovial fibroblasts can support osteoclast differentiation from monocyte-macrophage lineage precursor cells under a suitable condition, at least *in vitro*.

INVOLVEMENT OF RANKL/RANK PATHWAYS IN BONE DESTRUCTION IN RA

Remarkable progress has been made in recent years in the field of osteoclast research primarily due to the finding of the receptor activator of nuclear factor κB (NF-κB) ligand (RANKL)/RANK system[18]. RANKL is a member of the TNF superfamily of cytokines, which was originally identified as a membrane-bound survival factor for dendritic cells produced by activated T cells[19]. The expression of RANKL can be also induced in osteoblasts and bone marrow stromal cells by osteotropic hormones such as 1,25$(OH)_2D_3$ and parathyroid hormone[20]. In the presence of M-CSF, RANKL can stimulate osteoclast differentiation from hematopoietic precursor cells *in vitro*[20]. RANKL also acts on mature osteoclasts and activates the bone-resorbing activity and survival of the cells. RANKL binds to its receptor RANK, a transmembrane receptor belonging to the TNF receptor superfamily, which is expressed in monocyte-macrophage lineage osteoclast precursor cells as well as in mature osteoclasts and dendritic cells. Binding of RANKL to RANK induces intracellular signals including NF-κB activation and c-Jun N-terminus kinase activation. The other important actor in this system is osteoprotegerin (OPG) a soluble receptor of RANKL, belonging to the TNF receptor superfamily[19]. OPG specifically binds to RANKL, and inhibits RANKL activity by preventing its binding to RANK.

The essential role of RANKL/RANK signaling pathways in osteoclast development *in vivo* has been established by a series of targeted gene disruption experiments[19] comprising, the targeted disruption of either RANKL or RANK induced osteopetrosis in mice, a pathological bone disease which is characterized by an increased bone mass due to a deficiency in osteoclast differentiation[21,22]. We and another group found that mice deficient in TRAF6, a signaling molecule involved in RANK signaling, also showed osteopetrotic phenotypes. In contrast, the targeted disruption of OPG induces reduced bone mass in mice, reminiscent of osteoporosis, due to the increased number and activity of osteoclasts[18,23,24]. These results clearly demonstrate the essential role of RANKL/RANK pathways in osteoclast development and activation *in vivo*. The next question is whether the RANKL/RANK system is also involved in pathological bone destruction, such as in RA. We and others have revealed by Northern blotting, immunocytochemistry and *in situ* hybridization (Figure 2) that RANKL is highly expressed in synovial fibroblasts[12,15,25,26]. 1,25$(OH)_2D_3$ treatment increased the expression of RANKL in synovial fibroblasts and reduced the expression of OPG in the cells. RANKL expression was also detected in $CD4^+$ T lymphocytes in RA synovial tissues by *in situ* hybridization. Kong *et al*[27] demonstrated that activated $CD4^+$ T lymphocytes fixed with paraformaldehyde or culture supernatants from activated T cells can support osteoclast differentiation through the surface-bound and/or soluble RANKL they produce. They also showed that RANKL was expressed on the surface of activated T cells in synovial tissues of adjuvant arthritis rats[27]. These results suggest the important role of activated T lymphocytes in bone and joint destruction in RA. However, the role of T cells in osteoclast development is

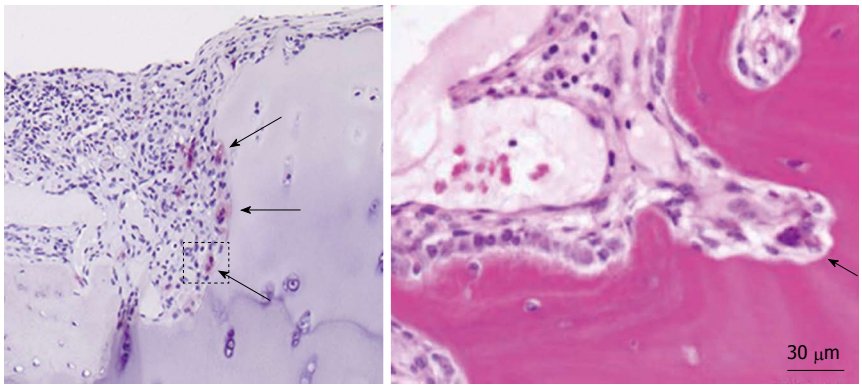

Figure 1 Inflammatory synovial proliferation and bone erosion (arrows) by osteoclasts in rheumatoid arthritis patients.

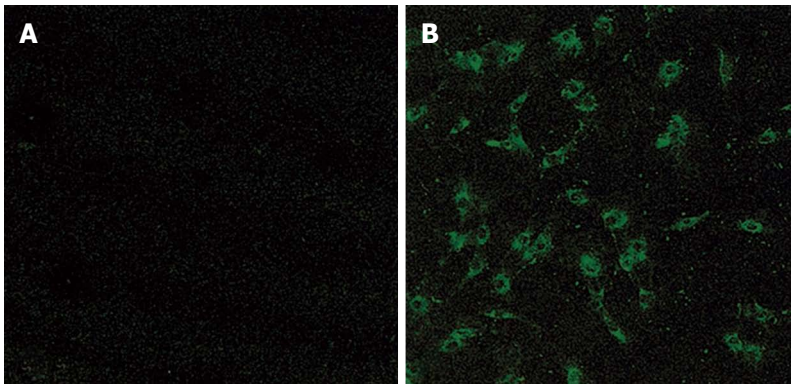

Figure 2 Immunostaining of synovial fibroblasts obtained from osteoarthritis (A) and rheumatoid arthritis (B) patients with anti-receptor activator of nuclear factor κB ligand antibody.

still controversial because activated T cells also produce many cytokines which inhibit osteoclast differentiation, such as interferon-β and IL-10. In any case, these studies indicate that RANKL produced by synovial fibroblasts and/or activated T lymphocytes in RA synovial tissues may play an essential role in osteoclast development and bone destruction in RA. Based on these findings, Kong *et al*[27] proposed that OPG can be a potent therapeutic agent against bone destruction in RA. Exogenous administration of recombinant OPG suppressed bone and joint destruction in rat adjuvant arthritis.

Reduced bone destruction in a patient with osteopetrosis and RA

In addition to the animal studies described above, the importance of osteoclasts in bone destruction in RA was further confirmed by the clinical finding in a RA patient with osteopetrosis[28]. Osteopetrosis is an inherited disorder characterized by an increase in bone mass[29]. In humans, osteopetrosis comprises a heterogeneous group of diseases, which are classified into three major groups on the basis of inheritance, age of onset, severity, and secondary clinical features: autosomal recessive infantile malignant osteopetrosis, autosomal recessive intermediate mild osteopetrosis, and autosomal dominant adult onset benign osteopetrosis. The most frequent form of osteopetrosis, which has autosomal dominant (ADO) inheritance (incidence 5:100000), is also called Albers-Schönberg disease or ADO type Ⅱ. ADO type Ⅱ is characterized by vertebral endplate thickening (rugger-jersey appearance), fragile bones with multiple fractures and delayed healing. Recent studies have shown that the *CLCN7* gene encoding type 7 chloride channel, which is essential for the acidification of the extracellular environment in resorption lacuna by osteoclasts, is a candidate gene for ADO type Ⅱ. We recently reported a very rare case of RA associated with ADO type Ⅱ. In spite of the severe inflammation and rapid progression of cartilage destruction in the patient, the progression of bone erosion was quite slow (Figure 3)[28]. These clinical findings further confirm the critical role of osteoclasts in bone destruction in RA but not in inflammation or cartilage destruction.

The mechanisms of action of aminobisphosphonate

Since osteoclasts are critically involved in bone destruction in RA, therapeutics which target osteoclasts could be good candidates for the treatment of RA. One of the most promising group of reagents which inhibit osteoclast function is bisphosphonates. Bisphosphonates (BPs), stable analogs of pyrophosphate, strongly inhibit bone resorption and have been used to treat various diseases driven by increased bone resorption, such as postmenopausal osteoporosis. Although BPs are poorly absorbed

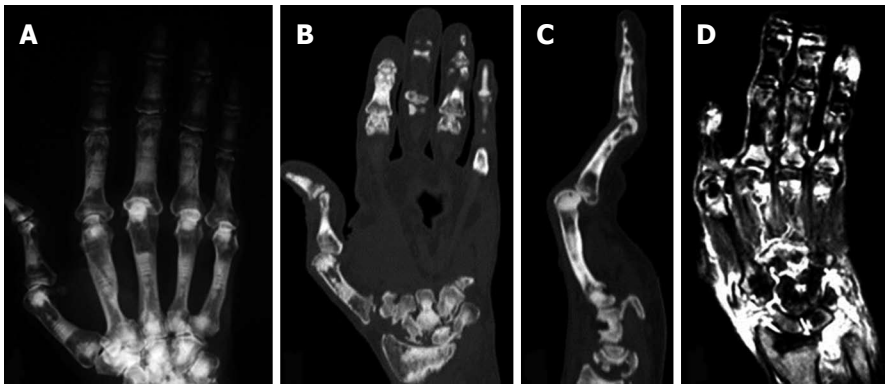

Figure 3 Plain X ray (A), computed tomography scan (B and C) and magnetic resonance imaging (D) of the right hand of an autosomal dominant Ⅱ patient with rheumatoid arthritis. Erosion of the carpal bones (B) and severe synovitis, as determined by the high intensity areas by T2-weighted magnetic resonance imaging images (D), were observed[14].

from the intestine, they are quickly deposited on the bone surface once absorbed. BPs are divided into two groups according to the structure of the side chains, a nitrogen-containing type (N-BPs) and a non-nitrogen-containing type. Non-nitrogen-containing BPs are reported to act through the intracellular accumulation of non-hydrolyzable ATP analogs that exert cytotoxic effects on OCs, while N-BPs inhibit the mevalonate pathway and prevent the post-translational prenylation of small GTP-binding proteins such as Ras, Rho, Rac and Cdc42. We recently reported that risedronate, one of the N-BPs, induced osteoclast apoptosis by suppressing the Erk pathway and increasing the expression of a pro-apoptotic Bcl family protein, Bim, while it reduced bone-resorbing activity of the cells through suppression of the Akt pathway[30].

Osteoporosis and osteoporosis-related fractures are common in RA patients[31-33] and several studies have demonstrated that bisphosphonates effectively increase bone mineral density and decrease fragile fractures in RA patients[34-36]. In spite of these strong and specific inhibitory effects of bisphosphonates on osteoclasts, only limited clinical data demonstrate the effectiveness of bisphosphonates in RA patients. Jarette *et al*[37] reported preliminary evidence that treatment with zoledronic acid plus methotrexate showed better results in reducing bone destruction than methotrexate alone. However, many other studies have failed to show positive effects of bisphosphonates against bone destruction in RA[38-40]. This may be because, in these studies, the treatment was initiated too late or the strength of the bisphosphonates used was not enough to treat the bone destruction in RA.

Effects of anti-RANKL antibody on bone destruction in RA

Denosumab is a fully human monoclonal antibody that specifically and avidly binds to RANKL. Previous clinical studies have demonstrated that administration 60 mg of denosumab subcutaneously every 6 mo to postmenopausal women with osteoporosis significantly reduced bone turnover markers, increased bone mineral density, and reduced osteoporosis-related fractures[41]. Because of the critical role of the RANKL-RANK system in osteoclast development and bone destruction in RA, clinical studies were conducted to analyze the effect of denosumab on RA[42-44]. Sharp *et al*[42] demonstrated that twice-yearly subcutaneous injections of denosumab (60 mg or 180 mg) with ongoing methotrexate treatment significantly reduced cortical bone loss in RA patients for up to 12 mo. In a phase Ⅱ clinical trial, subcutaneous administration of denosumab every 6 mo to patients with active RA suppressed the progression of subchondral bone erosions and systemic bone loss, although there was no an apparent reduction of joint inflammation or joint space narrowing. In addition, denosumab treatment over 12 mo increased mean lumbar spine and hip bone mineral density and reduced bone turnover markers such as sCTx-I and P1NP compared with placebo, regardless of baseline bone mineral density or marker levels or concomitant bisphosphonate or glucocorticoid use[44]. The rate of adverse events and serious infections requiring hospitalization did not differ between patients treated with denosumab and with placebo. These clinical observations, in addition to the results of the basic studies, clearly suggest that denosumab is effective in preventing bone erosion but not cartilage destruction in RA.

CONCLUSION

The ultimate goal of the treatment of RA is to prevent the bone and joint destruction and preserve the daily activity of patients. Recent studies have revealed that osteoclasts are involved in the pathogenesis of bone and joint destruction in RA and can be a potent therapeutic target of the disease[4,45]. Therapeutics targeting osteoclast formation or function can at least ameliorate the progression of these bone changes[27,43]. However, inhibition of osteoclast function by anti-resorptive agents alone do not completely prevent bone erosion in RA in spite of their preventive effects against systemic bone loss. Therefore, the combination of anti-resorption therapy and anti-inflammatory therapy could be an ideal therapy for RA. Thus, anti-RANKL therapy in combination with the

anti-inflammatory therapy is a promising strategy for RA treatment, and safe and effective therapies against RA may be expected in the near future.

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TOPIC HIGHLIGHT

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Femoral impaction grafting

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Abstract

Femoral impaction grafting is a reconstruction option applicable to both simple and complex femoral component revisions. It is one of the preferred techniques for reconstructing large femoral defects when the isthmus is non-supportive. The available level of evidence is primarily derived from case series, which shows a mean survivorship of 90.5%, with revision or re-operation as the end-point, with an average follow-up of 11 years. The rate of femoral fracture requiring re-operation or revision of the component varies between several large case series, ranging from 2.5% to 9%, with an average of 5.4%.

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Key words: Femoral impaction grafting; Femoral revision; Bone grafting; Revision total hip arthroplasty; Bone loss

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INTRODUCTION

Managing bone loss is one of the most challenging aspects of revision total hip arthroplasty. Femoral impaction grafting is a technically demanding and time consuming procedure, but if performed well, is capable of restoring bone stock in the revision setting with high rates of graft incorporation[1]. The technique was developed in Europe in the 1980's and popularized by the Exeter, UK group in the early 90's. Long-term follow-up data is now available showing excellent survivorship beyond 10 years[2,3]. Advances in instrumentation, and the use of longer stems to bypass areas of weak cortical bone distally, have reduced the risk of stem subsidence and femoral fracture[4,5]. The performance time and technically demanding aspects of the operation currently limit its more widespread use compared to other types of revision stems that rely on biologic fixation. The long-term success of impaction grafting ultimately depends on incorporation of particulate allograft into host bone. This process is characterized by an initial inflammatory phase followed by revascularization. Allograft is eventually resorbed and replaced with new host bone by 6-12 mo after the operation.

INDICATIONS

Femoral impaction grafting is an attractive option for restoring femoral bone stock, especially if patients are likely to require an additional reconstructive procedure in their lifetime. It can be used in revisions where the intramedullary canal is > 18 mm, as a fully porous coated stem in this situation is associated with an increased incidence of thigh pain. In femoral defects where there is not 4-6 cm of cortical bone distally to provide scratch fit of a porous coated stem, or the isthmus is non-supportive, femoral impaction grafting is a viable option. If there is minimal cancellous bone present after removal of a femoral stem,

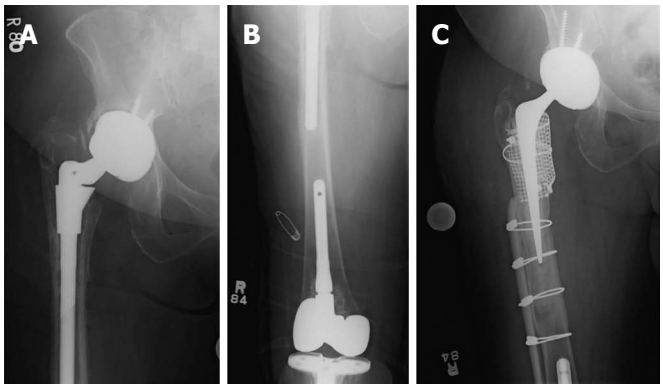

Figure 1 63 year-old female with an infected, loose right femoral component. A: A stem from an ipsilateral total knee arthroplasty prevented revision with a long extensively porous coated implant. A stage 1 revision was performed with retention of the pedestal to prevent cross-contamination followed by 6 wk of IV antibiotics with subsequent femoral impaction grafting; B: With subsequent femoral impaction grafting; C: 63 year-old female 3 mo after femoral impaction grafting. Allograft struts were applied to bypass a stress riser distally, and metal mesh was used to reconstruct the calcar.

impaction grafting is capable of creating a neomedullary canal that allows the use of a cemented stem with durable fixation. When a stem from an ipsilateral total knee arthroplasty prevents femoral component revision of a hip prosthesis with a long extensively porous coated implant, femoral impaction grafting is an option (Figure 1).

A continuous femoral tube must be confirmed intraoperatively before commencing with impaction of cancellous bone, otherwise another technique for revision should be considered. Segmental bone loss that can be converted to a contained defect with metal mesh, allograft struts or bulk allograft is amenable to impaction grafting. Although not commonly used for managing periprosthetic fracture, Tsiridis *et al*[6] reported a fracture union rate of 84% with 4 year follow-up when femoral impaction grafting was used to manage Vancouver B2 and B3 fractures.

Femoral impaction grafting requires the patient to be medically stable enough to tolerate a long operation. The technique becomes exceptionally challenging in reconstructions where there is near complete loss of the proximal 10 cm of the femur[7]. In these situations, an allograft prosthesis composite or megaprosthesis reconstruction is recommended. Although femoral impaction grafting can be used to manage infection, a two-stage operation is generally preferred over a single-stage revision.

SURGICAL TECHNIQUE

The patient is positioned laterally on the operating table and secured between two hip positioners, ensuring enough space is available to dislocate the hip before prepping and draping. A posterior or posterolateral approach is preferred in all cases and can easily be extended. Previous scars in line with the planned incision are incorporated. The fascia lata is incised along the mid to posterior portion of the femoral shaft and the gluteus maximus bluntly dissected in line with its fibers to allow adequate exposure of the hip joint and proximal femur. The short external rotators and posterior hip capsule are then taken down as a single layer to the level of the lesser trochanter distally and repaired back to the greater trochanter with drill holes at the conclusion of the case. The anterior capsule is elevated off the femoral neck to help deliver the femur out of the wound. The iliopsoas and the femoral insertion of the gluteus maximus tendon are usually taken down to ensure enough soft tissue tension is released to safely dislocate the femur without causing a fracture. A bone hook is placed underneath the femoral neck to lift the femoral head out of the socket instead of rotating through the leg to perform the dislocation.

Prior to removal of the femoral component, the surgeon should ensure enough space is cleared of soft tissue and bone laterally between the prosthesis and the greater trochanter to reduce the risk of femoral fracture during stem extraction. An extended trochanteric osteotomy is utilized if the stem cannot be removed easily. If a cemented stem is being revised, the cement is carefully removed with an osteotome, high-speed burr or ultrasonic device. If the cement plug is well fixed and is >2 cm from the tip of the planned revision stem, it need not be removed and can be left *in situ* to occlude the femoral canal distally.

Particulate allograft bone is the most common graft type utilized for impaction grafting. The structural support provided by the impacted graft depends on the size of the graft as well as how tightly the graft is packed at the time of revision surgery[8]. The optimal graft size and method of preparation is currently debated amongst surgeons. Commercially available bone mills typically produce graft sizes of 2 to 5 mm, however some published data suggests that larger sizes (7 to 10 mm) of graft material provide better stability[9]. Washing the graft prior to impaction removes fat and marrow contents, which theoretically improves the resistance to shear stresses and enhances frictional resistance providing a more mechanically stable environment to support the prosthesis and allow incorporation of the graft with host bone[10]. In general, smaller pieces of bone graft are impacted distally and larger ones used proximally at the time of reconstruction.

A continuous femoral tube must be confirmed intraoperatively before commencing with impaction of bone graft. This starts with assessing the size and location of femoral endosteal and cortical bone loss from preoperative radiographs. Areas of cortical bone destruction around the tip of the stem to be revised deserve close attention. These are frequently the site and cause of femoral fractures[4], and the surgeon should attempt to bypass these defects by two cortical diameters at the time

of impaction grafting. Otherwise these areas should be reinforced with allograft struts or plate fixation. Fractures have occurred through these stress risers when reinforcement with only metal mesh or cerclage wires was performed[3]. Prophylactic cerclage wires should also be used liberally to reinforce weak areas of cortical bone.

A threaded distal intramedullary plug is placed 2 cm beyond the tip of the planned revision stem whose length and offset are determined from templating pre-operative radiographs. A central guidewire is screwed into the occlusion plug through which cannulated instruments are advanced to impact bone graft with a slotted mallet. The largest phantom (femoral stem shaped bone tamp) that passes through the canal without impinging distally with the appropriate offset is selected. Next, a series of distal impactors are chosen and marked according to the depth to which they should be advanced. Impaction of bone graft starts distally and advances proximally until the femur is backfilled to the mid-portion of the diaphysis. The phantom is then used to impact bone graft while being sure the desired amount of anteversion is reproduced with each sequential impaction. Graft impaction continues until there is enough axial and rotational stability of the phantom to allow a trail reduction. Metal mesh and cerclage wires are then used to reconstruct the proximal femur. The phantom is left it place and then larger bone graft pieces impacted around the phantom with proximal tamping instruments. The phantom should be difficult to remove at the conclusion of graft impaction and axial and rotational stability achieved.

The canal is then dried with a suction device that threads into the phantom and a collarless, polished, tapered femoral stem cemented in place. The distal aspect of the neomedullary tube takes the shape of a thin cone, which requires the cement to be inserted with a low enough viscosity to squeeze through a narrow tipped nozzle.

After the cementation is complete and the femoral head reduced, the wound is copiously irrigated and the short external rotators and hip capsule repaired back to the proximal femur through drill holes with a heavy non-absorbable braided suture.

Deep drains are utilized, and the incision is closed in layers in routine fashion.

POST-OPERATIVE CARE

Total hip precautions are instituted after surgery and start with a hip abduction pillow placed between both lower extremities at the conclusion of the operation. Radiographs are taken shortly after surgery to assess whether there are any areas of cortical bone that may be deemed high risk for a post-operative fracture and to confirm there are no complications that would require early return to the operating room. Patients are frequently fitted for an abduction orthosis limiting hip flexion greater than 70 degrees to decrease torsional forces on the femoral stem and decrease the risk of implant loosening. The patient is mobilized on the first post-operative day and is toe touch weight bearing for 6 wk followed by gradual advancement of weight bearing to tolerance.

If the indication for femoral impaction grafting is primarily to reconstitute cancellous bone loss and cortical bone is otherwise structurally intact, it is reasonable to allow weight bearing to tolerance in the acute perioperative period. The hospital stay varies amongst different countries, but in the United States patients usually are discharged after 3 d. The patient returns for follow-up at 6 wk, 12 wk, 6 mo, 1 year and then every 2 years for clinical and radiographic surveillance.

OUTCOMES

The long-term survivorship of the prosthesis depends on the success of graft incorporation. Ling *et al*[11] performed histological analysis following post-mortem retrieval of revisions utilizing femoral impaction grafting. The authors described three zones of different cellular morphology and activity: A "deep zone" adjacent to the implant contained necrotic bone encased by cement, an "interface zone" consisted of osteoid in direct contact with methyl methacrylate and scattered giant cells. There was no evidence of viable mineralized bone in direct contact with cement in this zone. The "outer zone", or regenerated cortical zone, was composed of normal cortical bone, fatty bone marrow and a few contained areas of dead bone.

Histology from biopsy specimens taken at multiple time points over a 4 year period from 19 patients who underwent revision surgery with femoral impaction grafting showed a cellular response characterized by infiltration of fibrous tissue into impacted bone graft with new peripherally located bone formation by one year. Reabsorption of bone graft however can take years to complete. Areas of necrotic bone were identified adjacent to well-fixed stems at 4 years from the time of revision surgery[12].

Halliday *et al*[4] reported 90.5% survivorship of 226 hips with re-operation as the end point with 10-11 year follow-up using the Universal Exeter stem in all cases. Femoral fracture was the most common indication for re-operation in this series. The authors reported 17 (7.5%) intra-operative femoral fractures. Eight of these were managed at the time of the initial procedure without requiring further surgery. The reported rate of revision for aseptic loosening for any cause after the initial procedure was 7%. The authors noted poor quality bone around the tip of the femoral stem probably predisposed some patients to femoral fractures. This led the group to modify their technique by using longer femoral stems for most revision cases and the development of instrumentation that permits impaction grafting along the entire length of the stem to bypass these inherently weak areas of femoral cortical bone.

Lamberton *et al*[2] found a 84.2% 10 year survival rate in their cohort of 487 patients treated with femoral impaction grafting with revision for any reason as the

Table 1 Summary of survivorship data and rates of complications for femoral impaction grafting

Ref.	No. of femoral impaction grafting cases	Average follow-up (yr)	Outcome measures	Survivorship	Rate of femoral fracture	Rate of infection
Lamberton *et al*[2]	540	10	Revision	84.2%	5.4%	3.9%
Schreurs *et al*[3]	33	10.4	Revision	100%	9%	0.0%
Halliday *et al*[4]	226	10	Re-operation	90.5%	7.5%	2.2%
Ornstein *et al*[13]	1305	15	Revision	94%	2.5%	1.4%
Wraighte *et al*[14]	75	10.5	Revision	92%	2.6%	1.3%
Sierra *et al*[15]	42	10	Re-operation	82%	4.7%	4.8%
Summary	2221	11	Re-operation (including revision)	90.5%	5.3%	2.3%

primary end-point. With aseptic loosening as the end-point, the 10-year survival rate was 98%. The most common intra-operative complication was perforation of the femoral shaft (8.5%). Other intra-operative complications included fracture of the greater trochanter (3.5%), calcar (5.9%) and femoral shaft (1.9%). The authors used supplemental fixation in the form of cerclage wires, cables, cortical strut allograft, metallic mesh or dynamic compression plating in 56% of the 540 revisions in their series of 487 patients. 36% of the 540 revisions required the use of 2 or more types of reinforcement to manage deficient bone stock to make impaction grafting feasible. The post-operative rate of femoral fracture was 5.4%.

A retrospective review of the Swedish National Joint Registry[13] revealed 1305 cases of femoral impaction grafting in 1188 patients with a mean age of 71 years at the time of revision surgery. Kaplan-Meier survivorship at 15 years was 94% considering all causes of failure. There was no difference in survivorship of the femoral component with respect to age or gender in the study group. The authors found centers where over 100 cases of femoral impaction grafting were performed had better outcomes. Interestingly, there was not difference in the rate of survivorship in revisions using a long stemmed femoral component over a shorter stem. The majority of complications requiring revision after the initial femoral impaction grafting procedure occurred within four years. Infection and femoral fracture were the most common complications (47.5%), while aseptic loosening (15.7%) and subsidence (18.6%) were also cited as causes of failure.

Wraighte *et al*[14] retrospectively reviewed 75 patients who were treated with femoral impaction grafting and reported a 92% survivorship with revision for any reason as the end-point with a mean follow-up of 10.5 years. Intra-operative fracture was associated with an increased risk of post-operative subsidence of the femoral component. The median subsidence of the femoral stem was 2 mm at 1 year and 10-year follow-up. Femurs with greater pre-operative bone loss were at higher risk of subsidence after impaction grafting. The data from the study group however showed no association between long-term clinical outcome and subsidence of the femoral component. Patients being re-revised for infection were more prone to complications than patients being managed for aseptic loosening with impaction grafting. The median Harris Hip score was 80.6 at the mean follow-up duration of 10.5 years and 88% of patients were either pain free or reported only mild pain.

Sierra *et al*[15] retrospectively reviewed 567 cases of femoral impaction grafting from the Princess Elizabeth Orthopaedic Centre at Royal Devon and Exeter Hospital in Exeter, United Kingdom to determine the rate of post-operative periprosthetic fracture using a long stemmed (> 220 mm) femoral component. They established a cohort of 40 patients in whom 42 revisions were performed with a long stemmed femoral component and had a minimum follow-up of 5 years. The average age of their study group was 73.8 years. They found a substantial post-operative surgical complication rate of 33%, but only 2 of the 42 cases (4.7%) resulted in post-operative femoral fracture. The survival rate at 5 and 10 years with re-operation of the femur for any reason was 82%.

Schreurs *et al*[3] reported 100% survivorship of 33 femoral revisions managed with impaction grafting at a mean of 10.4 years with revision of the femoral component as the end-point. Three femoral fractures occurred post-operatively at three, six and twenty two months and successfully treated with open reduction and internal fixation. This decreased the survivorship to 85% at nine years with re-operation for any reason as the end-point. These fractures occurred at the tip of the stem where a segmental defect existed at the time of impaction grafting. In one case it was reinforced with metal mesh at the time of the initial procedure, and not reinforced in the other two. Two of the three post-operative fractures resulted from a fall and the other occurred unexpectedly. Three intra-operative complications resulted in femoral fracture that were not identified at the time of surgery, but successfully healed without an additional operation. Subsidence of the femoral stem within the cement mantle was common and averaged 3 mm over the case series. The largest change in stem position occurred within the first six months after impaction grafting. Interestingly, subsidence did not deleteriously affect Harris Hip scores. Seven patients with an average Harris Hip scores of 85 points, developed subsidence of the femoral stem within the cement mantle > 5 mm.

In conclusion, Femoral impaction grafting is primarily indicated for restoring bone stock in patients who require reconstruction of the femoral component, and for type Ⅳ femoral defects where the isthmus is not capable of supporting an implant that relies on biologic fixation. There are concerns about the risk of iatrogenic fracture both intra-operatively and post-operatively as well as

subsidence[16]. The procedure is technically challenging and time consuming. Femoral impaction grafting is not suitable for patients who are medically unable to tolerate a long procedure, or where an intact femoral tube cannot be restored. Despite the potential drawbacks of impaction grafting, this technique is associated with high survivorship rates at ten-year follow-up (Table 1), and represents a viable option when an extensively porous coated stem cannot be used.

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TOPIC HIGHLIGHT

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Anterior muscle sparing approach for total hip arthroplasty

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Abstract

The purpose of this review is to examine the validity of positive claims regarding the direct anterior approach (DAA) with a fracture table for total hip arthroplasty. Recent literature regarding the DAA was searched and specific claims investigated including improved early outcomes, speed of recovery, component placement, dislocation rates, and complication rates. Recent literature is positive regarding the effects of total hip arthroplasty with the anterior approach. While the data is not definitive at present, patients receiving the anterior approach for total hip arthroplasty tend to recover more quickly and have improved early outcomes. Component placement with the anterior approach is more often in the "safe zone" than with other approaches. Dislocation rates tend to be less than 1% with the anterior approach. Complication rates vary widely in the published literature. A possible explanation is that the variance is due to surgeon and institutional experience with the anterior approach procedure. Concerns remain regarding the "learning curve" for both surgeons and institutions. In conclusion, it is not a matter of should this approach be used, but how should it be implemented.

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Key words: Total hip arthroplasty; Anterior approach; Hip; Arthritis; Joint replacement

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INTRODUCTION

The direct anterior approach (DAA) for total hip arthroplasty was first described by Judet[1] in 1947, and recently popularized in North America by Matta *et al*[2,3]. It is attractive to patients and surgeons because of its muscle sparing approach, which allows for a faster recovery[4,5], less pain after surgery[6], and post-operative hip precautions are not necessary[7]. It can be performed on a standard operating table or with the use of a specialized orthopedic table that facilitates femoral exposure. The patient is positioned supine, which allows for accurate assessment of leg lengths intra-operatively. Fluoroscopy and computer navigation can also be utilized to provide real time information about component position during surgery.

The surgeon's level of experience with the approach does directly correlate with complication rates until reaching a plateau after the first 40-100 cases[8-10]. The low rate of dislocation consistently reported using the DAA for total hip arthroplasty[2,11] is a testament to the accuracy of component placement, as well as the preservation of important soft tissue structures that confer hip stability.

Advantages and disadvantages of the approach

The DAA is applicable for both primary[5] and revision total hip arthroplasty[12]. Bilateral hip replacement can easily be performed without re-positioning the patient. Achieving adequate femoral exposure is the most technically challenging aspect of the DAA for surgeons new to the technique.

There are some anatomic features of the native hip and pelvis that make the DAA more difficult, and all surgeons who desire to utilize this approach for total hip arthroplasty should be mindful of these morphologies. A wide or horizontal iliac wing can limit access to the femoral canal for broaching and placement of the femoral component. Acetabular protrusio brings the femoral canal closer to the center of the pelvis, which can obstruct access to the femur. A high neck shaft angle with decreased offset positions the femoral canal deeper in the thigh. Obese muscular males can limit the space available to place the components, and it takes considerable knowledge of how to position retractors as well as the leg in three-dimensional space to achieve enough exposure to do this accurately. A straight impactor that attaches to the acetabular component often impinges against the large muscular thigh distally, which can lead to more vertical and anteverted placement of the cup. An offset inserter is helpful in this situation. These are all technical aspects of the procedure that surgeons early in the learning curve are advised to consider in their patient selection process. Patients with a previous acetabular fracture associated with posterior heterotopic ossification, which requires excision, and when extensive exposure of the posterior acetabulum/column is necessary to address large posterior acetabular defects are relative contraindications[3].

Mast *et al*[12] described their operative experience in 51 patients with an average follow-up of 4.5 years using the DAA for revision total hip arthroplasty with an orthopedic table. When performing isolated acetabular liner exchange, cup revision or conversion of hip resurfacing to THA, the authors were able to perform these surgeries without proximal or distal extension of the standard approach.

CONTRAINDICATIONS

Mast *et al*[12] identify three scenarios that highlight the limitations of the anterior approach in revision surgery: (1) revision of long, extensively porous-coated femoral stems; (2) managing severe proximal bone loss or osteolysis; and (3) revision of a femoral stem with significant retroversion. It is worth pointing out that each of these three limitations involves the femoral exposure. Complications in this case series included loosening of the acetabular component (4%), heterotopic bone formation (2%), limb-length inequality (2%), trochanteric fracture (2%), with a reported complication rate of 9.8%. Interestingly, they reported no dislocations after revision surgery with a mean follow-up of 4.5 years.

Figure 1 Patient positioned supine on a specialized orthopedic table (A) with the operative leg prepped and draped (B).

SURGICAL TECHNIQUE

The surgeon can use a regular operating table or an orthopedic table designed to facilitate femoral exposure. The surgical technique described is with the use of an orthopedic table. The operative team consists of the surgeon, a single scrubbed assistant that stands on the opposite side of the table, a scrub nurse, a circulating nurse and the anesthesiologist. The patient is positioned supine on the operating table between a perineal post, which affords the benefit of being able to expeditiously utilize intra-operative fluoroscopy or computer navigation to assess leg lengths and ensure optimum placement of the components before leaving the operating room. Both feet are placed in boots that lock into a mobile spar that allows the leg to be positioned and rotated in any direction during the procedure. The original Judet orthopedic table has been modified to include a bracket that parallels the operative leg and supports a femoral hook, which holds the femur in an elevated position when broaching the canal. The operative extremity is draped from the iliac crest to the knee (Figure 1).

ACETABULAR EXPOSURE

The proximal aspect of the incision is marked 2-3 cm posterior and 1-2 cm distal from the anterior superior iliac spine, and extends distally in line with and over the tensor fascia lata muscle belly. The incision is placed laterally to the interval between the tensor fascia muscle and

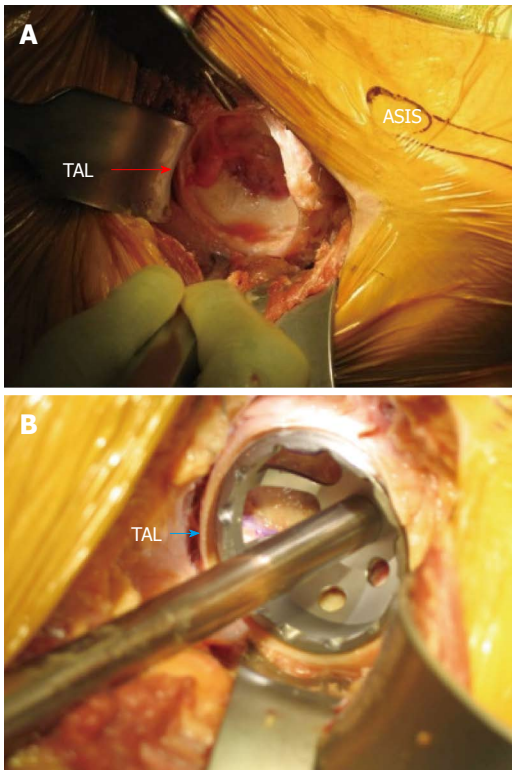

Figure 2 Acetabular exposure. A: Acetabular exposure with the direct anterior approach; B: Acetabular exposure using the direct anterior approach with trial component in place. The transverse acetabular ligament (TAL) is clearly identified by arrow. ASIS: Anterior superior iliac spine.

Figure 3 The supine position of the patient on the operating table facilitates the use fluoroscopy during surgery to assess component position and alignment.

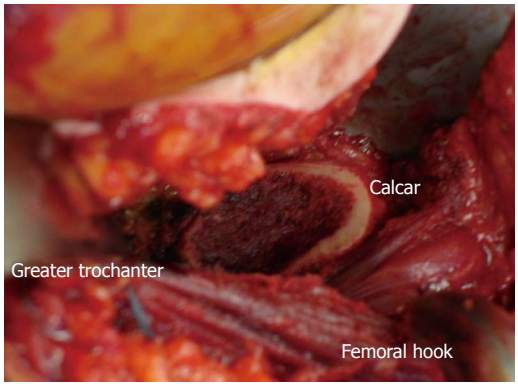

Figure 4 Exposure following femoral neck osteotomy with the direct anterior approach using a specialized orthopedic table.

the sartorius to minimize the risk of lateral femoral cutaneous nerve injury. By developing the interval within the tensor fascia, the lateral femoral cutaneous nerve remains medial to the sartorial fascia and is avoided in the superficial dissection.

The skin and subcutaneous tissues are dissected down to the translucent fascia over the tensor, where two or three perforating blood vessels are encountered. The fascia is then incised in line with the muscle just anterior to these perforating vessels. An Alice clamp is attached to the medial aspect of the fascial incision and provides counter traction as the surgeon uses his finger to bluntly sweep the tensor muscle off the sartorial fascia.

A blunt cobra retractor is placed over the superior lateral aspect of the femoral neck which enhances the interval exposure between the tensor muscle and gluteus medius laterally and the sartorial and rectus fascia medially. The lateral femoral circumflex vessels are found within this interval encased in a layer of fat in the middle of the wound. They are carefully dissected and cauterized, or tied off and transected, as bleeding from these vessels can be profuse and difficult to control if they retract. A Cobb elevator is then used to mobilize the indirect head of the rectus off the capsule at the base of the neck followed by placement of a second cobra retractor along the inferior medial portion of the femoral neck. A double bent homan retractor is then slid perpendicular to the inguinal ligament directly above the capsule and along the acetabulum (Figure 2).

The hip capsule is then incised as an inverted "T" parallel to the lateral aspect of the intertrochanteric line along the lateral portion of the femoral neck and extended medially along the inferior portion of the femoral neck. The capsule is tagged with non-absorbable suture and repaired at the conclusion of the case. This capsular closure provides an additional layer of soft tissue to theoretically minimize the risk of deep infection. Alternatively the capsule may also be excised.

A hip skid is then slid between the femoral head and the acetabulum to break up any adhesions to facilitate an atraumatic dislocation of the femoral head. The femoral neck cut is made in one of three ways: (1) with the hip reduced; (2) a "napkin ring" segment of bone is created and removed by making two parallel neck cuts which leaves a smaller segment of the femoral head; or (3) after dislocating the femoral head. After dislocation fixed bony landmarks such as the superior aspect of the femoral head or the lesser trochanter are used to determine the desired level of femoral neck resection. A corkscrew with a removable handle is placed in the femoral head prior to making the femoral neck cut. The corkscrew will allow the surgeon to remove the femoral head in a controlled fashion without damaging the tensor muscle with the

residual sharp spike of bone created by the distal end of the osteotomy. These steps allow expeditious removal of the femoral head after the neck cut. The femur is then externally rotated approximately 20 to 45 degrees, with slight adduction and flexion of the leg which enhances the exposure of the acetabulum for reaming and placement of the cup. Fluoroscopy and computer navigation can be used at this point to assess the placement of the socket, and adjustments made to component orientation if necessary (Figure 3).

FEMORAL EXPOSURE

After the acetabular component is seated, any traction on the operative leg is released and the femur is rotated back to a neutral position. If a femoral hook is used to assist with femoral exposure, it should be placed just distal and posterior to the vastus ridge. It should slide in easily and without resistance superficial to the vastus lateralis. The leg is then externally rotated so the calcar is facing directly anterior and the greater trochanter posterior. The operative leg is then positioned so the hip is extended 25-30 degrees by bringing the foot to the floor, and then maximally adducted. The surgeon laterally displaces the proximal femur and manually lifts the femoral hook to elevate the femur and uses a foot pedal to bring the motorized bracket arm up to dock the hook. If the surgeon attempts to elevate the femur by only using the motorized bracket arm with the hook in place, the femur can easily fracture.

The key to obtaining femoral exposure is performing sequential capsular and soft tissue releases along the medial aspect of the greater trochanter and femoral neck under tension (Figure 4). This ultimately allows the greater trochanter to clear the posterior wall of the acetabulum. With the operative leg hyper-extended and adducted, a long curved homan retractor is placed behind the greater trochanter to sufficiently tension these soft tissue attachments. This allows the surgeon to see and feel the femur move with each structure that is released. The goal is to release the minimum amount of soft tissue attachments to translate the femur laterally and elevate it up and out of the wound. The capsule is the first structure taken down with electrocautery, followed by the piriformis, the gemelli and the obturator internus until sufficient exposure is achieved. Preserving the obturator externus is important for maintaining hip stability and should not be released unless necessary as this effects the most direct medial pull of the femur to the pelvis.

Offset broach handles and occasional use of flexible reamers facilitate preparation of the femur and placement of the final femoral component. Fluoroscopy and computer navigation are again optional (Figure 3). They allow the surgeon additional information to intra-operatively assess the center of rotation, offset, leg lengths, femoral stem alignment, and fit within the canal.

The hip is reduced and can be checked for stability and component impingement. If the approach is performed with the utilization of a special table, lowering the foot to the floor and then adducting and externally rotating the operative leg can check anterior stability. Simply unhooking the boot from the mobile spar allows the surgeon to assess posterior stability and impingement.

The wound is copiously irrigated, the capsule re-approximated with heavy non-absorbable braided suture, and a deep drain drain is placed. The fascia of the tensor fascia lata muscle is closed with a running suture, and the subcutaneous and subcuticular layer closed with interrupted and a running 3-0 monocryl suture.

POST-OPERATIVE CARE

Patients are mobilized the day of surgery and post-operative hip precautions are not necessary. Post-operative pain and narcotic use is often significantly less compared to other surgical approaches for total hip arthroplasty[6]. Patients are more frequently discharged to home instead of extended care facilities, thus further decreasing the time of exposure to harmful pathogens[13]. The length of time in the hospital after total hip arthroplasty is significantly less in some European countries with the DAA[6,13].

If the patient has a pendulous abdomen that rests on the incision, precautionary steps are taken to minimize prolonged moisture on the incision. The senior author (Moskal JT) applies an abdominal binder at the conclusion of the case for patients with a pendulous abdomen to keep the pannus from resting on the incision until it has healed. Keeping the inguinal crease clean, dry and the incision covered with a sterile bandage also minimizes the risk of post-operative infection.

In a large prospective series, the average time to discontinuing the use of a cane or walker was 21 d, with 80% of patients discontinuing ambulatory assist devices by 7.6 d[11]. Gait analysis studies show quicker recovery of motor function for the DAA compared to other surgical exposures[14]. The patient returns for follow-up at 2 wk, 6 wk, 1 year, and then every 2 years for routine clinical and radiographic surveillance.

OUTCOMES

The literature, in general, makes numerous positive claims regarding the DAA with a fracture table for total hip arthroplasty including quicker recovery and return to unassisted ambulation, and reduced soft tissue damage, surgery time, pain, and risk of dislocation with early elimination of hip precautions[4,5,8,11,15,16].

In 2004, Sculco[15] wrote an early review of less extensive THA surgery. Sculco[15] stated in his review of minimally invasive total hip arthroplasty, "The rationale for performing hip arthroplasty through a less extensive exposure is to reduce hospital stay, speedy recovery, decrease surgical trauma. Certainly patients are happier with a smaller incision, and recovery is faster." As less invasive THA continues to evolve, it is important to consider patient satisfaction and the speed at which they recover is a

critical factor in their satisfaction and their return to normal activities of daily living.

The benefits of the anterior approach are mostly accrued from "muscle preservation" rather than the more traditional "muscle splitting" approaches[2,4,5,9,17-19]. Various authors have contributed to the literature focused on the mini-incision anterior approach, numerous aspects of this surgical technique are discussed: early outcomes and speed of recovery[4,5,9,14,17,20-22], component placement[2,4], dislocation rates[2,11,18,22-24], complication rates[2,4,9,11,21-23], and the impact of surgeon experience with this technique[2,4,9,11,22-25].

Early outcomes and speed of recovery

There are many ways to measure the early outcomes of THA and the speed of recovery from the surgery, such as time to full weight bearing, incidence of limping, biochemical muscle recovery, gait variables, range of motion, and traditional clinical measures[4,5,9,14,17,20-22].

In 2004, Siguier *et al*[22] reported that all patients were able to full weight bear within two days postoperatively and that most patients were able to discontinue walking aids within 8 d to 3 wk of surgery. There were no cases of limping secondary to gluteus medius insufficiency because the buttock muscles and greater trochanter were not affected by the surgical approach.

In an early investigational study, Pilot *et al*[17] were concerned with specific indicators of muscle recovery following anterior approach THA. They found no significant difference in inflammation as measured by interleukin-6 levels, in muscle damage as measured by heart type fatty acid binding protein, or in hemoglobin levels when comparing the mini-incision anterior approach with the standard posterolateral approach for THA (10 subjects in each group). Although they speculate that the term minimally invasive surgery is "at least doubtful in terms of being less traumatic" that there were no significant negative outcomes in terms of muscle recovery with minimally invasive surgery using the anterior approach.

In a very recent study, Bergin *et al*[19] reported the extent of muscle damage from the limited incision anterior approach (n = 29) as compared to the standard incision posterior approach (n = 28). The biochemical markers of inflammation, serum creatine kinase, C-reactive protein, interleukin-6, interleukin-1 beat, and tumor necrosis factor-alpha, were in general lower in the anterior approach group from post-surgery through post-operative day 2. The rise in creatine kinase was 5.5 times greater in the posterior approach group than in the anterior approach group post-surgery ($P < 0.05$) and nearly twice as high over the measurement period ($P < 0.05$). Serum creatine kinase levels indicated that the anterior approach causes significantly less muscle damage than the posterior approach[19].

Roth *et al*[21] looked at the early outcomes for 195 THA using the anterior approach in the supine position and found early restoration of full weight bearing and range of motion.

In a kinematic study comparing the DAA and the traditional anterolateral approach, Mayr *et al*[14] found that both gait and total range of motion were better with the DAA. Gait was improved in more categories than with the traditional anterolateral approach, including: significant improvement in cadence, stride time, stride length, walking speed, hip flexion at foot contact, maximum hip flexion in swing.

Nakata *et al*[4] compared the DAA and the mini-posterior approach in one of the few articles reporting on two different minimally invasive procedures. They found more rapid recovery of hip function and gait ability with the DAA. In the same year, Seng *et al*[9] also reported an earlier recovery and return to activities of daily living with the anterior approach.

In a more recent study, Klausmeier *et al*[20] compared the anterior approach with the anterolateral approach and a control group that did not have THA, their focus was the short term recovery of hip strength and motion. Hip abductor strength was lower in both of the THA groups when compared with the control group preoperatively, at six weeks, and at 16 wk. At 6 wk, the late stance peak abductor moment was not significantly different between the anterior approach and the control group; this measure was significantly lower for the anterolateral group. While the authors found no difference between the two approaches with regards to speed of recovery, or isometric strength and dynamic gait measures at six and sixteen weeks, the anterior approach was associated with improved gait velocity and peak flexor moment at 6 wk[20].

Most studies do not evaluate the differences in standard clinical measures such as Harris Hip Scores, SF-36, WOMAC, and VAS energy, daily activities, or overall quality, however Restrepo *et al*[5] did in 2010. In a study comparing the single-incision-modified Smith-Peterson anterior approach and the direct lateral approach, the outcomes using validated measures were found to be were significantly better for the anterior approach group at 6 wk, 6 mo, and 12 mo[5].

Other studies that reported on these factors consistently found that the anterior approach provided for faster recovery and improved early outcomes when employing the anterior approach[4,5,9,14,17,21,22].

Component placement

Component placement is an important factor in the success of THA, two sources reported on this outcome using the anterior approach[2,4]. Matta *et al*[2] had "safe zone" placement rates for the acetabular component; 96.07% (440 of 458 THA) in safe zone abduction angle and 93.01% (426 of 458 THA) in safe zone anteversion angle. Nakata *et al*[4] stated that significantly more acetabular components were placed in "safe zones" with DAA (98 of 99 THA, 98.99%) as compared to the mini-posterior approach (87 of 96 THA, 90.63%) (P = 0.008).

Dislocation rates

Dislocation rates are a common and useful metric when

discussing THA, 8 studies discuss the dislocation rate using the anterior approach[2,4,9,11,21-23,25]. Of the 5801 THA reported in these studies, there were 55 dislocations (0.95%). Dislocation risk tends to be less than 1.0%, excepting for the rate reported by Sariali *et al*[18] (1.53%).

Complication rates

Various complications were reported: total complications, nerve related complications, and fractures (dislocation reported above)[2,4,9,11,21-23,25]. The overall complication rates ranged from 2.03% to 15.79%[22,24]. The two highest rates of overall complications, 15.79% and 15.63%, were in studies focused on complication rates with anterior THA using fracture tables[23,24]. The overall complication rate from aggregated data was 7.74% (320 of 4136 THA)[2,4,9,11,22,24].

The rate of nerve related complications was reported to range from 0.00% to 14.81%[21,25]. Most rates of nerve related complicates were less than 2%; the rate reported by Bhargava *et al*[25] was clearly much higher than the others, possibly due to this study being focused on nerve related complications[2,4,11,19,21,22,24].

The rate of fracture complications ranged from 0.10% to 7.29%[22,24]. Most complication rates were less than 3%; the rate reported by Woolson *et al*[24] came from a study of complications in a community hospital and may have been influenced by the setting and surgeon experience[2,4,11,19,21-23].

Impact of surgeon experience with this technique

The level of experience that an orthopaedic surgeon has with any new technique clearly impacts the successful execution of that technique; various authors have reiterated this with regards to the DAA using a fracture table[4,9,11,23-25]. Jewett *et al*[23] and Woolson *et al*[24] found disturbingly high rates of complications with this technique when performed by surgeons still in the "learning curve." When Woolson *et al*[24] examined outcomes associated with the early experience of four community surgeons; the series was only of the early cases. Jewett *et al*[23] examined the complication rates for the first 800 cases performed using this technique and found that after the first 400 cases, intraoperative complications such as fracture no longer occurred. Bhargava *et al*[25] noted that the incidence of nerve impairment decreases as surgeon experience increases.

Two studies attempted to quantify the "learning curve" for the DAA using a fracture table[9,11]. Bhandari *et al*[11] found a clear decline in complications after the first 100 cases were performed by creating subgroups for analysis, one group contained surgeons with less than 100 cases and the other group contained surgeons with over 100 cases. Surgeons who had performed less than 100 cases had complication rates double that of more experienced surgeons[11]. Seng *et al*[9] sought to define the learning curve for joint arthroplasty surgeons in high volume practices. After six months and 57 cases, over 50% of DAA THA were performed comfortably and surgical time and intraoperative blood loss decreased[9].

CONCLUSION

What are the benefits of the anterior approach? In contrast to muscle-splitting approaches such as the direct lateral approach, the anterolateral approach, or the posterior approaches, the anterior approach is a muscle-sparing procedure thus no muscles are cut or detached. Muscle-splitting approaches require the cutting and detachment of soft tissues. This in turn disturbs the natural dynamic stabilization of the hip and makes it impossible for the hip to function normally until those structures have healed. Therefore, with muscle-splitting approaches, patients require at least six weeks of muscle healing plus additional time and rehabilitation effort to recover lost muscle strength. In short, patients must recover from both the surgical approach and the hip arthroplasty. Additionally, restrictions are required regarding patient movement and weightbearing to allow the soft tissues adequate time to heal.

In contrast to muscle-splitting approaches, with a muscle-sparing procedure, such as the DAA, no muscles are cut or detached. The patient must recover/heal from the surgical procedure only, not the approach. Recovery requires no additional time for healing of the muscle sleeve or its attachment, thus patients recover more quickly and may rehabilitate without restrictions. Experience suggests that patients benefit from a quicker recovery and elimination of postoperative restrictions, particularly younger and/or more active patients who need to return to work or return to other activities without restriction.

As more studies regarding the anterior approach for total hip arthroplasty are published, it becomes clearer that this approach does present distinct benefits for patient focused outcomes. However, there are concerns when incorporating new techniques into surgical practice; these often create a "learning curve" and unforeseen technical complications.

In conclusion, the DAA is a muscle-sparing approach with a quicker rehabilitation because the recovery is faster since the patients need only to recover from the procedure and not the approach. The question is not whether the orthopaedic community will embrace this technique but rather how should it be introduced into routine practice.

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TOPIC HIGHLIGHT

Shigeru Kobayashi, MD, PhD, *Series Editor*

Access related complications during anterior exposure of the lumbar spine

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Abstract

The new millennium has witnessed the emergence of minimally invasive, non-posterior based surgery of the lumbar spine, in particular *via* lateral based methodologies to discectomy and fusion. In contrast, and perhaps for a variety of reasons, anterior motion preservation (non-fusion) technologies are playing a comparatively lesser, though incompletely defined, role at present. Lateral based motion preservation technologies await definition of their eventual role in the armamentarium of minimally invasive surgical therapies of the lumbar spine. While injury to the major vascular structures remains the most serious and feared complication of the anterior approach, this occurrence has been nearly eliminated by the use of lateral based approaches for discectomy and fusion cephalad to L5-S1. Whether anterior or lateral based, non-posterior approaches to the lumbar spine share certain access related pitfalls and complications, including damage to the urologic and neurologic structures, as well as gastrointestinal and abdominal wall issues. This review will focus on the recognition, management and prevention of these anterior and lateral access related complications.

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Key words: Anterior spinal exposure; Lumbar spine; Complications

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INTRODUCTION

Anterior spinal access is often required for the treatment of spinal deformity, bony and/or discogenic infection, trauma, tumor and degenerative disease. Advantages of this approach include performance of a thorough discectomy and release, capability to implant high profile interbody fusion and non-fusion devices, debridement and excision of necrotic tissue, removal of migrated/misplaced devices, and a favorable milieu for interbody fusion with rich blood supply and graft/device placement under compression. The most common associated complications include damage to the vascular, urologic and neurologic structures, as well as gastrointestinal and abdominal wall issues.

VASCULAR INJURY

Anterior exposure of the spine at the L4-L5 and L5-S1 levels requires mobilization of the left common iliac vessels, as they course obliquely across the anterior aspect of the L5 body, traversing variable portions of the L4-L5 and L5-S1 disc spaces in the process. The most dorsally located, the left common iliac vein is the most likely vascular structure to be injured during anterior lumbar spinal surgery. Apart from intraoperative hemorrhage and the challenge associated with vascular control and repair,

Table 1 Reported incidence of major vascular injury during anterior spinal surgery *n* (%)

Ref.	Year	*n*	Arterial injury	Venous injury
Fantini *et al*[1]	2007	345	1 (0.3)	9 (2.6)
Brau *et al*[2]	2004	1315	6 (0.5)	19 (1.4)
Kulkarni *et al*[3]	2003	336	8 (2.4)	NA
Gumbs *et al*[4]	2005	64	0	2 (3.1)
Fritzell *et al*[5]	2003	72	0	2 (3.7)
Holt *et al*[6]	2003	450	0	7 (1.6)
Kaiser *et al*[7]	2002	98	0	3 (3.1)
Oskouian *et al*[8]	2002	207	2 (0.9)	7 (3.4)
Kuslich *et al*[9]	1998	591	0	10 (1.7)

NA: Not available.

thrombotic occlusion may occur in the postoperative period following seemingly uncomplicated iliac venorrhaphy, or simply as a result of prolonged retraction of the iliac vein or inferior vena cava. The ascending iliolumbar vein acts as an important dorsolateral tether to the left common iliac vein, therefore routine ligation and division will facilitate anterior exposure of the L4-L5 disc space[1]. Similarly, ligation and division of the L4 segmental vessels will release the aortic terminus and the terminal inferior vena cava (IVC), thus permitting retraction to the right side of the spine, further facilitating anterior exposure of the L4-L5 disc space. Previous osteomyelitis/discogenic infection, previous anterior spinal surgery, spondylolisthesis, osteophyte formation, transitional lumbosacral vertebra and anterior migration of interbody device have been identified as risk factors for injury to the major vascular structures during anterior spinal surgery[1]. With the sole exception of transitional anatomy, the identified conditions share the underlying pathogenesis of inflammation of the annular and pre-vertebral soft tissues, as well as of the periosteum, thereby limiting mobility of the overlying vascular structures. The vast majority of major vascular injuries to the great vessels of the abdomen occur during attempts at anterior exposure of L4-L5 and L5-S1.

The reported incidence of significant venous injury is in the 2%-4% range (Table 1). Arterial thrombosis occurs in less than 1% of cases, and is typically associated with fixed retraction of the large vessels, either *via* a table mounted mechanical system[2] or through Steinman pins placed directly into the vertebral body[3]. Although we do use a table mounted mechanical retractor system, the major vascular structures are manipulated only through the use of hand held retractors, with release of traction at regular intervals of no longer than fifteen minutes. In addition, attempts to mobilize heavily calcified vessels should be tempered, as loss of normal elasticity and recoil will predispose to plaque fracture and arterial thrombosis.

The use of lateral based approaches for discectomy and fusion of the lumbar spine cephalad to L5-S1 has nearly eliminated the occurrence of great vessel injury. That said, it is not uncommon to encounter the aforementioned ascending iliolumbar vein during performance of a lateral based approach to the L4-L5 disc from the left. In this setting, ligation and division of the ascending iliolumbar vein in controlled fashion is the preferred approach.

Principles of venous repair

Initial maneuvers following recognition of injury to a major venous structure (e.g., iliac vein or vena cava) are of critical importance and may very well determine outcome. Aggressive use of suction and/or traction at the venotomy site, prior to gaining control, can cause further damage to the injured vessel and must be avoided. Trendelenburg's position should be utilized. Control of hemorrhage should be obtained with compression proximal and distal to venotomy, typically through the use of Kitner peanut dissectors and/or sponge-sticks. Wylie renal vein retractors may also prove useful in this regard. No attempt to encircle the iliac vein or to apply vascular clamps should be made, as this will generally result in further venous disruption and increased bleeding. Once adequate visualization of the venotomy has been obtained, primary repair with 5-0 prolene suture on a cardiovascular needle may be carried out (Figure 1). Should a minimal access incision not permit formal suturing and tying, vascular clips may be placed at right angles to the long axis of the vessel in "railroad track" fashion (Figure 1C). Recent experience with endovascular repair of the left common iliac vein with a covered stent suggests that this will be a viable methodology as this technology becomes more widely available[10]. Topical hemostatic agents including Gelfoam® (Pfizer, New York, NY), Surgicel® Fibrillar™ and Surgiflo® (Ethicon, Somerville, NJ), and Tisseel (Baxter, Deerfield, IL) are important adjuncts to direct repair, and in many instances can be effective as the sole method of hemostasis.

Postoperative surveillance for iliac vein thrombosis

Successful repair of seemingly minor injuries of the iliac vein can result in thrombosis in the postoperative period. Remarkably, manifestations of leg swelling may not be readily apparent in the setting of bed rest and limited ambulation. Venous duplex scanning is notoriously unreliable in detecting thrombosis cephalad to the inguinal ligament. For this reason, iliac venous imaging by computed tomographic angiography (CTA) or magnetic resonance venography is performed routinely following iliac venous repair[1]. Detection of iliac vein thrombosis in the early postoperative period typically mandates placement of a vena caval filter, as anticoagulation is generally not an option.

Management of arterial injury

As noted above, arterial complications can be minimized by avoiding the use of fixed retraction systems on the large vessels, and by limiting the degree of arterial mobilization in the setting of heavy vessel calcification. Arterial hemorrhage can be managed with traditional lateral suture repair, applying vascular clamps above and below

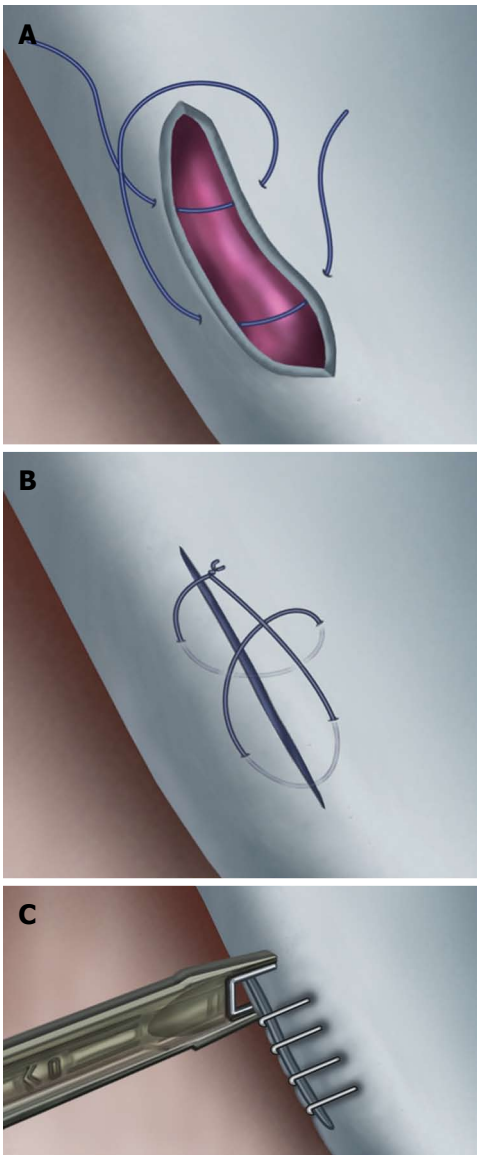

Figure 1 Lateral repair of iliac vein with 5-0 prolene suture placed in figure-of-eight fashion (A, B) and vascular clips placed in "railroad track" fashion (C).

the arteriotomy if necessary. Arterial thrombosis can be a more difficult problem in the patient with atherosclerotic disease. Continuous pulse oximetry of the lower extremity ipsilateral to the site of arterial retraction, typically the left, is a useful monitor to employ routinely. Management by catheter thrombectomy and repair of the culprit lesion, sometimes requiring adjunct methods of endarterectomy or bypass, will be required. Consideration to leg fasciotomy should be given, depending upon the degree and duration of extremity ischemia.

UROLOGIC INJURY

Blood supply to the ureter is segmental in nature, and as such, no attempt to skeletonize the ureter should be made. Rather, the ureter should be rotated medially along with the visceral sac. Incidence of ureteral injury during primary retroperitoneal exposure is exceedingly low, though has been reported[4]. In contrast, the ureter is at significant risk of injury during revision anterior spinal surgery. This is especially true in the setting of removal of anterior instrumentation, as the ureter may be encased in scar tissue immediately overlying the instrumentation. In this instance, delayed images taken during preoperative CTA will delineate the course of the ureters, and typically signal the need for ipsilateral ureteral stent placement. In addition, methylene blue is administered intravenously on a routine basis at the start of the revision anterior procedure.

Retrograde ejaculation

The sympathetic fibers of the hypogastric plexus are adherent to the posterior surface of the peritoneum at the level of L5-S1, thus further emphasizing the importance of *en bloc* mobilization of the visceral sac. Avoidance of electrical and/or thermal injury to the hypogastric plexus can be achieved by using a scalpel for the annulotomy and by using bipolar electrocautery sparingly and only as absolutely necessary. Modern series have reported low incidences of retrograde ejaculation. The ProDisc® (Synthes, West Chester, PA) lumbar total disc replacement (TDR) trial reported an incidence of 1.2% (1/82) in males undergoing TDR[11], while the Charité™ (DePuy, Raynham, MA) artificial disc trial reported an incidence of 4% (6/147) in males undergoing either TDR or anterior fusion[12]. A recent retrospective consecutive cohort study implicates the inflammatory reaction associated with recombinant human bone morphogenetic protein-2 (rhBMP-2) use as an adjunct to anterior lumbar interbody fusion (ALIF) at L5-S1 in generating an increased incidence of retrograde ejaculation[13]. A 6.3% incidence (15/239) of retrograde ejaculation was identified in male patients receiving rhBMP-2 as an adjunct to one (L5-S1) or two (L4-5/L5-S1) level ALIF, as compared to an incidence of 0.9% (2/233) absent rhBMP-2 use in the control arm. Noteworthy is that of 12 patients with retrograde ejaculation followed for at least 2 years postoperatively, six (50%) reported resolution.

GASTROINTESTINAL COMPLICATIONS

The most common gastrointestinal issue complicating the postoperative course of the patient undergoing anterior lumbar spinal surgery is ileus. Routine measures taken to reduce the incidence of ileus include preoperative mechanical bowel preparation, use of an orogastric tube intraoperatively, and avoidance of nitrous oxide as an anesthetic agent. Use of preoperative mechanical bowel preparation is especially worthwhile in the setting of a significant preoperative narcotic requirement, as gastrointestinal transit time may be dramatically prolonged. Methylnaltrexone bromide (Relistor®, Salix Pharmaceuticals, Raleigh, NC) injection is particularly useful in treating opiate induced constipation postoperatively. In cases of refractory ileus, as well as colonic pseudo-obstruction

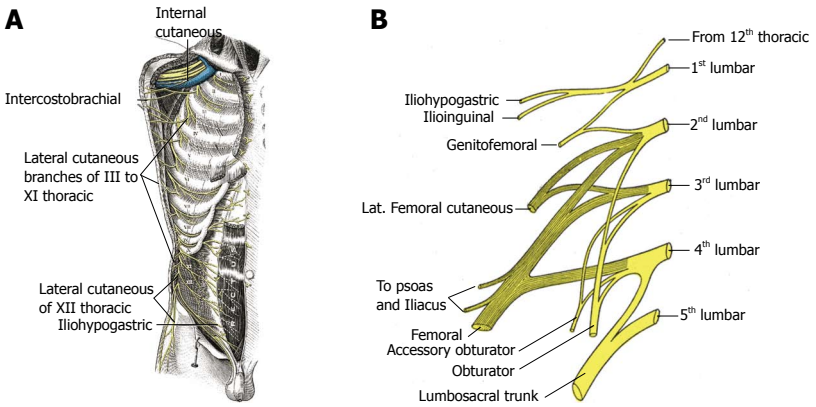

Figure 2 Anatomy of thoraco-abdominal nerves (A) and iliohypogastric and ilioinguinal nerves (B).

(Ogilvie's syndrome), neostigmine administered intravenously is frequently effective, although a monitored setting is required as bradycardia is a recognized side effect of this parasympathomimetic agent[14].

ABDOMINAL WALL COMPLICATIONS

Sometimes referred to as abdominal asymmetry, a change in contour of the abdominal wall is a recognized outcome following oblique flank incisions during the course of aortic, renal and/or anterior spinal surgery. The resulting prominence or bulge is not a true hernia, as there is no accompanying fascial defect, and consequently no risk of incarceration exists. Generally thought to occur as a result of denervation of the oblique musculature of the flank, an increased incidence has been noted with incisions extending into the eleventh intercostal space[15], suggesting an important role for the eleventh intercostal nerve in preserving normal muscular function of the abdominal wall. Innervation of the oblique and rectus abdominis musculature is by the anterior divisions of intercostal nerves VII-XII, referred to as thoraco-abdominal nerves (Figure 2A). Coursing between the internal oblique and transversus abdominal muscles, the thoraco-abdominal nerves perforate the rectus sheath and terminate as anterior cutaneous branches of the abdomen. Further innervation of the internal oblique and transversus abdominal muscles is by the iliohypogastric (superior branch) and ilioinguinal nerves (inferior branch), arising together from the anterior rami at T12 and L1 (Figure 2B). Preservation of the thoraco-abdominal neurovascular bundle in the interval between the internal oblique and transversus abdominal muscles is felt to be an important element in maintaining integrity of muscular function of the abdominal wall during performance of lateral transpsoatic interbody fusion.

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BRIEF ARTICLE

Finger movement at birth in brachial plexus birth palsy

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Abstract

AIM: To investigate whether the finger movement at birth is a better predictor of the brachial plexus birth injury.

METHODS: We conducted a retrospective study reviewing pre-surgical records of 87 patients with residual obstetric brachial plexus palsy in study 1. Posterior subluxation of the humeral head (PHHA), and glenoid retroversion were measured from computed tomography or Magnetic resonance imaging, and correlated with the finger movement at birth. The study 2 consisted of 141 obstetric brachial plexus injury patients, who underwent primary surgeries and/or secondary surgery at the Texas Nerve and Paralysis Institute. Information regarding finger movement was obtained from the patient's parent or guardian during the initial evaluation.

RESULTS: Among 87 patients, 9 (10.3%) patients who lacked finger movement at birth had a PHHA > 40%, and glenoid retroversion < -12°, whereas only 1 patient (1.1%) with finger movement had a PHHA > 40%, and retroversion < -8° in study 1. The improvement in glenohumeral deformity (PHHA, 31.8% ± 14.3%; and glenoid retroversion 22.0° ± 15.0°) was significantly higher in patients, who have not had any primary surgeries and had finger movement at birth (group 1), when compared to those patients, who had primary surgeries (nerve and muscle surgeries), and lacked finger movement at birth (group 2), (PHHA 10.7% ± 15.8%; Version -8.0° ± 8.4°, P = 0.005 and P = 0.030, respectively) in study 2. No finger movement at birth was observed in 55% of the patients in this study group.

CONCLUSION: Posterior subluxation and glenoid retroversion measurements indicated significantly severe shoulder deformities in children with finger movement at birth, in comparison with those lacked finger movement. However, the improvement after triangle tilt surgery was higher in patients who had finger movement at birth.

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Key words: Finger movement; Triangle tilt surgery; Brachial plexus birth palsy; Glenohumeral dysplasia; Pejorative sign

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INTRODUCTION

Normal shoulder development requires balanced dynamic muscle environment between the humeral head and the glenoid. Initial damage during birth to the brachial plexus, and its incomplete recovery results in full or partial paralysis of shoulder muscles during the child's development. The most common muscle imbalances after partial recovery occur between the internal and

the external rotators, and the abductors and adductors of the shoulder. The chronic evolution of the muscle imbalance causes changes to the developing bony structures, and formation of scapular and glenohumeral joint deformities.

Lack of finger movement at birth in obstetric brachial plexus injury (OBPI) represents a pejorative sign of prognosis. In these patients, the shoulder muscles are all weakened, and there is no muscle balance, indicating a severe initial injury that mostly affects the entire brachial plexus. However, the presence of finger movement at birth in asymmetrical brachial plexus injury (initial damage to C5-C6 or C5-C7) also predicts the development of severe bony deformities caused by severe muscle imbalance on the growing bony structures of the infant shoulde[1,2]. This progress to a posterior subluxation or complete dislocation of the humeral head. These secondary deformities, including internal rotator and adductor contractures, glenohumeral dysplasia, cause major long-term morbidity requiring surgical correction to improve limb function.

The severity of glenohumeral dysplasia and shoulder function associated with nerve repair in OBPI patients has been recently demonstrated[3]. In this report, we further evaluated the severity of glenohumeral dysplasia in OBPI patients with and without finger movement at birth, and correlated the outcome of primary and secondary surgeries in this patient population.

MATERIALS AND METHODS

Study 1

We conducted a retrospective study reviewing pre-surgical records of 87 patients with residual obstetric brachial plexus palsy. Their ages at the time of computed tomography (CT) or magnetic resonance imaging (MRI) scan were between 4 mo and 16 years (average 4.6 years). All the patients in this study have a CT/MRI of bilateral shoulders prior to any surgical procedure. We compared and correlated the pre-surgical results of posterior subluxation of the humeral head (PHHA), and glenoscapular version angle to the finger movement at birth. In studies that quantify obstetric brachial plexus deformities, the most common measurements are PHHA and glenoid retroversion.

Radiological measurements were taken using patients CT or MRI on the transverse sections at the level of the scapular spine as follows: (1) PHHA[4] calculated as percent humeral head anterior to the scapular line (Figure 1); and (2) Glenoscapular version angle (θ-angle difference between the glenoid and a line 90° to scapular line), was measured from either CT or MRI scans[5] as previously described[6, 7], and in the figure legend (Figure 1).

Study 2

This study consisted of 141 OBPI patients, who underwent primary surgeries and/or secondary surgery at the Texas Nerve and Paralysis Institute. All the patients in this study were injured severely enough to develop shoulder deformities that required surgical reconstruction. All surgeries were performed by the same surgeon (Nath RK), whose practice has focused on reconstructive surgery in this population for the past 15 years. The age of these patients ranges from 5 mo to 20 years at the time of visit. One group included 50 patients who underwent nerve reconstruction and secondary surgeries (muscle and bony), the second group included 82 patients, who underwent only secondary surgeries (no nerve surgery), and the third group included 9 patients, who have had only bony (triangle tilt) surgery.

Nerve repair, modified Quad, and triangle tilt surgeries were performed on these patients by the senior author and the surgeon (Nath RK) as described previously[8-11]. Information regarding finger movement was obtained from the patient's parent or guardian during the initial evaluation.

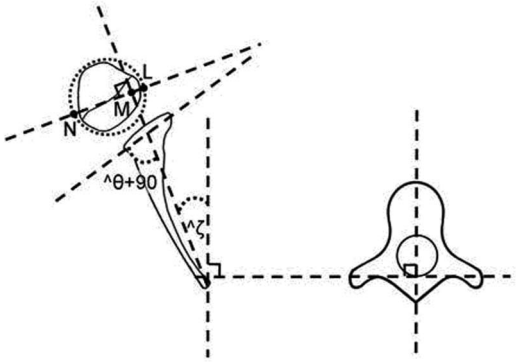

Figure 1 Schematic drawing showing the method of calculating glenoid version and percentage of humeral head anterior to scapular line. Measuring the glenoid version angle (θ): The scapular line is drawn between the medial margin of the scapula to the midpoint of the glenoid. Another line is drawn through the anterior and posterior aspects of the glenoid labrum. The angle between these two lines is measured, and 90° is subtracted. A negative value indicates a retroverted glenoid. A line perpendicular to the scapular line is drawn and the percentage of humeral head anterior to scapular line is defined as the ratio of the distance from the scapular line to the anterior portion of the head to the diameter of the humeral head (LM/LN × 100). Reproduced from Nath RK *et al*[7].

Statistical analysis

Statistical analysis was performed using Analyse-It plugin (Leeds, United Kingdom) for Microsoft Excel 2003 software. A *P*-value of < 0.05 was considered as statistically significant.

RESULTS

Study 1

No finger movement at birth was observed in 56% of the patients. Among 87 patients, 9 (10.3%) patients who lacked finger movement at birth had a PHHA > 40%, and glenoid retroversion < -12°, whereas only 1 patient (1.1%) with finger movement had a PHHA > 40%, and

retroversion < -8°.

Study 2

The improvement in glenohumeral deformity (PHHA, 31.8% ± 14.3%; and glenoid retroversion 22.0% ± 15.0%) was significantly higher in patients, who have not had any primary surgeries and had finger movement at birth (group 1), when compared to those patients, who had primary surgeries (nerve and muscle surgeries) and lacked finger movement at birth (group 2), (PHHA, 10.7% ± 15.8%; Version -8.0% ± 8.4%, $P = 0.005$ and $P = 0.030$, respectively).

The change in radiological measurments was not statistically significantly different in patients who have had primary surgeries (data not shown) with reference to finger movement at birth. No finger movement at birth was observed in 55% of the patients in this study group.

DISCUSSION

The integrity of the motor cortex and the corticospinal tract is critical for the movements of the extremities, and for the control of finger movements[12-17]. Finger movement at birth is an important indication of the functional and anatomical integrity of the brachial plexus.

There are numerous reports in the literature relating finger movements to brain region and brain damage[18-22], stroke[23-25], cerebral palsy[26-28], Parkinson's disease[29,30], carpal tunnel syndrome[31,32], traumatic injury[21,33-37]. However, there are only few reports correlating finger movements and obstetric brachial plexus injury[2,38] and hand injuries, despite the hands are important in performing daily activities[36].

Finger movement at birth was evaluated as one of the potential risk factors for permanent injury and predictors of future osseous shoulder deformity[2]. Glenoid retroversion was significantly more severe in patients with finger movement at birth, and thus associated with the development of a worse glenohumeral deformity. Posterior subluxation was also more severe in these patients, however not significantly.

Although, the mean radiological scores show that lack of finger movement at birth is actually protective against bony deformities of the shoulder, yet, some patients in this group faced severe bony deformities (up to PHHA-31, and version-16, data not shown). Therefore, these patients also suffer extensive functional impairment that necessitated for surgical treatment.

Permanently injured patients with finger movement at birth develop more severe bony deformities of the shoulder than patients without finger movement at birth due, in part, to asymmetrical muscle action on growing bony elements, also underwent surgical treatment at the Texas Nerve and Paralysis Institute.

The outcome of triangle tilt surgery in terms of radiological scores (PHHA and version) was significantly higher in patients who have not had any primary surgeries and had finger movement at birth (group 1), when compared to patients who had primary surgeries (nerve, nerve and muscle surgeries) and lacked finger movement at birth (group 2). Other investigators have reported that some OBPI patients achieved voluntary finger movement with double free-muscle transfer[38].

Our present study is unique in that it evaluates the relationship between finger movement at birth, and the outcome of the primary and secondary surgeries in OBPI patients. Finger movement at birth, may be used as a simple and rapid clinical test, as a predictor of the outcome. The finger movement data in this study is based on retrospective information which was obtained from patient families. The limitation of this study is that a population of transiently injured patients was not available for comparison. In addition, there are not many reports in the literature to compare the finger movement at birth and the surgical outcome in OBPI patients.

COMMENTS

Background

The severity of glenohumeral dysplasia and shoulder function associated with nerve repair in obstetric brachial plexus injury (OBPI) patients has been recently demonstrated. In this report, authors further evaluated the severity of glenohumeral dysplasia in OBPI patients with and without finger movement at birth, and correlated the outcome of primary and secondary surgeries in this patient population.

Research frontiers

Finger movement at birth has been evaluated as one of the potential risk factors for permanent brachial plexus injury, and predictors of future osseous shoulder deformity.

Innovations and breakthroughs

Although, there are numerous reports in the literature relating finger movements to brain region and brain damage, stroke, cerebral palsy, Parkinson's disease, carpal tunnel syndrome, traumatic injury, this is the first report proposing that finger movement may be used as a simple and rapid clinical test, and as a predictor of the surgical outcome in obstetric brachial plexus injury.

Applications

Finger movement at birth, may be used as a simple and rapid clinical test, as a predictor of the surgical outcome.

Terminology

Triangle tilt surgery: This operative technique includes osteotomies of the clavicle, neck of the acromion and scapula in order to release the distal acromioclavicular triangle and allow it to reorient itself in a more neutral position into the glenoid. The modified Quad procedure: Transfer of the latissimus dorsi and teres major muscles, release of contractures of subscapularis pectoralis major and minor and axillary nerve decompression and neurolysis.

Peer review

The limitation of this study is that a population of transiently injured patients was not available for comparison. In addition, there are not many reports in the literature to compare the finger movement at birth and the surgical outcome in OBPI patients.

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Patent (list all authors)

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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).

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Italics

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EDITORIAL

Distinguishing erosive osteoarthritis and calcium pyrophosphate deposition disease

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Abstract

Erosive osteoarthritis is a term utilized to describe a specific inflammatory condition of the interphalangeal and first carpal metacarpal joints of the hands. The term has become a part of medical philosophical semantics and paradigms, but the issue is actually more complicated. Even the term osteoarthritis (non-erosive) has been controversial, with some suggesting osteoarthrosis to be more appropriate in view of the perspective that it is a non-inflammatory process undeserving of the "itis" suffix. The term "erosion" has also been a source of confusion in osteoarthritis, as it has been used to describe cartilage, not bone lesions. Inflammation in individuals with osteoarthritis actually appears to be related to complicating phenomena, such as calcium pyrophosphate and hydroxyapatite crystal deposition producing arthritis. Erosive osteoarthritis is the contentious term. It is used to describe a specific form of joint damage to specific joints. The damage has been termed erosions and the distribution of the damage is to the interphalangeal joints of the hand and first carpal metacarpal joint. Inflammation is recognized by joint redness and warmth, while X-rays reveal alteration of the articular surfaces, producing a smudged appearance. This ill-defined, joint damage has a crumbling appearance and is quite distinct from the sharply defined erosions of rheumatoid arthritis and spondyloarthropathy. The appearance is identical to those found with calcium pyrophosphate deposition disease, both in character and their unique responsiveness to hydroxychloroquine treatment. Low doses of the latter often resolve symptoms within weeks, in contrast to higher doses and the months required for response in other forms of inflammatory arthritis. Reconsidering erosive osteoarthritis as a form of calcium pyrophosphate deposition disease guides physicians to more effective therapeutic intervention.

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Key words: Erosive osteoarthritis; Calcium pyrophosphate deposition disease; Rheumatoid arthritis; Spondyloarthropathy; Osteoarthritis; Hydroxychloroquine

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SEMANTICS

Semantics, philosophy and paradigms are at the core of how we name a disorder[1-11]. Thus, the term erosive osteoarthritis has been imbedded in the medical lexicon. The issue is complex. Even the term for the non-erosive phenomenon we recognize as osteoarthritis[7,8,10,12-26] is somewhat of a misnomer. Semantically, the suffix "itis" in osteoarthritis would suggest inflammation of a diarthrodial (synovial membrane-lined) joint. As osteoarthritis is associated with negligible inflammation[27,28], the suggestion has been made that osteoarthrosis is a more proper term[29]. Further, the term "erosions" has occasionally utilized in an imprecise manner to describe cartilage damage in osteoarthritis[27,28,30]. Actual erosions/disruption of subchondral bone does not occur.

INFLAMMATION

Inflammation of joints affected by osteoarthritis appears actually to be related to complications[31-35] and not to the primary disease. The most common complications are related to calcium pyrophosphate and hydroxyapatite crystals.

Erosive joint disease

The term "erosive osteoarthritis" has been utilized to describe a process which involves joints (interphalangeal and first carpal metacarpal) commonly affected by osteoarthritis, but is characterized by subchondral joint damage[36-38]. Joint tenderness, swelling, angulation, redness and warmth are often present, the latter two documenting an inflammatory process. Radiologic evaluation reveals abnormal articular surfaces, referred to as erosions. These erosions differ from what is found in the major forms of erosive arthritis, rheumatoid arthritis and spondyloarthropathy[3,39-42]. The term spondyloarthropathy defines a family of erosive arthritis including ankylosing spondylitis, psoriatic arthritis, reactive arthritis (replacing name of the war criminal, Reiter's syndrome), the arthritis of inflammatory bowel disease (ulcerative colitis and Crohn's disease) and an undifferentiated form). In contrast to the sharply delineated erosions of the latter, the term "crumbling" has been used to describe the joint damage characteristic of erosive osteoarthritis. The edges appear ill-defined or smudged[3,39,42]. There may be adjacent calcific flecks. This pattern actually describes the damage found in calcium pyrophosphate deposition disease[3,27,39,42].

Calcium pyrophosphate deposition disease

Not only is the character of osseous damage in erosive arthritis identical to that seen in other joints affected by calcium pyrophosphate deposition disease[3,39,43,44], the character of its response to therapeutic intervention is identical[43,44]. Hydroxychloroquine (Plaquenil) treatment, which has not effect on osteoarthritis, is extraordinarily effective in treatment of erosive osteoarthritis. Lower doses are required and the response rate is significantly more rapid in individuals with erosive osteoarthritis (now interpreted as a manifestation of calcium pyrophosphate deposition disease) than rheumatoid arthritis or spondyloarthropathy. Doses as low as 100 mg and control of inflammation within one to four weeks are not uncommon, in contrast to the three to six months required for recognizable response in patients with rheumatoid arthritis or spondyloarthropathy[44-46]. I suggest that the term "erosive osteoarthritis" has outlived its usefulness. Recognizing the characteristic damage as a manifestation of calcium pyrophosphate deposition disease directs attention to specific evidence-based interventions[39,44,47-59].

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REVIEW

Developmental dysplasia of the hip in the newborn: A systematic review

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Abstract

Developmental dysplasia of the hip (DDH) denotes a wide spectrum of conditions ranging from subtle acetabular dysplasia to irreducible hip dislocations. Clinical diagnostic tests complement ultrasound imaging in allowing diagnosis, classification and monitoring of this condition. Classification systems relate to the alpha and beta angles in addition to the dynamic coverage index (DCI). Screening programmes for DDH show considerable geographic variation; certain risk factors have been identified which necessitate ultrasound assessment of the newborn. The treatment of DDH has undergone significant evolution, but the current gold standard is still the Pavlik harness. Duration of Pavlik harness treatment has been reported to range from 3 to 9.3 mo. The beta angle, DCI and the superior/lateral femoral head displacement can be assessed *via* ultrasound to estimate the likelihood of success. Success rates of between 7% and 99% have been reported when using the harness to treat DDH. Avascular necrosis remains the most devastating complication of harness usage with a reported rate of between 0% and 28%. Alternative non-surgical treatment methods used for DDH include devices proposed by LeDamany, Frejka, Lorenz and Ortolani. The Rosen splint and Wagner stocking have also been used for DDH treatment. Surgical treatment for DDH comprises open reduction alongside a combination of femoral or pelvic osteotomies. Femoral osteotomies are carried out in cases of excessive anteversion or valgus deformity of the femoral neck. The two principal pelvic osteotomies most commonly performed are the Salter osteotomy and Pemberton acetabuloplasty. Serious surgical complications include epiphyseal damage, sciatic nerve damage and femoral neck fracture.

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Key words: Developmental dysplasia of the hip; Congenital; Pavlik harness; Ultrasound screening; Pelvic osteotomy

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INTRODUCTION

Developmental dysplasia of the hip (DDH) denotes a wide spectrum of pathologic conditions, ranging from subtle acetabular dysplasia to irreducible hip dislocation with proximal femoral displacement[1]. The reported incidence of DDH varies from 1.5 to 2.5 per 1000 live births[1-3]. Unlike "congenital dysplasia of the hip", DDH is not restricted to congenital malformation, but also includes developmental disturbance[4]. The radiological definition relies on the presence of an intact Shenton line (Figure 1)[5]. The Shenton line remains intact in "subluxation" but disrupted in "dysplasia"[6]. The term dysplasia tends to be used for a hip with a positive Ortolani sign, *i.e.*, a dislocated hip that can be relocated back into the acetabulum. The typical dysplastic hip has a ridge in the superior-posterior and inferior aspects of the acetabulum. The ridge, or neo-limbus, as described by Ortolani, is composed of very cellular hyaline cartilage. The femoral head glides in and out of the acetabulum, producing the palpable sensation known as Ortolani's sign. An additional diagnostic test used to detect dysplasia is the "Barlow manoeuvre", whereby hip flexion and adduction causes the femoral head to leave the acetabulum[7]. Good evidence exists to suggest that untreated dysplasia will culminate in degenerative joint disease. The term "dislocation" is reserved for any hip with a negative Ortolani's sign, *i.e.*, an unreducible hip, that is associated with "secondary adaptive changes of shortening, decreased abduction and asymmetry of the folds"[8].

CLASSIFICATION OF DDH

Graf classified DDH according to various ultrasound measurements (Table 1). The infant remains in a lateral decubitus position and coronal images are taken with subsequent measurement of alpha and beta angles[9]. The alpha angle refers to the angle between the acetabular roof and vertical cortex of the ilium. The beta angle is the angle formed between the vertical cortex of the ilium and the triangular labral fibrocartilage (echogenic triangle). Type 1 hips are deemed mature, type 3 are referred to as immature (Table 1). Dynamic coverage index (DCI) refers to ultrasound measured femoral head coverage with the hip in coronal flexion and adduction. Grill *et al*[10] and Alexiev *et al*[11] used DCI to help formulate a DDH classification system. DCI was greater than 50% in stable hips, DCI was 30%-50% in moderate subluxation, DCI was 10%-35% for severe subluxation; DCI was less than 10% for dislocation.

SCREENING FOR DDH

Screening for DDH may be based upon clinical and/or ultrasound methodology. With clinical screening only, the late dislocation rate is reported as between 0.5 and 0.8 per 1000 live births[9,12]. Some studies[13,14] have suggested that clinical examination for DDH should be delayed until after the newborn period, due to the high rate of spontaneous stabilisation in the first 4 wk of life. Vedantam *et al*[15] suggested that dislocatable hips at birth could be safely monitored with ultrasound for two weeks before determining the course of treatment, reducing the number of infants requiring treatment, without prejudicing the final outcome. Clegg *et al*[16] reported a late dislocation rate of 0% in the 11-year history of their universal ultrasound screening program, but an operative rate of 0.21/1000 live births. They attempted to make a financial case for universal ultrasound screening due to reduction in mean surgical cost by earlier diagnosis of dysplasia/dislocation with subsequent need for fewer, less invasive procedures. Universal ultrasound screening of newborns however, is not deemed cost-effective by most North American authors, although in Europe, non-selective screening is more widely used[17]. van der Sluijs *et al*[13] reported the terms of the Dutch screening programme, which recommended clinical and ultrasound screening of infants between the ages of three and five months with one or more of the following risk factors: breech delivery, family history, leg length discrepancy or limited abduction of the hip. The current United Kingdom programme recommends ultrasound screening of high risk infants at six weeks[18,19]. Sampath *et al*[14] reported a late dislocation rate of 0.22-0.68/1000 live births in selective ultrasound screening programs.

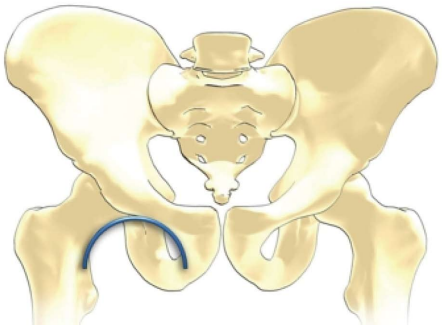

Figure 1 Diagram to demonstrate location of Shenton line. Shenton line is disrupted in developmental dysplasia of the hip[5].

NON-SURGICAL TREATMENT OF DDH: "A HISTORICAL EVOLUTION"

The treatment of children with DDH evolved markedly during the last century. Lorenz first proposed his method of forceful closed reduction and plastering in fixed maximal abduction. At the turn of the last century, most infants were not diagnosed to have dysplasia/dislocation until they started walking. The early 1900's saw the advent of the radiograph and blood transfusion, facilitating lower rates of morbidity from open reductions. Ortolani was the first to highlight the recognition of dislocation in infants below the age of 12 mo, using the clinical ma-

Table 1 The Graf classification[11]

Graf type	Angles
All type Ⅰ	Alpha angle > 60 degrees (normal)
Type Ⅰa	Beta angle < 55 degrees
Type Ⅰb	Beta angle > 55 degrees
All type Ⅱ	
Type Ⅱa	Alpha angle 50-59 degrees
Type Ⅱb	Alpha angle 50-59 degrees
Type Ⅱc	Alpha angle 43-49 degrees Beta angle < 77 degrees
Type D ("about to decenter")	Alpha angle 43-49 degrees Beta angle > 77 degrees
Type Ⅲ Type Ⅲa and Ⅲb distinguished on the grounds of structural alteration of the cartilaginous roof	Alpha angle < 43 degrees
Type Ⅳ (dislocated with labrum interposed between femoral head and acetabulum)	Alpha angle < 43 degrees

noeuvre that would come to bear his name. He supplemented this with his own version of an abduction brace.

In the 1950's, Arnold Pavlik published articles on hip dysplasia and "functional treatment" in response to high rates of avascular necrosis (AVN) and failed reductions using previous conservative treatments[2]. A system of a harness and stirrups was developed which is still in use today. The Pavlik harness is well established as the orthosis of choice for infants with DDH superseding multiple preceding devices[4,10,20-30]. The concept of manual, forceful reduction of the infant's hip with maintenance of limb flexion and abduction was updated to one of hip movement ("dynamic splintage") within a non-pathological range. This reduces the hip and corrects the acetabular dysplasia whilst also minimising the risk of femoral head AVN[7]. The principle centres upon the hip being a "basic joint of movement". Therefore, active and spontaneous motion results in "non-violent and unforced abduction and reduction". His landmark paper, *Zeitschrift fur Orthopaedie*, reported on 1912 hips, with an 85% rate of successful reduction and a 2.8% rate of AVN. This is in marked contrast to success rates of 30% using previously prevalent "passive mechanical" methods[9].

The Pavlik harness consists of two shoulder straps crossing on the back and fastened to a broad thoracic belt anteriorly (Figure 2)[31]. The legs are held in slings consisting of two straps and the hips are flexed to at least 90°. This flexion lines the proximal femoral metaphysis to point towards the triradiate cartilage, the conjoined physeal plate of the pelvic bones. The anterior strap keeps the hips in flexion, limiting extension. The posterior strap is adjusted to stop the lower limb breaking the midline, *i.e.*, to prevent adduction, rather than forcing abduction. Grill *et al*[10] noted that this is remarkably similar to the position of prenatal flexion of the thigh and the position of babies when traditionally carried on a mothers' back[2,32].

The main objective of harness application remains atraumatic, expedient relocation and maintenance of the

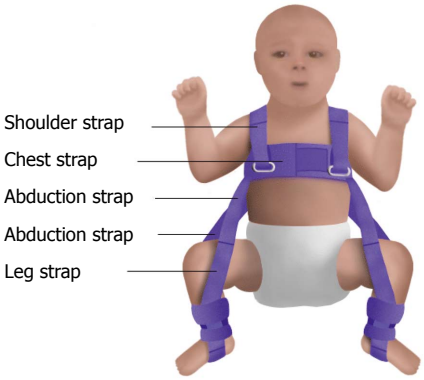

Figure 2 The Pavlik harness[31].

hip to resume normal development. Controlled reduction of the hip depends primarily on flexion and passive abduction. The concept of a "safe zone" for this movement was defined by Ramsey *et al*[27] as the "arc between the angle of abduction that can be comfortably attained and the angle that allows redislocation". Suzuki *et al*[33] reported that in some cases of dislocation, AVN rates could be reduced by the use of under thigh pillows during harness application. However, in cases of severe dislocation, some groups have stated that prevention of extreme abduction with under thigh pillows, was useless in reducing AVN[32]. In such cases, factors such as an inverted labrum, intraarticular interposition of pulvinar, elevated transverse ligament and hypertrophied round ligament are thought to be involved in the pathogenesis of AVN[3].

Weinstein *et al*[2] first highlighted the importance of quadriceps and gluteal muscle activity for optimal harness function. Iwaya *et al*[34] attributed the activity of the hamstrings in reducing dislocation. Relief of the adductor contracture was recognised by Pavlik as being indispensable for reduction. Early studies suggested that this was achieved *via* spontaneous lower limb movements. Modern thinking suggests the weight of the lower extremities plays a more significant role.

Use of the Pavlik harness is contraindicated when there is a major muscle imbalance, as in myelomeningocele (L2 to L4 functional level); major stiffness, as in arthrogryposis; or ligamentous laxity; as in Ehlers-Danlos syndrome[2].

PAVLIK HARNESS TREATMENT REGIMES

Various studies have recommended different durations of harness treatment. Erlacher[30] instructed his patients to wear the harness for approximately 6 mo, whilst Hirsch *et al*[35] believed in an average duration of 3 mo. Others have proposed regimes centred upon age at initiation of harness. Mubarak *et al*[36] suggested the harness should be worn for at least 3 mo by children younger than 3 mo of age, whereas in children older than 4 mo, it

should be worn for approximately double their age. They proposed weekly follow up with ultrasonography and appropriate harness adjustment. They believed such a regime would normally achieve hip stability within three weeks in cases of newborn true dislocation. Ramsey *et al*[27] recommended a mean treatment duration of 3.6 mo when treatment commenced before 1 mo, 7.0 mo between 1 and 3 mo, and 9.3 mo between 3 and 9 mo.

van der Sluijs *et al*[13] noted that one disadvantage of prolonged harness treatment destined to failure was a delay in the management of DDH using alternative strategies which could potentially be successful. Closed reduction at increasing ages is problematic, resulting in an increased incidence of open reductions and possibly higher rates of AVN. They concluded that the use of the Pavlik harness could be prolonged in patients with Graf type Ⅲ hips only if physical examination and ultrasonography showed improvement. A number of studies, including one in a cohort of Graf type Ⅲ/Ⅳ hips by Uçar *et al*[37] report that the likelihood of Pavlik harness treatment leading to a stable reduction markedly decreases after 3-4 wk duration. If the hip is not improved or reduced after 3 wk, some studies have suggested that the use of the harness be discontinued and the treatment plan changed[3,12,27,37-39].

MONITORING PAVLIK HARNESS TREATMENT WITH IMAGING

Grissom *et al*[40] and Polanuer *et al*[41] reported the results of ultrasound evaluation of the harness treatment in two cohorts of fifty patients. Their subjects remained in the harness with periodic adjustments to ensure proper fit and position with interval radiographs to monitor hip position. Ultrasound was deemed particularly useful in allowing good antero-posterior assessment of femoral-acetabular association in two dimensions. Several papers have reported the increased sensitivity of ultrasound scanning when compared with clinical examination[40,42]. One such study reported 100% sensitivity and 94% specificity for all dislocation/significant instability and noted the benefit of ultrasound monitoring for visualisation of soft tissue structures alongside the ability to assess hip position during harness adjustment. Viere *et al*[43] described "surreptitious reduction" as the process whereby hips treated by the harness remain dislocated and locked behind the posterior rim of the acetabulum. Ultrasound allows visualisation of such cases which can result in posterolateral acetabular deficiency with prolonged harness use.

Suzuki[44] reported the use of ultrasound in providing us with an indication of the likelihood of harness success by identifying three degrees of residual head displacement. Type A dislocations demonstrate contact between the femoral head and the acetabular wall, with no significant obstruction to the head returning to the bottom of the fossa. In type B dislocations the femoral head contacts the posterior margins of the socket. In type C dislocations the femoral head is displaced outside the socket, with its centre posterior to the acetabular rim. They suggested that the Pavlik harness was indicated in type A hips, appropriate for type B hips along with daily ultrasound monitoring and contraindicated in type C hips.

Whilst many authors showed that static ultrasound imaging could be a reliable way of detecting abnormality, Engesaeter *et al*[45] and Dias *et al*[46] reported poor reliability of static ultrasound and advocated solely dynamic assessment. A landmark study by Graf indicated that static and dynamic images should be used in conjunction[47]. Some studies have suggested the use of ultrasound in the prediction of poor acetabular development after walking age[11,48]. At a mean follow-up of 5 years, Alexiev *et al*[11] found that dynamic sonographic measures of stability such as a reduced DCI < 22% and a beta angle of < 43° showed 100% sensitivity for medium-term instability. They suggested that increased echogenicity of the cartilaginous roof on initial ultrasound was the most specific single predictor of residual dysplasia (sensitivity 100% and specificity 88%). The structurally normal cartilaginous roof is non-echogenic except for the labrum and ultrasound showed that in all successfully reduced hips in this series[11], the echogenic cartilage reverted to non-echogenic tissue. White *et al*[49] agreed that a DCI < 22% was predictive of failure. An inverted labrum and superior femoral head displacement correlated with poor outcome. Authors reported that a femoral head positioned below the labrum was strongly correlated with Pavlik harness success. They found that hips which displayed Pavlik failure had a significantly greater beta angle and significantly less lateral femoral head coverage at the time of presentation. Such cases are more likely to have an inverted labrum and to present later. They identified two new ultrasonographic markers, superior femoral head displacement relative to the labrum and total femoral head displacement. They found the latter to be the more reliable marker of failure.

The use of ultrasonography is not problem-free. Gwynne Jones[48] showed the considerable inter- and intra-observer variability of ultrasound measurement in neonatal hips. Ultrasound can detect abnormalities in the first few weeks of life which resolve spontaneously and scans at 4, 6 or 9 wk are more specific than earlier scans but this limits usefulness in screening.

In spite of these issues, many authors agree that the use of ultrasonography is the most significant development in the management of DDH since the development of the Pavlik harness itself[50-53].

PAVLIK HARNESS TREATMENT OUTCOMES

Overall, success rates of 7%-99% have been reported in cases of DDH using the Pavlik harness[8,38,39,54-58]. Cer-

tain studies have given lower peak success rates of 50%-80%[8,13,15,43,59]. Weinstein *et al*[2] highlighted the role of the harness in infants with limited hip abduction and documented acetabular dysplasia with or without subluxation. Following appropriate harness application, the contracted hip adductors stretch, allowing a full range of abduction within two weeks. Relief of adductor contracture is a key component of success, necessitating adductor tenotomy in some instances as originally proposed by Pavlik.

Failure of the device has been linked to improper use and poor compliance as noted by Lerman *et al*[38] and Mubarak *et al*[36]. The reported incidence of AVN ranges from 0%-28%[60-64]. Use of the Pavlik harness is associated with excessive flexion causing injury to the femoral nerve, excessive abduction causing AVN, and conversely insufficient flexion or abduction for maintenance of a stable reduction[65]. The maximum period for use of the harness is unknown. Some studies have suggested that long-term unsuccessful treatment is associated with a high rate of AVN, deformity of the femoral head and deficiency of the posterior acetabulum. van der Sluijs *et al*[13] disagreed with this and suggested that continued use of the harness could increase the number of successful reductions as long as abduction of the hip was continually improving, without risk of AVN or residual dysplasia[66]. By 12 wk, they reported that half of the type Ⅲ hips which eventually responded to bracing were not yet reduced. Consequently, a substantial proportion of these hips would have been potentially treated by surgery if Pavlik harnessing was limited to the conventional 4 wk. They reported that development of the hip was related to Graf type, rather than duration of bracing. The authors reported that prolonged bracing did not increase AVN, with their rates of AVN in Graf type Ⅲ and Ⅳ hips (16%), being equivalent to that of a previous study[33] where bracing was shorter. Suzuki[44] described the "type 1 error", occurring with incorrect prolonged use of the Pavlik harness in hips that remained unreduced in a posteriorly dislocated position. In such hips, the femoral head became adherent to the posterior capsule. This was reported to require open reduction from an anterior approach. The "type 2 error" occurs in hips that are too loose for successful treatment with the harness and require a more stable orthosis. Excessive duration of Pavlik harness use can therefore lead to erosion of the posterior acetabulum. Swaroop *et al*[18] highlighted the benefits of ultrasound in recognising failed improvement in abduction at three weeks.

The treatment of dislocated but reducible hips has proved problematic, with previous studies reporting success rates of 60%-70%[67,68]. The failed cases ultimately require operative treatment with closed or open reduction and hip spica casting. Swaroop *et al*[18] reported an increase in successful reductions of Ortolani positive hips, with two specific changes in treatment protocol; routine use of serial office based ultrasound examinations and transition to fixed hip abduction orthosis in hips remaining stable after three weeks in a Pavlik harness. The use of abduction braces in failed Pavlik harness treatment is contentious. Hedequist *et al*[69] suggested that it may be successful because cases of inferior dislocation were often resistant to Pavlik treatment and could be aggravated by flexion. Whilst numerous studies have highlighted the increased risk of AVN with more rigid devices, Hedequist *et al*[69] and Eberle[70] reported on a series of Ortolani positive hips treated with rigid devices after Pavlik failure, who were followed up until the development of a normal appearing ossific nucleus. They reported no incidence of AVN in their patients. Clearly, the numbers in these series were small and further study could establish more accurate incidence of AVN with abduction orthosis.

CONSEQUENCES OF PAVLIK HARNESS FAILURE

Harness failure has historically been associated with impaired femoral head/acetabular development and AVN. Rates of AVN following Pavlik treatment vary widely in historical studies from 0% to 28%[23,24,27,71], due to differences in definition of AVN and length of follow-up, indication for treatment and severity of dislocation.

The diagnosis of AVN has traditionally been made according to the Salter criteria[63]: (1) Failure of appearance of the ossific nucleus of the femoral head during 1 year or more after reduction; (2) Failure of growth in an existing ossific nucleus during 1 year or more after reduction; (3) Broadening of the femoral neck during 1 year after reduction; (4) Increased radiographic density of the femoral head followed by the radiographic appearance of fragmentation; and (5) Residual deformity of the femoral head and neck when reossification is complete.

Early studies did not analyse the reasons for any failure. Felipe and Carlioz mentioned 7 failures in 112 hips without discussing contributing factors or subsequent management, whilst the European Paediatric Society reported a failure rate of 14%, and also did not analyse reasons for failures[43]. An early study by Wilkinson suggested that an irreducible dislocation (Ortolani negative) hip was a contraindication to the use of the harness. Others[2,8,38,59,63,72] have disagreed. Viere *et al*[43] reported an early series in which despite recognition of an increased risk of harness failure, 11 of 27 such patients were treated successfully with the harness. They recommended a harness trial in patients with an Ortolani negative dislocation below the age of 7 mo, with discontinuation of treatment if concentric reduction was not achieved within 4 wk.

A number of early studies have highlighted delay in treatment beyond the age of 3 wk[67] and 7 wk[43], poor stability of the reduced hip, the initial acetabular index and an Ortolani negative clinical examination as risk fac-

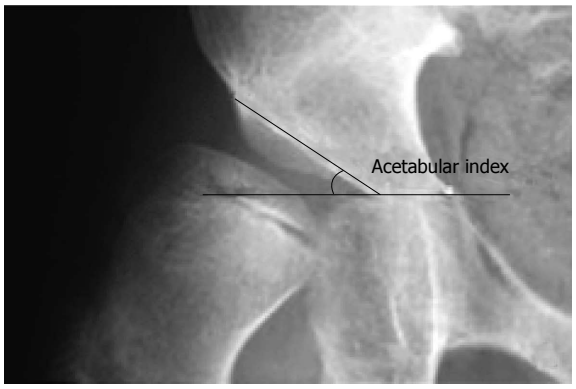

Figure 3 Calculation of acetabular index[95].

tors for Pavlik harness failure[63]. Inoue *et al*[73] highlighted poor treatment technique, including improper application of the harness leading to rigid fixation of the hip in a "frog-leg" position. Traditionally, there have been differing opinions concerning the relationship between instability and acetabular dysplasia, with some authors finding that instability could lead to dysplasia[63,74] and vice-versa[33,59].

Male gender is a recently cited factor[75] with some disagreement between studies[38]. Viere *et al*[43] and Lerman *et al*[38] found a statistically increased likelihood of failure with bilateral involvement, whereas Harding *et al*[67] and more recently, Borowski *et al*[76] found no increased association with bilaterality. A retrospective study by Kitoh *et al*[7] found that patients with bilateral DDH were approximately six times as likely to fail Pavlik harness treatment as those with unilateral DDH, whereas Borowski *et al*[76] found no significant association. Despite progression in radiological imaging, a number of studies have reported the severity of initial clinical examination to be the most powerful univariate predictor of failure of Pavlik harness treatment[38,43].

ALTERNATIVE NON-SURGICAL TREATMENT METHODS FOR DDH

Historically, there have been a number of alternative reduction devices used in DDH, such as stirrup devices proposed by LeDamany, Frejka, Lorenz and Ortolani[72]. However, the majority of the literature has shown the Pavlik harness to be superior in terms of successful reduction and AVN rates. The Frejka pillow for example has been associated with poor outcomes and high rates of AVN because it has the tendency to forcibly abduct the hips. Czubak *et al*[77] showed 89% successful reduction using the Frejka pillow, compared to 95% with the Pavlik harness and found the Pavlik harness to be more effective in hips diagnosed before 24 wk. They noted AVN in 12% and 7% of hips treated with the Frejka pillow and Pavlik harness respectively. The Rosen splint[72] is still used in many Scandinavian centres. Whilst reported to have high rates of success and few complications, it is only of use in newborns. Its use otherwise is associated with AVN and increased risks of skin irritation and pressure sores[18].

Recently various devices essentially based on the Pavlik harness have shown promising results. The "Wagner stocking" was reported by Pach *et al*[78] to have high rates of successful reduction and AVN rates in the region of 2.6%, comparable to some studies of the Pavlik harness. Clearly the evidence behind this is small compared to that concerning the Pavlik harness and longitudinal studies of outcomes are needed for significant comparison.

SURGICAL TREATMENT OF DDH

Failure to achieve hip reduction *via* closed techniques may dictate surgical open reduction techniques combined with femoral or pelvic osteotomy. Femoral osteotomies are performed to correct excessive anteversion or valgus deformity of the femoral neck. The pelvic osteotomies principally used for DDH include: (1) Salter innominate osteotomy[79-91] or (2) Pemberton pericapsular osteotomy[83,92-94]. Selection of a or b has been linked to the acetabular index (Figure 3)[31,95]. The Acetabular Index is the angle between the Hilgenreiner line and a line drawn from the triradiate epiphysis to the lateral edge of the acetabulum. This angle should decline with age and typically is less than 20 degrees by the time the child is 2-year-old. The Pemberton osteotomy tends to be favoured in cases where the acetabular index is greater than 40 degrees[96]. The Salter osteotomy is an open wedge osteotomy which retroverts and extends the acetabulum around a fixed axis such that the acetabular roof covers the femoral head both superiorly and anteriorly[97,98]. This osteotomy is designed to deliver more anterior femoral head coverage with less posterior coverage provided par consequence. Success depends upon a mobile pubic symphysis[99]. Böhm *et al*[100] reviewed the cases of 61 patients who had 73 Salter osteotomies and reported 15 failures; defined by the need for revision surgery or obtaining a Harris Hip Score of less than 70 points. The Pemberton Osteotomy is an incomplete transiliac osteotomy which starts approximately 10 mm superior to the anterior inferior iliac spine and advances posteriorly, ending at the ilioischial limb of the triradiate cartilage[101]. Wu *et al*[102] evaluated the results of 106 children (116 hips) with DDH treated with a Pemberton acetabuloplasty, reporting good to excellent results in 87% (with follow up ranging from 2 to 10 years). Complications of surgery for DDH include: AVN of the femoral head, sciatic nerve damage, K-wire breakage or migration, damage to the epiphyseal centre, femoral fracture and leg-length discrepancy[83].

CONCLUSION

DDH refers to a broad spectrum of conditions from mild acetabular dysplasia to irreducible hip dislocation. Screening programmes for DDH still vary worldwide

and more large-scale, longitudinal studies are needed to allow standardisation of policy across regions. Ultrasound imaging allows DDH classification based upon alpha/beta angles and the DCI. The appropriate management of DDH can have lasting consequences for lifetime morbidity. Non-surgical treatment methods for DDH have undergone historical evolution with the Pavlik harness remaining the treatment of choice worldwide. The Pavlik harness has undoubtedly led to progression in the successful treatment of DDH with a reduction in the incidence of short-term complications and developmental disturbance. Pavlik harness treatment does require meticulous clinical follow up often in conjunction with routine ultrasound imaging. Harness failure can however lead to femoral and acetabular developmental disturbance along with devastating AVN. Alternative non-surgical treatment methods have been reported for DDH such as the Wagner stocking and Frejka Pillow. Surgical management is a last resort for patients where harness treatment has failed. A combination of open reduction with femoral/pelvic osteotomy may be required.

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REVIEW

Pathophysiology, diagnosis, and treatment of discogenic low back pain

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Abstract

Discogenic low back pain is a serious medical and social problem, and accounts for 26%-42% of the patients with chronic low back pain. Recent studies found that the pathologic features of discs obtained from the patients with discogenic low back pain were the formation of the zones of vascularized granulation tissue, with extensive innervation in fissures extending from the outer part of the annulus into the nucleus pulposus. Studies suggested that the degeneration of the painful disc might originate from the injury and subsequent repair of annulus fibrosus. Growth factors such as basic fibroblast growth factor, transforming growth factor β1, and connective tissue growth factor, macrophages and mast cells might play a key role in the repair of the injured annulus fibrosus and subsequent disc degeneration. Although there exist controversies about the role of discography as a diagnostic test, provocation discography still is the only available means by which to identify a painful disc. A recent study has classified discogenic low back pain into two types that were annular disruption-induced low back pain and internal endplate disruption-induced low back pain, which have been fully supported by clinical and theoretical bases. Current treatment options for discogenic back pain range from medicinal anti-inflammation strategy to invasive procedures including spine fusion and recently spinal arthroplasty. However, these treatments are limited to relieving symptoms, with no attempt to restore the disc's structure. Recently, there has been a growing interest in developing strategies that aim to repair or regenerate the degenerated disc biologically.

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Key words: Intervertebral disc; Degeneration; Diagnosis; Treatment; Discogenic low back pain; Classification; Internal disc disruption; Internal annular disruption; Internal endplate disruption

Core tip: Discogenic low back pain is the most common type of chronic low back pain. Why lumbar disc degeneration leads to pain is one of the most important topics in medical field. Studies have revealed that pathologic features of painful discs were the formation of the zones of vascularized granulation tissue, with extensive innervation in annular fissures. Provocation discography now still is the only available means by which to identify a painful disc. There are a multitude of treatments used in clinical practice to treat chronic low back pain, with little consensus amongst clinicians as to which is the best approach.

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INTRODUCTION

Chronic low back pain is a serious medical and social problem, and one of the common causes responsible for disability. It is estimated that, in all populations, an individual has an 80% probability of having low back

pain at some period during their life time, and about 18% of the population experiences low back pain at any given moment[1,2]. According to US National Center for Health Statistics reports, 14% of new patients that went to a hospital for treatment were patients with low back pain, which represents 13 million people. About 3% of all patients discharged from hospitals have symptomatic low back pain. The expense of treating low back pain is higher than $100 billion each year[3].

The prerequisite for successfully treating low back pain is to make an accurate pathological diagnosis. Despite the inherent challenge in elucidating the specific etiology of chronic low back pain, diagnostic procedures can reveal its source in 90% of patients. DePalma *et al*[4] found that the prevalence of zygapophysial joints, sacroiliac joints, and lumbar discs was 31%, 18%, and 42%, respectively. They confirmed the disc as the most common etiology of chronic low back pain in adults. Crock[5] first proposed the concept of internal disc disruption (IDD), which indicated the discogenic pain syndrome caused by disc degeneration and non-nerve root referred pain. IDD causing discogenic low back pain accounts for 26%-42% of chronic low back pain patients[4,6,7]. IDD had been assigned as a separate clinical entity to differentiate it from other types of disc degenerative low back pain, such as lumbar disc herniation, degenerative disc disease (DDD) and lumbar segment instability[8]. Lumbar X-ray images of IDD patients show no characteristic changes in degenerative disc diseases such as intervertebral space narrowing, osteophyte formation, endplate sclerosis, and gas formation within disc space[8].

This paper reviews the pathophysiology, diagnosis, and treatment of discogenic low back pain according to the existing literature.

PATHOPHYSIOLOGY

The intervertebral disc is the main joint between two consecutive vertebrae in the vertebral column. Each disc consists of three different structures: an inner gelatinous nucleus pulposus, an outer annulus fibrosus that surrounds the nucleus pulposus, and two cartilage endplates that cover the upper and lower surfaces of vertebral bodies. The cells that form the annulus fibrosus, particularly in the outer region, are fibroblast-like and arranged parallel to the collagen fibers, whereas those in the inner annulus fibrosus are chondrocyte-like. The nucleus pulposus contains collagen fibers that are randomly distributed and elastin fibers that are radially organized embedded in a highly hydrated aggrecan-containing gel. Chondrocyte-like cells synthesize type Ⅱ collagen, proteoglycans, and non-collagenous proteins that form the matrix of the nucleus pulposus and the cartilage endplate. Fibroblast-like cells synthesize type I and type Ⅱ collagen for the annulus fibrosus[9]. Proteoglycans consist of a core protein from which radiate chains of glycosaminoglycans containing keratin sulphate and chondroitin sulphate. Multiple proteoglycans are joined to a hyaluronic acid chain to form aggrecan. Aggrecans are held together by type Ⅱ collagen, which is cross-linked by type Ⅸ collagen. Aggrecan is the most common proteoglycan in the disc, and comprises approximately 70% of the nucleus pulposus and 25% of the annulus fibrosus. Aggrecan provides a high level charge density, which creates a high osmotic pressure for retaining water within the nucleus pulposus[10]. A young healthy disc behaves like a water bed, with the high water content of the nucleus and inner annulus enabling the tissue to act like a fluid. Only the outermost annulus acts as a tensile "skin" to restrain the nucleus.

Disc cells synthesize their matrix and break down existing matrix by producing and activating degradative enzymes, including matrix metalloproteinases (MMPs) and "a disintegrin and metalloproteinase" (ADAMS). Degradation of the matrix allows it to be refreshed by newly-synthesized components. Several growth factors, such as bone morphogenetic protein-2 (BMP-2), BMP-7 (also known as osteogenic protein-1; OP-1), growth differentiation factor-5 (GDF-5), transforming growth factor-β (TGF-β), insulin-like growth factor-1 (IGF-1), and others have been found to stimulate matrix production, while interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) inhibit the synthesis of matrix by enhancing its catabolism[9,10].

Disc degeneration will occur if the matrix is not normal. At a molecular level, degeneration will be expressed by the production of abnormal components of the matrix or by an increase in the mediators of matrix degradation, such as IL-1 and TNF-α, and of MMPs and a reduction in the levels of tissue inhibitors of metalloproteinases (TIMPs). Several factors have been considered to cause disc degeneration. Genetic predisposition, mechanical load, and nutritional factors are widely regarded as important contributors to the degenerative process[11]. However; detailed characterization of this complex interplay remains elusive. With the disc degeneration, there is a net loss of proteoglycans and water from the nucleus, leading to poor hydrodynamic transfer of axial stresses to the outer anulus fibrosus. The disc degeneration may result from an imbalance between the anabolic and catabolic processes or the loss of steady state metabolism that is maintained in the normal disc. Alterations in both anabolic and catabolic processes are thought to play key roles in the onset and progression of disc degeneration.

Disc degeneration usually appears in magnetic resonance imaging (MRI) T2-weighted images as a decline in signal intensity, *i.e.*, the so-called "black" disc. MRI may identify a degenerative disc and an annular tear, but it will not help differentiate between a disc which is pathologically painful and one which is physiologically aging[12]. Disc degeneration is a very complicated biological process. Previous views on disc degeneration and the mechanism underlying it were mainly based on histological and biochemical studies using human disc herniation specimens from surgery and animal models of aging and degenerative discs[13,14]. However, the main histological

changes and the exact molecular mechanisms underlying the painful pathological disc remain unknown.

With the development and popularization of lumbar fusion, a greater number of painful pathological disc specimens can be obtained, which are beneficial for studies regarding the pathogenesis of painful disc degeneration. Based on our previous histological studies[15-17], we found that the composition and structure of painful disc differed from those of non-painful degenerative disc. Specifically, normal fibroblasts in the annulus fibrosus were replaced by cartilage-like cells. The annulus fibrosus lamellar structure was disordered and fractured. The normal highly hydrated gelatin-like nucleus pulposus, whose matrices showed obvious fibrosis, and cartilage-like cells, were completely replaced with fibroblasts, was substituted by fibrous tissues. The histological changes in the nucleus pulposus were divided into 3 major types: obvious fibrosis, vascular invasion, and inflammatory granulation tissue formation. In addition, we found that the characteristic change in painful pathological discs was the formation of inflammatory vascular granulation tissues with extensive innervation along the tears in the posterior annulus fibrosus, along with mass expression of some growth factors such as basic fibroblast growth factor (bFGF), TGF-β1, and connective tissue growth factor (CTGF). Vascular granulation tissue was not formed in asymptomatic degenerative discs, and only a few growth factors were expressed. Asymptomatic degenerative discs with tears are not painful, because these discs have not been innervated[15].

Blood vessels only exist in the longitudinal ligaments and the outermost layers of the annulus fibrosus in a normal disc. The ingrowth of vascularized granulation tissue along the tear deep into the inner annulus and nucleus pulposus in the painful disc probably begins soon after the injury when repair of the tear starts from the margin of the annulus fibrosus[15]. Owing to the absence of blood vessels in the inner annulus fibrosus and nucleus pulposus, it is unlikely that vascularized granulation tissue which is induced by the tear should originate from there. Different animal models of outer annular injury have proved that the healing of the annulus might initiate a progressive degeneration of the disc[18-24]. In addition, the whole process of healing of annulus fibrosus injury, including inflammatory reaction, formation of granulation tissue, and tissue reconstruction had been observed, implying that the disc has actually been torn and there has been a process of healing in progress[16].

According to recent researches on injury and repair, growth factors have been considered to be essential to regulate and control the whole process of repair of an injury. Some growth factors, such as bFGF, TGF-β, and CTGF, may be important as promoters in tissue repair. Growth factors that control cellular proliferation and differentiation *in vitro* have been identified. These factors mediate cellular interactions *in vivo*, which not only contribute to development and growth, regeneration, and wound healing, but also may incite abnormal changes[16]. Growth factors through their each receptor signal transduction pathway, promote cellular proliferation and collagen synthesis of matrix cells such as fibroblast and vascular endothelial cells, which exert a strong effect on adjustment and control of wound and repair[16]. Previous studies have indicated that bFGF as an important mitogen accelerator may directly act on the mitotic cycle of tissue repair cells (for example fibroblast), resulting in shortening of G1 phase, prolongation of G2 and M phases, thus mitotic cycle is shortened, and cell division and proliferation accelerates. TGF-β, as a multi-functional growth factor, not only can attract inflammatory cells and tissue repair cells to aggregate in the wound region, but also directly act on fibroblasts to stimulate synthesis of type I procollagen, formation of granulation tissue, and tissue reconstruction in the later stage of repair[25-27]. Nagano *et al*[28] in an animal model of disc degeneration found that bFGF was a proliferation stimulating factor promoting proliferation of chondrocytes to replace normal annular cells in degenerated discs in an autocrine or paracrine manner. Tolonen *et al*[29] studied expression of bFGF and TGF-β in painful degenerative discs, and found that growth factors strongly express in both the annulus fibrosus and the nucleus pulposus. Their study suggests that these growth factors promote cellular remodeling, and create a cascade in the process of disc degenerateion.

Disc tissues are different from other tissues because they comprise the largest avascular tissue. In other tissues, injury healing proceeds from the inside to the outside. On the contrary, healing in disc tissues proceeds from the outside to inside[16]. When the annulus fibrosus is lacerated or injured, vascular tissues can only gradually develop from the outer to the inner annulus fibrosus. Endothelial cells migrating into discs form the principal parts of a new capillary vessel. With the help of various growth factors, endothelial cells migrating into the avascular disc tissues differentiate, proliferate, and gradually form complicated capillary networks. Our studies[15-17] suggested that as annulus fibrosus injuries stimulated local vascular inflammatory reactions, cells including macrophages and mast cells in inflammatory regions produce a large number of growth factors such as bFGF, TGF-β1, and CTGF. The cells in normal disc are separated from the circulatory system. These increased growth factors acted on the intervertebral disc cells, and promoted disc cell dedifferentiation and proliferation, as well as large-scale extracellular matrix synthesis via signal transduction. This may be the main cause of painful disc fibrosis and degeneration. The strong expression of proliferating cell nuclear antigen (PCNA) in painful discs seemed to be an evidence of this hypothesis. PCNA, a nucleoprotein of nonhistone, is an essential auxiliary protein of DNA polymerase-δ[16]. It can markedly increase activity of DNA polymerase-δ, and its expression level is believed to be an important measure of cell proliferation activity[30].

The normal disc is believed to be an organ that is poorly innervated supplied only by sensory and sym-

pathetic perivascular nerve fibers. In the early 1980s, Bogduk[31] clarified the innervation of the outer layers of the annulus. The posterior part of the human disc was supplied not only from the sinuvertebral nerve but also received direct branches in its posterolateral aspect from the ramus communicans or the ventral ramus. Branches from the grey ramus communicans also supplied the lateral aspect of the disc. Anterior discal nerves were observed to arise solely from the sympathetic plexus surrounding the anterior longitudinal ligament. The sensory fibers that innervated the disc are mainly nociceptive and, to a lesser extent, proprioceptive. The sympathetic fibers are considered vasomotor efferents, and also sympathetic afferents conveying pain impulses[32]. The close association of the postganglionic efferent and sympathetic afferent fibers reflected a similar pattern to that seen in certain enteric organs, leading them to suggest that low back pain is a kind of visceral pain[33-35]. In human degenerated disc, as well as in animal models of disc degeneration, the number of nerve fibers in the disc increases[15,36,37]. Furthermore, the nociceptive nerve fibers grow into what are usually aneural inner parts of the annulus and even into the nucleus. In addition to the sensory nerve fibers, there is growing evidence that sympathetic afferents are also increased in degenerated disc and that they play a significant role in low back pain[38-40]. In human normal disc, protein gene product 9.5-positive nerve fibers, either associated with blood vessels or distant from them, innervate the outer layers of the annulus. These nerve fibers are also positive for acetylcholinesterasem NFP, SP, CGRP, VIP, neuropeptide Y, C-flanking peptide and synaptophysin. The nerves entering the rat disc have an identical expression pattern[32]. Mechanical stimuli which are normally innocuous to disc nociceptors can, in certain circumstances, generate an amplified response which has been termed 'peripheral sensitization'. This may explain why some degenerative discs are painful and others not. There is growing evidence that these pain receptors in painful disc are peripherally sensitized by the activity of sympathetic efferents which may initiate a pain impulse in response to ischaemia, pressure changes or inflammatory irritation[32].

It is accepted that the lumbar disc, which are the main source of discogenic back pain in humans, are innervated segmentally. However, the ventral portions of the rat lower lumbar discs are innervated by upper (L1-L2) dorsal root ganglion neurons and the nerve fibers innervating the posterolateral portion of the disc come from the upper and lower dorsal root ganglion (L3-L6)[38,39]. Nerve fibers reach the lumbar disc through the sinuvertebral nerves or from branches of the paravertebral sympathetic trunks[40]. Clinical studies have indicated those local anaesthetic blocks of L2 nerve root can relief discogenic low back pain[41].

DIAGNOSIS

The diagnostic criteria for IDD established by the International Association for the Study of Pain (IASP) are emergence of a concordant pain response during discography, internal annular disruption shown by CT after discography (CTD) and at least one adjacent disc without concordant pain[42]. The term IDD was first coined by Crock[5] on the basis of a large group of patients whose disabling back and leg pain became worse after operation for suspected disc prolapse. He reported this condition, characterizing it by disruption of the internal architecture of the disc, discogenic back pain in the absence of peripheral disc shape abnormality, and the absence of nerve root compression. At present, IDD has been described as a distinct clinical entity to be distinguished from other painful processes such as degenerative disc disease and segmental instability[8]. In our a previous study, according to discography, we classified discogenic low back pain into two types that were annular disruption-induced low back pain (IAD) and internal endplate disruption-induced low back pain (IED), which have been fully supported by clinical and theoretical bases[43]. The term IAD should be more reasonable than the term IDD clinically and pathologically. Clinically, these two types of low back pain should be confirmed by lumbar discography. The diagnostic processes, radial tear and pain responses are identical. During the process of contrast medium injection, the contrast medium was either flowing to the outside of disc through a radial annular tear, or flowing to the vertebral body through the radial endplate tear. The concordant pain responses would be induced in either way.

According to the "Modified Dallas Discogram Description" method[44,45], the degrees of annular disruption could be classified into four grades. The definitions are Grade 0: the contrast medium is confined within the normal nucleus pulposus; Grade 1: the contrast medium flows into the inner third of the annulus through annular fissure; Grade 2: the contrast medium flows into the middle third of the annulus; Grade 3: the contrast medium flows into the outer third of the annulus, and extends circumferentially less than 30° arc at the disk center; Grade 4: the contrast medium flows into the outer third of the annulus, and extends circumferentially more than 30° arc at the disk center; and Grade 5: the contrast medium leakage into the outer space. Grades 0, 1 and 2 are normal, while Grades 3 and above are indicative of annular disruption. We combined the discogram and CT scan after discography to evaluate the degree of endplate disruption in IED patients. The disruptive degrees were classified into four grades (Figure 1): Grade 0 (no disruption), Grade 1 (contrast medium flows into the cartilage endplate through tear), Grade 2 (contrast medium flows into the bony endplate), Grade 3 (contrast medium flows into the cancellous bone of vertebra under endplate, showing local dispersion) and Grade 4 (contrast medium disperses extensively in the cancellous bone)[43]. In this group of patients with IED, all intervertebral discs that showed concordant pain responses had endplate disruptions more severe than Grade 3, which was consistent with the distributions of blood vessels and nerves in the

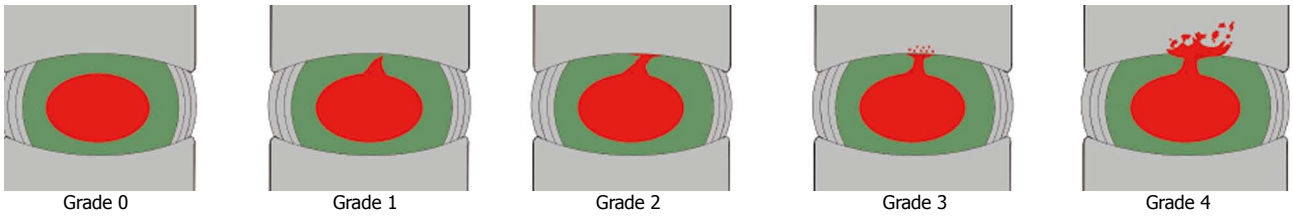

Figure 1 Endplate disruption grading method schematic diagram.

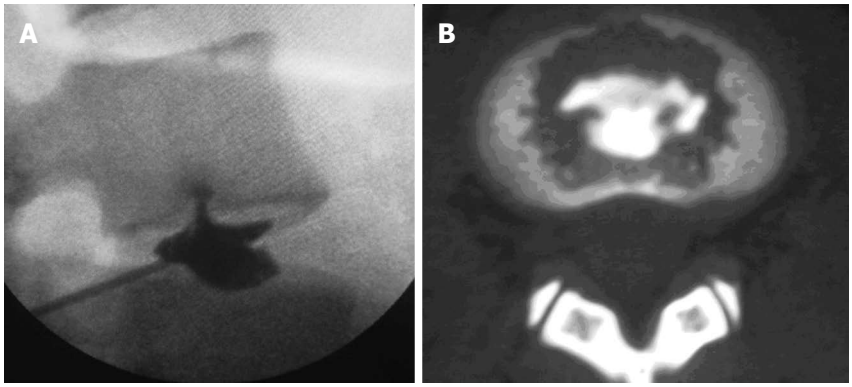

Figure 2 Discography and computed tomography. A: Discography showing a radial disruption on the lower endplate of L4 vertebra and that the contrast medium flows into the cancellous bone of the lower endplate of L4 vertebra through the fissure; B: Computed tomography scan showing the contrast medium dispersed in the lower endplate of L4 vertebra, with Grade 4 endplate disruption.

endplate (Figure 2)[43].

Theoretically, any innervated vertebra and its peripheral structures might be the source of low back pain. An intervertebral disc has such a structure that, except for the peripheral parts around annulus fibrosus, the endplate also has nerve supplies. Normally, one vertebral endplate has two nerve supplies: one enters the endplate along with perivertebral blood vessels, while the other that belongs to the sinuvertebral nerve branch that enters the endplate through the intervertebral foramen. The nerve density within the endplate is similar to that of the annulus, indicating that the endplate is also an important source of discogenic low back pain[46]. Recently, we published a clinical study article[47], 21 patients with chronic back pain originating from the endplate injuries were selected to explore the methods of diagnosis and surgical treatment. Pain level of disc was determined through discography in each patient. All 21 patients with a diagnosis of back pain originating from endplate injuries according to discography were treated with anterior or posterior fusion surgery. After operation, through a mean follow-up of three years and five months, we found that in all the 21 patients, 20 (20/21) reported a disappearance or marked alleviation of low back pain and experienced a definite improvement in physical function. The study suggests that discography and fusion surgery may be very effective methods for the diagnosis and treatment, respectively, of chronic back pain originating from the endplate injuries. In fact, endplate damage-induced low back pain occurs quite often clinically. In clinical research, we found that endplate damage-induced low back pain accounted for 16.7% of chronic discogenic low back pain. Epidemiological investigation showed that the incidence of endplate damage among populations without low back pain was 30%[48].

Theoretically, the pathogenesis of endplate disruption-induced discogenic low back pain is presumed to be consistent with that of annular disruption. A large number of animal experiments have indicated that damage to the outer layer of the annulus could induce a progressive degeneration of the entire disc[19-23]. Similarly, animal models have indicated that needle punctures from the vertebral side all the way through the endplate into the disc could induce a progressive degeneration of the entire disc[49]. It was found that the apoptosis of nucleus pulposus cells increased and the proteoglycan content decreased after endplate injury in the endplate damage animal model[50]. The ingrowth of nerves and blood vessels is a characteristic of tear discs, and is also directly correlated with discogenic low back pain. Freemont *et al*[51] found that blood capillaries grew in companion with nerve endings into the painful discs through endplates.

Basic and clinical studies have overwhelmingly illustrated the nerve supply of the disc and pathomorphologic correlates[6-9,15,18,36,37,52-58]. Based on controlled evaluations, the lumbar intervertebral discs have been shown to be sources of chronic low back pain without disc herniation in 26% to 42%[4,6,7]. Because of the variety of anatomic and pathophysiologic causes of chronic low back pain, it is a difficult diagnosis for clinicians to make. Clinicians primarily use advanced imaging techniques, such as MRI to diagnosis low back pain. Studies show that MRI findings such as disc degeneration do not correlate with the presence or severity of low back symptoms. Lumbar

provocation discography is a procedure that is used to characterize the pathoanatomy and architecture of the disc and to determine if the disc is a source of chronic low back pain. Recently, the American Pain Society developed and published multiple guidelines[59,60] in managing low back pain which did not recommend discography as a diagnostic test because of poor evidence for its sensitivity, specificity, and predictive value. However, subsequently, these guidelines were severely criticized[52]. There were deficiencies and inappropriate evaluation in almost all areas; inappropriate studies were included and appropriate studies were excluded. The basic deficiency of these guidelines by Chou and Huffman[59] was their failure to recognize the discography must not be performed in asymptomatic volunteers or patients with mild low back pain. They also utilized outdated guidelines from AHCPR and European COST guidelines[52]. In the interim, questioning the validity of discography warrants questioning the role of the disc as a discrete pain generator, or more specifically, challenges the concept of symptomatic internal disc disruption. If one considers discography to be a useless test, then one may have to abandon the concept of the disc as a discrete pain generator and abandon the pursuit of intradiscal therapies, whether surgical or non-surgical[52]. Recent systematic reviews have concluded that there is strong evidence that lumbar discography can identify the subset of patients with chronic discogenic pain[61,62].

TREATMENT

Treatment for discogenic low back pain has traditionally been limited to either conservative management or surgical fusion. However, to accurately assess the effect of any therapy for treating discogenic low back pain, the natural history of such pain should be known beforehand. Recently, our a clinical study indicated that the natural history of discogenic low back pain was continuous and chronic[63]. This result indicates that most patients are expected to experience low back pain after a longer time interval, and their pain severity is expected to remain nearly the same. The elucidation of natural history of discogenic low back pain has important clinical significances for decision-making of treatments.

There are a multitude of treatments used in clinical practice to treat chronic low back pain, with little consensus amongst clinicians as to which is the best approach. Pharmacologic treatment usually includes analgesics, nonsteroidal anti-inflammatory drugs, and muscle relaxants, but the evidence for their efficacy is not compelling. In randomized trials, the differences in pain after a patient has taken nonsteroidal anti-inflammatory agents as compared with placebo have generally been in the minimally detectable range[64]. A meta-analysis revealed that opioids seem to have a small effect in improving function and relieving pain for the patients with chronic low back pain[65]. Long-term treatment with narcotics is generally discouraged, given the associated risks of tolerance and side effects. Physical therapy, exercise, manipulation, and back school seem to have some effects, but it is unknown if effects are sustained for the long term[64]. Exercise therapy by the McKenzie method is a popular treatment for low back pain among physical therapists. Clinical studies have indicated that the McKenzie method is slightly more effective than manipulation or is equal to strengthening training for patients with chronic low back pain[66,67].

If conservative treatment fails, then epidural injections are commonly performed for chronic discogenic pain. Epidural injections are administered by accessing the lumbar epidural space by multiple routes including interlaminar, caudal, and transforaminal[68-79]. Epidural procedures continue to be debated regarding their effectiveness, indications, and medical necessity. Recent systematic reviews indicated that effectiveness of epidural injections for treatment of discogenic low back pain was fair[80]. The underlying mechanism of action of epidurally administered steroid and local anesthetic injection is still not well understood. It is believed that the achieved neural blockade alters or interrupts nociceptive input, the reflex mechanism of the afferent fibers, self-sustaining activity of the neurons, and the pattern of central neuronal activities[80]. Further, corticosteroids have been shown to reduce inflammation by inhibiting either the synthesis or release of a number of pro-inflammatory mediators and by causing a reversible local anesthetic effect[81-85].

As alternative treatments, percutaneous treatments directed at altering the internal mechanics or innervation of the disc by heat (intradiscal electrothermal annuloplasty, IDET, and biacuplasty) have recently been advocated[7,86,87], but data supporting their use are controversial[86]. IDET was first used to treat discogenic low back pain in 1996, using a concection technology with a 5 cm active tip placed at the uncleoannuar junction. Two randomised trials have shown either no effect or benefit in only a small number of highly selected subjects[88-90]. Further, of the 6 observational studies[91-96], 4 studies showed positive results, one study showed negative results, and one study showed undermined results. Recent a systematic review evaluated these studied, and concluded that the evidence is fair for IDET[97]. Biacuplasty is one of the minimally invasive treatment methods. It creates heat across the posterior annulus using a cooled bipolar radiofrequency device[98]. The initial study results are promising[99,100], but the effectiveness needs to be evaluated further to use randomized controlled trials.

During recent decades, surgical fusion of the lumbar spine has been performed in increasing number on patients with chronic low back pain[4]. However, the reported results vary considerably in different studies, and the complication rate after fusion surgery in the lumbar spine is not negligible[101-105]. Consequently, artificial disc replacement has been proposed as a substitute for spinal fusion with the aim of treating back pain while preserving vertebral motion at the operated levels and protecting adjacent levels from undergoing degenerative changes, but so far, only several studies have been reported on the

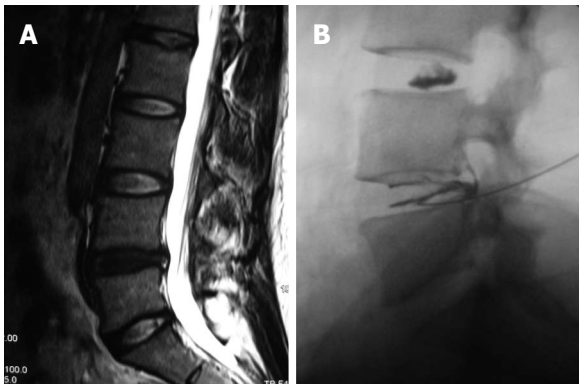

Figure 3 Magnetic resonance imaging and discography. A: A 35-year-old woman had a 5-year history of low back pain. Sagittal T2 weighted magnetic resonance imaging showed L4/5 disc degeneration with a high intensity zone in the posterior annulus fibrosus; B: Discography showed L4/5 disc disruption with exact pain reproduction. After discography, 10 mg methylene blue was injected into the painful disc through discographic needle. Low back pain was almost totally relieved. No recurrence was observed at a 12-mo follow-up interval.

results of lumbar disc prosthesis[106-108]. Recent a systematic review suggested that the spine surgery community should be prudent to adopt this technology on a large scale because harm and complications may occur after some years[109]. The results with longer follow-up need to be observed further.

Based on the recent insights into signal transduction mechanisms that might lead to the induction of pain by degenerative discs, it is conceivable that therapies aiming at disrupting pro-inflammatory signaling pathways and the pathway of nerve conduction might be successful in the foreseeable future. Such therapies might not have the ability to reverse the progressing tissue destruction which occurs with aging but may transform a symptomatic to asymptomatic disc degeneration and thereby greatly improve life quality of the affected patients[10]. Recently, a minimally invasive method, intradiscal methylene blue injection for the treatment of painful disc degeneration, had been reported (Figure 3)[110,111]. This successful outcome subsequently was demonstrated by the animal experiments which indicated that methylene blue indeed had destroyed the nerve endings or nociceptors and alleviated inflammatory response in the degenerated discs[112,113].

Recently, there has been a growing interest in developing strategies that aim to repair or regenerate the degenerated disc biologically. Treatments for degenerated discs have two main objectives: restoration of the disc' s structure and elimination of pain[114]. The benefits of biologically based treatments appear to be limited to restoring disc structure. Whether disc regeneration would result in pain relief remains unclear. That said recent data from animal studies have shown changes in cytokine expression following growth factor injection, indicating a possible mechanism for pain relief. Further, the first human clinical trial for growth factor injection therapy is currently underway and may shed light on the clinical outcome. Mesenchymal stem cells (MSCs) may also help relieve pain by reducing inflammation. A recent study indicates that MSCs can induce the production of anti-inflammatory cytokines[115]. However; additional studies are needed to elucidate the underlying mechanisms of pain relief.

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MINIREVIEWS

Bone morphogenetic protein in complex cervical spine surgery: A safe biologic adjunct?

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Abstract

The advent of recombinant DNA technology has substantially increased the intra-operative utilization of biologic augmentation in spine surgery over the past several years after the Food and Drug Administration approval of the bone morphogenetic protein (BMP) class of molecules for indications in the lumbar spine. Much less is known about the potential benefits and risks of the "off-label" use of BMP in the cervical spine. The history and relevant literature pertaining to the use of the "off-label" implantation of the BMP class of molecules in the anterior or posterior cervical spine are reviewed and discussed. Early prospective studies of BMP-2 implantation in anterior cervical spine constructs showed encouraging results. Later retrospective studies reported potentially "life threatening complications" resulting in a 2007 public health advisory by the FDA. Limited data regarding BMP-7 in anterior cervical surgery was available with one group reporting a 2.4% early (< 30 d) complication rate (brachialgia and dysphagia). BMP use in the decompressed posterior cervical spine may result in neurologic or wound compromise according to several retrospective reports, however, controlled use has been reported to increase fusion rates in select complex and pediatric patients. There were no cases of *de novo* neoplasia related to BMP implantation in the cervical spine. BMP-2 use in anterior cervical spine surgery has been associated with a high early complication rate. Definitive recommendations for BMP-7 use in anterior cervical spine surgery cannot be made with current clinical data. According to limited reports, select complex patients who are considered "high risk" for pseudoarthrosis undergoing posterior cervical or occipitocervical arthrodesis or children with congenital or traumatic conditions may be candidates for "off-label" use of BMP in the context of appropriate informed decision making. At the present time, there are no high-level clinical studies on the outcomes and complication rates of BMP implantation in the cervical spine.

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Key words: Cervical spine; Bone morphogenetic protein; Bone morphogenetic protein

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DECADE OF BONE MORPHOGENETIC PROTEIN EMERGENCE IN THE UNITED STATES

Biological augmentation of spinal surgery procedures has substantially increased in the United States over the past decade with the advent of genetic engineering techniques and the Food and Drug Administration (FDA) approval and marketing of several synthetic products. A great deal of therapeutic potential has been associated with the "Bone Morphogenetic Protein" (BMP) class of molecules since the Nobel Prize nominated work of Marshall Urist in 1965 demonstrated their ability to transduce intracellular signaling pathways towards the genesis of bone and cartilage tissues[1]. Basic science studies laid the groundwork for later pre-clinical studies that demonstrated definitive evidence of rhBMP-2 induced os-

teoinduction in a small series of 11 humans[2]. The more recent foray of these powerful signal transduction agents into the clinical realm has brought to light both powerful efficacy and the potential for serious and even fatal complications.

In 2002, the FDA granted pre-market approval of rhBMP-2 (rhBMP-2 - Infuse Bone Graft, Medtronic Sofamor Danek, Memphis, TN) for use in adult patients undergoing single-level anterior lumbar interbody fusion (ALIF) from L2 to S1 for degenerative disk disease[3]. Two years later, a second subtype of recombinant BMP molecule was also approved by the FDA, BMP-7 (rhBMP-2 - OP-1 Putty, Stryker Biotech, Hopkinton, MA) as an alternative to autograft in patients requiring revision posterolateral (intertransverse) lumbar spinal fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion (patients with osteoporosis, smokers, and diabetes)[4].

Any new therapeutic procedure, technique, or medication will bring a finite number of associated complications. In the ensuing time period following the translation of these biological adjuncts into the operating room, a series of reports has sparked great concern about potential adverse sequelae. In July of 2010, a 33% higher concentration formulation of Medtronic's rhBMP-2 product featuring a compression-resistant matrix (AMPLIFY Matrix - 2.0 mg/cc compared to INFUSE 1.5 mg/cc) that was designed to induce *de novo* bone formation without iliac crest bone graft (ICBG) was rejected by the FDA due to possible increased cancer risks in susceptible individuals[5]. In 2011, secondary analysis of Medtronic-funded studies found an increased cancer risk associated with rhBMP-2 (AMPLIFY) in patients undergoing posterolateral lumbar fusion. Reports of increased retrograde ejaculation following ALIF procedures[6,7] and that complication rates associated with BMP are 10 to 50 times higher than the original estimates in industry-sponsored peer-reviewed publications have recently been publicized[6]. The ensuing media attention to these studies has resulted in a decline in the use of biologics in spine surgery applications[8].

Much less is known about the "off-label" use of the BMP class of molecules in the cervical spine. To understand the incidence and spectrum of reported complications associated with BMP use in the cervical spine, the relevant clinical studies reported in the literature are reviewed and discussed.

ANTERIOR CERVICAL SURGERY WITH BMP

The efficacy of rhBMP-2 use in the anterior cervical spine has been evaluated by several groups as "off-label" indications have been found in parallel with those approved by the FDA.

Prospective studies

An early pilot study in 2003, was designed as a prospective randomized trial comparing rhBMP-2 to cancellous autogenous ICBG inside a fibular allograft in 33 patients. All patients underwent plated anterior cervical discectomy and fusion (ACDF) for degenerative cervical disk disease[9]. At 2-years follow-up, both groups demonstrated solid fusion in all patients. Interestingly, the rhBMP-2 group had superior improvement in neck disability and arm pain scores. In this pilot study, anecdotal observation of two cases of heterotopic bone anterior to the graft in the rhBMP-2 group and one in the autograft group were made. Given the limited numbers of patients, conclusive statements on potential adverse events could not be made. In 2004, a second pilot study prospectively followed 20 patients that underwent ACDF with rhBMP-2 contained within a bioabsorbable spacer demonstrated bridging bone across the interspace in 100% of patients[10]. Buttermann confirmed these reports in a prospective nonrandomized consecutive series of 66 patients with either ICBG or BMP-allograft. Two patients in the ICBG group had pseudarthrosis compared to one patient in the BMP-allograft group at 2-3 year follow-up. However, 50% of the patients in the BMP allograft group had "neck swelling" presenting as dysphagia compared to 14% in the ICBG group[11].

Retrospective studies

Several retrospective studies raised concerns about the use of BMP in the anterior cervical spine. In 2005, Boakye *et al*[12] reported an uncontrolled retrospective report of good clinical outcomes and solid fusion with rhBMP-2 implanted inside of a polyetherehterketone (PEEK) spacer for single and multi-level ACDF in 24 patients. By 2006, retrospective reviews of 151 patients who underwent either anterior cervical corpectomy (n = 13) or ACDF (n = 138) augmented with high dose INFUSE (up to 2.1 mg/level) reported a complication rate of 23.2% due to hematoma requiring surgical evacuation or readmission due to swallowing/breathing difficulties or dramatic swelling in the absence of a hematoma[13]. A subsequent retrospective report of 69 patients confirmed the high complication rate associated with BMP-2 use in ACDF constructs with 27.5% having clinically significant swelling[14]. In 2007, retrospective reports of significantly more dysphagia following ACDF with rhBMP-2 and increased anterior soft tissue shadow for the first 6 wk postoperatively on lateral C-spine radiograph were accompanied by similar clinical outcomes at 2-years[15].

Radiographic reports

These early reports of excellent fusion rates were later accompanied by radiographic reports of endplate erosion and subsidence associated with rhBMP-2. In 2007, a prospective study of cervical interbody fusion with allograft and rhBMP-2 demonstrated significant subsidence of cervical interbody grafts of a mean height of 53% that occurred in more than half of the operative levels[16]. Further radiographic studies comparing polyetherehterketone (PEEK) cages and BMP for spinal fusion demonstrated an enhanced fusion rate with a concomitant

prevertebral soft-tissue swelling in patients who underwent ACDF. Radiographic evidence of a resorptive phase of BMP-2 resulting in endplate absorption has been reported by several groups to occur in 100% of patients undergoing ACDF[15,17,18].

FDA public health advisory

In March of 2007, a case report of a 54 year-old male presenting with neck swelling and difficulty swallowing 5 days after ACDF with rhBMP-2 resulting in respiratory distress and reintubation was published[19]. By July of that year, early "off-label" use of BMP in the cervical spine resulted in at least 38 reports of complications over the preceding 4 years[20]. This provided the impetus for the FDA to issue a public health advisory of "life-threatening complications" due to severe swelling and airway compromise. Many practitioners continue to implant BMP in the cervical spine despite this advisory in a select group of patients in the context of thorough patient education and informed decision making.

BMP use after the FDA advisory

Following the FDA advisory in 2007, reports of acute airway obstruction between postoperative days 2 and 7 remained a significant concern. Yaremchuk reported in 2010 a retrospective review of 260 patients who underwent cervical procedures augmented by BMP between 2004 and 2009. Patients treated with BMP had significantly longer hospital stays, higher hospital charges, a higher number of tracheotomies, unplanned intubations after surgery, dysphagia, dyspnea, respiratory failure, readmissions, intensive care unit admissions, and 90-d mortality rates. Despite these warnings, surgeons have advocated rhBMP-2 use in the anterior cervical spine in a controlled manner. A retrospective study by Tumialan *et al*[21] reported 200 patients that underwent one to four level ACDF with PEEK spacer, titanium plate, and rhBMP-2 reported a fusion rate of 100%, an incidence of clinically significant dysphagia of only 7%, and suggested that the incidence of dysphagia may be decreased by a lower dose of rhBMP-2 that is placed only within the PEEK spacer.

Anterior cervical surgery with BMP-7 (OP-1)

Data on the use of OP-1 in the anterior cervical spine is much more sparse than that of rhBMP-2. A PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/) query for "BMP-7" or "OP-1", and "anterior cervical" yielded only one study in the literature at the present time. In 2009, surgeons in Australia reported early outcomes and complications (within 30 d) of a prospective consecutive cohort study of 123 patients who underwent ACDF with a controlled dose of OP-1 augmentation. They reported a 2.4% complication rate (transient brachialgia and dysphagia), no reoperations, and concluded that BMP-7 can be used safely in anterior cervical procedures. This report remains to be reproduced by other groups and long-term data on fusion and complication rates have yet to be reported.

POSTERIOR CERVICAL SURGERY WITH BMP

Therapeutic applications of rhBMP-2 in the posterior cervical spine avoid the putative inflammatory effects on critical anterior airway structures suggesting indications may be more plausible. However, there have been few reports on the safety and efficacy of the "off-label" use of BMP products in the posterior cervical spine. At the present time, there are no prospective studies on the use of BMP in posterior cervical spine procedures.

A potential role for OP-1 in posterior cervical spine surgery in patients considered to be high risk for psuedoarthrosis was examined in a 2007 invited submission of the American Association of Neurosurgical Surgeons Joint Section on Disorders of the Spine and Peripheral Nerves. This report by Furlan *et al*[22] was an uncontrolled prospective non-randomized study of 14 patients undergoing posterior cervical or occipitocervical spine surgery that resulted in no "allergic reactions" and no postoperative hematomas. In this patient population that included heavy smokers, patients with genetic disorders (mucopolysaccharidosis), rheumatoid arthritis, lupus, and previous nonunions, a fusion rate of 80% was reported at mean follow-up of 24 mo. All patients underwent MR imaging between 6 months and 1 year postoperatively and one patient who underwent posterior occipitocervical fusion demonstrated an asymptomatic linear opacification in the soft tissues representing heterotopic ossification.

In 2009, a retrospective evaluation of 77 patients undergoing posterior cervical arthrodesis with either rhBMP-2 absorbable sponge or ICBG demonstrated a trend towards more posterior cervical wound complications requiring treatment in the rhBMP-2 group (14.6%) *vs* the ICBG group (2.8%), however, this result did not reach statistical significance[23]. In 2011, Xu *et al*[24] reported a retrospective review of 204 patients that underwent posterior spinal fusion augmented with and without rhBMP-2 over a 4-year period and found at 2-year mean follow-up there was no significant difference between the two cohorts in duration of hospitalization, CSF leakage, infection, hematoma, C5 palsy, wound dehiscence, reoperation rates, or Nurick/ASIA scores. There were no patients in the rhBMP-2 group with instrumentation failure, however, a trend was observed towards increased rates of instrumentation failure in the non-BMP group due to 11 patients (7.1%) with this complication (P = 0.06). Patients receiving rhBMP-2 did have a significantly increased fusion rate (P = 0.01), however, they also had higher rates of recurrent/persistent neck pain (chi-square test P = 0.003, log-rank test P = 0.01)[24].

Case reports have suggested the potential for catastrophic neurological complications with rhBMP-2 use in the posterior cervical spine following laminectomy. Anderson *et al*[25] reported two cases of posterior cervical

decompression and instrumented fusion procedures resulting in a substantial decline in neurological status due to exuberant seroma formation causing cord compression at 5 d and 2 wk postoperatively.

A role for rhBMP-2 augmentation in the pediatric population for congenital and traumatic conditions has been supported by recent case reports. In 2007, a 4-mo-old infant with Down syndrome who suffered a high cervical spine injury due to craniovertebral instability and two previous failed arthrodesis attempts later underwent successful salvage fusion procedure with rhBMP-2 augmentation. The patient subsequently went on to fusion without a reported complication at 4 years follow-up[26]. The surgical challenges of occipitocervical stabilization in infants with complex trauma may also benefit from BMP-2 augmentation. Benzel *et al*[27] reported a case of a 12-mo-old female with traumatic atlanto-occipital dislocation after a motor vehicle accident that was stabilized by autologous rib graft, Mersilene suture, ethibond sutures as "cross-connectors" and rhBMP-2 augmentation with excellent alignment and modest but progressive neurological improvement by 12 wk.

CONCLUSION

Recombinant DNA technology has hastened the arrival of powerful biologically engineered molecules capable of intracellular signal transduction pathways into the operating theatre. Approval by regulatory agencies and the subsequent proliferation of these products to "off-label" indications such as the cervical spine has provided new clinical data and novel complications associated with their use. At the present time, widespread international utilization of BMP products has been self-limited by a prohibitively high cost. In the coming years, as proprietary patents expire and generic formulations become commercially available, an international dialogue in the academic community will aid in the understanding of not only the clinical efficacy of biologics, but also help to mitigate potential harm.

Several studies have reported excellent fusion rates and the avoidance of donor site morbidity with the use of rhBMP-2 in the anterior cervical spine. However, concomitant increased complication rates are reported that may involve catastrophic airway compromise. The soft-tissue complications may be dose dependent, with higher rates reported for higher concentrations by several authors.

Patients who are considered high risk for pseudoarthrosis undergoing posterior cervical or occipitocervical arthrodesis or children with complex congenital or traumatic conditions may be candidates for "off-label" use of BMP according to limited current reports. At the present time, there are no high level clinical studies of the outcomes, complication rates, safety and efficacy of BMP use in the cervical spine.

When painted with broad strokes, the powerful effects of BMP are implicated by several studies to result in increased complication rates in the cervical spine. In a comprehensive database review of the Scoliosis Research Society Morbidity and Mortality database of 55862 spinal fusion procedures, multivariate analysis demonstrated that anterior cervical spinal fusion with BMP remains a significant predictor of complications after adjusting for patient age and revision procedures[28].

In a retrospective cohort study of the Nationwide Inpatient Sample database (a sample of 20% of United States community hospitals) consisting of 328468 spinal fusion procedures, BMP use was associated with greater complications for anterior cervical fusions and greater hospital charges[29]. Nonetheless, in select complex cervical patients, the use of BMP in a controlled fashion may have benefits that outweigh the risks as supported by several authors[21,22,26,27].

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Unicompartmental knee prosthetization: Which key-points to consider?

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Abstract

Unicompartmental knee arthroplasty (UKA) has evolved into a suitable option for diseased knees that cannot be managed with arthroscopic treatment and at the same time are not good candidates for total knee replacement. Since meticulous execution of the surgical technique is essential to optimizing UKA outcome, some procedural key-points are mandatory. Templates (phantoms) are then used to size the required prosthetic component (using these radiographs. Arthritic varus (or valgus) knees with an asymptomatic patello-femoral joint are typically ideal for UKA. Metal-backed tibial components should be favourite instead of all-polyethylene tibial components to avoid polyethylene creep that may occur in fixed bearings. Moreover, a proper thickness of the polyethylene layer is mandatory, in order to avoid early failure.

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Key words: Knee; Unicompartmental knee prosthesis; Procedure; Surgery

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UNICOMPARTMENTAL KNEE ARTHROPLASTY

Unicompartmental knee arthroplasty (UKA) has evolved into a suitable option for diseased knees that cannot be managed with arthroscopic treatment and at the same time are not good candidates for total knee replacement (TKR). On initial consideration, UKA has several potential advantages over TKR, namely preservation of bone stock, cruciate ligament conservation, and sparing of the contralateral compartment and the patello-femoral joint[1]. Since meticulous execution of the surgical technique is essential to optimizing UKA outcome[2], some procedural key-points are mandatory. Preoperatively, appropriate implant selection requires the use of weight-bearing radiographs of the affected knee to better delineate true varus or valgus features of the arthritic compartment. Templates (phantoms)[3] are then used to size the required prosthetic component (Figure 1) using these radiographs. Arthritic varus (or valgus) knees with an asymptomatic patello-femoral joint are typically ideal for UKA[4]. If there is concern regarding the cartilaginous condition of patello-femoral joint, magnetic resonance imaging and subsequent arthroscopic evaluations[5] are suggested prior to selecting the definitive prosthetic solution as skyline knee radiographs may not be an accurate reflection of the joint condition. If patello-femoral joint disease is present, a TKR should be performed as there is a high likelihood that revision after UKA will be is a more suitable option as progression of

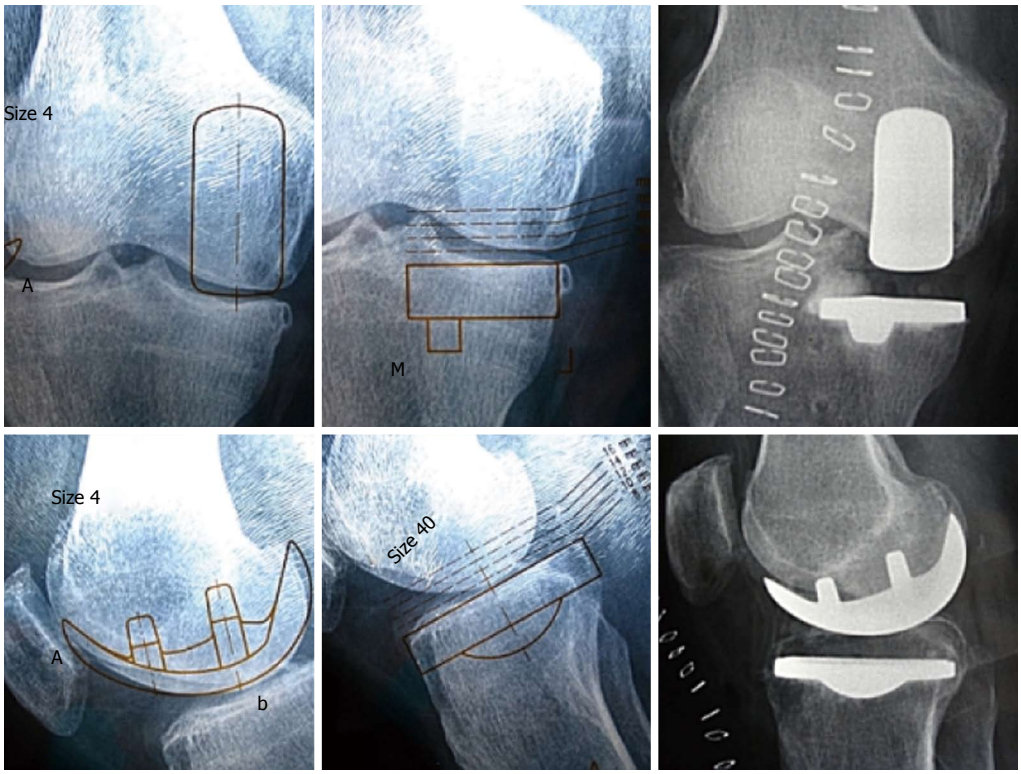

Figure 1 Example of a preoperative surgical plan of a medial unicompartmental knee arthroplasty right knee. Weight-bearing radiographs are templated against acetate phantoms. Immediate post-operation radiographs show correct positioning of the prosthetic implants.

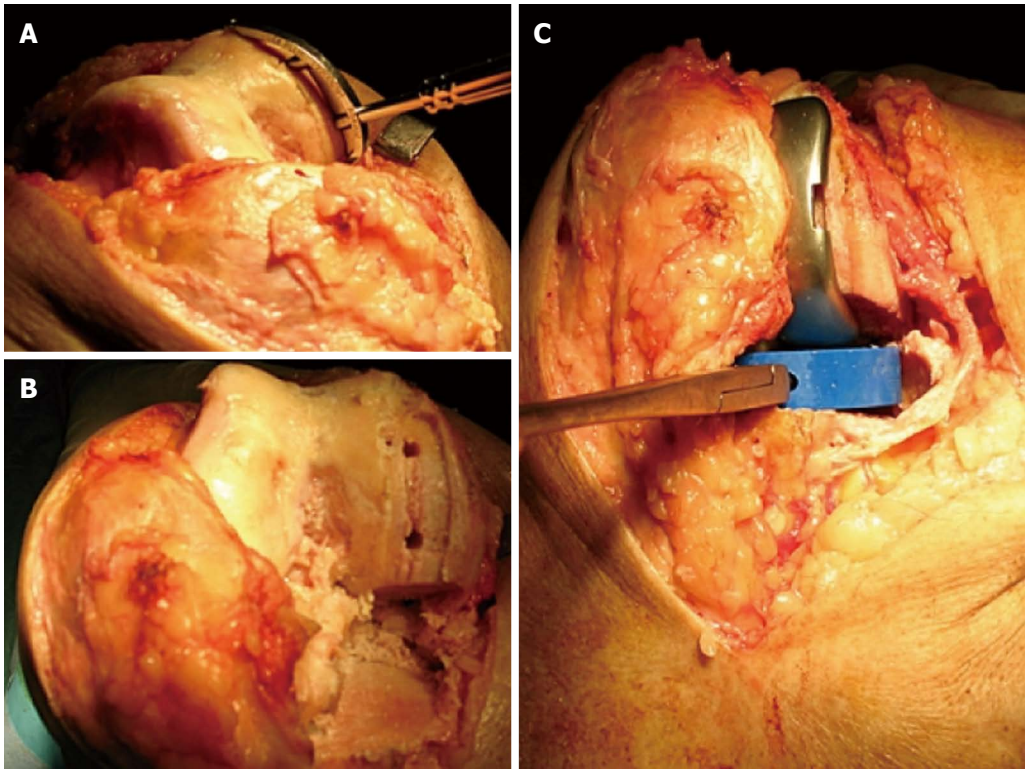

Figure 2 Knee bone cuts and positioning of trial components. A: A curved instrument available in different sizes allows to check the curvature of the condylus to prosthetize along with the amount of bone to remove; B: Femoral and tibial bony cuts. At this stage of the operation is essential to check eventual meniscal fragments, bony particulate and bony prominences that is made possible through a standard parapatellar approach; C: Femoral and tibial trials inserted with patella in place. Accurate trials size to choose definitive implants must be carefully checked.

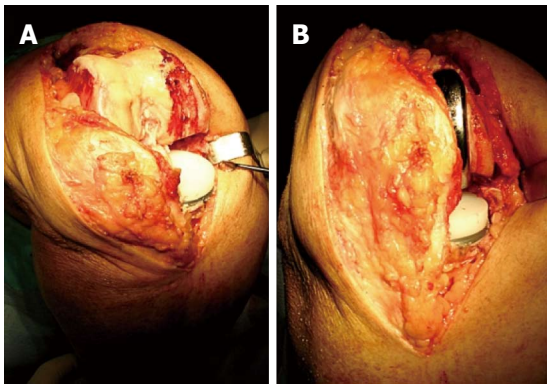

Figure 3 Cemented prosthetic components in place and patellar tracking assessment. A: Cemented tibial metal-back component in place with proper thickness of polyethylene insert; B: Cemented femoral and tibial components inserted along with patella in place. At this moment it is possible to verify ligament balance and patellar tracking.

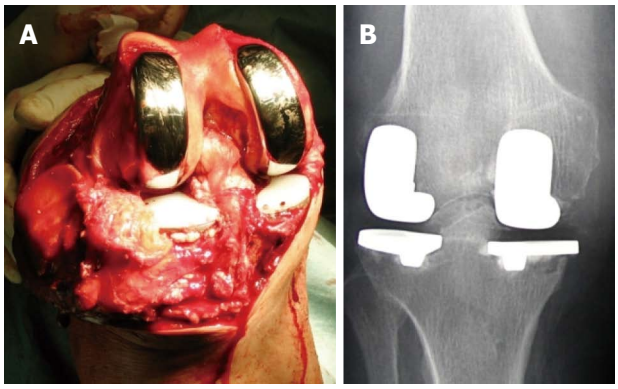

Figure 4 Bi-unicompartmental knee arthroplasty. A: In selected cases, bi-unicompartmental knee replacement is a feasible prosthetic solution that allows to maintain ligamentous compartments; B: This permits to have a more physiologic knee functionality, replacing only the affected parts of the articulation.

arthritis may involve not only the un-prosthetized contralateral compartment, but also the patello-femoral joint with progressive degeneration[6] and consequent surgical prosthesis revision. In general, metal-backed tibial components should be favourite instead of all-polyethylene tibial components to avoid polyethylene creep[7] that may occur in fixed bearings. Moreover, a proper thickness of the polyethylene layer is mandatory, in order to avoid early failure[8]. At the time of surgery, traditional Von Langenbeck's medial or lateral parapatellar surgical approach should be performed since the entire articulation (anterior and posterior compartments) should be evaluated to avoid leaving intra-articular bony particulate, residual sections of meniscus, posterior condylar bony cams, posteriorly extruded cement, and hidden osteophytes that may significantly contribute to implant failure[9] (Figure 2). Moreover, since all the three compartments are visualized, Von Langenbecks's approach allows thorough evaluation of ligament balance, avoiding over- and under-corrections, and permits a good assessment of patellar tracking (Figure 3). The same approach is mandatory in bi-unicompartmental knee replacement, an alternative prosthetic solution[10,11] that employs two unicompartmental prostheses and is utilizable in selected patients with asymptomatic patello-femoral articulation (Figure 4). In contrast, the use of minimally invasive approaches leads to reduced access to surgical landmarks[12] and is more likely to result in anatomic malalignment. Bent narrow Hohmann retractors are recommended instead of straight ones in order to minimize soft tissue stress during retraction and in a less invasive way protect the posterior neurovascular bundle during power-saw cutting of the condylus and the tibial plate. To conclude, it is also strongly suggested to use pulsed lavage irrigation to increase cement penetration and decrease both bone and poly-methyl-methacrylate debris particles[13,14] that may be responsible for third-body polyethylene abrasive wear.

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MINIREVIEWS

Common surgical complications in degenerative spinal surgery

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Abstract

The rapid growth of spine degenerative surgery has led to unrelenting efforts to define and prevent possible complications, the incidence of which is probably higher than that reported and varies according to the region of the spine involved (cervical and thoracolumbar) and the severity of the surgery. Several issues are becoming progressively clearer, such as complication rates in primary versus revision spinal surgery, complications in the elderly, the contribution of minimally invasive surgery to the reduction of complication rate. In this paper the most common surgical complications in degenerative spinal surgery are outlined and discussed.

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Key words: Spine surgery; Complication; Failed back surgery; Instability; Disc herniation

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INTRODUCTION

Spine surgery has grown exponentially over recent decades, with fusion performed for degenerative conditions comprising the lion's share[1]. A recent evidence based review of the literature reported the overall rate of reported complications to be 16.4%[2]. The focus of this particular paper will be those complications that are related to the surgical operation; general medical complications and surgical wound infection are not included (Table 1). The conditions mentioned here are outlined briefly but in reasonable detail; a more elaborate report would be beyond the scope of this paper.

DURAL TEARS

Dural tears happen accidentally during spine surgery. The reported incidence varies from 15.9% in revision surgery[3] to 3.5% in primary lumbar discectomy[4]. These tears are usually the result of direct trauma or laceration, with the Kerrison punch being the instrument most commonly implicated[5]. Intraoperative technical difficulties that appear to predispose to accidental durotomies are dural scarring, adhesions and fibrosis, particularly in revision surgery, an eroded and thin dura as seen in long-standing spinal stenosis, and large disc herniations making dural retraction and nerve root dissection difficult[6].

When recognized intraoperatively, dural tears need to be made watertight to prevent cerebrospinal fluid (CSF) leaks. This is usually accomplished by direct suturing and/or the use of fibrin glue, in addition to muscle or fat graft to cover the area of the tear[3-5,7]. In a large retrospective series, primary repair was successful in the majority of cases, with only 1.8% requiring reoperation for a second defect repair[3]. Similarly, results from the Spine Patient Outcomes Research Trial (SPORT) study

show that incidental durotomy, although associated with increased operative time, blood loss and inpatient stay, does not impact long-term clinical outcome[8-10]. If unrecognized however, these tears can have significant consequences, such as CSF leakage and/or the development of fistulas or pseudomeningoceles. CSF leaks present with headache, nausea, vomiting, and/or photophobia as soon as patients assume an upright posture after surgery[7]. A pseudomeningocele is a CSF-filled cyst that develops from the dura tear. In addition to symptoms related to CSF leakage, compression from the cyst may also result in back pain or even nerve root compression[11,12]. The clinical diagnosis may be confirmed by magnetic resonance imaging (MRI) or computed tomography (CT) myelography. Treatment consists of bed rest, epidural blood patch or fibrin glue, percutaneous or open placement of subarachnoid drain and open direct repair of the dural tear[7,11,12]. As the incidence of iatrogenic CSF fistulas or pseudomeningoceles is between 0.02%-2%, there is limited available evidence on the long term outcome of patients presenting with this complication[7,11,12]. Nevertheless, it seems that open direct dural repair as soon as the dural tear is diagnosed provides the best outcomes[7].

RECURRENT DISC HERNIATION

A recurrent disc herniation is defined as the presence of herniated disc material at the same level and site in a patient that has experienced a pain free interval after discectomy. The reported incidence varies between 5%-23%[13-16]. The only risk factors that have consistently shown a strong association are diabetes mellitus[17,18] and the shape and size of the herniation[19]. Symptomatic recurrent herniations are much less common than radiographic ones (10.2% *vs* 23.1%)[16]. So, care must be taken before attributing the recurrence of low back pain or nerve root symptoms to the herniation. In addition, imaging of the post-operative spine can be difficult to evaluate. A mass lesion at the previously operated level should be differentiated between pseudomeningocele, scar tissue and recurrent disc herniation. Gadolinium-enhanced MRI appears to be the imaging modality of choice in such patients[14,20,21], although intraoperative findings are not in agreement with imaging results in up to 33% of cases[22]. Once the diagnosis is made, treatment options are similar to primary herniations, i.e. conservative (pharmacological modalities, physiotherapy) or surgical. Although revision surgery on the spine is generally associated with poorer outcomes and higher rates of complications, repeat discectomies appear to be an exception, with most authors reporting results similar to those of primary discectomies[15,22-24].

INSTABILITY

Clinical spinal instability is defined as the loss of the spine's ability to maintain its patterns of displacement under physiologic loads. There is no initial or additional neurologic deficit, no major deformity, and no incapacitating pain[25]. Causes of instability are degenerative[26,27] erosion of structures by neoplastic disease[28], trauma[29], spondylolisthesis[30] and iatrogenic (post-laminectomy)[31,32]. In the post-operative patient, instability is most commonly seen after laminectomy without fusion, although even simple discectomy may be complicated by this condition. Clinically, patients may present with low back pain with or without radicular symptoms. Radiographic criteria for spinal instability include translation and angulation of one vertebra relative to another in standing and in flexion-extension radiographs, with Posner's radiographic criteria showing the best correlation with clinical findings and surgical outcomes[25,33,34]. The treatment of post-operative spinal instability is either bracing or instrumented spinal fusion, with surgery exhibiting superior results[34,35].

Table 1 Surgical complications in spinal surgery

Complications
Dural tears
Instability
Junctional kyphosis
Recurrent disc herniation
Pseudarthrosis (non-union)

PSEUDARTHROSIS (NON-UNION)

Pseudarthrosis refers to a failure in osseous union of the intended spinal fusion. Although pseudarthrosis is not always correlated with symptoms or poor results[36,37], most authors agree that a solid fusion results in better clinical outcomes and certainly mitigates any need for reoperation[38-40]. Radiographic confirmation is required to make the diagnosis; signs include a cleft in the fusion mass, failure of incorporation of bone graft, progressive resorption of bone graft, loosening and/or breakage of implants and progressive deformity[41]. Pseudarthrosis can be further graded by the Lenke classification, in the case of posterolateral fusions[42], or by the Brantigan, Steffee, Fraser classification, in cases where PLIF cages are used[43]. Radiography however is dreadfully unreliable in detecting non-union (its accuracy ranges from 82%-68%[44,45]) when compared to surgical exploration. Flexion-extension views may be helpful in detecting instability in the fused segments, although their value in the lumbar spine has been questioned[46,47]. Helical CT scanning has demonstrated better accuracy[48,49] although surgical exploration remains the "gold standard"[50]. When the diagnosis has been made, the decision to operate or not should be made on an individual basis. A period of close observation, during which bracing and activity limitation are employed is certainly reasonable early on, in the hope that delayed union, rather than non-union, will ultimately occur. In the symptomatic patient who shows evidence of pseudoarthrosis later on, revision surgery is warranted. It has been shown that pseudoarthrosis repair can lead to improved clinical results[39,44], although this revision surgery carries a significant risk of recurrent non-union and a persistently poor outcome[39,40,51]. When surgically treat-

ing pseudarthrosis, it is important to remember that better graft material than that used in the index procedure should be used in an optimized environment. This means aggressive removal of fibrous tissue, extensive decortication where appropriate, use of autologous bone, (preferably iliac crest), use of biological modifiers such as electrical stimulation or BMP, replacement of implants when anchorage is questionable, conversion to circumferential fusion whenever possible and if necessary, extension of the fusion and correction of alignment[52,53].

JUNCTIONAL KYPHOSIS

Junctional kyphosis can occur at either end of an instrumented spinal fusion as a result of the increased mechanical demands in the zone adjacent to the fusion. In its strict definition, this occurs when the sagittal Cobb angle between the last instrumented vertebra and two vertebrae further away from this is greater than 10° or when postoperatively there is an increase in the same angle by ⩾ 10°[54]. Incidence appears to be greatest at the proximal end of long fusions, with reported rates ranging from 26%-43%[55-57] while distal junctional kyphosis occurs in 21.7%-30.2% of patients overall[58,59]. Although specific risk factors have not yet been identified in an evidence based manner, most authors argue that normalization of global sagittal alignment would prevent the development of junctional failure[59-61]. Junctional kyphosis is a radiographic sign which does not always produce symptoms and which shows no correlation with clinical outcomes in most studies[55,56,59,62]. As such, treatment should be reserved for those patients who are symptomatic or where there is obvious deformity. There is a single study in the literature addressing treatment of symptomatic proximal junctional kyphosis. The corrective procedures performed were Smith-Petersen osteotomies in the majority of cases, with rib osteotomies and vertebral column resection in exceptional cases[63]. Reported results were good with a minimum follow-up of two years.

NEUROLOGICAL COMPLICATIONS

The occurrence of a post-operative neurological deficit is probably the most dreaded of all spinal complications. Despite its notoriousness, the reported incidence is only 0%-2% in most reports[64]. Injury to the nervous elements can either be direct at the time surgery, such as laceration, traction or compression of an exiting nerve root, or indirect, due to disruption of blood supply or compression. Notably, injury to the peripheral nerves may occur due to improper patient positioning, with resulting nerve palsies. Direct injury can be caused by trauma from surgical instruments of from misplacement of screws and/or hooks[65]. Disruption of the blood supply usually happens during correction of spinal deformity. The use of intraoperative neurophysiological monitoring has reduced the occurrence of neurological complications, with the Stagnara wake-up test still being used in cases with increased risk of postoperative neurological deficits[66]. Compression occurs intraoperatively from cotton patties, fat grafts or dura sealing products. In these cases, deficits will manifest immediately after surgery. Compression can also be caused from a mass lesion, such as hematoma, pseudomeningocele, epidural abscess or recurrent disc herniation. The presentation of neurologic symptoms will be insidious and almost certainly never in the immediate post-operative period.

A meticulous neurologic examination as soon as the patient wakes from surgery is of critical importance to distinguish deficits that occur intraoperatively from those that develop in the early post-operative period. The significance of this baseline examination is emphasized by the fact that imaging of the post-operative spine so soon after surgery will often be of limited value. Determining the cause of the neurological lesions depends on recollection of intraoperative events by the surgeon and his team, timing of presentation of symptoms and imaging findings, if any. Depending on the cause, management varies from patiently monitoring the course and progress of any deficits to immediate surgical exploration and correction of the underlying cause.

CONCLUSION

Surgical complications in spine surgery are not uncommon. Their significance can be minor, noticeable only as mere radiographic findings, or catastrophic, presenting with pain, neurological symptoms and progressive deformity. We chose not to include adjacent segment disease (ASD) in this overview. In our view, ASD constitutes the natural progression of the disease that was originally treated with surgery or perhaps a manifestation of wrong level selection and under-treatment. Hopefully, as our understanding of spinal pathologies becomes clearer and our therapeutic arsenal more sophisticated, the rate of complications will decrease further, minimizing the risks and distress to patients.

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MINIREVIEWS

Polymethylmethacrylate bone cements and additives: A review of the literature

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Abstract

Polymethylmethacrylate (PMMA) bone cement technology has progressed from industrial Plexiglass administration in the 1950s to the recent advent of nanoparticle additives. Additives have been trialed to address problems with modern bone cements such as the loosening of prosthesis, high post-operative infection rates, and inflammatory reduction in interface integrity. This review aims to assess current additives used in PMMA bone cements and offer an insight regarding future directions for this biomaterial. Low index (< 15%) vitamin E and low index (< 5 g) antibiotic impregnated additives significantly address infection and inflammatory problems, with only modest reductions in mechanical strength. Chitosan (15% w/w PMMA) and silver (1% w/w PMMA) nanoparticles have strong antibacterial activity with no significant reduction in mechanical strength. Future work on PMMA bone cements should focus on trialing combinations of these additives as this may enhance favourable properties.

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Key words: Polymethylmethacrylate; Bone cement; Cement nanoparticle; Vitamin E additive; Arthroplasty; Artificial joint fixation; Post-operative infection; Mechanical weakness; Fat additive; Antibiotics

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INTRODUCTION

Bone cement, or polymethylmethacrylate (PMMA), has been used in surgical fixation of artificial joints for over 50 years. The primary function of bone cement is to transfer forces from bone to prosthesis. This review explores the development of bone cements, the role of bone cement additives, identifies applications and discusses future directions.

HISTORICAL BACKGROUND

The pioneering work on PMMA technology is widely credited to German chemist Dr. Otto Rohm. He patented the PMMA product Plexiglass in 1933, which was used in submarine periscopes and airplane canopies[1], leading to an exponential increase in demand and interest during the pre-war and war era. Kulzer (1936) was at the forefront of mouldable cement technology after discovering that the dough formed by mixing ground PMMA powder and a liquid monomer hardens when benzoyl peroxide is added and the mixture heated to 100 ℃ in a stone mould[2]. The first clinical use of this PMMA mix-

ture was in an attempt to close cranial defects in monkeys in 1938. Surgeons used the heat stable polymer Paladon 65 to close cranial defects in humans. The material was assembled in plates in the laboratory and later moulded in the surgical suite[2].

The era of modern PMMA bone cements stems from the patent by Degussa and Kulzer (1943), describing how MMA polymerizes at room temperature if a co-initiator, such as a tertiary aromatic amine, is added[2]. Dental surgeons were the first to use this technology for dental fixatives and fixtures.

The first bone cement use in orthopaedics is widely credited to English surgeon, Dr. John Charnley, who used "dental acrylic" in 1958 for total hip arthroplasty[3]. Initial clinical results were poor for mechanical and biological reasons, related to both cement and loading surface[2]. Dr. Charnley developed a new product called "bone cement" (Plexiglass) which had more adaptable biological characteristics[4] and which he marketed aggressively to the global orthopaedic community. American orthopaedic surgeons trained with Dr. Charnley at the Wrightington Hospital in the 1960's and 1970's to learn his pioneering technique[5]. When returning to America, these surgeons often took bags of bone cement with them, an illegal trade which was only eliminated in the mid-1970's after the Food and Drug Administration approved the use of bone cement technology in the United States[5]. This material still had many shortcomings. Over the last two decades, additives have been developed to address these shortcomings[6].

PMMA PROPERTIES AND ADDITIVES

Mechanical weakness

A common complication of cemented arthroplasty is loosening of the cemented prosthesis. Mechanical weakness in the bone cement, primarily attributed to the addition of barium sulphate and zirconium oxides (for radiological detection), increases the risk of loosening[7]. Stabilisation of the bone cement matrix improves the transfer of load across the cement-prosthesis interface, reducing the likelihood of crack formation in the cement. Various additives such as steel fibres, glass fibres, carbon fibres and titanium fibres have been developed to improve mechanical strength[8-10]. Rubber toughened cement (PMMA matrix interspersed with rubber particles; Moeseley Rubber Co. Pvt. Ltd., United States) has 167% greater fracture toughness (the structural strength to withstand further cracking in fractured materials) than non-reinforced control (PMMA), although compressive strength and elasticity are compromised (raw data not available)[11]. PMMA reinforced with embedded continuous stainless steel coil (2.5 turns of coil; distal tip of prosthesis) significantly increases compressive stress 4.5-fold (control *vs* reinforced; 0.039 ± 0.001 MPa *vs* 0.009 ± 0.001 MPa) and tensile stress 4.5-fold (control *vs* reinforced; 4.272 ± 0.015 MPa *vs* 0.95 ± 0.005 MPa) on 3-dimensional finite element computational analysis[12]. This reinforcement increases mechanical strength, thus decreasing the likelihood of fracture formation. The use of additives with rubber toughened cements and stainless steel coils may improve other properties and needs to be investigated.

Interface integrity

The long-term stability of cemented hip arthroplasty is also dependent on the integrity of the bone-cement interface. Interface integrity is related to the strength of bonding and the degree of cement penetration (extent of interdigitation into bone). Increased migration behavior and micromotions of the prosthesis and bone cement are a result of abrasion. The production of wear particles from roughened metallic surfaces and from the PMMA cement promotes local inflammatory activity, resulting in chronic complications to hip replacements[13]. Lower bone cement viscosity affects the mechanical strength of the connection, giving an immediate limitation to the benefits of certain water-based additives, like antibiotics, in comparison to those in powder form[14]. The addition of an amphiphilic bonder, such as glutaraldehyde, may lead to significant improvements in the longevity of cemented metal stems[13,15]. Strength is maximized by increasing the amount of trabecular bone in the cement[16]. Interface integrity should be the optimal outcome of any additive trial. Powder based additives should generally be preferred to their water based counterparts, with greater importance placed on ensuring increased trabecular bone in cement matrix and/or amphiphilic bonders.

Osteoconduction

Osteoconduction refers to a process in which the three-dimensional structure of a substance is conducive to the on growth and/or ingrowth of newly formed bone. Bone growth on an implant surface depends on the action of differentiated bone cells; pre-existing pre-osteoblasts/osteoblasts activated by trauma or recruited from primitive mesenchymal cells by osteoinduction[17,18]. Bone conduction is dependent on the conditions for bone repair as well as the biomaterial used and its reactions[19]. More than 60% by weight of bioactive ceramic powders should be added to PMMA powders to achieve satisfactory osteoconductive properties after setting[20].

Thermal reduction

The polymerisation of bone cement is an exothermic process that can cause tissue necrosis. The high peak curing temperatures of acrylic bone cements is a major concern that needs to be addressed. The use of oxygen plasma increases the maximum curing temperature of bone cement. For example, 100 W of oxygen plasma applied to PMMA powdered polymer (Sigma-Aldrich Chemie, Germany) increases the maximum temperature from 83.48 ± 7.35 ℃ to 96.50 ± 4.52 ℃ (no reported significance)[21]. This is explained by the catalytic activity in polymerization, which results in more rapid heat release. A number of additives have also been tested for

their potential effects on heat reduction. PMMA bone cement modification with 1-dodecyl mercaptan (DDM, Acros Organics, United States) lowers peak temperatures by 4-6 ℃ (no reported significance), possibly by acting as a chain stopping agent[21]. Endothermic reactions involving ammonium nitrate (Acros Organics United States) also help to reduce temperatures (73.64 *vs* 96.5 ℃; no reported significance). Zeolites (ZSM-5, Acros Organics, United States) further improve the exothermic profile of bone cements, reducing temperature from 90.12 to 86.9 ℃ with DDM, and from 73.64 to 72.66 ℃ with ammonium nitrate (no reported significance)[21]. In addition to limiting PMMA toxicity, the antioxidant N-Acetylcysteine (NAc) has also been shown to significantly reduce heat release in a dose dependent manner[22]. The maximum polymerization temperature was 42.6 ℃ with 1.00% (w/w) NAc, compared to 57.0 ℃ in the absence of NAc.

Radio-opacifying additives

Ceramic particles, such as barium sulfate and zirconia (zirconium oxide), are incorporated into bone cement to allow visualization through X-ray imaging[23]. They have an adverse influence on the biocompatibility of PMMA, leading to mechanical weakness[23-25]. Barium sulfate ($BaSO_4$; Horii Pharmaceutical, Osaka, Japan) at 10% w/w monomer has a compressive load test strength of 85(± 5) MPa[26]. Increasing concentrations of $BaSO_4$ (20%; 30%; 40% w/w monomer) reduce this strength (86 ± 4 MPa; 87 ± 8 MPa; 69 ± 10 MPa), although only the reduction between 30% and 40% is statistically significant ($P < 0.02$)[26]. The 10% w/w monomer has a fracture load of 88 ± 10 MPa in the three point bending load test, and this strength reduces in proportion to increasing barium concentration[26]. Furthermore, impact load testing of 10% w/w monomer reveals a strength of 3.1 ± 0.9 kJ/m^2, which is the same as for the 20%, 30% and 40% w/w monomers ($P < 0.01$)[26]. Thus, increasing concentrations of barium sulfate (10%-40%) reduce mechanical strength of cement. Additionally, conventional barium sulfate (Reade Materials; Providence, RI, United States) promotes poor osteoblast (bone forming cells) function at the surface of PMMA, in human osteoblast cell culture lines (CRL-11372), as seen by scanning electron microscopy and atomic force microscopy[25]. Kobayashi *et al*[27] analysed the effect of barium concentrations in PMMA additives (10%, 30% wt and empty control; Simplex® and Spineplex®, Stryker Instruments) in animal models at 12 and 90 d. Higher concentrations of barium sulfate were associated with stronger foreign body reaction at 90 d, suggesting lower levels of biocompatibility at higher concentrations. Further work is needed weighing the benefit of higher cement visualization against the lower biocompatibility at higher $BaSO_4$ concentrations in humans.

Iodine-containing acrylic bone cement has comparable biocompatibility to the barium sulfate-containing equivalent, while maintaining its useful radiopaque properties[28]. Analysis suggested that there was no significant difference in mechanical strength (fracture toughness and four-point loading test) between iodine and barium sulfate based cements.although further work needed to assess clinical application of iodine based cement[28].

Table 1 Exothermic activity of polymethylmethacrylate mixed with nano-MgO (12.8 nm) *vs* polymethylmethacrylate control[25]

	1 s	1 min	2 min	10 min	107 min
PMMA (℃)	44.98	45.82	50.10	52.5	47.85
PMMA and nano-MgO (℃)	39.65	40.36	46.99	48.85	44.10

PMMA: Polymethylmethacrylate.

The use of ceramic nanoparticles, such as magnesium oxide (MgO; 12.8 nm; Sigma Aldrich; St. Louis, MO, United States) and $BaSO_4$ (80-500 nm; Reade Materials; Providence, RI, United States), improves osteoblast adhesion (PMMA + nanoMgO 3.25 cells/mm^2; PMMA + nano$BaSO_4$ 3.6 cells/mm^2; cell density on adhesion assay and fluorescence microscopy) compared to conventional PMMA (2.6 cells/mm^2), although this improvement is not statistically significant ($P < 0.1$)[25]. The addition of nano$BaSO_4$ (100 nm; Sachtleben, Duisburg, Germany) to PMMA (CMW1 bone cement; DePuy Orthopaedics Inc., Warsaw, IN, United States) at 10% w/w has no significant difference on uniaxial compression strength ($P = 0.08$) or uniaxial tensile strength (ultimate stress and elastic modulus; $P = 0.3$ and $P = 0.4$ respectively)[29]. The addition of nanoMgO (at 10% w/w per total PMMA cement) also reduces the exothermic nature of *in vitro* PMMA solidification (Table 1), thus minimizing tissue necrosis[25]. Overall, nanoMgO and nano$BaSO_4$ improve osteoblast adhesion, with nanoMgO minimizing tissue necrosis and nano$BaSO_4$ having no impact on mechanical strength. Further work is needed to fully assess the mechanical parameters of nanoMgO and the exothermic activity of nano$BaSO_4$.

Organobismuth compounds also have radio-opaque properties that have been tested in bone cement. One particular study found that 5%, 10%, 15% and 20% (w/w) bismuth salicylate in bone cement with a 2/1 solid/liquid ratio [MMA, 1% (v/v) dimethyl-4-toluidine, 1.25% (w/w) benzoyl peroxide, Merck] had higher radiopacity than standard admixtures containing barium sulphate (Merck)[30]. Furthermore, 10% bismuth salicylate preparations had a higher percentage of injectability than their 10% barium sulphate counterpart (85.89% *vs* 81.90%; no reported significance)[30]. The addition of contrast agents, such as gadolinium and manganese, to produce a signal-inducing bone cement formulation has also been useful for magnetic resonance imaging. Gadolinium in gadoterate meglumine-water cement (Dotarem 0.5 mmol/mL; Laboratory Guerbet, Paris, France, 12 g PMMA and 5 mL MMA) had a higher contrast-to-noise ratio (CNR) in air than the manganese-containing cement (5 mL $MnCl_2$ solution, 100 mg/L deionised water) with a maximum CNR of 157.5 in a fast T1W turbo-spin echo sequence[31].

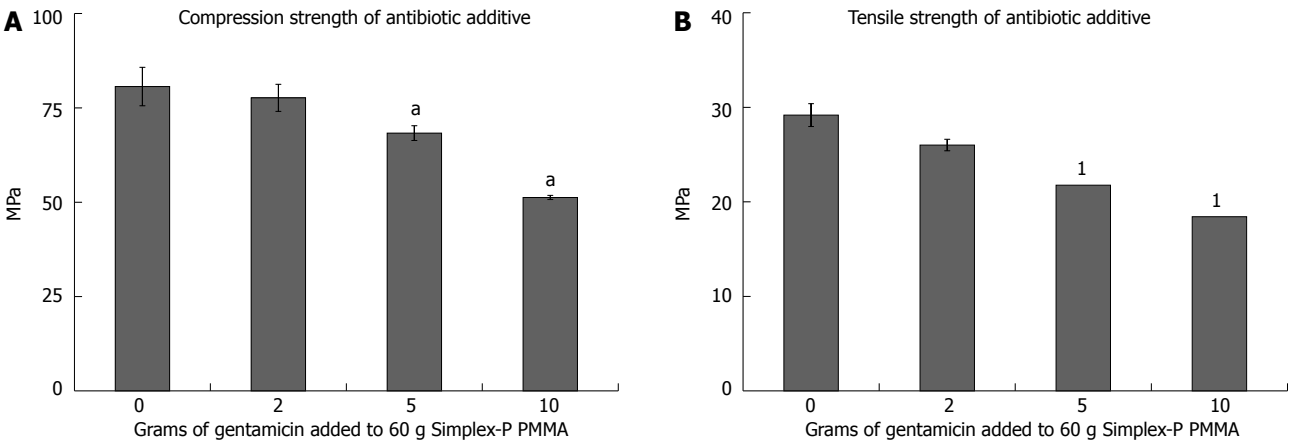

Figure 1 Mechanical strength of antibiotic (gentamicin) additives[38]. A: Compression strength, [a]$P < 0.05$ *vs* 0 g addition of Gentamicin; B: Tensile Strength, [1]invalid result as cements failed to fracture in a non-brittle manner.

Antibiotic additives

There is a high incidence of post-operative infections (0.25%-2.0%) in individuals receiving total joint replacements[32]. In cases where PMMA is used this rate increases to 13%[33]. Use of antibiotic-loaded bone cement for prophylaxis and prosthesis related infections has been documented since the 1970s, with erythromycin one of the earliest additives used[34,35]. Despite achieving clinical efficacy, erythromycin was found to diffuse poorly from the cement matrix into surrounding bone[34,35]. Aminoglycosides, such as gentamicin and tobramycin have since become popular additives for bone cements, due to their broad spectrum activity and low allergy profiles[36,37].

One study found that addition of gentamicin (2/60 g cement) did not significantly alter compressive or diametral tensile strength compared to control PMMA (Simplex-P; Figure 1). However, higher gentamicin levels of 5/60 g or 10/60 g, significantly reduced compressive strength ($P < 0.05$), although results for tensile strength could not be interpreted[38]. Although higher doses of gentamicin mean greater antibiotic availability, the mechanical properties of the additive are adversely affected.

Another study compared four antibiotics (sodium oxacillin, sodium cefazolin powder, gentamicin powder and gentamicin sulphate aqueous solution; 40 mg/mL of PMMA mixture), evaluating them for compressive (80, 70 and 65 MPa; 2g gentamicin powder, 250 mg aqueous gentamicin and 800 mg aqueous gentamicin solution respectively) and diametral tensile strength (27, 23 and 15 MPa; 2 g gentamicin powder, 250 mg aqueous gentamicin and 800mg aqueous gentamicin solution respectively) in comparison to control PMMA (Simplex-P)[39]. Powered gentamicin (2/40 g) made no statistically significant difference to compressive or diametral tensile strengths whereas aqueous forms produced weakened bone cements, as result attributed to the water in the mixture[39]. We recommend use of 2/60 g, or less, of antibiotic in powdered form. This lowers post-operative infection rates while only causing modest reductions in compressive (< 5% reduction) and tensile (< 5% reduction) strength.

Vancomycin has also been used as a bone cement additive, with concentrations less than 5% having no effect on the mechanical properties of the bone cement[40,41]. However, this has been found to be less efficacious than similar concentrations of tobramycin and gentamicin[37,42]. Interestingly, when used in combination with tobramycin, a synergistic effect appeared[43,44], with a 68% greater elution of tobramycin ($P = 0.024$), and 103% greater elution of vancomycin from the bone cement ($P = 0.007$), compared to controls containing only one antibiotic[43].

Vitamin E additives

The polymerisation process utilises a redox system, comprising benzoyl peroxide (BPO) as an initiator and *N,N*-dimethyl-4-toluidine (DMT) as an activator. This produces benzoate and amine free radicals which are thought to induce local inflammation and alter macrophage activity[45]. Vitamin E is a free radical "scavenger" in the oxidative process[46]. Mixed Vitamin E (MVE) additive (1 part liquid MVE: 1.8 part solid cement) shows increased cytocompatibility (as measured by total cellular DNA, cellular proliferation and differentiation *vs* control PMMA group) and decreased exothermic activity (peak temperature: 15% wt MVE-MMA 53 ℃ *vs* PMMA 76 ℃), reducing the likelihood of bone necrosis. However, setting time is increased (20.7 min 15% wt MVE-MMA mixture *vs* 12.2 min PMMA control), which exposes the operative site to the environment for longer[46]. Compositions of > 25% wt MVE-MMA have no effect on compressive strength, but significantly reduce tensile strength (Figure 2), although this still remains within the range for clinical usage[46]. The use of 15% vitamin E yields a lower compressive strength compared to additive concentrations of 10% and 20% (Figure 2), though this could be attributed to experimental error. Greatest clinical scope exists for 10% vitamin E additives as they have a positive effect on free radical oxidation and exothermic activity, with only modest reduction (< 5%) in tensile strength.

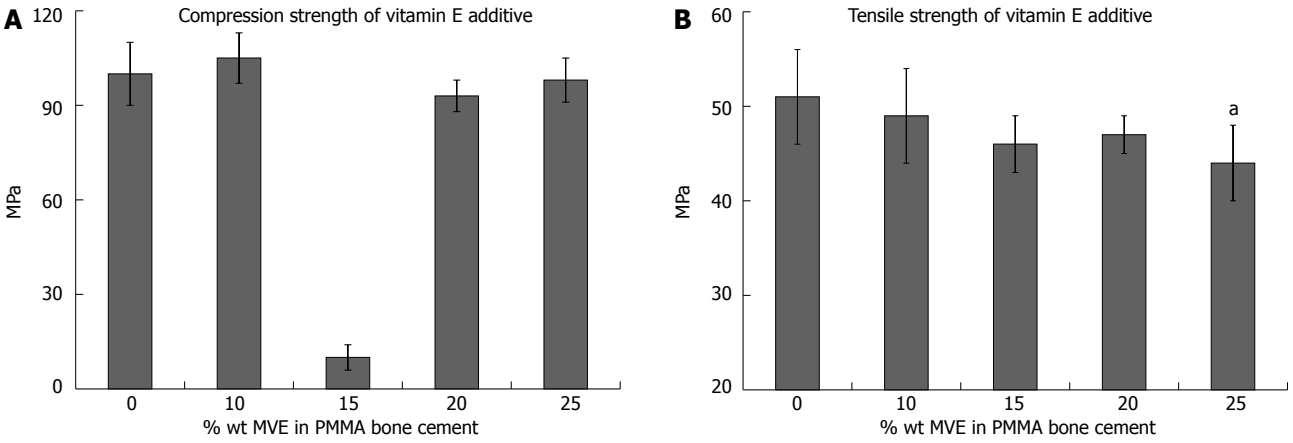

Figure 2 Mechanical strength of vitamin E additives[46]. A: Compression strength, great reduction at 15% appears to be an anomaly, but requires further review; B: Tensile strength, $^{a}P < 0.05$ *vs* 0%.

Table 2 Diametral tensile strength of polymethylmethacrylate and MMA:AA: MA co-polymer mixtures[47]

PMMA quantity (g)	MMA:AA:AMA quantity (g)	MMA:AA:AMA ratio	Tensile strength (Mpa)
20	0	-	31.3 ± 9.0
19	1	80:20:10	39.3 ± 3.0
17	3	80:20:10	36.2 ± 4.7
19	1	70:30:10	33.1 ± 4.2
17	3	70:30:10	26.6 ± 6.1

PMMA: Polymethylmethacrylate.

Monomer and nanoparticle additives

The co-polymer [poly (methylmethacrylate-acrylic acid-allylmethacrylate) or poly (MMA-AA-AMA); MMA, Kanton Chemical Co. Japan; AA, Alfa Aesar, Ward Hill, MA, United States; AMA, Acros Organics, Morris Planes, NJ, United States] reduces bone cement shrinkage (a problem in traditional compositions) as it absorbs body fluids and swells to compensate for shrinkage. An MMA:AA:AMA ratio of 80:20:10 resulted in improved mechanical strength (Table 2). In contrast, 70:30:10 did not yield any significant improvements, possibly due to increased acrylic acid concentration[47]. Co-polymerisation with MMA:AA:AMA also resulted in improved fracture toughness, due to a roughened surface, as identified with scanning electron microscopy. Further, cross-linked poly (MMA-AA-AMA) copolymer is able to induce bone ingrowths at the interface of bone and copolymer[48].

Bone cement composites have been trialed with nanoparticle additives, such as multi-walled carbon nanotubes and nano-sized titanium fibers. While there were measurable improvements in the flexural strength and bending capacity by 12.8% and 3.7% respectively, adverse effects on surrounding cell *in vitro* biocompatibility were observed[9] At the optimal concentration of 1% by wt, nano-titania fibers-give a significant increase in fracture toughness (67%), flexural strength (20%) and flexural modulus (22%), compared with control PMMA cement, while retaining handling properties and *in vitro* biocompatibility[9].

Recently, nanoparticles have been trialed *in vitro* as bactericidal agents. PMMA (DePuy International Ltd., UK and Biomet, Merck, Germany) with and without gentamicin was loaded with chitosan (CSNP, CarboMec Inc) and quaternary ammonium CS derived nanoparticles (QCSNP) at weight ratios of 15% and 30%, and then examined for their antibacterial (*Staphylococcus aureus* and *Staphylococcus epidermidis*, analysed by sphectrophotometry), mechanical (tensile and three point bending test, Young's and bending modulus) and cytotoxic properties (3T3 mouse fibroblast assay)[49]. Bone cement mixed with CSNP and QCSNP significantly ($P < 0.05$) decreased cell count for both strains (500 to 200 CFU/cm^2 for CSNP; 500 to 40 CFU/cm^2 for QCSNP)[49]. Cytoxicity assay and mechanical testing showed no significant difference between CSNP, QCSNP and control PMMA[49]. Further *in vivo* assessment of CSNP and QCSNP as potential bone cement additives is suggested for future studies.

Silver ions (AgNP) inactivate enzymes vital to bacteria and disable the mechanism for bacterial DNA replication[50]. Clinical application is limited by the difficulty of incorporating and dispersing AgNP into acrylics. *In situ* generation of AgNP (University of Texas Health Science Center, Texas) has been trialed[51]. Silver benzoate (AgBz; 1.0% w/w of total monomer; Sigma Aldrich) was blended with PMMA and extra benzoyl peroxide (B; 0.5%, 1.0%, 1.5% and 2.0% w/w; Sigma Aldrich) and diamethyl-p-toludine (D; 0.5, 1.0, 1.5 and 2.0% w/w; Sigma Aldrich) added. AgNP released silver ions *in vitro* for over 28 d (analysed by Atomic Absorption Spectrometry), inhibited 99.9% of bacterial growth at 48 h (*Acinetobacter baumannii, Pseudomonas aeruginosa, Proteus mirabilis and Staphylococcus aureus*; *in vitro* antimicrobial assay) and showed a continued antibacterial effect against *P. aeruginosa* for over 28 d (1.5B: 0.5D 1% AgBz, 1B: 1D 1% AgBz and 0% AgBz; 4.8, 6.3 and 0 mm inhibition; long term antimicrobial assay)[51]. However, AgNP (1%) mixtures have reduced mechanical strength (three point bending flexural test) compared to controls. Further work is needed to assess optimum loading, other mechanical properties and long term antimicrobial activity against other bacterial strains.

Table 3 Summary of polymethylmethacrylate bone cement additives

Additive	Summary
Gentamicin	Reduces post-operative infection rates. Powdered format (2/60 g or 2/40 g) shows no significant impact on mechanical strength, however increased gentamicin concentration decreases mechanical strength
Vitamin E	Improves cement cytocompatibility and reduces peak temperature. 10% vitamin E concentration does not significantly affect mechanical strength. Increasing concentrations associated with increased setting time and decreased mechanical strength
Polymer MMA:AA:AMA	Reduces bone cement shrinkage and improves fracture toughness. 80:20:10 significantly improves mechanical strength *vs* control
NanoMgO and NanoBaSO$_4$	Improves osteoblast adhesion, nanoMgO (12.8 nm) minimizes tissue necrosis and nanoBaSO$_4$ (100 nm) improves mechanical strength
Barium sulfate	Allows radiological identification of cement. 10% concentration is not associated with significant decrease in mechanical strength *vs* control. As concentration increases, mechanical strength decreases
Chitosan nanoparticles	*In vitro* studies show significant antibacterial activity against *S. aureus* and *S. epidermidis* with no significant difference in cytoxicity and mechanical strength *vs* control PMMA
Silver nanoparticles	AgNP (1%) has strong and continued antibacterial activity (against *A. baumannii*, *P. aeruginosa*, *P. mirabilis* and *S. aureus*) but with reduction in mechanical strength. Nanosilver (5-50 nm) has antibacterial activity against *S. epidermidis*, MRSE and MRSA with no significant difference in cytotoxicity *vs* control

PMMA: Polymethylmethacrylate; MRSE: Methicillin-resistant *S. epidermidis*; MRSA: Methicillin-resistant *S. aureus*.

Nanosilver (5-50 nm; 0.1%, 0.5% and 1.0% w/w monomer) mixed with PMMA (Coripharm, Dieberg, Germany), PMMA mixed with 2% w/w gentamicin sulphate (Schering-Plough, Brussels, Belgium) and PMMA control were compared for antimicrobial activity (on microplate proliferation assays) against *S. epidermidis*, methicillin-resistant *S. epidermidis* (MRSE) and methicillin-resistant *S. aureus* (MRSA)[52]. PMMA control had no antimicrobial effect, whereas 1% Nanosilver and 2% gentamicin loaded cements completely inhibited *S. epidermidis*. Furthermore, 1% Nanosilver completely inhibited MRSA and MRSE growth whereas gentamicin had no effect. This may be due to gentamicin resistance in tested strains[52]. The antimicrobial effect of Nanosilver was dose dependent, with higher concentrations of Nanosilver having higher antimicrobial effect. *In vitro* cytotoxicity was not significantly different (human osteoblast quantitative elusion testing and qualitative growth) between Nanosilver and PMMA controls[35]. Further, biocompatibility (measured by human osteoblast on growth) was similar between Nanosilver and the control group.

FUTURE APPROACHES

The focus of bone cement research is better mechanical quality, curing time and biocompatibility. Biomaterials, such as calcium phosphates and hydroxyapatite, more efficiently induce bone growth. Advances in the biocompatibility of PMMA bone cements might be achieved by introducing osteogenic agents, such as bone morphogenic proteins or transforming growth factors, to cement surfaces that contact the surrounding bone[53].

PMMA for vertebroplasty has greater stiffness than vertebral cancellous bone, causing higher incidences of fracture of neighboring vertebral bodies[54]. More porous bone cement has been developed by introducing an aqueous phase in PMMA cements, which is released *in vivo* with powder particles and thus increases risk of embolism. Beck and Boger (2009) showed that delaying the addition of the aqueous phase to acrylate mixture minimizes the amount of particles released[54].

CONCLUSION

As demonstrated in this review, there are many bone cement additives, none of which is perfect as strength often being adversely affected with minor additions of an additive (Table 3). There is scant data focusing on the effect of combining various additives. We suggest that this approach may yield bone cements that display the beneficial properties of each additive, while still maintaining structural integrity. Low index (< 15%) vitamin E and low index (< 5 g) antibiotic impregnated additives should be investigated further. These target inflammatory and infective pathologies, respectively, related to long term failure in bone cements, with only modest reductions in mechanical strength of the cement matrix. Mechanical strength and interface integrity should be improved through the use of rubber-toughened cements, amphiphilic bonders and/or increasing trabecular bone concentration in the cement matrix. Chitosan (15% w/w PMMA) and silver (1% w/w PMMA) nanoparticles have strong antibacterial activity with no significant reduction in mechanical strength. The field of nanoparticle technology holds promise.

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BRIEF ARTICLE

Longitudinal evaluation of time related femoral neck narrowing after metal-on-metal hip resurfacing

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Abstract

AIM: To track the short-term neck narrowing changes in Birmingham metal-on-metal hip resurfacing (MOMHR) patients.

METHODS: Since 2001, the Center for Hip and Knee Replacement started a registry to prospectively collect data on hip and knee replacement patients. From June 2006 to October 2008, 139 MOMHR were performed at our center by two participate surgeons using Birmingham MOMHR prosthesis (Smith Nephew, United States). It is standard of care for patients to obtain low, anteriorposterior (LAP) pelvis radiographs immediately after MOMHR procedure and then at 3 mo, 1 year and 2 year follow up office visits. Inclusion criteria for the present study included patients who came back for follow up office visit at above mentioned time points and got LAP radiographs. Exclusion criteria include patients who missed more than two follow up time points and those with poor-quality X-rays. Two orthopaedic residency trained research fellows reviewed the X-rays independently at 4 time points, *i.e.*, immediate after surgery, 3 mo, 1 year and 2 year. Neck-to-prosthesis ratio (NPR) was used as main outcome measure. Twenty cases were used as subjects to identify the reliability between two observers. An intraclass correlation coefficient at 0.8 was considered as satisfied. A paired *t*-test was used to evaluate the significant difference between different time points with $P < 0.05$ considered to be statistically significant.

RESULTS: The mean NPRs were 0.852 ± 0.056, 0.839 ± 0.052, 0.835 ± 0.051, 0.83 ± 0.04 immediately, 3 mo, 1 year and 2 years post-operatively respectively. At 3 mo, NPR was significantly different from immediate postoperative X-ray ($P < 0.001$). There was no difference between 3 mo and 1 year ($P = 0.14$) and 2 years ($P = 0.53$). Femoral neck narrowing (FNN) exceeding 10% of the diameter of the neck was observed in only 4 patients (5.6%) at two years follow up. None of these patients developed a femoral neck fracture (FNF).

CONCLUSION: Femoral neck narrowing after MOMHR occurred as early as 3 mo postoperatively, and stabilized thereafter. Excessive FNN was not common in patients within the first two years of surgery and was not correlated with risk of FNF.

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Key words: Hip joint; Arthroplasty; Complications; Hip resurfacing; Femoral neck narrowing

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INTRODUCTION

Metal-on-metal hip resurfacing (MOMHR) was approved in the United States by the Food and Drug Administra-

tion in May 2006, buoyed by promising survivorship data from the United Kingdom[1]. This technique, primarily due to its bone conserving nature, has become an alternative to total hip arthroplasty in younger patients. Femoral neck narrowing, potentially posing as a risk factor for femoral neck fracture, is a complication unique to this type of arthroplasty; though at present, there is no consistent evidence showing correlation between neck narrowing and neck fracture after MOMHR.

The incidence of neck narrowing after MOMHR was reported from 77% to 98%[2-3]. Although the exact etiology of neck narrowing is still unknown, possible contributing factors for neck narrowing may include stress shielding, damage to the blood supply, bone necrosis in the residual femoral head, alteration in hip biomechanics or secondary to wear debris[5-12].

Spencer's study showed-neck narrowing after resurfacing may stabilize after 2 years[2]. Shimmin demonstrated that the mean time to fracture after MOMHR is 3 to 4 mo, while Cooke *et al* reported that bone mineral density is significantly decreased at 3 mo postoperatively and recovers back to normal thereafter[13,14]. As a result of this data it is unclear when exactly neck narrowing occurs and whether or not it had any impact as a risk factor for early femoral neck fracture with MOMHR. Thus the purpose of this study was to more closely evaluate the changes that occur in the femoral neck in MOMHR patients. We measured neck narrowing radiographically immediately after surgery and at 3 mo, 1 year and 2 years postoperatively. We hypothesized that neck narrowing occurs early after MOMHR and then stabilizes long before the 2 year time point.

MATERIALS AND METHODS

This study was a retrospective longitudinal evaluation of prospectively collected patients' data from the Center for Hip and Knee Replacement Registry. From June 2006 to October 2008, 139 MOMHR were carried out at our center by two senior surgeons using the Birmingham MOMHR prosthesis (Smith Nephew, Memphis, TN, United States). All operations were performed using a modified enhanced posterior soft tissue repair approach[15]. The components were fixed using an uncemented hydroxyapatite porous coated cobalt chrome acetabular component and a cemented femoral component. As a part of our standard of care, all patients had low anterior-posterior (LAP) pelvis radiographs immediately after MOMHR procedure and were advised follow-up X-rays at 3 mo, 1 year and 2 years post-operatively. All radiographs were taken with great toes in contact to maintain consistent femoral rotation.

Inclusion criteria for the present study were all patients who came back for follow up office visit at the above mentioned time points and obtained LAP radiographs. Exclusion criteria included patients who missed more than two follow up time points and those with poor-quality X-rays. Symmetry of the trochanter was evaluated qualitatively on all follow up radiographs to ensure identical femoral neck version. We had function follow up of all 139 MOMHR. None of them had femoral neck fracture or revision at 2 years time point. Seventyone hips were excluded due to lack of proper X-rays; 68 hips (61 patients) fulfilled the inclusion criteria and were included into the study. Out of these 49 (72%) were in men and 19 (28%) were in women. The mean age at the time of surgery was 50.6 ± 9.6 years, the average body mass index was 29.4 ± 5.2 kg/m^2. The primary preoperative diagnosis was osteoarthritis in 53 (78%), osteonecrosis in 11 (16.2%), dysplasia in 2 (3%) and inflammatory arthritis in 2 (3%).

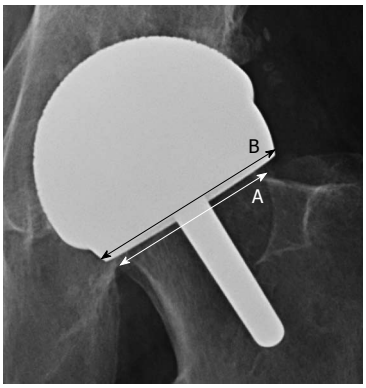

Figure 1 Radiograph showing measurement of Femoral Neck and Prosthesis. A: Neck-to-prosthesis ratio was calculated by dividing the femoral neck diameter at the prosthesis; B: Neck-to-prosthesis ratio was calculated by the diameter of the prosthesis at the opening edge.

Neck-to-prosthesis ratio, as described by Spencer *et al*[2], was used as the main outcome measure. "A" is the diameter of the femoral neck exactly at the prosthesis; "B" is the diameter of the implant exactly at the level of its opening edge (Figure 1). By dividing A by B the neck-to-prosthesis ratio was calculated. The means of the ratios between the two observers was taken for statistical analysis. Neck narrowing was indicated by reduced ratio (A/B) over the period of time. Femoral neck narrowing greater than 10% was considered significant.

Two independent observers reviewed the X-rays at 4 time points, *i.e.*, immediately after surgery, 3 mo, 1 year and 2 year. All the measurements were performed using Centricity Enterprise Web V3.0 (2006 GE Medical System) digital radiographic software. Twenty cases were used as subjects to calculate an intraclass correlation coefficient which evaluates the intra-observer and inter-observer reliability between the two observers (a value more than 0.8 was considered significant). After ensuring good reliability the remaining patients' X-rays were analyzed.

Statistical analyses were performed using SPSS 12.0 (SPSS for Windows, Rel. 12.0.0, 2003; SPSS Inc, Chicago, Ill). A paired *t*-test was used to evaluate the significant difference between different time points. A two-sided *P*-value < 0.05 was considered to be statistically significant.

RESULTS

Intraclass correlation coefficient calculated to analyze the reliability of the intraobserver and interobserver radiological measurements of diameters of femoral neck and

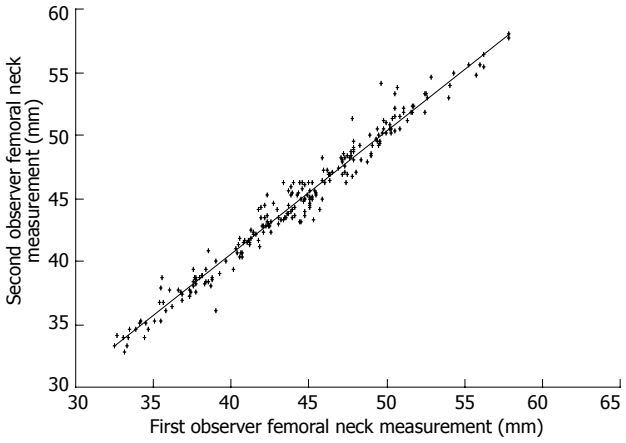

Figure 2 Inter-rater reliability comparison graph of paired femoral neck measurements.

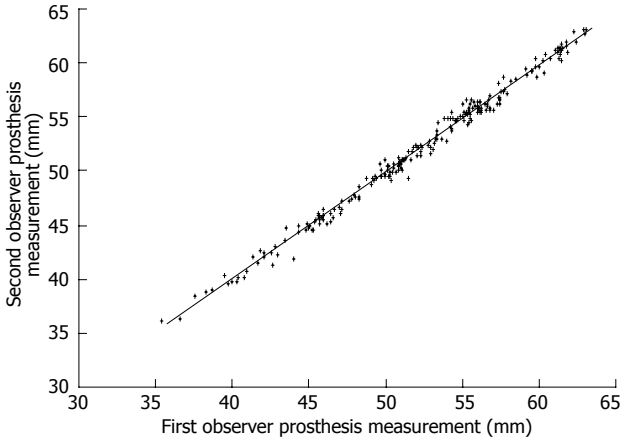

Figure 3 Inter-rater reliability graph of paired prosthesis measurements.

the femoral component showed significant degree of correlation (correlation coefficient = 0.924; 95%CI of 0.903-0.941) (Figures 2 and 3).

The neck-to-prosthesis ratios (NPRs) were 0.852 ± 0.056 immediately after surgery, 0.839 ± 0.052 at 3 mo, 0.835 ± 0.051 at 1 year and 0.83 ± 0.04 at 2 years post-operatively (Figure 4). When comparing to the immediate postoperative NPRs, the percent change was 1.9 ± 3.2 (0.05%-12.6%) at 3 mo, 1.9 ± 4.4 (0.1%-17%) at 1 year, and 3.6 ± 4.8 (0.07%-20%) at 2 years post-operatively. At 3 mo, femoral neck narrowing (FNN) was observed in 74% (48) of hips, which was significantly different from immediate postoperative X-ray ($P < 0.001$). Out of these 48 hips 23 were in men and 15 in women. There was no difference between neck to prosthesis ratio between 3 mo and 1 year ($P = 0.14$) and between 1 year and 2 years ($P = 0.53$). Excessive FNN, *i.e.*, narrowing that exceeded 10% of the diameter of the neck, was observed in only 4 patients at two years follow up. None of these patients developed a femoral neck fracture.

DISCUSSION

This aim of this study was to evaluate the short term

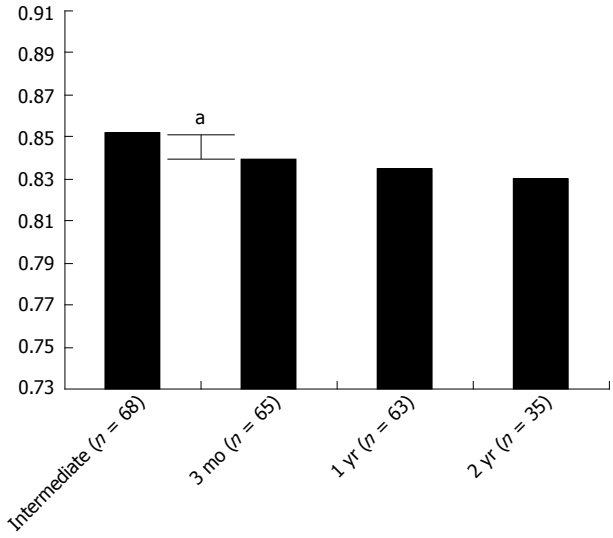

Figure 4 Neck-prosthesis ratio at follow-up (a) indicates significant change in neck-to-prosthesis ratio from immediate postoperative to 3 mo postoperatively.

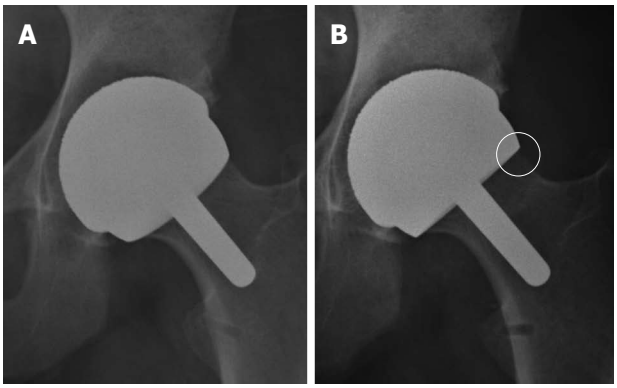

Figure 5 Femoral neck narrowing after Birmingham metal-on-metal hip resurfacing prosthesis occurs as early as 3 mo postoperatively and the neck-to-prosthesis ratio stabilizes thereafter. A: Immediate postoperative X-ray; B: Cirle showing neck narrowing at 3 mo postoperatively.

FNN after MOMHR. To the best of our knowledge, this is the first longitudinal evaluation of time related FNN after MOMHR focusing on short term outcome. Previous studies have focused on neck narrowing at 2 years or more, and their results have consistently reported absence of significant neck narrowing after 2 years post-operatively[1-4,16]. Spencer *et al*[2] reported that neck narrowing occurs within the first 2 years after surgery with no significant progression observed to a follow up of 7 years. Hing *et al*[4] showed that there was no statistically significant difference between the neck diameter at 3 years and 5 years indicating that thinning had stabilized previous to the 3 years time point. Joseph *et al*[3] also found no significant neck thinning after 2 years. Results of our study demonstrate that FNN after Birmingham MOMHR prosthesis occurs as early as 3 mo postoperatively and the NPR stabilizes thereafter (Figure 5). Our results of early neck narrowing may be supported by observations of Cooke *et al*[14] who found that bone mineral

density changes after resurfacing are mainly confined to femoral neck and that it reduces by 3 mo post-operatively but is recovered to normal by 12 mo with no significant change thereafter.

The incidence of neck narrowing in our cohort was 74% (48 hips). This was similar to what Hing *et al*[4] observed (125 hips; 77%) in their study on 163 Birmingham Hip Resurfacing arthroplasties but was less than that reported by Spencer *et al*[2] who found neck narrowing in 90% of prosthesis at 2 years post operatively. It is possible that the uncemented implant used in that study may result in a different loading pattern as compared to BHR. Joseph et al. did a comparative study examining both the Cormet 2000 in 35 cases and Birmingham Hip Resurfacing in 26 cases[3]. They observed neck narrowing in 98 % (60/61) of cases but found no statistical difference in the measurements between the two implant types. We also noticed that 15 out of 19 female had neck narrowing, while only 23 out of 49 male did ($P = 0.017$). One of the possible reason might be the femoral neck of female was significantly narrower than male. In our group the femoral neck diameter were 44.0 ± 3.5 mm and 37.7 ± 3.6 mm for male and female respectively. While the stem diameter of the femoral component is the same in spite of the size of the component, these results in the stem to neck ratio in female are greater than male. However, further researches were needed to investigate the effect of femoral neck diameter on neck narrowing.

Although the exact etiology of neck narrowing is still unknown, possible contributing factors for neck narrowing may include stress shielding, damage to the blood supply, bone necrosis in the residual femoral head, alteration in hip biomechanics or secondary to wear debris.

In the current literature, bone remodeling secondary to stress shielding after hip resurfacing has been studied by several finite element analyses[7-9]. Although bone remodeling is a feature of normal bone metabolism, hip resurfacing may result in stress shielding with resorption and narrowing of the femoral neck resulting from altered load. We believe that this resorption stabilizes by 3 mo; however, it requires further investigation.

Changes in blood supply to femoral head after hip resurfacing is controversial. Steffen *et al*[5] demonstrated compromised blood supply to the femoral head during hip resurfacing. Also, notching of the femoral neck during surgery has been shown to cause a reduction in blood flow of 50%[6]. In the retrieval analysis of failed Birmingham or Cormet resurfacing, Little *et al*[17] observed evidence of osteonecrosis in all but one case at revision. However, Howie *et al*[18] and Campbell *et al*[19] reported that retrieved femoral head maintained good blood supply and that avascular necrosis of femoral head is not a common cause of failure of resurfacing. The reason for this difference in observation may be attributed to different histological criteria used for determining osteonecrosis. It is still unclear if changing of blood supply plays a role in neck narrowing.

It has been shown that metal-on-metal articulations if malpositioned cause increased wear rates[10]. This wear induced debris can cause an inflammatory reaction and subsequent osteolysis which leads to neck thinning[10-12]. Also, in some patients hypersensitivity due to metal ion release may be a cause of neck thinning[20].

Although the clinical significance of neck narrowing is still unknown, the main concern is whether it could be predictive of future risk of femoral neck fractures. There is no consistent evidence in the literature showing that neck narrowing can lead to fracture. Shimmin did a national review of 3497 Birmingham hips which were inserted by 89 surgeons. Fracture of the femoral neck occurred in 50 patients, an incidence of 1.46%. They also found out that the mean time to fracture was 15.4 wk postoperatively. In our cohort, though we observed a 74% rate of neck narrowing, we did not have any fracture cases and therefore, we were not able to evaluate if there is correlation between neck narrowing and fracture.

We note the limitations of this study. First, as in all previous studies, we did not assess FNN in the sagittal plane. Computed tomography scan or roentgen stereophotogrammetric analysis may provide more accurate information; however, routine use of these methods on every resurfacing patient was not performed for this investigation. Our measurements were recorded using digital radiographs which may have improved our accuracy compared to previous studies done using a conventional radiography[1,2,16]. To reduce errors, all observations were made twice by two independent observers and all values were expressed as ratios. Similar to previous studies, we showed that this method of measuring neck-prosthesis ratio is statistically reliable. We had an intraclass correlation coefficient of 0.924. Second, this is a retrospective study. Only 68 out of 139 patients fulfilled the inclusion criteria. Although 96% (65/68) and 93% (63/68) patients had 3-mo and 1-year data, only 51% (35/68) had 2-year data. Selection bias may affect the result. Thirdly, the sample size of this study is relatively small. Potentially, this study could be under powered.

In conclusion, our study shows that neck narrowing occurs as early as 3 mo after MOMHR and is generally not progressive for up to 2 years as was previously believed. This pattern of early neck narrowing may be explained by bone adoption to initial stress shielding of the neck below the implant. Further study is required to determine the exact cause of this early neck narrowing. In our study, thinning of the femoral neck did not progress to any adverse clinical consequences and we are currently unsure of its clinical significance. It still remains to be seen whether patients with FNN may be more susceptible to femoral neck fracture.

COMMENTS

Background

Metal-on-metal hip resurfacing (MOMHR) was approved in the United States by the Food and Drug Administration in May 2006, buoyed by promising survivorship data from the United Kingdom. This technique, primarily due to its bone conserving nature, has become an alternative to total hip arthroplasty in younger patients. Femoral neck narrowing, potentially posing as a risk factor for

femoral neck fracture, is a complication unique to this type of arthroplasty.

Research frontiers

The incidence of neck narrowing after MOMHR was reported from 77% to 98%. Although the exact etiology of neck narrowing is still unknown, possible contributing factors for neck narrowing may include stress shielding, damage to the blood supply, bone necrosis in the residual femoral head, alteration in hip biomechanics or secondary to wear debris. As a result of this data it is unclear when exactly neck narrowing occurs and whether or not it had any impact as a risk factor for early femoral neck fracture with MOMHR.

Innovations and breakthroughs

This study was to more closely evaluate the changes that occur in the femoral neck in MOMHR patients. The authors measured neck narrowing radiographically immediately after surgery and at 3 mo, 1 year and 2 years postoperatively. The authors hypothesized that neck narrowing occurs early after MOMHR and then stabilizes long before the 2 year time point.

Applications

This pattern of early neck narrowing may be explained by bone adoption to initial stress shielding of the neck below the implant. In this study, thinning of the femoral neck did not progress to any adverse clinical consequences and we are currently unsure of its clinical significance. It still remains to be seen whether patients with femoral neck narrowing may be more susceptible to femoral neck fracture.

Peer review

The manuscript is very interesting and can be accepted with minor corrections that are reported through the text.

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BRIEF ARTICLE

Incidence and analysis of radial head and neck fractures

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Abstract

AIM: To investigate several complications like persistent radial head dislocation, forearm deformity, elbow stiffness and nerve palsies, associated with radial head fractures.

METHODS: This study reviewed the clinical records and trauma database of this level Ⅰ Trauma Center and identified all patients with fractures of the radial head and neck who where admitted between 2000 and 2010. An analysis of clinical records revealed 1047 patients suffering from fractures of the radial head or neck classified according to Mason. For clinical examination, range of motion, local pain and overall outcome were assessed.

RESULTS: The incidence of one-sided fractures was 99.2% and for simultaneous bilateral fractures 0.8%. Non-operative treatment was performed in 90.4% (*n* = 947) of the cases, surgery in 9.6% (*n* = 100). Bony union was achieved in 99.8% (*n* = 1045) patients. Full satisfaction was achieved in 59% (*n* = 615) of the patients. A gender related significant difference (*P* = 0.035) in Mason type distribution-type Ⅲ fractures were more prominent in male patients *vs* type Ⅳ fractures in female patients-was observed in our study population.

CONCLUSION: Mason type Ⅰ fractures can be treated safe conservatively with good results. In type Ⅱ to Ⅳ surgical intervention is usually considered to be indicated.

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Key words: Elbow; Radial head; Radial neck; Fracture; Children; Adult

Core tip: To investigate several complications like persistent radial head dislocation, forearm deformity, elbow stiffness and nerve palsies, associated with radial head fractures. An analysis of clinical records revealed 1047 patients suffering from fractures of the radial head or neck classified according to Mason. Non-operative treatment was performed in 90.4% (*n* = 947) of the cases, surgery in 9.6% (*n* = 100). Full satisfaction was achieved in 59% (*n* = 615) of the patients. A gender related significant difference (*P* = 0.035) in Mason type distribution-type Ⅲ fractures were more prominent in male patients *vs* type Ⅳ fractures in female patients-was observed in our study population.

Kovar FM, Jaindl M, Thalhammer G, Rupert S, Platzer P, Endler G, Vielgut I, Kutscha-Lissberg F. Incidence and analysis of radial head and neck fractures. *World J Orthop* 2013; 4(2): 80-84 Available from: URL: http://www.wjgnet.com/2218-5836/full/v4/i2/80.htm DOI: http://dx.doi.org/10.5312/wjo.v4.i2.80

INTRODUCTION

Fractures of the radial head are common and account for one third of all fractures of the elbow and approximately 1.5%-4% of all fractures in adults[1-3]. As much as 85% of these fractures occur between the third and sixth decade of age. According to the literature the mean age is between 45 and 45.9 years, and in an average, female patients are 7 to 16.8 years older than male patients[4-8]. Injury mechanism is a fall on the outstretched arm with the elbow in pronation and partial flexion, or in a rare case, direct trauma[1,6,7,9]. In children the incidence for radial head and neck fractures is up to 1.3%[10].

Radial fractures can be classified by the Mason-Johnston classification[11,12]. According to this classification, radial head fractures can be divided in to 3 types: a type I fracture is a nondisplaced fracture, a type Ⅱ fracture is a displaced fracture, and a type Ⅲ fracture is a comminuted fracture. Johnston added a fourth type: a radial head fracture with dislocation of the elbow[7,11,12].

Thus, the aim of this study was to analyze the epidemiology of radial head and neck fractures, specifically to describe age distribution, male female ratio, and the influence of fracture types and stabilization technique on the overall outcome, seen in this Level I Trauma Center between 2000 and 2010.

MATERIALS AND METHODS

Study population

In a ten year period, 1047 non-selected trauma patients where included in our study at a Level I Trauma Center, Department auf Trauma Surgery, Medical University of Vienna, Austria. Data were collected prospectively and evaluated retrospectively, in our computerized patient record's database. We collected data on all victims admitted to the hospital with diagnosed radial head and neck factures, but only patients with complete data and follow up have been included into the present study.

Members of the Department of Trauma Surgery did data collection and an independent member of the Department not involved in the study did a random cross check to exclude possible errors. Internal revision board (IRB) approval was not requested due to the fact that it is a retrospective data study only. The study was conducted according to the principles of Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) to the best of our knowledge. Collected data included variables such as age, gender, mechanism of injury, method of treatment, and clinical and radiological outcome after treatment. We generated two subgroups, juvenile fractures of the radial head and neck (< 18 years), and fractures in adults. Exclusion criteria for this study were missing pertinent clinical or radiographic data of follow-up monitoring leading to incomplete dataset. Treatment methods were depending on the fracture type and the physicians' choice. Radial head prosthesis was implanted in patients with comminuted fractures, if the salvage of the radial head was not possible. For clinical examination, range of motion, local pain, and bony union were assessed routinely.

Table 1 Description of studypopulation *n* (%)

Total	1047 (100)
Male	499 (47.7)
Female	548 (52.3)
Age (range), yr	36 (2-95)
Follow up (wk)	3 (0-350)
Children	77 (7.4)
Adults	970 (92.6)
Left	501 (47.9)
Right	538 (51.4)
Utriusque	8 (0.8)

Clinical and radiographic examination

For analysis of incidence and outcome of radial head a neck fractures, all records of follow-up monitoring were meticulously reviewed for each patient. Follow-up monitoring included patient's accurate clinical and radiographic examination in our outpatient clinic at admittance and at each follow-up visit. Radiographic assessment included standard radiographs (antero-posterior and lateral view). Additional radiocapitellar views or computer tomography (CT) scans were performed if the standard finding was doubtful. Radiologic scoring was performed according to Johnston's modification of the Mason classification[11,12].

Statistical analysis

For statistical analyses we used the SPSS software package (SPSS, Chicago, IL, United States). Medians and Interquartile rages are shown for continuous variables unless otherwise stated. Discrete variables are presented as counts and percentages. The nonparametric Mann-Whitney *U* test was used for continuous variables and the χ^2 test for discrete variables. A two-tailed *P* value less than 0.05 was considered statistically significant.

RESULTS

During the ten-year study period, 1047 trauma patients met the inclusion criteria. The mean age was 36 years (range 2 to 95), 499 (47.7%) were males and 548 (52.3%) were females, 970 (92.6%) patients were adults, 77 (7.4%) were children. (Table 1) In our study population a total of 859 (82.1%) fractures type I, 149 (14.2%) type Ⅱ, 28 (2.7%) type Ⅲ and 11 (1.1%) type Ⅳ have been observed. (Table 2) In 538 patients (51.4%) the radial head fracture or neck fracture was on the right side, and 501 cases (47.9%) had the fracture on the left side. In 8 cases (0.8%) a simultaneous bilateral fracture was observed. Mean follow up was 3 wk (range 0 to 350). 71 (6.6%) had follow-up less than one week, 267 (25.5%) had follow-up of exactly one week.

We divide our total patient population in two subgroups: adults and children to analyse our treatment results. In the children group 69 (90%) cases were treated

Table 2 Distribution of fracture types I-IV in our study population *n* (%)

Mason		Male	Female
Type Ⅰ	859 (82.1)	409 (47.6)	450 (52.5)
Type Ⅱ	149 (14.2)	67 (45.0)	82 (55)
Type Ⅲ	28 (2.7)	20 (71.4)	8 (28.6)
Type Ⅳ	11 (1.1)	3 (27.3)	8 (72.7)

conservatively compared to 8 (10%) cases treated with surgery. In comparison to those findings, in the adult group 91% (n = 880) cases were treated conservative compared to 9% (n = 90) cases treated with surgery.

In the total study population, 11 prostheses (1%) were implanted. In seven cases cemented radial head prostheses, in three cases bio prostheses and in one case total elbow prosthesis were implanted.

In eight cases sensitivity impairment was observed in type Ⅰ fractures, treated conservatively. Those patients were from the geriatric study pool and had full function on the affected extremity. Two patients, both type Ⅲ, developed a non-union, one after stabilization with a T-plate, and one after open reduction in the first procedure and transfixation during the revision surgery. In one case, type Ⅲ, a palsy of the ulna nerve occurred after closed reduction. Synostosis was observed in a type Ⅲ fracture, treated with a prosthesis. Re-osteosynthesis was indicated in one case, because the primary screw fixation was locking the range of motion (ROM) in the elbow joint. After re-osteosynthesis the patient gained full ROM without pain. Luxation after initial treatment occurred in two cases, one in a type Ⅰ fracture, stabilized with a T-plate, and in the second case, a type Ⅲ fracture, treated with a prosthesis of the radial head. No death or amputation occurred in our study population.

A gender related significant difference (P = 0.035) in Mason type distribution was observed in our study population. type Ⅲ fractures were more prominent in male patients (n = 20, 71.4%) *vs* type Ⅳ fractures in female patients (n = 8, 72.7%).

A significant difference in type Ⅱ distribution was observed between children and adults. While 26% of the children (n = 20) type Ⅱ fracture, only 13% of the adult subgroup (n = 129) suffered from the same fracture type (P = 0.004). Correlating with age revealed that within children younger than ten years, only half of the patients suffered from type Ⅰ (53%, n = 17), and type Ⅱ (40.6%, n = 13) (P < 0.001). In the children older than ten years, and adults, type Ⅰ was predominant. 84% (n = 38) in children from 11 till 18 years, and 83% (n = 804) in the adult subgroup (P < 0.001).

Median ROM (flexion/extension) according to Mason classification was: type Ⅰ 135 [interquatile range (IQR) 105-150], type Ⅱ 130 (IQR 108-150), type Ⅲ 130 (IQR 108-150) and type Ⅳ 140 (IQR 110-150). For the total study population 77% (n = 802) gained ROM > 100°, 22% (n = 225) ROM 50°-100°, and 2 (n = 20) < 50°. Median ROM (internal/external rotation) was 94% (n = 985) > 100°, 4% (n = 43) 50°-100°, and 2% (n = 19) < 50°. Total pain distribution at the end of follow up was non 59.3% (n = 621), mild 37.6% (n = 394) and severe in 3.1% (n = 32) (P = 0.031).

Different forms of conservative treatment did not influenced time of immobilization and pain at the end of follow-up. (Table 3) 75% of patients treated with surgery reported no pain at the end of follow-up compared to 57% of patients, treated conservatively (P = 0.03) (Table 4). No influence according to Mason classification could be observed.

DISCUSSION

In our study, we aimed to investigate the effect of fracture type and stabilization technique on overall outcome. Additionally we also looked at possible gender related influences. Due to the limited range of follow up, we believe that the total number of 1047 included cases over a period of ten years allows a warrantable analysis of our study population.

Incidence of fracture types according to Mason was comparable to findings in the already published literature[7,13]. The average age in years for specific fracture types (Ⅰ-Ⅳ) in the adult subgroup was similar to those numbers published by Duckworth *et al*[13]. For the distribution of fracture types in the children subgroup, we could detect similar results compared to Kaas *et al*[7]. The number of observed simultaneous bilateral fractures during an inclusion period of ten years is in accordance with previous published data[14]. Haematoma aspiration was performed in a total of 23 cases (2%), but no significant influence on pain and functionality could be observed. This is in contrast to the finding by Ditsios *et al*[1], postulating that haematoma aspiration leads to a imminent decrease in pain for the patient.

Our results demonstrate a statistical significance for the male female ratio in both subgroups. In current publications male-female ratio of 2:3, with female patients being significantly older is reported[4]. We found a full satisfactionary outcome after 3 wk on average in 59% (n = 615) of the patients, after radial head and neck fractures.

The assessment of longitudinal stability is a basic step before deciding the most suitable surgical option and to avoid complications[15]. If open reduction and internal fixation fails to achieve a satisfactory result, resection arthroplasty and radial head prosthesis are additional options, but both are linked with poorer outcome results[3,15-17]. Despite the fact that numerous papers have been published dealing with the optimal treatment of radial head fractures, no consensus or general accepted guideline exists[16,18-23].

There are several limitations of the current study we have to mention in relation to our results. The first and most gravid is the fact that the study was retrospectively performed. Also some critical readers may esteem the long inclusion duration of ten years as limitation. The fact that the study population represents a wide range of

Table 3 Immobilization time in conservative treatment

	Type Ⅰ				Type Ⅱ				Type Ⅲ				Type Ⅳ
	n	Median	Min	Max	*n*	Median	Min	Max	*n*	Median	Min	Max	*n*
Cast upper arm	256	1	1	6	51	2	1	6	0				0
Cast lower arm	7	2	2	4	1	2	2	2	0				0
Dorsale splint	7	4	1	4	1	1	1	1	0				0
Elastic bandage	3	1	1	3	4	2	1	3	0				0
Filmulin bandage	526	1	1	12	34	1	1	8	1	3	3	3	0
Gilchrist	0	0			1	2	2	2	0				0
Cork splint upper arm	0	0			1	3	3	3	0				0
Cork splint lower arm	1	1	1	1	0				1	1	1	1	0
Mitella	8	1	1	1	0				0				0
Non	9	0	0	0	3	0	0	0					0
Surgery	10				53				26				11

Table 4 Summary treatment strategies and pain *n* (%)

	Total	Surgery	Pain non	Pain mild	Pain severe
Type Ⅰ	859 (82.1)	10	3 (30)	7 (70)	0
Type Ⅱ	149 (14.2)	53	41 (77.4)	10 (18.9)	2 (3.8)
Type Ⅲ	28 (2.7)	26	21 (80.8)	4 (15.4)	1 (3.8)
Type Ⅳ	11 (1.1)	11	10 (90.9)	1 (9.1)	
		Conservative			
Type Ⅰ		849	488 (57.5)	335 (39.5)	26 (3.1)
Type Ⅱ		96	57 (59.4)	36 (37.5)	3 (3.1)
Type Ⅲ		2	1 (50)	1 (50)	
Type Ⅳ		0			

age and heterogeneity in the accident cause and fracture type may also be seen as a disadvantage. Several surgeons, attendings and residents, performing the surgeries might also influence the results. We also want to mention the special patient population when it comes to suicidal jumps and motor vehicle accidents, with people of challenging social background that might have an influence on the outcome, compliance and follow up. Also the inclusion of extreme fracture cases with severe soft tissue trauma may have an influence on our results. Despite these limitations we believe that the results justify our conclusion, even if further prospective clinical trials have to be conducted to approve our findings.

Conservative treatment is the primary goal. Mason type I fractures can be treated safe conservatively with good results[1,12,24]. In type Ⅱ to Ⅳ surgical intervention is usually considered to be indicated[23]. A gender related significant difference ($P = 0.035$) in Mason type distribution was observed in our study population. type Ⅲ fractures were more prominent in male patients ($n = 20$, 71.4%) *vs* type Ⅳ fractures in female patients ($n = 8$, 72.7%). Different forms of conservative treatment did not influence the pain at the end of follow-up. 75% of patients treated with surgery reported no pain at the end of follow-up compared to 57% of patients, treated conservatively ($P = 0.03$).

The decision which of the described techniques should be used in a patient can still be considered a fine line, and has to be based on the individual case and surgeons experience.

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COMMENTS

Background

To investigate several complications like persistent radial head dislocation, forearm deformity, elbow stiffness and nerve palsies, associated with radial head fractures.

Research frontiers

Radial fractures can be classified by the Mason-Johnston classification.

Innovations and breakthroughs

Fractures of the radial head are common and account for one third of all fractures of the elbow and approximately 1.5%-4% of all fractures in adults. As much as 85% of these fractures occur between the third and sixth decade of age. According to the literature the mean age is between 45 and 45.9 years, and in an average, female patients are 7 to 16.8 years older than male patients. Injury mechanism is a fall on the outstretched arm with the elbow in pronation and partial flexion, or in a rare case, direct trauma. In children the incidence for radial head and neck fractures is up to 1.3%.

Applications

An accurate classification of radial head fractures is the first step in successful treatment.

Peer review

The manuscript is an interesting one. It summaries a 10 year prospective study related to an important population suffering radial head and neck fractures.

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BRIEF ARTICLE

Bipolar hemiarthroplasty for femoral neck fracture using the direct anterior approach

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Abstract

AIM: To evaluate whether walking ability recovers early after bipolar hemiarthroplasty (BHA) using a direct anterior approach.

METHODS: Between 2008 and 2010, 81 patients with femoral neck fracture underwent BHA using the direct anterior approach (DAA) or the posterior approach (PA). The mean observation period was 36 mo. The age, sex, body mass index (BMI), time from admission to surgery, length of hospitalization, outcome after discharge, walking ability, duration of surgery, blood loss and complications were compared.

RESULTS: There was no significant difference in the age, sex, BMI, time from admission to surgery, length of hospitalization, outcome after discharge, duration of surgery and blood loss between the two groups. Two weeks after the operation, assistance was not necessary for walking in the hospital in 65.0% of the patients in the DAA group and in 33.3% in the PA group ($P < 0.05$). As for complications, fracture of the femoral greater trochanter developed in 1 patient in the DAA group and calcar crack and dislocation in 1 patient each in the PA group.

CONCLUSION: DAA is an approach more useful for BHA for femoral neck fracture in elderly patients than total hip arthroplasty in terms of the early acquisition of walking ability.

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Key words: Direct anterior approach; Bipolar hemiarthroplasty; Posterior approach; Femoral neck fracture; Muscle presentation; Walking ability

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INTRODUCTION

The direct anterior approach (DAA) is an intermuscular approach to reach the hip joint using the distal part of the Smith-Petersen approach without muscle detachment[1-3]. This approach has been reported to be useful in total hip arthroplasty (THA) for hip osteoarthritis due to it facilitating recovery of walking ability early after the operation[2,4-8]. When bipolar hemiarthroplasty is performed for femoral neck fracture in the elderly, early recovery is important to prevent a decrease in activities of daily living (ADL)[9-11]. Therefore, assuming that walking ability recovers early after bipolar hemiarthroplasty using DAA, we performed a prospective study on the usefulness of DAA in comparison with the posterior approach (PA).

MATERIALS AND METHODS

Between January 2008 and January 2010, 81 patients with femoral neck fracture underwent bipolar hemiarthroplasty using DAA or PA, and 79 of them were included as subjects after excluding patients with a pathological fracture. The patients were alternately assigned to the DAA group or PA group in the order they were hospitalized. The mean observation period was 36 mo (24-48 mo). As for the prosthesis type, the Centrax/Accolade TMZF (β titanium alloy: titanium-molybdenum-zirconium-iron) stem (Stryker) was used in all patients (Figure 1). Surgery was performed as soon as possible after admission. Anticoagulants/antiplatelet drugs were not suspended. The operators were 6 surgeons with 2-8 years clinical experience in the orthopedic department. The author (Baba T) played the role of a teaching assistant in all operations.

DAA was performed employing the method of Oinuma *et al*[2] using the distal part of the Smith-Petersen approach in the supine position on a standard surgical table. The fascia of the tensor fasciae latae muscle was incised at a site about 2 cm laterally to the skin incision to prevent lateral femoral cutaneous nerve injury and the intermuscular space between the tensor fasciae latae muscle and sartorius muscle was bluntly entered. The anterior articular capsule was exposed, incised and resected as much as possible to expose the femoral head. For stem insertion, the surgical table was extended so that the hip joint could be extended to 15°. The superior and posterior portions of the articular capsule were partly incised so that the greater trochanter could be elevated with a retractor. Finally, the size and stability were confirmed under fluoroscopy during the operation. PA was performed in the lateral recumbent position. The gluteus maximus muscle was divided along muscle fibers and short external rotators were detached. A T-shaped incision was made in the articular capsule and the femoral head was resected. Finally, the short external rotators and the articular capsule were sutured to the original position as much as possible.

In both groups, full weight bearing was permitted from the day after the operation. In the DAA group, no abduction pillow was applied. The PA group used an abduction pillow during rest on the bed for about 2 wk. An antibiotic was administered at the time of the introduction of anesthesia and at 3 hourly intervals thereafter (total of 3 times) on the day of the operation and twice a day for the subsequent 4 d. The drain was removed 2 d after the operation and fondaparinux as an anticoagulant for deep veins was administered at an appropriate dose according to the body weight and renal function for 14 d. The patients visited the hospital for examination 1 mo after discharge and underwent plain X-ray examination and clinical evaluation at 3 monthly intervals for 1 year and at 6 monthly intervals thereafter. When they were transferred to another hospital to continue rehabilitation, they visited our hospital 1 mo after the transfer and the subsequent schedule was the same as above.

The age, sex, body mass index (BMI), time from admission to surgery, length of hospitalization, outcome after discharge, walking ability, duration of surgery, blood loss and complications were compared.

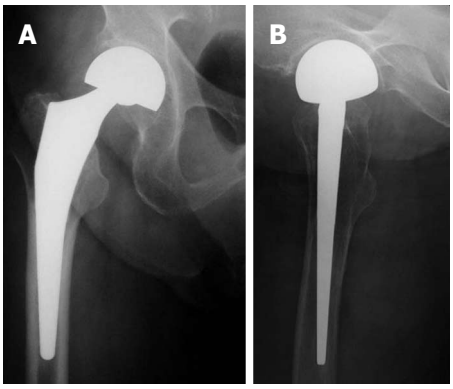

Figure 1 Since the anteroposterior width of Accolade TMZF stem is narrow and rasping of the greater trochanter is not necessary, this stem could be readily used for the direct anterior approach. Anteroposterior and lateral views on X-ray radiography after bipolar hemiarthroplasty.

Table 1 Demographic characteristics of patients

	DAA	PA	*P* value
Sex (male:female)	7:33	8:31	NS[1]
Age (yr)	76.7 ± 7.3	74.9 ± 7.7	NS[2]
BMI (kg/m^2)	20.6 ± 3.6	21.6 ± 3.0	NS[2]
Time from admission to surgery	2.9 ± 2.5	2.9 ± 2.0	NS[2]

There was no significant difference in the age, sex, BMI, time from admission to surgery. Values are the mean ± SD. [1]χ^2 test, [2]Student's *t*-test. BMI: Body mass index; DAA: The direct anterior approach; PA: The posterior approach; NS: Not significant.

Statistical analysis

Continuous data were analyzed using Mann-Whitney *U* test and Student's *t*-test and data grouped into categories were analyzed with the chi-squared test. A $P < 0.05$ was considered significant.

RESULTS

The DAA group consisted of 40 patients (7 males and 33 females) with a mean age of 76.7 ± 7.3 years. The PA group consisted of 39 patients (8 males and 31 females) with a mean age of 74.9 ± 7.7 years. Two patients in the DAA group died of liver cancer and myocarditis and 1 in the PA group died of renal failure. These deaths were not associated with the femoral neck fracture. The other patients were followed up to the final evaluation time point. There was no significant difference in the age, sex and BMI between the two groups (Table 1). Surgery was performed 2.9 d (mean) after admission in both the DAA group and the PA group. Surgery was performed within 2 d after admission in 24 of the 40 patients in the DAA group and 23 of the 39 patients in the PA group.

The mean hospitalization period was 29.9 (14-50) d in the DAA group and 29.3 (17-58) d in the PA group, showing no difference. Therefore, the place of residence

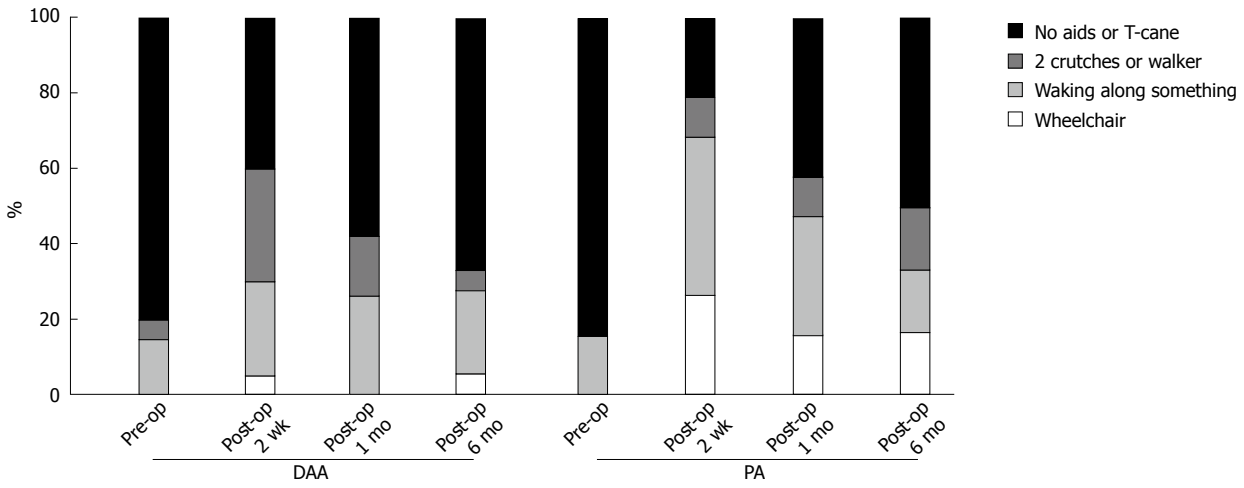

Figure 2 Walking ability before injury and after the operation. DAA: Direct anterior approach; PA: Posterior approach; op: Operation.

at the time of injury and the place to which the patient was discharged from our hospital were investigated. In the DAA group, the former and latter were home and home, respectively, in 38 patients and a facility and facility in 1, and home and a rehabilitation hospital in 1. Of the 40 patients, 39 were discharged to the place of residence before injury. In the PA group, the former and latter places were home and home, respectively, in 21 patients and home and a rehabilitation hospital in 18. Of the 39 patients, only 21 were discharged to the place of residence before injury. Walking ability before injury and after the operation was classified into the following 4 categories: unaided walking (including walking using a T-cane because in our hospital we instruct patients to use a T-cane even when unaided walking is possible), walking using two crutches (including walkers for the elderly), walking along something (assisted walking) and use of a wheelchair (Figure 2). Two weeks after the operation, assistance was not necessary for walking in the hospital (unaided walking, walking using a T-cane, walking with 2 crutches) in 65% (26/40) of the patients in the DAA group and in 33.3% (13/39) in the PA group (Mann-Whitney *U* test; $P < 0.05$). After 6 mo, unaided walking or walking using a T-cane was possible in 67.5% (27/40) in the DAA group and in 66.6% (26/39) in the PA group, without a significant difference between the two groups. The duration of surgery was 65.3 ± 39 min in the DAA group and 76.7 ± 33 min in the PA group. The intraoperative blood loss was 121 ± 82 g in the DAA group and 146 ± 56 g in the PA group. Warfarin was administered in 3 patients in the DAA group and Bayaspirin in 3 in the DAA group and 5 in the PL group but these drugs were not suspended during the perioperative period.

As for complications, fracture of the apex of the femoral greater trochanter developed in 1 patient in the DAA group and calcar crack in 1 patient and dislocation in 1 in the PA group. Neither infection of the superficial layer or deep area nor fatal deep venous thrombosis was observed. No special treatment was performed for the fracture of the apex of the femoral greater trochanter. The calcar crack was reinforced by wiring as much as possible. The fracture of the apex of the femoral greater trochanter or calcar crack did not delay the initiation of weight bearing after the operation, presenting no special clinical problems.

DISCUSSION

To improve ADL for femoral neck fracture in the elderly, we paid attention to DAA as an intermuscular approach. Excellent results of THA using DAA have been reported[12-14]. DAA is advantageous for the early postoperative recovery of muscle strength and is associated with a low dislocation rate. However, it has also been reported that muscle strength 6-12 mo after the operation does not differ between DAA and other approaches[4,15]. Since THA is mostly performed for hip osteoarthritis, the long-term recovery of muscle strength is important and the advantage of DAA (early recovery of muscle strength) is not so marked. Rather than this advantage, the low dislocation rate may be useful for THA. On the other hand, in bipolar hemiarthroplasty in the elderly, it is important to use methods that: (1) does not induce dislocation, even in patients such as dementia patients with difficulty in recognizing contraindicated limb positions; and (2) facilitate early regaining of walking ability without a decrease in the preoperative muscle strength rather than the long-term recovery of muscle strength. In addition, less invasive, safe and accurate surgical methods may reduce peri- and postoperative complications, contributing to ADL improvement. Therefore, we performed this study, comparing two groups who were treated by DAA as an intermuscular approach or PA as an approach with muscle detachment using the same prosthesis system and who were similar in age and sex and the waiting period. As a result, the DAA group clearly showed a better walking ability early after the operation.

Dislocation after bipolar hemiarthroplasty is one of the complications, although the reported dislocation rate varies from 1.5% to 13.4%[16-20]. Risk factors of dislocation include difficulty in recognizing dislocation-inducing limb positions due to dementia and mental/neurological

disorders, decreased muscle strength due to hemiplegia or Parkinson's disease, and frequent falling. These risks cannot be avoided because this fracture mainly occurs in elderly people. Concerning the difference in the dislocation rate between surgical approaches, many studies have shown that the anterior approach is advantageous in reducing dislocation in THA[1,3], whereas Sierra RJ *et al*[18] reported no association between the dislocation rate after bipolar hemiarthroplasty and the surgical approach. In our study, dementia and Parkinson's disease were observed in 5 and 1 patient, respectively, in the DAA group and 3 and 3 patients, respectively, in the PA group. The number of high-risk patients for dislocation was similar between the two groups but two episodes of posterior dislocation occurred in a patient with dementia in the PA group. After using a hip abduction orthosis, this patient did not develop dislocation. Dislocation-inducing limb positions in the PA group may involve a higher risk in bipolar hemiarthroplasty in elderly patients than in THA because patients have difficulty in adequately understanding these positions. Since dislocation-inducing limb positions after an operation using DAA rarely occur during ADL, few instructions regarding such positions are necessary.

Oinuma *et al* described patients appropriate for implantation of a THA by DAA system as: (1) females; (2) without obesity; (3) with osteoarthritis excluding Crowe 3 and 4; and (4) showing a wide range of motion[21,22]. When these criteria are applied to bipolar hemiarthroplasty, femoral neck fracture frequently occurs in females without deformation showing a normal range of motion. In our DAA group, the mean BMI was 20.1 and there were few obese patients. These conditions are appropriate for the use of DAA. In particular, using DAA, stem manipulation on the femoral side is considered to be difficult. However, since femoral neck fracture was not accompanied by flexion contracture or deformation, anterior transfer of the femur was straightforward in bipolar hemiarthroplasty compared with THA. Fracture of the apex of the greater trochanter in our study was clearly a surgical manipulation problem and adequate attention should have been paid to osteoporotic bone. Due to the surgical technique, it is necessary to select stems not occupying the medullary cavity and preserving the greater trochanter. Long straight stems are difficult to insert using DAA. The Accolade TMZF stem (Stryker) used in this study has a tapered wedge achieving stem fixation on the medial and lateral sides of the femoral medullary cavity in a wedge shape[23]. Since the anteroposterior width of the stem is narrow and rasping of the greater trochanter is not necessary, this stem could be readily used for DAA. Concerning tapered wedge fixation in patients with frail medullary cavity shapes or bone, the stem alignment tends to be flexed but this presents no clinical problems and satisfactory mid-term results have been reported[24,25]. Indeed, there were no clinical problems associated with the use of the Accolade stem in our patients.

In conclusion, DAA is an approach more useful for bipolar hemiarthroplasty for femoral neck fracture in elderly patients than THA in terms of the early acquisition of walking ability due to muscle preservation and the low dislocation rate.

COMMENTS

Background

The direct anterior approach (DAA) is an intermuscular approach to reach the hip joint using the distal part of the Smith-Petersen approach without muscle detachment. This approach has been reported to be useful in total hip arthroplasty (THA) for hip osteoarthritis due to it facilitating recovery of walking ability early after the operation.

Research frontiers

When bipolar hemiarthroplasty is performed for femoral neck fracture in the elderly, early recovery is important to prevent a decrease in activities of daily living.

Innovations and breakthroughs

Assuming that walking ability recovers early after bipolar hemiarthroplasty using DAA, the authors performed a prospective study on the usefulness of DAA in comparison with the posterior approach (PA).

Applications

DAA is an approach more useful for bipolar hemiarthroplasty for femoral neck fracture in elderly patients than THA in terms of the early acquisition of walking ability due to muscle preservation and the low dislocation rate.

Peer review

The authors treated femoral neck fracture cases treated bipolar hemiarthroplasty and compared between groups using the DAA and the group using the PA. The manuscript is neat. The concluded that DAA useful in elderly patients than PA in terms of the early acquisition of walking ability due to muscle preservation and anesthetic management during surgery in the supine position.

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CASE REPORT

Combined distal tibial rotational osteotomy and proximal growth plate modulation for treatment of infantile Blount's disease

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Abstract

Infantile Blount's disease is a condition that causes genu varum and internal tibial torsion. Treatment options include observation, orthotics, corrective osteotomy, elevation of the medial tibial plateau, resection of a physeal bar, lateral hemi-epiphysiodesis, and guided growth of the proximal tibial physis. Each of these treatment options has its disadvantages. Treating the coronal deformity alone (genu varum) will result in persistence of the internal tibial torsion (the axial deformity). In this report, we describe the combination of lateral growth modulation and distal tibial external rotation osteotomy to correct all the elements of the disease. This has not been described before for treatment of Blount's disease. Both coronal and axial deformities were corrected in this patient. We propose this combination (rather than the lateral growth modulation alone) as the method of treatment for early stages of Blount's disease as it corrects both elements of the disease and in the same time avoids the complications of proximal tibial osteotomy.

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Key words: Infantile Blount's disease; Tibia vara; Growth modulation; Eight plate; Hemi-epiphysiodesis; Rotational osteotomy; Genu varum; Lateral tension plate; Distal tibial osteotomy; External rotation osteotomy; Guided growth

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INTRODUCTION

Infantile tibia vara (infantile Blount's disease) is an orthopedic condition that affects young children causing varus deformity of the knee. The treatment of this condition differs according to the degree of involvement of medial proximal tibial physis. Multiple treatment options had been described for this condition[1-10]. These included observation; orthotic[4]; corrective osteotomy (acute or gradual correction)[3,5-9,10,11]; elevation of the medial tibial plateau[2,12,13]; resection of a physeal bar[1]; lateral hemi-epiphysiodesis[14]; and guided growth of the proximal tibial physis[8].

Infantile Blount's disease causes marked varus deformity that originates from the proximal tibial physis. The pathology of infantile Blount's disease involves internal tibial torsion as an element of the condition[15]. Treatment of Blount's disease should address all the elements of the disease; otherwise the child will be left with partially uncorrected deformity. Some of the surgical techniques used to treat infantile Blount's disease focus only on the coronal deformity (genu varum deformity) and does not treat the axial (internal tibial torsion) part of the disease[2,8,12-14].

There has been increasing interest in treating infantile Blount's disease by guide growth modulation[8]. The

principle of guided growth modulation depends on inhibiting the growth on the lateral aspect of the proximal tibial physis while allowing the medial part of the physis to continue growing resulting in correction of the genu varum deformity. This will not result in correction of the internal tibial torsion that is part of the pathology of infantile Blount's disease[8].

In this case report, we describe a novel method to treat infantile Blount's disease by combining a proximal lateral tibial growth modulation with distal tibial osteotomy to achieve both full correction of the deformity and decrease the risks of complications to the patient.

CASE REPORT

Three years old girl, Hispanic, morbidly obese, presented to the outpatient clinic with the bilateral severe genu varum deformity. Clinical examination showed that the child has bilateral internal tibial torsion of about 30 degrees bilaterally. The radiographs showed affection of the medial proximal growth plate (Langenskiold stage 2). The mechanical axis of the right side was 3.6 cm medial to the center of the knee and the mechanical axis of the left side was 3.2 cm medial to the center of the knee. The angle between the mechanical axis of the femur and the mechanical axis of the tibia (mechanical tibio-femoral angle) was 20° varus on the right side and 17° varus on the left side. The girl had the diagnosis of bilateral infantile tibia vara with bilateral internal tibial torsion (Figure 1).

The child underwent surgery to perform lateral proximal tibial growth modulation by inserting lateral tension band plate (eight plate) (Orthofix, Lewisville, Texas) (reversible plate hemi-epiphyiodesis) to correct the varus deformity. In addition, distal external rotation osteotomy of the tibia and fibula was performed to bring the foot to 5° external rotation compared to the knee axis. The external rotation osteotomy was done at the level of the distal tibia and fibula (junction proximal ¾ with the distal ¼). After rotation of the distal part, 3 crossing K-wires were passed across the osteotomy to stabilize it. Bilateral above knee casts were applied and patient was instructed to be non weight bearing for 6 wk on wheel chair (Figure 2).

Ten months later, follow up of the patient shows that she had full correction of both the varus deformity and the internal rotation deformity that was previously present. The radiographs showed correction of the varus deformity of the knee. The mechanical axis on the right side is 0.4 cm medial to the center of the knee and on the left side was 1.1 cm lateral to the center of the knee. The angle between the mechanical axis of the femur and mechanical axis of the tibia (mechanical tibio-femoral angle) was 0° on the right side and 7° valgus on the left side. The osteotomy side distally was completely healed. The 8 plates were removed bilaterally (Figure 3).

Consent was obtained from the mother to publish the case of her daughter.

DISCUSSION

Infantile Blount disease is a condition affecting the medial part of the proximal tibial physis. The condition is usually referred to as "infantile tibia vara" describing the frontal plane deformity; nevertheless, patients with infantile Blount disease have also internal tibial torsion deformity as well[15].

Tibial osteotomy is usually the standard of treatment for these children. The correction after tibial osteotomy can be done acutely with internal or external fixation. Acute correction carries the risk of compartment syndrome, under and overcorrection of the deformity[16-19]. A prophylactic anterior compartment fasciotomy and insertion of a drain is recommended for patients with Blount disease who are undergoing acute deformity correction to decrease the chance of compartment syndrome[20]. Gradual correction by external fixator lead to more accurate correction of the deformity with less chance of compartment syndrome, however, external fixators are usually not very well tolerated by the children due to their marked obesity and need to have bilateral fixators applied simultaneously in most cases. Another inherent problem with proximal tibial osteotomy to treat infantile tibia vera is that it is usually done away from the center of the deformity as the center of rotation and angulation (CORA) in cases of Blount disease lies at (or very close to) the level of the proximal tibial physis. Most of osteotomies are performed distal to the correct CORA because fixing very proximal osteotomies (at the level of the physis) is very technically challenging. This will result in displacement of the mechanical axis. Osteotomies done away from the CORA requires translation with the angular correction otherwise it will lead to shift of the mechanical axis of the limb[21].

Recently, there has been growing interest in using guided growth in treating early cases of infantile Blount's disease[8,22]. The procedure has the advantage of being minimally invasive, gradual correction with minimal risk and avoiding most of the complications of osteotomies. Also, the correction will occur at the center of deformity (CORA) avoiding any deviation of the mechanical axis of the corrected limb. The patient is followed until his/her mechanical axis of the limb reaches neutral alignment (or slight valgus) and then the tether (plate or staples) is removed. The tether is applied to the proximal lateral growth plate of the tibia, and it is not necessary to restrict the growth of the proximal fibular physis. Using the guided growth to treat early stages of infantile Blount disease will gradually correct the varus deformity but should theoretically have no influence on the internal tibial torsion. This will cause incomplete correction of the deformity and persistence of negative foot progression angle.

A recent retrospective study described the use of lateral tension plate to treat infantile Blount's disease[8]. Twelve children (18 limbs) had treatment of infantile Blount disease with application of lateral proximal tibial tension band plates. The success rate of growth manipulation in

Figure 1 The girl had the diagnosis of bilateral infantile tibia vara with bilateral internal tibial torsion. A: 3 years old girl, standing showing genu Varum; B: Pre operative clinical picture showing the marked internal rotation of both lower extremities. Note the relation between the feet direction and the patella (outlined by skin marker); C: Pre operative radiograph showing the gneu varum, mechanical axis deviation and the proximal medial tibial physeal changes.

Figure 2 Immediate post operative radiograph for the right leg showing application of the lateral plate to proximal tibial growth plate and distal tibial/fibular osteotomy fixed by 3 K wires.

Figure 3 Ten months post operative showing. A: Correction of both the genu varum and the internal rotation of the leg (clinical picture); B: Correction of the varus deformity and healing of the osteotomy sites (radiograph).

this group was 89%. Despite this high success rates, the authors stated that in 3 patients (25% of the population), there was persistence of a significant internal tibial torsion.

We propose a combination of the lateral growth modulation with distal tibial/fibular rotational osteotomy that can effectively and safely correct both elements of the pathology of the Blount's disease. The application of lateral tether will correct the varus deformity and the distal external rotation osteotomy will correct the internal tibial torsion.

The advantages of this combination are the following: (1) It has the advantage of using growth tethering which is: The deformity is corrected at CORA which is biomechanically the best option. The deformity is corrected gradually with a chance to monitor the effect of treatment and obtain the exact desired amount of correction; (2) The internal rotation deformity will be corrected and not left without treatment; and (3) The external rotation osteotomy is done in a safer area (distally rather than proximally) with less concern regarding development of compartment syndrome[23,24].

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CASE REPORT

Biepicondylar fracture dislocation of the elbow joint concomitant with ulnar nerve injury

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Abstract

In this article, we present a case of humeral biepicondylar fracture dislocation concomitant with ulnar nerve injury in a seventeen year-old male patient. Physical examination of our patient in the emergency room revealed a painful, edematous and deformed-looking left elbow joint. Hypoesthesia of the little finger was also diagnosed on the left hand. Radiological assessment ended up with a posterior fracture dislocation of the elbow joint accompanied by intra-articular loose bodies. Open reduction-Internal fixation of the fracture dislocation and ulnar nerve exploration were performed under general anesthesia at the same session as surgical treatment of our patient. Physical therapy and rehabilitation protocol was implemented at the end of two weeks post-operatively. Union of the fracture lines, as well as the olecranon osteotomy site, was achieved at the end of four months post-operatively. Ulnar nerve function was fully restored without any sensory or motor loss. Range of motion at the elbow joint was 20-120 degrees at the latest follow-up.

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Key words: Elbow injury; Fracture dislocation; Biepiconylar humeral fracture; Ulnar nerve injury

Core tip: Elbow joint posterior fracture-dislocations accompanied by neurovascular injuries are generally require surgical intervention. In this article, we present a case of humeral biepicondylar fracture dislocation concomitant with ulnar nerve injury in a seventeen year-old male patient. We obtained a successful clinical result by applying open reduction-internal fixation of the fracture dislocation and ulnar nerve repair at the same session as surgical treatment of this case. Although elbow fracture-dislocations with neurovascular complications are rarely seen, assessment of the neurovascular status in emergency room should always be a crucial part of physical examination which may affect the clinical result of the treatment.

Konya MN, Aslan A, Sofu H, Yıldırım T. Biepicondylar fracture dislocation of the elbow joint concomitant with ulnar nerve injury. *World J Orthop* 2013; 4(2): 94-97 Available from: URL: http://www.wjgnet.com/2218-5836/full/v4/i2/94.htm DOI: http://dx.doi.org/10.5312/wjo.v4.i2.94

INTRODUCTION

Elbow joint is the second most common site of upper extremity dislocations in young adults[1]. Mechanism of injury in posterior elbow dislocation is generally described as falling on an outstretched hand[2]. Recent studies in the literature have shown that elbow joint is

more likely to dislocate when it is in slightly abducted and flexed position. Posterior dislocation of the elbow joint occurs when compressive forces are directed on to the outstretched hand through the radius and ulna, along with the valgus stress at the elbow joint[3]. These biomechanical forces also contribute to associated fractures at the dislocated joint. Sport related injuries are the etiology in 10%-50% of all elbow dislocations. More than 90% of the cases are posterior dislocations. Isolated cases can be successfully treated with closed reduction; however, dislocations accompanied by fractures or neurovascular injuries are more prone to different complications and generally require surgical intervention[1-3].

In this article, we present a case of humeral biepicondylar fracture dislocation concomitant with ulnar nerve injury in a seventeen year-old male patient.

CASE REPORT

Seventeen year-old male patient was admitted to the emergency department after falling on to left arm. Physical examination of the patient in the emergency room revealed a painful, edematous and deformed-looking left elbow joint. Hypoesthesia of the little finger was also diagnosed on the left hand. Radiological assessment ended up with a posterior fracture dislocation of the elbow joint accompanied by intra-articular loose bodies (Figure 1). Closed reduction in the emergency room was failed and surgical treatment was planned for the patient. Under general anesthesia, the patient was admitted to the operation table in prone position. A pneumatic arm tourniquet was applied and then sterile dressing of the left upper extremity was set. Following a twenty centimeters long skin incision, ulnar nerve was explored and total disruption of the nerve was diagnosed (Figure 2).

V-shaped olecranon osteotomy was applied in order to achieve open anatomic reduction of the distal humeral joint surface as well as the removal of the loose bodies inside the joint. Lateral collateral ligament (LCL) was ruptured with avulsion fracture of the lateral epicondyle (Figure 2). Fixation of the lateral epicondyle together with the LCL was carried out by using a headless screw. A nerve stimulator was used to explore and find out the distal end of the ulnar nerve. Following release of the two ends, microsurgical repair with anterior transposition was applied for disrupted ulnar nerve. Medial collateral ligament (MCL) was also ruptured with avulsion fracture of the medial epicondyle. Fixation of the medial epicondyle together with the MCL was achieved by using a headless screw. Plate and screw fixation was chosen for olecranon osteotomy site (Figure 2).

Following wound closure, a posterior long arm splint was applied. Physical therapy and rehabilitation protocol was implemented at the end of two weeks post-operatively. Active and passive stretching exercises were put into practice following a 3-wk passive ROM rehabilitation program. Galvanic current electrotherapy nerve stimulation was also applied at the same time.

Figure 1 Pre-operative posterior elbow fracture dislocation with avulsed medial and lateral epicondyle fracture radiography.

Union of the fracture lines, as well as the olecranon osteotomy site, was achieved at the end of forth months post-operatively and the plate was removed after one year (Figure 3). Ulnar nerve function was fully restored with minimally hypoesthesia and no motor loss. Finger co-ordination was fully recovered and the reduced grip strength was improved at the end of six months. Disability of the Arm-Shoulder-Hand (DASH) Score was used to evaluate healing status during the post-operative follow-up period. Quick DASH score was measured as 27.5 at the end of 1 year.

Range of motion at the elbow joint was between 20 to 120 degrees and there was not sensory or motor loss except slight hypoesthesia of the fourth and fifth fingers by the end of one year post-operatively (Figure 4).

DISCUSSION

Stability of the elbow joint is supplied by the primary and secondary stabilizers playing role in different stages of motion. Main primary stabilizer is the anatomical structure of the ulnohumeral joint. Coronoid process is especially the most important part of this anatomical structure. Secondary stabilizers are the radial head, joint capsule, and the origins of flexor and extensor tendons[4]. Fracture dislocation of the elbow joint is often accompanied by disruption of one or more bony stabilizers, and thus pathophysiology of the elbow fracture dislocation is complicated. Generally, the stability of the joint cannot be secured by closed reduction because of the impaired

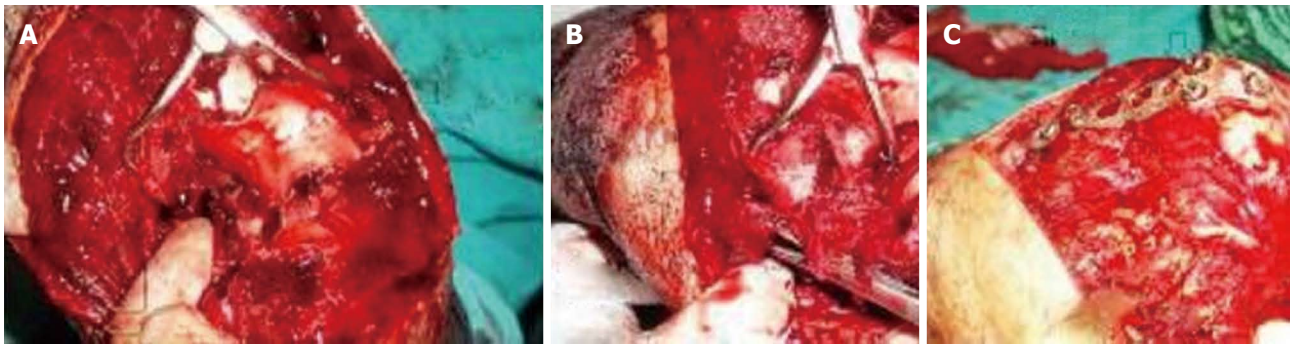

Figure 2 Intra-operative view. A: Avulsed medial epicondyle and lateral epicondyle with osteotomized olecranon; B: Avulsed medial epicondyle with nervus ulnaris; C: Plate and screw fixation of olecranon and repaired nervus ulnaris.

Figure 3 Early post-operative radiography with olecranon plate. A: Union of the fracture lines, as well as the olecranon osteotomy site, was achieved at the end of forth months post-operatively; B: Elbow radiography after removal olecranon after one year.

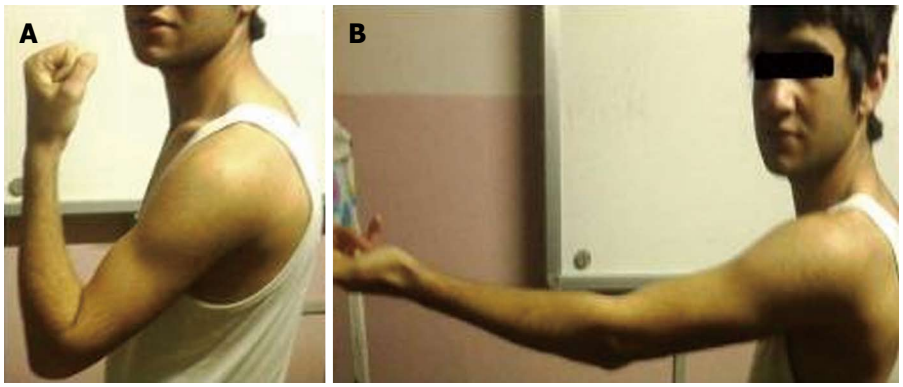

Figure 4 Elbow range of motion after one year. A: Fully restored flexion; B: Only 20 degrees extension disability.

function of these bony fragments which are very small in size but play crucial role in the biomechanical stability[5].

Biepicondylar fracture dislocation of the elbow joint was reported by several authors in the literature[6-9]. Bono *et al*[10] presented a case of intraosseous median nerve entrapment following posterior elbow dislocation in a seven year-old child. Abu Jayyap *et al*[11] reported biepicondylar fracture dislocation with complete radial nerve transection. In another study, median nerve entrapment and ulnar nerve palsy following elbow fracture dislocation in a child was discussed[12]. Acute ulnar nerve entrapment following closed reduction of a posterior fracture dislocation of the elbow joint was also highlighted as a potential risk in the literature[13]. Our patient had biepicondylar fracture dislocation of the elbow concomitant with complete ulnar nerve disruption.

Twelve months clinical outcome of our case was evaluated by the use of DASH scale. This scale is a 30-item self-report questionnaire which was developed to evaluate the functional status and symptoms of the patients with musculoskeletal disorders of the upper extremity[14]. Validity and reliability of this questionnaire in Turkish were tested and used in different studies. The scale is scored between 0 to 100 points and the higher scores indicate a

high level of disability[15]. DASH score of our case was measured as 27.5 at the end of one year.

In conclusion, we obtained a successful clinical result by applying open reduction-internal fixation of the fracture dislocation and ulnar nerve repair at the same session as surgical treatment of the case. As far as we could reach, we did not find any similar case reported in the literature. Although a few article can be considered close to our case report in the literature. We believe that although elbow dislocations with neurovascular complications are rarely seen, assessment of the neurovascular status in the emergency room should always be a crucial part of physical examination which may affect the clinical result of the treatment.

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Best approach for the repair of distal biceps tendon ruptures

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Abstract

The preferred treatment of distal biceps tendon ruptures is by operative repair. However, the best approach for repair (single *vs* double incision) is still subject of debate. Grewal and colleagues recently presented the results of a randomized clinical trial evaluating two different surgical approaches for the repair of distal biceps tendon ruptures. Despite the fact that this article currently presents the highest level of evidence for the surgical repair of distal biceps tendon ruptures, we have some comments on the study that might be interesting to discuss. We think that some of the results and conclusions presented in this study need to be interpreted in the light of these comments.

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Key words: Distal biceps tendon; Elbow; Operation technique; Repair; Rupture

Core tip: The preferred treatment of distal biceps tendon ruptures is by operative repair. However, the best approach for repair (single *vs* double incision) is still subject of debate. Despite the fact that this article currently presents the highest level of evidence for the surgical repair of distal biceps tendon ruptures, we have some comments on the study that might be interesting to discuss. We think that some of the results and conclusions presented in this study need to be interpreted in the light of these comments.

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TO THE EDITOR

With great interest we have read the article of Grewal and colleagues[1]. We have however, some comments on this trial and think that the conclusions of this article should be interpreted in this light. The preferred treatment of distal biceps tendon ruptures is by operative repair[2,3]. A systematic review by Chavan *et al*[4] showed that refixation of the distal biceps tendon is best done with a cortical button. However, the best approach for repair (single *vs* double incision) is still subject of debate. Grewal *et al*[1] recently presented the results of the largest randomized clinical trial evaluating two different surgical approaches for the repair of distal biceps tendon ruptures. In this great piece of research were 91 acute distal biceps tendon ruptures randomized between a single incision repair with use of suture anchors (n = 47) or double incision repair with use of transosseous drill holes (n = 44). The postoperative treatment protocol was identical for both groups. Primary outcome measure was the American Shoulder and Elbow Surgeons elbow score and secondary outcome measures included number of complications, elbow range of motion, elbow strength, Patient Rated Elbow Evaluation and Disabilities of

Arm, Shoulder and Hand scores. After two years were outcome measure questionnaires completed by 91% of the patients. One patient in the single incision group had died. Six patients (three in both groups) were lost to follow up. Both at short term (3-6 mo) and long term (12-24 mo) there was no difference in mean outcome scores. The final isometric flexion strength was significantly better in the double incision technique. In addition, there were significantly more (minor) complications seen in the single incision group (predominately because of transient neuropraxias of the lateral antebrachial cutaneous nerve in this group). Despite the fact that this article currently presents the highest level of evidence for the surgical repair of distal biceps tendon ruptures, we have some comments on the study that might be interesting and relevant for the readers to be discussed.

Besides the difference in approach, there is also a difference in fixation technique used between both groups. This raises the question whether the presented differences between the groups (number of complications and especially the isometric flexion strength) is related to different approach used, or to the difference in fixation technique used. The article of Grewal *et al*[1] suggests the first, though it can not be ruled out that the latter might be of even or greater importance. Previous studies[4,5] concluded that suture anchor repair is a stronger fixation technique than transosseous drill holes.

Current study does not mention whether or not the biceps ruptures were complete or partial. If partial ruptures were included, the question rises whether or not these are divided equally between both groups. Since more dissection is required in complete ruptures, this might reasonably result in more complications.

The technique of drilling the holes is not described in detail; it is for example not clear in which direction the drill holes were made for both groups. This is of importance since drilling in the wrong direction can cause injury to the posterior interosseous nerve[6].

The authors found more transient neuropraxias of the lateral antebrachial cutaneous nerve in the single incision group. This might be caused by more traction on the nerve during the single incision surgical approach. However, the single incision group represents more patients that are operated after 2 wk (38%) *vs* the double incision group (25%). It is of interest whether this difference is significantly, as longstanding ruptures often need more dissection and possible more retraction of the soft tissues. From other part of the body we also know that that chronic pathology is more difficult to treat than acute ones[7].

In conclusion, we think that Grewal and colleagues performed an excellent study, which represents a major contribution to the "distal biceps tendon reconstruction literature". However, we think some of the results and conclusions presented in this study need to be interpreted with care. We hope that the authors can present some more information based on the above-mentioned comments in order to enrich the common knowledge in the repair of distal biceps tendon ruptures.

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EDITORIAL

Trochanteric area pain, the result of a quartet of bursal inflammation

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Abstract

Bursitis is quite responsive to therapeutic intervention, once the afflicted area is accurately identified. This is especially notable for some hip complaints. Patients' use of the term "hip" can relate to anything from the low back to groin to lateral thigh pain. Trochanteric area surface localization of "hip" pain may afford an opportunity for immediate cure. Effectiveness of therapeutic intervention is predicated upon injection of not one or two, but all four peri-trochanteric bursa with a depot (minimally water-soluble) corticosteroid. The term trochanteric bursitis suggests that the inflammation is more focal than what is clinically observed. While easier to express, perhaps it is time to refer to inflammation in this area, naming all four affected bursae.

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Key words: Trochanter; Bursitis; Bursa; Hip; Injection; Corticosteroids; Dexamethasone; Triamcinolone

Core tip: The designation hip pain requires localization to identify effective treatment. Once tenderness is localized to the area of the greater trochanter, it is quite amenable to treatment. However, there are four bursa represented and injection of only one usually does not resolve the problem. Injection of all four with a corticosteroid that is minimally water soluble is required.

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HIP PAIN

Bursitis is quite responsive to therapeutic intervention, once the afflicted area is accurately identified. This is especially notable for some hip complaints. Patients' use of the term "hip" can relate to anything from the low back to groin to lateral thigh pain[1-6]. The affected area is typically identified by where the patient points. Lateral thigh localization suggests involvement of bursae in the vicinity of the greater trochanter[7-15]. Pain on external rotation with abduction is highly suggestive of the diagnosis. Direct palpation of the greater trochanter is usually diagnostic, although slipping ilial-tibial band syndrome must be considered[15] and of course, the bursae may rarely be infected (*e.g.*, tuberculosis)[16].

Non-operative orthopedics is a field in which results are typically expected in days (more commonly weeks or months) rather than producing the gratification of immediate and safe resolution of the problem that is so commonly the result of surgical intervention. One diagnosis that I find especially rewarding is that of involvement of peri-trochanteric bursae in individuals with "hip" pain. Such pathology has a female predominance. It is present unilaterally in 15% of women, 8.5% of men; bilaterally, in 6.6% of women, 1.9% of men[17,18]. It is rewarding to both physician and patient, as it is especially responsive to injection of the appropriate bursae with triamcinolone and lidocaine[19-23]. The lidocaine gives immediate relief of patient symptoms, confirming the diagnosis, while the

triamcinolone provides lasting relief. It is performed with a 22 gauge spinal (3-1/2 inch) needle and is sometimes performed under radiological guidance[24]. This injection provides a depot corticosteroid effect, in contrast to the time-limited effect of dexamethasone, whose water solubility results in rapid systemic, rather than localized distribution. Passive movement of the hip through full range of motion subsequent to injection is critical to assure mobilization of the steroid throughout the bursae[25]. This intervention is usually effective, even when it is a post-surgical event or in the presence of a leg length discrepancy[26-28], although presence of lower extremity osteoarthritis reduces effectiveness[18].

A recent article[29] questioned the efficacy of such injection therapy. However, the identified treatment approach was flawed in its injection of only one or two bursa(e), a common approach[30]. I too found disappointing results with that approach. However, there are actually four significant bursae in that location: gluteus medius, gluteus minimus, subgluteus medius and subgluteus minimus bursae[31].

Retrospective assessment of the last 50 individuals in my practice in whom all four bursae were injected revealed immediate elimination of pain in 49. Pain relief persisted more than 6 mo in 47 individuals. Two individuals had recurrent "hip" pain 3 mo after the initial injections. Their pain responded to repeat injection of the four bursae and they have been pain free since. Involvement of bursae was often (30 instances) bilateral. Because of insurance company limitations, unilateral injections were initially performed, with plan to inject the contralateral the following week. An unexpected observation was resolution of pain in the contralateral bursa, as well as in those injected. Given the effect of bursitis on gait[32,33], perhaps injection of the most symptomatic side eliminated the mechanical effect of altered gait. That may have allowed the contralateral side to heal. A systematic effect of the injected depot corticosteroid is unlikely, as injection of the above-named peri-trochanteric bursae did not affect concurrent anserine bursitis (which itself is extremely responsive to injection of a depot corticosteroid), nor did it affect concurrent bicipital or supraspinatus tendonitis. As injection of all four bursae is so effective, the role for diagnostic studies (*e.g.*, magnetic resonance imaging) seems an unnecessary expense[34-37].

It is intriguing that so many exotic approaches (*e.g.*, shock wave therapy and even surgery) to this problem have been pursued[38-48], when a simple injection approach is so frequently and fully effective. Non-steroidal anti-inflammatory drugs may reduce discomfort[49], but have significant systemic effects and do not resolve the underlying inflammation. Injection of only one or two of the four bursae results in partial, but statistically significant pain relief[8]. Comparison with elimination of pain in 98% of afflicted individuals by injection of all four bursae suggests the latter provides a greater opportunity for clinical benefit. The term trochanteric bursitis suggests that the inflammation is more focal than what is clinically observed. While easier to express, perhaps it is time to refer to inflammation in this area, naming all four affected bursae (*i.e.*, gluteus medius, gluteus minimus, subgluteus medius and subgluteus minimus bursitis).

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EDITORIAL

Mechanical solution for a mechanical problem: Tennis elbow

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Abstract

Lateral epicondylitis is a relatively common clinical problem, easily recognized on palpation of the lateral protuberance on the elbow. Despite the "itis" suffix, it is not an inflammatory process. Therapeutic approaches with topical non-steroidal anti-inflammatory drugs, corticosteroids and anesthetics have limited benefit, as would be expected if inflammation is not involved. Other approaches have included provision of healing cytokines from blood products or stem cells, based on the recognition that this repetitive effort-derived disorder represents injury. Noting calcification/ossification of tendon attachments to the lateral epicondyle (enthesitis), dry needling, radiofrequency, shock wave treatments and surgical approaches have also been pursued. Physiologic approaches, including manipulation, therapeutic ultrasound, phonophoresis, iontophoresis, acupuncture and exposure of the area to low level laser light, has also had limited success. This contrasts with the benefit of a simple mechanical intervention, reducing the stress on the attachment area. This is based on displacement of the stress by use of a thin (3/4-1 inch) band applied just distal to the epicondyle. Thin bands are required, as thick bands (*e.g.*, 2-3 inch wide) simply reduce muscle strength, without significantly reducing stress. This approach appears to be associated with a failure rate less than 1%, assuming the afflicted individual modifies the activity that repeatedly stresses the epicondylar attachments.

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Key words: Epicondylitis; Tennis elbow; Adaptive equipment; Mechanical overload; Elbow; Inflammation

Core tip: Lateral epicondylitis is a mechanical problem with a mechanical solution. While there have been many approaches, some quite exotic, to this phenomenon, there is a very effective non-invasive treatment: application of a 3/4-1 inch forearm band just below the elbow, of course associated with modification of the activity that is stressing the epicondylar attachments.

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CHARACTER OF LATERAL EPICONDYLITIS

Popularly referred to as tennis elbow, lateral epicondylitis is a relatively common clinical problem[1,2] that has apparently confounded many attempts at its resolution. Easily recognized on induced pain/replication of symptoms by palpation of the lateral protuberance on the elbow, the term lateral epicondylitis identifies a disorder localized to that lateral epicondyle. The "itis" suffix in the term epicondylitis is misleading. Histological evaluation does not support categorizing it as an inflammatory process[3-5]. Microscopic examination actually reveals angiofibroblastic and mucoid degeneration, attributed to mechanical overloading[3]. Indeed, ultrasound evaluation reveals me-

chanical damage to tendons[6-9].

ANALGESIC AND ANTI-INFLAMMATORY INTERVENTION

The multitude of approaches to management of a clinical problem suggests either that it is quite responsive to intervention or that the optimal approaches have yet to be identified. Many of the approaches to treatment of lateral epicondylitis seem to be predicated on the subsequently falsified hypothesis that the epicondylitis represented an inflammatory process[3-9]. These attempts have included use of oral or topical non-steroidal anti-inflammatory drugs[10-12], injections[13] of corticosteroids[10,13-20], anesthetics (*e.g.*, bupivacaine)[21] or even botulinum toxin[22] injection, none of which have had documented long-term clinical benefit[3]. Simply treating the pain symptom with analgesics has also provided inadequate relief[10,11,21,23].

INJURY-PREDICATED INTERVENTION

Based on recognition that epicondylitis represents an injury, another approach has been to inject autologous blood[24-27] or platelet-rich plasma[3,18,21,24,28,29]. This is predicated on the hypothesis that these injections provide growth factors, which stimulate healing. Similarly, skin-derived stem cells have been injected with this goal[30]. The enthesitis (irritation of tendon insertions) occasionally leads to calcification/ossification of those attachments. Speculation that the ossification/calcification process is the source of pain, radiofrequency[31] and shock wave[32,33] treatments have also been pursued. Surgical approaches have included percutaneous tenotomy and arthroscopic approaches[23,26,34-39].

PHYSIOLOGIC APPROACHES

More physiologic approaches have included physiatric/physical therapy techniques including manipulation, therapeutic ultrasound, phonophoresis, iontophoresis, acupuncture and exposure of the area to low-level laser[11,19,38,40-43]. An intriguing approach has been dry needling[25,34]. This is especially remarkable, as the lateral epicondyle has been listed[44], I believe erroneously[45], as a fibromyalgia trigger point and needling has been utilized as an approach to treatment of fibromyalgia[46]. The efficacy of all these approaches has been limited[3,13-16,25,28,29,38,47]. The study by Creaney *et al*[25] showed statistically significant clinical improvement in 60%-72%, but not complete relief. This is a greater response than with other approaches, but none identify complete resolution.

MECHANICAL INTERVENTION

The efficacy of these variably invasive approaches contrasts with a simple mechanical intervention. The irritation that appears to be the source of the pain derives from stresses produced by the muscles which attach to the lateral epicondyle[48]. Reducing the stress on the attachment area seems a reasonable approach. Logically, a band applied to the forearm, just distal to the elbow, would be expected to reduce stress on muscle attachment to the epicondyle, and it does. Early attempts to utilize this approach, however, were only marginally effective, because commercially available bands have an unintended effect. Those several inch wide bands only reduced effective muscle strength. The reduced available muscle power did reduce stress on the epicondyle, but did so inadequately and use of such armbands was less effective than immobilization of the elbow[12]. The latter, of course, results in muscle atrophy and loss of strength.

My personal approach has been to utilize Velcro bands of 0.75 to 1 inch in width and to assure their application 1 inch below the epicondyle. That position is critical. Such placement has no effect on muscle strength, but displaces the stresses on the epicondyle, such that it was now at the site of the band and thus distal to the epicondyle. Pain was immediately reduced and eliminated within several weeks. Patients were advised to wear the bands continually, except when sleeping, and to continue their use for two weeks beyond their perception of any residual elbow pain. Recurrences have responded equally well, once the activity responsible for the epicondyle stress is modified. I have had only 5 patients who have not responded (with complete resolution of elbow symptoms) in the three decades that I have utilized this approach. That represents less than 1% failure rate, and that was in individuals who would or could not modify the activity[2,42,49,50] that was repeatedly stressing the epicondylar attachments.

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EDITORIAL

Use of intercostal nerves for different target neurotization in brachial plexus reconstruction

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Abstract

Intercostal nerve transfer is a valuable procedure in devastating plexopathies. Intercostal nerves are a very good choice for elbow flexion or extension and shoulder abduction when the intraplexus donor nerves are not available. The best results are obtained in obstetric brachial plexus palsy patients, when direct nerve transfer is performed within six months from the injury. Unlike the adult posttraumatic patients after median and ulnar nerve neurotization with intercostal nerves, almost all obstetric brachial plexus palsy patients achieve protective sensation in the hand and some of them achieve active wrist and finger flexion. Use in combination with proper muscles, intercostal nerve transfer can yield adequate power to the paretic upper limb. Reinnervation of native muscles (*i.e.*, latissimus dorsi) should always be sought as they can successfully be transferred later on for further functional restoration.

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Key words: Intercostal nerve; Brachial plexus reconstruction; Reinnervation; Root avulsion

Core tip: Intercostal nerves are a very good choice for elbow flexion or extension and shoulder abduction when the intraplexus donor nerves are not available. Use in combination with proper muscles, intercostal nerve transfer can yield adequate power to the paretic upper limb. Reinnervation of native muscles (*i.e.*, latissimus dorsi) should always be sought as they can successfully be transferred later on for further functional restoration.

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INTRODUCTION

Nerve transfer or neurotization procedure can provide a useful function in cases of brachial plexus palsy with global spinal nerve root avulsion or irreparable proximal lesion. During a neurotization procedure a healthy donor nerve is separated from its territory, and its proximal stump is then connected directly or *via* a nerve graft to the distal stump of an injured nerve or implanted directly into a more critical denervated muscle target.

Sacrificing a donor nerve must be worthwhile. More specifically, the function gained has to be of greater value than the function lost and the donor nerve must contain adequate number of motor fibers to affect target reinnervation. Additionally, sufficient brain plasticity must take place to affect the restored function. These principles are operable in cases when intercostal nerves are used to neurotize different targets.

Yeoman *et al*[1] first in 1963 transferred several intercostals nerves into the musculocutaneous nerve using the

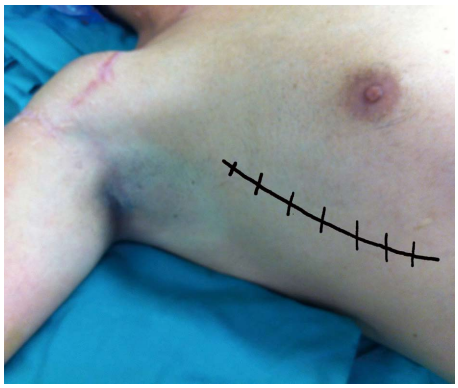

Figure 1 A curved incision starts at the anterior axillary line at the level of the upper chest and extents caudally towards the midline of the abdomen at the level of the umbilicus, depending on the number of intercostals nerves to be harvested.

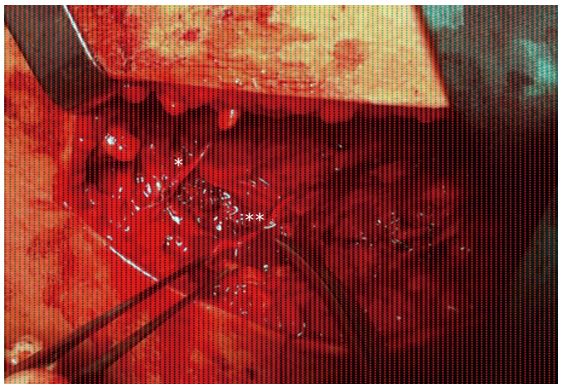

Figure 2 The motor branch is identified on top of the innermost intercostal muscle and dissected from the costochondral junction anteriorly to the posterior axillary line posteriorly. The intercostal nerves are passed to the axilla through a subcutaneous tunnel so they can be sutured to the recipient nerve. Note the intercostal nerve 5 (*) and the intercostal nerve 6 (**) after their dissection and mobilization.

ulnar nerve as a graft. This technique was modified and further developed by Kotani *et al*[2] and Tsuyama *et al*[3] ten years later. The pioneers in brachial plexus surgery such as Millesi, Narakas, Celli, Morelli, Terzis, and Gu commonly used intercostal nerve transfer for brachial plexus reconstruction[4-13].

ANATOMY AND PHYSIOLOGY OF THE INTERCOSTAL NERVES

Intercostal nerves are the ventral primary rami of spinal nerves T1 to T11. The ventral primary ramus of T12 spinal nerve is the subcostal nerve. T1 takes part in the brachial plexus and T12 does not actually occupy an intercostal space. Therefore 10 thoracic nerves from T2 to T11 constitute the anterior branch of intercostal nerves. In the intercostal space there are three muscular layers: (1) external intercostal muscle; (2) internal intercostal muscle; and (3) the innermost intercostal muscle. The upper intercostal nerves (T3, T4, T5 and T6) run parallel to their ribs in between the middle and innermost intercostal muscles, while the lower intercostal nerves (T7, T8, T9, T10 and T11) lie superficial either to transversus thoracic or transversus abdominis muscles.

There are some anatomic differences between the intercostal nerves. The first intercostal nerve is a tiny ramus of the first thoracic nerve and runs along the lower margin of the first rib. This is a purely sensory nerve and travels towards the sternum to innervate the skin near the midline. The second intercostal nerve has a large sensory lateral branch that innervates the skin in the anterior portion of the axilla and forms a connection with the medial cutaneous nerve of the arm. Furthermore, this nerve, because of its very high location is not accessible for neurotization. The anterior portion of the second and third intercostal nerves runs deep to the external intercostal muscle under the rib margin. The fourth intercostal nerve is slightly thinner than the third, its sensory component supplies the skin of the nipple-areolar area, and must be avoided for harvesting. Intercostal nerves from the 7 to the 11 supply muscles and skin of the anterior abdominal wall and theoretically will carry on higher number of axons than the upper intercostal nerves.

An intercostal nerve contains no more than 1200-1300 myelinated fibers and only 40% of them are motor fibers. Freilinger *et al*[14] studied the motor fiber content in the six, seventh and eight intercostal nerves and found a relatively constant level between 30% and 40% in the six intercostal nerve. The highest percentage (40%) was reached just after the lateral cutaneous branch had left the main trunk. Each intercostal nerve innervates multifunctional muscles and affects the respiratory function and posture including trunk flexion-extension and rotation. After intercostal nerve transfer to a given muscle, central motor programs responsible for respiration and posture will be connected to the innervated muscle. Initially, the function will occur only after voluntary respiratory effort, but with time voluntary control over the restored function will be achieved. These changes of control imply central adaptation, involving rearrangement of motor programs for a given muscle function and respiration[15].

During nerve transfer procedure, there is always a great risk of wasting transferred motor nerve fibers into inappropriate channels. For this reason, the distal site of coaptation must be as close as possible to the entry point of the motor nerve into the muscle target. This requires harvesting greater length of the donor nerve (Figures 1 and 2). However, the more the dissection proceeds distally, the lower the available number of motor fibers in the intercostal nerve.

To avoid an interposed nerve graft, Celli *et al*[4] suggested dissection of the intercostal nerve from its origin in the back and tracing it anteriorly for a length of 30-40 cm. Morelli *et al*[8], in order to maintain the maximal number of motor fibers, suggested transection of the intercostal nerve close to its origin followed by lengthening with a long intermediate nerve graft to reach the target.

INDICATIONS

Intercostal nerves can be used for primary nerve repair

Table 1 Intraoperative scoring system used to estimate the severity score

Score	Description of lesion
0	Avulsion
1	Rupture/avulsion
2	Rupture
3	Rupture/traction
4	Traction
5	Normal

in early or in late cases when free muscle transfer is indicated. The primary nerve transfer contains direct coaptation with single muscle target (musculocutaneous nerve, axillary nerve, triceps branch, and direct coaptation with nerves of multiple muscle targets (ulnar and median nerves); However, innervation of muscle targets for muscle transfer contains (1) neurotization of long thoracic nerve for stabilization of scapula and shoulder abduction; (2) neurotization of the thoracodorsal nerve and using in a second stage the latissimus dorsi muscle as pedicle flap for restoration of elbow flexion or extension; and (3) neurotization of free muscles transferred for shoulder, elbow, or hand reanimation. In patients with history of rib fractures, chest tube placement, or thoracotomy appropriate electrodiagnostic studies of intercostal nerves involved should be performed preoperatively.

DATA ANALYSIS

Brachial plexus palsy with multiple root avulsion is a devastating injury due to paucity of proximal motor donors. The only alternative for restoration of useful function is the use of neurotization procedures. However, the available donor nerves for transfer are few.

Yeoman *et al*[1] first described intercostal nerve transfer for brachial plexus reconstruction. Subsequently, several authors have reported their experience with intercostal nerve transfer[4,16-29]. In order to restore maximum function of the arm, as many intercostal nerves as possible are harvested and transferred. However, the optimal number of intercostal nerves used for nerve transfer remains controversial. Nagano *et al*[26] showed 70% good to excellent results using two intercostal nerves for musculocutaneous nerve neurotization. Chuang *et al*[17] reported higher success rate when they used three intercostal nerves. Kawai *et al*[23] supported that at least two intercostal nerves are needed to achieve useful elbow flexion, but using more than two intercostal nerves the results were not significantly better than those obtained when only two intercostal nerves were used.

There is a controversy on which intercostal nerves are the best for transfer. For brachial plexus reconstruction purposes, nine intercostal nerves are available: T3 through T11. Chuang *et al*[17] in their series showed no difference in the functional outcomes after using upper *vs* lower intercostals.

Different series have advocated the advantages of direct method of intercostal nerve coaptation without tension to the recipient nerve *vs* using nerve graft[10,20,25,27,30-33]. None of the patients in series of Friedman *et al*[20] who had interposed nerve graft between the transferred intercostal nerve and the musculocutaneous nerve obtained useful elbow flexion. Sedel[34] reported useful elbow flexion in five out of nine patients using nerve grafts. Songcharoen[28] showed muscle grading 3 or more in 65% of patients after intercostal to musculocutaneous nerve transfer (Table 1). Probably, when direct nerve repair is utilized, the distance to the target is shorter, and the regenerating axons pass through only one coaptation site instead of two when nerve graft has been used.

In late brachial plexus cases, when native muscle targets have been wasted, free muscle transfer innervated by intercostal nerves seem to be a viable procedure[16,18,35-39]. When planning a muscle transfer for upper extremity reanimation, in order to obtain the maximum result it is imperative to choose the correct muscle for needed function. Due to the greater power demands needed for proximal joint animation, free latissimus dorsi, rectus femoris or vastus lateralis muscles should be used for elbow flexion restoration, and the use of free gracilis muscle should be limited to hand reanimation.

The overall results after intercostal nerve transfer differ in many series. Chuang *et al*[17] showed that 67% of patients obtained a muscle strength of grade 4 or higher after intercostal to musculocutaneous nerve neurotization. Ruch *et al*[40] reported that 47% of patients obtained good or excellent results after musculocutaneous nerve neurotization with intercostal nerve transfer. Krakauer *et al*[24] showed that 6 out of 8 patients achieved a muscle grading of 3 or more after musculocutaneous nerve neurotization with intercostal nerves. Malessy *et al*[30] reviewed intercostal to musculocutaneous nerve transfers in adult patients performed in 6 different centers and found that a grade of 3 or more was achieved in 78% of the cases. Kawai *et al*[23] showed a muscle grading of +3 or more in 42% of patients after intercostal to musculocutaneous nerve transfer. Kawabata *et al*[41] reported his experience with intercostal nerve transfer in obstetric brachial plexus palsy patients and found that 84% of their patients achieved a muscle power of grade 4. Terzis *et al*[12] showed excellent results (M4 to M5-) in 5 out of 6 obstetric brachial plexus palsy patients when using intercostal to musculocutaneous nerve transfer and excellent result in 5 out of 11 patients when intercostal nerves were used for triceps nerve reinnervation[12].

Restoration of protective sensation it is imperative to maximize the upper extremity function. Kotani *et al*[2] reported limited recovery of sensibility in 11 out of 15 cases treated with intercostal nerve transfer for sensory restoration of the hand. Millesi[7,25] showed recovery of protective sensation in 15 out of 18 patients. Kawai *et al*[23] reported superficial pain recovery and some touch sensation in 5 out of 13 cases. Ihara *et al*[21] stated that intercostal nerve neurotization of the median nerve provided some touch sensation in 12 out of their 15 cases but no two-point discrimination was recorded. Doi *et al*[37]

showed tactile gnosis after intercostal nerve transfer to the ulnar nerve in all their patients. Terzis *et al*[12] reported complete recovery of protective sensation and active wrist and finger flexion after intercostal to ulnar and/or median nerve neurotization in obstetric brachial plexus palsy patients.

CONCLUSION

Intercostal nerve transfer is a valuable procedure in devastating plexopathies. Intercostal nerves are a very good choice for elbow flexion or extension and shoulder abduction when the intraplexus donor nerves are not available. The best results are obtained in obstetric brachial plexus palsy patients, when direct nerve transfer is performed within six months from the injury. Unlike the adult posttraumatic patients after median and ulnar nerve neurotization with intercostal nerves, almost all obstetric brachial plexus palsy patients achieve protective sensation in the hand and some of them achieve active wrist and finger flexion. Use in combination with proper muscles, intercostal nerve transfer can yield adequate power to the paretic upper limb. Reinnervation of native muscles (*i.e.*, latissimus dorsi) should always be sought as they can successfully be transferred later on for further functional restoration.

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EDITORIAL

Cervical adjacent segment pathology following fusion: Is it due to fusion?

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Abstract

Adjacent segment pathology affects 25% of patients within ten years of anterior cervical diskectomy and fusion (ACDF). Laboratory studies demonstrate fused segments increase adjacent level stress including elevated intradiscal pressure and increased range of motion. Radiographic adjacent segment pathology (RASP) has been associated to ACDF in multiple statistically significant studies. Randomized controlled trials (RCTs) comparing anterior cervical discectomy and arthroplasty (ACDA) and ACDF have confirmed ACDF accelerates RASP. The question of greatest clinical interest is whether ACDA, artificial disc surgery, results in fewer adjacent level surgeries than ACDF. Current RCT follow up results reveal only non statistically significant trends favoring ACDA yet the post operative periods are only two to four years. Statistically significant increased RASP in ACDF patients however is already documented. The RCT patients' average ages are in the mid forties with an expected longevity of up to forty more years. Early statistically significant increased RASP in the ACDF patients supports our prediction that given sufficient follow up of ten or more years, fusion will lead to statistically significant higher rate of adjacent level surgery compared to artificial disc surgery.

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Key words: Cervical; Diskectomy; Fusion; Arthroplasty; Adjacent; Degeneration

Core tip: Cervical artificial disc surgery has brought the expectation of a lower rate of adjacent segment pathology. Randomized controlled trials (RCTs), currently have only two to four years follow ups and the results regarding adjacent segment surgery indicate only non statistically significant trends favoring the anterior cervical discectomy and arthroplasty (ACDA). Higher rates of radiographic adjacent level pathology, after anterior cervical diskectomy and fusion (ACDF) is already documented. We predict that as the RCT average age mid forty-year-old patients continue to their almost forty year expected longevity, adjacent level surgery rates after ACDF will also increase in comparison to the ACDA patients.

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ADJACENT SEGMENT PATHOLOGY

The advent of anterior cervical discectomy and arthroplasty (ACDA) has brought the expectation of reduced adjacent level disease that may lead to additional surgery[1,2]. Randomized control trials (RCT), conducted in the United States for a variety of cervical artificial discs have a control arm consisting of anterior cervical discectomy and fusion (ACDF). Thus, these studies may give definitive answers to the much discussed and debated question; Does fusion surgery lead to adjacent segment pathology?

Adjacent segment pathology (ASP) is a serious problem after ACDF. Hilibrand *et al*[3] reported that 25% of patients experienced symptomatic clinical ASP (CASP) within ten years of ACDF. Fused cervical segments have been documented to increase adjacent level stress in multiple ways including: increased pressure and increased range of motion[4-9].

Radiographic adjacent segment pathology (RASP), has been linked to ACDF in multiple statistically significant studies[10]. Baba *et al*[11] reported 25% new spinal stenosis adjacent to ACDF. Gore *et al*[10] reported 25% new and 25% progression of degenerative disc changes at adjacent segments within five years of ACDF. Goffin *et al*[12] reported that 92% of patients developed RASP within five years of ACDF. They concluded that RASP was correlated also to CASP as an independent effect above the natural history of cervical degenerative disc disease. Not all randomized RCTs looked at RASP but those that have, confirmed that ACDF accelerates RASP. Coric *et al*[13] found much less RASP after the artificial disc compared to fusion. At two year follow-up, 24.8% of ACDF patients compared to 9% of ACDA had RASP with very high statistical significance, (P = 0.0001). Beaurain *et al*[14] for the Moby-C RCT, also at two year follow-up 34.6% RASP with ACDF compared to 17.5% after ACDA. Looking at all the available data, most will agree that there is an overwhelming and robust evidence for increased RASP with ACDF as opposed to ACDA.

But does fusion lead to more adjacent level surgeries than an artificial disc? Currently published and/or available data from RCTs show a trend, albeit statistically insignificant, towards increased ASP surgeries[1]. Most current RCT reports have only a two year follow up and not surprisingly there is no statistically significant difference between ACDF and ACDA with respect to CASP. Two, or even four year follow ups are too short a time when dealing with DDD that may take decades to become symptomatic. Most of the RCT patients were in their 40's and they are expected to live 30 or 40 more years. The increased RASP and the trend of increased CASP in the ACDF patients portend what is obvious. Cervical fusion accelerates adjacent segment pathology and will lead to increased adjacent segment surgery. We predict that given sufficient length of follow-up (at least 10 years), fusion will lead to statistically significant increased rate of adjacent level surgery as opposed to artificial disc.

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MINIREVIEWS

Orthopaedic perspective on bone metastasis

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Abstract

The incidence of cancer is increasing worldwide, with the advent of a myriad of new treatment options, so is the overall survival of these patients. However, from an orthopaedic perspective, there comes the challenge of treating more patients with a variety of metastatic bone lesions. The consequences of such lesions can be significant to the patient, from pain and abnormal blood results, including hypercalcemia, to pathological fracture. Given the multiple options available, the treatment of bone metastasis should be based on a patient-by patient manner, as is the case with primary bone lesions. It is imperative, given the various lesion types and locations, treatment of bone metastasis should be performed in an individualised manner. We should consider the nature of the lesion, the effect of treatment on the patient and the overall outcome of our decisions. The dissemination of primary lesions to distant sites is a complex pathway involving numerous cytokines within the tumour itself and the surrounding microenvironment. To date, it is not fully understood and we still base a large section of our knowledge on Pagets historic "seed and soil" theory. As we gain further understanding of this pathway it will allow us develop more medical based treatments. The treatment of primary cancers has long been provided in a multi-disciplinary setting to achieve the best patient outcomes. This should also be true for the treatment of bone metastases. Orthopaedic surgeons should be involved in the multidisciplinary treatment of such patients given that there are a variety of both surgical fixation methods and non-operative methods at our disposal.

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Key words: Bone metastases; Diagnosis; Pathophysiology; Surgical treatment, Medical treatment

Core tip: This paper discusses the pathophysiology and patient implications of bone metastasis. We aim to describe the orthopaedic input into the management of this condition, especially in a multi-disciplinary setting. We believe that orthopaedics do not have a significant enough involvement in the treatment of long bone metastasis, although from this paper we feel we have many options to offer. The future of metastasis treatment may be targeted at the molecular level but current management options do require an understanding of musculoskeletal oncology to obtain best patient outcomes through operative and non-operative means.

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INTRODUCTION

The American Cancer Society estimates that 1.64 million cases of cancer will be diagnosed in the United States in 2012[1]. Approximately 50% of these cases involve tumours of the breast, prostate, lung, kidney and thyroid. These tumours commonly metastasize to bone and account for 80% of all skeletal metastases[2]. This compares to an estimated 2890 cases of primary bone tumours that will be diagnosed during the same period[1]. These figures emphasize the importance of being able to recognise, investigate, manage and intervene appropriately in the course of metastatic disease in order to preserve function

and quality of life while minimizing complications.

The microenvironment associated with bone is ideal for tumour progression. Bone is a highly vascular mineral which produces adhesion molecules and is a source of angiogenic and bone resorbing molecules, all of which are conducive to the spread and development of tumours[3,4]. It also contains immobilised growth factors, which, when released, further enhance tumour cell proliferation[3,5].

Earliest evidence of skeletal metastases dates from 400 BC[6]. The term "metastasis" was first used by Hippocratic physicians, is of Greek origin and means the "change in the seat of a disease".

Throughout the 19th century, further investigation was carried out to elicit the mechanism behind the development of metastases. This era gave rise to pagets "seed and soil" theory, which postulated that tissues ("soil") receiving tumour cells could either be congenial or hostile[7]. The preferential development of bone metastases first postulated by Stephen Paget in 1889 noted that "in a cancer of the breast the bones suffer in a special way, which cannot be explained by any theory of embolism alone". Hence he proposed the widely acknowledged "seed and soil hypothesis". Circulating disseminated cancer cells activate bone to provide the ideal "soil" in which the aforementioned "seeds" can grow.

Others explained metastases on a purely stochastic basis[8]. It is now accepted that both methods occur, approximately 60% of metastatic sites can be predicted on a purely haematological and/or lymphatic route basis, the remainder of metastases involve intricate interactions between the tumour and host sites at the cellular and molecular level.

The identification of bone metastases is a significant development for patients. Their treatment can change completely as does their outcome. Not only can this news have a physical effect on patients' lives but also an emotional effect. As the treatment of metastatic disease is multidisciplinary in nature, it is imperative that orthopaedic surgeons are involved at an early stage and not just following pathological fracture or the development spinal stenosis.

DIAGNOSIS

Bone metastases and their associated complications (bone pain, pathological fractures, spinal cord compression, loss of independence and mobility and abnormal electrolytes) are the major morbidities associated with advanced disease and the symptoms with which patients will present[9].

The critical aspect in the investigation of a patient with potential metastases involves recognition of the above symptoms as possible progression of the primary tumour to bone. Imaging has an important role in the detection, diagnosis, prognostication, treatment planning, and follow-up monitoring of bone metastases.

Despite the relative insensitivity of plain radiographs in detecting small or early metastases, initial investigations should always include plain radiography. The presence of sclerosis or osteolysis on the X-ray can aid in diagnosis of the metastatic lesion, with sclerosis typically indicating a prostatic lesion and osteolytic lesions secondary to a breast primary[9,10].

Technetium-99m (99mTc) bone scintiscanning (*i.e.*, radionuclide bone scanning) is the most cost-effective and widely available whole-body screening test for the assessment of bone metastases. Combined analysis with plain radiography and 99mTc bone scintiscans improves diagnostic accuracy in detecting bone metastases and assessing the response to therapy[10].

Computed tomography (CT) scanning is an invaluable modality in those cases where bone scan confirms a focal abnormality but plain radiography cannot confirm any metastases. All bony metastatic lesions are depicted well on CT, including those of an osteoblastic, osteolytic and mixed nature.

Despite the expensive nature of the modality, magnetic resonance imaging (MRI) is very sensitive in the detection of metastases. Although some studies have suggested whole body MRI as a possible alternative to 99mTc bone scanning in the skeletal evaluation of bone metastases, this would be an impractical and expensive choice. MRI is primarily used in the evaluation of vertebral metastases for spinal cord compression or soft tissue involvement[11].

Histological diagnosis of metastases can be obtained from core biopsy of the effected bone, or CT guided biopsy should the former prove difficult. Alternatively, in the case of a patient presenting with a pathological fracture in the setting of known metastases, bone reamings at the time of surgical fixation can also be histologically analysed for the presence of circulating tumour cells.

MECHANISM OF METASTATIC LESION FORMATION

Metastasis involves a number of complex cell-cell interactions that ultimately leads to the development and growth of cancer cells in a distant visceral or bony site. Cells from the primary tumour must detach and extravasate. Following this they must migrate through the endothelium into the surrounding blood vessels, attach to the endothelium of a distant site after surviving the turbulent arterial blood supply, then migrate through the endothelium and extracellular matrix of the distant organ. Finally these circulating tumour cells must develop in the distant organ and facilitate the growth of further cancer cells[12].

The capacity to enter the circulation requires that neoplastic cells must have intrinsic properties that facilitate this process. The tumour cell must have the ability to induce neovascularization and be capable of crossing from the tumour stroma to the vasculature by invading the basement membrane of the vascular endothelium[13]. This process is facilitated by cell adhesion molecules (CAMs). Several categories of CAMs exist, including intercellular adhesion molecules (ICAMs), selectins and cadherins[14,15].

Once in the circulation, embolization of the tumour

Table 1 Mirels classification of metastatic bone lesions

Variable	Score		
	1	2	3
Site	Upper limb	Lower limb	Peritrochanter
Pain	Mild	Moderate	Functional
Lesion	Blastic	Mixed	Lytic
Size	< 1/3	1/3-2/3	> 2/3

cell is facilitated by adhesion to P- and L-selectins, located on platelets and leucocytes respectively. Adhesion to the endothelium of the metastatic tissue is mediated *via* E-selectin. Upon adhesion, an integrin signalling pathway is initiated, the net result of which is up-regulation of both the anti-apoptotic machinery and proteolytic activity in the microenvironment, thus facilitating the extravasation of tumour cells out of the circulation, and their invasion into the host tissue[16].

Disseminated tumour cells also contain integrins, a transmembrane receptor family which allows their attachment to several peptide sequences present on certain bone matrix proteins. These cell-surface molecules are involved in signal transduction and have been implicated in the mediation of cell migration, differentiation and apoptosis. Many studies have shown the correlation of increased integrin expression with malignant potential[17].

While our understanding of the molecular mechanisms of metastases has improved significantly since the earliest observations of Billroth[18], we remain ignorant of the intricacies of metastases. Selective therapeutic agents targeted exclusively at metastatic cells have yet to be developed[19] and much remains to be discovered about the critical determinants of metastatic process. However, the accelerated advances in the fields of molecular biology and genetics augurs well for the future.

TREATMENT OPTIONS FOR SKELETAL METASTASES

Bisphosphonates

Current medical options for the treatment of bone metastases primarily involves the use of bisphosphonates[20]. These are potent inhibitors of osteoclast activity and bone resorption and are widely used in both metabolic bone disease and metastatic disease. The mechanism of action of bisphosphonates targets the key stage of metastatic development where the disseminated circulating tumour cell stimulates further bone resorption. The disruption of this interaction, for either a palliative or preventative means, decreases the amplification of the metastatic process.

More recent studies have investigated the direct anti-tumour effects of bisphosphonates. It is believed that along with their inhibition of bone resorption, bisphosphonates may induce apoptosis of certain disseminated cancer cells, such as breast cancer cells. Furthermore, it is now believed from *in vivo* studies that bisphosphonates alter the properties of adhesion molecules in the bone matrix thus inhibiting the direct attachment of circulating tumour cells to the bone microenvironment[12,20]. However, despite their benefits in the treatment of symptomatic metastatic disease, they have not improved survival in patients with bone metastases[20].

Table 2 Capanna classification, classification according to tumour type

Classification according to tumour type	
Class 1	Solitary metastatic lesion Primary with good prognosis Interval after primary over 3 years
Class 2	Pathological fracture at any site
Class 3	Impending fracture in a major weight bearing bone
Class 4	Osteoblastic lesions at all sites Osteolytic or mixed lesions in non-structural bones Osteolytic lesion with no impending fracture in major weight-bearing bone Lesions of the iliac wing, anterior pelvis or scapula

Surgery

There is no strict rationale governing the surgical management of skeletal metastases. Clinical, medical, radiological and surgical factors, coupled with the inherent biology of the primary tumour all contribute to the decision making process. Furthermore, surgery in the setting of metastatic disease requires reliable data about patient survival and quality of life[21]. Earliest recommendations were simple and called for surgical intervention in the clinical scenario where fractures were "predicable"[22], the idea that the patient should have a reasonable life expectancy before considering surgery is relatively new[23].

Protocols for the treatment of bone metastases of the appendicular skeleton have been published. Mirels described a weighted scoring system in an attempt at quantifying the risk of sustaining a pathological fracture[24] and consequently the relative urgency for orthopaedic surgical intervention (Table 1). Mirels' system remains in wide use today despite the recent introduction of newer protocols[25]. The newer system describes the guidelines to surgical indications, types of surgery and recommended implants. Capanna classifies all patients with bony metastases into 4 categories (Table 2). Patients accumulate a representative numerical value for their metastatic lesion depending on figures awarded for potential survival (Table 3), the size of the lesion, the biomechanics of the bone involved and the potential response to adjuvant therapy. This dictates the recommended surgical intervention and the prosthetic implant to be used (Table 4).

However, despite involved classification systems and resultant surgical recommendations, each case of metastatic disease warrants treatment on an individual basis. Huge strides have been made in the techniques of surgical management for achieving secure fixation of pathological fractures despite what is often extensive bony destruction[26,27]. The use of internal fixation devices and prostheses along with methyl methacrylate has greatly assisted the orthopaedic surgeon in managing

Table 3 Capanna classification, potential survival

Survival	Sources of metastasis
< 1 yr (1 point)	Unknown Primary
	Melanoma
	Lung
	Pancreas
	Thyroid (undifferentiated)
	Stomach
1-2 yr (3 points)	Colon
	Breast (not responding to adjuvants)
	Liver
	Uterus (responding to adjuvants)
> 2 yr (6 points)	Thyroid (differentiated)
	Myeloma
	Lymphoma
	Breast (responding to adjuvants)
	Rectum
	Prostate
	Kidney

Table 4 Capanna classification, recommended surgical procedure and prosthetic type

Survival	Biomechanics	Size defect	Response to adjuvant therapy
< 1 yr = 1 pts	Tibia = 1pt	Small (1/3) = 1 pt	Yes = 0
1-2 yr = 3 pts	Femur, humerus = 2 pts	Large (1/2) = 2 pts	No = 3
> 2 yr = 6 pts	Subtrochanteric, supracondylar = 3 pts	Defective or pathological fracture = 3 pts	
	< 5 points =	Minimal or simple osteosynthesis	
	5-10 points =	Reinforced osteosynthesis	
	10-15 points =	Megaprosthesis or intercalary spacer	

pathological fractures. Despite improved fixation, healing of pathological fractures remains a challenge, overall 35% of pathological fractures can be expected to heal in 6 mo[28], highest healing rates are seen with multiple myeloma (67%) and the lowest rates were seen with lung carcinoma (0%).

It is imperative that whatever fixation device is used the construct should be durable enough to reliably last the remainder of the patient's life expectancy[29] and it is our recommendation that the entire diseased bone be stabilised at one operative sitting (Figure 1).

Although the general orthopaedic surgeon will commonly deal with pathological fractures in their day to day practice, we are commonly referred patients with spinal metastases. As with any patient, a complete history and examination is necessary, including a thorough neurological examination. Radiology should include an MRI to assess spinal cord compression and the extent of spinal metastases. Neurological status may necessitate urgent decompression with stabilisation of the adjacent vertebrae. However, prior to major surgery, it is important to liaise with the patients' oncology service to ascertain overall outcome. In palliative cases, radiotherapy may be

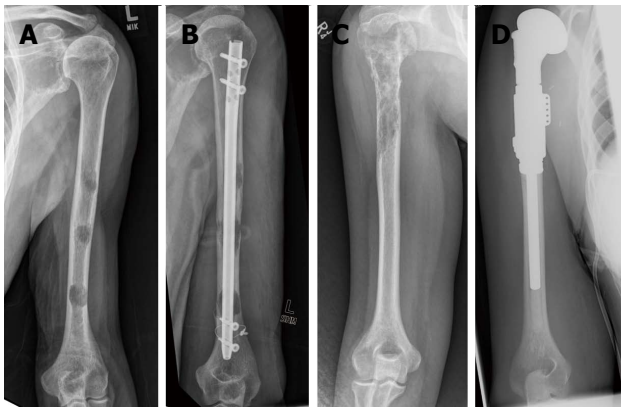

Figure 1 Different fixation methods for metastases of the humerus. A, B: Show the pre and post-operative X-rays of a 71-year-old male with painful metastatic lesions secondary to renal cell carcinoma. The humerus was stabilized using a locked intramedullary nail with a prophylactic distal cerclage wire, excellent pain relief was achieved; C, D: Show the pre and post-operative status of a 40-year-old female with painful metastatic breast carcinoma. The painful lesion was excised and replaced with an endoprostheses, good symptomatic relief was achieved.

an option, if the patient is medically unfit to undergo and survive spinal surgery.

Radiotherapy

The indications to treat bone metastases with radiation therapy include pain, risk of pathological fracture and spinal cord compression. The goals of radiation therapy are to palliate pain, decrease the use of narcotic analgesics, improve ambulation and restore function and prevent complications of pathological fracture.

External-beam radiation is the most common treatment and remains the cornerstone of palliative treatment with hundreds of thousands of patients undergoing treatment each year in the United States. Radiotherapy for bone metastases attempts to exploit the radiosensitivity characteristics inherent to tumour cells such as significant vascularization, high rates of proliferation and non-differentiation[30]. The exact mechanism of action of radiation therapy is unknown and remains speculative[31]. It was only recently that animal models established that radiation had its effect on tumour cells and that the benefit did not accrue from an indirect effect on the peripheral surrounding normal cells[32,33].

Clinically, several choices exist regarding the use of radiation therapy for bone metastases. Opinions differ on the best regimen for each patient, the most suitable radiation dosage, the appropriate adjuvant therapies and their timings and the best delivery mechanism.

The radiation therapy oncology group (RTOG) conducted a prospective randomized trial (RTOG 74-02)[34]. Patients with a solitary metastasis were randomized to receive 2000 cGy using 4 Gy fractions delivered over a short 5-day period or 4050 cGy delivered using 2.7 Gy fractions over a 3 wk period. There was no significant difference in outcomes measured by pain relief. Similar results were seen in patients with multiple metastases who were randomized to receive 3000 cGy in 10 fractions

over 2 wk or 1500 cGy in 5 fractions over 1 wk or 2000 cGy in 5 fractions over 1 wk or 2500 cGy in 5 fractions over 1 wk.

Since the RTOG trial[34] there have been several trials evaluating dose fractionation schemes[34,35] with no schedule or dose demonstrating significantly better outcome. Single-fraction radiotherapy has been advocated as a cost effective way to palliate bony metastases. A single dose of 8 Gy has been shown to have significantly better response rates when compared to a single dose of 4 Gy[36]. When a single dose regimen was compared to a multifraction regimen (20 Gy/5 fractions or 30 Gy/10 fractions), no differences were noted in time to symptomatic improvement, time to complete pain relief or time to first increase in pain up to 12 mo post-treatment[37].

It is now accepted that accelerated regimens may be appropriate in certain clinical settings for instance if the life expectancy is less than 3 years or where social circumstances decree that the patient cannot return on a daily basis. A protracted course may be more appropriate where the disease is more indolent or where the patient has a good performance status with a longer life expectancy or a solitary bone metastasis where the primary is well controlled[38].

Chemotherapy

The decision to use chemotherapy for the management of bone metastases relies on several factors. Firstly, the histology of the tumour must be known and secondly, it is important to know whether the patient has previously received chemotherapy because even the most chemosensitive tumours, such as lymphomas, are frequently resistant on relapse[38].

Certain tumours are considered highly chemosensitive. Such tumours frequently respond rapidly and often chemotherapy results in a significant reduction in the tumour burden. Complete or near complete remissions can be seen in certain chemosensitive tumours. Highly chemosensitive bone tumours may be considered for a trial of chemotherapy unless the involved bone is mechanically unstable.

Chemotherapy should rarely be considered for the management of metastatic tumours if the primary tumour is not chemoresponsive or chemosensitive. Response rates for these tumour types are so low that responses are considered anecdotal and it is reasonable to consider the tumour to have no effective chemotherapy.

CONCLUSION

Unfortunately the incidence of primary tumours is increasing, with that comes the challenge of dealing with metastatic disease. An individualised approach is recommended for each patient, taking into account the nature and biology of the primary lesion, life expectancy and the most appropriate surgical option. An increased understanding of the biology of the metastatic process may produce new treatment options to arrest this pathway at a variety of positions. Surgical management relies upon basic principles, but also on a fundamental knowledge of the nature of bone metastases.

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BRIEF ARTICLE

Errors in visual estimation of flexion contractures during total knee arthroplasty

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Abstract

AIM: To quantify and reduce the errors in visual estimation of knee flexion contractures during total knee arthroplasty (TKA).

METHODS: This study was divided into two parts: Quantification of error and reduction of error. To quantify error, 3 orthopedic surgeons visually estimated preoperative knee flexion contractures from lateral digital images of 23 patients prior to and after surgical draping. A repeated-measure analysis of variance was used to compare the estimated angles prior to and following the placement of the surgical drapes with the true knee angle measured with a long-arm goniometer. In an effort to reduce the error of visual estimation, a dual set of inclinometers was developed to improve intraoperative measurement of knee flexion contracture during TKA. A single surgeon performed 6 knee extension measurements with the device during 146 consecutive TKA cases. Three measurements were taken with the desired tibial liner trial thickness, and 3 were taken with a trial that was 2 mm thicker. An intraclass correlation coefficient (ICC) was calculated to assess the test-retest reliability for the 3 measurements taken with the desired liner thickness, and a paired *t* test was used to determine if the knee extension measurements differed when a thicker tibial trial liner was placed.

RESULTS: The surgeons significantly overestimated flexion contractures in 23 TKAs prior to draping and significantly underestimated the contractures after draping (actual knee angle = 6.1° ± 6.4°, pre-drape estimate = 6.9° ± 6.8°, post-drape estimate = 4.3° ± 6.1°, $P = 0.003$). Following the development and application of the measurement devices, the measurements were highly reliable (ICC = 0.98), and the device indicated that 2.7° ± 2.2° of knee extension was lost with the insertion of a 2 mm thicker tibial liner. The device failed to detect a difference in knee extension angle with the insertion of the 2 mm thicker liner in 9/146 cases (6.2%).

CONCLUSION: We determined the amount of error associated with visual estimation of knee flexion contractures, and developed a simple, reliable device and method to improve feedback related to sagittal alignment during TKA.

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Key words: Extension; Knee; Arthroplasty; Flexion contracture

Core tip: Fixed flexion contractures of even 1° have been reported to result in inferior outcomes after total knee arthroplasty. Despite the importance of correcting flexion deformities during surgery, the knee angle is often estimated visually. We developed an intraoperative measurement device that was highly reliable (intraclass correlation coefficient = 0.98) and was able to detect a loss of knee extension with the placement of a 2 mm thicker trial polyethylene liner in 93.8% of cases.

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INTRODUCTION

During total knee arthroplasty (TKA), surgeons often visually evaluate the angle of knee extension when determining if additional soft tissue releases or bony resection are required to correct flexion contractures. However, with the knee draped and tourniquet inflated, errors in the estimation of knee extension angle may occur as the surgeon can no longer visualize the location of the hip joint. The purposes of this two-part study were to (1) determine the effect of surgical draping and tourniquet inflation on visual estimation of knee flexion contractures, and (2) develop and evaluate an inexpensive manual tool to provide surgeons with accurate and reliable measures of knee extension angle during TKA.

MATERIALS AND METHODS

Patients electing to undergo primary TKA (n = 23, age = 64.5 ± 10.9 years, body mass index = 32.2 ± 5.9 kg/m^2) volunteered to participate in this IRB-approved study designed to better understand the magnitude of errors in visual estimation of knee flexion contractures during TKA. Once the patient had been anesthetized and in a supine position, a member of the surgical team lifted the operative limb into 20°-30° of hip flexion with the foot rotated so that the second toe was pointed towards the ceiling in order to neutrally align the knee. The preoperative knee flexion contracture was then measured using a long-arm goniometer prior to the placement of surgical draping and tourniquet. Digital photographs of the lateral aspect of the surgical limb were taken prior to and after the placement of standard surgical drapes and inflation of the tourniquet. The camera location for all of the photographs was perpendicular to the operative leg and consistently placed 183 cm from the table. The knee was centered within the camera's field of view, and the hip, knee, and ankle were fully visible prior to draping, after the knee had been partially draped, and after the knee had been fully draped and the tourniquet inflated.

Three board-certified orthopedic surgeons individually estimated the degree of knee flexion contracture from each of the photographs. The order of the resulting 69 images was randomized and the surgeons were blinded to their previous responses as well as the responses of the other surgeons.

The aforementioned results demonstrated a need to reduce the risk of uncorrected flexion contractures by providing surgeons with more accurate and reliable methods to measure knee flexion contractures during TKA. A simple, inexpensive tool that consisted of two inclinometers, both of which featured a freely moving angle indicator arm with an inferior counterweight, was developed with an inferior counterweight was developed (Biomet, Warsaw, IN, United States). After placement of the trial components, the inclinometers were used to measure the resulting degree of flexion contracture. The tibial inclinometer was designed to slide over the handle of the tibial trial inserter, and a set screw was tightened to ensure that it was properly fixed to the handle of the inserter. A drill pin was then inserted into the femoral trial, and the femoral inclinometer was placed on the drill pin (Figure 1). As the leg was positioned in approximately 30° of hip flexion, the degree of knee flexion contracture was measured as the difference between the 2 angles indicated on the tibial and femoral inclinometers. Simply put, if the two inclinometers were divergent when viewing from the lateral aspect of the knee, then full extension had not been achieved whereas if the two inclinometers were convergent, then the knee was in hyperextension. Full extension (0°) was present if the two were parallel.

Figure 1 Intraoperative use of the knee flexion contracture measuring device.

The resulting value was the combination of the angular difference between the femur and tibia, but also included the relative degree of flexion or extension of the femoral component and the degree of posterior slope of the proximal tibial cut (Figure 2). For example, a surgeon performing cruciate-retaining TKA preferred to make the proximal tibial cut with 3° of posterior slope. If in this example the femoral component was properly aligned in the sagittal plane (neither flexed nor extended), then the difference between the study device's two inclinometers would be -3° (the two pins would be convergent indicating hyperextension). The knee itself; however, would truly be in full extension (0°) as the 3° posterior slope of the tibial component would create the appearance of hyperextension.

Statistical analysis

To evaluate the errors of visual estimation, a repeated-measure analysis of variance was used to compare the estimated angles prior to and following the placement of the surgical drapes and tourniquet inflataion with the preoperative flexion contracture measured with the long-arm goniometer. To evaluate the efficacy of the novel device, we assessed the consistency of measurement and the ability to detect a change in angle. A single surgeon performed 6 knee flexion contracture measurements with the study device during 146 TKA procedures (141

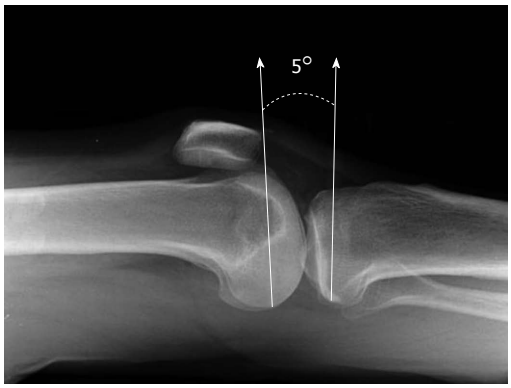

Figure 2 The effect of posterior slope of the proximal tibial cut on the measurements with the study device. If the femoral and tibial components were both placed perpendicular to the long axis of each bone as pictured, then the study device would indicate the presence of a 5° flexion contracture. However, if the proximal tibia was cut with 5° of posterior slope, it would give the false impression that full extension had been achieved as the two inclinometers would be parallel.

patients). Three of the measurements were made with the intended polyethylene thickness, and 3 measurements were taken with the insertion of a trial liner that was 2 mm thicker than the intended liner. An intraclass correlation coefficient (ICC) was calculated to assess the test-retest reliability for the 3 repeated flexion contracture measurements. To evaluate ability to detect a change in knee angle, we compared the measurements with the 2 different liner thicknesses using a paired *t* test. All statistical analyses were performed using SPSS Statistics version 20 (IBM, Armonk, NY, United States).

RESULTS

Prior to draping, the surgeons significantly overestimated the degree of flexion contracture but significantly underestimated the degree of contracture after draping (goniometric measurement = 6.1° ± 6.4°, pre-drape visual estimate = 6.9° ± 6.8°, post-drape visual estimate = 4.3° ± 6.1°, $P = 0.003$).

When evaluating the novel intraoperative measurement device, the measurements were highly reliable (ICC = 0.98), and the device indicated that 2.7° ± 2.2° of knee extension was lost with the insertion of a 2 mm thicker tibial liner. The device failed to detect a difference with the insertion of the 2 mm thicker liner in 9/146 cases (6.2%).

DISCUSSION

The purposes of this two-part study were to determine the effect of surgical draping and tourniquet inflation on visual estimation of knee flexion contractures, and develop and evaluate an inexpensive manual tool to provide surgeons with accurate and reliable measures of knee extension angle during TKA. It was evident after Part I of this study that the ability to correctly estimate the degree of extension during TKA becomes more difficult when the knee is draped.

On average, the three study surgeons visually estimated the knee extension angle to be 2.6° less when the knee was draped compared to estimates made prior to draping. This highlights the need for an intraoperative technique that allows more accurate evaluation of sagittal alignment to avoid fixed flexion contractures. Postoperative flexion contractures of even 1° may negatively affect clinical outcomes[1-6]. By limiting a patient's ability to properly accept weight during gait, flexion contractures cause patients to walk with a bent-knee gait, increasing contact forces in the patellofemoral joint of the involved knee[7,8]. Furthermore, postoperative flexion contractures have been demonstrated to create mechanical overloading of the contralateral knee during gait, potentially contributing to the progression of osteoarthritis in the contralateral knee[9]. As such, great care should be taken to properly correct flexion contractures during TKA.

The novel device used in this study provided a consistent method to intraoperatively measure knee flexion contractures without the added expense or operative time associated with computer-assisted navigation or other electronic sensors.

COMMENTS

Background

Fixed flexion contractures of even 1° have been reported to result in inferior outcomes after total knee arthroplasty (TKA). Despite the importance of correcting flexion deformities during surgery, the knee angle is often estimated visually.

Research frontiers

When visually estimating knee flexion contractures, surgeons significantly underestimated the contractures after draping.

Innovations and breakthroughs

The authors developed an intraoperative measurement device that was highly reliably and was able to detect a loss of knee extension with the placement of a 2 mm thicker trial polyethylene liner in 93.8% of cases.

Applications

The simple, inexpensive device used in this study may allow surgeons to more consistently correct flexion deformities during TKA.

Peer review

This is a well done, interesting paper, presenting strong data.

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BRIEF ARTICLE

Biomechanical characteristics of bone in streptozotocin-induced diabetic rats: An *in-vivo* randomized controlled experimental study

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Abstract

AIM: To investigate the *in vivo* effects of type I diabetes on the mechanical strength of tibial bone in a rodent model.

METHODS: The biomechanical effect of diabetes on the structural integrity of the tibia in streptozotocin induced diabetic Wistar rats was analysed. Induction of diabetes was achieved by an intra-peritoneal injection and confirmed by measuring serial blood glucose levels (> 150 mg/dL). After 8 wk the tibiae were harvested and compared to a control group. Biomechanical analysis of harvested tibiae was performed using a three-point bending technique on a servo hydraulic MTS 858 MiniBionix frame. Maximum force applied to failure (N), stiffness (N × mm) and energy absorbed (N/mm) were recorded and plotted on load displacement curves. A displacement control loading mode of 1 mm/min was selected to simulate quasi-static loading conditions. Measurements from load-displacement curves were directly compared between groups.

RESULTS: Fourteen streptozotocin induced diabetic Wistar rats were compared against nineteen non-diabetic controls. An average increase of 155.2 g in body weight was observed in the control group compared with only 5 g in the diabetic group during the experimental study period. Levels of blood glucose increased to 440.25 mg/dL in the diabetic group compared to 116.62 mg/dL in the control group.The biomechanical results demonstrate a highly significant reduction in the maximum load to failure from 69.5 N to 58 N in diabetic group compared to control (P = 0.011). Energy absorption to fracture was reduced from 28.2 N in the control group to 23.5 N in the diabetic group (P = 0.082). No significant differences were observed between the groups for bending stiffness.

CONCLUSION: Streptozotocin-induced diabetes in rodents reduces the maximum force and energy absorption to failure of bone, suggesting a predisposition for fracture risk.

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Key words: Streptozotocin; Rodent; Bone; Biomechanics

Core tip: The bones of streptozotocin-induced diabetic Wistar rats are more fragile with reduced toughness, characterized by a reduction in the capacity to absorb energy and with lower forces required to induce fracture in comparison to those in the control group. Our findings confirm previous studies and lend weight to the literature describing the detrimental relationship between the mechanical properties of bone subjected to diabetes mellitus. Further research needs to be conducted to ascertain whether uncontrolled diabetes in a human population affects the structural and biomechanical properties of bone.

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INTRODUCTION

Bone is a composite of organic collagen and inorganic crystalline hydroxyapatite. Bone loss in diabetes mellitus (DM) has been attributed to metabolic abnormalities, abnormal calcium concentration within cells, and high blood glucose levels[1]. DM interferes with the formation of the collagen network, therefore affecting the biomechanical integrity of bone. Any basis for reduction in bone integrity and material strength has yet to be accurately defined. A lack of insulin in *in vitro* experiments results in a reduction in ossification and calcification and a reduction in cartilage formation[2]. Furthermore, in rat studies the proliferation of osteoblasts and nucleotide synthesis[3,4] *in vitro* are associated with insulin binding through expression of insulin receptors[5]. Production of advanced glycation end products has also been implicated in the reduction of bone material strength in diabetes, through the non-enzymatic cross-linking of collagen[6,7]. Despite molecular evidence for this theory, mechanical data on the effect of diabetes on bone remain conflicting and sparse.

Clinical and experimental studies demonstrate that diabetes is associated with molecular and cellular changes with resultant alterations to bone physiology[8]. Patients with type 1 DM have been observed to exhibit a disproportionately high risk of fracture with reduced bone mass, leading to speculation that diabetic bone has reduced strength[9,10]. Furthermore studies indicate that diabetes exerts a similar effect on bone to that observed in the normal ageing process, with a predisposition to fracture susceptibility, delayed union and osteoporosis[11]. The biomechanical properties of bone in diabetes have been poorly addressed in the literature with conflicting results. Fleischli *et al*[12] demonstrated no differences in the material properties of human metatarsal bones when comparing younger diabetics to older non-diabetic donors. In a subsequent study on cadaveric human tibiae no significant differences were demonstrated between diabetic and non-diabetic specimens[13]. Animal studies suggest a reduction in bone mineral density as a direct consequence of DM. This is exhibited by bone loss in trabecular bone and failure to accrue cortical bone due to premature cessation of growth[14]. Further biomechanical experimental animal studies have demonstrated either increased stiffness[9,15] or reduced stiffness[16-18]. These variances are confusing but may be accounted for due to a number of factors. Stiffness as an indicator of overall bone strength alone is not the only significant biomechanical factor that can be affected by diabetes. Taken in isolation, changes in stiffness may be a consequence of a reduction in total whole bone strength. Any decoupling of stiffness or strength as a ratio may account for the reported differences observed in studies. Changes to strength may not only be an effect of the material strength of the tissues but also a consequence of differences in the size and shape of the bone being tested. Furthermore, the length of time that the rats were exposed to a diabetic state may also account for differences in results.

The aim of the current study is to examine and quantify the mechanical behavior of bone in streptozotocin-induced diabetic rats compared to normal controls.

MATERIALS AND METHODS

Animal model

The experimental protocol was ethically approved by the General Directorate of Veterinary Services (license No: K/7559/29-10-09) and by the Bioethics Committee of University of Athens Medical School, Hellas. The study was conducted in accordance with Hellenic legislation for experimental animal studies (P.D.160/91) and in compliance with European Union law (86/609/EEN.2015/92) and the Convention on Vertebrate Animals Protection for experimental or other scientific purposes (123/1986). Forty male Wistar rats aged 3 mo, weighing between 200-300 g were supplied by the Institute Pasteur. Wistar rats represent a close homology to the human type 1 DM phenotype, demonstrating comparable genetic and physiological characteristics. All animals had free access to food and water. Animals were randomly assigned to a control (C) or diabetic (D) group. Those assigned to the D group were induced to a diabetic state by an intra-peritoneal injection of streptozotocin at a dose of 55 mg/kg body weight. Streptozotocin is an agent known to be specifically toxic to the beta cells in the islets of Langerhans in the pancreas. The mechanism of action is thought to be mediated by alkylation of DNA bases, resulting in reduction of nicotinamide adenine dinucleotide. This, therefore, eliminates production of insulin and induces a hyperglycaemic state. After 1 wk, body weight estimation,

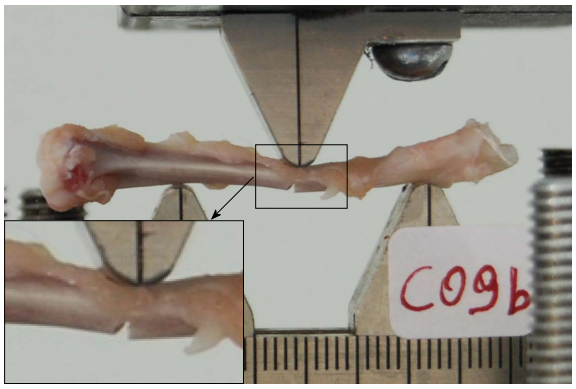

Figure 1 Mini-Bionix Frame with application of three-point bending at the mid diaphysis.

and glucose blood sampling was conducted to determine animals in a hyperglycemic state, defined as blood sugar > 150 mg/dL. Twenty-six animals were originally induced with streptozotocin to a diabetic state. Seven out of those 26 animals were excluded from the study (3 died and 4 did not respond) leaving 19 animals in the D group. The diabetic state was defined as polyuria and minimal weight gain post streptozotocin injection. Fourteen rats remained in the C group and compared with the 19 rats in the D group. Eight weeks after induction of diabetes, the animals were euthanized according to the Convention on Vertebrate Animals Protection for experimental scientific purposes (123/1986) using isoflurane gas and sodium-pentobarbital. Tibial bones were carefully dissected of soft tissue from each animal in each group, isolated and harvested for mechanical testing.

Biomechanical testing

Biomechanical analysis was performed by three-point bending mechanical tests. The experiments were conducted using a servo hydraulic MTS 858 Mini Bionix frame (MTS Systems, Eden Prairie, MN, United States). Tibiae were placed horizontally on the frame on rounded edges at a distance of 24 mm. Attention was paid to ensure all the specimens were placed in exactly the same manner with regards to position and orientation in an effort to minimize variability. The load was applied at the mid-shaft of the diaphysis using a punch with a rounded notch (Figure 1). The displacement control loading mode was selected. The rate of the imposed displacement was selected as 1 mm/min in an effort to simulate quasi-static loading conditions. The displacement was imposed continuously until fracture. The load-displacement curves and the maximal load at fracture in Newtons (N) were recorded. Failure was defined and observed by a propagation of an almost vertical fracture starting almost universally at the lower cortical bone surface. This is expected in bending tests of a brittle material because of the relatively lower tensile strengths compared to the respective opposite compressive strength.

Maximum force applied to failure (N), stiffness (N × mm) and energy absorbed (N/mm) were recorded and plotted on load-displacement curves. The maximum load is represented by the maximum compressive force applied until fracture. Deformation (strain) was defined as the degree of transverse displacement at the loading point. The initial non-linear curve corresponds to the adaptation of the specimens on the rounded edges of the loading device. The almost perfectly linear portion represents the linear elastic behavior of the tissue and the slope is equal to the stiffness. The nonlinear portion corresponds to the non-elastic (plastic) behavior of the tissue.

Statistical analysis

Statistical analysis on the groups was conducted using analysis of variance. An overall P value of < 0.05 was considered to be statistically significant.

RESULTS

Weight and glucose measurements

Table 1 demonstrates weight measurements and glucose measurements of both groups over the experimental study period. An average increase of 155.2 g in body weight was observed in the C group compared with only 5 g in the D group during the experimental study period. Levels of blood glucose increased to 440.25 mg/dL in the D group compared to 116.62 mg/dL in the C group.

Biomechanical analysis

Table 2 summarizes the differences in maximum force to failure, stiffness and energy-absorbed values recorded between the two groups. Maximal load to failure in C was 69.5 ± 10.3 N (mean ± SD) compared with a reduction to 58 ± 13.2 N (mean ± SD) in the D group. This demonstrated a statistically significant difference (P = 0.011). Stiffness measurements demonstrated no significant differences between the two groups. A statistically significant reduction (P = 0.019) was observed in measurements for energy absorption from 28.2 ± 5 N in the control group to 23.5 ± 5.6 N in the D group.

DISCUSSION

Our experimental randomized controlled study demonstrated the effect of diabetes on bone strength.

The literature on the association between bone strength and fracture risk in DM remains weak. The bone changes directly observed in DM can be attributed to a multitude of interrelated factors. Both the material and geometric properties of bone are implicated in influencing mechanical strength. Macroscopic structure (size and shape), architecture (cortical and cancellous components) and the bone substance (organic and inorganic components) are all influenced by DM. Furthermore, changes in collagen, elastin and proteoglycan concentrations, formation of advanced glycation end products and the orienta-

Table 1 Weight and blood glucose comparison between groups

	Prior to induction		One weekpost-induction		Ateuthanasia	
	C group	D group	C group	D group	C group	D group
Weight (g)	263.5	272.5	367	284.7	418.7	277.5
Glucose (mg/dL)	135.5	128.5	121.37	359.37	116.62	440.25

C group: Control group; D group: Diabetic group.

Table 2 Summary of biomechanical data (mean ± SD)

	Max force (N)	Stiffness (N × mm)	Energy (N/mm)
Diabetic group	58.0 ± 13.2	101.1 ± 30.2	23.5 ± 5.6
Control group	69.5 ± 10.3	118.4 ± 23.0	28.2 ± 5.0
P value	0.011	0.082	0.019

tion of collagen fibers are all important determinants of mechanical integrity, which are also affected.

In our study, we aimed to directly quantify whether an uncontrolled diabetic state directly alters the mechanical properties of appendicular long bone of tibiae, to add to the quality of published evidence that DM adversely affects bone quality. Immature rodents were used in an attempt to mimic the presentation of DM in humans, which typically occurs prior to skeletal maturity. Wistar rats were selected for the animal model as this genotype represents a close homology to DM in humans. We observed statistically significant changes in the D group, with reductions in maximum force and energy absorbed to failure demonstrating that the DM alters mechanical properties after as little as 8 wk. Interestingly, in our study we found no statistically significant differences in stiffness between C and D groups. Reported information on stiffness is conflicting in the literature, with some demonstrating increased[9] and other decreased values[16,18]. These variances are confusing but may be accounted to a number of factors. Stiffness as an indicator of overall bone strength alone is not the only significant biomechanical factor that can be affected by diabetes. Taken in isolation, changes in stiffness may be a consequence of a reduction in total bone strength. Any decoupling of stiffness or strength as a ratio may account for the reported differences observed in studies. The changes to strength therefore may not only be an effect of material strength of the tissues but also as a consequence of differences in the size and shape of the bone being tested. When values for stiffness are normalized against the geometry and structural shape of the bone, these differences in stiffness can be accounted for.

A number of experimental rodent studies exist documenting the biomechanical effects of bone in streptozotocin induced DM. These studies exhibit various experimental protocols. To our knowledge, eight studies exist evaluating bone mechanics using a type 1 diabetic model in rodent studies[9,14-16,19-22]. All these studies exhibit differences in their methodology, specifically duration of induced DM, species of rodent and diabetogen used to initiate DM. However, despite their differences these studies consistently demonstrate reductions in ultimate force to failure in the D groups, in keeping with the result of our study. The three studies which report on values for energy to failure[15,16,22] all demonstrate a reduction in energy to failure in the diabetic groups, in keeping with our analysis.

Our findings lend weight to the argument that DM (in a type 1 DM rodent model) reduces the mechanical behavior of bone. However, the changes that occur are probably not only to be result of changes in mechanical properties but are probably also due to inherent detrimental changes which occur in the structural material properties. This theory has been confirmed in a mouse model where significant differences were observed in the strength-structure relationship, with reductions to the tissue mineral density of bone in DM, which became apparent after only 10 wk[23].

Our experimental model subjected the D group of rats to uncontrolled levels of hyperglycaemia. This experimental protocol represents a scenario, which would only be representative of the small proportion of the human DM population who poorly control their blood glucose levels. It is likely be that our experimental model represents a worse case scenario. Conversely the duration that the rats were exposed to an uncontrolled hyperglycaemic state was only 8 wk. This is unlikely to represent the chronic human diabetic state. It is possible that subjecting the animals to a longer period of hyperglycaemia would cause further deterioration in the material properties of bone. This has been confirmed by Nyman *et al*[23] in a mouse model exposed to DM for up to 18 wk, in which further deterioration in mechanical properties was observed with longer exposure.

There are several limitations to our study. Firstly the duration of induced DM was only 8 wk, which may not be representative of the changes that occur chronically. It could be postulated that any effects on mechanical properties could be under-estimated and the further detrimental changes could have occurred if DM was allowed to continue. The experimental model also represents a scenario where DM remains unchecked with hyperglycemia allowed to develop without control. This model is unlikely to be representative of a clinical scenario where DM is treated and therefore represents a worse case presentation. Furthermore, this study did not investigate the effects of DM on bone structure and architecture. No histomorphometric analysis was conducted to investigate

whether the mechanical changes to the material observed, exhibited correlation to bone quality.

Although the pathogenesis of osteopenia in diabetes is a poorly understood phenomenon, decreased bone formation, mineralization and absorption seem to be associated with inferior mechanical properties of bone turnover in diabetes. These changes may be not so frequently observed in humans, as most people do not allow serum glucose levels to go unchecked and manage DM with strict administration of insulin therapy. Significant changes to bone biomechanics may, therefore, only be representative of a small cohort of human diabetics who have long-standing prolonged disease which is resistant to or poorly controlled by insulin therapy.

The bones of streptozotocin-induced diabetic Wistar rats are more fragile with reduced toughness characterized by a reduction in the capacity to absorb energy and with lower force required to induce fracture, in comparison to those in the control group. Our findings confirm previous studies and add weight to the literature investigating the detrimental relationship between the mechanical properties of bone subjected to DM.

COMMENTS

Background

Clinical and experimental studies demonstrate that diabetes is associated with molecular and cellular changes with resultant alterations to bone physiology. Patients with type 1 diabetes mellitus (DM) have been observed to exhibit a disproportionately high risk of fracture with reduced bone mass, leading to speculation that diabetic bone has reduced strength. The resultant biomechanical changes and properties of bone in DM have been poorly addressed in the literature with conflicting results.

Research frontiers

Experimental studies demonstrating alterations to physiology and structural changes to bone in DM is sparse and conflicting. Uncontrolled DM has been suggested to result in detrimental biomechanical properties of bone. Furthermore, studies indicate that diabetes exerts a similar effect on bone to that observed in the normal ageing process, with a predisposition to fracture susceptibility, delayed union and osteoporosis.

Innovations and breakthroughs

This study lends weight to the literature that an uncontrolled DM state in a rodent population induced by streptozotocin results in reduction in the biomechanical properties of bone, specifically with reduction in ultimate strength to failure and capacity to absorb energy.

Applications

By understanding how an uncontrolled diabetic state detrimentally alters bone biomechanics, future strategies to target diabetic patients may result in better bone health and reduction in osteoporosis and fracture risk.

Terminology

Wistar rats represent a close homology to the human type 1 DM phenotype, demonstrating comparable genetic and physiological characteristics. Thus, they likely to be the closest animal model representative of an uncontrolled diabetic state in humans.

Peer review

The authors examined the effects of an induced DM state and its relationship to the biomechanical properties of bone. Results revealed decreased bone quality and reduction in energy absorbing capacity. The results are interesting and may represent a close homology to the effects seen in the bone health of patients who have DM.

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BRIEF ARTICLE

Olecranon anatomy: Use of a novel proximal interlocking screw for intramedullary nailing, a cadaver study

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Abstract

AIM: To define the optimum safe angle of use for an eccentrically aligned proximal interlocking screw (PIS) for intramedullary nailing (IMN).

METHODS: Thirty-six dry cadaver ulnas were split into two equal pieces sagitally. The following points were identified for each ulna: the deepest point of the incisura olecrani (A), the point where perpendicular lines from A and the ideal IMN entry point (D) are intersected (C) and a point at 3.5 mm (2 mm safety distance from articular surface + 1.5 mm radius of PIS) posterior from point A (B). We calculated the angle of screws inserted from point D through to point B in relation to D-C and B-C. In addition, an eccentrically aligned screw was inserted at a standard 20° through the anterior cortex of the ulna in each bone and the articular surface was observed macroscopically for any damage.

RESULTS: The mean A-C distance was 9.6 mm (mean ± SD, 9.600 ± 0.763 mm), A-B distance was 3.5 mm, C-D distance was 12.500 mm (12.500 ± 1.371 mm) and the mean angle was 25.9° (25.9° ± 2.0°). Lack of articular damage was confirmed macroscopically in all bones after the 20.0° eccentrically aligned screws were inserted. Intramedullary nail fixation systems have well known biological and biomechanical advantages for osteosynthesis. However, as well as these well-known advantages, IMN fixation of the ulna has some limitations. Some important limitations are related to the proximal interlocking of the ulna nail. The location of the PIS itself limits the indications for which intramedullary systems can be selected as an implant for the ulna. The new PIS design, where the PIS is aligned 20° eccentrically to the nail body, allows fixing of fractures even at the level of the olecranon without disturbing the joint. It also allows the eccentrically aligned screw to be inserted in any direction except through the proximal radio-ulnar joint. Taking into consideration our results, we now use a 20° eccentrically aligned PIS for all ulnas. In our results, the angle required to insert the PIS was less than 20° for only one bone. However, 0.7° difference corresponds to placement of the screw only 0.2 mm closer to the articular surface. As we assume 2.0 mm to be a safe distance, a placement of the screw 0.2 mm closer to the articular surface may not produce any clinical symptoms.

CONCLUSION: The new PIS may give us the opportunity to interlock IMN without articular damage and confirmation by fluoroscopy if the nail is manufactured with a PIS aligned at a 20.0° fixed angle in relation to the IMN.

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Key words: Interlocking screw; Intramedullary nailing; Ulna fracture; Ulna anatomy

Core tip: Limitations of intramedullary nailing (IMN) of the ulna, which make IMN a secondary choice, include problems experienced at the proximal interlocking screw (PIS). A new PIS system may solve most common problems with an eccentrically aligned screw. This new PIS system may be very advantageous if the fluoroscopy time, operation time and the need for additional incision in other systems is considered. However, the screw must be designed at a safe angle to have these advantages. According to our results, a 20.0° is the optimum angle of alignment for this screw.

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INTRODUCTION

Intramedullary nailing (IMN) of the forearm has gained much popularity but still has some technical limitations, especially in relation to IMN of the ulna[1,2]. The proximal interlocking screw (PIS) is one of the critical steps in IMN of the ulna. Location of the PIS limits the indications for which IMN of the ulna can be used with currently available IM systems. IM systems are useless in fractures where the olecranon is involved. In addition, IM systems may be insufficient in proximal ulna fractures and may require extra caution to avoid damage to the articular surface when placed around the olecranon[1,2]. Currently available IMN systems of the ulna have the same inherent problems as all IMN, requiring an extra incision for the interlocking screw and prolonged radiation exposure of the surgical team because of the use of fluoroscopy.

A newly developed PIS system[3] solves these problems with an eccentrically aligned PIS (Figure 1) which is inserted through a hole located at the proximal tip of the nail.

In this *in vitro* study, we aim to identify the optimum angle of the eccentrically aligned PIS to the IMN in relation to the olecranon articular surface.

MATERIALS AND METHODS

Ulna bones of 36 dry bony cadavers were used. The proximal parts of the ulnas were split sagitally into two equal pieces. The deepest point of the incisura olecrani (A) was identified for each ulna. A horizantal line was drawn longitudinally at the middle of the medulla and a vertical line was drawn from point A perpendicular to this line. The point where these lines intersected (C) and the ideal IMN entry point (D) were also identified for each ulna. Then a point (B) was identified, located on the A-C line and 3.5 mm posterior to point A. 3.5 mm is the sum safe distance from the articular surface (2 mm) and the radius of PIS (1.5 mm) (Figure 2). Then, we calculated the angles of the screws when inserted from point D through to point B using the following formula: tanα = B-C/C-D (Figure 2).

Figure 1 Eccentrically aligned proximal interlocking screw.

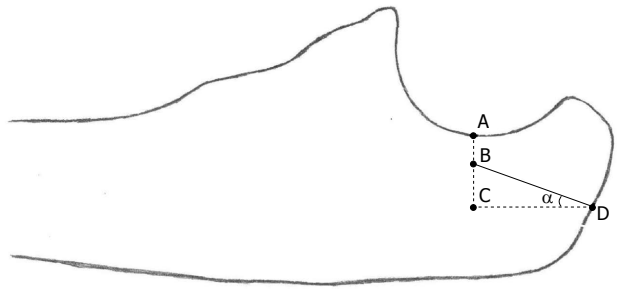

Figure 2 Olecranon anatomy, related to a novel proximal interlocking screw for intramedullary nailing. A: Deepest point of the incisura olecrani; B: The point, which is 3.5 mm posterior to A point and targeted during insertion of the proximal interlocking screw; C: The point where the line from the middle of the medulla and the line perpendicular to point A intersect; D: Ideal entry point for intramedullary nail.

In addition, taking into consideration the measured angles, a screw alligned eccentrically in relation to the IMN was inserted at a standard 20° through the anterior cortex of the ulna in each bone as a PIS and the articular surface was observed macroscopically for any damage.

RESULTS

The mean A-C distance was 9.600 mm (range 8.500-11.000 mm, SD = 0.763 mm). The mean A-B distance was 3.5 mm for each ulna. The mean C-D distance was 12.500 mm (range 10.000-14.600 mm, SD = 1.371 mm). The mean angle was 25.9° (range 19.3°-29.2°, SD = 2.0°) (Table 1). Lack of articular damage was observed macroscopically for each bone after the 20.0° eccentrically aligned screws were inserted.

DISCUSSION

Intramedullary nail fixation systems have well known biological and biomechanical advantages for osteosynthesis. However, in addition to these well-known advantages, intramedullary nail fixation of the ulna has some limitations[1,2]. Some important limitations are related to the PI of the ulna nail. The location of the PIS itself limits the indications for which intramedullary systems can be selected as an implant for the ulna.

Table 1 The A-C distance, C-D distance and angle for each ulna

Ulna No.	A-C distance (mm)	C-D distance (mm)	Angle (°)
1	9.7	11.2	24.9
2	9.4	13.8	23.1
3	9.0	12.0	24.6
4	8.5	14.3	19.3
5	8.9	13.4	21.9
6	11.0	14.6	27.2
7	10.1	13.6	25.9
8	10.4	12.4	29.1
9	11.0	13.4	29.2
10	11.0	14.6	27.2
11	9.0	11.7	25.2
12	8.7	10.6	26.1
13	10.2	14.0	25.6
14	10.5	13.2	27.9
15	9.3	12.9	24.2
16	9.8	12.4	26.9
17	10.0	14.5	24.1
18	9.5	12.8	25.1
19	9.5	12.7	25.3
20	8.8	10.7	26.3
21	10.1	13.5	26.0
22	11.0	14.5	27.3
23	9.0	10.7	27.2
24	9.6	12.1	26.7
25	9.9	12.5	27.1
26	8.7	11.3	24.7
27	8.9	10.2	27.9
28	10.8	13.6	28.2
29	9.0	11.0	26.6
30	9.0	10.6	27.4
31	8.9	10.1	28.1
32	8.6	12.5	22.2
33	9.3	12.7	24.5
34	10.1	13.1	26.7
35	9.8	12.4	26.9
36	8.7	10.0	27.4
Total, mean ± SD (range)	9.600 ± 0.763 (8.500-11.000)	12.500 ± 1.371 (10.000-14.600)	25.9 ± 2.0 (19.3-29.2)

Intramedullary fixation systems are inadequate for fractures of the proximal ulna especially if the olecranon is involved. There is usually not enough bone stock to put a PIS into proximal fractures even if the fracture is slightly distal to the olecranon[4]. If the fracture is to the proximal part of the ulna or at the level of the olecranon, the screw should be inserted perpendicular or oblique to the articular surface[5-7]. This requires the selection of a PIS to avoid disturbing the joint, and this may not provide adequate stability. Moreover, there may be irritatation of the ulnar nerve if the PIS is aligned parallel to the articular surface of the olecranon[5]. Gehr and Friedl developed an intramedullary device for olecranon fractures, although this device cannot be used for segmental fractures, which also involve distal fractures, and they reported ulnar nerve irritation. The new PIS design allows the fixing of fractures even at the level of the olecranon without disturbing the joint when the PIS is aligned 20.0° eccentrically to the nail body. It also allows the eccentrically aligned screw to be inserted in any direction except through the proximal radio-ulnar joint.

Radiation exposure tends to be underestimated by surgeons[8,9]. Proximal interlocking always requires fluoroscopic confirmation. Currently available intramedullary nails for the ulna require quite long fluoroscopy time, even up to 150 min[7]. By contrast, with the new PIS system floroscopy usage is optional, provided preoperative measurements are done properly.

The PIS usually requires an additional incision[6,10,11]. In the new PIS system, the screw is inserted from the proximal tip of the nail. There is no need for an additional incision for PI other than the incision used for insertion of the IM nail, which means no additional soft tissue damage.

An eccentrically aligned PIS with a fixed angle may provide important advantages. The angle between the nail and screw has critical importance to the articular surface of the olecranon.

Taking into consideration our results, we use a 20° eccentrically aligned PIS for all ulnas by. In our results, the angle required to send the PIS was less than 20° (19.3°) for only one bone (No. 4). However, 0.7° difference corresponds to placement of screw only 0.2 mm closer to the articular surface. As we assume 2.0 mm to be a safe distance, a 0.2 mm closer placement of the screw to the articular surface may not produce any clinical symptoms. Moreover, as far as we know, there are no previous studies which have considered the safe distance between the screw and the articular surface of the olecranon. As a result, the lack of macroscopic articular surface damage in case 4, like all others, may be evidence of the safety of this system.

As a result, this new PIS system may be very advantageous if the fluoroscopy time, operation time and the need for additional incision compared to other systems is considered. However, the screw must be positioned at a safe angle to have these advantages. According to our results, a 20° is the optimum angle of alignment for the screw.

COMMENTS

Background

Intramedullary nail fixation systems have well known biological and biomechanical advantages for osteosynthesis. Limitations of intramedullary nailing (IMN) of the ulna, which makes IMN a secondary choice, includeproblems experienced at the proximal interlocking screw (PIS).

Research frontiers

Location of the PIS limits the indications for use of IMN of the ulna in currently available intramedullary systems. A new PIS system may solve most common problems with an eccentrically aligned screw. The purpose of this *in vitro* study was to define the optimum safe angle of eccentrically aligned PIS for IMN.

Innovations and breakthroughs

Intramedullary systems may be insufficient in proximal ulna fractures and may require extra caution not to damage the articular surface when placed around the olecranon. Currently available IMN systems of the ulna have the same inherent problems as all IMN, requiring an extra incision for the interlocking screw and prolonged radiation exposure of the surgical team because of the use of fluoroscopy. The new PIS may give the authors the opportunity to interlock the IMN without articular damage and confirmation by fluoroscopy if the nail is manufactured with a PIS aligned at a 20° fixed angle in relation to the IMN.

Applications

The new PIS design allows fixing fractures even at the level of the olecranon without articular damage and confirmation of fluoroscopy.

Terminology

Intramedullary nailing: A rod of metal, or other material for fixation of fragments

of fractured bones, in this study for ulna fractures. Interlocking screw: A screw which passes through the IMN perpendicular to its long axis and prevents the nail to migrate or rotate within the bone.

Peer review

This new PIS system may be very advantageous if the fluoroscopy time, operation time and the need for additional incision at other systems is considered. However, it must be designed at a safe angle to have these advantages. According to these results, 20° is the optimum angle of alignment for this screw.

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BRIEF ARTICLE

Comparison of straight median sternotomy and interlocking sternotomy with respect to biomechanical stability

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Abstract

AIM: To increase the stability of sternotomy and so decrease the complications because of instability.

METHODS: Tests were performed on 20 fresh sheep sterna which were isolated from the sterno-costal joints of the ribs. Median straight and interlocking sternotomies were performed on 10 sterna each, set as groups 1 and 2, respectively. Both sternotomies were performed with an oscillating saw and closed at three points with a No. 5 straight stainless-steel wiring. Fatigue testing was performed in cranio-caudal, anterio-posterior (AP) and lateral directions by a computerized materials-testing machine cycling between loads of 0 to 400 N per 5 s (0.2 Hz). The amount of displacement in AP, lateral and cranio-caudal directions were measured and also the opposing bone surface at the osteotomy areas were calculated at the two halves of sternum.

RESULTS: The mean displacement in cranio-caudal direction was 9.66 ± 3.34 mm for median sternotomy and was 1.26 ± 0.97 mm for interlocking sternotomy, $P < 0.001$. The mean displacement in AP direction was 9.12 ± 2.74 mm for median sternotomy and was 1.20 ± 0.55 mm for interlocking sternotomy, $P < 0.001$. The mean displacement in lateral direction was 8.95 ± 3.86 mm for median sternotomy and was 7.24 ± 2.43 mm for interlocking sternotomy, $P > 0.001$. The mean surface area was 10.40 ± 0.49 cm² for median sternotomy and was 16.8 ± 0.78 cm² for interlocking sternotomy, $P < 0.001$. The displacement in AP and cranio-caudal directions is less in group 2 and it is statistically significant. Displacement in lateral direction in group 2 is less but it is statistically not significant. Surface area in group 2 is significantly wider than group 1.

CONCLUSION: Our test results demonstrated improved primary stability and wider opposing bone surfaces in interlocking sternotomy compared to median sternotomy. This method may provide better healing and less complication rates in clinical setting, further studies are necessary for its clinical implications.

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Key words: Median sternotomy; Interlocking stenotomy; Stability; Osseos healing; Biomechanics

Core tip: Sternal healing after median sternotomy can be compromised by an unstable closure. In this *in vitro* study, we found that the biomechanical characteristics of the median interlocking sternotomy were superior to those of the straight median sternotomy. The zigzag cuts made the sternotomy line significantly more stable and provided more surface area

for bony healing. These improved features are highly associated with improved bony healing. We believe that the interlocking sternotomy will decrease the complications associated with sternotomy in clinical basis by providing a better bony healing.

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INTRODUCTION

Median sternotomies are the most commonly performed osteotomy in the world[1]. Sternotomy is the best transsternal approach for accessing lesions localized to the vertebral bodies of the upper thoracic spine[2,3], and it is a standard incision for thoracic and cardiac surgery.

Despite the popularity of median sternotomy, complications such as nonunion, persistent pain, and infection occur in 0.3% to 5% of cases and are associated with a 14% to 47% mortality rate if mediastinitis supervenes[4]. The morbidity, mortality, and expenses associated with these complications continue to make their prevention and treatment of great importance.

The continuous motion between the halves of the divided sternum resulting from the lack of immobilization causes postoperative sternal instability[5], which is the most important factor in postoperative morbidity and mortality. Providing greater stability[3,4,6] and promoting primary osseous healing is crucial for preventing these complications[7-11].

More than 40 different techniques have been described for closing median sternotomy[12-16]. The biomechanical characteristics of different sternal closures may substantially improve sternotomy reduction and stability[17-19]. In particular, interlocking sternotomy appears to offer better stability and greater surface area for bone healing than other techniques. However, the biomechanical characteristics of this technique have not been assessed. Accordingly, in this experimental study, we compared the biomechanical characteristics of interlocking sternal closure with those of straight sternal closure in a study of sheep sterna.

MATERIALS AND METHODS

We obtained sterna freshly isolated from the sterno-costal joints of the ribs of 20 sheep (Ovis ammon aries) in same age and weight from slaughterhouse. We had institutional ecthical approval from Marmara University ethical committee. Median straight (Figure 1A) and interlocking (Figure 1B) sternotomies were performed on 10 sterna each.

Sternotomy procedure

Interlocking sternotomy was created with 3 zigzag osteotomy lines approximately 150 degrees to each other in the coronal plane. Each osteotomy line was perpendicular to the previous line in the axial plane (Figure 2). Median sternotomy was performed as a straight osteotomy line in the cranio-caudal (CC) direction. We measured the dimension of the cut surface and simply calculated the area of surface for interlocking sternotomy and median sternotomy.

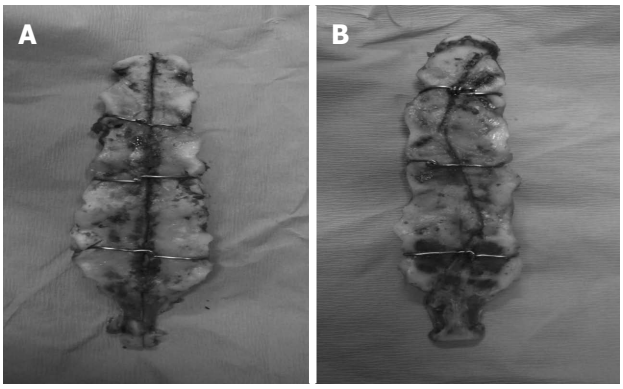

Figure 1 Sternotomy. A: Fixated median straight sternotomy, anterior view; B: Fixated interlocking sternotomy, anterior view.

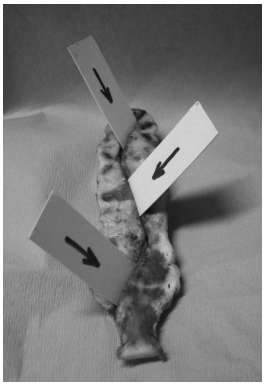

Figure 2 Sternotomy planes of interlocking sternotomy. Each zigzag osteotomy line was perpendicular to the previous line in the axial plane, which are showed with arrows.

Both sternotomies were performed with an oscillating saw and closed at three points with No. 5 straight stainless-steel wiring (Figure 1). The wire tension during closure is done by free hand, with 5 times twisting the wire for each suture.

The sterna were attached to custom fixtures designed to produce displacement in one of three directions: (1) CC shear; (2) anterio-posterior (AP) shear; and (3) lateral (distraction) shear. The test was done in CC, AP and distraction directions sequentially. The fixtures designed to have 3 grasping jigs in 3 directions like the x, y and z dimensions.

Biomechanical testing

Fatigue testing was performed by a computerized materials-testing machine (High Capacity 8802, Instro, Norwood, MA, United States). The sterna were attached (Figure 3) to custom fixtures designed to produce dis-

Table 1 Biomechanical characteristics of median sternotomies in fresh sheep sterna 4 d after surgery

Characteristic	Median straight sternotomy (n = 8), mean (range)	Median interlocking sternotomy (n = 8), mean (range)	Difference (95%CI)
CC displacement, mm	9.66 ± 3.34 (5.24 to 15.35)	1.26 ± 0.97 (0.3 to 2.8)	6.08 to 10.71 $P < 0.001$
AP displacement, mm	9.12 ± 2.74 (5.48 to 14.78)	1.20 ± 0.55 (0.3 to 2.5)	6.06 to 9.77 $P < 0.001$
Lateral displacement, mm	8.95 ± 3.86 (5.1 to 17.1)	7.24 ± 2.43 (3.26 to 11.11)	-1.32 to 4.74 $P > 0.001$
Surface area, cm²	10.40 ± 0.49 (9.6 to 10.9)	16.8 ± 0.78 (15.3 to 18.3)	-7.01 to 5.78 $P < 0.001$

CC: Cranio-caudal; AP: Anterio-posterior.

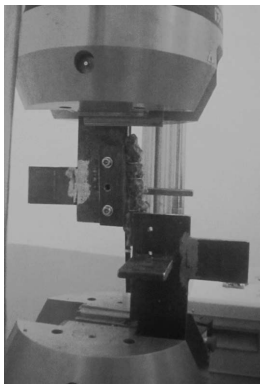

Figure 3 The sterna were attached to custom fixtures designed to produce displacement in one of three directions.

placement in one of three directions: (1) CC shear; (2) AP shear; and (3) lateral (distraction) shear. The displacement between the halves of the sternum was measured and recorded automatically by the testing device.

Fatigue testing was performed by cycling between loads of 1 and 400 N per 5 s (0.2 Hz) for 60 cycles of distraction and release. One sterna in each group was distracted for 180 cycles. The test was ended if the wires were torn from the bone or if the bone broke.

Statistical analysis

Mean displacement was measured after completion of distraction in all three directions and was compared between the two groups with Student's t test for independent groups. The data conformed to the assumptions of the t test, and all tests were two-tailed. Alpha was set at 0.05. The "SPSS 16.0" statistical software program was used in the analyses was used.

RESULTS

Two sterna in each group broke during the calibration of the testing machine so they were excluded from analyses. Fractures were related to fixation apparatus not related to test, and after the fractures it was revised and test began from the beginning. Displacement in all directions was smaller in the interlocking sternotomies (Table 1).

The mean displacement in CC direction was 9.66 ± 3.34 mm for median sternotomy and was 1.26 ± 0.97 mm for interlocking sternotomy, $P < 0.001$. The mean displacement in AP direction was 9.12 ± 2.74 mm for median sternotomy and was 1.20 ± 0.55 mm for interlocking sternotomy, $P < 0.001$. The mean displacement in lateral direction was 8.95 ± 3.86 mm for median sternotomy and was 7.24 ± 2.43 mm for interlocking sternotomy, $P > 0.001$. The mean surface area was 10.40 ± 0.49 cm² for median sternotomy and was 16.80 ± 0.78 cm² for interlocking sternotomy, $P < 0.001$. The displacement in AP and cranio-caudal directions is less in group 2 and it is statistically significant. Displacement in lateral direction in group 2 is less but it is statistically not significant. Surface area in group 2 is significantly wider than group 1.

DISCUSSION

Normal breathing, coughing, and movement apply pressure to the sternum, creating a combination of lateral displacement forces and anterior-posterior shear and cranial-caudal shear[20]. After sternotomy, these forces can interfere with bony healing and cause serious complications[21-23]. An unstable sternotomy can increase postoperative sternal pain, which can lead to atelectasis and pneumonia, secondary to a decreased inspiratory effort[9]. Other serious complications related to instability include sternal dehiscence, deep sternal infection, fulminant medistinitis, osteomylelitis, and chronic sternal instability[4,24-26]. These complications are associated with a 14% to 47% mortality rate[4]. Providing a more stable osteotomy and improving sternal osteosynthesis is the best way to prevent these complications[3,4,27,28].

More than 40 different techniques with various materials have been described for sternal closure[12-16]. Most techniques revolve around a different pattern of wire cerclage, rigid plate fixation, or various non-rigid methods of closure[29-36]. The techniques those provide more rigid fixation are associated with relatively fewer wound infection and even mortality[3]. However, one has to consider the movements of sternal halves at AP and CC directions. Current methods provide sufficient lateral stability, but does not provide adequate AP and CC stability[20]. Due to this three dimensional movement of sternum during physiological activities, providing stability in AP and CC directions is important as well as stability in lateral direction.

The sternal fixation with using plate and screw provides relatively more stability in AP and CC directions. However, this method has some serious disadvantages[3]. Drilling into the sternum increases the obvious risks to the heart and bypass conduits[3], and the costs of plate fixation are about 10 times higher than those of wire fixation[6]. In addition, the screw holes closest to the midline tend to break through the adjacent bone[6]. That is

why the plate and screw fixation does not gain popularity. Also, in an *in vitro* study, Saito *et al*[35] compared wire fixation with wire fixation plus an intrasternal pin. The intrasternal pin was presented, as a technical modification required increasing stiffness in the AP and CC directions. Intrasternal pin fixation did provide significantly more stability than did wire fixation alone. However, the clinical application of this technique is not reported yet.

Current methods aiming to increase the stability of sternotomy are focused on different implants and configuration of suturing with wire. On the other hand, it is well known that, improving the stability of an osteotomy line can be increased by selecting the correct osteotomy technique[37,38]. In our study, we focused on decreasing AP and CC interfragmentary motion at the same time by changing the configuration of the osteotomy line itself. In our literature search we determined, two clinical studies have shown that the stability of the sterna can be increased by the sternotomy configuration itself. Joshi *et al*[36] performed a lazy-S-shaped sternotomy, which minimized post-operative pain, was also associated with better respiratory function, and reduced rates of sternal dehiscence and mediastinitis. Lee *et al*[39] performed curvilinear paramedian sternotomy and found this technique ensuring precise open reduction and internal fixation. These results may indicate that the changing the sternotomy technique prevents CC motion, on the other hand, these sternotomy techniques still does not prevent the AP motion.

In our study, we focused on decreasing AP and CC interfragmentary motion at the same time by changing the configuration of the osteotomy line itself. The interlocking osteotomy created an inherently more stable closure that was less affected by displacement and shear forces and that provided a greater mean surface area than that provided by straight sternotomies. Although the interlocking sternotomy indirectly reduced lateral displacement, the amount of displacement was not statistically significant.

Increasing the opposing surface areas of an osteotomy is important for primary bone healing[36]. The interlocking sternotomy maximizes the opposing surfaces of the sternal halves. By preventing the slippage of sternal ends in the AP and CC directions, the interlocking sternotomy ensures appropriate approximation during closing and should substantially improve the osseous healing.

In this *in vitro* study, we found that the biomechanical characteristics of the median interlocking sternotomy were superior to those of the straight median sternotomy. The zigzag cuts made the sternotomy line significantly more stable and provided more surface area for bony healing. Our method does not require any extra equipments or implants. The wires are used as fixation material, already employed and the surgeons are familiar with. Also this technique does not require surgeons to make great changes in their routine practice. It is possible to make this sternum incision with sternotomy saws in routine use. We believe that the interlocking sternotomy provide a significantly more stable sternotomy without extra costs. Although no clinical or animal experiment study has been performed with interlocking sternotomy, our biomechanical study may be evidence of superiority in primary osseos healing if interlocking sternotomy is performed in clinical practice.

COMMENTS

Background

The continuous motion between the halves of the divided sternum resulting from the lack of immobilization causes postoperative sternal instability, which is the most important factor in postoperative morbidity and mortality. Providing greater stability and more surface area promoting primary osseous healing is crucial for preventing these complications.

Research frontiers

Interlocking sternotomy appears to offer better stability and greater surface area for bone healing than other techniques. However, the biomechanical characteristics of this technique have not been assessed. In this study, authors compared the biomechanical characteristics of interlocking sternal closure with those of straight sternal closure in a study of sheep sterna and compared the surface area of two osteotomies.

Innovations and breakthroughs

More than 40 different techniques with various materials have been described for sternal closure. The techniques those provide more rigid fixation are associated with relatively fewer wound infection and even mortality. Current methods provide sufficient lateral stability, but do not provide adequate anterio-posterior (AP) and cranio-caudal (CC) stability. Interlocking sternal closure provide stability in AP, CC and in lateral direction and more surface area.

Applications

Authors believe that the interlocking sternotomy provide a significantly more stable sternotomy and more surface area for bony healing so decreasing the complications without extra costs.

Terminology

The interlocking sternotomy is a zigzag cut in three dimension. CC movement is a movement of one half of sternum superior while the other half inferior.

Peer review

The sterna were attached to custom fixtures designed to produce displacement in one of three directions: (1) CC shear, (2) AP shear, and (3) lateral (distraction) shear. The displacement between the halves of the sternum was measured and recorded automatically by the testing device. The zigzag cuts made the sternotomy line significantly more stable and provided more surface area for bony healing.

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BRIEF ARTICLE

Relationship of knowledge about osteoporosis with education level and life habits

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Abstract

AIM: To assess possible relationships of knowledge and related factors with educational level and osteoporosis-related life habits.

METHODS: This was a cross sectional study conducted on 268 women (≥ 35 years old) from June 2011 to August 2011. The sample collection was done in outpatient clinics in three university hospitals in Isfahan, Iran. We used a demographic questionnaire containing questions that evaluated osteoporosis-related life habits, including exercise, smoking, intake of calcium and vitamin D supplements and so on. We also used the Osteoporosis Knowledge Assessment Tool to measure osteoporosis knowledge of women.

RESULTS: The mean level of knowledge about awareness of osteoporosis, its risk factors and preventive factors were 56, 55 and 22, respectively. The relationship of education level and awareness of osteoporosis, its risk factors and preventive factors was significant, with R = 0.76, R = 0.73 and R = 0.83, respectively (P < 0.001). The relationship of education level and osteoporosis-related life habits was not significant (R = 0.03 and P = 0.56). The relationship of osteoporosis-related life habits and awareness of osteoporosis and its risk factors was significant, with R = 16%, P = 0.006 and R = 16%, P = 0.008, respectively, but the relationship of osteoporosis-related life habits and preventive factors was not significant (R = 0, P = 0.99).

CONCLUSION: Iranian women with a higher education level have significantly better knowledge about osteoporosis than women with a lower educational level but they do not use this knowledge in their life.

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Key words: Osteoporosis; Knowledge; Education; Life habits; Relationship

Core tip: Osteoporosis, a serious health problem that diminishes quality of life, is a systemic skeletal disorder, characterized by reduction in bone mass, increasing bone fragility and fracture risk. Iranian women with a higher education level have significantly better knowledge about osteoporosis than women with a lower educational level but they do not use this knowledge in their life.

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INTRODUCTION

Osteoporosis, a serious health problem that diminishes quality of life, is a systemic skeletal disorder, characterized by reduction in bone mass, increasing bone fragility and fracture risk[1,2]. It has often been viewed as a disease affecting women[3]. Approximately 40%-50% of women sustain osteoporotic fractures in their lifetime[1,2]. The progress of decrease in bone mass is typically asymptomatic but in many women is manifested with clinical presentations, including acute back pain, fragility fractures (hip, vertebra, proximal femur and tibia), compression of mid-thoracic and upper lumbar vertebrae and progressive deformation of the spinal column that leads to limited back mobility and reduction in height[4-7]. Based on bone mineral density (BMD) testing, the World Health Organization (WHO) clinically defines osteoporosis by a BMD T-score ≥ 2.5 SD below the mean bone mass density in healthy, young normal women[8,9].

Many risk factors for osteoporosis have been identified: female sex, with a prevalence 4 times that of men; Asiatic and Caucasian races; old age, with a high percentage of osteoporosis among women over 70 years old; a family history of osteoporosis or fragility fractures; low body weight (less than 51.8 kg); premature menopause (menopause before 45 years of age); nulliparity; prolonged lactation; prolonged amenorrhea unrelated to menopause; inadequate consumption of a diet containing calcium and vitamin D; poor intestinal absorption of calcium; lactose intolerance; excessive caffeine and alcohol consumption; smoking; sedentary lifestyle; and prolonged treatment with thyroid hormones, glucocorticoids, anticonvulsants, aluminum antacids and anticoagulants[1,10].

The most important preventive habits are weight-bearing exercises (*e.g.*, going up and down stairs, jogging, aerobics, swimming and isometrics, for at least 30 min daily), diet or supplements containing adequate levels of calcium and vitamin D, and absence or cessation of smoking and moderate or less alcohol and caffeine consumption[7,11]. A study in the United States revealed that a high proportion of women were unaware of the association between cigarette smoking and osteoporosis[12].

Physical activities continue to stimulate increases in bone diameter throughout the lifespan. These exercise-stimulated increases in bone diameter diminish the risk of fractures by mechanically counteracting the thinning of bones and increases in bone porosity. Exercise should be dynamic, exceed a threshold intensity and strain frequency, be relatively brief but intermittent, and also be supported by unlimited nutrient energy and adequate calcium and vitamin D3 supplements[13].

A study of American women (≥ 25 years) showed that knowledge about osteoporosis was limited[14]. Although calcium intake was sufficient in most cases, the amount and type of physical activity was not enough for their age. Other studies of Caucasian and African-American women found that most had heard about osteoporosis but few women had adequate exercise or the recommended intake of calcium per day[15,16]. Another study in Australia showed that Asian women living in Australia also had a low calcium intake (< 800 mg/d) and their knowledge about osteoporosis was limited[17]. A study in Mexico of women aged 50-59 years showed that about 90% of subjects had knowledge about the relationship of menopause and osteoporosis but most subjects were not aware of other risk factors and incorporated life habits that increase the risk of osteoporosis[18]. Two studies of women of Hispanic origin in the United States have shown different results. One study found that more than 37% of women had habits preventing osteoporosis, including taking calcium supplements and getting enough physical exercise. It was mostly attributed to prior health education, knowledge about osteoporosis and bone-mass evaluations offered by healthcare services[19]. The other study of both Hispanic and African-American women found that most women in both groups had little knowledge of behaviors that increase and maintain bone mass, less than 50% of women had regular physical exercise, and less than 10% had adequate calcium intake[20]. Bisphosphonates are antiresorptive drugs widely used to treat osteoporosis. Denosumab 60 mg subcutaneously every 6 mo is an approved treatment for women with postmenopausal osteoporosis (PMO) who are at high risk for fracture[21,22].

In this study, we aimed to assess the possible relationships of the level of knowledge and related factors with educational level and osteoporosis-related life habits (including exercise, calcium and vitamin D intake) among Iranian women aged ≥ 35 years.

MATERIALS AND METHODS

Ethics

This work was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association and was approved ethically by Al-Zahra University Hospital Trust (988/l.786). All patients provided informed written consent.

Patients and settings

This was a cross sectional study conducted on 268 women (≥ 35 years old) from June 2011 to August 2011. The sample collection was done in outpatient clinics (except orthopedic and rheumatology) in three university hospitals in Isfahan, Iran.

We used a demographic questionnaire containing questions that evaluated osteoporosis-related life habits (including exercise, smoking, daily consumption of milk,

Table 1 Relationship of level of knowledge about osteoporosis with education level and related life habits with a Persian version of the osteoporosis knowledge assessment tool

	Awareness of osteoporosis	Risk factors	Preventive factors	Osteoporosis-related life habits
Education level	R = 0.76/ $P < 0.001$	R = 0.73/ $P < 0.001$	R = 0.83/ $P < 0.001$	R = 0.03/ $P = 0.56$
Osteoporosis-related life habits	R = 16/ $P = 0.006$	R = 16/ $P = 0.008$	R = 0/ $P = 0.99$	

intake of calcium and vitamin D supplements, usage of certain drugs such as contraceptives and exposure to sunlight) and the Osteoporosis Knowledge Assessment Tool (OKAT), an instrument to measure knowledge about osteoporosis of women[23]. The Persian version of the OKAT was tested in a pilot study and 10 adult women filled out a scale for "cognitive debriefing" which was evaluated by four orthopedic surgeons for a "clinician's review"[24].

Statistical analysis

We used Cronbach's alpha to evaluate the internal consistency of OKAT, which was 77%. To evaluate education level, Spearman's correlation was used. Pearson's correlation was applied to determine the relationship of the level of knowledge and osteoporosis-related life habits. $P < 0.05$ was considered as significant. SPSS for Windows, Version 16.0, was used for statistical analyses.

RESULTS

The study involved 268 adult women older than 35 years. Ninety seven percent were married and 94.8% of them did not have other diseases (4% had thyroid disease, 2.6% had diabetes and 2.2% had other diseases). Regarding the education level, 68.6%, 16.4% and 15% of participants had the education level below high school diploma, high school diploma, and academic education, respectively. Nonsmokers comprised 97.4% of the sample. Ninety five point nine percent of women did not exercise regularly. Among the women in the study, 41% had at least 30 min exposure to sunlight every day. Ninety seven point six percent and 98.2% of participants had no intake of calcium and vitamin D supplements, respectively. Only 19.8% regularly consumed daily milk. Forty percent of women were post-menopausal, of whom just 1.3% have received replacement hormone therapy. Ninety eight point five percent of women in our study did not undergo any assessments to evaluate osteoporosis. Sources of their information were television (40%), radio (27%), books (14%), newspapers (11%) and other people (8%).

The mean level of knowledge about osteoporosis, its risk factors and preventive factors were 56, 55 and 22, respectively. Thus, mean level of knowledge about osteoporosis was 44.3 in total. Means were calculated between "0 to 100". The relationship of education level and awareness of osteoporosis, its risk factors and preventive factors was significant with R = 0.76, R = 0.73 and R = 0.83, respectively ($P < 0.001$). The relationship of education level and osteoporosis-related life habits was not significant (R = 0.03 and $P = 0.56$). The relationship of osteoporosis-related life habits and awareness of osteoporosis and its risk factors was significant with R = 16, $P = 0.006$ and R = 16, $P = 0.008$, respectively, but the relationship of osteoporosis-related life habits and preventive factors was not significant (R = 0, $P = 0.99$) (Table 1).

DISCUSSION

Women's knowledge about osteoporosis was poor or limited among our subjects; therefore, health educational programs and health services regarding osteoporosis are necessary. This finding is consistent with previous studies in Taiwan, Brazil, Australia and the United States[14,23,25,26]. In contrast, a study in Sweden showed that performing a general intervention program concerning the knowledge of osteoporosis in participants is not effective[27].

We found that there was a significant relationship of level of knowledge and education but the relationship of education level and osteoporosis-related life habits was not significant. The relationship of osteoporosis-related life habits and awareness of osteoporosis and its risk factors was significant but there was no significant relationship of osteoporosis-related life habits and preventive factors. The present results show that Iranian women with a higher education level have significantly better knowledge about osteoporosis than women with a lower educational level, similar to Chinese women in Singapore and Salvadoran women in Brazil[26,28], but they do not use this knowledge in their life. For instance, among women of our study which included participants with a high education level, 95.9% did not exercise regularly, 97.6% and 98.2% did not have an adequate intake of calcium and vitamin D supplements and only 19.8% had regular daily milk. So, similar to studies in Australia and Brazil, intake of calcium in our study was low[17,26]. This was in contrast to the study of Terrio *et al*[14] in the United States in which the intake of calcium was sufficient in most cases.

It indicates the importance of skin sun exposure in order to raise serum vitamin D levels. We can conclude that Iranian women's knowledge about osteoporosis does not lead to improving the preventive habits of osteoporosis and, with regards to the absence of a significant relationship between education level and osteoporosis-related life habits, in addition to increasing women's knowledge, we must change osteoporosis-related life habits, together with women's diet and behavior patterns. Therefore, we should provide better programs for the evaluation of osteoporosis, establish continuous teaching programs, and prepare more appropriate educational materials for osteoporosis and improve specific health messages in public media.

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COMMENTS

Background

Osteoporosis, a serious health problem that diminishes quality of life, is a systemic skeletal disorder, characterized by reduction in bone mass, increasing bone fragility and fracture risk.

Research frontiers

Osteoporosis, a serious health problem that diminishes quality of life, is a systemic skeletal disorder, characterized by reduction in bone mass, increasing bone fragility and fracture risk. In this study, the authors assessed possible relationships of the level of knowledge and related factors with educational level and osteoporosis-related life habits (including exercise, calcium and vitamin D intake) among Iranian women aged ⩾ 35 years.

Innovations and breakthroughs

Iranian women's knowledge about osteoporosis does not lead to improving the preventive habits of osteoporosis and, with regards to the absence of a significant relationship between education level and osteoporosis-related life habits, in addition to increasing women's knowledge, osteoporosis-related life habits, together with women's diet and behavior patterns must change. Therefore, better programs for the evaluation of osteoporosis should be provided, continuous teaching programs established, and more appropriate educational materials for osteoporosis and improved specific health messages in public media should be prepared.

Applications

By understanding how knowledge about osteoporosis leads to improving the preventive habits of osteoporosis, this study may represent a future strategy for improving women's knowledge about osteoporosis.

Peer review

The authors examined women's knowledge about osteoporosis and demonstrated that it does not lead to improving the preventive habits of osteoporosis and, with regards to the absence of a significant relationship between education level and osteoporosis-related life habits, in addition to increasing women's knowledge, the authors must change osteoporosis-related life habits, together with women's diet and behavior patterns. Therefore, the authors should provide better programs for the evaluation of osteoporosis, establish continuous teaching programs, and prepare more appropriate educational materials for osteoporosis and improve specific health messages in public media.

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META-ANALYSIS

Ponseti method compared with soft-tissue release for the management of clubfoot: A meta-analysis study

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Abstract

AIM: To compare the functional outcomes of patients who underwent open surgery *vs* Ponseti method for the management of idiopathic clubfoot and to determine whether correlations exist between functional outcome and radiographic measurements.

METHODS: A meta-analysis of the literature was conducted for studies concerning primary treatment of patients with idiopathic clubfoot. We searched PubMed Medline, EMBASE, and the Cochrane Library databases from January 1950 to October 2011. Meta-analyses were performed on outcomes from 12 studies. Pooled means, SDs, and sample sizes were either identified in the results or calculated based on the results of each study.

RESULTS: Overall, 835 treated idiopathic clubfeet in 516 patients were reviewed. The average follow-up was 15.7 years. Patients managed with Ponseti method did have a higher rate of excellent or good outcome than patients treated with open surgery (0.76 and 0.62, respectively), but not quite to the point of statistical significance (Q = 3.73, P = 0.053). Age at surgery was not correlated with the functional outcome for the surgically treated patients (r = -0.32, P = 0.68). A larger anteroposterior talocalcaneal angle was correlated with a higher rate of excellent or good outcomes (r = 0.80, P = 0.006). There were no other significant correlations between the functional and radiographic outcomes.

CONCLUSION: The Ponseti method should be considered the initial treatment of idiopathic clubfeet, and open surgery should be reserved for clubfeet that cannot be completely corrected.

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Key words: Idiopathic clubfoot; Congenital talipes equinovarus; Ponseti method; Surgical release; Ponseti-Laaveg score

Core tip: This study analyzed a large cohort of patients with idiopathic clubfoot and presented differences in the functional and radiographic outcomes based on the management employed. Although no statistically significant difference was noted in the overall functional outcomes between patients managed with the Ponseti method or open surgery, patients treated with the Ponseti method had a higher rate of excellent or good outcomes. Serial manipulation and casting has been widely accepted as the initial treatment of idiopathic clubfeet, and soft-tissue release is reserved for clubfeet that cannot be completely corrected. A strict brace compliance remains the major challenge of the Ponseti method.

Lykissas MG, Crawford AH, Eismann EA, Tamai J. Ponseti method compared with soft-tissue release for the management of clubfoot: A meta-analysis study. *World J Orthop* 2013; 4(3): 144-153 Available from: URL: http://www.wjgnet.com/2218-5836/full/v4/i3/144.htm DOI: http://dx.doi.org/10.5312/wjo.v4.i3.144

INTRODUCTION

During the second half of the twentieth century, the primary treatment of idiopathic clubfoot has ranged from gentle manipulations to aggressive surgical treatment. Surgical management predominated because it was considered as a method that could obtain full and lasting correction. Over time and based on long-term follow-up studies surgeons realized that the results of surgical intervention are unpredictable[1-3]. Extensive soft-tissue releases can result in scarring which may lead to stiffness, recurrent deformity, and pain[4]. It was this observation along with the promising results of the Ponseti method[5,6] that shifted treatment of idiopathic clubfoot towards a more conservative approach consisting of manipulations and serial casting, and frequently minimal invasive surgery. Open surgery is usually reserved for more severe cases that failed serial casting. However, even in these cases, current surgical procedures are less aggressive than procedures performed three decades ago.

Although there are a plethora of studies that have assessed the functional and radiographic outcomes following different treatment protocols, there are only a few studies that directly compare open surgery and Ponseti method for the management of idiopathic clubfoot[1,7-9]. This can be mainly attributed to variable and simplistic grading systems for scoring the severity of the deformity as well as the differing evaluation systems for assessing outcomes. Only one study in the current literature prospectively compares surgical management and Ponseti method, but there are no prospective randomize controlled trials[7].

The present meta-analysis aims to address two topics. The main purpose is to compare the functional outcomes between patients undergoing open surgery *vs* Ponseti method for the treatment of idiopathic clubfoot. A secondary aim is to determine if functional outcomes and radiographic measurements correlate.

MATERIALS AND METHODS

Literature search

A meta-analysis of the literature was conducted for studies concerning management of patients with idiopathic clubfoot with either soft-tissue release or Ponseti method. The search was performed with use of the following electronic bibliographic databases: Medical Literature Analysis and Retrieval System online (PubMed Medline), Excerpta Medica Database (EMBASE), and The Cochrane Library. The medical subject headings or text words utilized included: "clubfoot", "congenital talipes equinovarus", "soft-tissue release", "surgery", and "Ponseti method". The bibliographies of the retrieved articles as well as the "related articles" option in PubMed Medline were also searched to assess for potentially inclusive papers that were missed by the initial search.

Criteria for eligibility

Since several methods and systems have been used to describe the functional and radiographic outcome of patients treated with open surgery or Ponseti method, we performed an initial search to identify the most commonly used functional scores and radiographic parameters. These included: Laaveg-Ponseti score (Figure 1)[5], anteroposterior talocalcaneal angle (TCA-AP), lateral talocalcaneal angle (TCA-LT), anteroposterior talus-first metatarsal angle (TMT-AP), lateral talus-first metatarsal angle (TMT-LT), anteroposterior calcaneus-fifth metatarsal angle (CMT-AP), lateral first-fifth metatarsal angle (MTT-LT), and talocalcaneal index (TCI) (Figure 2). The Laaveg-Ponseti score is a 100-point evaluation system with scores between 90 and 100 considered as excellent, 80 and 89 as good, 70 and 79 as moderate, and below 70 as poor. According to our initial search of the literature, this was the most commonly used functional score in patients who underwent soft-tissue release or Ponseti method from its description in 1980 until today. In contrast to other systems, it can be used to study the correlation between the functional outcome and radiographic measurements since it relies only on clinical aspects, not including any radiographic parameters[10].

Based on the initial search findings, studies selected for the analyses were original studies fulfilling the following eligibility criteria: (1) assess idiopathic clubfoot; (2) assess primary treatment of idiopathic clubfoot; (3) use the functional evaluation score of Laaveg-Ponseti; (4) use of at least three of the radiographic outcome measures found to be the most commonly used in the literature and described above; (5) evaluate more than ten feet; (6) evaluate human subjects; and (7) was published from January 1950 through October 2011.

Potentially inclusive papers were manually reviewed and were discussed among the authors, and a decision was made regarding inclusion. If there was any disagreement among authors regarding the inclusion of an article, the senior author made the final decision.

Extraction of data

Data were carefully extracted and computerized on the following variables from those published articles that meet our inclusion criteria: (1) radiographic findings at final follow-up (main outcome variable); (2) Laaveg-Ponseti score at final follow-up (main outcome variable); (3) time period during which the procedure was performed; (4) duration of follow-up; (5) number of patients/feet; (6) unilateral or bilateral involvement; (7) sex of the patient; (8) age at treatment; (9) level of evidence; (10) publication year; and (11) authors' names.

Statistical analysis

Due to the possibility of variation between studies, the more conservative, random-effects model was selected over a fixed-effects model. Random effects models account for both within-study and between-study variation and are more preferable when assessing observational studies. Pooled means, SDs, and sample sizes were either identified in the results of each study or calculated based

Category	Points
Satisfaction (20 points)	
I am	
(1) very satisfied with the end result	20
(2) satisfied with the end result	16
(3) neither satisfied nor unsatisfied with the end result	12
(4) unsatisfied with the end result	8
(5) very unsatisfied with the end result	4
Function (20 points)	
In my daily living, my club foot	
(1) does not limit my activities	20
(2) occasionally limits my strenuous activities	16
(3) neither satisfied nor unsatisfied with the end result	12
(4) usually limits my strenuous activities	8
(5) limits me in walking	4
Pain (30 points)	
My club foot	
(1) is never painful	30
(2) occasionally causes mild pain during strenuous activities	24
(3) usually is painful after strenuous activities only	18
(4) is occasionally painful during routine activities	12
(5) is painful during walking	6
Position of heel when standing (10 points)	
My club foot	
Heel varus, 0° or some heel valgus	10
Heel varus, 1°-5°	5
Heel varus, 6°-10°	3
Heel varus, greater than 10°	0
Passive motion (10 points)	
Dorsiflexion	1 point per 5°
Total varus-valgus motion of heel	1 point per 10°
Total anterior inversion-eversion of foot	1 point per 25°
Gait (10 points)	
Normal	6
Can toe-walk	2
Can heel-walk	2
Limp	-2
No heel-strike	-2
Abnormal toe-off	-2

Figure 1 Functional rating system for clubfoot. Reproduced from by Laaveg *et al*[5].

Figure 2 Radiographic parameters most commonly measured on plain films. Anteroposterior (A) and lateral (B) standing foot radiographs of a patient with clubfoot showing the anteroposterior talocalcaneal angle (a), anteroposterior calcaneus-fifth metatarsal angle (b), anteroposterior talus-first metatarsal angle (c), lateral talocalcaneal angle (d), lateral talus-first metatarsal angle (e), and lateral first-fifth metatarsal angle (f).

on the results. Effect sizes with 95%CI were calculated using the mean and SE for each study. Subgroup analyses were performed in order to compare the Ponseti method and surgical treatment studies on all outcome measures. Variability between treatment types was assessed with Cochran's Q statistic, which measures the presence or absence of heterogeneity between studies based on a χ^2 distribution. It is calculated as the weighted sum of squared differences between individual study effects and pooled effects across studies. The I^2 index was also calculated as a measure of the extent of heterogeneity between studies. Larger Q and I^2 values indicate

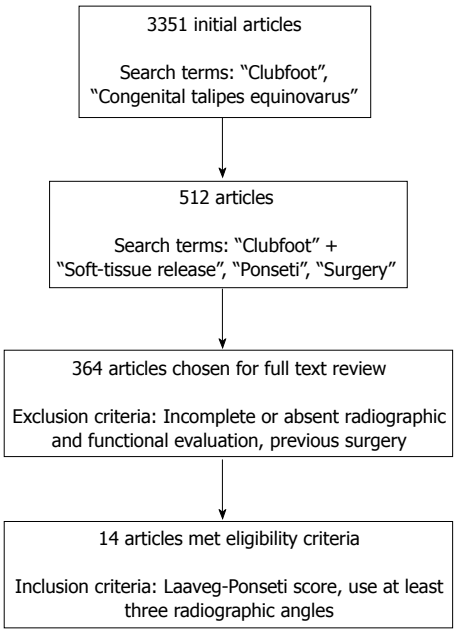

Figure 3 Flow chart summary of the literature.

greater variability. The number of feet with good or excellent outcomes on the Laaveg-Ponseti scale was also compared to the number of feet with poor or fair outcomes using event rates of successful outcomes rather than effect sizes.

Meta-analyses were performed using the Comprehensive Meta-Analysis software (2.0, Bio-Stat, Englewood, NJ, United States). A P value of 0.05 or less was considered as statistical significant.

RESULTS

Literature search

Based on the title and the abstract, the initial electronic search yielded 512 articles as potentially eligible. After obtaining the full text of 364 articles, a total of fourteen articles were found to fulfill the inclusion criteria[1,3,5,6,9-18]. Two studies were excluded because the measures were in terms of medians and ranges, and thus, effect sizes could not be calculated[9,18]. A flow chart summary of the literature search is shown in Figure 3.

Meta-analyses were performed on outcomes from 12 studies[1,3,5,6,10-17]. Nine studies evaluated functional and radiographic outcome following soft-tissue release, two studies after Ponseti method, and one study compared outcomes in patients who underwent Ponseti method or open surgery for the management of idiopathic clubfoot. Three studies were therapeutic level of evidence Ⅲ studies[1,3,13]. The rest of the studies were observational level of evidence Ⅳ case series[5,6,10-12,14-17].

In summary, 835 treated idiopathic clubfeet in 516 patients were reviewed. Among these patients, 369 patients (611 feet) were treated with soft-tissue release and 147 patients (224 feet) were managed with the Ponseti method. The male-to-female ratio was 2.5:1. The unilateral-to-bilateral involvement ratio was 1.25:1. The mean age at initiation of treatment was 8.8 ± 4.8 mo. The average follow-up was 15.7 ± 10.8 years. The minimum follow-up was one year and the maximum 42 years.

Functional outcome

At the final follow-up, functional outcomes, as measured with the Laaveg-Ponseti score, did not differ between patients treated with Ponseti method and patients treated with soft-tissue release (86.3 and 82.0, respectively, Q = 0.45, P = 0.50) (Table 1). However, when compared categorically, patients managed with Ponseti method did have a higher rate of excellent or good outcome than patients treated with open surgery (0.76 and 0.62, respectively), but not quite to the point of statistical significance (Q = 3.73, P = 0.053) (Figure 4, Table 1).

For all patients studied, a longer length of follow-up was correlated with worse functional outcomes (r = -0.82, P = 0.023). Age at surgery was not correlated with functional outcome for patients treated with open surgery (r = -0.32, P = 0.68).

Radiographic outcome

The radiographs taken at the time of the final follow-up did not show any significant differences between patients treated with manipulation and serial casting (Ponseti method) and patients treated with soft-tissue release regarding the TCA-AP (15.8° and 18.9°, respectively) (Q = 2.09, P = 0.15), TCA-LT (29.9° and 26.6°, respectively) (Q = 0.33, P = 0.57), TCI (45.7° and 46.1°, respectively) (Q = 0.002, P = 0.96), and the TMT-AP angles (0.96° and 6.04°, respectively) (Q = 0.55, P = 0.11) (Table 2).

Statistically significant differences were noted between patients managed with the Ponseti method and patients treated with open surgery in TMT-LT (5.51° and 12.08°, respectively) (Q = 10.74, P = 0.001), MTT-LT (15.4° and 25.2°, respectively) (Q = 10.48, P = 0.001), and CMT-AP angles (-6.49° and 3.86°, respectively) (Q = 16.12, P < 0.001) (Table 3).

Heterogeneity in outcomes

For the Laaveg-Ponseti score and all radiographic measurements, except TCA-LT, greater variability was recorded in patients who underwent open surgery compared with patients managed with the Ponseti method, as indicated by the higher Q values and I^2 values (Table 4).

Correlations between functional outcome and radiographic measurements

A larger TCA-AP angle was correlated with a higher rate of excellent or good outcomes (r = 0.80, P = 0.006). Functional outcomes were not significantly correlated with MTT-LT (r = -0.80, P = 0.20), TMT-AP (r = -0.80, P = 0.20), and TCA-AP (r = 0.70, P = 0.19) angles or the TCI (r = -0.30, P = 0.62) (Table 5).

DISCUSSION

Idiopathic clubfoot is a complex three dimensional deformity with an incidence of between 0.64 and 6.8 per

Table 1 Comparison of Laaveg-Ponseti score between patients treated with the Ponseti method and surgically managed patients

Studies	Level of evidence	Mean follow-up (yr)	Time period of procedure	Patients (*n*)	Feet (*n*)	Laaveg-Ponseti score mean (95%CI)	Excellent/good Laaveg-Ponseti rating rate (95%CI)
All Treatments				500	810	86.2 (84.2-88.2)	0.73 (0.67-0.78)
Ponseti method				147	224	86.3 (84.2-88.3)	0.76 (0.69-0.81)
Ippolito *et al*[1]	Ⅲ	19	1979-1984	32	49	85.4 (83.9-86.9)	0.78 (0.64-0.87)
Laaveg *et al*[5]	Ⅲ	18.8	1950-1967	70	104	87.5 (85.3-89.7)	0.74 (0.65-0.82)
Cooper *et al*[6]	Ⅳ	34	1950-1967	45	71	-	0.78 (0.63-0.88)
Soft-tissue release				353	586	82.0 (69.5-94.5)	0.62 (0.48-0.74)
Ippolito *et al*[1]	Ⅲ	25	1973-1977	32	47	74.7 (71.4-78.0)	0.43 (0.29-0.57)
Dobbs *et al*[3]	Ⅲ	31	1972-1979	45	73	65.3 (62.9-67.7)	0.33 (0.23-0.44)
Fridman *et al*[10]	Ⅳ	6.4	1986-2003	50	71	86.9 (84.1-89.6)	0.80 (0.69-0.88)
Schuh e *et al*[11]	Ⅳ	4.5	1986-2000	86	130	95.6 (94.0-97.2)	-
Singh *et al*[12]	Ⅳ	13.8	1980-1996	18	33	-	0.82 (0.65-0.92)
Prasad *et al*[13]	Ⅳ	-	-	30	50	-	0.58 (0.44-0.71)
Munshi *et al*[14]	Ⅲ	3.5	-	-	50	87.3 (83.1-91.5)	0.78 (0.65-0.87)
Herbsthofer *et al*[15]	Ⅳ	6.7	1984-1994	38	62	-	0.47 (0.35-0.59)
Abulsaad *et al*[16]	Ⅳ	3.9	2000-2004	54	70	-	0.69 (0.57-0.78)
Difference between treatments						Q = 0.45, P = 0.50	Q = 3.73, P = 0.053

Treatment type	Study	Year	Statistics					Event rate and 95%CI
			Event rate	Lower limit	Upper limit	*Z*	*P*	
Ponseti Method	Ippolito *et al*[1]	2003	0.78	0.64	0.87	3.62	< 0.001	
Ponseti Method	Cooper *et al*[6]	1995	0.78	0.63	0.88	3.49	< 0.001	
Ponseti Method	Laaveg *et al*[5]	1980	0.74	0.65	0.82	4.69	< 0.001	
Ponseti Method			**0.76**	**0.69**	**0.81**	**6.85**	**< 0.001**	
Soft Tissue Release	Ippolito *et al*[1]	2003	0.43	0.29	0.57	-1.02	0.31	
Soft Tissue Release	Singh *et al*[12]	2005	0.82	0.65	0.92	3.33	0.001	
Soft Tissue Release	Prasad *et al*[13]	2009	0.58	0.44	0.71	1.13	0.26	
Soft Tissue Release	Herbsthofer *et al*[15]	1998	0.47	0.35	0.59	-0.51	0.61	
Soft Tissue Release	Fridman *et al*[10]	2007	0.80	0.69	0.88	4.71	< 0.001	
Soft Tissue Release	Dobbs *et al*[3]	2006	0.33	0.23	0.44	-2.87	0.004	
Soft Tissue Release	Abulsaad *et al*[16]	2008	0.69	0.57	0.78	3.03	0.003	
Soft Tissue Release	Munshi *et al*[14]	2006	0.78	0.65	0.87	3.71	< 0.001	
Soft Tissue Release			**0.62**	**0.48**	**0.74**	**1.66**	**0.097**	
Combined			**0.73**	**0.67**	**0.78**	**6.78**	**< 0.001**	

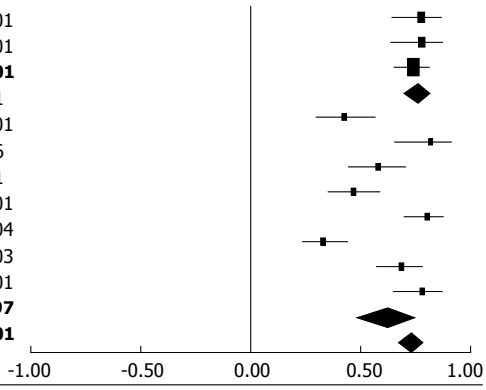

Figure 4 Success rate of Ponseti method *vs* soft-tissue release for clubfoot management based on Laaveg-Ponseti score.

1000 live births[19]. Pathogenesis of idiopathic clubfoot remains obscure, but there is increased evidence for a multifactorial etiologic model. Both genetic and environmental factors have been implicated. Muscle growth impairment[20,21], primary germ plasm defect in the talus[22], vascular anomalies[23-25], medial retraction fibrosis[26], and intrauterine factors[19], such as oligohydramnios, placental insufficiency, drugs, infective pathogens, and amniocentesis prior to the eleventh week[27], have been proposed as potential etiologic factors in the pathogenesis of idiopathic clubfoot. Studies have shown that the deformity has a heritable factor, but is not inherited in a simple autosomal dominant or recessive mendelian fashion[28-32]. Although there is no evidence to support sex linkage, males are affected more commonly than females in all ethnic groups. The reported male-to-female ratio is 2.5:1[33]. This is in accordance to our findings. The male-to-female ratio in 516 patients with idiopathic clubfoot reviewed in our study was 2.5:1. We also recorded a unilateral-to-bilateral involvement ratio of 1.25:1.

The success rates in different series are difficult to compare because of variation in severity of the deformity between study groups and, more importantly, absence of common assessment protocols. In the present meta-analysis, in an effort to use a "common language" between patients treated with open surgery or Ponseti method, we used the subjective assessment method published by Laaveg *et al*[5]. It is based on functionality, presence of pain, foot and ankle range of motion, and patient's satisfaction. In contrast to other systems, it can be used to study the correlation between the functional outcome and radiographic measurements since it relies only on clinical aspects, not including any radiographic parameters[15]. Although it may have been interesting to compare outcomes based on the degree of deformity prior to treatment, only five of the 12 studies included in this meta-analysis evaluated clubfeet at birth. Even in these few studies, the system used deferred, and a comparison in terms of severity of the deformity was not possible. It should also be noted that this study has the disadvantages

Table 2 Comparison of anteroposterior talocalcaneal angle, lateral talocalcaneal angle, and talocalcaneal index between patients treated with the Ponseti method and surgically managed patients

Studies	Patients	Feet	Talocalcaneal		
			AP mean (95%CI)	Lateral mean (95%CI)	Index mean (95%CI)
All treatments	430	655	16.2 (14.9-17.5)	26.9 (23.9-29.9)	46.0 (41.4-50.7)
Ponseti method	147	224	15.8 (14.5-17.2)	29.9 (19.3-40.5)	45.7 (33.4-58.0)
Ippolito *et al*[1]	32	49	16.1 (14.6-17.6)	38.8 (37.1-40.4)	54.9 (51.7-58.0)
Laaveg *et al*[5]	70	104	14.5 (12.8-16.2)	20.9 (19.8-22.0)	35.5 (33.5-37.5)
Cooper *et al*[6]	45	71	17.0 (15.1-18.9)	30.0 (28.4-31.6)	47.0 (43.5-50.5)
Soft-tissue release	283	431	18.9 (15.0-22.8)	26.6 (23.5-29.8)	46.1 (41.0-51.1)
Ippolito *et al*[1]	32	47	14.1 (12.2-16.0)	33.2 (30.7-35.7)	47.3 (42.9-51.7)
Dobbs *et al*[3]	45	73	12.8 (11.1-14.4)	23.3 (21.8-24.8)	36.1 (32.9-39.3)
Fridman *et al*[10]	50	71	20.8 (19.3-22.3)	22.5 (20.9-24.0)	43.3 (40.9-45.6)
Singh *et al*[12]	18	33	28.4 (27.0-29.8)	30.9 (29.2-32.6)	59.3 (56.2-62.4)
Prasad *et al*[13]	30	50	18.5 (16.2-20.8)	27.4 (24.6-30.1)	45.8 (43.3-48.4)
Herbsthofer *et al*[15]	38	62	16.1 (14.6-17.6)	23.0 (21.3-24.7)	39.1 (36.0-42.2)
Abulsaad *et al*[16]	54	70	16.4 (15.1-17.6)	21.4 (19.9-23.0)	42.2 (39.7-44.7)
Docquier *et al*[17]	16	25	24.3 (21.5-27.1)	32.2 (29.6-34.8)	56.5 (51.1-61.9)
Difference between treatment			$Q = 2.09$, $P = 0.15$	$Q = 0.33$, $P = 0.57$	$Q = 0.002$, $P = 0.96$

Table 3 Comparison of talus-1st metatarsal, 1st-5th metatarsal, and calcaneus-5th metatarsal angles between patients treated with the Ponseti method and surgically managed patients

Studies	Patients	Feet	Talus-1st metatarsal		1st-5th metatarsal	
			AP mean (95%CI)	Lateral mean (95%CI)	Lateral mean (95%CI)	AP mean (95%CI)
All treatments	516	655	1.27 (-0.23-2.77)	6.24 (5.00-7.48)	15.6 (16.7-17.9)	-5.11 (-6.83 - -3.40)
Ponseti method	147	224	0.96 (-0.59-2.51)	5.51 (4.20-6.82)	15.4 (14.7-16.1)	-6.49 (-8.33 - -4.65)
Ippolito *et al*[1]	32	49	0.94 (-1.01-2.89)	6.39 (4.40-8.38)	15.5 (14.2-16.7)	-6.8 (-9.20 - -4.40)
Laaveg *et al*[5]	70	104	-	-	14.7 (13.5-15.9)	-4.9 (-6.92 - -2.88)
Cooper *et al*[6]	45	71	1 (-1.56-3.56)	5 (3.60-6.40)	16 (14.8-17.2)	-8 (-10.33 - -5.67)
Soft-tissue release	283	431	6.04 (-0.06-12.13)	12.08 (8.38-15.79)	25.2 (19.3-31.0)	3.86 (-0.84 - 8.57)
Ippolito *et al*[1]	32	47	8.28 (5.97-10.59)	9.4 (6.69-12.11)	22.1 (20.3-23.9)	-0.62 (-3.04 - 1.80)
Dobbs *et al*[3]	45	73	15.95 (13.24-18.66)	7.68 (4.06-11.30)	18.1 (15.4-20.8)	10.32 (8.55 - 12.09)
Fridman *et al*[10]	50	71	3.97 (1.27-6.67)	-	-	1.32 (-0.70 - 3.34)
Singh *et al*[12]	18	33	11.9 (9.89-13.91)	15.7 (13.14-18.26)	28.2 (25.9-30.5)	-
Prasad *et al*[13]	30	50	6.92 (2.49-11.35)	18.54 (11.90-25.18)	46.2 (38.7-53.7)	5.8 (2.22 - 9.38)
Herbsthofer *et al*[15]	38	62	10.29 (7.68-12.90)	-	-	9.95 (7.90 - 12.00)
Abulsaad *et al*[16]	54	70	-5.43 (-6.85-4.02)	-	-	-
Docquier *et al*[17]	16	25	-3.5 (-6.52-0.48)	10.9 (6.43-15.37)	15.9 (12.7-19.1)	-3.9 (-7.04 - -0.76)
Difference between treatment			$Q = 2.50$, $P = 0.11$	$Q = 10.74$, $P = 0.001$	$Q = 10.48$, $P = 0.001$	$Q = 16.12$, $P < 0.001$

adherent to low level of evidence studies analyzed and the relatively loose entry criteria.

Extensive soft-tissue release was the preferred method of treatment for many decades because it often provides definitive correction of the deformity. Full correction by addressing all components of the deformity was recommended. Surgical approaches most commonly used can be classified into three main categories: the Turco posteromedial incision[34], the Crawford's circumferential Cincinnati incision[35], and the two-incision Carroll approach[36]. Ponseti *et al*[33] pioneered his manipulative and serial casting technique in the late 1940s and first published his method in 1963. He proposed simultaneous correction of all components of clubfoot by abducting the foot under the talus while a counter pressure is applied to the talar head. Based on long-term follow-up studies of patients who underwent extensive soft-tissue releases for the management of idiopathic clubfoot before 1980, it has been shown that aggressive surgical management results in poor long-term foot function due to pain, stiffness, and degenerative arthrosis[1-4]. Until today, there is a lack in the literature of studies evaluating adults with clubfeet treated with selective posteromedial release techniques, as these were described after 1983. The present meta-analysis, by including data of clubfeet treated with both aggressive and comprehensive release techniques, demonstrated that patients managed with the Ponseti method had a higher rate of excellent or good outcomes than patients treated with open surgery.

Noncompliance of the family to follow the brace protocol is associated with unexpected high recurrence rate ranging from 30% to 45%[7,57-49]. According to a recent study, there is no association between the poor bracing compliance and the families educational level, income or cultural origin[50]. Distance from the treatment centers and accessibility to the health care system are important parameters that may also adversely affect compliance, and secondarily the success rate. In addition, concurrent

Table 4 Between and within-study heterogeneity in outcomes of clubfoot treatment

	Overall		Ponseti method		Soft-Tissue release	
	Q	I^2	*Q*	I^2	*Q*	I^2
Laaveg-Ponseti score	468.8[a]	98.7	2.3	57.2	465.8[a]	99.1
Excellent/Good Laaveg-Ponseti ratings	72.5[a]	86.2	0.35	0	55.6[a]	87.4
TCA-AP	346.8[a]	97.1	4.1	50.9	312.5[a]	97.8
TCA-LT	496.3[a]	98.0	320.8[a]	99.4	158.1[a]	95.6
TCI	274.5[a]	96.4	114.3[a]	98.3	265.5[a]	95.4
TMT-AP	376.3[a]	97.6	0.001	0	365.2[a]	98.1
TMT-LT	67.3[a]	91.1	1.3	20.5	21.0[a]	80.9
MTT-LT	203.8[a]	96.6	2.3	12.0	89.0[a]	95.5
CMT-AP	328.7[a]	97.6	4.0	50.6	121.5[a]	95.9

[a]$P < 0.05$ *vs* patients who underwent open surgery, significant variability. TCA-AP: Anteroposterior talocalcaneal angle; TCA-LT: Lateral talocalcaneal angle; TCI: Talocalcaneal index; TMT-AP: Anteroposterior talus-first metatarsal angle; TMT-LT: Lateral talus-first metatarsal angle; MTT-LT: Lateral first-fifth metatarsal angle; CMT-AP: Anteroposterior calcaneus-fifth metatarsal angle.

Table 5 Correlations between functional and radiographic outcomes after clubfoot treatment

	Length of follow-up *r* (*P* value)	Laaveg-Ponseti excellent/good outcomes *r* (*P* value)
TCA-AP	-0.31 (0.39)	0.80 (0.006)
TCA-LT	0.43 (0.22)	-0.26 (0.46)
TCI	0.13 (0.73)	0.48 (0.16)
TMT-AP	0.27 (0.49)	-0.36 (0.34)
TMT-LT	-0.66 (0.16)	-0.06 (0.91)
CMT-AP	-0.26 (0.53)	-0.64 (0.091)
MTT-LT	0.11 (0.82)	-0.13 (0.79)

TCA-AP: Anteroposterior talocalcaneal angle; TCA-LT: Lateral talocalcaneal angle; TCI: Talocalcaneal index; TMT-AP: Anteroposterior talus-first metatarsal angle; TMT-LT: Lateral talus-first metatarsal angle; MTT-LT: Lateral first-fifth metatarsal angle.

illnesses may affect management of clubfeet with the Ponseti method.

In an effort to objectively evaluate idiopathic clubfoot, assess treatment, and classify residual deformities, a large number of angular measurements have been proposed on the anteroposterior and lateral radiographic projections[51-53]. The TCA-AP and the TCA-LT, as well as the TCI (sum of TCA-AP and TCA-LT angles) are the most widely used parameters and reflect the anatomic relationship between the talus and the calcaneus. Among the other radiographic angles usually used in clinical practice, TMT-LT and MTT-LT angles measure midfoot cavus deformity, whereas TMT-AP and CMT-AP angles are expressions of forefoot adduction that characterize clubfoot. Our study did not reveal statistically significant difference in TCA-AP and TCA-LT angles between clubfeet treated with open surgery or the Ponseti method. The average TCI was measured above 40 in clubfeet managed with Ponseti method as well as in surgically treated clubfeet. A statistically significant difference was recorded in TMT-LT, MTT-LT, and CMT-AP angles.

Although radiographic evaluation has been extensively used as a measure of success of idiopathic clubfoot treatment, several authors have questioned the correlation between functional and radiographic outcomes as well as the prognostic value of radiographs[6,14,54,55]. Evaluation of radiographs is difficult to reproduce due to complexity of the deformity in various planes with multiple bone involvement, the small size or complete absence of ossific nuclei, particularly that of the navicular, the considerable overlap between radiographic values of normal feet and clubfeet, and difficulty in positioning the stiff and deformed foot[56]. Furthermore, the use of different functional systems does not allow direct comparison between studies in order to identify any association between these radiographic parameters and the functional outcome. In the present meta-analysis, the Laaveg-Ponseti score was used to study the correlation between the clinical scoring and angular measurements since it does not rely on any radiographic parameters. A higher TCA-AP angle was associated with a better functional outcome. This is in agreement with several previous studies[57,58], although many authors have found strong correlation between the functional rating and TCA-LT[5,18,34,59,60] or TCI[52,57,61]. Herbsthofer *et al*[15] demonstrated no correlation between angular measurements and functional outcome. It is our opinion, however, that several radiographic parameters representing each of the clubfoot deformities should be used to provide a comprehensive radiological assessment of the three dimensional clubfoot deformities. By measuring TCA-AP, MTT-LT, and TMT-AP angles, the heel varus, midfoot cavus, and forefoot adduction, can be radiologically assessed and correlated with the functional outcome. In contrast, using a severity evaluation system that is based exclusively on radiographic criteria may overestimate the value of radiographs.

Long-term follow-up studies of treated clubfeet evaluating function beyond skeletal maturity are rare[1-3,6,62]. The studies with the longer follow-up were those of Cooper *et al*[6] with an average of follow-up of 34 years, Ippolito *et al*[1] with an average duration of follow-up of 25 years, and Dobbs *et al*[3] with a mean of follow-up of 30 years. Cooper *et al*[6], evaluated 71 clubfeet in 45 patients treated with the Ponseti method. Seventy-eight percent of the patients had an excellent or good outcome. Mild arthrosis in the foot and ankle was found

in 35% of the patients. Twenty-seven percent of the patients had an excellent or good outcome. Ippolito *et al*[1] compared the results of adult patients with idiopathic clubfoot treated during infancy either with the Ponseti method or extensive soft-tissue release. They recorded better long-term functional outcomes when the former technique was used. The mean Laaveg-Ponseti score was 85.4 and 74.7 for the Ponseti method and surgically treated group, respectively. Seventy-eight percent of the patients treated with the Ponseti method had an excellent or good outcome. In contrast, only 43% of the patients treated with extensive soft-tissue release had an excellent or good outcome. Thirty percent of the surgically treated patients and 38% of the patients treated with the Ponseti method were found to have recurrences requiring additional intervention. Among these recurrences, 86% in the surgical group and 27% in the Ponseti group were major. Dobbs *et al*[3] followed 73 clubfeet who had undergone either an extensive combined posterior, medial, and lateral release or a posterior release and plantar fasciotomy. They reported a correlation between the extent of soft-tissue release and the degree of functional impairment. Moderate to severe evidence of arthrosis in the foot and ankle was found in 56% of surgically treated patients. The mean Laaveg-Ponseti score was 65.3. Our study was in agreement with these findings, suggesting that foot function deteriorates over time in patients treated with open surgery. However, it should be noted that surgically treated patients in the last two long-term studies, as well as 20.87% of surgically treated clubfeet included in our study, were operated with extensive soft-tissue releases which does not represent the current surgical practice.

This study analyzed a large cohort of patients with idiopathic clubfoot and presented differences in the functional and radiographic outcomes based on the management employed. Although no statistically significant difference was noted in the overall functional outcomes between patients managed with the Ponseti method or open surgery, patients treated with the Ponseti method had a higher rate of excellent or good outcomes. Serial manipulation and casting has been widely accepted as the initial treatment of idiopathic clubfeet, and soft-tissue release is reserved for clubfeet that cannot be completely corrected. A strict brace compliance remains the major challenge of the Ponseti method.

COMMENTS

Background

During the second half of the twentieth century, the primary treatment of idiopathic clubfoot has ranged from gentle manipulations to aggressive surgical treatment. Although there are a plethora of studies that have assessed the functional and radiographic outcomes following different treatment protocols, there are only a few studies that directly compare open surgery and Ponseti method for the management of idiopathic clubfoot. This can be mainly attributed to variable and simplistic grading systems for scoring the severity of the deformity as well as the differing evaluation systems for assessing outcomes.

Research frontiers

The present study analyzed a large cohort of patients with idiopathic clubfoot and presented differences in the functional and radiographic outcomes based on the management employed. The findings suggest that foot function deteriorates over time in patients treated with open surgery.

Innovations and breakthroughs

In the present long-term study, although no statistically significant difference was noted in the overall functional outcomes between patients managed with the Ponseti method or open surgery, patients treated with the Ponseti method had a higher rate of excellent or good outcomes. Serial manipulation and casting has been widely accepted as the initial treatment of idiopathic clubfeet, and soft-tissue release is reserved for clubfeet that cannot be completely corrected. A strict brace compliance remains the major challenge of the Ponseti method.

Applications

The study results suggest that serial manipulation and casting is the accepted initial treatment of idiopathic clubfeet, and soft-tissue release is reserved for clubfeet that cannot be completely corrected.

Terminology

Ponseti method is the conservative treatment of idiopathic clubfoot consisting of manipulations and serial casting, and frequently minimal invasive surgery.

Peer review

This is an excellent meta-analysis in which authors analyze a large cohort of patients with idiopathic clubfoot and presented differences in the functional and radiographic outcomes based on the management employed. The results are interesting and suggest that Ponseti method has a higher rate of excellent or good outcomes.

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CASE REPORT

Profunda femoris artery pseudoaneurysm following revision for femoral shaft fracture nonunion

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Abstract

Femoral artery pseudoaneurysms (FAPs) have been described following internal fixation of intertrocantheric, subtrocantheric and intracapsular femoral neck fractures as well as core decompression of the femoral head. The diagnosis of FAP is usually delayed because of non-specific clinical features like pain, haematoma, swelling, occasional fever and unexplained anaemia. Because of the insidious onset and of the possible delayed presentation of pseudoaneurysms, orthopaedic and trauma surgeons should be aware of this complication. We report a case of Profunda Femoris arterial branch pseudoaneurysm, diagnosed in a 40-year-old male 4 wk after revision with Kuntscher intramedullary nail of a femoral shaft nonunion. The diagnosis was achieved by computed tomography angiography and the lesion was effectively managed by endovascular repair. The specific literature and suggestions for treatment are discussed in the paper.

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Key words: Arterial injury; Pseudoaneurysm; Nonunion; Femoral shaft; Endovascular repair

Core tip: Femoral artery pseudoaneurysms (FAPs) are a reported possible complication of intramedullary nailing for acute femoral shaft fractures. In this report we describe the delayed occurrence of a FAP after revision surgery for femoral shaft nonunion, its diagnosis and management by endovascular repair and discuss the pertinent findings in the medical literature.

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INTRODUCTION

A pseudoaneursym is a collection of blood leaking from a damaged arterial wall. The damage can be caused by traumatic or iatrogenic perforations. Femoral artery pseudoaneurysms (FAPs) have been described to arise after different surgical procedures, including internal fixation of intertrocantheric, subtrocantheric and intracapsular femoral neck fractures, intramedullary nailing of femur, core decompression of femoral head for osteonecrosis and revision total hip arthroplasty[1-4].

Because of the insidious onset and possible delayed presentation of FAPs, orthopaedic and trauma surgeons should be aware of this complication. FAPs may close spontaneously if the tear is small enough to allow for clotting and sealing. On the other hand, rupture of the aneurysm can trigger thrombosis, distal embolization and compression of adjacent structures. Compartment syndrome of the tigh has also been observed after formation of a pseudoaneurysm of the femoral artery or of its branches[1].

As far as treatment is concerned, small-sized FAPs can be managed by coil or balloon embolisation, stent

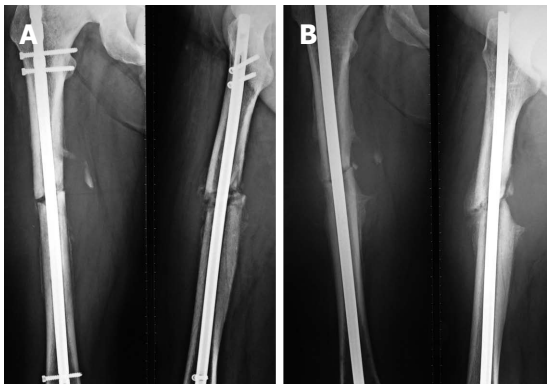

Figure 1 X-ray appearance of pseudoaneurysm. A: Anteroposterior and lateral radiograph of femoral shaft nonunion 8 mo after interlocking IM nailing; B: An ovoid, soft tissue mass behind the fracture site is visible 1 mo after exchange nailing.

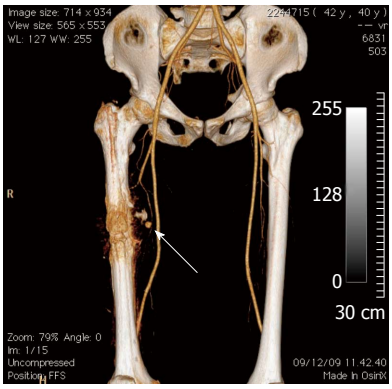

Figure 2 Computed tomography appearance of pseudoaneurysm. Computed tomographic angiogram showing pseudoaneurysm of profunda femoris artery (arrow).

graft repair, transducer-directed compression and other percutaneous or endoluminal treatments[2].

We report a case of a profunda femoris arterial branch pseudoaneurysm, diagnosed in a 40-year-old male 4 wk after revision with Kuntscher intramedullary nail for a femoral shaft nonunion.

To the best of our knowledge this is the first report of femoral pseudoaneurysm occurring after intramedullary nailing for nonunion of the femoral shaft.

CASE REPORT

A 40-year-old male cyclist in good health was involved in a collision with a car that was travelling at 45 miles (65 km) per hour. He sustained an isolated, closed femoral shaft fracture. There were no concomitant abdominal or thoracic injuries. His Injury Severity Score was 9. On X-rays he showed a type 32-A2 fracture according to the AO-ASIF classification[5].

The patient consented to have surgical treatment in the form of unreamed intramedullary nailing (T2 Femur Nail, Stryker Trauma). This was done on the day of injury. There were no reported intraoperative complications. Postoperative radiographs revealed a minimum gap between the proximal and distal fragments. The patient was discharged 4 d after surgery with progressive weight bearing on a assisted rehabilitation protocol. He obtained a complete range of motion after 1 wk and full weight bering after 1 mo, but he complained of a degree of pain during ambulation.

X-rays at 8 mo follow-up revealed nonunion (Figure 1A). After consulting the patient, a revision with intramedullary exchange nailing was planned with reamed insertion. This involved the removal of a previously placed implant and reaming the medullary canal to a larger diameter. The diameter of the new nail (Kuntscher Nail, Stryker Trauma) was 2 mm larger than that of the previous nail and the intramedullary canal was over-reamed by 1 mm more than the diameter of the new nail. Postoperatively, the hemoglobin level never fell down under 9.0 g/dL, without any signs and symptoms of hypovolemia.

Four weeks after surgery, a tender swelling over the medial thigh was noted, and radiographs revealed an ovoid soft tissue mass behind the fracture site (Figure 1B). A residual hematoma (confirmed by duplex ultrasound) was diagnosed, and observation was recommended based on intact distal pulses and neurological function.

However, 3 wk later the enlargement of the mass had continued and associated pulsatile swelling was noticed. A pseudoaneurysm instead of a simple hematoma was suspected. Further investigation, including computer tomographic angiography, confirmed a lesion originating from a profunda femoris arterial branch adjacent to the fracture site (Figure 2).

The patient was therefore referred to an Interventional Radiology department. An angiogram confirmed a rapidly enhancing pseudoaneurysm sac arising from a branch of the right profunda femoris artery. Using a microcatheter, the segmental branch feeding the pseudoaneurysm was selectively cannulated (Figure 3A) and a total of five microcoils (3 mm × 3 cm) were deployed in the vessel distally and proximally to the pseudoaneurysm neck. After embolisation, a control angiogram showed satisfactory hemostasis with occlusion of the feeding vessel, no further filling of the pseudoaneurysm, and no extravasation of contrast (Figure 3B). The compressive discomforts were quickly relieved.

Over the next 6 mo, intact neurovascular status without recurrent painful swelling or reported complications were observed. No additional complications arose during follow-up. The femoral shaft nonunion healed at 6 mo follow-up (Figure 4).

DISCUSSION

There are different causes of FAP caused by orthopaedic procedures reported in the literature. Arterial damage can occur because of bone spikes, screws, drills, displaced implants and retraction of surrounding tissues[6]. Others reports stress the point that locking screws are potential causes of FAPs in case of penetration of inner cortex[7]. The most likely cause of the pseudoaneurysm seen in this case report was over penetration of the drill bit during the intramedullary exchange nailing with reamed inser-

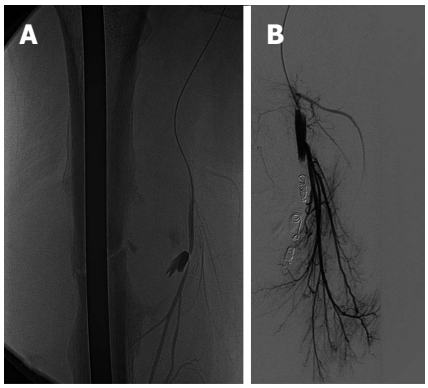

Figure 3 Embolisation. Elective (microcatheter) right deep femoral angiography pictures showing the pseudoaneurysm adjacent to the fracture site. A: Before coil embolization; B: After coil embolization (digital subtraction angiography).

Figure 4 Fracture healing. Anteroposterior and lateral radiograph of the femoral shaft 6 mo from revision surgery, showing fracture union.

tion. The drilling probably injuried the arterial wall with subsequent external hemorrhage.

Early diagnosis of a pseudoaneurysm of the femoral artery or one of its banches can be done if non-specific clinical signs are evaluated and any swelling over the medial aspect of the proximal thigh is investigated properly. However, these findings may be normal when the injury only involves a minor vessel.

The time frame necessary to detect traumatic pseudoaneurysms varies from hours to years depending on the involved region and clinical signs. Clinical manifestations include an enlarging pulsatile swelling, audible bruit, palpable thrill, pain, edema and compressive neuropathy. Without a clear history of trauma, the lesion may mimic some soft tissue conditions like abscesses or neoplasms. Because of the presence of heat and tenderness in the surrounding area, the inflammation during the organisation of the hematoma may appear as a postoperative infection[8]. Therefore, a high index of suspicion and radiological imaging [particularly computed tomography (CT) angiography and duplex ultrasonography] plays a major role in obtaining a diagnosis. Multidetector CT angiography enables 3-dimensional reformatting of the lower limb vasculature. Although the image quality can be impaired by metallic implants, it is a quick and non-invasive method, with high sensitivity (90%-95%) and specificity (98%-100%) for detecting arterial injury after trauma[9].

The management of pseudoaneurysms depends mostly on their location and size. Small asymptomatic lesions or those involving non-critical vessels may be observed for 4-6 wk to detect possible spontaneous recovery. However, active intervention is indicated in larger (> 3 cm) symptomatic lesions. Current therapeutic approaches include open surgical repair, ultrasound-guided compression, ultrasound-guided thrombin injection and endovascular repair using coil embolization or stent-graft insertion as seen in this case.

In conclusion, to the best of our knowledge this is the first report of a delayed pseudoaneurysm caused by drilling during a revision intramedullay nailing for femoral shaft nonunion. Therefore, a pseudoaneurysm should be suspected not only in fracture cases, but also in revisions of nonunions. Due to the rarity of the condition, in case of suspicion the early use of CT angiography is highly recommended. Endovascular repair is an effective minimally invasive treatment for delayed pseudoaneurysms of the femoral artery.

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CASE REPORT

Solid fusion after lumbosacral arthroplasty

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Abstract

A 55-year-old female was diagnosed with L5-S1 degenerative disc disease (DDD). Initial scores by the visual analogue scale (VAS) were 5 (back) and 9 (leg) and the Oswestry disability index (ODI) was 32. Arthroplasty was performed. Clinical and radiographic monitoring took place thereafter at one month, three months, six months and annually. At one month, VAS scores were 2 (back) and 3 (leg), ODI was 12 and ROM was 2.1° by radiographs. At two years, VAS scores were 1 (back) and 2 (leg), ODI was 6 and ROM was approaching 0. Five years after surgery, the entire operated segment (L5-S1) was solidly fused. A malpositioned disc implant may impair normal spinal movement, culminating in heterotopic ossification or complete fusion of the operated segment.

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Key words: Total disc replacement; Lumbar spine; Heterotopic ossification; Fusion, Arthroplasty; Solid fusion

Core tip: A 55-year-old female was diagnosed with L5-S1 degenerative disc disease. Initial scores by the visual analogue scale were 5 (back) and 9 (leg) and the Oswestry disability index was 32. Arthroplasty was performed. Clinical and radiographic monitoring took place thereafter at one month, three months, six months and annually. A malpositioned disc implant may impair normal spinal movement, culminating in heterotopic ossification or complete fusion of the operated segment.

Jang SH, Lee HY, Cho JY, Lee SH. Solid fusion after lumbosacral arthroplasty. *World J Orthop* 2013; 4(3): 157-160 Available from: URL: http://www.wjgnet.com/2218-5836/full/v4/i3/157.htm DOI: http://dx.doi.org/10.5312/wjo.v4.i3.157

INTRODUCTION

Total disc replacement (TDR) is currently advocated for degenerative disc disease (DDD) as a substitute for fusion surgery in certain cases. In theory, TDR may preserve normal range of motion (ROM) in diseased segments and prevent adjacent segment degeneration (ASD)[1-3]. However, a number of complications undermining these benefits have been observed following lumbar TDR, such as heterotopic ossification, facet arthrosis, subsidence, ASD and device migration[1-5]. This report details an unusual occurrence of solid spinal fusion subsequent to lumbosacral TDR and the factors likely contributing to device failure.

CASE REPORT

A 55-year-old female was hospitalized for low back pain radiating to the left thigh and calf. Her past medical history was otherwise unremarkable. Initial scores by the visual analogue scale (VAS) were 5 (back) and 9 (leg) and the Oswestry disability index (ODI) was 32. Radiographic findings were indicative of DDD at the L5-S1 level. After six weeks of unproductive nonsurgical therapy (NSAID, physical therapy), she underwent lumbosacral TDR. Preoperative ROM was 8.6° by radiographs and preoperative computed tomography and magnetic resonance image shows no stenosis or facet arthroplasty at the L5-S1

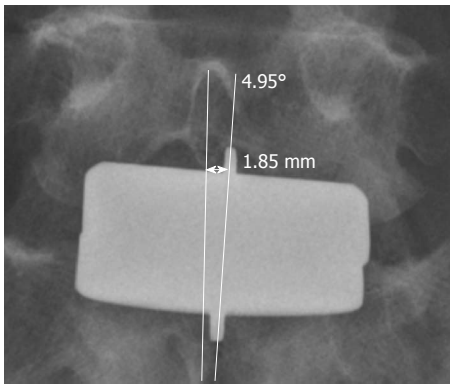

Figure 1 In the anteroposterior view, the superior endplate of the implant deviated 1.85 mm to the left of midline with 4.95° angular displacement.

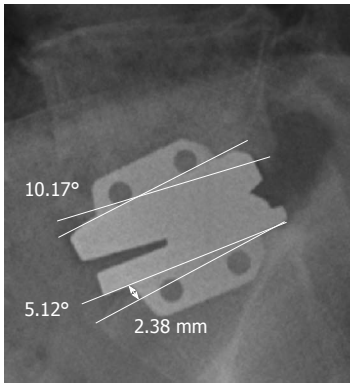

Figure 2 In the lateral view, angular gaps of 10.17° and 5.12° existed between the upper and lower implant endplates, respectively, and 2.38 mm of the lower anterior vertical keel did not insert completely into the S1 upper endplate.

level. The procedure entailed standard left-sided anterior retroperitoneal[4] insertion of a Maverick® (Medtronic Sofamor Danek, Inc., Memphis, TN, United states) implant, requiring 120 min to complete. Estimated blood loss was 200 cc.

In the immediate postoperative period, the patient's condition was satisfactory. There were no significant early complications. Nevertheless, radiographs showed that the superior endplate of the implant deviated 1.85 mm to the left of midline in anterior-posterior (AP) view, with 4.95° angular displacement (Figure 1). In the lateral view, angular gaps of 10.17° and 5.12° existed between the upper and lower implant endplates, respectively, and 2.38 mm of the lower anterior vertical keel did not insert completely into the S1 upper endplate (Figure 2). The patient's clinical course was uneventful. Four days postoperatively, VAS scores were 3 (back) and 4 (leg) and she was discharged seven days after surgery in a stable condition. Clinical status and standing lateral radiographs were evaluated at each follow-up visit. At one month, VAS scores were 2 (back) and 3 (leg), ODI was 12 and ROM was 2.1° by radiographs (Figure 3). At two years, VAS scores were 1 (back) and 2 (leg), ODI was 6 and ROM was approaching 0° (Figure 4). VAS scores and ODI

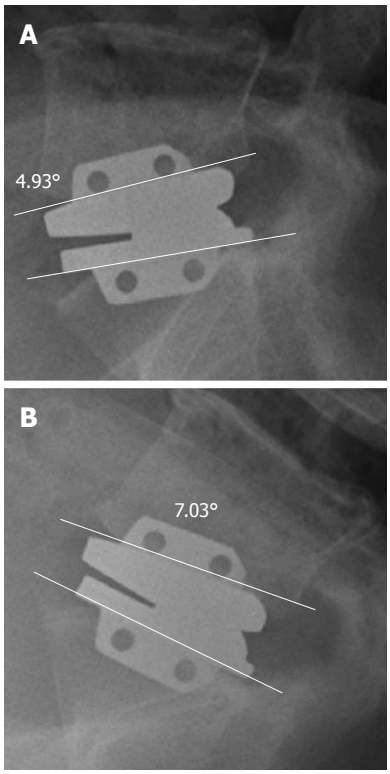

Figure 3 One month after the operation, range of motion of the implant was checked 2.1° (Left: Extension; Right: Flexion).

were unchanged at three years, but calcific bony spurs (heterotopic calcification) were noted on radiographs at the anterior and posterior implant margins (Figure 5). At the final follow-up (five years), VAS scores of 1 (back) and 1 (leg) and ODI of 3 were recorded. By radiographs, the L5-S1 segment was completely fused (Figure 6).

DISCUSSION

The increasing surgical use of artificial discs has raised concern due to related heterotopic ossification (HO). While the etiology of HO remains unclear, perioperative bleeding, implant milieu and ancillary patient conditions (*i.e.*, diffuse idiopathic skeletal hyperostosis) have been implicated[5].

The incidence of HO has been cited as 4.3% in two years of follow-up by Tortolani *et al*[6] who found no effect on ROM or clinical outcomes attributable to HO. They also remarked that the onset of HO was unlikely past the sixth postoperative month. On the other hand, Lemaire *et al*[7] reported a 3% rate of HO after a minimum follow-up of 10 years, all manifested later than five years postoperatively. Finally, Park *et al*[5] detected HO at a rate of 30.5% within 17 mo (on average) after TDR. Four cases actually emerged beyond the third postoperative year. They further cautioned that HO may progress during follow-up, making long-term monitoring imperative. Of note, Fransen *et al*[8] believe nonsteroidal anti-inflammatory drugs (NSAIDs) to be protective in this regard.

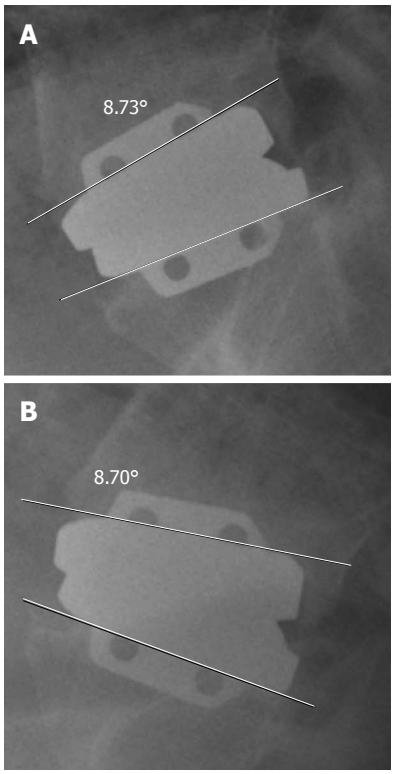

Figure 4 Two years after the operation, radiograph (Above: Extension; Beow: Flexion) shows range of motion of the implant was almost 0°.

Implant placement was unsatisfactory in our patient, deviating to the left of midline with angular gaps between the implant endplates and adjacent vertebrae. The implant was also misaligned in the AP plane, improperly inserting into the body of S1 (Figures 1 and 2). In retrospect, we believe that decompression at the L5-S1 posterior lip was excessive, creating a sunken base posteriorly for the implant and impairing its placement as described above. Normal movement clearly appeared compromised as a consequence. ROM was only 2.1° one month after surgery (Figure 3), HO had developed after two years and at the final 5-year follow-up, the operated segment was solidly fused (Figures 5 and 6). According to Huang *et al*[9], the risk of ASD after TDR (followed 8.7 years) is higher when ROM is low (less than 5°). A malpositioned implant may thus produce an outcome over time that is tantamount to fusion surgery, with heightened potential for ASD.

There are obvious limitations to the observations drawn from this single patient. Results here are based on the Maverick® implant specifically and may not apply to all TDR devices. Furthermore, we could not closely pinpoint the onset of HO or spinal fusion once follow-up visits were extended to annual intervals. Nevertheless, we feel that implant positioning may be critical in development of HO by impacting ROM.

In conclusion, a malpositioned implant may impair normal spinal movement, leading to HO or complete fusion of the operated segment. As a preventative measure, careful preparation of the bony endplate and precise alignment of the implant in the coronal and sagittal planes is warranted.

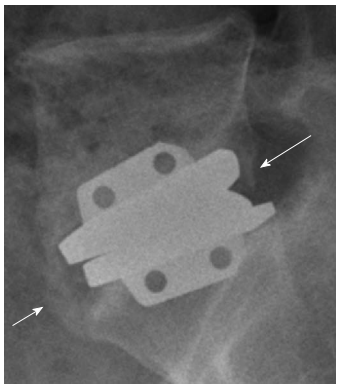

Figure 5 Three years after the operation, calcified spurs (heterotopic ossification) were identified (arrow) at the anterior and posterior margin of the implant.

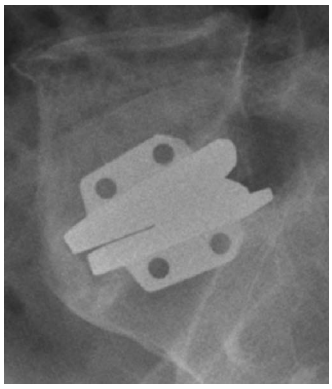

Figure 6 At the last follow-up (5 years), more prominent bony masses were identified and the L5-S1 segment was fused completely.

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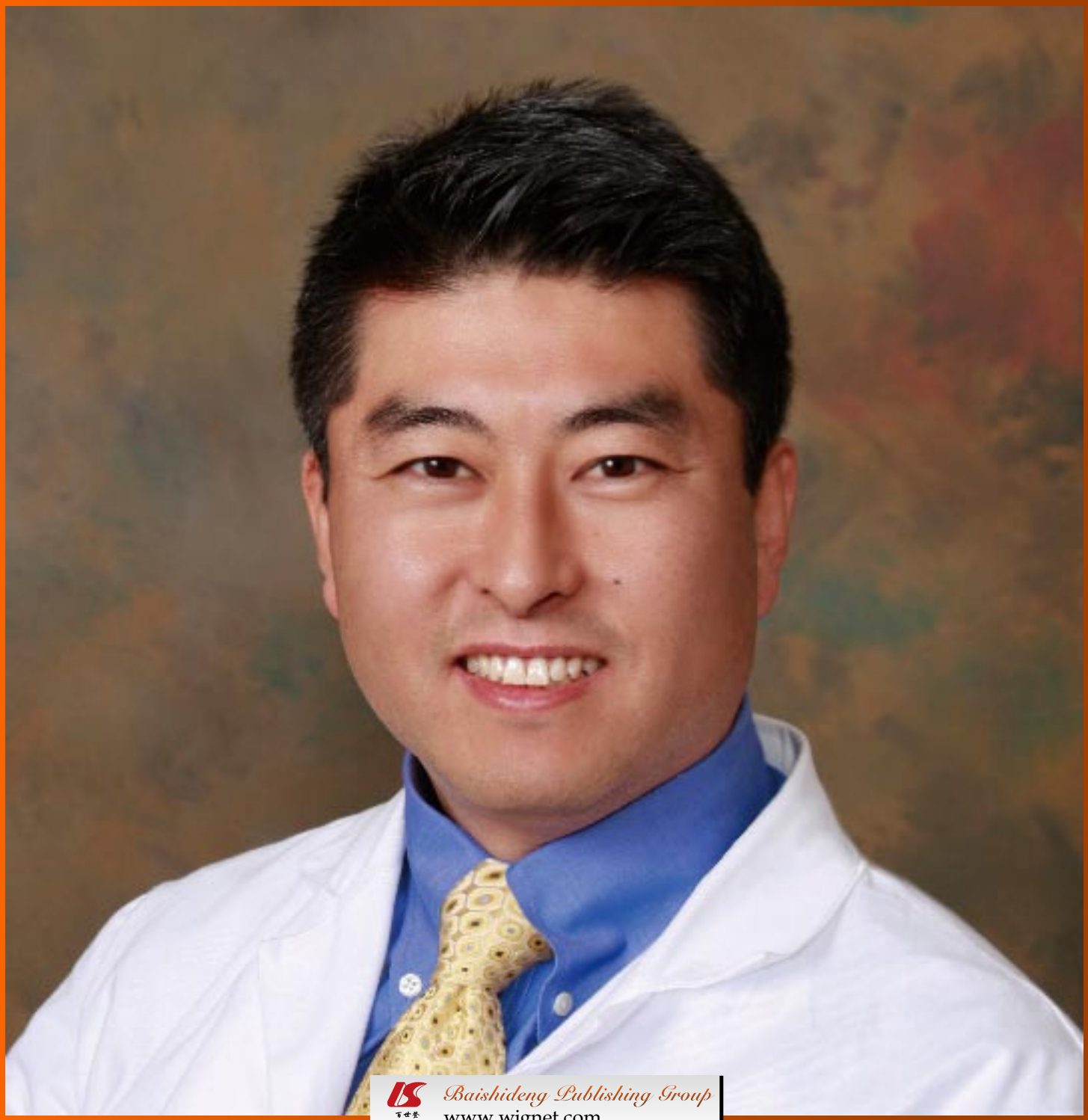

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EDITORIAL

Trunnionosis: A pain in the neck

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Abstract

Metal-on-metal (MoM) hip replacements have proven to be a modern day orthopaedic failure. The early enthusiasm and promise of a hard, durable bearing was quickly quashed following the unanticipated wear rates. The release of metal ions into the blood stream has been shown to lead to surrounding soft tissue complications and early failure. The devastating destruction caused has led to a large number of revision procedures and implant extractions. The resulting research into this field has led to a new area of interest; that of the wear at the trunnion of the prosthesis. It had been previously thought that the metal debris was generated solely from the weight bearing articulation, however with the evolution of modularity to aid surgical options, wear at the trunnion is becoming more apparent. The phenomenon of "trunnionosis" is a rapidly developing area of interest that may contribute to the overall effect of metallosis in MoM replacements but may also lead to the release of metal ions in non MoM hip designs. The aim of this paper is to introduce, explain and summarise the evidence so far in the field of trunnionosis. The evidence for this phenomenon, the type of debris particles generated and a contrast between MoM, non MoM and resurfacing procedures are also presented.

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Key words: Wear; Trunnion; Ions; Arthroplasty; Hip

Core tip: Metal ions, derived from Metal-on-Metal (MoM) hip replacements have been a subject of interest since the catastrophic failure of this bearing surface. However, debris generation is not solely limited to the articulating surface, but can arise from the interface between the head and neck at the trunnion. Furthermore, it appears that the phenomenon of 'trunnionosis' is not limited to only MoM prosthesis, but to all modular designs and may therefore contribute to the problem of metallosis.

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INTRODUCTION

The devastating effects of metal on metal hip arthroplasty are well recognized and described in the literature[1,2]. The term adverse reaction to metal debris (ARMD) is an umbrella term that has been used to describe the effects of metal ion deposition within soft tissues in the body. Patients who become symptomatic and develop ARMD frequently need revision of their prostheses[3], whilst those who are asymptomatic but suffer with high serum metal ion levels represent a more controversial group to treat[4].

Historically, early hip replacements consisted of a non modular femoral head with a single neck option, the so called "monobloc". This meant that restoring leg length and offset was difficult, and may have resulted in instability and abductor dysfunction. As a result, modularity was introduced into the design of hip prostheses and has become increasingly common in the last two decades. Modularity can be exhibited at the junction between the head and the neck with the junction being made at the trunnion or the neck and the body. The neck head junction typically consists of a trunnion which typically has a machined taper allowing for an interference fit. The taper interface is where the femoral head (female taper surface) attaches to the trunnion (male taper) of the femoral stem. The attraction of this degree of modularity to the operating surgeon is clear. Armed with these options, alterations to the offset, version and length of the final implanted device can be achieved independent of the femoral stem fixation, thus restoring the hip centre[5].

A recent area of interest involves the head and neck interface. The evidence is still unclear but there are concerns that this extra junction between the head and the trunnion may be exacerbating the problem of metal on metal replacements and may be a source of metal wear debris. This potential wear process has been given the term "trunnionosis".

Metal on metal (MOM) hip replacements and hip resurfacing offer a useful model for the study of trunnionosis. Since metal-on-metal revision procedures are now frequently performed, the retrieved prostheses are being sent for analysis at regional centres. This enables a thorough and detailed analysis of the prostheses, including the trunnion/taper sites, to be performed. Given that hip resurfacing and MOM hip replacements use the same bearing, but hip resurfacing has no trunnion or modularity, differences in metal wear debris can be compared between the two. The study of trunnionosis has a potential impact on all modular hip replacement prostheses regardless of the bearing surface used.

The aim of this paper is to present the early and growing body of evidence to support the presence of wear debris generated from the taper junction and relate it to the clinical outcome.

WHAT IS THE EVIDENCE?

The use of large diameter heads in total hip replacements is thought to improve stability of the articulating surfaces[6,7]. However in the context of metal-on-metal, it has been associated with an increased wear and subsequent failure rate[8]. Elkins *et al*[9] developed a finite element model to evaluate the relationship between implant stability and trunnion wear. The head/neck interface consisted of the tapered trunnion and head bore. When assembled on the trunnion, a moment arm exists between the center of rotation of the head and the trunnion contact pressure centroid. Stability, measured in terms of femoral head subluxation, improved with increased diameter, although diminishing benefit was seen for size increases beyond 40 mm. By contrast, at the trunnion interface, unabated increase in stress was observed for femoral heads exceeding 40 mm, with the greatest effect seen for larger values of head diameter. Linear wear at the trunnion interface demonstrated a similar dependence upon head size, accelerated wear observed for femoral head diameters exceeding 40 mm for both gait and sit-to-stand motions. This seemed to suggest that *ex-vivo*, large-diameter heads for MoM THA have a tendency to undergo deleterious wear generation at the head/trunnion interface, albeit with an associated improvement in construct stability. It also appeared that trunnionosis-inducing wear increased substantially for head diameters greater than about 40 mm.

Considering *in-vivo* evidence, there is a growing body of evidence to suggest the presence of trunnionosis. A study from Japan undertaken by Yoshikawa *et al*[10], sought to investigate the likely source of the metal ions that led to adverse reaction to metal debris (ARMD) in ten out of thirty eight revised MoM THRs. All ARMD cases showed metal debris-like deposits on head-neck junction on the trunnion and massive periprosthetic tissue scarring at time of revision. Histological analysis and metal ion measurements confirmed that the periprosthetic tissue necrosis occurred due to toxicity due to excess accumulation of cobalt and chromium ion levels. Most interestingly, the energy dispersive X-ray spectrometry findings suggested that the deposits resulted from a tribochemical reaction on trunnion rather than any other area of the prosthesis.

Garbuz *et al*[11] performed a randomized clinical trial to compare outcomes and serum metal ion levels in two groups of patients, one receiving the Durom femoral resurfacing component and the other group a large-head MoM THA (M/L Taper stem made of titanium, with a large Metasu head *via* a Cr-Co alloy metal sleeve adapter and Morse taper in order to match the 12/14 taper of the stem. One of the hypotheses was that since the articulating portion of these implants is identical, there should be no difference in serum metal ions between the two groups. They found that although both groups had raised metal ion levels, the levels were much higher in large-head metal-on-metal hip replacement group. One reasonable conclusion drawn was that the markedly elevated serum cobalt and chromium levels related to the two areas of modularity for the attachment of the femoral head to the stem.

Furthermore, Beaulé *et al*[12] performed a similar comparative study involving cohorts of 26 patients matched according to gender femoral head size and BMI. One group received a modular stem THA while the other group received a MoM hip resurfacing prosthesis. Once again, the acetabular components and bearing surfaces used in both groups were identical. Cobalt ion levels were significantly higher in the cohort of patients who received a THA at 6, 12 and 24 mo.

Similar conclusions were drawn by Langton *et al*[13]. Their group analysed the 206 ASR hip resurfacing and 51 ASR THA systems, each used with an identical acetabular component. The THA head attaches to the stem *via* a cobalt-chromium taper junction in two sizes 11/13 and 12/14. As the bearing diameter increased in the resurfacing group, there was a significant decreasing trend of ion concentration. For the THA group, there was a non significant increase as bearing diameter increased. They speculated that the generation of metal debris from taper junctions explained the poor performance of the larger sized THA joints and also the increased failure rates of the smaller sizes relative to the pure resurfacings. The patterns of material loss suggested to them that the tapers were splayed open by mechanical forces.

In a bid to quantify wear, corrosion and to determine the main mechanism of material loss at the taper, a retrospective study of 78 large metal-on-metal hip replacements retrieved after revision was conducted by Matthies *et al*[14]. Corrosion was assessed using light microscopy and scanning electron microscopy (SEM). Evidence of at least mild taper corrosion was seen in 90% cases, with 46% severely corroded. SEM confirmed the presence of corrosion debris, pits and fretting damage. However, volumetric wear of the taper surfaces was significantly lower than that of the bearing surfaces ($P = 0.015$). They concluded that corrosion appeared to be the predominant mechanism of material loss at the taper junction.

Langton *et al*[15] prospectively investigated the failure of 111 failed and explanted DePuy MoM THA. One hundred and four of these (94%) had been revised secondary to adverse reactions to metal debris. On visual inspection, 38 of the tapers (34%) showed no identifiable surface change. Volumetric and linear wear analysis showed little or no distinction between these tapers and the unused, sterile tapers used as a control. However the remaining 73 tapers were found to have clear visual surface changes, the patterns of which were markedly similar. The investigating group noted an area of significant damage in a localised circumferential band that corresponded to the insertion of the base of the trunnion. The damage was so severe that in some cases it was palpable. Proximal to this band, the trunnion had left an imprint of its machining grooves. Scanning electron microscopy images confirmed the above findings. Furthermore, the ridges formed by the trunnion grooves appeared flattened with multiple pits. These pits were localised, approximately ten microns in diameter and appeared to be partially filled with inclusion bodies. Further analysis showed that the pits were rich in chromium and the presence of small amounts of chlorides and oxides suggested that there was evidence of local corrosion. The surface around these pits was identical to the manufactured alloy.

Nassif *et al*[16] assessed the trunnion taper junction of fifty large metal-on-metal retrieved implants to determine damage modes and severity of wear. All had heads of greater than 40 mm. The female tapers were examined visually for gross wear and deformation and discoloration associated with oxidative wear was also recorded. Trunnion counterparts were further analyzed using a laser profilometry system to determine location and severity of wear and to measure linear and then correlated to taper geometry and head size. They found that all taper types demonstrated discoloration consistent with corrosive damage, while gross mechanical damage was found in 16% of examined tapers. Corrosive damage of the trunnion interface was present on 58% of implants demonstrating circumferential discoloration of varying severity. Implants that employed "11/13" taper geometries had a significantly higher evidence of mechanical wear and toggling compared to "12/14". Implants from all manufacturers demonstrated consistently high incidence of oxidative wear. Patients with more severe tissue destruction (abductor damage and bone loss) had an 80% incidence of corrosive wear at the trunnion junction. Less severe soft tissue damage was associated more with mechanical wear, but had only a 50% incidence of corrosive wear. They concluded that taper-trunnion micromotion and corrosion in large head MOM THA did not correlate with head size however were significantly affected by trunnion taper geometries with "11/13" taper designs being more susceptible. Nonetheless, corrosive damage is present across all taper designs.

Meyer *et al*[17] also failed to find a correlation between head size and metal ion release. In a retrieval analysis of 114 patients who had revisions of large-diameter head MoM articulations, electrochemical reactions between the stem and adapter were performed. All patients presented with early clinical symptoms; 59 patients had radiographic signs of loosening. However ninety-four percent of patients had instability at the cone/taper interface. Intra operatively, one hundred four patients had metal ion induced foreign body reactions and necrosis. The largest amounts of metal released were titanium or iron. However, their analysis showed a risk for galvanic corrosion and loosening at the cone/taper interface.

A further retrieval study by Hexter *et al*[18], quantified taper corrosion in 161 failed MoM components (head components $n = 128$; femoral stem $n = 33$) from nine hip types with the use of a qualitative subjective scoring system. They unexpectedly noted a region on the female taper surface that contained ridges that directly corresponded with the ridged microthread on the trunnion. The ridges were not present on unimplanted (control) female taper surfaces. Historically the ridged microthread was introduced to trunnions to minimise the risk of burst fracture of ceramic heads. They called this phenomenon "imprinting". The corrosion and imprinting scores were strongly correlated ($r = 0.694$, $P = 0.001$). Corrosion was largely confined to the area of the female taper interface where imprinting had occurred, at the region that had been in contact with the trunnion microthread. Scanning electron microscopy showed evidence of fretting corrosion and substantial mechanical wear within the ridged region on the female taper surface. Their group proposed a process of "mechanically-

assisted crevice corrosion," starting with joint fluid entering the taper junction as a result of pumping of fluid along the machined microthread of the trunnion. This results in galvanic corrosion of the anodic surface (the cobalt-chromium femoral head or taper sleeve). The pattern of corrosion of the head taper is determined by the surface profile of the screw thread of the trunnion, thus leaving an imprinted appearance. Thus they speculated that these ridges exacerbate the mechanical wear at this junction in metal-on-metal hip bearings.

IS THIS A PROBLEM EXCLUSIVE TO MOM REPLACEMENT?

Wear at the neck/stem interface is not exclusive to MoM replacements, however due to the recent interest in this area, more attention has been given to this process. The effect of trunnion wear is also evident with non metal-on-metal bearing surfaces. Several studies have shown that even when using polyethylene inserts, there are still detectable levels of metal ions within the blood, albeit at a much lower rate compared to that of metal on metal bearing recipients. Using identical femoral and acetabular components, MacDonald *et al*[19] randomised two groups of patient to receive either a metal or a polyethylene acetabular insert. At a minimum of 2 years, patients who had metal-on-metal inserts had on average a 7.9-fold increase in erythrocyte cobalt, a 2.3-fold increase in erythrocyte chromium, a 1.7-fold increase in erythrocyte titanium, a 35.1-fold increase in urine cobalt, a 17.4-fold increase in urine chromium and a 2.6-fold increase in urine titanium. Patients receiving a polyethylene insert had no change in erythrocyte titanium, urine cobalt, or urine chromium and a 1.5-fold increase in erythrocyte cobalt, a 2.2-fold increase in erythrocyte chromium, and a 4.2-fold increase in urine titanium.

Isaac *et al*[20]measured whole blood metal ion levels for a series of ceramic-on-metal total hip replacements and compared them metal-on-metal prostheses. The median increase in chromium and cobalt levels at 12 mo was 0.08 μg/L and 0.22 μg/L respectively for the CoM bearings, compared to 0.48 μg/L and 0.32 μg/L for the MoM implants. These findings may suggest that even in patients with well functioning metal or ceramic-on-polyethylene total hip replacements, metal ion release at the modular femoral head-neck junctions remains a source of serum cobalt and chromium particle debris release.

HOW SIGNIFICANT IS THE WEAR DEBRIS DERIVED FROM THE TRUNNION?

It is beginning to become evident that material loss does appear to occur at the region of the trunnion interface. The question still remains about the significance of this debris produced. Hart *et al*[21] retrieved 53 large head metal-on-metal hip replacements and attempted to determine the relative contributions of the bearing and taper surfaces to the total wear volume. Volumetric wear of the bearing surfaces was measured using a coordinate measuring machine and of the taper surfaces using a roundness measuring machine. They found that the mean taper wear volume was lower than the combined bearing surface wear volume ($P = 0.015$). On average the taper contributed 32.9% of the total wear volume, and in only 28% cases was the taper wear volume greater than the bearing surface wear volume.

IS IT THE SAME PARTICLES AS THAT DERIVED FROM THE WEIGHT BEARING SURFACE?

There is no clear evidence pointing to whether the wear particles generated at the taper are dissimilar to those generated at the weight bearing surfaces. However there does appear to be evidence to support the notion that taper derived particles may be more biologically active and destructive to soft tissues.

Langton *et al*[15] have reported data involving 369 explanted metal-on-metal devices from various manufacturers from patients who all suffered with adverse reaction to metallic debris. Volumetric wear analysis of the bearing surfaces and taper junctions was carried out using a coordinate measuring machine. The relationships between total metallic loss and metal ion concentrations and the macroscopic and histological tissue appearance of THA patients were compared to those in resurfacing patients. Resurfacing explants retrieved from patients who had suffered ARMD were found to have significantly higher median rates of volumetric wear than the THAs [10.16 *vs* 2.25 mm^3/year ($P < 0.001$)]. Total volumetric material loss from taper junctions ranged from 0.01 to 21.55 mm^3. When volumetric taper wear was combined with bearing surface wear in the THR patients this total rate of material loss was still significantly less than in the resurfacing patients 2.52 mm^3/year *vs* 10.16 mm^3/year ($P < 0.001$). Despite this, macroscopic tissue destruction and extent of ALVAL (aseptic lymphocyte-dominated vasculitis-associated lesion) infiltration was found to be significantly greater in the THA patients. This may suggest that taper debris may be more able to more readily stimulate a destructive immune cascade than debris from primary bearing surfaces.

Several of the studies mentioned in this paper have also speculated that the material released at the taper may be more biologically active than that derived from the weight bearing surfaces[14,21].

HAS THE DESIGN OF MODERN PROSTHESES CHANGED AND DOES THIS HAVE ANY SIGNIFICANCE?

A direct correlation between design changes to prostheses and trunnionosis is still unclear however several of the studies already mentioned are noticing some

correlations that may be of significant importance. Langton *et al*[15] have highlighted, in their opinion, several changes to the design of large head metal-on-metal hips that may contribute to the phenomenon of trunnionosis. Modern prosthetic designs tend to have a shorter and slimmer trunnions. This is thought to increase the impingement free range of movement by reducing the trunnion skirt. This does however mean that the base of the trunnion now sits very close to the taper which may lead to an increase in edge loading at the trunnion base. In addition, the slimmer and smaller diameter taper means that the surface area of contact between the taper and the trunnion is less. This may reduce the chance of a successful interference fit and thus increase the potential for micromotion as also concluded by Nassif *et al*[16]. Another change in modern trunnion design in that most tend to have a ridge surface machined into the material to accommodate ceramic heads. As shown by Langton *et al*[4] and Hexter *et al*[18], these grooves leave imprints on the majority of tapers and thus increase wear rate and material loss. This could also lead to increased corrosion.

CONCLUSION

Despite contributing less to the total material loss than the bearing surfaces, the head-stem taper junction appears to represent an important source of implant-derived wear debris. Analysis of metal ion levels in THA appear to be higher than hip resurfacings with comparable acetabular designs, Evidence is growing following analysis if the retrieved prostheses show clear patterns of material loss at the taper/trunnion junction, which is likely to involve corrosion. It has been speculated that the material released may be more biologically active than that from the bearing surface. What is certain is that as further analysis is undertaken, the significance or not surrounding the process of trunnionosis will become clearer.

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Normal and abnormal spine and thoracic cage development

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Abstract

Development of the spine and thoracic cage consists of a complex series of events involving multiple metabolic processes, genes and signaling pathways. During growth, complex phenomena occur in rapid succession. This succession of events, this establishment of elements, is programmed according to a hierarchy. These events are well synchronized to maintain harmonious limb, spine and thoracic cage relationships, as growth in the various body segments does not occur simultaneously at the same magnitude or rate. In most severe cases of untreated progressive early-onset spinal deformities, respiratory insufficiency and pulmonary and cardiac hypertension (*cor pulmonale*), which characterize thoracic insufficiency syndrome (TIS), can develop, sometimes leading to death. TIS is the inability of the thorax to ensure normal breathing. This clinical condition can be linked to costo-vertebral malformations (*e.g.*, fused ribs, hemivertebrae, congenital bars), neuromuscular diseases (*e.g.*, expiratory congenital hypotonia), Jeune or Jarcho-Levin syndromes or to 50% to 75% fusion of the thoracic spine before seven years of age. Complex spinal deformities alter normal growth plate development, and vertebral bodies become progressively distorted, perpetuating the disorder. Therefore, many scoliotic deformities can become growth plate disorders over time. This review aims to provide a comprehensive review of how spinal deformities can affect normal spine and thoracic cage growth. Previous conceptualizations are integrated with more recent scientific data to provide a better understanding of both normal and abnormal spine and thoracic cage growth.

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Key words: Spine; Thorax; Thoracic cage; Growth; Early-onset spinal deformity; Children

Core tip: Development of the spine and thoracic cage is a complex series of events involving multiple metabolic processes, genes and signaling pathways. During growth, complex phenomena follow a rapid succession. This succession of events, this establishment of elements, is programmed according to a hierarchy. Complex spinal deformities alter normal growth plate development and vertebral bodies become progressively distorted, perpetuating the disorder. Therefore, many scoliotic deformities can become growth plate disorders over time.

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INTRODUCTION

Growth is the basis of development. Normal spines are characterized by symmetric and harmonious growth, although spinal growth is the product of more than 130 growth plates working at different paces. In severe spinal deformities, growth becomes asymmetrical as a result of growth plate disorganization. Complex spinal deformities alter normal growth plate development, and vertebral

bodies become progressively distorted, perpetuating the disorder. Therefore, many scoliotic deformities can become growth plate disorders over time[1-5].

Development of the spine and thoracic cage is a complex series of events involving multiple metabolic processes, genes and signaling pathways. During growth, complex phenomena follow each other in rapid succession. This succession of events, this establishment of elements, is programmed according to a hierarchy. These events are well synchronized to maintain harmonious limb, spine and thoracic cage relationships, as growth in the various body segments does not occur simultaneously at the same magnitude or rate[5-9].

The slightest error or modification can lead to a malformation or deformity that has negative effects on standing and sitting height; thoracic cage shape, volume and circumference; and lung development. These distortions alter the virtuous circle of growth[1,6,8,10-12].

Spinal deformities influence the various skeletal and organic components of the thoracic cage and cavity; however, these influences are not fully understood[1-3,5,8,10,11].

Only comprehensive knowledge of normal growth parameters allows a better understanding of both normal and abnormal spine and thoracic cage growth and of the pathologic changes in a growing spine and chest resulting from a spinal deformity[1-3].

As a spinal deformity progresses, not only is spinal growth affected, but the size and shape of the thoracic cage are also modified. In a "domino effect", this distortion of the thorax eventually interferes with lung development and cardiac function, leading affected children to develop potentially lethal TIS and *cor pulmonale*[11]. Cardiac and respiratory problems can develop after precocious vertebral arthrodesis or as a consequence of pre-existing severe vertebral deformities and can vary in pattern and timing according to the existing degree of the deformity[1-3,5,7-10,12-15].

The aim of this work is to provide a comprehensive review of how spinal deformities can affect normal spine and thoracic cage growth.

RESEARCH

This review aims to provide a comprehensive review of how spinal deformities can affect normal spine and thoracic cage growth. The work is based on a search of English and French literature from 1970 to 2013 in the PubMed database. A manual search of the references cited in the retrieved articles was also performed. Some of the data presented in this article were gathered from studies performed in the 1980s and 1990s and their applicability to populations of different ethnicities, geographical regions and developmental stages has yet to be elucidated. The universal applicability of these results is therefore open to debate. Previous conceptualizations have been integrated with newer scientific data to provide a basis for a better understanding of both normal and abnormal spine and thoracic cage growth.

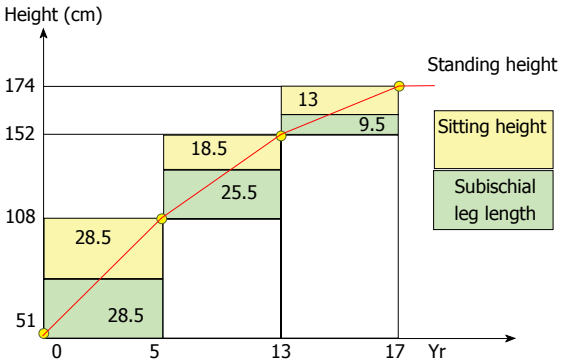

Figure 1 Sitting and standing height. From birth to age five, the development of the trunk is substantial. Between age 5 and puberty, the lower extremities grow more than the trunk and the spinal growth rate decreases from 2.2 to 1.1 cm/year. During puberty, the trunk grows more than the lower extremities. At the beginning of puberty, the remaining standing height is approximately 20 cm, of which 2/3 is at the level of the trunk and 1/3 is at the level of the lower extremities. At Risser I (menarche), the remaining growth of the trunk is approximately 3 to 4 cm.

GROWTH OF THE SPINE

Neurocentral synchondrosis

Neurocentral synchondrosis is a physis in the spine located at the junction of the pedicle and the vertebral body and is important in the growth of the vertebral body and the posterior arch. In a growing pig model, unilateral transpedicular screw fixation traversing the neurocentral synchondrosis can produce asymmetric growth of the synchondrosis and create scoliosis with the convexity on the side of the screw fixation. However, in humans, neurocentral synchondrosis fuses at approximately age nine, and by five years of age, the spinal canal has already grown to approximately 95% of its final size. Therefore, perivertebral arthrodesis performed after age five has no influence on the size of the spinal canal[1,2,4,16].

Sitting height

Sitting height correlates strictly with trunk height and is, on average, approximately 34 cm at birth and 88 and 92 cm at the end of growth for girls and boys, respectively. In children with severe spinal deformities, loss of sitting height is related to the severity of the deformity. For this reason, it is important to monitor changes in the sitting height rather than in the standing height in children with scoliosis. During the first three years of life or if a child has a neurologic disorder or a collapsing spine, it is recommended that the sitting height be measured in the supine position.

Growth is a succession of acceleration and deceleration phases comprising three periods (Figure 1). The first period is from birth to age five and is characterized by a gain in sitting height of 27 cm, with 12 cm of growth occurring during the first year of life. The second period is from age five to ten years and is a quiescent phase, as sitting height increases by 2.5 cm/year. The third period corresponds to puberty and is characterized by a gain in sitting height of approximately 12 cm[1-3]. At the begin-

Figure 2 Spine at birth. At birth, only 30% of the spine is ossified. At birth, the T1-S1 segment measures approximately 20 cm and reaches 45 cm at skeletal maturity.

Table 1 Evaluation of T1–T12 and L1–L5 spinal segments from birth to skeletal maturity

Developmental stage	Spinal segment			
	Boys		Girls	
	T1-T12	L1-L5	T1-T12	L1-L5
Newborn	11	7.5	11	7.5
Child	18	10.5	18	10.5
Young	22	12.5	22	12.5
Adult	28	16	26	15.5

Values are averages and expressed in cm[15].

ning of puberty, the average remaining growth in the sitting height is approximately 12.5 cm for boys and approximately 11.5 cm for girls; 2/3 of this growth occurs during the "peak height velocity" or "acceleration phase". The average remaining growth in sitting height during the "deceleration phase" is approximately 4 cm for boys and 3.5 cm for girls [1-4,10].

T1-S1 spinal segment

Assessment of the T1-S1 spinal segment is important, as many spinal deformities originate in this segment. At birth, the T1-S1 segment measures approximately 20 cm and reaches 45 cm at skeletal maturity (Figure 2). The height of the spine accounts for 60% of total sitting height, and the head and pelvis account for the remaining 40%. The T1-S1 segment accounts for approximately 50% of the sitting height; two-thirds of this segment is thoracic spine, and one-third is lumbar spine. The T1-S1 segment grows approximately 10 cm during the first five years of life (2 cm/year), approximately 5 cm between ages five and 10 (1 cm/year), and approximately 10 cm between age 10 and skeletal maturity (1.8 cm/year) (Table 1). In patients who developed scoliosis before four years of age, early surgery does not modify the deformation produced by the scoliosis or preserve respiratory function, even when the anterior growth of the spine is arrested. Therefore, it is very important for a surgeon to consider the state of skeletal maturity and the amount of growth remaining in the spinal segment to be fused[1,2,5,6,11].

T1-T12 spinal segment

T1-T12 is the posterior pillar of the thoracic cage and an important segment. It measures, on average, approximately 12 cm at birth, 18 cm at five years of age, and 27 cm at skeletal maturity. The thoracic spine constitutes 30% of the sitting height, and each single thoracic vertebra and its disc account for 2.5% of the sitting height. In normal children, the longitudinal growth of the thoracic spine is approximately 1.3 cm/year between birth and five years, 0.7 cm/year between the ages of five and 10 years, and 1.1 cm/year during puberty. A precocious arthrodesis of the T1-T12 segment affects thoracic growth and lung development. In young children with progressive deformities, there is a decrease in longitudinal growth and a loss of the normal proportionality of trunk growth[1-3,5,11]. Untreated progressive early-onset spinal deformities have been associated with short trunk, short stature and, often, respiratory insufficiency. In untreated patients, the loss of vital capacity in those with early-onset scoliosis has been shown to be 15% greater than in those with adolescent idiopathic scoliosis. Emans *et al*[15] showed that pelvic inlet width, measured by computerized tomograms or plain radiographs, is an age-independent predictor of the expected thoracic dimensions in unaffected children and adolescents. That study also established normal range standards for chest and spine dimensions to assist in the assessment of treatment outcomes[2,15].

The twelve thoracic vertebral bodies have costal facets that articulate with the costal heads of the ribs on each side and two transverse processes that articulate with the tubercles these ribs. Together, these synovial articulations constitute the costo-vertebral joint and play an essential role in elevating and depressing the ribs to increase the anterior-posterior and transverse diameters of the thoracic cavity during respiration.

Respiratory problems can develop after a precocious vertebral arthrodesis or as a consequence of pre-existing severe vertebral deformities and can vary in pattern and timing according to the existing degree of deformity. Variations in the extent of experimental arthrodesis also have different effects on both growth and thoraco-pulmonary function. Early spinal fusion for progressive scoliosis further limits spinal growth, leading to diminished thoracic height and a long-term loss of vital capacity. Therefore, early spinal fusion, especially if performed in the thoracic region, is a cause of respiratory insufficiency and adds loss of pulmonary function to the pre-existing spinal deformity. Karol *et al*[13] reported that a thoracic spine height of 18 cm or more is necessary to avoid severe respiratory insufficiency. In addition, they showed that children undergoing a precocious spinal fusion ex-

hibit reductions in thoracic depth and shorter T1-T12 segments compared to normal subjects. The forced vital capacity may decrease by 50% of the predicted volume if more than 60% of the thoracic spine, eight thoracic vertebrae, is fused before eight years of age. In their clinical work, Karol *et al*[13] confirmed some of the previously published experimental findings published [5].

L1-L5 spinal segment

The lumbar vertebrae have well-developed vertebral bodies and spinous, transverse, and superior articular processes that provide attachment sites for ligaments and muscles (erector spinae and transversospinalis muscles). The L1-L5 length is, on average, approximately 7.5 cm at birth and 16 cm at skeletal maturity. The lumbar spine constitutes approximately 18% of the sitting height, and a single lumbar vertebra and its disc account for 3.5% of sitting height. At 10 years of age, the lumbar spine has reached approximately 90% of its final height but only 60% of its definitive volume. A perivertebral arthrodesis of the lumbar spine performed after 10 years of age results in a minimal loss of sitting height[1,2].

GROWTH OF THE CHEST

Thoracic cage volume, circumference and shape

At birth, the thoracic cage volume is approximately 6% of its final size and reaches 30% by age five and 50% by age 10. Between age 10 and skeletal maturity, the thoracic cage volume doubles before it ultimately stops growing. Not all types of thoracic growth progress at the same speed. At five years of age, the trunk has reached approximately 66% of its final height, whereas thoracic volume is only 30% of its definitive size.

The thoracic circumference corresponds to 95% of the sitting height and increases during the first five years of life and during puberty. On average, the thoracic perimeter is 32.3 cm in boys and 31.5 cm in girls at birth, and it attains a mean value of 89.2 cm and 85.4 cm, respectively.

The thoracic cage shape varies with age. At birth, the difference between the thoracic depth and width is minimal, and the thoracic depth/thoracic width ratio is very close to 1. Conversely, at skeletal maturity, the thoracic depth/thoracic width ratio is less than 1, as width increases more than depth. For this reason, the overall thoracic cage shape evolves from ovoid at birth to elliptical at skeletal maturity. At the end of growth, the thorax has an average depth of 21 cm in boys and 17.7 cm in girls and an average thoracic width of 28 cm and 24.7 cm in boys and girls, respectively. At skeletal maturity, the thoracic depth and width represent approximately 20% and 30% of sitting height, respectively. The thoracic cage is part of the rib-vertebral-sternal complex[1-4,6,8-11].

Emans *et al*[15] reviewed a total of 198 CT scans of healthy patients ranging from 0 to 21 years of age and showed that pelvic inlet width, measured by computerized tomograms or plain radiographs, is an age-independent predictor of the expected thoracic dimensions in unaffected children and adolescents.

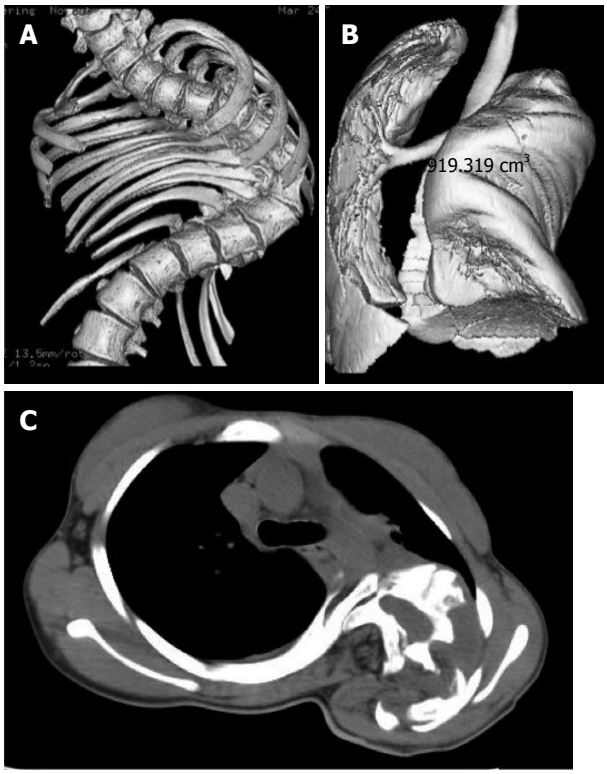

Figure 3 Thoracic cage distortion and lung compression. Lung (A) and thoracic cage (B) growth volumes increase in a non-linear fashion over the first twenty years of life. The volumes of both structures are proportional to height in the absence of spinal disease. Spinal deformities alter normal spine and thorax growth, prevent the lungs from expanding and lead to thoracic insufficiency syndrome (C).

Lung growth

Lung growth is a complex topic because different pulmonary structures and regions grow at different rates. At birth, a newborn has the same number of conducting airways as an adult. Tracheal caliber increases 2 to 3 fold between birth and skeletal maturity. In contrast, the peripheral regions of the lung that contain alveoli and pulmonary capillaries (acinar regions) undergo substantial postnatal growth and development. From infancy to adulthood, alveolar number increases by up to 6 fold. The alveolar-capillary surface area increases by more than 10 fold as a result of increased alveolar number, complexity and septation, as well as capillary development. Therefore, early-onset scoliosis adversely affects thoracic growth at a critical period of maximum respiratory growth, which induces irreversible changes in the thoraco-pulmonary structure[11,17-20].

Lung and thoracic cage growth volume increase in a non-linear fashion over the first twenty years of life, with rapid growth occurring before 4 years of age and during the pubertal growth spurt[11]. In the absence of spinal disease, the volumes of both the lungs and thorax are proportional to height, and norms for lung function in children, including lung volumes, are based primarily on standing height (Figure 3). Therefore, double extrinsic

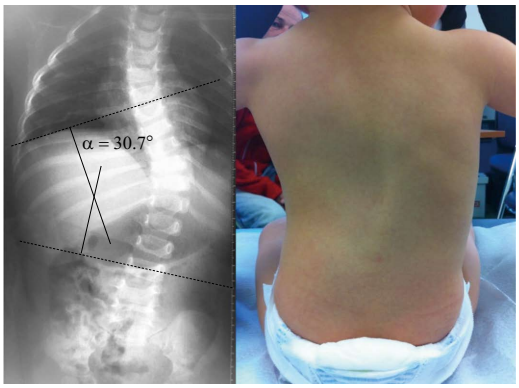

Figure 4 Early-onset spinal deformity. Thirteen-month-old female with progressive infantile scoliosis.

disturbances of the chest wall functions are a potential source of respirator failure, as thoracic cage deformities prevent hyperplasia of lung tissue and intrinsic alveolar hypoplasia. It is important to preserve both thoracic growth and lung volume during this critical period of life[7,11].

In a review of 1050 normal CT scans of the chest with three-dimensional volumetric reconstruction of the pulmonary system, Gollogly *et al*[18] showed that lung parenchyma volume is a function of age (Figure 4).

Effects of early-onset scoliosis on thoracic cage development

It is known that spinal deformations adversely affect thoracic development by changing the shape of the thorax and reducing its normal motility. The "rib-vertebral-sternal complex", which encloses the three-dimensional thoracic cavity, tends to constitute an elastic structural model similar to a cube in shape[7]. However, in the presence of scoliosis, it becomes flat, rigid and elliptical and prevents the lungs from expanding. These deformities can be lethal in the most severe cases as a result of reciprocal interactions and influences among the various skeletal and organic components of the thoracic cage and cavity that are not well understood.

Several studies have focused on the anatomical influences of experimental arthrodesis on spinal growth, chest development, and thoraco-pulmonary function. These reports have demonstrated that early arthrodesis, as well as severe spinal deformities, can adversely affect the development of the spine and the thorax by changing their shape and reducing normal mobility[5-10,21].

Post-mortem studies showed that patients with early-onset deformities have fewer alveoli than expected and exhibit emphysematous changes in the existing alveoli[11,17]. These studies suggest that mechanical compression is not a factor in reducing the number of alveoli; this reduction is most likely due to a premature cessation of alveolar proliferation. Indeed, from the late fetal stage to four years of age, the number of alveoli increases by a factor of 10, and the development of the bronchial tree ends at approximately eight to nine years of age.

Canavese *et al*[5-9] evaluated the consequences of disturbed growth of vertebral bodies on the development of the ribs, sternum, and lungs. These consequences are much more evident when arthrodesis is performed at the critical T1-T6 segment of the thoracic spine. The development of the thoracic cage and lungs is a complex process that requires perfect synergy among the various components of the rib-vertebral-sternal complex. Alterations to any of these elements affect and change the development and growth of the others. Therefore, to preserve thoracic motility and permit a normal development of the respiratory tree, treatment should not only focus on the spine but also consider the rib-vertebral-sternal complex as a whole[5,6,8-11].

Maximal compensatory lung growth may well be limited to a specific time after birth and diminish after the period of alveolar multiplication is complete. Published estimates of this period of alveolar multiplication vary from 1 to 8 years of age. The optimal timing of surgical intervention to expand the thoracic cage, minimizing progressive postnatal pulmonary hypoplasia and maximizing compensatory lung growth, still needs to be determined. It is likely to be earlier rather than later in childhood[5-11,18-20], as the "golden" period for both thoracic spine and thoracic cage growth occurs between birth and 4 years of age and coincides with lung development[11,17-20].

DISCUSSION

Only comprehensive knowledge of normal growth parameters allows a better understanding of the pathologic changes in a growing organism resulting from an early-onset spinal deformity. As the spinal deformity progresses, in a "domino effect", not only are spinal growth is affected, but size and shape of the thoracic cage are also modified. This distortion of the thorax interferes with lung development. Over time, the spinal disorder changes in nature from a mainly orthopedic issue to a severe pediatric systematic disease, with thoracic insufficiency syndrome[1-11,22,23] and *cor pulmonale*[14].

In normal children, the longitudinal growth of the thoracic spine is approximately 1.3 cm/year between birth and 5 years of age, 0.7 cm/year between the ages of 5 and 10 years and 1.1 cm/year during puberty.

The thoracic spine from T1 to T12 is the posterior pillar of the thoracic cage and is an important segment. A precocious arthrodesis of this segment can have repercussions on thoracic growth and lung development. In young children with progressive deformities, arthrodesis can result in decreased of longitudinal growth and a loss of normal proportionality of trunk growth. Karol *et al*[13] showed that a thoracic spine height of 18-22 cm or more is necessary to avoid severe respiratory insufficiency. They showed that children undergoing a precocious spinal fusion have a reduced thoracic depth and a shorter T1-T12 segment compared to normal subjects[13]. The forced vital capacity may decrease by 50% of the predicted volume if more than 60% of the thoracic spine, or 8 thoracic verte-

brae, is fused before 8 years of age[11,17-19, 21-24].

Untreated progressive early-onset spinal deformity has been associated with short trunk, short stature and often respiratory insufficiency. In untreated patients, the loss of vital capacity in those with early-onset scoliosis is 15% greater than in those with adolescent idiopathic scoliosis[1-5,11,12,24]. Moreover, spinal fusion is a cause of respiratory insufficiency and adds a loss of pulmonary function[13] to the pre-existing spinal deformity.

The time between birth and 8 years of age is the golden period for thoracic spine and thoracic cage growth and coincides with lung development. From birth to four years, the number of alveoli increases by a factor of 10, and the development of the bronchial tree ends at 8 to 9 years of age. Gollogly *et al*[18] showed in a CT scan study that lung parenchyma volume is a function of age. The lung parenchyma volume is approximately 400 cc at birth, 900 cc at 5 years of age, 1500 cc at 10 years of age, and is approximately 4500 cc for boys and 3500 for girls at skeletal maturity. Therefore, early-onset scoliosis adversely affects thoracic growth at the critical period of maximum "respiratory growth", inducing irreversible changes in the thoraco-pulmonary structure[1-11,18-20,24].

Campbell *et al*[22,23] described thoracic insufficiency syndrome, the inability of the thorax to ensure normal breathing. They showed that an opening wedge thoracostomy can increase the thoracic volume ("parasol effect")[11]. It is important to perform this procedure before the end of bronchial tree development at 8 years of age[1-4,6,8-11,17-20,22,23,25]. However, this procedure has drawbacks, including an increase in the stiffness of the thoracic cage resulting in an increase in the amount of energy needed to breathe.

The crankshaft phenomenon is the progression of a spinal deformity when the anterior portion of the spine continues to grow while the posterior portion is blocked by arthrodesis[26,27]. Golberg *et al*[12] showed that in patients who develop scoliosis before the age of 4, early surgery does not modify the deformation produced by the scoliosis and does not preserve respiratory function, even when the anterior growth of the spine is arrested. Therefore, it is very important for a surgeon to consider the state of skeletal maturity and the amount of growth remaining in the spinal segment to be fused. Similarly, Dubousset *et al*[21] showed that severe spinal deformities lead to penetration of the apical portion of the deformity inside the thoracic cage ("endo-thoracic hump") and described the "spinal penetration index"[21].

It is now known that spinal deformations adversely affect the development of the thorax by changing its shape and reducing its normal motility. Metha *et al*[24] demonstrated that a unilateral deformity of the spine or the thorax induces scoliosis and thoracic cage deformities with asymmetrical lung volume[24]. Moreover, Canavese *et al*[6] reported that the "rib-vertebral-sternal complex", which encloses the three-dimensional thoracic cavity, tends to constitute an elastic structural model similar to a cube in shape. In the presence of scoliosis, it becomes flat, rigid and elliptical and prevents the lungs from expanding. These deformations can be lethal in the most severe cases and result from mutual interactions and influences among the various skeletal and organic components of the thoracic cage. Alterations in some elements affect the development and growth of the others[6-11]. These influences are much more evident when an arthrodesis is carried out in the "critical portion" (T1-T6 segment) of the thoracic spine[1-3,5,7-11]. Early spinal fusion, especially if performed in the thoracic region, results in respiratory insufficiency and adds loss of pulmonary function to the pre-existing spinal deformity[11,17-19, 21-24]. Therefore, arthrodesis carried out in the thoracic spine at an early age does not address the impact of the deformity on lung parenchyma development or the preservation of pulmonary function. Its ability to prevent deformity progression has been questioned. In children with spinal deformities with strong progression potential, expansible materials can be used to support the expansion of the thoracic cage and lung growth[1-3,5,11,20,22-25].

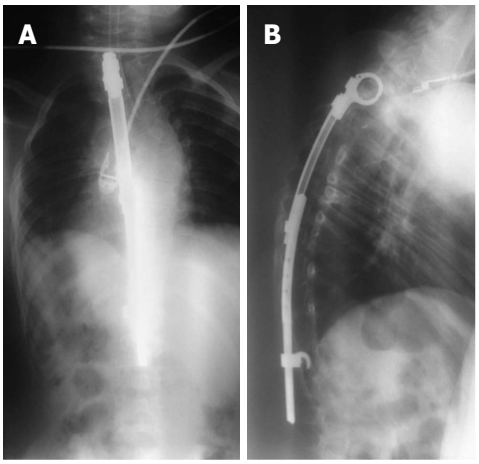

Figure 5 Controlled growth. Eight-year-old male with congenital scoliosis treated with "spine to rib" vertical expandable prosthetic titanium rib. Treatment of the growing spine is a unique challenge and involves preservation of the thoracic spine, thoracic cage, and lung growth without reducing spinal motion.

Modern techniques and instrumentation control only one plane of the deformity, as distraction forces are applied to the spine or to the thoracic cage. Over the past few years, several studies demonstrated that near-normal growth can be attained with the vertical expandable prosthetic titanium rib, growing rods or a Shilla-type procedure. All of these techniques aim to restore normal spinal growth by controlling the progression of the deformity[26-30].

However, there is currently no instrumentation that is able to control the three-dimensional nature of early-onset spinal deformities. To preserve thoracic motility and permit the normal development of the respiratory tree, treatments should not focus only on the spine but should consider the "rib-vertebral-sternal complex" as a whole[2-6]. In very young children, surgery should be limited as much as possible and extensive arthrodesis of the spine should be avoided (Figure 5).

CONCLUSION

A deformed spine does not grow normally!

A critical analysis of all growth parameters over time will allow for an improved understanding the full magnitude of the deficits induced by early-onset spinal deformities. Spinal and thoracic growth obey strict rules and can be controlled only by adhering to their requirements.

Four different scenarios can be identified: (1) The clinical picture worsens, and the abnormal growth leads to a deficit that sustains the deformity and continues to worsen ("snowball effect"). Reduced body mass index due to weight loss weakens the respiratory muscles and makes breathing more difficult; (2) The clinical picture remains stable; (3) The clinical picture improves slightly with the improvement of clinical parameters, including weight, vital capacity, and sitting height; and (4) The clinical picture returns to normal. In this ideal scenario, all clinical parameters return to normal and the deficit induced by the deformity is eliminated. Unfortunately, this is unlikely to happen, as most children with severe spinal deformities present with a short trunk, significant loss of vital capacity, and disproportionate body habitus at skeletal maturity. Surgical strategies must consider the complete life span of the patient and should provide answers to two basic questions: (1) What is the functional benefit? and (2) What is the morbidity risk?

It must be emphasized that the thoracic cage is part of the deformity (rib-vertebral-sternal complex). There is a normal interaction between the spine, thoracic cage, and lungs. Both early-onset spinal deformities and precocious spinal arthrodesis alter spinal growth and affect the development the thorax by changing its shape and reducing its normal mobility. Treatment of the growing spine is a unique challenge and involves preservation of the thoracic spine, thoracic cage, and lung growth without reducing spinal motion. It is no longer generally accepted that a short, straight spine produced by an early fusion is better that a long, curved spine.

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FIELD OF VISION

Multi-factorial sustainability approach is necessary to preserve knee function following osteoarthritis diagnosis

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Abstract

Knee function preservation following a diagnosis of osteoarthritis may benefit from healthy patient lifestyles, exercise or activity habits, and daily living routines. Underlying societal issues and social roles may contribute further to both ecological and knee function preservation concerns. Based on sustainability theory and social ecology concepts we propose that factors such as health history, genetic predisposition, socio-environmental factors and local-regional-global physiological system viability contribute to knee function preservation. Addressing only some of these factors or any one factor in isolation can lead the treating physician, surgeon and rehabilitation clinician to less than optimal treatment effectiveness. An example is presented of a 57-year-old man with medial tibiofemoral osteoarthritis. In the intervention decision-making process several factors are important. Patients who would benefit from early knee arthroplasty tend to place osteoarthritic knee pain elimination at the top of their list of treatment expectations. They also have minimal or no desire to continue impact sport, recreational or vocational activities. In contrast, patients who are good candidates for a knee function preservation treatment approach tend to have greater expectations to be able to continue impact sport, recreational or vocational activities, are willing and better able to implement significant behavioral changes and develop the support systems needed for their maintenance, are willing to tolerate and live with minor-to-moderate intermittent knee pain, and learn to become more pain tolerant.

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Key words: Knee surgery; Treatment planning; Comprehensive care

Core tip: Total knee arthroplasty likely provides the best chance for knee osteoarthritic pain elimination. What is less understood by the patient is the needed reduction in recreational sport or vocational activities that will likely follow this intervention and the negative impact that elimination of these activities will potentially have on local-regional-global physiological systems, psychosocial factors, and quality of life. Patient satisfaction regarding the selection of either early knee arthroplasty or knee joint preservation is largely based on their expectations and the likelihood that these expectations are realistic.

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INTRODUCTION

To sustain natural systems there must be an ongoing balance between environmental, social, and economic considerations[1]. A key element of sustainability theory is to identify the most vulnerable component. In the knee, ar-

ticular cartilage, which has a poor healing capacity is the last line of defense from osteoarthritis (OA). Environmental sustainability benefits through the development of nature friendly cities, gardens, and parks. Knee function preservation may similarly benefit from healthy lifestyles, exercise or activity habits, and daily living routines. Underlying societal issues and social roles may contribute further to both ecological and knee function preservation concerns. Based on sustainability theory and social ecology concepts we propose that factors such as health history, genetic predisposition, socio-environmental factors and local-regional-global physiological system viability contribute to knee function preservation[2,3]. Addressing only some of these factors or any one factor in isolation can lead the treating physician, surgeon and rehabilitation clinician to less than optimal treatment effectiveness.

As an example we present a 57-year-old man with medial tibiofemoral compartment knee pain who displays a 33% reduction in articular cartilage thickness on standing, weightbearing radiographs. He has a strong desire to continue recreational soccer and tennis with his club teams. On a 10-cm visual analog scale he rates his medial knee pain with walking as 3-5, using up his pain medication prescription in approximately 3 mo. He considers himself to be 10 kg overweight [body mass index (BMI) = 29] and is interested in reducing his bodyweight. Intervention now with high tibial osteotomy and an individualized therapeutic exercise program[4-7] that makes appropriate use of social cognitive theory principles[8] to effect needed behavioral changes would greatly enhance this patient's likelihood for continuing recreational soccer and tennis participation. Without this needed intervention, by the time he is 60-years of age his condition may have progressed to two or more knee compartments and his bodyweight may have increased another 10 kg (BMI = 32) leading his treating orthopaedist to recommend total knee arthroplasty.

Total knee arthroplasty likely provides the best chance for knee OA pain elimination[9-11]. What is less understood by the patient is the needed reduction in recreational sport or vocational activities that will likely follow this intervention and the negative impact that elimination of these activities[12,13] will have on local-regional-global physiological systems, psychosocial factors, and lifestyle. Assuming a life expectancy of 85 years of age; the next 25 years following TKA will likely include reduced medial right knee pain, but also reduced participation in social roles and responsibilities that have largely contributed to his being the person that he is, thereby decreasing quality of life. In contrast, early intervention with high tibial osteotomy[14], weight loss, and behavioral change-inducing individualized therapeutic exercises with a social cognitive theory approach[8,15] when he was 57 years of age may have been sufficient to enable him to continue recreational soccer and tennis participation. Simultaneously this intervention may have served as the conduit to effecting both physiological and psychosocial benefits, improved coping skills, self-efficacy and stress resilience levels, and the maintenance of decision-making independence regarding the activities he chooses to perform, as well as the frequency and intensity of those activities. Maintenance of cognitive as well as functional independence is essential to healthy aging and early knee OA treatment intervention including a less invasive surgical procedure has the potential to serve as the needed conduit to improved general health and needed psychobehavioral changes in addition to knee function preservation. The key ingredient in this decision-making process is the patient's willingness and ability to comply with the necessary lifestyle changes and with an individualized therapeutic exercise program that relies on social cognitive theory approach concepts of modeling, self-efficacy development, reciprocal determinism between patient and environment, and vicarious learning to effect positive behavioral changes that improve physical and emotional health, general health, and preserve knee function.

In the decision-making process to direct the patient to the best clinical care pathway several factors are important. Patients who would benefit most from early knee arthroplasty tend to place knee OA pain elimination at the top of their list of treatment expectations. They also have minimal or no desire to continue impact sport, recreational or vocational activities. They are less likely to be willing or be able to make significant changes to existing negative health behaviors such as excessive bodyweight[13] or smoking. Finally, before selecting this pathway they should understand that this intervention was designed primarily for elderly patients and it is that population that appears to be the most satisfied with that treatment approach[11,16-18]. However, the knee function expectations of that group are not very high[11]. In contrast, patients who are good candidates for a knee function preservation approach such as meniscal repair, meniscal transplantation, chondroplasty, or osteotomy[19] tend to have greater expectations to be able to continue impact sport, recreational or vocational activities. They also tend to be more willing and better able to implement significant behavioral changes, to develop the support systems needed for their maintenance, are willing to tolerate and live with minor-to-moderate intermittent knee pain and are willing to learn to become more pain tolerant. Satisfaction regarding the selection of either clinical care pathway is largely based on patient expectations and the likelihood that these expectations are realistic[2,3,11]. Patients should understand that the knee function preservation clinical care pathway was designed for young or middle-aged patients who have the capacity for commitment, implementing, and achieving the needed behavioral changes. In the battle against knee OA treating clinicians are trying to preserve knee function. Selecting a salvage procedure such as knee arthroplasty too early in the disease progression before completely understanding patient expectations[20] may lead to less than optimal treatment effectiveness. This is particularly

true for more active patients who are willing to live with intermittent knee pain to be able to continue impact activities deemed to be of high quality of life value.

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TOPIC HIGHLIGHT

Hisataka Yasuda, PhD, *Series Editor*

Role of RANKL/RANK in primary and secondary breast cancer

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Abstract

Bone is one of the most preferential metastatic target sites of breast cancer. Bone possesses unique biological microenvironments in which various growth factors are stored and continuously released through osteoclastic bone resorption, providing fertile soil for circulating breast cancer cells. Bone-disseminated breast cancer cells in turn produce osteotropic cytokines which modulate bone environments. Under the influences of breast cancer-produced cytokines, osteoblasts express elevated levels of Ligand for receptor activator of nuclear factor-κB (RANKL) and stimulate osteoclastogenesis *via* binding to the receptor receptor activator of nuclear factor-κB (RANK) and activating its downstream signaling pathways in hematopoietic osteoclast precursors, which causes further osteoclastic bone destruction. Establishment of crosstalk with bone microenvironments (so called vicious cycle) is an essential event for metastatic breast cancer cells to develop bone metastasis. RANKL and RANK play a central role in this crosstalk. Moreover, recent studies have demonstrated that RANKL and RANK are involved in tumorigenesis and distant metastasis independent of bone microenvironments. Pharmacological disruption of the RANKL/RANK interplay should be an effective therapeutic intervention for primary breast tumors and bone and non-bone metastasis. In this context, denosumab, which is neutralizing monoclonal antibody against RANKL, is a mechanism-based drug for the treatment of bone metastases and would be beneficial for breast cancer patients with bone metastases and potentially visceral organ metastases.

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Key words: Bone metastasis; Osteoclasts; Bone resorption; Osteoblasts; Stromal cells; Epithelial-mesenchymal transition; Bone pain

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INTRODUCTION

Due to dramatic advancement of cumulative anti-cancer treatments, surgeons and medical oncologists are confidently able to control primary tumors these days. In contrast, however, metastasis to distant organs is still uncontrollable and has been one of the primary causes of increased mortality and morbidity in cancer patients. Hence, control of distant organ metastasis is very important and an ultimate goal in the treatment and management of cancer patients.

Breast cancer frequently spreads to bone as well as lung, liver and brain[1]. Notably, bone metastases are not readily detected, because they are asymptomatic until patients complain bone pain in most cases. Furthermore,

it usually develops at later stages of illness and many cancer patients die before bone metastases are clinically detected and become problematic. However, over the last a decade bone metastasis has come under the spotlight since it causes many problems in the management of cancer patients who survive long enough to develop bone metastases due to improved anti-cancer therapies. Metastases to bone *per se* do not directly affect survival of cancer patients but virtually worsen quality of life in these patients by causing devastating bone pain and skeletal-related events (SREs) including pathological fractures, spinal compression and hypercalcemia, which indirectly lead to earlier death[1]. Furthermore, treatments of bone metastases significantly increase medical care cost[2]. Of note, there is increased frequency of bone metastases in breast, lung and prostate cancer of which incidence is sharply rising in developed countries. It is, therefore, evident that control of bone metastasis will be critical to properly manage cancer patients under good quality of life and also reduce healthcare costs.

In this article, mechanism of bone metastasis in breast cancer is overviewed at cellular and molecular levels with a special focus on the role of ligand for receptor activator of nuclear factor-κB (RANKL) and receptor activator of nuclear factor-κB (RANK). Furthermore, the pharmacological actions and clinical benefits of the anti-RANKL neutralizing monoclonal antibody denosumab in the management of bone metastasis in breast cancer are reviewed and discussed.

CANCER METASTASIS TO DISTANT ORGANS

There are multiple biological steps in distant metastasis of cancer[3]. However, it can be divided into two broad processes from the view point of organ-selective metastasis, namely before and after cancer cells arrest in target organs (Figure 1). Before cancer cells reach distant target organs, they grow and invade into the surrounding tissues at primary site, induce angiogenesis to support primary tumor development and enter the circulation (intravasation), escape from host immune cell attack by forming cell aggregates and migrate to their target organ. Cancer cells migrating in the circulation are called circulating tumor cells (CTCs), which are proposed to be a promising target to interrupt distant metastatic cascades[4]. This process is likely common for all metastatic cancer cells regardless of the target organ.

Next process is unique depending on the target organ in which CTCs migrate. After CTCs reach their target organ, here bone, they egress circulation (extravasation) and arrest in the target organ. These cancer cells are called disseminated tumor cells (DTCs). It is shown that there is a significant correlation between the detection of DTCs in bone marrow and higher risk of recurrence and disease-specific death in breast cancer[5]. DTCs change their phenotype under the influence of bone environments to adjust to and proliferate and survive in bone (Figure 1). Consistent with this notion, we found that the bone-seeking clone of the MDA-MB-231 human breast cancer shows altered biological phenotype from parental and brain-seeking clone that allow them to selectively home and colonize bone[6,7]. Establishment of the interactions with bone environments is the most critical step for disseminated breast tumor cells to develop bone metastases. Hence, dissection of bone environments at cellular and molecular levels in the context of cancer cell colonization is important to understand the mechanism of bone metastasis in breast cancer.

RANKL EXPRESSION AND VICIOUS CYCLE IN BONE ENVIRONMENTS

Bone is a storehouse of growth factors such as insulin-like growth factors (IGF), transforming growth factor-β (TGF-β), fibroblast growth factors, platelet-derived growth factors and bone morphogenetic proteins[8]. These growth factors are continually released into the bone marrow cavity *via* osteoclastic bone resorption during physiological bone remodeling (Figure 2). Thus bone is fertile soil for metastatic cancer cells to colonize. In this regard, bone represents the organ that exteriorized the concept of "Seed and Soil" theory proposed by Paget[9] more than 120 years ago. Bone-derived IGF is shown to promote proliferation and suppress apoptosis in breast cancer cells by activating Akt/NF-κB pathway[10]. On the other hand, bone-derived TGF-β stimulates the production of osteoclast-activating cytokines such as parathyroid hormone-related protein (PTH-rP)[11], prostaglandin E_2 (PGE_2)[12] and interleukin-11 (IL-11)[13] in breast cancer cells. These factors in turn further stimulate osteoclastic bone resorption, followed by enhanced release of bone-stored growth factors, thus establishing "vicious cycle" (Figure 2)[7,14-16].

Of note, these osteoclast-activating cytokines do not directly activate osteoclasts but they first bind and activate osteoblasts/stromal cells which express the receptors for these cytokines[17]. These cytokines up-regulate the production of RANKL that is a potent stimulator of osteoclast differentiation, activation and survival[18,19]. RANKL then interacts with its receptor RANK expressed in the hematopoietic osteoclast precursors and promotes osteoclastogenesis and bone resorption by mature osteoclasts (Figure 2). Thus the partnership between RANKL on osteoblasts and RANK on the hematopoietic osteoclast precursors plays a central role in the establishment and acceleration of the vicious cycle that is the driving force in the development and progression of bone metastases. Inhibition of bone metastasis by osteoprotegerin (OPG), a natural antagonist of RANKL, in preclinical models[20] verifies the importance of RANKL-RANK interplay in bone metastasis. Accordingly, design of pharmacological agents that interrupt the vicious cycle by targeting RANKL/RANK interplay would be a promising approach to effectively and selectively treat bone metastases in breast cancer patients.

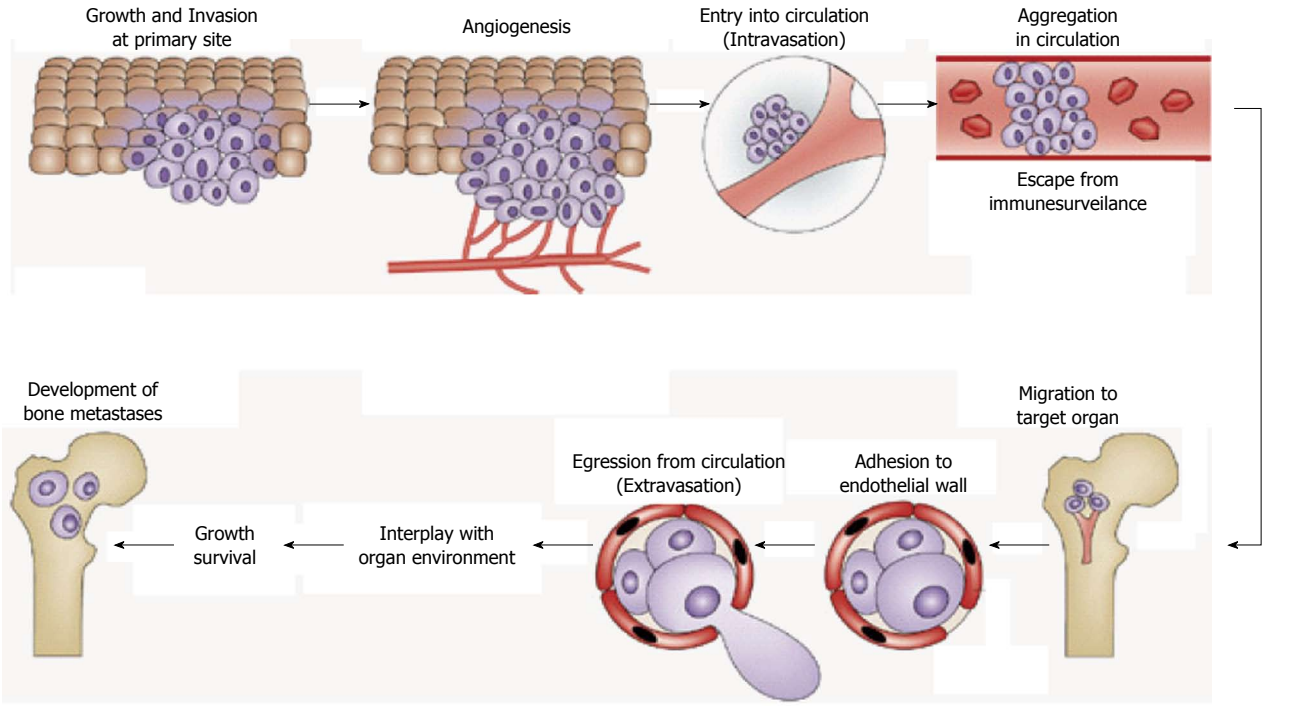

Figure 1 Steps of distant metastasis. Distant metastasis of cancer can be divided into two broad processes including before and after cancer cell arrest in target organs. Before the arrival at distant target organs, cancer cells go through growth, invasion, angiogenesis, intravasation, escape from host immune surveillance, and migration to their target organ. Cancer cells in the circulation are called circulating tumor cells (CTCs). This process is common for all metastatic cancer cells. CTCs reached their target organ subsequently show extravasation and finally arrest in the target organ. These cancer cells are called disseminated tumor cells (DTCs). DTCs change their phenotype *via* interactions with bone. Establishment of the interactions with bone environments is the most critical step for disseminated breast tumor cells to develop bone metastases. This process is unique depending on the target organs. Adapted from Ref. 14 and modified.

RANKL/RANK AND MAMMARY GLAND MORPHOGENESIS

Mice deficient in RANKL or RANK exhibited disturbed mammary gland morphogenesis due to decreased differentiation and proliferation and increased apoptosis in mammary epithelial cells during lactation[21]. Later it was shown that RANKL[22] and RANK[23] were virtually involved in ductal side-branching, alveolar differentiation and lumen formation in mammary gland. Furthermore, RANKL was found to stimulate cell proliferation and suppressed apoptosis *via* inhibition of NF-κB kinase alpha (IKKα)-cyclin D1 signaling and Id2-p21 signaling in mammary epithelial cells[24,25]. Of note, prolactin- or progesterone-receptor null mice displayed identical mammary gland phenotype to RANKL- or RANK-deficient mice[26,27] and prolactin or progesterone stimulated RANKL expression at transcriptional levels in mammary epithelial cells. These results suggest that prolactin and progesterone promote mammary gland morphogenesis through transcriptionally up-regulating the expression of RANKL, which subsequently stimulates cell proliferation and inhibits apoptosis in mammary epithelial cells. Progesterone-RANKL-RANK axis plays an important role in lactating mammary gland morphogenesis in physiological condition.

RANKL/RANK AND BREAST CANCER

Recent clinical studies demonstrated that progestin-containing hormone replacement therapy and contraceptives were significantly associated with increased incidence of breast cancer[28], suggesting the link between progesterone and breast cancer risk. Progesterone is shown to stimulate the proliferation of mammary stem cells[25,29], which possess the potential to transform preneoplastic cells. Of note, however, these mammary stem cells lack progesterone receptors, suggesting that the growth-stimulatory effects of progesterone are indirect and likely mediated by other neighboring molecules of which production is stimulated by progesterone. Administration of medroxyprogesterone acetate caused elevated induction of RANKL expression in mammary epithelial cells and RANKL promoted proliferation and inhibited apoptosis in mammary epithelial cells and mammary stem cells[26,27]. In addition, RANK is recently found to promote mammary tumorigenesis involving epithelial-mesenchymal transition[30]. Conversely, suppression of RANKL expression in mammary epithelial cells and mammary stem cells blocked progesterone-induced mammary morphogenesis and tumorigenesis, respectively. Together these results strongly suggest that progesterone-RANKL-RANK axis plays a critical role in the initiation of mammary tumors in an autocrine manner. Disruption of this axis could be a novel approach for the treatment and prevention of mammary gland tumor and carcinogenesis, respectively[25].

Of interest, Tan *et al*[31] have reported that $CD4^+$ $CD25^+FOXP3^+$ regulatory T lymphocytes infiltrating into mammary tumors produce elevated amounts of RANKL,

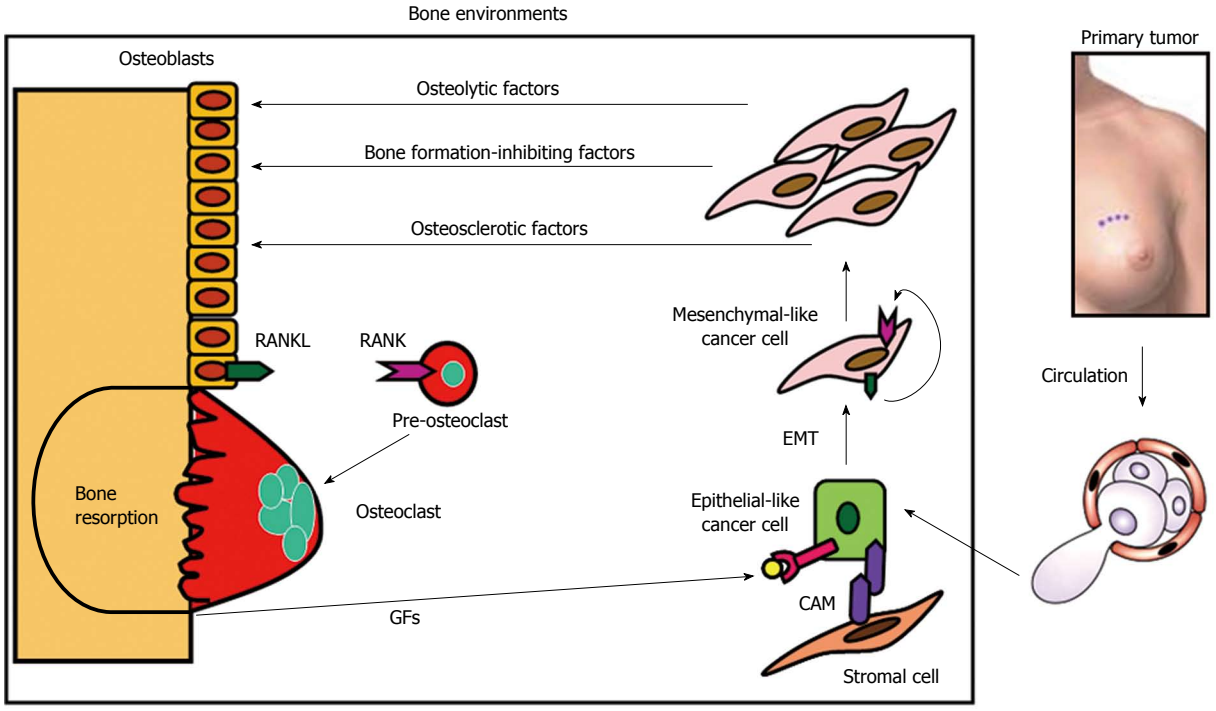

Figure 2 Vicious cycle between bone and breast cancer cells in bone metastasis. Bone-derived growth factors (GFs) such as insulin-like growth factors (IGF) and transforming growth factor-β (TGF-β) that are continually released *via* osteoclastic bone resorption promote proliferation and suppress apoptosis and stimulate the production of parathyroid hormone-related protein (PTH-rP), prostaglandin E_2 (PGE_2) and interleukin-11 (IL-11) in metastatic breast cancer cells migrating from primary site *via* circulation. Bone is fertile soil for metastatic cancer cells representing the concept of "Seed and Soil" theory proposed by Paget[9]. These osteolytic factors further stimulate osteoclastic bone resorption, followed by enhanced release of bone-stored growth factors, thus establishing "vicious cycle". Prostate cancer may produce osteosclerotic factors and multiple myeloma is shown to produce bone formation-inhibiting factors[14-16]. These osteolytic factors up-regulate the production of ligand for receptor activator of nuclear factor-κB (RANKL) in osteoblasts/stromal cells, which then interacts with its receptor receptor activator of nuclear factor-κB (RANK) in the osteoclast precursors promoting osteoclastogenesis and bone resorption. RANKL and RANK play a central role in the establishment of the vicious cycle. Metastatic breast cancer cells themselves occasionally express RANKL and RANK to develop an autocrine stimulation of carcinogenesis or tumorigenesis. RANKL/RANK expression in breast cancer cells could be a predicting indicator for subsequent occurrence of bone metastasis. Some metastatic breast cancer cells reside in stromal cell niche *via* cell-cell contact that is mediated by cell adhesion molecules (CAMs) and stay dormant. Metastatic breast cancer cells undergo epithelial-mesenchymal transition (EMT) by changing cell shape from epithelial to mesenchymal and acquire more aggressiveness in the presence of bone-derived TGF-β.

which then stimulates mammary tumor cell proliferation and protects from apoptosis in a paracrine manner, leading to increased tumor burden and pulmonary metastases. Earlier studies have reported that the regulatory T cells, which negatively regulate tumor immunity, accumulate in the bone marrow cavity in patients with prostate cancer with bone metastases and multiple myeloma[32,33]. Thus, the paracrine regulation by regulatory T cell-derived RANKL contributes to the stimulation of tumor growth and metastasis in breast cancer. Targeting regulatory T cell RANKL may reverse anti-tumor immunity and could be a unique therapeutic intervention for breast cancer patients with bone metastasis.

Substantial cases of primary human breast tumors expressed RANK and RANKL. Of interest, RANKL expression was increased in breast cancers in young women. Furthermore, RANKL expression levels are also well-correlated with the number of mammary stem cells[34-37]. These results raise the possibility that breast cancers in premenopausal young women are more aggressive than those in postmenopausal old women. Further studies in clinical settings are required to prove this important notion. However, if this turns out to be the case, disruption of RANKL-RANK interplay would be more appropriate and effective in premenopausal breast cancer patients.

Inhibition of RANKL/RANK interplay using OPG-Fc combined with tamoxifen is shown to enhance anti-cancer action of tamoxifen, leading to a reduction in cancer colonization in bone and bone destruction in a preclinical animal model of estrogen receptor-positive breast cancer[38]. Combination of RANKL/RANK inhibitors with anti-cancer agents appears to be a practical therapeutic approach for breast cancer patients and its efficacy needs to be evaluated in clinical settings.

RANKL/RANK AND BREAST CANCER METASTASIS TO BONE

Circulating RANKL and OPG are proposed to be predicting biomarkers of bone metastases in breast cancer patients[39,40], although whether non-membrane-bound soluble RANKL is present at substantial levels in circulation in breast cancer patients is still controversial. Similarly, immunohistochemical examination of clinical samples showed that RANKL expression was elevated in breast, lung, prostate and thyroid cancers that metastasized to bone compared to those at primary site[41]. Moreover,

there was a positive correlation between RANK expression levels in primary breast tumors and frequency of bone metastasis and poor survival[41]. On the other hand, survival of patients with breast cancers with increased expression of OPG, which disrupts RANKL-RANK interplay, is found to be prolonged[42]. Thus, RANKL/RANK/OPG expression ratio in tumors could be a diagnostic indicator for the subsequent occurrence of bone metastasis in the clinical course of breast cancer patients. The mechanism of increased frequency of skeletal metastasis in breast cancers that showed elevated RANKL or RANK expression is unknown. These breast cancers may be chemoattracted to bone by RANK or RANKL expressed in resident cells in bone marrow.

RANKL/RANK AND EPITHELIAL-MESENCHYMAL TRANSITION IN BREAST CANCER

Cancer cells are genetically unstable[43]. They readily change their biological phenotype and acquire new malignant capacities according to the environments to which they are exposed[44]. Epithelial-mesenchymal transition (EMT) is a process in which the epithelial-like cancer cells change their cell shape to mesenchymal fibroid morphology, accompanying with increased aggressiveness including mobility, invasiveness, distant metastasis and resistance to chemotherapy[45]. Since bone is a preferential target site of metastasis for breast cancer, it is plausible to reason that breast cancer cells show EMT when they arrest in and colonize bone. We found that mRNA expression of Snail, a well-recognized mesenchymal marker[46], was markedly increased in breast cancer in bone compared with that at orthotopic mammary fat pad in mice, while E-cadherin, a representative epithelial marker, was profoundly decreased in these cells in bone. Snail is a transcription repressor and known to inhibit E-cadherin expression. These results suggest that bone environments cause EMT in breast cancer cells metastasized in bone. Subsequent *in vitro* experiments to examine which constituent of bone environments promotes EMT in breast cancer cells showed that TGFβ, which is stored in bone and continually released in active forms from bone by bone resorption[10], promoted EMT. TGFβ is a powerful stimulator of EMT[47]. Of note, we found that OPG inhibited TGFβ-stimulated EMT, suggesting an involvement of RANKL and RANK interplay. Consistent with this result, RANKL also stimulated EMT *via* up-regulating Snail expression in breast cancer cells. These results suggest that RANKL produced in breast cancer cells mediates TGFβ-promoted EMT in an autocrine manner. They also suggest that intrinsic expression of RANK in breast cancer cells may exacerbate their malignant behaviors once these breast cancer cells arrest in bone in which RANKL is abundantly available in autocrine and paracrine fashion. It is therefore expected that suppression of RANKL actions in bone not only inhibits bone metastases but also consequent acquisition of aggressive autonomous behaviors of breast cancer. Consistent with our results, Palafox *et al*[30] recently have reported that RANK induces EMT in human mammary epithelial cells and promotes tumorigenesis and metastasis. Study on the role of RANKL/RANK in EMT in breast cancer in bone may allow us to design novel therapeutic approaches.

RANKL/RANK AND BONE CANCER PAIN

Bone pain is one of the major complications that seriously affect quality of life in cancer patients with bone metastases[1]. More than 70% of cancer patients with bone metastases suffer from devastating bone pain. Although the precise mechanism of bone pain is still unclear, the long-standing clinical observations that specific inhibitors of osteoclastic bone resorption bisphosphonates (BPs) reduce bone pain[48] suggest a potential role of osteoclasts, which play a central role in osteolytic bone metastases. Osteoclasts dissolve bone minerals by releasing protons through the vacuolar type proton pump ($V\text{-}H^+\text{-}ATPase$)[49], thereby locally creating acidic microenvironments in bone. Acid is a well-known cause of pain[50]. Consistent with this notion, we reported that acidosis created by bone-resorbing osteoclasts is partially responsible for inflammation-induced bone pain[51-53]. The important role of osteoclasts in causing bone cancer pain is further supported by the finding that OPG reduced bone cancer pain in animal models[54-56]. Furthermore, a recent clinical report describes that denosumab reduces bone pain due to cancer metastasis to bone[57]. These results support the notion that RANKL causes bone pain by activating osteoclastic bone resorption that creates acidic microenvironments by releasing protons. Blockade of RANKL/RANK interplay thus is a promising novel therapeutic intervention for bone pain in cancer patients with bone metastases.

DENOSUMAB IN BREAST CANCER PATIENTS WITH BONE METASTASIS

Denosumab is a fully human IgG2 monoclonal neutralizing antibody to RANKL[19]. Denosumab is administered *via* subcutaneous injection and because of its large molecular weight, denosumab is not excreted from kidney, and it is not metabolized in liver[58]. Different from bisphosphonates that inhibit bone resorption by inducing apoptosis in mature bone-resorbing osteoclasts, denosumab inhibits not only bone resorption by mature osteoclasts but also osteoclast formation from hematopoietic precursors and survival[59].

Phase Ⅱ clinical study showed significant effectiveness and safety of denosumab in the treatment of breast cancer patients with bone metastases[60]. Body *et al*[61] described that denosumab was effective at blocking bone resorption and preventing SREs in breast and prostate cancer patients who had not responded adequately to earlier bisphosphonate therapy. These results provide

with useful information for the question as to whether denosumab should be a first line treatment to prevent SREs in cancer patients and if cancer patients who previously were refractory to bisphosphonate treatment can be treated with denosumab. Stopeck *et al*[62] reported that denosumab was significantly more effective than zoledronic acid at delaying the first onset of SRE in breast cancer patients with bone metastasis. Concise description about the results of these clinical studies on breast, prostate and lung cancers and multiple myeloma is reported elsewhere[63].

Regarding adverse effects, denosumab as well as bisphosphonates is associated with osteonecrosis of the jaw (ONJ). There was no difference in the incidence rate of ONJ between bisphosphonate- and denosumab-treated cancer patients with skeletal metastases in the randomized double-blind controlled trial[64]. However, the incidence of hypocalcemia was significantly higher in cancer patients receiving denosumab than bisphosphonates[65]. Cautious periodical monitoring of blood ionized calcium levels and supplementation of calcium and vitamin D are strongly recommended for cancer patients receiving denosumab.

CONCLUSION

In conclusion, Because large bodies of scientific information on bone microenvironments have been accumulated at cellular and molecular levels, steps associated with the development and advancement of bone metastasis are relatively well characterized. In particular, the importance of the interactions between metastatic cancer cells and bone cellular constituents including osteoclasts and osteoblasts is unique and specific for bone metastasis. RANKL and RANK are expressed in a variety of bone marrow-resident cells including osteoblasts/stromal cells, hematopoietic cells and immune cells at substantial levels and play primary and essential roles in mediating these interactions. Thus RANKL/RANK is a logic target in design of bone-modifying agents that inhibit bone metastasis by interrupting the vicious cycle.

In addition to the critical role in bone metastasis, early results obtained in RANKL- or RANK-deficient mice clearly demonstrated that RANKL and RANK were important in normal mammary gland morphogenesis during lactation. However, these findings did not attract intense interests until recently. Over the last several years, however, the importance of RANKL and RANK not only in normal mammary morphogenesis but also in the acquisition of aggressive neoplastic phenotype including promoted cell proliferation, resistance to apoptosis, carcinogenesis, tumorigenesis, suppressed tumor immunity and EMT have been revisited. Furthermore, involvement of RANKL/RANK in the development and advancement of tumors other than breast cancer is also revealed[19,20]. These results raise the possibility that RANKL/RANK can be categorized as oncogene. Based on this concept, the bone-modifying agents including bisphosphonates and denosumab are able to inhibit cancer cell colonization in bone and secondary metastasis to distant organs from bone as well as bone metastasis. This direction of research may lead us to gain novel insights into cancer biology and ideas for the development of effective therapeutic approaches.

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TOPIC HIGHLIGHT

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Historically significant events in the discovery of RANK/RANKL/OPG

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Abstract

After it was suggested 30 years ago that the osteoblast lineage controlled the formation of osteoclasts, methods were developed that established this to be the case, but the molecular controls were elusive. Over more than a decade much evidence was obtained for signaling mechanisms that regulated the production of a membrane - bound regulator of osteoclastogenesis, in the course of which intercellular communication in bone was revealed in its complexity. The discovery of regulation by tumor necrosis factor ligand and receptor families was made in the last few years of the twentieth century, leading since then to a new physiology of bone, and to exciting drug development.

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Key words: Receptor activator of nuclear factor κB ligand; Osteoprotegerin; Receptor activator of nuclear factor κB; Osteoclasts; Bone biology

Core tip: The history of discovery of receptor activator of nuclear factor κB ligand began with the hypothesis that the osteoblast lineage controls osteoclast formation. The hypothesis was confirmed by experiments showing first, that osteoblastic cells were necessary for osteoclast activation, then some years later that osteoblasts were necessary for osteoclast formation in a contact-dependent process. Ultimate confirmation came from mouse genetics, discovering inhibition of osteoblast formation by a secreted tumor necrosis factor (TNF) ligand, followed by discovery of promotion of osteoclast formation by a membrane-bound member of the TNF ligand family that signalled through its receptor in hemopoietic cells to promote osteoclast formation.

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INTRODUCTION

Since the 1970's we have advanced in understanding of bone biology from scarcely appreciating that there are cells in bone to seeing now a wonderful complex of intercellular communication, involving not only the cells of bone but also those of the hemopoietic and immune systems, and control systems far beyond the early simple ideas of hormone regulation. Many cytokines contribute to the balanced outcome of these cell communication processes, the brain and sympathetic nervous systems play central roles, and the skeleton even behaves as an endocrine organ itself.

This chapter consists of reflections on the scientific background and events that set the scene for the eventual discovery of the control of osteoclast formation by members of the tumor necrosis factor (TNF) ligand and receptor families, and of the impact of these discoveries.

THE OSTEOCLAST

From the time of their discovery in 1873[1] as the multinucleated cells responsible for bone resorption, osteoclasts provoked great interest, first in their study for many years by light and electron microscopy, when they were recognised to possess unique ultrastructural characteristics which both distinguished them from other cell types and seemed likely to provide them with an advantage in achieving motility to aid in bone resorption[2]. Apart from their multinuclearity, a striking feature of the osteoclast was noted as the presence of the "ruffled border", a complex structure of deeply interfolded finger-like projections of the plasma and cytoplasmic membranes adjacent to the bone surface. Adjacent to and surrounding the ruffled border is the clear zone, an area of cytoplasm devoid of cellular organelles except for numerous cytoplasmic actin filaments. The clear zone became known as the "sealing zone", since the plasma membrane in this region comes into very close apposition with the bone surface to ensure osteoclast attachment, and to separate the bone-resorbing area beneath the ruffled border from the unresorbed area, which maintains in a closed compartment a favourable microenvironment for bone resorption[2].

From the mid - 1970's the organ culture of fetal and newborn bone provided for the first time means of deducing more of the function of living osteoclasts, and in the 1980's the first osteoclasts were studied as isolated cells in culture. These approaches began to provide biochemical explanations for the earlier structural observations. Osteoclasts were considered to bring about dissolution of bone mineral by creating an acid microcompartment under the ruffled border, adjacent to the bone surface[3], with acidification achieved by the passage of hydrogen and chlorides ions through the ruffled border[4,5]. The functions of the acid milieu are to promote dissolution of mineral and to provide the appropriate pH for optimal action of the protease, cathepsin K, in the dissolution of bone matrix. Osteoclasts were found to be rich in tartrate-resistant acid phosphatase (TRAP), which is a commonly used histochemical marker for osteoclasts, although not exclusive to those cells. It is nevertheless a convenient marker for *in vitro* generated cells when combined with identification of calcitonin receptors[6,7] and the ability to form resorption pits when grown on thin slices of cortical bone or dentine. Some other properties include possession of vitronectin receptors, vacuolar ATP-ase, and chloride-7 channels and secretion of cathepsin K. This combination of properties provides the phenotype that equips osteoclasts uniquely to resorb bone.

DEVELOPMENT OF CONCEPTS OF THE ORIGIN OF OSTEOCLASTS

Ideas of the cellular origin and development of osteoclasts were much more contentious, and remained so until the 1980's. Autoradiographic evidence had led Tonna[8] to conclude that osteoclasts arise from fusion of osteoblasts and that osteoclasts can dissociate again into osteogenic precursor cells. Fornadley *et al*[9] believed that osteoclasts and osteoblasts originate from a common osteoprogenitor cell, and at a later stage may return to the osteoprogenitor pool. In 1974, Rasmussen *et al*[10] proposed that endosteal mesenchymal cells differentiate into pre-osteoclasts which may then form an osteoclast by fusion. At a certain time and place the osteoclast then dissociates into pre-osteoblasts, giving rise to osteoblasts and osteocytes. These views of a connective tissue cell origin of osteoclasts were all subsequently superseded in the face of compelling evidence for a hemopoietic origin of osteoclasts.

The first convincing evidence that osteoclasts and osteoblasts came from different lineages came in the mid-1970's. Studies using a variety of model systems including quail-chick chimera experiments, parabiosis experiments and the restoration of bone resorption in osteopetrosis by bone marrow and spleen cell transplantation, showed that osteoclasts are supplied to bone *via* the circulatory system, and are formed by fusion of mononucleated precursors derived from hemopoietic progenitor cells[11-13]. The important finding common to these experiments was that the precursors of the osteoclast could travel *via* the blood to an area where osteoclasts were needed, whereas osteoblasts were recruited from local precursors. This suggested that local precursors could not differentiate into osteoclasts and consequently that the lineages of osteoblasts and osteoclasts are different[13]. Although such experiments did not show definitively that the osteoclast is derived from the hemopoietic stem cell, since bone marrow is diverse and contains stromal cells in addition to hemopoietic cells, the accumulated evidence strongly suggested that the osteoclast is derived from the fusion of mononucleated precursors of hemopoietic origin. It rather fitted with Maureen Owen's conclusion on the basis of extensive studies in rabbits[14], that osteoclasts are very sparsely distributed in bone - "anyone who has looked at histologic sections of bone will have been struck by the paucity of osteoclasts compared with the number of osteoblasts". It seemed therefore that osteoclasts only come where and when they are needed, and it made no sense for their development and arrival to be orchestrated by any circulating factors - these would more likely be local. This is consonant with the thinking of Chambers in his considering the osteoclast as a "wandering" cell, whose formation would logically be programmed by genuine bone cells[15].

BIRTH OF BONE CELL BIOLOGY

In 1970 there was little prospect of isolating cells from bone in sufficient numbers and purity to characterize them adequately, although the first enzymatically digested cells from newborn rodent bone had been cultured in the 1960's[16]. Another possibility was to develop a tumor

of bone cell origin and use it to study hormone action. Experimental tumors had been described that retained hormone-responsiveness throughout prolonged animal passage[17], allowing studies of hormone-receptor interactions and effects of hormones on specific cell functions[18], so it seemed logical to develop bone tumors with the aim of learning something of the properties of cells of bone origin.

That was the reasoning behind the decision to induce an osteogenic sarcoma in the rat and investigate the hormone responsiveness of the tumor cells. Tumors were induced in rats by serial injections of ^{32}P-orthophosphate that resulted in a high incidence of osteogenic sarcoma development[19]. The tumors were readily transplantable within the same strain of rats, retaining their phenotypic properties throughout many years of transplantation. Membrane and cell preparations from the tumors showed dose-dependent increases in adenylyl cyclase and cellular cAMP respectively, to parathyroid hormone (PTH) and to prostaglandins of the E series[20-22]. The tumors were rich in alkaline phosphatase, made a bone-like ground substance and mineralized it. The stability of the phenotype was such that a few years later stable clonal cell lines were derived from the osteogenic sarcoma[23,24], one of which, UMR106, has been used extensively by our own and many other laboratories.

What the osteogenic sarcoma provided was a tumor of the osteoblast lineage that could be used for studies of certain aspects of hormone action, particularly PTH, prostaglandins and metabolites and vitamin D. It has always been important to recognize that the cells are not osteoblasts, but can at best be described as malignant cells originating in bone, that possess a number of features in common with cells of the osteoblast lineage. The osteogenic sarcoma and the clonal cells derived from it proved valuable in many ways, since at that time, the early 1970's, knowledge of the cells of bone was primitive, so much the case that only a little later in the 1970's was there evidence for the separate developmental origin of the osteoclast and osteoblast lineage (v supra).

The experimental pathways offered by the UMR106 and related clones were matched by the ROS17.2/8 cells[25,26], a further rat osteosarcoma clonal line enriched in a number of osteoblast properties. A major advance though, came when cells were extracted from newborn rodent bone by sequential enzymatic digestion[27,28]. Although such cultures were inevitably heterogeneous, they could be enriched in properties identified with the osteoblast, and could be studied *in vitro* up to a few subculture passages. The two osteosarcoma approaches and the rodent osteoblast culture methods came together at the same time, the end of the 1970's, and in many ways signalled the birth of bone cell biology.

The UMR106 and ROS 17.2/8 cells were useful in studying mechanisms of hormone or cytokine action on cells that possessed a number of osteoblast-like properties. Careful comparisons between primary bone cells and clonal osteosarcoma cells that were enriched in a number of the phenotypic features of osteoblasts, allowed general conclusions about osteoblast function to be drawn[23,29,30]. At the simplest level, the hormone and prostaglandin responsiveness of osteosarcoma and calvarially-derived osteoblast cultures were very similar, and we chose to apply this principle of regularly comparing the behaviour of osteosarcoma cells with primary cultured cells. The phenotypic properties of osteoblasts were studied in such rodent cell culture systems, and the observations made in those systems extrapolated to adult bone *in vivo*, leading to concepts of the "osteoblast phenotype". It was this work that led to the thoughts that that the osteoblast lineage might control osteoclasts.

COULD OSTEOBLASTS REGULATE OSTEOCLASTS?

It was reassuring in this work that, when comparing osteogenic sarcoma cells with calvarial osteoblast-rich cultures in their adenylyl cyclase responsiveness to prostaglandins, their metabolites and analogues, their relative efficacies in repeated dose-response studies were very closely similar. At this time also the laboratories of Larry Raisz and Armen Tashjian had shown in two different organ culture systems that prostaglandins were powerful stimulators of bone resorption[31,32]. What was most striking, however, was that the dose responses to prostaglandins, metabolites and analogues in promoting bone resorption in organ culture so very closely mimicked the cyclic AMP response in the cells isolated either from osteosarcoma or calvariae [20,21,33,34]. This was despite the fact that these were such very different assay systems, one requiring the generation in organ culture of osteoclasts that resorbed bone, and with a read-out after 48 h or longer, the other a response within only a few minutes in cells of the osteoblast phenotype. These observations helped lay the foundation for the hypothesis, that in order to generate active osteoclasts, bone-resorbing agents act first on cells of the osteoblast lineage[35] (Figure 1).

The thinking behind this drew also on observations made shortly before that by Alan Boyde, who showed that PTH had many actions upon osteoblasts or "osteoblast-like cells", including cell shape changes resulting in less tight packing of cells that were evident in organ cultures[36,37] and isolated cells[38]. This drew attention to "lining" cells - those cells that were by far the most abundant on bone surfaces. The lining cells were envisaged as providing a barrier between osteoclasts and the bone mineral surface[36]. The proposal in the hypothesis was that this was a barrier to be breached when bone resorbing hormones acted upon them[35]. In addition to this physical process, of making the bone available to osteoclasts that would initiate resorption, the concept was that the osteoblastic lineage cells in response to activators, would generate signal(s) leading to the recruitment, maturation and activation of osteoclasts[39] (Figure 2). We considered the lining cells to be the most likely of the osteoblast

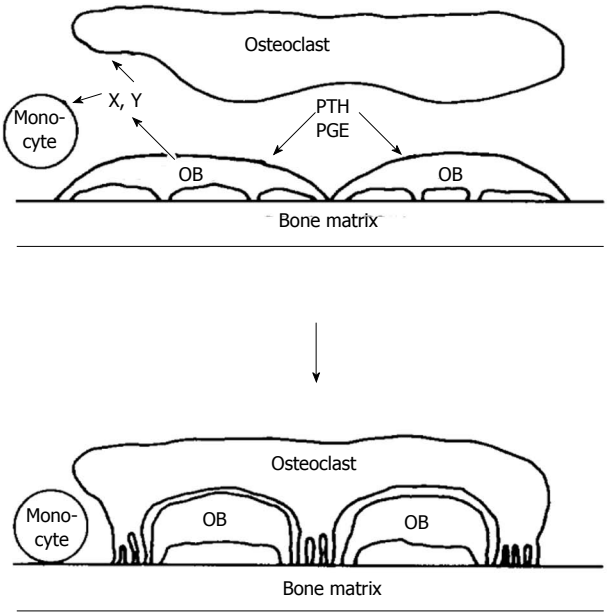

Figure 1 Schematic representation of osteoblast involvement in hormone - stimulated bone resorption (reproduced with permission). OB: Osteoblast; PTH: Parathyroid hormone; PGE: Prostaglandin E.

lineage cells to mediate the actions of resorbing agents in promoting formation of active osteoclasts - with the least likely of all being fully active, synthesizing osteoblasts.

Chambers[15] came to the same conclusion about osteoblast control of the osteoclast, but arrived at this for other reasons. Coming from work on macrophages, he argued that since the osteoclast derives from a "wandering" cell, it made sense to have its activity programmed by an authentic bone cell, *i.e.*, the osteoblast. He subsequently did much to establish this as fact.

These developments gave rise to a major interest in intercellular communication in bone. The hypothesis of osteoblast lineage control, attractive as it might have seemed to its proponents, was not received with wide enthusiasm by the field, with a common view being that intercellular communication in bone was unlikely. It was testable though, and the next several years would bring much activity along those lines. It was still the case that we were not well educated about the cells of bone, and this applied particularly to osteoclasts. Scarcely a thought was given to osteocytes, because there was simply no way we could approach their study, although there was an old literature on osteocytes that indicated they had an interesting association with lysis around their lacunae[40-42].

OSTEOBLAST REGULATION OF OSTEOCLASTS

Organ cultures of fetal or embryonic bone continued to provide valuable information concerning the actions of hormones, cytokines and drugs on bone resorption, but were not readily adaptable to testing the idea that cells of the osteoblast lineage might control osteoclasts - that was out there to be proved or disproved. Now that it was possible to culture cells with the properties expected of osteoblasts, and with quite an increase in understanding of where osteoclasts come from, the next several years proved to be enlightening.

Regulation of the osteoclast by the osteoblast lineage was still only a hypothesis. Over the next several years methods were developed to address the question, using cells isolated from newborn rat bone and plated onto thin slices of cortical bone, dentine or ivory[43-48]. Resorption by isolated osteoclasts was assessed by measuring the areas or numbers of resorption pits produced by the cells in response to treatment with bone resorbing agents. A number of methods were used to isolate the cells from newborn bone, all of which yielded osteoclasts inevitably mixed with a large excess of other cells, many of them osteoblastic cells and fibroblasts.

Osteoclasts rapidly attached to the bone slice surfaces, and other cells, including osteoblasts, that adhered less tightly, were removed as much as possible by vigorous washing. By limiting the time of cell adherence to less than 15 min, "functionally pure" osteoclast populations could be prepared, *i.e.*, cultures in which treatment overnight with bone-resorbing agents (*e.g.*, PTH, IL-1, TNFα, *etc.*) resulted in no stimulation of resorption. Alternatively, deliberate contamination with osteoblasts could be achieved, either by allowing long settlement times before washing, or by adding osteoblasts (or surrogate osteoblasts in the form of certain osteogenic sarcoma cells) to the cultures. In the latter conditions the bone-resorbing agents could stimulate resorption that could be quantitated.

These experiments showed convincingly that the bone resorbing agents stimulate resorption by a mechanism which requires the presence of contaminating osteoblasts that made contact with the precursors of osteoclasts. This was true of PTH, 1,25-dihydroxyvitamin D, TNFα and β, IL-1, and thyroid hormone[46-50]. The question whether cell contact was essential was a crucial one. Although some evidence was obtained that the activation of resorption by "functionally pure" osteoclast cultures could be produced by the transfer of medium from osteoblasts that had been treated by resorbing agents[51,52], this was insufficiently consistent to allow purification of such activity. The overall conclusion from the data supported the hypothesis that osteoblastic cells were needed for osteoclast activity.

An important question was whether osteoclast formation from hemopoietic precursors also required participation of accessory cells. The isolated osteoclast assay summarized above was considered to be an assay predominantly of osteoclast activity, as measured by resorption of bone, dentine or ivory. In some circumstances though, osteoclast formation clearly took place, and required cell contact. What was a "functionally pure" culture at the beginning of an experiment was not so after a period of time because of the proliferation of osteoblast lineage and other cells in these crude cultures. For example, when cells were isolated from endosteal

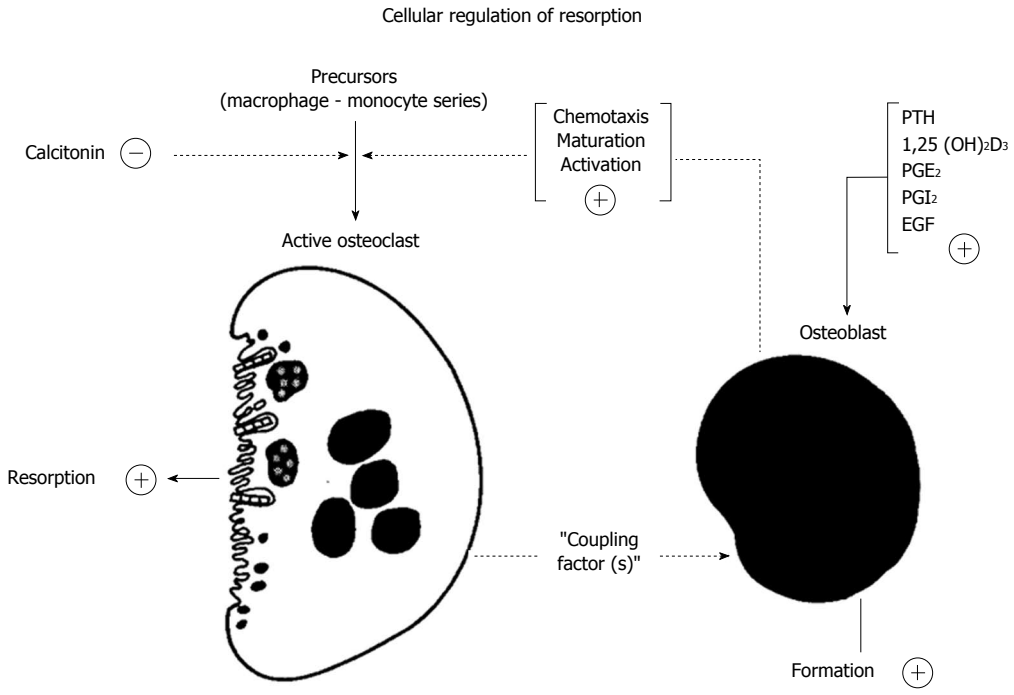

Figure 2 Proposed participation of cells in the osteoblast lineage in the action of the bone - resorbing hormones (reproduced with permission from Ref. 39). PTH: Parathyroid hormone; PGE_2: Prostaglandin E_2; EGF: Epidermal growth factor.

surfaces of newborn rat (mouse) bone and grown on bone for several days, resorption that was unresponsive to PTH in the first 24 h became responsive thereafter, because of continuing increases in osteoblast numbers. This was illustrated by results of growing isolated rat osteoclasts on bone for several days[53]. Osteoblast numbers increased 3-fold from 24 h to 48 h, and cultures that were not responsive to PTH in the first 24 h became responsive thereafter. Furthermore the actual numbers of osteoclasts continued to increase beyond 24 h, indicating the generation of new osteoclasts osteoclasts under the culture conditions. Observations such as this were instructive, indicating that osteoblastic cells might indeed be needed for osteoclast formation as well as for their activity. Convincing evidence for that was to come a few years later (v infra). Importantly also, it had become clear that great care and attention to detail should be exerted in attempting to use the isolated newborn bone cell cultures as an osteoclast activity assay - often it was more than that.

CONTROL OF OSTEOCLAST FORMATION

Once it became firmly established that osteoblasts and osteoclasts had entirely different origins, with hemopoietic cells arriving in the bone environment and being used to form osteoclasts where they were needed in bone, generated from "wandering" precursors, how did this happen? Burger *et al*[54], using a co-culture system in which hemopoietic cells from embryonic mouse liver were co-cultured with fetal long bone rudiments from which the periosteum had been stripped, showed that that living bone cells are required for osteoclast development. However it was the development of murine bone marrow cultures by Naoyuki Takahashi in the group of Tatsuo Suda, that led to major advances, with reproducible assays of osteoclast formation[55,56]. These were used first to show that treatment with bone resorbing agents such as $1,25(OH)_2D_3$ could promote osteoclast formation in a dose-dependent manner, with osteoclast quantitation carried out by counting TRAP positive multinucleated cells that were also CT receptor positive by receptor autoradiography. In the course of these studies, Takahashi *et al*[55] made an observation that turned out to be a crucial one. They noted consistently that more than 90% of the TRAP-positive mononucleated cell clusters and multinucleated cells formed in mouse marrow cultures in response to bone resorbing stimuli were located near colonies of alkaline phosphatase-positive mononucleated cells (possibly osteoblasts). This was consistent with the idea that osteoblastic cells are involved in osteoclast formation, in addition to the evidence produced in the few earlier years of their influence on osteoclast activity. They set out to determine whether close contact between osteoclast progenitors and osteoblastic cells was necessary in order for osteoclast formation to occur.

A simple experimental design was developed by Takahashi to examine this possibility further, and this had a major impact on the field. That was the establishment of a co-culture system in which osteoblast-rich cells from mouse calvariae were grown with osteoclast precursors (from spleen), either on the same surface or separated by a 0.45 μm filter (Figure 3)[57]. Osteoclast formation was measured and shown to require direct contact between the participating cells. Similar results were obtained with

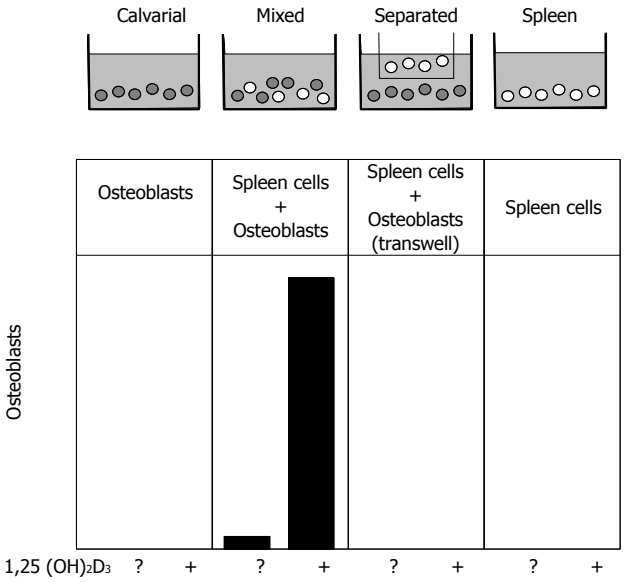

Figure 3 Representation of the co-culture method that showed the contact-dependent promotion of osteoclast formation by stromal osteoblasts.

the bone marrow-derived stromal cell lines[58,59], any of which could be substituted for primary osteoblastic stromal cells in co-cultures with spleen cells, to result in the formation of osteoclast-like cells in the presence of $1,25(OH)_2D_3$. These studies highlighted the fact that the ability to promote osteoclast formation was one distributed within the osteoblast lineage, clearly demonstrable in cells early in the lineage, and later shown to be a property also of fibroblasts[60] and of chondrocytes[61], and even claimed recently for osteocytes[62,63]. On the other hand we did not consider it likely that precursors would be presented to mature, bone-forming osteoblasts in a way that would favour these members of the osteoblast lineage having a role in osteoclast generation. A later illustration of this point came from the finding that genetic ablation of mature osteoblasts, driven through the osteocalcin promoter, had no influence on the ability of mice to form osteoclasts[64].

HORMONE AND CYTOKINE CONTROL OF OSTEOCLAST FORMATION

With increasing acceptance of a role for cells of the osteoblast lineage in controlling osteoclast formation and activity by a contact-dependent mechanism, it was important to understand how this process was regulated by hormones and cytokines that stimulate osteoclast formation. PTH and PTHrP, acting through their common receptor, promoted osteoclast formation in marrow cultures by a cAMP-dependent mechanism[48,65] as did PGE_2, and the effect of interleukin-1 (IL-1) resulted from the generation of PGE_2 as an intermediate effector[66]. It remains the case that there is no evidence for the existence of functional PTH/PTHrP receptors in osteoclasts, capable of supporting a direct stimulatory effect of PTH on the osteoclast. A second signaling mechanism for regulation of osteoclastogenesis by osteoblasts was provided by the steroid hormone, $1,25(OH)_2D_3$ which had very similar effects on osteoclast formation in marrow cultures and in co-cultures of osteoblasts with hemopoietic cells[7]. $1,25(OH)_2D_3$ signals by combining with its receptor and translocating to the nucleus to influence transcriptional events. Finally, a membrane bound receptor complex involving a 130 kDa glycoprotein (gp130)[67] provides for osteoclast formation under the influence of the group of cytokines that use this signalling mechanism [IL-6, IL-11, leukemia inhibitory factor (LIF) and oncostatin M (OSM)].

Thus the concept of stromal/osteoblastic regulation of osteoclastogenesis through local signaling mechanisms was firmly established, along with its regulation by a number of circulating and local factors. Despite the fact that they fell into three main classes with respect to their initial signaling mechanisms, it seemed that they converged in later actions to use a common pathway to promote osteoclast formation. Figure 4 depicts the state of understanding of this process from the late 1980's until the matter was resolved about ten years later, with the search for the common mechanism occupying many of us in bone cell biology research throughout those years.

EFFORTS TO IDENTIFY ODF AND SOFA

While understanding of the regulation of osteoclastogenesis had improved somewhat, with signaling through the three pathways as depicted in Figure 4, by the 1990's there had been no real progress towards identifying the molecular mechanisms by which contact between osteoblast lineage cells and hemopoietic cells could lead to osteoclast formation. The stromal cell-hemopoietic cell co-culture data provided the strongest evidence for the existence of a contact-dependent process, likely a stromal cell membrane molecule requiring contact between the stromal cell and a hemopoietic precursor. This hypothetical substance was termed "stromal osteoclast forming activity" (SOFA)[68], or "osteoclast differentiation factor" (ODF)[56] (Figure 4). Although involvement of matrix factors was not excluded, we favoured the idea that such a membrane molecule existed[56].

It was not surprising that for a time, attention was directed at the colony - stimulating factors as possible candidate specific molecular regulators of osteoclast formation, but they were eventually excluded. A mutation in the coding region of the Macrophage colony-stimulating factor (M-CSF) gene in the mouse impaired the ability to form multinucleated osteoclasts, resulting in one variant of murine osteopetrosis, the *op/op* mouse. M-CSF appeared to play a role in both proliferation and differentiation of osteoclast progenitors[69,70]. On the other hand, M-CSF inhibited the bone resorbing activity of isolated osteoclasts[71], and osteoclasts were found to be rich in M-CSF receptors[72]. As was the case with M-CSF, both GM-CSF and IL-3 reduced bone resorption in organ

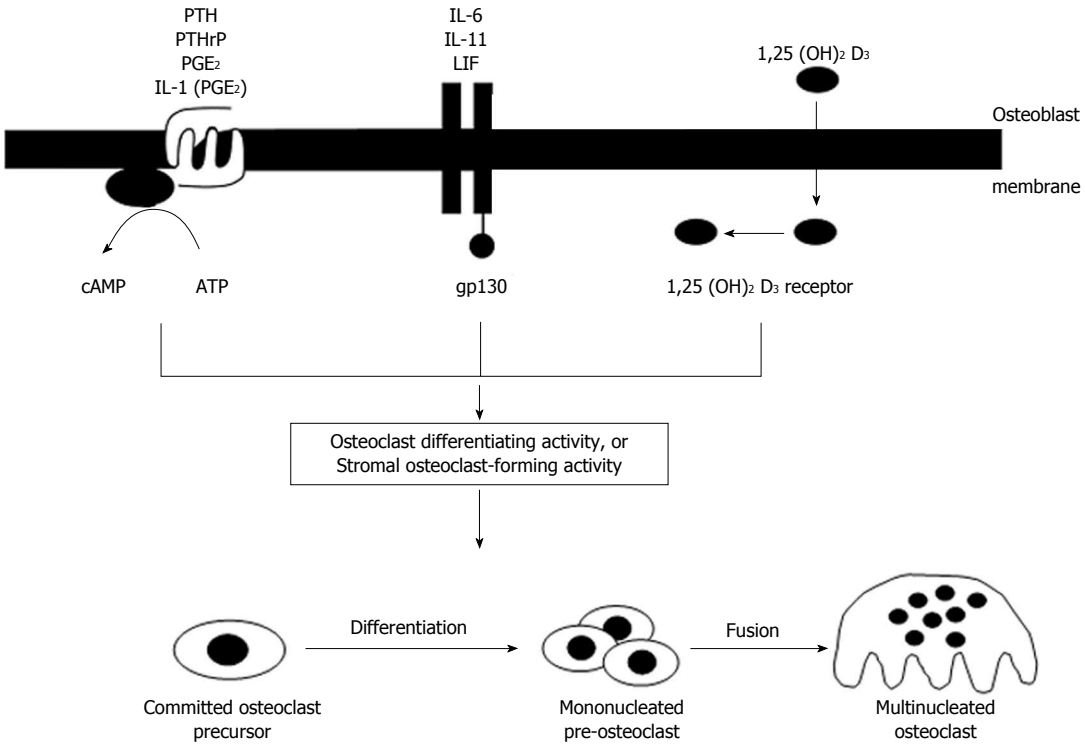

Figure 4 Concepts of regulation of osteoclastogenesis from the mid-1980's until the discovery of the molecular regulation mechanisms. Three different signaling pathways converged to promote formation of osteoclasts through undefined mechanisms. IL: Interleukin; PTH: Parathyroid hormone; LIF: Leukemia inhibitory factor.

culture[73]. All three cytokines inhibit the generation of osteoclasts in mouse bone marrow cultures. However, when marrow hemopoietic cells were pretreated with CSFs before co-culture with osteoblast/stromal cells and 1,25(OH)$_2$D$_3$, each of the CSFs enhanced osteoclast formation, with M-CSF the most effective[69]. The conclusion from these various observationswas that M-CSF, GM-CSF, and IL-3 secreted by cells in the bone marrow (stromal-osteoblasts) contribute to the development of osteoclast-like cells by enhancing proliferation of precursors. In the case of M-CSF, this is also necessary for the differentiation of osteoclasts later in the development pathway. However none of these hemopoietic growth factors fulfilled criteria required of one which is a product of the osteoblast lineage and is specific for osteoclast formation.

A claim was made for identification and isolation of an "osteoclast colony-stimulating factor"[74]. However the biological assay used in that isolation work was the mixed marrow culture system (containing both stromal and hemopoietic elements). Therefore the material isolated had no actions which distinguished it from several cytokines and hormones capable of promoting osteoclast formation with the mediation of stromal cells/osteoblasts. No convincing evidence was produced in that or in subsequent work from the same group that the isolated factor could promote authentic osteoclast formation from purely hemopoietic cells. Lee *et al*[75] showed that the activity which they had isolated promoted formation of TRAP-positive cells from bone marrow cells cultured in Bacto agar, as did IL-3 and stem cell factor. The results are similar to those of Kurihara *et al*[76], using spleen cells from 5-FU-treated mice. On the other hand, when strict criteria for osteoclast identification were used, none of the CSFs were able to induce osteoclast differentiation in semi-solid cultures of mouse bone marrow cells[56]. Furthermore, Chambers *et al*[68] established a number of osteoclastogenic cell lines from the H-2KbtsA58 transgenic mouse, but the osteoclastogenesis with these cell lines still required the presence of stromal cells and 1,25(OH)D.

Some continued to argue that osteoblastic stromal cells are not required for osteoclast differentiation[77]. Much of the lack of agreement is in the interpretation of the data. In experiments in which very strict criteria of osteoclast identification were applied, the need for stromal/osteoblast participation was convincing. This is not so when a single criterion is used, as in the case of TRAP staining in the experiments of Lee *et al*[75].

A DRAMATIC CONCLUSION

Of the many multifunctional cytokines that had some role in osteoclast formation, none provided an explanation for the molecular regulation of osteoclast formation and activity. Dramatic resolution of the question came in 1997 with the discovery by two groups independently that osteoclast formation is controlled physiologically by regulated interactions among members of the TNF ligand and receptor families. Finally, after many years of hypothesizing, testing those hypotheses, refining them,

arguing about what turned out to be false leads, and acquiring useful information along the way, the denouement came in what seemed to be the twinkling of an eye. What made this rapid progress possible was due in no small measure to the fact that the history of research in this area made it obvious what experiments to do, and how to do them, once a really promising candidate molecule came along. These few months surely marked a major point in the history of the study of bone biology - not the end of history though, by any means, because new doors were opened.

The discovery of osteoprotegerin (OPG), a soluble member of the TNF receptor superfamily, revealed it as a powerful inhibitor of osteoclast formation[78,79]. This provided the means of identifying and cloning the elusive stimulator of osteoclast formation, which proved to be a TNF ligand family member that came to be called receptor activator of nuclear factor κB ligand (RANKL), as the common factor mediating osteoclast formation in response to all known stimuli[80,81]. As a membrane protein, RANKL fulfilled the predictions of earlier work, that osteoclast differentiation required contact-dependent activation of hemopoietic precursors. The communication with the hemopoietic lineage results from RANKL binding to its receptor on the osteoclast lineage, RANK, thereby initiating signaling essential for osteoclast differentiation. RANKL was the unknown "osteoclast differentiating activity" of Figure 3. The bone-resorbing cytokines and hormones, with disparate signaling mechanisms, were found to converge in promoting RANKL production[82], just as they had previously been predicted to promote production of "ODF" or "SOFA"[56]. The decoy receptor, OPG, was found to have an essential physiological role as a paracrine regulator of osteoclast formation, produced by the osteoblasts and binding RANKL, with constitutive production of OPG necessary to limit the osteoclast formation resulting from RANKL stimulation[83].

Studies in genetically altered mice established clearly the essential physiological role of these TNF ligand and receptor family members in controlling osteoclast formation and activity, filling in the gaps that had been eluding us for many years[84]. The concepts that drove the research to such outcomes had been developed over years of study of bone cell biology, predominantly with *in vitro* studies using rodent systems, but drawing on some *in vivo* observations also. The control of osteoclast formation and activity by the osteoblast lineage predicted a control mechanism that was so important from the evolutionary point of view that it was likely to be highly conserved. That certainly proved to be so, both in respect of the overall mechanism and of the conserved sequences of the central molecules. The physiology of the bone resorption regulatory system was in a short time laid out before us with convincing evidence of the essential regulatory function of RANKL, not only in promoting osteoclast formation, but also their survival and activity[85], as was predicted from the earlier demonstration of activation of osteoclasts through contact with osteoblastic cells[44].

Each of four research groups arrived independently and at about the same time at the identification and cloning of RANKL. Two of these groups in the final stages of their work had the specific aim of identifying the long sought-after membrane promoter of osteoclast formation. The other two, working in immunology, were studying the T cell-dependent immune response, identifying RANKL in the process, and subsequently became aware of its role in bone.

The discovery of the crucial parts played by the members of the TNF ligand and receptor family (RANKL, RANK, OPG) was characterized by a number of outstanding feats of cell and molecular biology and protein chemistry. When reviewing things historically, some partisanship might be expected. This author, who was a close observer of all the related events, and was one of those who would like to have made the discovery, nominates the work carried out at the Snow Brand Milk Products Company, Japan, as the most commendable single scientific achievement. They had found that a human embryonic lung fibroblast cell line IMR90, secreted into the medium an activity that inhibits osteoclast formation in mouse marrow culture. They saw this as an opportunity to identify a key player in osteoclast control, which they began to call "osteoclastogenesis inhibitory factor (OCIF)", and set out to purify and then sequence it. All such protein purification work is heavily dependent on the robustness and throughput of the biological assay used to monitor purification. The bioassay they used in their work was the one developed originally by Takahashi[57], in which they looked for inhibition of $1,25(OH)_2D_3$ - treated osteoclast formation in mouse bone marrow cultures. The assay is technically demanding and time-consuming, with a very slow turnaround time (greater than 7 d), and indeed with no features favourable for protein purification. The fact that they succeeded in purifying and sequencing the heparin-binding protein that they called osteoclast-inhibitory factor (OCIF)[79], must be regarded as an outstanding technical achievement. Using this sequence they cloned OCIF, showing it to be identical with OPG[81], as a novel member of the TNF receptor family.

Because OCIF/OPG strongly inhibited osteoclast formation in cocultures or marrow cultures treated with $1,25(OH)_2D_3$, PTH, or IL-11, it seemed to them evident that OCIF would achieve its inhibition of osteoclast formation by binding to the responsible effector molecule, *i.e.*, ODF/SOFA. They had the means at their disposal to address this question, knowing that certain mouse marrow stromal cells would be expected to express ODF/SOFA strongly on the cell surface when given appropriate stimuli. They used expression cloning of the ligand for OCIF/OPG with a cDNA library of mouse ST2 cells that had been treated in this way, and identified a cDNA encoding a 316 amino acid type Ⅱ transmembrane protein of the TNF ligand family[81]. Expression of the protein

confirmed its ability to promote osteoclast formation.

A different path was followed by the Amgen group. In the course of a fetal rat intestine cDNA sequencing project they noted an expressed sequence tag (EST) with features suggesting that it might be a member of the TNF receptor family, based on known domain structures. This was confirmed when a full length clone was prepared and sequenced, revealing a 401 amino acid glycoprotein with features of a secreted member of the TNF receptor family[78]. This was at that stage essentially an "orphan" receptor, but they had resources at their disposal that allowed them to pursue molecules of likely interest when they were were discovered. They did this using transgenic mice, and found that hepatic expression of the novel protein yielded mice that survived with profound osteopetrosis. This they showed to be due to inhibition of late stages of osteoclast differentiation, and furthermore, recombinant protein inhibited osteoclast formation *in vitro* and increased bone density when administered to normal mice. They named the protein "OPG", and they too recognised that it could provide a crucial approach to unravelling the molecular mechanisms of control of osteoclast formation.

Using recombinant OPG-Fc fusion protein as an immunoprobe, they identified a mouse myelomonocytic line that expressed on its surface a molecule which could be readily detected. An expression library prepared from these cells was constructed and screened for binding in pools of transfected COS7 cells. A single plasmid clone was identified, and when expressed, gave rise to on OPG-binding protein on the surface of the expressing cells. They called this 316 amino-acid protein OPG ligand (OPGL), and showed that there was 87% conservation between mouse and human protein sequences[86]. OPGL was able to promote osteoclast formation from hemopoietic precursors in the presence of M-CSF, and to stimulate bone resorption and elevate the blood calcium levels when administered *in vivo*.

The publication[78] of identification of OPG (later agreed as RANKL) was a landmark event in the field, but although Tsuda *et al*[79] published some months later, their independent contributions were equally outstanding. From the ways in which each of these groups discovered OPG/OCIF, and with any appreciation of the concepts that had developed over the previous decade or more of osteoclast control, it was quite apparent that this discovery would prove to be central to completing the picture of the local control of osteoclastogenesis.

Remarkably enough, two other groups were successful in identifying and cloning RANKL[87,88], each of them in fact publishing this work some months before either the Snow Brand or the Amgen groups. Wong et al identified and characterized a TNF-related activation-induced cytokine (TRANCE) during a search for apoptosis-regulatory genes in murine T cell hybridomas, finding it to be predominantly expressed on T cells and in lymphoid organs and controlled by the T cell receptor through a calcineurin-regulated pathway[87]. The putative receptor for TRANCE was detected on mature dendritic cells. They were not aware at that time of any involvement of TRANCE in bone biology, and in their survey of tissue distribution of TRANCE mRNA in mouse tissues, bone was not examined. It might be noted that this omission remains the case almost always, when new molecules of whatever variety are discovered, unless it takes place in the context of investigators who have a direct interest in bone.

In studying the processing and presentation of antigens by dendritic cells to T cells, Anderson *et al*[88] characterized receptor activator of NF-kB (RANK), a new member of the TNF receptor family derived from dendritic cells, and its ligand RANKL, which they recognized to be identical to TRANCE[68]. A soluble form of RANKL augmented the ability of dendritic cells to stimulate T cell proliferation in a mixed lymphocyte reaction and increased the survival of RANK-positive T cells. Again, these workers were not aware at the time of their first publication of any link between RANK/RANKL and bone. Interestingly though, the type I membrane protein, RANK, contained four extracellular cysteine-rich domains, as was the case with OPG, published earlier that year[78].

OSTEOCLAST REGULATION AND FUNCTION

These discoveries filled in the gaps that had been eluding us for many years[56]. The concepts that drove the research to such outcomes had been developed over years of study of bone cell biology. The ODF/SOFA hypothesis predicted a control mechanism that was sufficiently important from the evolutionary point of view that it was likely to be highly conserved, and that has certainly proven to be so, both in respect of the overall mechanism and of the conserved sequences of the central molecules. By treating with RANKL and M-CSF it was now possible for the first time to prepare osteoclasts in relatively large numbers without the participation of stromal/osteoblastic precursors, including the preparation of human osteoclasts from peripheral blood[89,90]. The physiology of the bone resorption regulatory system was in a short space of time laid out before us with convincing evidence of the essential regulatory function of RANKL, not only in promoting osteoclast formation, but also their survival and activity[85], as was predicted from the earlier demonstration of activation of osteoclasts through contact with osteoblastic cells[44].

The remainder of this Issue is devoted to details of the ways in which this physiological control system functions, how the knowledge has led to drug development, and how this communication system is crucial not only to the control not only of osteoclast biology and hence bone remodeling, but also to other biological systems.

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TOPIC HIGHLIGHT

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Role of osteoclasts in regulating hematopoietic stem and progenitor cells

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Abstract

Bone marrow (BM) cavities are utilized for hematopoiesis and to maintain hematopoietic stem cells (HSCs). HSCs have the ability to self-renew as well as to differentiate into multiple different hematopoietic lineage cells. HSCs produce their daughter cells throughout the lifespan of individuals and thus, maintaining HSCs is crucial for individual life. BM cavities provide a specialized microenvironment termed "niche" to support HSCs. Niches are composed of various types of cells such as osteoblasts, endothelial cells and reticular cells. Osteoclasts are unique cells which resorb bones and are required for BM cavity formation. Loss of osteoclast function or differentiation results in inhibition of BM cavity formation, an osteopetrotic phenotype. Osteoclasts are also reportedly required for hematopoietic stem and progenitor cell (HSPC) mobilization to the periphery from BM cavities. Thus, lack of osteoclasts likely results in inhibition of HSC maintenance and HSPC mobilization. However, we found that osteoclasts are dispensable for hematopoietic stem cell maintenance and mobilization by using three independent osteoclast-less animal models. In this review, I will discuss the roles of osteoclasts in hematopoietic stem cell maintenance and mobilization.

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Key words: Osteoclasts; Hematopoietic stem and progenitor cell; Mobilization; Receptor activator of nuclear factor kappa B ligand; Osteomac; Osteopetrosis; *op/op*; C-Fos; Osteoprotegerin

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INTRODUCTION

Bones reportedly play crucial roles in regulating bone marrow (BM) hematopoiesis by preparing BM cavities and bone marrow "niches" to support hematopoietic stem cell (HSC) maintenance[1-8]. Niches consist of osteoblasts, endothelial cells, reticular cells and osteomacs and are regulated by their products, such as Angiopoietin 1 and Cxcl12 (Figure 1)[9-19]. Functional BM cavities are required for HSPC mobilization from BM cavities to the periphery[20-24]. Thus, BM cavities play crucial roles in regulating HSC maintenance and HSPC mobilization to the periphery and loss of BM cavities is predicted to promote impaired HSPC maintenance and mobilization. However, the impact of lack of BM cavities on the hematopoietic system remains unclear.

Osteoclasts are unique in their capacity to resorb bones: perturbation of osteoclast differentiation or function results in loss of BM cavities, a condition termed osteopetrosis[25-30]. Macrophage colony stimulating factor (M-CSF) and receptor activator of nuclear factor kappa B ligand (RANKL) are cytokines[31-35] that play a crucial

role in inducing osteoclastogenesis[36-41]. Loss of M-CSF and RANKL, and c-Fos, a transcription factor required for osteoclastogenesis, via mutation or gene-targeting in animal models, impairs osteoclastogenesis and BM cavity formation, an osteopetrotic phenotype[25,26,28]. In contrast, loss of osteoprotegerin (OPG), a decoy RANKL receptor that inhibits osteoclastogenesis[42-45], accelerates osteoclastogenesis in mice and promotes an osteoporotic phenotype[46,47]. Osteoclast activity is reportedly upregulated following serial granulocyte colony-stimulating factor (G-CSF) injection[48], which stimulates HSPC mobilization to the periphery[49-61]. Furthermore, osteoclasts reportedly induce HSPC mobilization[62-64]. Osteoclasts were also reportedly involved in regulating the HSC niche in the bone marrow[65-70]. Thus far, however, hematopoiesis and HSPC mobilization in animals lacking M-CSF, RANKL, c-Fos or OPG remained uncharacterized before our study.

HEMATOPOIETIC STEM CELLS ARE MAINTAINED IN OSTEOPETROTIC MICE

The chemotherapeutic agent 5-fluorouracil (5-FU) kills cycling cells. Since hematopoietic stem cells (HSCs) are maintained in a quiescent state, HSCs are resistant to 5-FU induced cell death. Thus, serial 5-FU injection has been utilized to evaluate HSC cell function and maintenance *in vivo*[71-74]. We hypothesized that osteopetrotic mice show a reduced HSC pool and function due to lack of BM cavities and niches. Indeed, we found that *op/op* mice were lethally susceptible to serial 5-FU injection[75]. However, RANKL- and c-Fos-deficient mice were not as susceptible to serial 5-FU injection as *op/op* mice were[75]. These results suggest that osteoclasts and BM cavities are not required for HSC maintenance, while M-CSF likely functions in resistance to 5-FU-induced myelosuppression. Indeed, we found that serum M-CSF concentrations increase during 5-FU-induced myelosuppression and that various tissues from M-CSF-deficient *op/op* mice exhibit serious bacterial infections, suggesting that M-CSF expression antagonizes infection during myelosuppression[75].

HSPCS ARE MOBILIZED FOLLOWING SERIAL G-CSF INJECTION INTO OSTEOPETROTIC MICE

Serial G-CSF injection is utilized clinically to mobilize HSPCs for transplantation[49-51]. Similarly, serial G-CSF injection in mice induces HSPC mobilization to the periphery and is often utilized to evaluate HSPC mobilization capacity in mouse models[20,52-61]. We analyzed HSPC mobilization capacity following serial G-CSF injection in three independent osteoclast-less and thereby BM cavity-less animals, *op/op* mice (M-CSF-deficient mice), c-Fos and RANKL-deficient mice. HSPC mobilization to the periphery was evaluated by flow cytometry to detect the phenotypically HSPC-rich fraction; Lineage-negative, Sca1-positive and c-Kit-positive (LSK), and functional assays such as colony formation and competitive repopulation assay. Since BM cavities or osteoclasts reportedly function in HSPC mobilization[20], we speculated that osteopetrotic animals do not show HSPC mobilization into the periphery due to their loss. Interestingly, however, we found that serial G-CSF injection mobilized HSPCs at levels in all three osteopetrotic mice, compared to control mice, indicating that osteoclasts and BM cavities are not required for HSPC mobilization to the periphery[75].

HSPC MOBILIZATION IS IMPAIRED IN OSTEOPOROTIC OPG-DEFICIENT MICE

Since HSPC mobilization was detected in osteoclast-less osteopetrotic mice, we evaluated HSPC mobilization in OPG-deficient mice, which exhibit osteoporotic phenotypes due to accelerated osteoclastogenesis[75]. In contrast to osteopetrotic mice, osteoporotic OPG-deficient mice showed reduced HSPC mobilization capacity compared to wild-type mice, suggesting that osteoclasts negatively regulate HSPC mobilization following serial G-CSF injection.

SPLEEN IS NOT THE PRIMARY TISSUE TO MAINTAIN HSPCS IN AN OSTEOPETROTIC CONDITION

In osteopetrotic patients and animal models, extramedullary hematopoiesis reportedly occurs in the spleen[76,77]. Indeed, we found an increased proportion of the LSK cell fraction in *op/op* mouse spleen compared to control mouse spleen[75]. Thus, we reasoned that there is a pool of mobilized HSPCs in osteopetrotic mice in the spleen prior to mobilization. We then removed spleens from *op/op* mice and analyzed HSPC mobilization capacity of HSPCs following serial G-CSF injection (Figure 2). HSPC mobilization was significantly elevated in splenectomized *op/op* mice compared to splenectomized controls or non-splenectomized *op/op* mice, suggesting that the spleen is not the primary tissue to maintain HSPCs and that it may even antagonize HSPC mobilization in osteopetrotic mice[75]. At present, the localization of HSPCs in osteopetrotic mice is not clear, but we found that small bone lacunae are distributed in osteopetrotic bones and that c-Kit-positive hematopoietic cells are located in such lacunae[75]. These lacunae in osteopetrotic bones likely contribute to the HSPC pool in these animals.

F4/80-POSITIVE OSTEOMACS ARE REDUCED IN *OP/OP* MICE BUT ARE DETECTED NORMALLY IN C-FOS-, RANKL- AND OPG-DEFICIENT MICE

Recently, F4/80-positive bone-lining cells termed "osteo-

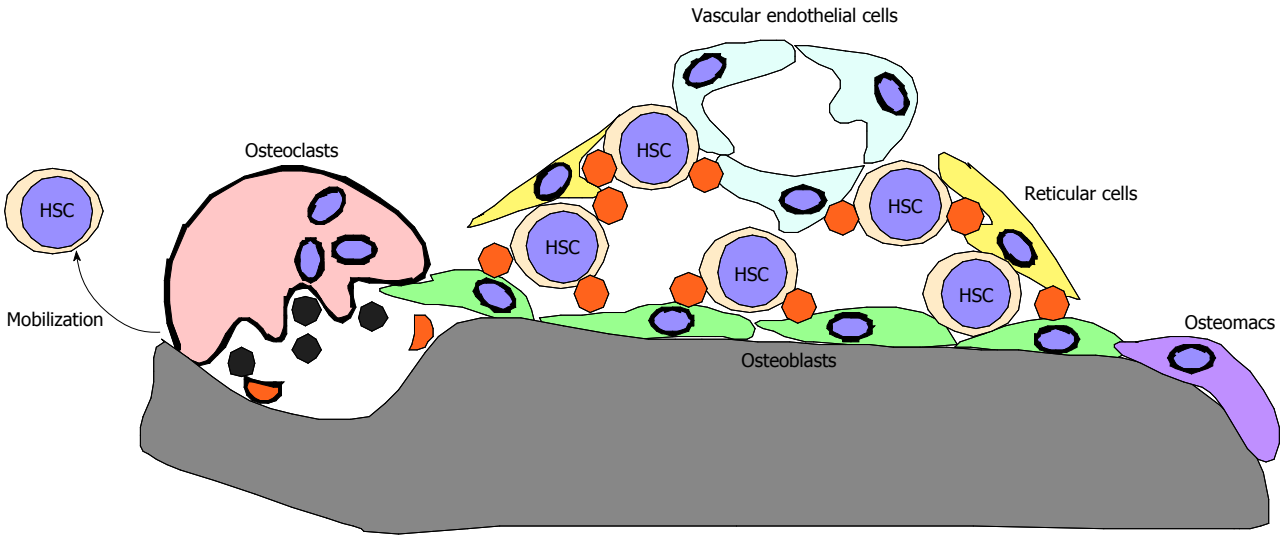

Figure 1 Components of bone marrow niches. Bone marrow niches are composed of cell types such as osteoblasts, reticular cells and vascular endothelial cells and factors expressed by these cells; HSC: Hematopoietic stem cell.

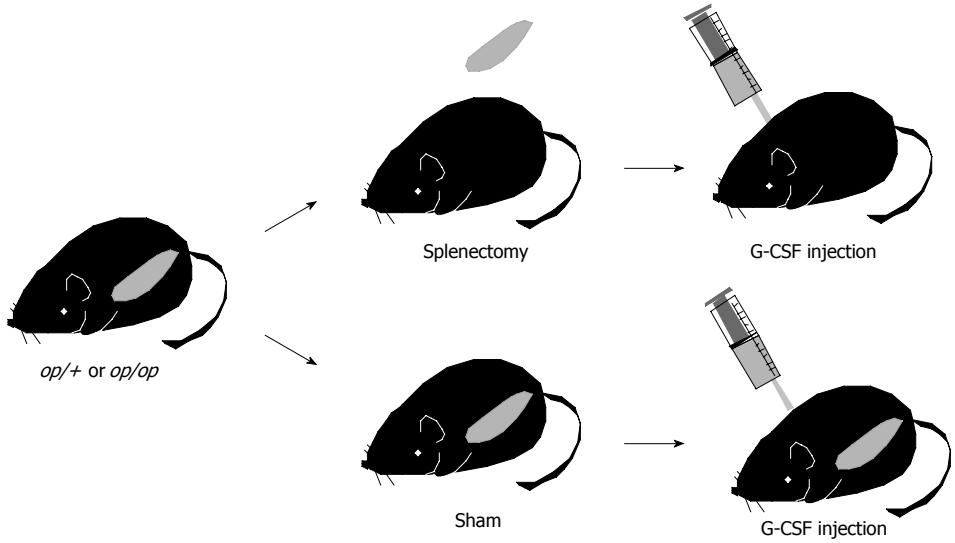

Figure 2 Splenectomy strategy. Splenectomy or sham surgery was performed on *op/op* and control mice. Seven days later, mice were injected with 250 μg/kg per day granulocyte colony-stimulating factor daily for 5 d and hematopoietic stem cell mobilization to peripheral blood was analyzed using flow cytometry and colony-forming assays. G-CSF: Granulocyte colony-stimulating factor.

macs" have been identified[78] and demonstrated to play a crucial role in regulating hematopoiesis *in vivo*[18]. Osteomacs reportedly regulate osteoblast function and help retain HSPCs in BM cavities and osteomac loss is predicted to mobilize HSPCs to the periphery[18]. Since osteomacs were once thought to be identical to osteoclasts, increased mobilization seen in osteoclast-less animals was considered due to the loss of osteomacs/osteoclasts. Indeed, we observed decreased numbers of osteomacs in *op/op* mouse bones[75]. However, F4/80-positive osteomacs were detected normally in RANKL-deficient and c-Fos-deficient mice, indicating that osteomacs are not osteoclasts[75]. F4/80 is reportedly not expressed in osteoclasts[79], further suggesting that osteomacs are a different cell type.

PHARMACOLOGICAL INHIBITION OF OSTEOCLASTS BY BISPHOSPHONATE AND RANKL NEUTRALIZING ANTIBODY DOES NOT INHIBIT HSPC MOBILIZATION

Although we analyzed osteoclast function in regulating hematopoiesis in osteopetrotic mice, the role of osteoclasts in hematopoiesis in adult animals remained unclear. Previously, osteoclast activity was reported to increase following G-CSF injection, but treatment with pamidronate, an osteoclast-inhibiting bisphosphonate, did not inhibit HSPC mobilization to the periphery, suggesting that increased osteoclast activity is not required for HSPC mobilization following G-CSF injection[48]. In contrast,

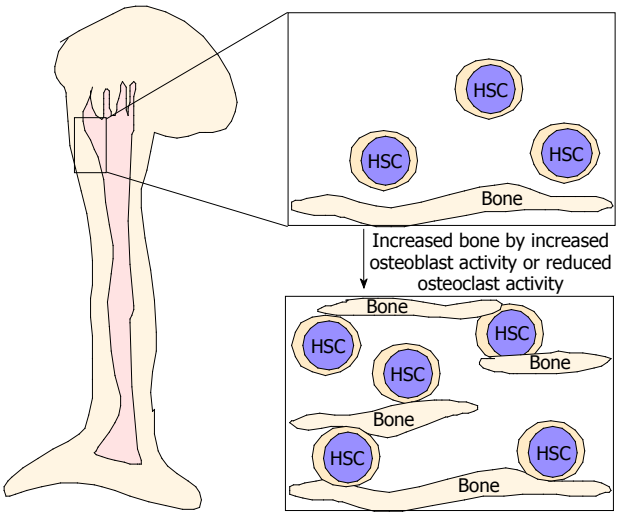

Figure 3 Increased bone mass is associated with an increased hematopoietic stem cell pool. Hematopoietic stem cells (HSC) are located in bone marrow cavities with surrounding niche cells. Increased bone mass due to either increased osteoblast activity or reduced osteoclast activity likely contributes to HSC expansion.

osteoclasts are reportedly required for HSPC mobilization since mobilization is induced by bleeding or LPS injection, which increases osteoclastogenesis[62]. Similarly, injection of HGF, SDF1 or RANKL also stimulated HSPC mobilization and increased osteoclast formation[62]. RANKL- or G-CSF-induced HSPC mobilization is abrogated in young female PTPe-deficient mice, which exhibit mild osteoclast dysfunction[62]. Thus, the role of osteoclasts in regulating HSPC mobilization in adults remained controversial and so we did the next experiments to resolve this controversy. We treated wild-type adult mice with an osteoclast-inhibiting agent: the bisphosphonate alendronate or a neutralizing antibody against RANKL (RANKL Ab). Both of these reagents strongly inhibit osteoclast activity and are used to treat osteoporosis patients[80-97]. Indeed, we observed increased bone mass following treatment with alendronate and RANKL Ab in wild-type adult mice[75]. Even in this osteoclast-inhibiting condition, HSPC mobilization to the periphery was normal or even highly induced compared with control mice, suggesting that osteoclast activity is neither required for nor antagonistic to HSPC mobilization[19].

ROLES OF OSTEOCLASTS AND BM CAVITIES IN HEMATOPOIESIS AND HSPC MOBILIZATION

In most mammalian and avian species, including humans and mice, hematopoiesis occurs in BM cavities and HSC daughter cells are mobilized to the periphery. To continuously supply hematopoietic cells throughout an animal's life, HSCs must self-renew and be capable of producing multiple lineages[98]. Protection of HSCs from various stresses is crucial to maintain lifelong hematopoiesis. To maintain function, HSCs locate in a specific microenvironment in BM cavities termed the "niche", where cells normally remain quiescent. Niches consist of various cell types, including osteoblasts, reticular cells, endothelial cells and osteoclasts, and corresponding products of these cells, such as Cxcl12 (SDF1), Angiopoietin 1 and N-Cadherin. Increased osteoblastogenesis reportedly increases the HSC pool, while degradation of Cxcl12 or surrounding extracellular matrix protein is required for HSPC mobilization to the periphery[9,10,20]. Since osteoclasts express high levels of matrix-degrading enzymes, such as matrix metalloprotenase 9 (MMP9) and Cathepsin K[99-105], and osteoclast activity increases following G-CSF injection[48], osteoclasts were predicted to be critical for HPSC mobilization through degradation of Cxcl12 and matrix protein[62]. In our study, we found that HSPC mobilization to the periphery was induced at comparable or even higher rates than that seen in controls following serial G-CSF injection of three independent osteoclast-less and therefore BM-less mice, phenotypes also seen in wild-type mice treated with two independent osteoclast inhibiting agents[75]. These findings suggest that osteoclasts and BM cavities are dispensable for HSPC maintenance and mobilization. However, it is important to note that we did not induce HSPC mobilization by bleeding or injection of LPS or cytokines, but rather treated wild-type adult mice with one bisphosphonate and one antibody. Nonetheless, our study, at least in part, demonstrates that osteoclast-less and BM cavity-less conditions or conditions in which osteoclasts are severely inhibited do not necessarily prohibit HSPC mobilization.

HEMATOPOIESIS IN OSTEOCLAST-LESS, THEREBY BM-LESS, ANIMALS

As described above, even in osteopetrotic bones, HSCs were located in bones[75], suggesting that these bones play a role in providing an HSC pool. Parathyroid hormone (PTH) reportedly has dual effects in bone and single or intermittent PTH injection leads to increased osteoblastic activity, whereas continuous PTH stimulation results in increased osteoclast activity and decreased bone mass[106-111]. Interestingly, increased osteoblastic activity due to elevated PTH signaling in constitutive active PTH receptor transgenic mice reportedly increases bone mass and the size of the HSC pool *in vivo* and osteoblasts are thought to serve as critical niche components[9,10]. Similarly, we found that increased bone mass due to reduced osteoclastic activity may contribute to an increased HSC pool[75]. Thus, increased bone mass, due to either increased osteoblast activity or reduced osteoclast function, likely increases the HSC pool *in vivo* (Figure 3). Expanding HSCs *ex vivo* is considered difficult since senescence is crucial for maintaining HSCs and cell cycling disrupts HSC function. Increased niche size by either increased osteoblast activity or inhibited osteoclast function likely serves as a mechanism to increase the HSC pool *in vivo* (Figure 3). Further studies are needed to elucidate the

role of bones as a HSC niche.

BM CAVITY FORMATION AND BONE STRENGTH

We have shown that osteoclasts and BM cavities are not required for HSPC maintenance and mobilization. So why do BM cavities develop with osteoclasts? We found that, indeed, bone mineral density was significantly higher in osteopetrotic bones than that seen in control bones since BM cavities of osteopetrotic bones were filled with bone[75]. However, osteopetrotic bone strength was low compared with control bones. Since cortical bone thickness is lower in osteopetrotic than in control bones, BM cavities likely developed along with development of cortical bones. At present, the roles of BM cavities are not well clarified and further studies are needed to elucidate their roles in bone and in hematopoiesis.

PHARAMACOLOGICAL INHIBITION OF OSTEOCLASTS

Osteoclasts emerge in the presence of M-CSF and RANKL: mutational inactivation of M-CSF or targeted disruption of RANKL results in osteoclast differentiation failure and BM cavity-less osteopetrotic phenotypes[25,28]. Recently, a neutralizing antibody against RANKL, named Denosumab, was utilized to treat osteoporosis patients and found to promote significantly reduced osteoclast activity and elevated bone mineral density compared with non-treated placebo controls[90]. Similarly, neutralizing antibody against mouse RANKL increases bone mass[94]. That antibody could be a useful tool to analyze effects of osteoclast-inhibiting conditions in mouse models. The increasing number of osteoporosis patients is now a pressing problem in developed countries and many are treated with osteoclast-inhibiting agents such as bisphosphonates. Future analysis of the effects of these drugs on the systems other than the bone system, such as hematopoiesis, is required to evaluate potential adverse affects of these agents in the future.

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TOPIC HIGHLIGHT

Hisataka Yasuda, PhD, *Series Editor*

RANKL, a necessary chance for clinical application to osteoporosis and cancer-related bone diseases

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Abstract

Osteoporosis is a common bone disease characterized by reduced bone and increased risk of fracture. In postmenopausal women, osteoporosis results from bone loss attributable to estrogen deficiency. Osteoclast differentiation and activation is mediated by receptor activator of nuclear factor-κB ligand (RANKL), its receptor receptor activator of nuclear factor-κB (RANK), and a decoy receptor for RANKL, osteoprotegerin (OPG). The OPG/RANKL/RANK system plays a pivotal role in osteoclast biology. Currently, a fully human anti-RANKL monoclonal antibody named denosumab is being clinically used for the treatment of osteoporosis and cancer-related bone disorders. This review describes recent advances in RANKL-related research, a story from bench to bedside. First, the discovery of the key factors, OPG/RANKL/RANK, revealed the molecular mechanism of osteoclastogenesis. Second, we established three animal models: (1) a novel and rapid bone loss model by administration of glutathione-S transferase-RANKL fusion protein to mice; (2) a novel mouse model of hypercalcemia with anorexia by overexpression of soluble RANKL using an adenovirus vector; and (3) a novel mouse model of osteopetrosis by administration of a denosumab-like anti-mouse RANKL neutralizing monoclonal antibody. Lastly, anti-human RANKL monoclonal antibody has been successfully applied to the treatment of osteoporosis and cancer-related bone disorders in many countries. This is a real example of applying basic science to clinical practice.

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Key words: Osteoclast; Osteoblast; Receptor activator of nuclear factor-κB ligand; Denosumab; Receptor activator of nuclear factor-κB; Osteoprotegerin

Core tip: This review describes a success story from discovery of osteoprotegerin/receptor activator of nuclear factor-κB ligand (RANKL)/receptor activator of nuclear factor-κB (RANK) to clinical application of a fully human anti-RANKL monoclonal antibody to the treatment of osteoporosis and cancer-related bone disorders. RANKL is a key molecule for osteoclast differentiation and activation. Inhibition of RANKL activity with anti-RANKL antibody reduces osteoclastogenesis, resulting in inhibition of bone resorption. Three animal disease models of osteoporosis, hypercalcemia, and osteopetrosis by treating normal mice with soluble RANKL (sRANKL), adenovirus expressing sRANKL, and anti-mouse RANKL neutralizing antibody, respectively, can be established in 2-14 d and the establishment of these animal models could help accelerate research on bone metabolism.

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INTRODUCTION

Morphogenesis and remodeling of bone depends on the integrated activity of osteoblasts which form bone and osteoclasts which resorb bone. There have been many

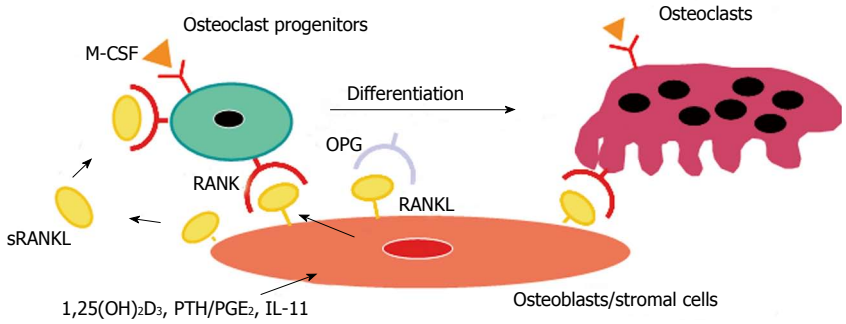

Figure 1 A model illustrating a mechanism by which osteoblasts/stromal cells regulate osteoclast differentiation and activation. Three distinct signals stimulated by 1,25(OH)$_2$D$_3$, PTH/PGE$_2$, and interleukin (IL)-11 induce receptor activator of nuclear factor-κB ligand (RANKL) expression on osteoblasts/stromal cells. RANKL mediates a signal for osteoclastogenesis through RANK produced on osteoclast progenitors. Osteoprotegerin (OPG) inhibits osteoclastogenesis by interrupting the binding of RANKL and RANK. Macrophage colony-stimulating factor (M-CSF) produced by osteoblasts/stromal cells is also indispensable for proliferation and differentiation of osteoclast progenitors. Soluble RANKL (sRANKL) is produced by digestion of RANKL with metalloproteinases and may regulate osteoclastogenesis.

attempts to develop pharmaceuticals to treat osteoporosis and other metabolic bone disorders. The major difficulty in the development of such drugs is the lack of clarification of the mechanisms regulating differentiation of the bone cells including osteoblasts and osteoclasts. In the late-1990s, dramatic findings of the key factors of osteoclast differentiation opened a new era in research of osteoclast biology and the development of anti-resorptive pharmaceuticals for osteoporosis[1-11].

Discovery of key factors to understand the molecular mechanism of osteoclastogenesis

We previously identified and cloned an osteoclastogenesis inhibitory factor named OCIF[2,3]. We used human fetal lung fibroblasts, IMR-90 cells, as the cell source and purified OCIF using the *in vitro* osteoclastogenesis assay established by Takahashi *et al*[12] and Udagawa *et al*[13]. Since fibroblasts are present ubiquitously in the body, it was surprising to find that these cells produce a novel osteoclastogenesis inhibitory factor. IMR-90 cells produce a number of cytokine and growth factors including hepatocyte growth factor (HGF)[14]. Suda *et al*[15] proposed a working hypothesis that osteoclasts are generated by cell-to-cell interaction with a hypothetical membrane-bound factor called osteoclast differentiation factor (ODF) on osteoblasts. To explore this hypothesis we attempted to find a novel osteoclastogenesis inhibitory factor that could be an inhibitor of the hypothetical factor, ODF[2,3]. Simonet *et al*[1] independently found the identical factor through the rat EST project and named it osteoprotegerin (OPG). They found a novel tumor necrosis factor (TNF) receptor family member in the comprehensive genomic sequencing project and identified it as an osteoclastogenesis inhibitor by overexpression of its cDNA in transgenic mice. Notably, two independent groups identified the same factor at almost the same time by different strategies.

Thereafter, Yasuda *et al*[4] and Lacey *et al*[5] independently identified a ligand of OCIF/OPG with expression cloning and named it ODF and OPG ligand (OPGL), respectively. ODF/OPGL was found to be identical to TNF-related activation-induced cytokine (TRANCE)[16] and RANKL[17], which were cloned as factors regulating T-cell and dendritic cell functions. We confirmed that ODF was the long-sought after ligand regulating osteoclast differentiation and activation[4]. As standard nomenclature of the same molecule, OPG and RANKL were proposed by the ASBMR President's Committee on Nomenclature, respectively[18].

We further identified RANK as a receptor for RANKL on osteoclasts[6]. Although RANK was known to be a receptor for RANKL in the T-cell and dendritic cell interaction[17], the receptor responsible for the RANKL-mediated osteoclastogenesis had not been identified. Some ligands of the TNF family bind to several receptors of the TNF receptor family. It was suspected that RANKL might bind to another member of the TNF receptor family, but not to RANK. We molecularly cloned the RANKL receptor from mouse osteoclast progenitors by panning and identified it as RANK[6]. A polyclonal antibody against soluble RANK (sRANK) mimicked the RANKL function by clustering of RANK. In contrast, sRANK and Fab fragment of anti-RANK polyclonal antibody completely inhibited RANKL-mediated osteoclastogenesis by binding to RANKL and RANK, respectively. Hsu *et al*[7] also led to the same conclusion using transgenic mice overexpressing soluble RANK. The importance of OPG/RANKL/RANK was demonstrated *in vivo* with gene-deficient mice[19-23]. The summary of these results is illustrated in the model of osteoclast differentiation (Figure 1). The details of OPG/RANKL/RANK are described elsewhere[8-11].

To investigate the effects and functions of RANKL *in vivo*, transgenic mice overexpressing mouse soluble RANKL (sRANKL-TG mice)[24] and RANKL-deficient mice[21] were generated. They are useful animal models but it takes several months to interbreed them with other TG mice or gene-deficient mice. Alternatively, we attempted to establish three animal disease models by treating normal mice with either sRANKL, adenovirus vector harboring mouse sRANKL cDNA (Ad-sRANKL), or anti-mouse RANKL neutralizing mono-

clonal antibody. It takes two to 14 d to make these animal models using normal mice. Thus, the establishment of these quick animal models could help accelerate research on bone metabolism.

ESTABLISHMENT OF THREE ANIMAL MODELS OF METABOLIC BONE DISEASES

A novel and rapid bone loss model by administration of GST-RANKL to mice

Osteoporosis remains a major public health problem through its associated fragility fractures. Several animal models for the study of osteoporotic bone loss, such as ovariectomy (OVX) and denervation, require surgical skills and several weeks to establish[25-31]. We tried to establish a novel and rapid bone loss model by the administration of glutathione-S transferase (GST)-RANKL to mice[32,33] (Figure 2). GST-RANKL is a fusion protein of GST and the extracellular domain of human RANKL (aa 140-317). GST-RANKL showed stronger activity in osteoclastogenesis using mouse bone marrow macrophages (BMM) and the mouse macrophage cell line, RAW264 cells, respectively, compared with a commercially available soluble RANKL (sRANKL) (Figure 2A, B). Mice were injected intraperitoneally with GST-RANKL and used to evaluate existing anti-osteoporosis drugs. GST-RANKL decreased bone mineral density (BMD) within 50 h in a dose-dependent manner. The marked decrease in femoral trabecular BMD demonstrated by pQCT and the 3D images obtained by micro computer tomography (CT) were indistinguishable from those observed in the OVX model. Histomorphometry revealed significant increase in osteoclastic activity in the GST-RANKL-injected mice. In addition, serum biochemical markers of bone turnover such as calcium, C-terminal cross-linked telopeptides of collagen I (CTx), and tartarate-resistant acid phosphatase-5b (TRAP-5b) were also significantly increased in the GST-RANKL-injected mice in a dose-dependent manner. One of the gold standard models for osteoporosis is OVX which mimics osteoporosis in postmenopausal women. Moreover, the GST-RANKL-induced bone loss model was successfully applied to C57/B6 male and female mice, ICR mice, and Fisher rats. Very recently we successfully shortened the experimental period from 50 to 24 h and established a 1-d bone loss model with one injection of GST-RANKL in mice and rats (Tomimori *et al*, unpublished).

To apply this bone loss model in the evaluation of pharmaceuticals for osteoporosis, we tested bisphosphonates (BPs), PTH and a selective estrogen receptor modulator (SERM), which are commonly used for the treatment of osteoporosis. We successfully evaluated BPs and PTH within 4 d and 2 wk, respectively, and a combination of GST-RANKL injections and OVX allowed evaluation of a SERM in 18 d. As major pharmaceuticals for osteoporosis have been evaluated using the GST-RANKL-induced bone loss model, it could also be used to evaluate novel drug candidates. In fact, using the bone loss model we evaluated an inhibitor of Btk/Tec tyrosine kinases that are essential for signal transduction through RANK in osteoclast differentiation in approximately 50 h[32].

We also evaluated a denosumab-like anti-human RANKL neutralizing monoclonal antibody as a new osteoporosis therapeutic drug candidate in 10 d[33]. We made anti-human RANKL monoclonal antibodies and selected a neutralizing antibody using the *in vitro* osteoclastogenesis assay with RAW264 cells. This antibody bound to and neutralized the activity of human but not mouse RANKL. The anti-human RANKL neutralizing antibody (100 g/mouse) or PBS was injected subcutaneously into mice 7 and 4 d before the GST-RANKL injection. Antibody treatment of the model mice completely inhibited the decrease in femoral trabecular BMD. In contrast, BMD in PBS-injected control mice was unaffected by the antibody treatment.

Notably, two or three injections of GST-RANKL induced a weak coupling, whereas longer treatments induced strong coupling[33]. Because OVX-induced bone loss is accompanied with a high turnover of bone remodeling, the GST-RANKL model is similar in mechanism to that of OVX-induced bone loss. Bahtiar *et al*[34] also used GST-RANKL to develop a high bone turnover model. Other models for high-turnover bone disease with sRANKL have been reported, using continuous infusion[35] and subcutaneous injections of sRANKL[36]. Some of the mice exhibited hypercalcemia. The infusion model requires a large amount of sRANKL and insertion of osmotic pumps subcutaneously into rats, while the injection model requires twice-daily subcutaneous injections into mice for 10 d. As a local bone loss model GST-RANKL was injected into mouse calvaria several times to induce osteoclastogenesis and bone loss near the injection sites within several days[37,38].

A summary of the characteristics of the GST-RANKL-induced bone loss model in comparison to the OVX model is shown in Table 1. First of all, the GST-RANKL-induced bone loss model is rapid, being established within 24-50 h. Second, it is easy, as two or three intraperitoneal injections of sRANKL are sufficient to induce osteoporotic bone loss. Third, it is simple. The mechanism of bone loss in the model is simply due to a stimulation of osteoclast differentiation and activation with endogenous sRANKL. Lastly, it is useful for evaluation of major pharmaceuticals and/or candidates for osteoporosis. A Btk/Tec tyrosine kinase inhibitor, BPs, anti-human RANKL neutralizing monoclonal antibody, PTH and a SERM were evaluated within 50 h, 3 d, 10 d, 2 wk, and 18 d, respectively. Overall, the GST-RANKL model is the simplest, fastest, and easiest osteoporosis model and could be a gold standard for the evaluation of novel drug candidates of osteoporosis as well as OVX[32,33].

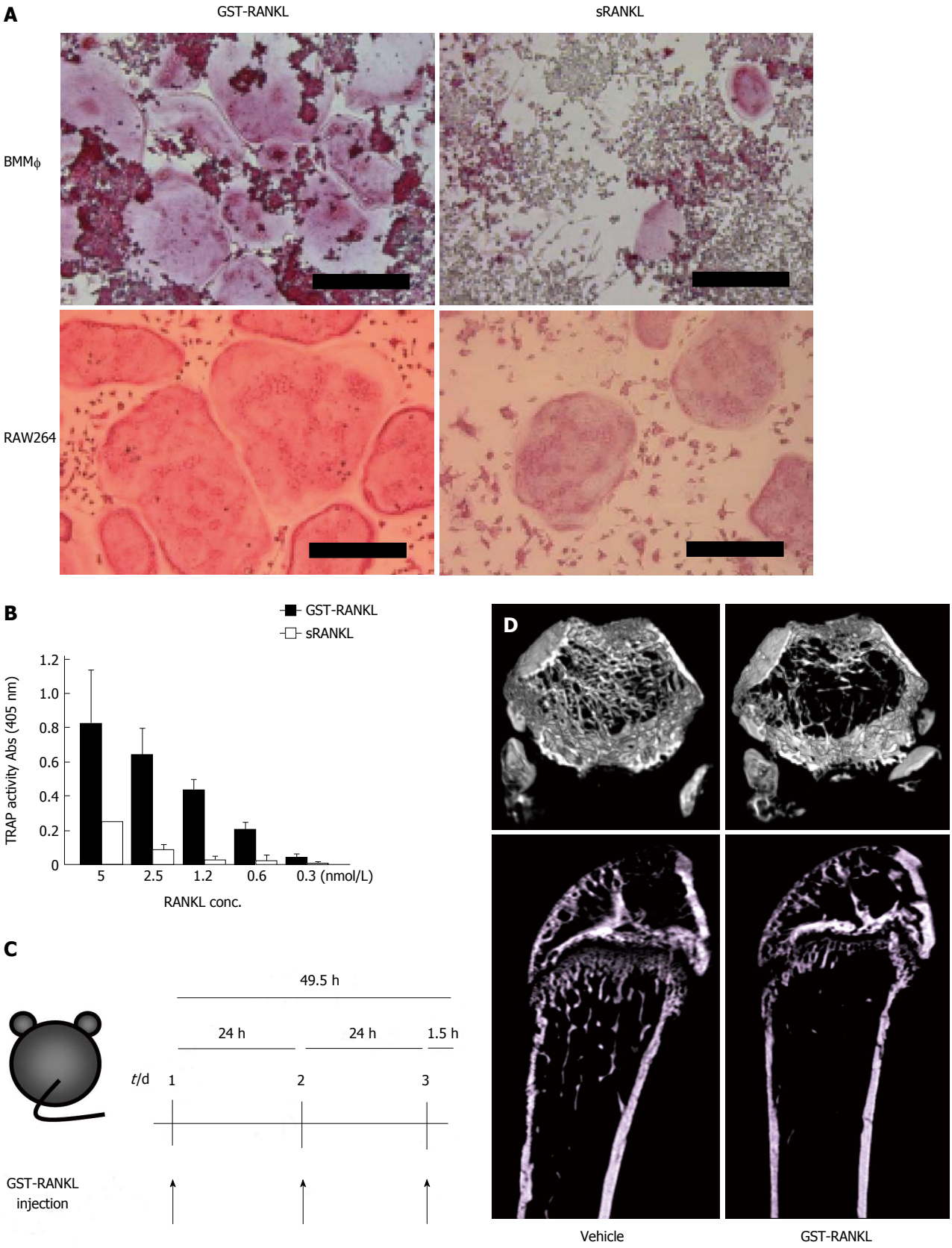

Figure 2 Establishment of GST-RANKL-injected bone loss model. A: Osteoclasts were generated with 5 nmol/L glutathione-S transferase-receptor activator of nuclear factor-κB ligand (GST-RANKL) or sRANKL from bone marrow macrophages (BMM) and RAW264 cells in the presence and absence of M-CSF, respectively. The cells were fixed and stained for tartarate-resistant acid phosphatase (TRAP). Bars = 250 m; B: Activities of GST-RANKL and sRANKL were compared using *in vitro* osteoclastogenesis assay with RAW264 cells by TRAP solution assay. The TRAP activity represents the number of osteoclasts. C: Experimental design. PBS (vehicle) or GST-RANKL was injected intraperitoneally at 24-h intervals for 3 d into 7-wk-old female mice. Mice were sacrificed 90 min after the last injection; D: Micro computer tomography 3D images of femurs of mice treated with vehicle or 2 mg/kg GST-RANKL. The upper and lower panels are 3D cross-sectional and longitudinal images, respectively.

Table 1 Comparison of features between ovariectomy and GST-RANKL bone loss models

Technique	OVX model	GST-RANKL bone loss model
Technique	OVX	Intraperitoneal injections
Term for establishment	> 4 wk	24-50 h
Term for evaluation of BP	> 4 wk	3 d
Term for evaluation of PTH	> 4 wk	14 d
Term for evaluation of SERM	> 4 wk	18 d
Term for evaluation of anti-human RANKL	No	9 d
Term for evaluation of Tec tyrosine kinase inhibitor	NA	50 h
Evaluation of male animals	No	Yes
Term for pharmacological experiments	Several mon	Several wk/d
Advantages	Human disease model	Rapid, easy, simple, and inducible model

GST-RANKL: Glutathione-S transferase-receptor activator of nuclear factor-κB ligand; OVX: Ovariectomy; NA: Not available; BP: Bisphosphonates; SERM: Selective estrogen receptor modulator; PTH: Parathyroid hormone.

Table 2 Comparison of serum soluble RANKL concentrations among various mouse models

Mouse model	sRANKL (ng/mL)	Phenotype
Ad-sRANKL injection (High)	1500	Severe osteoporosis /hypercalcemia
Ad-sRANKL injection (Low)	233	Severe osteoporosis /hypercalcemia
sRANKL-Tg mice	30	Severe osteoporosis
GST-RANKL injection	3.5[1]	Osteoporosis
Wild mice	0.1	Normal

[1]Serum glutathione-S transferase-receptor activator of nuclear factor-κB ligand (GST-RANKL) concentration 4 h after injection of 1 mg/kg GST-RANKL. sRANKL: Soluble RANKL; Ad-sRANKL: Harboring mouse sRANKL cDNA.

A novel mouse model of hypercalcemia with anorexia by overexpression of sRANKL using an adenovirus vector

Hypercalcemia is a significant complication in human malignancies, including squamous cell, renal cell, and breast carcinomas. Humoral hypercalcemia of malignancy (HHM) is caused by the overproduction of parathyroid hormone related protein (PTHrP) by tumors[39,40]. PTHrP mobilizes calcium from bone by inducing the expression of RANKL[41]. RANKL is overexpressed in the marrow microenvironment in myeloma patients; the RANKL to OPG ratio is markedly increased compared to that in healthy controls[42].

Symptoms of hypercalcemia manifest as a reflection of the extent and rate of increase of serum ionized calcium. Mild to moderate hypercalcemia is usually asymptomatic[43], whereas moderate to severe hypercalcemia is usually symptomatic[44] and includes anorexia, constipation, vomiting, nausea, weakness and mental confusion.

In a previous study, we generated sRANKL-TG mice[24]. The sRANKL-TG mice exhibited severe osteoporosis accompanied with enhanced osteoclastogenesis, but no hypercalcemia. To analyze the relationship between the serum concentration of sRANKL and hypercalcemia and generate a simple and quick hypercalcemia model, Ad-sRANKL was injected intraperitoneally into male C57BL/6 mice[45]. Table 2 summarizes the results of serum sRANKL and calcium levels. Serum sRANKL increased markedly on day 7, while serum calcium increased with a peak on day 7 and returned to the baseline level on day 14. Food intake and body weight significantly declined on day 7. Taken together, the mice appeared to have anorexia as a symptom of hypercalcemia.

In addition, increases in markers for bone resorption (TRAP-5b) and formation (ALP, alkaline phosphatase) with a marked decrease in BMD measured by dual-energy X-ray absorptiometry were observed on day 14. The severe bone loss was confirmed by microCT (Figure 3). These results reflect accelerated bone formation following activation of osteoclasts, indicating coupling between bone formation and resorption.

Serum sRANKL level in the Ad-sRANKL group on day 7 was 15000 times higher than those in wild type mice. In sRANKL-TG mice, serum sRANKL was within normal range around 30 ng/mL[24]. Serum sRANKL level in the Ad-sRANKL group was about 50 times higher than that in the transgenic mice, which do not exhibit hypercalcemia even though they have severe osteoporosis and enhanced osteoclastogenesis. These observations suggest that 30 ng/mL sRANKL in serum is insufficient to induce hypercalcemia and that severe osteoporosis with enhanced osteoclastogenesis does not always accompany hypercalcemia. There may be a threshold sRANKL concentration for induction of hypercalcemia with anorexia.

Several experimental animal models of hypercalcemia have been described: a model with vitamin D treatment, a tumor transplant model and an infusion model using PTHrP[46-49]. These models have not shown a clear relationship between body weight loss and anorexia. Sato *et al*[49] showed that the recovery from hypercalcemia is accompanied by an improvement in body weight using a model of HHM, but the association of body weight loss with a decrease in food intake was not clearly shown in this model.

In summary, we established a novel model of hypercalcemia in normal mice injected intraperitoneally with Ad-sRANKL[45]. Overexpression of sRANKL activated osteoclasts to resorb bone, resulting in an increase in serum calcium. Hypercalcemic mice exhibited typical symptoms such as anorexia and weakness. The Ad-sRANKL-injected hypercalcemia model is the first one in which overexpressed sRANKL directly activates osteoclasts to increase serum calcium level. This simple and rapid model mimics HHM in terms of exhibiting anorexia and weakness and could be useful for investigating coupling between bone formation and resorption in high-turnover bone diseases, as well as for ex-

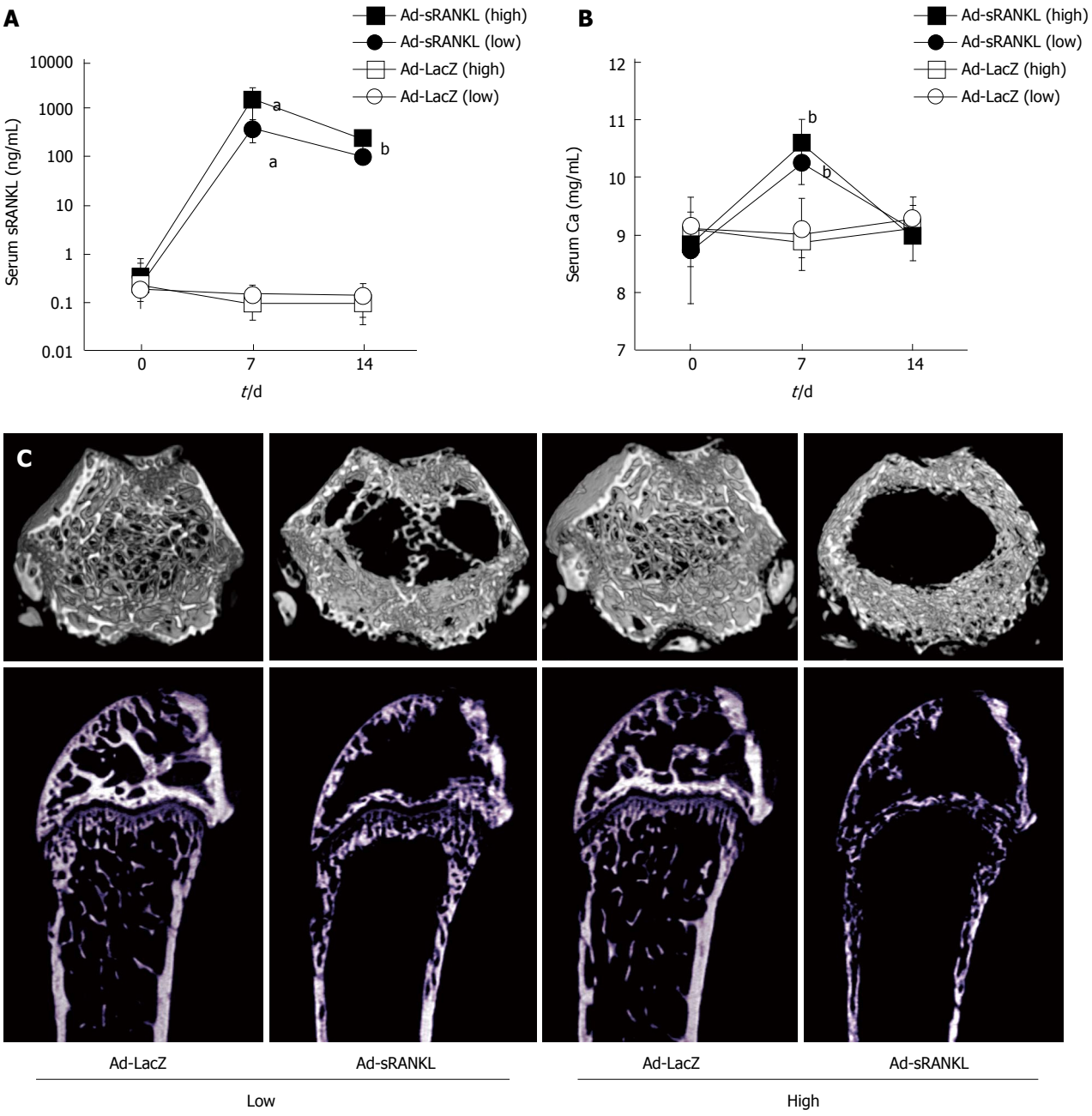

Figure 3 Establishment of Ad-sRANKL-injected osteoporosis/hypercalcemia model. Time-dependent changes in serum soluble receptor activator of nuclear factor-κB ligand (sRANKL) (A) and Ca (B) levels. Adenovirus vector harboring mouse sRANKL cDNA (Ad-sRANKL) or Ad-LacZ was injected intraperitoneally into 6-wk-old male C57BL/6 mice at 1.0×10^9 pfu/mouse in high-dose groups and 3.0×10^8 pfu/mouse in low-dose groups. Serum levels of sRANKL and Ca were measured on day 0, 7 and 14 after injection. Data are presented as the mean ± SD (n = 5 or 6). Ad-sRANKL high dose (filled squares), Ad-sRANKL low dose (filled circles), Ad-LacZ high dose (open squares), Ad-LacZ low dose (open circles). $^aP < 0.05$, $^bP < 0.01$ *vs* Ad-LacZ control; C: Micro computer tomography images of femurs in each group of mice. All mice were sacrificed on day 14 after injection and femurs were collected. The upper and lower panels are 3D cross-sectional and longitudinal images, respectively.

amining hypercalcemia with anorexia[45].

A novel mouse model of osteopetrosis by administration of a denosumab-like anti-mouse RANKL neutralizing monoclonal antibody

A fully human anti-RANKL monoclonal antibody (denosumab) is clinically used for the treatment of osteoporosis and cancer-related bone disorders[50-54]. It is a strong inhibitor of RANKL and is very stable in the blood stream for several months after single subcutaneous injection. Since denosumab does not cross react with rodent RANKL, its evaluation *in vivo* can be done only with non-human primates[55,56] or human *RANKL*-knock-in mice (HuRANKL mice)[57]. After replacing the exon 5 in mouse *RANKL* with that in human *RANKL*, denosumab can bind to and neutralize the chimeric mouse e/human RANKL in the HuRANKL mice. Cynomolgus monkeys have been used for the preclinical

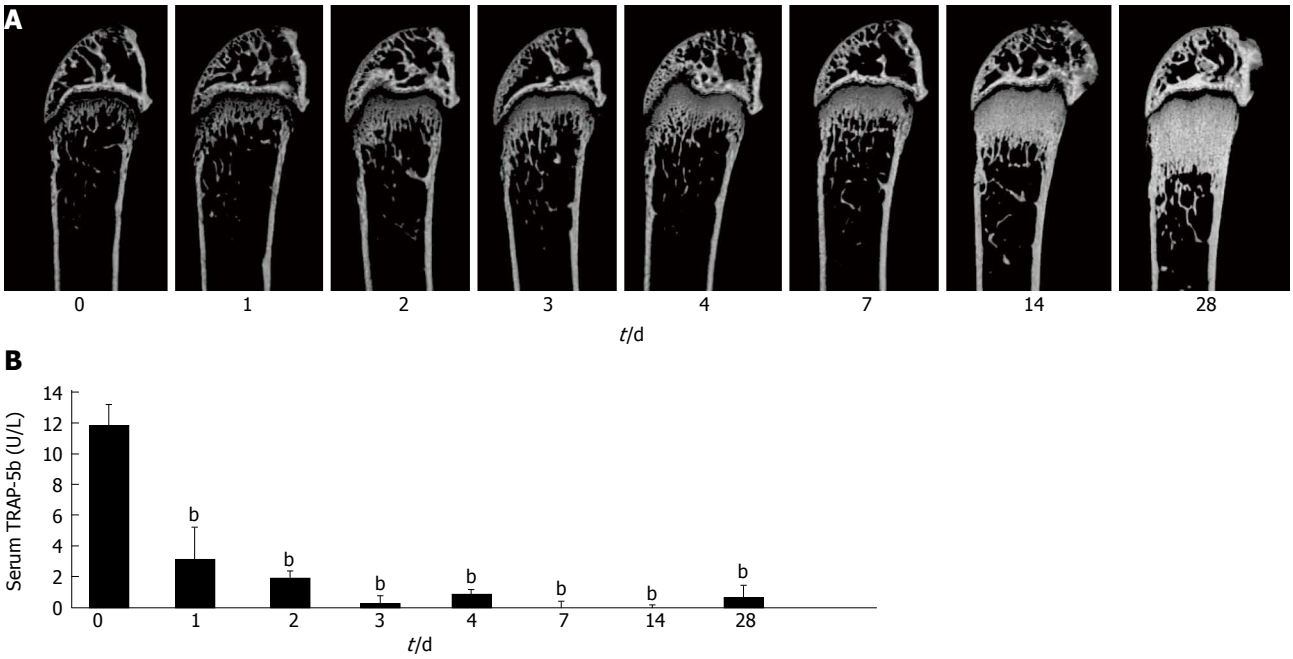

Figure 4 Establishment of anti-RANKL-injected osteopetrosis model. A: Time course of the effect of anti-mouse receptor activator of nuclear factor-κB ligand (RANKL) neutralizing antibody (clone, OYC1) on bone mass (day 0-28). OYC1 (5 mg/kg) was administered subcutaneously to 6-wk-old female mice (n = 5 or 6) on day 0. Mice were sacrificed on day 0, 1, 2, 3, 4, 7, 14, and 28. Bone structure in the trabecular area was analyzed by micro computer tomography; B: Serum TRAP-5b levels were measured by ELISA. Data are shown as the mean ± SD. $^{b}P < 0.01$ (ANOVA) *vs* value on day 0.

animal experiments of denosumab[55,56]. To investigate the effect of RANKL inhibition in normal mice, we prepared anti-mouse RANKL neutralizing monoclonal antibody (OYC1) and established a novel mouse model of osteopetrosis by administration of the anti-mouse RANKL antibody to normal mice[58].

Single subcutaneous injection of the antibody markedly increased bone mass in a time-dependent manner for 4 wk (Figure 4A). Histomorphometry showed remarkable decreases in osteoclast surface and number, as well as decreases in osteoblast surface, mineral apposition rate, and bone formation rate after 2 wk. These results are consistent with the previous report on HuRANKL mice treated with denosumab[57], which showed a negative coupling between bone resorption and formation. Decreases in bone resorption marker (TRAP-5b) and formation marker (ALP) were also observed in anti-RANKL-antibody-treated mice. There was almost no serum TRAP-5b activity for 4 wk, and anti-RANKL antibody was detected in serum of the treated mice even 4 wk after the injection (Figure 4B).

Histological and microCT analyses showed that the anti-RANKL antibody-treated mice exhibit an osteopetrotic phenotype, similar to the observation in OPG-treated mice[1,3]. The osteopetrotic phenotype was evident 2 d after a single injection in normal mice. The effect of a single injection (5 mg/kg body weight) of anti-RANKL antibody on bone mass is roughly equivalent to that of three daily injections (24 mg/kg body weight) of OPG, indicating that the efficacy and stability of anti-RANKL antibody *in vivo* was much higher than those of OPG[3,58].

Osteopetrosis is generally caused by failure of osteoclast-mediated resorption of skeleton. There are numerous mouse models of osteopetrosis without osteoclasts, including c-fos-deficient mice[59], op/op mice[60], RANKL-deficient mice[21] and RANK-deficient mice[22,23]. The anti-RANKL antibody-treated mouse is an inducible osteopetrosis model. It is possible to investigate the difference between BPs and anti-RANKL antibody in normal mice. It is also possible to test the effects of switching pharmaceuticals, *e.g.*, BP to denosumab and PTH to denosumab, and to test the effects of combinations of pharmaceuticals, *e.g.*, PTH and denosumab. We have demonstrated that the combination of a denosumab-like anti-mouse RANKL monoclonal antibody and PTH synergistically increases bone mass in normal mice. We also showed that PTH increases bone formation in osteoclast-deficient mice treated with the anti-RANKL antibody, suggesting that PTH requires no osteoclasts for its bone anabolic activity. The anti-mouse RANKL neutralizing antibody (OYC1) is a surrogate antibody for denosumab and is useful for investigating unidentified functions of RANKL in mice[58]. In fact, several important functions of RANKL were identified in other tissues in addition to bones. They include fever control in the brain[61], proliferation of mammary gland epithelial cells[62] and stem cells[63,64], proliferation of mammary cancer cells[65,66], hematopoiesis in bone marrow[67], development of epithelial cells in the thymic medulla[68], lymphogenesis[69], proliferation of regulatory T cells *via* activation of dendritic cells[70], and development of Microfold cells in intestinal epithelium[71].

These inducible models of osteoporosis and osteo-

petrosis using normal mice exhibit exactly mirror images in terms of the change in bone mass and are useful to advance research on osteoclast biology as well as bone metabolism *in vivo*.

IMPLICATIONS OF DISCOVERING THE OPG/RANKL/RANK SYSTEM

The discovery of the OPG/RANKL/RANK system guided us to the mechanisms of osteoclast differentiation and activation[8-11]. Inhibition of the RANKL/RANK signal in bone can increase bone mass and is useful for treatment of osteoporosis. OPG and soluble RANK have been developed as pharmaceutical candidates, and anti-human RANKL neutralizing antibody (denosumab) has been clinically used for osteoporosis and cancer-related bone disorders[50-54]. The past decade has witnessed significant progress in the development of the anti-human RANKL neutralizing antibody as a pharmaceutical agent. This is an outstanding story starting from the discovery of RANKL and advancing to the clinical application of anti-RANKL antibody[72].

At present denosumab is clinically used for the treatment of osteoporosis and cancer-related bone diseases in Japan, Europe, United States and many other countries. A phase II clinical trial for rheumatoid arthritis is ongoing in Japan. The future treatment option of rheumatoid arthritis thus looks promising.

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REVIEW

Feet injuries in rock climbers

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Core tip: While injuries of the upper extremity are widely discussed in rock climbers, reports about the lower extremity are rare. Nevertheless almost 50 percent of acute injuries involve the leg and feet and most frequently are strains, contusions and fractures of the calcaneus and talus. The chronic use of tight climbing shoes leads to overstrain injuries also. As the tight fit of the shoes changes the biomechanics of the foot an increased stress load is applied to the fore-foot. Thus chronic conditions as subungual hematoma, callosity and pain resolve. Also a high incidence of hallux valgus and hallux rigidus is described.

Schöffl V, Küpper T. Feet injuries in rock climbers. *World J Orthop* 2013; 4(4): 218-228 Available from: URL: http://www.wjgnet.com/2218-5836/full/v4/i4/218.htm DOI: http://dx.doi.org/10.5312/wjo.v4.i4.218

Abstract

While injuries of the upper extremity are widely discussed in rock climbers, reports about the lower extremity are rare. Nevertheless almost 50 percent of acute injuries involve the leg and feet. Acute injuries are either caused by ground falls or rock hit trauma during a fall. Most frequently strains, contusions and fractures of the calcaneus and talus. More rare injuries, as *e.g.*, osteochondral lesions of the talus demand a highly specialized care and case presentations with combined iliac crest graft and matrix associated autologous chondrocyte transplantation are given in this review. The chronic use of tight climbing shoes leads to overstrain injuries also. As the tight fit of the shoes changes the biomechanics of the foot an increased stress load is applied to the fore-foot. Thus chronic conditions as subungual hematoma, callosity and pain resolve. Also a high incidence of hallux valgus and hallux rigidus is described.

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INTRODUCTION

Rock climbing is a fast growing sport with followers around the globe[1]. While alpine climbing has its inherent dangers, sport, indoor and competition climbing showed a minor injury risk[1-15]. Also, most of the injuries occurring are of minor severity and often due to overuse[1,3,16]. In rock climbing mostly only the hands and feet are used to be holding onto the rock or artificial climbing wall; thus placing extreme forces on the distal extremities[9,13,17-59]. However in falls frequently the feet are getting the most load while landing[21].

INJURY DISTRIBUTION

The literature data on injury distribution between the upper and lower extremity is inconsistent[1]. Many scientific climbing papers only present case studies or common hand injuries[17,19,30,41,48,54,55,60-63] and are there-

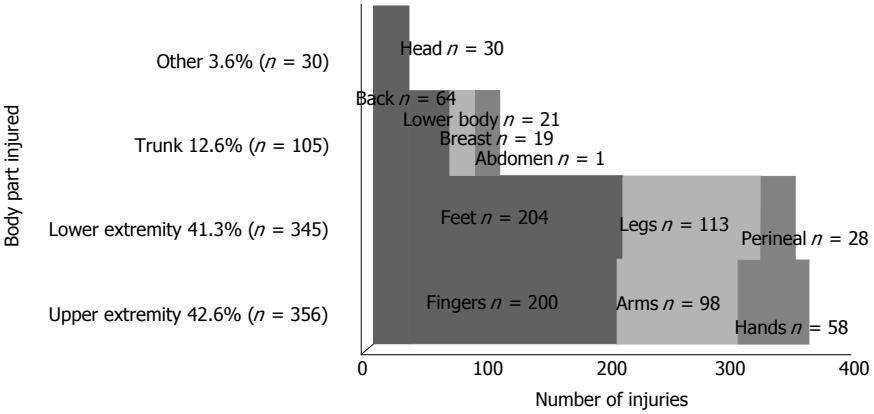

Figure 1 Distribution of Injuries by body part.

Table 1 The ten most frequent localization of climbing specific diagnoses 1/98-12/01[61] *n* (%)

Acute and chronic injuries	*n* = 604
Fingers	247 (41.0)
Forearm/elbow	81 (13.4)
Foot	55 (9.1)
Hand	47 (7.8)
Spine/torso	43 (7.1)
Skin	42 (6.9)
Shoulder	30 (5.0)
Knee	30 (3.6)
Others	37 (6.1)
Polytraumatic	5 (0.8)

fore not suitable for injury distribution analysis. So far, most research indicates that the upper extremity to be the most injured body region in non-alpine rock-climbing[2,3,5,6,10,14,15,40,60,64-72]. Schöffl *et al*[61] analysed 604 injured climbers (sport climbing, indoor climbing) and reported 247 of 604 (40.9%) injuries involved the hand, 9.1% the foot. In contradiction two studies that analysed climbing injuries treated in American hospitals or emergency rooms[5,73] reported that most climbing injuries involved the lower extremities and resulted from big swings into the wall or big falls[5,73]. Bowie *et al*[5] found most fractures (63%) in rock climbers on the lower extremity, primarily the ankle, tibia or fibula. The authors suggest that these findings may be partially explained by the minor nature of many rock climbing related injuries recalled by participants in the other surveys. Backe *et al*[6] reported that out of all acute climbing injuries 50% involved the foot, toe and ankle. Largiadèr *et al*[74] found in an inquiry among 332 climbers, that 34.4% suffered from injuries and that 34.6% of these were feet injuries. In another recent study on rock climbing injuries, traumatic injuries involved the lower extremities (foot, toe and ankle) in 50% while upper extremities accounted for 36% of the injuries[6]. Killian *et al*[75] found a significant correlation between the incidence of ankle sprains and bouldering as well as in between ankle sprains and sport climbing. Neuhof *et al*[2] in contrast found a even injury distribution between the upper (42.6%) and lower extremities (41.3%) (Figure 1). In summary, most of the studies found that overuse injuries are mainly affecting the upper extremity, while acute traumatic injuries are more frequently located on the lower extremity[1,76]. Also, besides the acute lower limb injuries the incidence of chronic feet problems increases in the higher levels of sport climbing[23,25,75,77,78]. Scientific research in rock climbing up to date focused extensively on upper limb injuries. This may be based on the fact that various upper limb injuries as *e.g.*, pulley injuries[44,60,79], lumbrical shift syndrome[32], extensor hood syndrome[80] or epiphyseal fatigue fractures in young climbers[63] are new pathologies and rather specific for the sport. Studies and reports on lower limb injuries and overuse syndromes are rare[23,25,33,75,77,78]. Nevertheless as *e.g.*, the study by Neuhof *et al*[2] showed, that the mostly injured region were the feet (19.2%), these injuries are of a high importance and need to be examined further[1] (Table 1)[61].

INJURIES OR OVERSTRAIN

Climbing shoes

Up until about 40 years ago, most alpine climbing and rock climbing was done in heavy mountain boots. An extra pair of socks was often worn, and the foot was held in a leather cast that protected it but also took away any sensitivity and the need for strength in the toes. Leather boots were replaced by the legendary E.B. in the 1970 s, and a new generation of rock shoes with sticky rubber was just around the corner. Shoes today have become specialized into the type of rock climbing one wants to do. Attributes like downturn, the concave shape that places pressure on the toes, and asymmetry, concentrating the pressure on the big toe, are basic elements of modern climbing shoes[21,75] (Figure 2). These special climbing shoes should facilitate the ability to stand on friction with straight toes and on edges with bent toes with precision and proper contact[33,75,77,81]. The majority of climbing foot injuries result from wearing climbing shoes unnaturally shaped or too small in size[33,75,77,81]. The shoe seize reduction forces the foot to conform the shoe and changes the biomechanical position of the foot

Figure 2 Modern climbing shoe.

Figure 3 A standing climber's barefoot and while wearing climbing shoes.

within the shoe. The foot shortens through supination and contraction of the digits[33,75,77,78]. In front pointing the proximal and mostly also the distal interphalangeal joints are flexed and the metatarsophalangeal joints are over extended (crimping toes)[78]. Lateral X rays within the climbing shoe show that the normal foot weight distribution onto the first and fifths metatarsal head and the heal is not given any more. The foot is front pointing onto the distal toe phalanges[75,77,78]. The plantar flexion of the metatarsal heads results in a tightening of the plantar fascia[33,35,75,77,78]. High ability climbers experience more foot deformities and injuries compared to climbers of lower ability due to the common practice of wearing climbing shoes sized smaller than normal street wear shoes (Figures 3 and 4A, B, C)[75,77,78]. Schöffl *et al*[78] reported about an average shoe seize difference between normal shoes and climbing shoes of 2.3 ± 0.73 continental seizes in high ability rock climbers [mean climbing level 9.7 (UIAA MedCom metric scale[82])]. Killian *et al*[75] reported about typically 1 to 2 seizes reduction (mean 1.699) in average climbers [mean climbing level 7.0 (UIAA MedCom metric scale[82])]. 80%-90% of the climbers reported[75,78] of suffering pain while using their climbing shoes, and that they accept to suffer this discomfort for improved performance[78]. Frequent problems are callosity, nail bed infections, pressure marks, neurologic complaints and subungual hematoma[33,75,77,78]. In the long term, using tight fit climbing shoes can lead to the development of a hallux valgus deformity[77,78]. van der Putten *et al*[77] even developed, based on their biomechanical analysis of climbers feet, a special climbing shoe sizing system, which includes an algorithm to accommodate differences between left and right foot.

For the further analysis acute injuries, mostly from falls and overuse (overstrain) injuries, due to the tight fitting climbing shoes must be distinguished.

Injuries to the feet

The most frequent inciting factor for injury to the lower extremity in rock climbing is a fall[1-3,5,83]. For further explaining the different ways injuries occur while climbing, a differentiation between two different types of falls is necessary: a wall-collision fall and a ground fall[21].

A wall-collision fall is one where the climber impacts the wall in a more or less vertical plane, while a ground fall is one where the climber impacts in more or less the horizontal plane[21]. In a wall-collision fall the climbers takes a fall while lead climbing. When falling the tensioning of the rope pulls him to, or against the rock face. In accordance to fall height, belay technique and rope stretch the impact onto the rock face varies[21] (Figure 5). Contrary to how it might appear, short falls, with a high impact factor (generally not far from the ground or the belay) can be the most dangerous. In these types of falls the climber is actually pulled back into the rock and the angle that he/she puts the foot (or arm) out at on impact creates a lot of stress on that particular spot. Also, auto-breaking devices, like the Gri-Gri® (Petzl, France) and Sirius® (TRE, Germany), can increase the fall factor[21]. Typical injuries are contusions or compound fractures[21]. A ground fall from as little as 8 feet high can lead to serious fractures of the calcaneus, talus and ankle joint (Figures 6, 7)[21]. Other ground fall injuries are distortions and ligamental injuries (ankle sprains)[6,21,73]. These injuries are on the increase with the growth in bouldering as a sport, but they are also fairly common with sport climbers who fall before reaching the first bolt or are dropped by their belayer[21]. One typical injury mechanism in indoor climbing, especially bouldering (ropeless climbing on low height with mattress belay) is a fall onto the mattresses and the foot getting stuck in the intermediate section between 2 mattresses[1,3,14,76,84,85]. As this injury mechanism was quite frequent 10 years ago it was addressed by the Medical Commission of the UIAA[85] (International Mountaineering Association) and nowadays the International Federation of Sport Climbing (IFSC) has a rule that these intersections must be closed in competitions (Figure 8)[76].

Typical feet injuries in rock climbers[1,2,7,8,10,21,73,78,84]: (1) Contusion; (2) Calcaneus fracture; (3) Talus fracture; (4) Ankle fracture; and (5) Ankle sprain with lateral ligament injury.

Neuhof *et al*[2] evaluated 1962 sport climbers and their injuries over a 5 year period and found a total of 699 injuries. 345 of these (41.3%) were on the lower

Figure 4 X-ray. A: Climber's bare foot while standing; B: Same subject's foot in climbing shoe. Note "crimping" toes and hallux valgus position of the large toe; C: Lateral plane of the same foot in a climbing shoe-note that the forefoot does not rest on the head of the metacarpalia 1 and 5 as normal but on the crimping toes; D: Post surgery (Case 1); E: Subchondral bone cyst in a 42 year old female climber causing chronic pain within the climbing shoes; F: After removal of the cyst and iliac crest bone graft using the OATS®; G: Osseous integration after 3 mo.

Figure 5 Wall-collision fall.

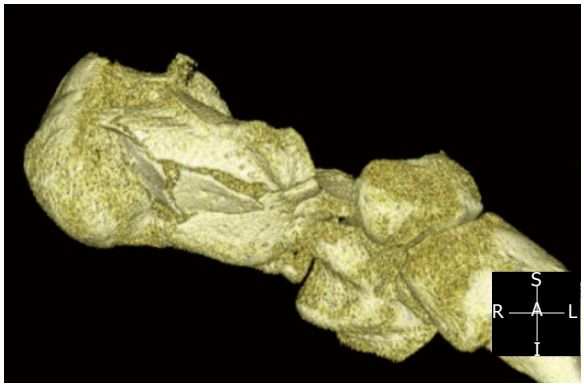

Figure 6 Calcaneus fracture after a ground fall (Computed tomography scan).

extremity, 29.2% were on the feet. Most of the fractures (48.6%) and most of all contusions (42.5%) were on the feet, while most ligamental injuries and tendon injuries were on the fingers. Ankle sprains are frequent in boulderers and sport climbers with a significant correlation[75] to these climbing activities. Killian *et al*[75] reported about an incidence of 0.23 for ankle sprains and of 0.03 for feet fractures in rock climbers. Nelsen *et al*[73] found that ankle injuries accounted for 19.2% of all climbing injuries. Backe *et al*[6] reported that out of all acute climbing injuries 50% involved the foot, toe and ankle. The most common type was a ligament injury, followed by contusions and lacerations. Gerdes *et al*[10] also reported that sprains and strains were most common on the fingers (31.9%) and the ankle (23%). Fractures were most common on the foot (24.6%) and the ankle (22.1%). Especially in the older athletes also short falls can lead to feet and ankle fractures caused by the increased brittleness of the bone that occurs with aging[86].

These typical injuries undergo standard orthopedic trauma guidelines and in case of displaced fractures mainly operative reconstruction (open reduction and internal fixation). Considering that climbers are mostly young and highly active patients we also favor a surgical repair in most talus and calcaneus fractures (Figures 6,

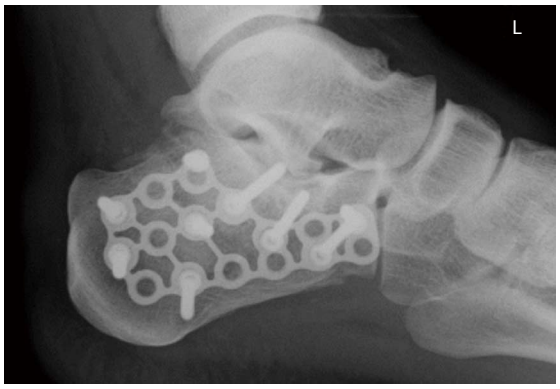

Figure 7 The same patient as above after surgery.

Figure 8 Closed mattress intersections at the International Federation of Sport Climbing Bouldering World Cup Munich 2011.

Figure 9 Computed tomography scan of a 20 year old female climber with osteochondritis dissecans of the medial talus shoulder.

7) to achieve an optimal outcome. While these standard guidelines are known and presented in the specific literature some rare injuries in climbers should be specifically addressed in this review. In particular we will focus on posttraumatic ostechondritis dissecans of the talus after climbing falls and the management of peroneal tendon dislocations in elite climbers.

Management of large osteochondritis dissecans defects of the talus: matrix associated autologous chondrocyte transplantation with combined iliac crest bone graft (Case 1)

Posttraumatic osteochondritis dissecans is a well-known pathology after ankle sprains and dislocation[87-91]. As the initial X-ray often does not show the injury they are often detected only secondarily, if the patient still complains of ankle pain after more than 6 wk. In persistent ankle pain and a plain standard radiograph an MRI is indicated. The following case presentation is one out of several climbers with a similar pathology.

The patient was a female climber, 20 years old, who had an ankle sprain due to a ground fall from bouldering. 1.5 years after the trauma an osteochondritis dissecans was diagnosed in another hospital and an arthroscopic drill-hole procedure was performed. One year later she was still complaining about ankle pain and presented in our outpatient clinic. X-ray, MRI and CT scan revealed an osteochondritis dissecans with a large osseous defect at the medial talus shoulder (Figure 9).

While the management of chondral lesions of the talus with autologous chondrocyte transplantation is a standard procedure with positive results in over 90%[88,89,91], large osseous defects in combination with osteochondral lesions are more difficult to manage[87]. Mostly these lesions are treated with osteochondral autografts (OATS)[90,92]. Nevertheless one problem with OATS is that the talus shoulder demands a cartilage cover on two plains, on the horizontal surface and on its respective medial or lateral side. Based on our previous work on matrix associated autologous chondrocyte transplantation (MACT) with combined iliac crest bone graft in large defects of the talus[87] we performed a similar procedure in this young female climber. A 4th degree cartilage defect was already confirmed arthroscopically in addition to the CT and MRI images in another hospital. A drilling of the defect during the prior arthroscopy did not help to restore blood flow into the osteochondritic area and thus failed. Therefore a osteograft with cartilage transplant was necessary. After arthroscopic harvesting of two osteochondral cylinders of the ipsi-lateral knee we performed secondary a medial osteotomy with debridement and resection of all dead tissue of the ankle joint. Then the medial talus shoulder was reconstructed with a bicortical iliac crest implant, which was secured through countersink mini titanium screws. Following the bone transplant was covered with a MACT (NOVOCART®, TETEC Tissue Engineering Technologies, Braun Aesculap, Germany) (Figures 4D and 10).

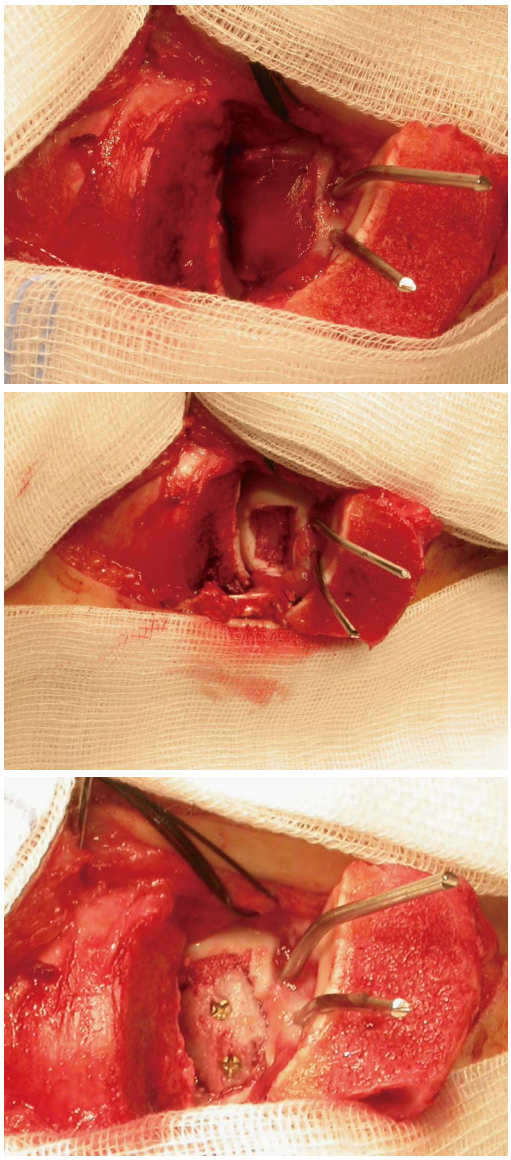

Figure 10 Medial talus shoulder reconstruction with iliac crest implant and associated autologous chondrocyte transplantation

Figure 11 Magnetic resonance imaging 3 mo after the procedure. The bone graft is integrated, the cartilage graft intact and osteotomy closed.

Figure 12 Typical climbers foot position which transfers a high load onto the peroneal tendons retinaculum.

The postsurgical procedure included 6 wk of cast immobilization followed by a step-wise load increase. Full weight bearing was allowed after 12 wk. MRI controls were performed after removal of the osteotomy screws after 3 and 6 mo. Standard MRI after 3 mo showed an osseous integration of the iliac crest graft and a contrast fluid enhancement of the MACT. After 6 mo morphological und biochemical magnetic resonance imaging showed the complete osteointegration of the bone graft and cartilage repair of the talus[93,94](Figure 11).

Pain decreased on a visual analog scale from 8 to 2. She could climb again at the same level as before the injury and American Orthopaedic Foot and Ankle Society Ankle-Hindfoot score[95] raised from 63 to 84 points.

Peroneal tendon dislocations in climbers (Case 2)

Acute peroneal tendon dislocations are rare and mostly seen in skiers[96-99]. Nevertheless evaluating 911 climbing injuries over 4 years (2009-2012)[100] we had 3 climbers with this pathology. All reported about a snap of the peroneal retinaculum while having the foot in a plantar flexion with maximum inversion and applying high tension onto the large toe while climbing (Figure 12). These acute peroneal tendon dislocations can be seen similar to pulley injuries in the fingers[60] in climbers. With the high strength impact onto the superior peroneal retinaculum, which serves analogous to the hand as a pulley, the retinaculum, which is also enhanced by the calcaneofibular ligament, fails and the peroneal tendons dislocate. In all 3 cases the peroneal tendon grove of the fibula was of normal shape, therefore no anatomical predisposition was given. In general literature recommend a non-

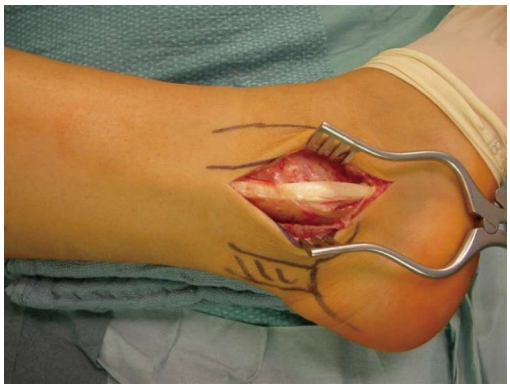

Figure 13 Peroneal tendon dislocation through climbing.

surgical approach if the dislocation is treated immediate and the tendons stay in their normal position within the cast[96,97]. Nevertheless in active patients, especially in "feet depending" sports a surgical repair is recommended[96,97]. Surgical techniques are mostly described for chronic subluxation and contain a peroneal groove deepening, a tenoplasty or a bone block transfer[96-99,101]. Only in acute cases a direct repair of the ruptured structures may be possible, sometimes in combination with a periostal flap[96,101]. We performed a surgical repair in all cases (Figure 13), in two cases a direct repair was possible and in one case an additional periostal flap was necessary. Afterwards a 6 wk cast immobilisation was performed. Climbing activity was allowed 8 wk after injury. All athletes regained a full climbing ability with no reoccurance or consisting problems.

OVERUSE INJURIES AND CHRONIC CONDITIONS

As described above rock climbing shoes are worn with a tight fit, roughly two seizes smaller than normal shoes[75,77,78]. This tight fit increases, due to the biomechanical chances of force distribution in the foot, the injury incidence in falls onto the foot or against the wall[75]. In addition to these acute conditions these malpositioning of the foot within the climbing shoe cause chronic conditions and complaints. Schöffl *et al*[78] evaluated 30 high level male sport climbers for chronic foot deformations. Every climber was at least climbing on a UIAA 9.0 level [mean climbing level 9.7 (UIAA MedCom metric scale[82])] and climbing more than 5 years (mean climbing years 12.8 years). Training hours per wk were a mean 12.3 h, which refers to roughly 10 h per wk within the small climbing shoes. The shoe seize difference between climbing shoes to standard shoes was in mean 2.3 seizes. 87% of the climbers were willingly accepting pain within the climbing shoes to achieve a better performance. Also 87% reported about chronic feet problems and pain within the climbing shoes. All climbers had callosity and pressure marks dorsally on their toes (100% dig.ped.1, 95% dig.ped.2, 85% dig.ped.3, 43% dig.ped.4, 8% dig.ped.5) (Figure 14A). Further conditions were: dead toe nails, broken and missing toe nails, nail bed infections, dermatomycosis, blisters, claw toes, subungual hematoma (Figure 14B) and hallux valgus (Figure 14C). For their incidence and distribution see Figure 15[78].

In comparison Largiadèr *et al*[74] reported only about 28% of climbers with feet nail dystrophy and feet deformities in 21%. Nevertheless their climber population was different, as most of their climber were only climbing in the 6th UIAA grade, thus having a shorter trainings time and less climbing years and therefore a reduced exposition to the very tight shoes in comparison to Schöffl *et al*[78]. Killian *et al*[75] surveyed 100 climbers through a questionnaire on feet conditions. 73 were male, 27 female, the mean climbing level was 5.109 US (7.0 UIAA[16]). 81% of the climber`s complaint about discomfort through the climbing shoes. Pain in the toes or hallux valgus was the most frequent complaint. They found a significant correlation between climbing ability and extent of shoe seize reduction, however no correlation between the extend of shoe seize reduction or skill level and the incidence of pain or discomfort. 65% of the climbers surveyed experienced either tingling or numbness a condition also frequently reported about by Peters[33] and Largiadèr *et al*[74]. These neurological complaints and neurinomas are known to be greatly exacerbated through constricting shoes[102]. van der Putten *et al*[77] also found frequently mycosis, splinter hemorrhage, nail fractures, hallux valgus, bunions, and callosity on their questioned 30 climber. Nevertheless as there paper focuses on the biomechanical development of a climbing shoe exact numbers of the distribution of these conditions were not given.

Schöffl *et al*[78] and Killian *et al*[75]also looked upon the long term effects of the wear of tight climbing shoes. Through radiographic analysis of a standing climber within a climbing shoe and barefoot Schöffl *et al*[78] demonstrate how the climbing shoes forces the foot into a hallux valgus position (Figures 4, 5). The hallux valgus angle increases from 14° barefoot to 21° within the shoe.[78] They found in 53% of the long time high level climbers a hallux valgus, in 20% bilateral (hallux valgus defined as a 20° difference between the axis of the first metatarsal and the axis of the proximal phalanx of the toe). The general incidence in a group of male adults (age: 17-44) is only 4.5%[103]. Killian *et al*[75] found an average incidence of a hallux valgus of 34% in climbers of all difficulty levels, but of 53% of the group of climbers in the 5.12 range (UIAA metric 8.3-9.0). Over the recent years we saw an increasing number of climbers with a hallux rigidus condition, even requiring a surgical therapy (cheilectomy or fusion)[21]. Rock climbing is still possible afterwards, nevertheless the risk of osteoarthritis in the adjunct joints increases. Sometimes also enchondroma (preexisting and not as a result of climbing activities) or bone cysts can cause chronic pain within the climbing shoes. Figure 4E, F, G (case 3) show a 42 year old female climber with chronic feet problems, revealing a large

Figure 14 Feet injuries. A: Pressure marks on the toes due to tight climbing shoes; B: Subungual hematoma caused by tight climbing shoes; C: Hallux valgus in a 20+ year long climber.

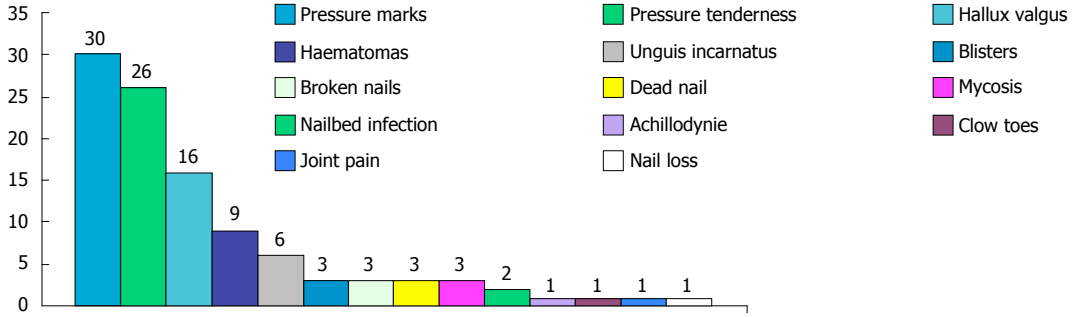

Figure 15 Chronic Feet Problems in Long time high ability rock climbers (n = 30)[78].

subchondral cyst of the big toe. The cyst was resected and the bone defect filled through a cortical-spongious bone graft from the iliac crest. To guarantee a press fit we used the OATS® (osteoarticular transfer system, Arthrex® Inc., Naples, FL, United States) instruments to harvest the graft and to shape the implant site as well. Postoperatively a cast was applied. Complete osseous integration was achieved and she could continue climbing without pain after 3 mo.

CONCLUSION

Considering the known high incidence of feet problems of rock climbers it is astonishing that only little scientific work has been done so far in this topic. Most climbing studies focus on the upper extremity, mainly the hand and fingers. With numbers of up to 90% of examined and questioned climbers with chronic feet conditions more work needs to be done in this respect. To reduce these complaints climbers need to be advised not to wear their shoes too tight and have an additional loose fit training shoe[21]. Also the industry producing climbing shoes must be involved, and new fitting strategies with less stretching outer materials and biomechanical adjusted constructions impaired. New shoes should have a inner lining to reduce bunions and callosity, while still guaranteeing a good perception of the rock. While high level climbing athletes may be in the need of a tight fit shoe the vast number of recreational climbers need the opposite. A comfortable fitting shoe which supports the foot and does not hurt.

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REVIEW

Healing of subcutaneous tendons: Influence of the mechanical environment at the suture line on the healing process

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Abstract

Tendon ruptures remain a significant musculoskeletal injury. Despite advances in surgical techniques and procedures, traditional repair techniques maintain a high incidence of rerupture or tendon elongation. Mechanical loading and biochemical signaling both control tissue healing. This has led some researchers to consider using a technique based on tension regulation at the suture line for obtaining good healing. However, it is unknown how they interact and to what extent mechanics control biochemistry. This review will open the way for understanding the interplay between mechanical loading and the process of tendon healing.

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Key words: Tendon; Healing; Mechanical loading; Mechanotransduction; Rupture; Repair

Core tip: Ruptured tendons heal poorly compared to skin, muscles and bones. Immobilization during repair has been shown to be detrimental for the healing process. Mechanical loading of the tendon callus gives rise to intracellular signaling, increases gene expression and protein synthesis. However, early loading reported clinical complications. A surgical technique based on control of the mechanical environment at the suture line provided satisfactory results. Therefore, understanding the interplay between loading and the healing process seems necessary. This review focuses on the biological processes that regulate tendon repair and timing of mechanical loading during the healing process. How do tendon cells sense mechanical forces?

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INTRODUCTION

This article is limited to the subcutaneous tendons, *i.e.*, tendons that do not glide through synovial sheaths responsible for their nutrition. It describes the function, structure and mechanobiology of tendons, reviews the phases of tendon healing and reviews the influence of the mechanical environment at the site of repair on the healing process.

TENDON STRUCTURE

Healthy tendons are brilliant white in color and have a fibroelastic texture. Tendons demonstrate marked variation in form; generally, extensor tendons are more flattened than flexor tendons which tend to be round or oval[1,2]. The dry mass of human tendons is approximately 30% of the total tendon mass, with water accounting for the remaining 70%[1,3]. Lemoine *et al*[3] reported that men had a significantly greater amount of tendon dry mass than

women. Many authors have explained this dissimilarity on the fact that estrogen directly alters collagen kinetics and inherently higher estrogen levels in women may therefore chronically depress collagen production as tendon cells have estrogen receptors[4,5]. Thus, blunted collagen production via estrogen could explain the lower amount of dry mass in female tendons as collagen comprises 90% of dry mass[3,4].

Tenoblasts and tenocytes constitute about 90% to 95% of the cellular elements of tendons. They lie between the collagen fibers along the long axis of the tendon[6]. The remaining 5% to 10% of the cellular elements consists of chondrocytes at the insertion sites, synovial cells and vascular cells, including capillary endothelial cells and smooth muscle cells of arterioles[1]. Tenocytes are mature tendon cells. They are active in energy generation and synthesize collagen and all components of the extracellular matrix network[7].

Extracellular matrix

Extracellular matrix (ECM) of tendons largely consist of collagens and proteoglycans and are dominated by type I collagen as it accounts for 65% to 80% of the dry mass of tendons. However, other collagens (*e.g.*, type Ⅱ, Ⅲ, Ⅴ, Ⅵ, Ⅸ, Ⅺ) are also present[2,8]. Collagen molecules consist of polypeptide chains (tropocollagen). Soluble tropocollagen molecules form cross-links to create insoluble collagen molecules. Three such chains combine together to form a densely packed, helical tropocollagen molecule (triple-helix polypeptide chain). In turn, five tropocollagens constitute a microfibril and microfibrils aggregate together to form fibrils. Fibrils are then grouped into fibers, fibers into fiber bundles (primary bundles) and fiber bundles into fascicles (secondary bundles), tertiary bundles and the tendon itself. A collagen fiber is the smallest tendon unit that can be tested mechanically and is visible under light microscopy[1,2]. Some of the larger collections of fascicles are visible in gross dissections[2].

The principal role of the collagen fibers is to resist tension, although they still allow for a certain degree of compliance (*i.e.*, reversible longitudinal deformation). Such apparently conflicting demands are probably resolved because the collagen is arranged in hierarchical levels of increasing complexity, beginning with tropocollagen[1,2]. At various levels of tendon organization, including the whole tendon, fascicles and fibrils, a helical architecture (often with superimposed "crimp", *i.e.*, a zigzag undulation of collagen fibrils) occurs in certain tendons. This helical organization of tendon components makes them comparable to man-made ropes and the presence of crimp contributes to their inherent flexibility[9-11]. Roukis *et al*[10] have suggested that the twisting that characterizes the tendon of tibialis posterior reduces the need for longitudinal slippage between fascicles during triplanar movements of the foot. The angle of torsion of the inner fibrils in a helical tendon fascicle may be less oblique than that of the outer fibrils and this may give the tendon regionally distinct compliance[10]. The fibers of the Achilles tendon twist through its descent, thus elastic recoil within the tendon are possible[12]. This point will be detailed under subheading elastic recoil of the tendon.

The ground substance of the extracellular matrix network surrounding the collagen and the tenocytes is composed of proteoglycans, glycosaminoglycans, glycoproteins and several other small molecules[1]. Proteoglycans make up less than 1% of the dry weight of most tensile tendons[8]. Proteoglycans are strongly hydrophilic, enabling rapid diffusion of water-soluble molecules and the migration of cells[1]. Additionally, the proteoglycans have the function of providing a viscous environment, allowing the collagen fibrils, fibers or fascicles to slide relative to each other, as well as to stretch and dissipate the force of sudden loads[8,13].

TENDON ENVELOPE

The epitenon, a fine loose connective-tissue sheath containing the vascular, lymphatic and nerve supply to the tendon, surrounds the tendon as a whole and forms the gross structure of the tendon[14,15]. The epitenon extends deeply as the endotenon, which is a thin reticular network of connective tissue investing each tendon fiber. The endotenon protects tendon vasculature and allows fascicles to slide over one another in particularly malleable parts of the tendon[2,14]. Due to the epitenon being directly continuous with the endotenon, the points of continuity help to bind it firmly to the surface of the tendon[14]. The epitenon is further enclosed by paratenon, a loose areolar connective tissue separated from the epitenon by a thin layer of fluid to allow tendon movement with reduced friction[2,14,15]. The paratenon may be quite vascular and is a source of the blood supply to the tendon itself[8].

Myotendinous junction

The myotendinous junction (MTJ) is the interface between muscle and tendon; it is tailored for transmitting the mechanical force generated by a muscle contraction to the extracellular matrix of the muscle and onto the tendon[16-18]. The characteristic morphology of the MTJ is the folding of the sarcolemma into finger-like projections at the interface between muscle and tendon at sites of myocyte termination[16,17]. The projections increase the area of muscle-tendon contact to more than 10 fold over the cross-section of the muscle fiber. Thus, the local stress (force per unit area) is reduced. Additionally, the longitudinal arrangement of the projections ensures that the stresses experienced by the MTJ are shear stresses[19,20]. Mechanical loading of the MTJ activates cell-signaling pathways that instruct the cells located at the interface to secrete and deposit proteins to form a specialized extracellular matrix at the MTJ. However, lack of the expression of these proteins has been shown to lead to structural damage of the interface during contraction[18].

Osteotendinous junctions

The osteotendinous junctions (OTJ) are sites of stress

concentration at the region where tendons attach to bone[21]. These regions are characterized by the presence of a unique transitional tissue called "entheses" at the interface, which can effectively transfer the stress from tendon to bone and vice versa through its gradual change in structure, composition and mechanical behavior[21,22]. There are two types of entheses, based on how the collagen fibers attach to bone[14,21,22]. Direct insertions (also called the fibrocartilaginous entheses), such as the insertion of the Achilles tendon and patellar tendon, are composed of four zones in order of gradual transition: tendon, uncalcified fibrocartilage, calcified fibrocartilage and bone[21,22]. The continuous change in tissue composition from tendon to bone is presumed to aid in the efficient transfer of load between the two materials[22]. Indirect insertions (also called fibrous entheses), such the insertion of the deltoid tendon into the humerus, have no fibrocartilage interface. The tendon passes obliquely along the bone surface and inserts at an acute angle either directly to the bone or indirectly to it *via* the periosteum[21,22]. The main factors affecting the type of insertion seem to be strain, site, length and angle of insertion. When a tendon runs parallel to the bone, the insertion is more likely to be indirect, while when the tendon enters the bone perpendicularly, the insertion is direct[22].

The majority of tendons attach not only to bone, but also to adjacent fascia. This is a basic strategy for dissipating stress concentration at entheses and thus reducing the risk of failure or local wear and tear. One of the classic examples of subcutaneous tendons that have both bony and fibrous attachments is the quadriceps tendon. This not only attaches to the superior pole of the patella, but also sends a sheet of fibers anterior to the patella that become continuous with the patellar tendon[23].

TENDON NUTRITION

Tendons are still vascularized and the presence of vessels is important for the normal functioning of tendon cells and the ability of tendons to repair[2]. Tendons receive their blood supply from three sources: the peritendinous tissues (the extrinsic source) that have a richer blood supply than the tendons themselves[24]. In the tendon itself, the vessels run longitudinally, parallel to the fascicles and within the endotenon and anastomoses between parallel vessels are common[25]. Intrinsic sources include vessels that enter tendons at their myotendinous junctions and at entheses[2]. Nevertheless, the direct role of the blood vessels in tendon nutrition has been called into question. Edwards has reported that tendons may be cut and transplanted with impunity[25]. Recently, many investigators have pointed out that diffusion from surrounding tissues may play a significant role in metabolic exchange in intact tendons[26-28].

TENDON INNERVATION

Tendon innervation originates from cutaneous, muscular and peritendinous nerve trunks[1]. The majority of nerve fibers are located within the paratenon and not the tendon itself[29]. Paratenon nerves form rich plexuses that send a few branches penetrating the epitenon. These branches are described to cross the myotendinous junction and to continue into the endotenon septa[30]. Deep in the tendon tissue proper, where innervation is reported to be relatively scarce, the nerves follow the blood vessels running along the axis of the tendon[2,30]. Four types of nerve endings have been identified: free nerve endings, Ruffini corpuscles, Pacinian corpuscles and Golgi tendon organs[30]. Vessel-associated fibers are autonomic nerves that immunolabel for neuropeptide Y and noradrenaline (vasoconstrictive factors) and for vasoactive intestinal peptide (VIP), a vasodilator factor. It has been suggested that the nerve fibers regulate blood flow within the tendon. Furthermore, free nerve fibers containing substance P and calcitonin gene-related peptide (CGRP) might be involved in collecting sensory information (including pain) and relaying this to the central nervous system[29]. Zaffagnini *et al*[31] have reported the presence of Ruffini and Pacinian corpuscles within the pes anserinus tendons, particularly at their tibial attachment sites. Benjamin *et al*[32] confirm that Pacinian corpuscles can be found on the surface of subcutaneous entheses.

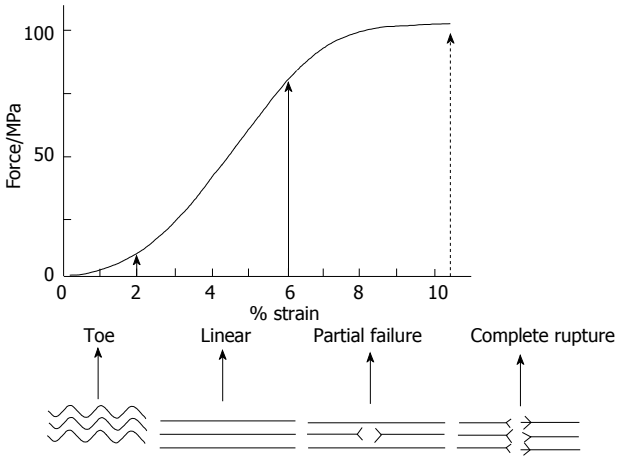

Figure 1 Stress-strain relationship for progressive loading of a tendon showing three distinct regions (toe, linear and partial failure) prior to complete rupture approximate stress forces (MPa) and strain values (% strain) is shown. Reprinted from [40] with permission from the Oxford University Press.

Biomechanical properties of the tendon

Tendons transmit force from muscle to bone and act as a buffer by absorbing external forces to limit muscle damage[1]. We will discuss the response of the tendon to mechanical stimuli at fibrillar and cellular levels. At rest, a tendon has a wavy configuration, a result of crimping of the collagen fibrils. The stress-strain curve of tendons usually exhibits three distinct regions[33], which can be correlated to deformations at different structural levels (Figure 1). In the first region that is usually called the toe region, a very small stress is sufficient to strain (elongate)

the tendon up to 2% of its length and the straightening of the macroscopic crimp in the collagen fibrils[34]. In the second region of the curve, at higher strains, the stiffness of the tendon increases[13,35]. If the strain placed on the tendon remains at less than 4%, the tendon behaves as a mechanical spring and returns to its original length and crimps when unloaded[35]. The most probable processes are thought to be the ability of the fascicles to slide independently against each other. This allows them to transmit tension despite the changing angles of a joint as it moves and allows tendons to change shape as their muscles contract[2,36]. Sliding within fascicles occurs between fibrils and this may account for up to 50% of the longitudinal deformation (*i.e.*, strain) of a tendon[37]. Sliding of fibrils or fascicles relative to each other occurs within the proteoglycan-rich matrix surrounding them[13]. The presence of the endotenon between fascicles and/or fiber bundles facilitates the sliding movement[2,14,38]. Lubricin, a molecule often associated with joint lubrication, is also present between the fascicles of certain tendons[39].

At strain levels between 4% and 8%, the tendon becomes progressively easier to extend but its length still returns to its original value. However, the wave pattern does not reappear[34]. On the other hand, recent work has suggested that strain values of 6% and even up to 8% may be physiological. Within the physiological range, particularly towards the higher range, microscopic degeneration within the tendon may start to occur, especially with repeated and/or prolonged stressing[40]. Beyond 8% to 10% strain, macroscopic failure occurs from intrafibril damage by molecular slippage[40-42]. The probable process has previously been investigated using synchrotron radiation diffraction. Initially, collagen fibril elongation occurs as a result of molecular elongation. When the stress increases the stretching of the collagen triple helices and the cross-links between the helices, a considerable gliding of neighboring molecules occur[43,44].

Response of tendon cells to mechanical load

There is now considerable evidence to suggest that tendons and tendon cells can respond to altered mechanical load. In man, collagen synthesis in the patellar tendon increases by nearly 100% as a result of just a single bout of acute exercise and the effect is still evident 3 d later[45]. At a cellular level, there seems to be no difference in the response of tenocytes to mechanical load between cells that have been extracted from different tendons, *e.g.*, those associated with antagonistic muscles[46]. However, in a given tendon, different stress patterns provoke different cellular reactions depending on the amount and duration of the tensional stress applied. Cell proliferation, for example, is stimulated by short periods of repetitive tension but inhibited by more extended periods[47]. The response seems to depend on gap junctional communication between neighboring cells, for when gap junctions are blocked, the cells no longer increase collagen synthesis in response to stretching forces applied *in vitro*. The modulation of ECM synthesis involves two types of gap junctions: those characterized by the presence of connexin 32 and those containing connexin 43. The former junctions stimulate and the latter inhibit collagen synthesis[48]. In addition to its effects on collagen synthesis, the repetitive stretching of tenocytes *in vitro* up regulates proinflammatory cytokine production and the gene expression of mediators such as Cox-2, prostaglandin E2 and matrix metalloproteinase (MMP)-1[49,50]. Smaller levels of repetitive tensile stress reduce the production of proinflammatory agents. Thus, repetitive small magnitude stretching seems to be anti-inflammatory, whereas large magnitude stretching is pro-inflammatory. If the findings also prove to be applicable *in vivo*, then it follows that moderate exercise may be beneficial for reducing tendon inflammation[50]. It is interesting to note that tenocytes themselves may produce IL-1β, especially if they are located next to a site where the tendon is injured. Expression is highest 1 day after injury but can persist for several days[51]. The significance of IL-1β production in an injured tendon is that it can induce the expression of a wide range of pro-inflammatory agents such as Cox2, MMP1, MMP3, MMP13, ADAMTS-4 and IL-6. It also triggers the further expression of IL-1β mRNA[52] and this is presumably a mechanism for rapidly raising its local concentration. It should be noted, however, that in addition to such actions, IL-1β reduces the elastic modulus of tenocytes by disrupting actin filaments[53]. The authors suggest that this acts as a protective mechanism against mechanical overuse of tendon cells during healing. How do tendon cells sense mechanical forces? This question will be answered in detail in this review.

Suppression of proteoglycan and collagen synthesis in cultured tenocytes can be induced by glucocorticoids[54,55]. These are among the substances commonly used by clinicians to suppress inflammation in patients with tendon injuries. Glucocorticoids can also suppress tenocyte proliferation and progenitor cell recruitment[56]. If such effects also occur *in vivo*, then this may explain why the integrity of the tendon as a whole may be affected by corticosteroid treatment. In contrast to corticosteroids, nitric oxide generally benefits tendon healing and enhances collagen synthesis[57]. Nitric oxide synthetases are normally expressed at low levels and are up regulated by mechanical stimuli[58,59]. The absence of nitric oxide from tendons during wound healing is associated with prolonged inflammation[60].

ELASTIC RECOIL OF TENDONS

Tendons can recoil elastically when a stretching force is removed. The elastic recoil property seems to be structurally related to crimp and/or knots within fibrils in regions where fibrils are twisted or bent. When a tendon is physiologically stretched *in vivo*, the crimp numbers within it may decrease by nearly 50%[61].

The ability of tendons to stretch and recoil enables them to save energy in running by allowing the limb to have shorter muscle fascicles or slower muscle fibers that

can generate force more economically[12]. The fibers of the Achilles tendon spiral through 90 degrees during its descent, such that the fibers that lie medially in the proximal portion become posterior distally. In this way, elongation and elastic recoil within the tendon are possible and stored energy can be released during the appropriate phase of locomotion. In addition, this stored energy allows the generation of higher shortening velocities and greater instantaneous muscle power than could be achieved by contraction of the triceps surae alone[12,15]. The stiffness of tendons varies with sex, age and physical activity. The Achilles tendon of women can recoil elastically more than that of men[62]. Stiffness is greater in young men than in young boys; however, it decreases with training in adults[63,64]. The greater compliance of tendons in young boys may reduce the risk of sport injuries[63]. The elasticity of a fatigued tendon tends to be greater, as evidenced by its ability to lengthen further with the same load[65].

Studies in goats have shown that it is the muscle rather than the tendon that provides the extra length within the muscle-tendon unit necessary for limb lengthening by distraction osteotomy. While the muscle may elongate by almost 10% of its initial length, the tendon only does so by 3%-4%[66]. Elastic recoil of tendon stumps will elongate the spontaneously healed tendon. This emphasizes the necessity for tension relief at the site of repair in the early phase of tendon healing.

TENDON RUPTURE

Tendon rupture occurs spontaneously or following direct trauma such as severance of a tendon by sharp objects or being caught between bones and traumatizing agent. A spontaneous rupture may be defined as a rupture that occurs during movements and activities that should not, and usually do not, damage the involved musculotendinous units[67]. Although many investigators reported that spontaneous rupture of a tendon is preceded by degenerative changes, there is little agreement with regard to its etiology. Degenerative changes of the tendon have been linked to genetic abnormalities of the collagen tissues[68], chronic diseases or metabolic disorders[69] and neurological conditions[70]. Fluoroquinolones and locally or systemically administered corticosteroids have been implicated in the etiology of tendon rupture[71-74]. In the literature, there are four basic types of tendon degeneration: hypoxic, mucoid degeneration, lipomatosis and calcification of the tendon. Extensive tendo lipomatosis by itself may lead to rupture of the tendon without degenerative changes in the collagen tissues[75]. For reasons that are not clear, most reported cases of tendo lipomatosis have been in the quadriceps or patellar tendon. The described histopathological changes predispose the tendon to rupture through decrease of its tensile strength[67]. Strength of the tendons and resistance to tensile forces are related to the angles of tendon crimps in providing a resistance to sudden elongation and to the diameter of the collagen fibers[61,76]. Järvinen *et al*[77] investigated the crimp angle and the diameter of the collagen fibers in spontaneously ruptured tendons and compared them to healthy tendons. They concluded that the collagen fibers in ruptured tendons are substantially thinner than in normal tendons. The crimp angle of the collagen fibers is also significantly decreased in ruptured tendons[77].

HEALING OF TENDON RUPTURE

After tendon rupture, the body restores tendon continuity through a cascade of events can be divided into three overlapping phases: tissue inflammation, cell proliferation and remodeling phases[78-80].

Inflammatory phase

This phase starts immediately post injury and persists for about 24 h[78]. In this phase, injured blood vessels that are in the tendon envelope cause the formation of a hematoma, which activates the release of various chemotactic factors such as vasodilators and proinflammatory molecules[78,79]. The chemotactic factors attract inflammatory cells (*e.g.*, neutrophils, monocytes and macrophages) that migrate to the wound site and clean the site of necrotic materials by phagocytosis. Tendon fibroblasts recruited to the site begin to synthesize various components of the ECM[81]. Moreover, during this phase, the angiogenic factors initiate the formation of a vascular network[82]. These processes include an increase in DNA and ECM, which establishes continuity and partial stability at the site of injury[78].

Proliferative phase

In this phase that lasts a few weeks, tendon fibroblasts synthesize collagen and other ECM components and deposit them at the wound site[78]. These components are initially arranged randomly within the ECM, which at this time is composed largely of type Ⅲ collagen[83]. An extensive blood vessel network is present and the wound has a scar-like appearance[84]. During this phase, the repair tissue is highly cellular and contains relatively large amounts of water and an abundance of ECM components[78,79].

Remodeling phase

This phase that begins by nearly the 6th week after injury is characterized by decreased cellularity, reduced matrix synthesis, decrease in type Ⅲ collagen, and an increase in type I collagen synthesis[78,79]. Type I collagen fibers are organized longitudinally along the tendon axis and are responsible for the mechanical strength of the regenerate tissue[85]. During the later remodeling phase, covalent bonding between collagen fibers consequently increases tendon stiffness and tensile strength. In addition, both the metabolism of tenocytes and tendon vascularity de-

cline[78,79].

ROLE OF FIBROBLASTS IN TENDON HEALING

It is known that the fibroblasts during healing generate and exert force on the ECM. This force is referred to as fibroblast contraction, which is essential for wound closure[86]. However, excessive cell contraction may lead to tissue scarring. On the other hand, inhibiting fibroblast contraction results in impaired wound healing[87]. Therefore, an optimal level of fibroblast contraction is desirable to facilitate wound closure while minimizing scar tissue formation.

Cell contraction involves the actin cytoskeleton[88]. The interaction between actin and myosin generates cell contraction[89] and the contractile forces transmit through actin filaments to integrins and the ECM[90].

In the literature, most studies concerned with cell contraction focus on skin fibroblasts[78]. Using a cell force monitor, contractile forces of tendon and skin fibroblasts were measured over time. It was found that tendon and skin fibroblasts exhibited different patterns of contraction where tendon fibroblasts produced a lower maximum contraction force than skin fibroblasts[91]. In healing tissues, myofibroblasts are thought to play a major role in tissue contraction. These cells have phenotypic characteristics of both fibroblasts and smooth muscle cells, including the formation of stress fibers parallel with the long axis of the cell[92] Mechanical loading also influences myofibroblast differentiation. Increased tension on granulation tissue in rats increases the formation of stress fibers and the expression levels of a-SMA and ED-A fibronectin[93], which are two protein markers of myofibroblasts[78].

HOW DO TENDON CELLS SENSE MECHANICAL FORCES?

As described above, tendon cells respond to mechanical forces by altering gene expression, protein synthesis and cell phenotype. These early adaptive responses may proceed, initiate long-term tendon structure modifications, and thus lead to changes in the tendon's mechanical properties. After that, we need to understand how tendon cells sense mechanical forces and convert them into cascades of cellular and molecular events that eventually lead to changes in tendon structure. This question comprises of the definition of mechanotransduction and necessitates a review of mechanotransduction mechanisms. Cellular components implicated in the transduction of mechanical forces are extracellular matrix, cytoskeleton, integrins, G proteins, receptor tyrosine kinases (RTKs), mitogen-activated protein kinases (MAPKs) and stretching-activated ion channels.

ECM

ECM is composed of cell-produced proteins and polysaccharides[94,95]. It defines tissue shape, structure and acts as the substrate for cell adhesion, growth and differentiation[96]. Mechanical loading increases ECM protein production by promoting the release of growth factors which mediate collagen secretion[97,98].

ECM transmits mechanical loads, stores and dissipates loading-induced elastic energy. Moreover, mechanical deformations in the ECM can transmit to the actin cytoskeleton and cause the remodeling of the actin cytoskeleton[99,100], which is known to control cell shape, affect cell motility and mediate various cellular functions, including DNA and protein syntheses[101].

Cytoskeleton

The cytoskeleton is composed of microfilaments, microtubules and intermediate filaments[101,102]. The cytoskeleton responds to extracellular forces, participates in transmembrane signaling and provides a network for translocating signaling molecules. Mechanical forces applied to the cell surface transmit directly to the cytoskeleton and cause changes in its structure[103]. Consequently, these changes due to applied mechanical forces can initiate transduction cascades within the cell through the activation of integrins and the stimulation of G protein receptors, RTKs and MAPKs[78].

Integrins

Integrins are transmembrane proteins composed of a and b subunits[104]. It mediates mechanotransduction between the extracellular matrix and the cell through "outside in" and "inside out" fashions[104,105]. Mechanical forces stimulate the conformational activation of integrins in cells and increase cell binding to the extracellular matrix[106].

G proteins

G proteins are membrane proteins that are involved in mechanotransduction. Mechanical forces may simultaneously activate G proteins and integrins[107].

RTKs and MAPKs

RTKs and MAPKs are a class of cell membrane proteins that are phosphorylated when subjected to cyclic stretching or shear stress. They can travel into the nucleus and alter gene expression[107,108]. It has been shown that cyclic stretching activates MAPKs in patellar tendon fibroblasts[109].

Stretching-activated ion channel

The activation of these channels permit calcium (Ca^{2+}) and other ions (*e.g.*, sodium and potassium) to influx, followed by membrane depolarization[110].

Mechanical stretching induced Ca^{2+} signal transmission involves the actin microfilament system because an actin polymerization inhibitor was found to abolish Ca^{2+}

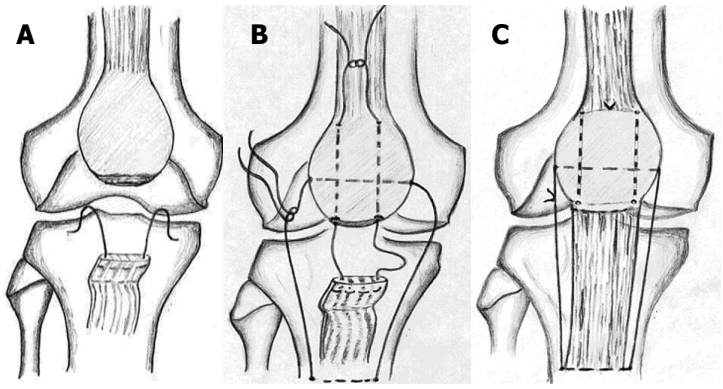

Figure 2 Drawing illustrates repair of the patellar tendon and making of the "suture line tension regulating suture". A: The modified Kessler suture in the proximal portion of an avulsed patellar tendon; B: The modified Kessler suture and the reinforcement device before tying the threads into a knot; C: The final appearance after tying the threads into knots. Reprinted from [124] with permission from the Springer.

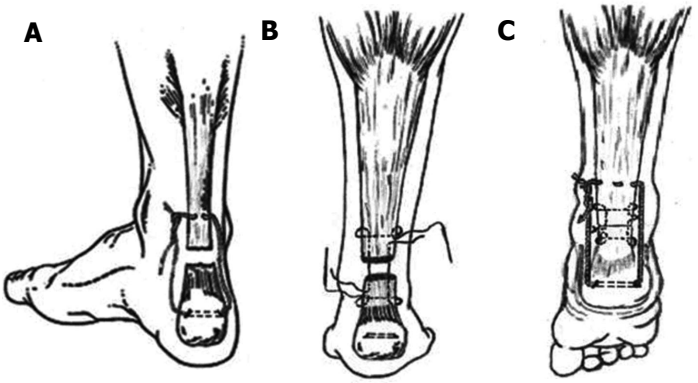

Figure 3 Drawing illustrates repair of the ruptured Achilles tendon. A: Thread of the reinforcement suture when it passes through the osseous tunnel in the calcaneus and by interweaving through the proximal stump of the Achilles tendon; B: Tendon stumps that were held together by Kessler's suture; C: Final appearance of the reinforcement suture and the repaired Achilles tendon. Reprinted from [125] with permission from the Elsevier.

responses induced by mechanical stimulation[111]. This means that calcium is an important mediator in cellular mechanotransduction.

TIMING OF MECHANICAL LOADING

It has been agreed that injured tendons require mechanical loading for optimal healing but early loading is not without risks of adverse effects. Loading might create excessive damage to the repair tissue leading to failure of the healing process or mostly plastic deformation (elongation) of the callus with subsequent tendon lengthening[112]. Lengthening during tendon healing is one potential clinical adversity. It is therefore important to understand the interplay between the loading and healing process.

The inflammatory phase of tendon repair seems to prepare the way for the formation of a fibrous callus. If early inflammation is inhibited, the fibrous callus can lose a third of its strength due to inferior material properties (lower stress at failure). During the inflammatory phase, there is little mechanical strength and mostly plastic deformation[112]. About the effect of loading during the inflammatory phase, Eliasson *et al*[113] noticed suppression of genes related to inflammation and extracellular matrix components. Moreover, they observed the loaded tendons by the third day also had a lower expression of collagens Ⅲ and I than unloaded ones, emphasizing, again, the value of mechanical protection in the early phase[113]. Once some elasticity has been obtained in the early fibrous callus, however, deformed tissues will resume their pre-load shape and cyclic loading will lead to biological signals[114]. It is remarkable that the investigators have suggested the period between the 4th and 6th postoperative week for the institution of mechanical loading at the tendinous interface as well as at the tendon-bone junction[114-117]. Eliasson *et al*[113] reported that later during healing, loading was related to a higher expression of extracellular matrix-related and tendon-specific genes, perhaps suggesting that the tissue was to some extent undergoing transformation from scar to tendon regeneration.

CLINICAL APPLICATIONS FOR MECHANICAL LOADING OF THE REPAIRED TENDONS

Because of the great distraction forces that arise from the muscles, long-lasting devices have been used for reinforcement of the repaired tendon[118-120]. However, prolonged reinforcement adversely influences the healing progress. Current knowledge indicates the appropriate time during the healing process for loading to start, but a suitable method for initiation of the mechanical loading during the healing process needs to be found. In our practice, we use an absorbable reinforcement device for tension regulation at the suture line. The utility of absorbable devices for reinforcement has been mentioned in several studies[121-123]. In two published studies[124,125], we used a reinforcement device made of Vicryl (polyglactin 910) suture, which has initial tensile strength equal or superior to nonabsorbable sutures[126,127]. Thereby, it serves initially as "a suture line tension-relieving suture". By the

fourth postoperative week, the suture loses about 75% of its tensile strength[128]; fortunately, this coincides with the remodeling phase.

We used the technique for the repair of a fresh rupture of the patellar and Achilles tendon in two groups of patients (Figures 2 and 3). Our philosophy is based on the protection of the tendon callus in the early healing phase. The spontaneous loss of tensile strength of the suture let the callus be exposed to the muscle tone, which continually changes. Continuous change of the muscle tone, theoretically, equals the cyclic mechanical loading in its effect. The group treated for patellar tendon rupture resumed their pre-injury activities at an average of 6.1 mo; knee motion reported no extension lag or flexion deficit and radiologically no patella alta, patella baja or degenerative changes in the patellofemoral joints were noted[124]. The group treated for Achilles tendon rupture returned to pre-injury daily activities by the fourth month and reported no tendon lengthening or reruptures[125]. Moreover, it is doubtless that we can attribute the noticed preservation of thigh and calf girths to our technique. The lack of tension on the immobilized musculotendinous unit is a major factor in the development of atrophy in the muscles[129,130]. This is due to the muscle spindle relaxing and afferent impulses to type-I fibers ceasing. The human soleus muscle contains a high portion of type-I muscle fibers as they are responsible for postural tone and are continually activated while the person is standing[131]. Our technique is designed to protect the suture line and places the muscle fibers under tension as long as the Vicryl suture preserves its tensile strength (Figures 2 and 3). By the end of the fourth week, patients were allowed active joint motion and weight bearing as tolerated.

In addition to alteration of the morphological character, lack of tension in immobilized muscle also alters its physiological properties that appear as a liability to rerupture. In a study of transected sheep Achilles tendons that had spontaneously healed, the rupture force was only 56.7% of normal at twelve months[132]. One possible reason for this is the absence of mechanical loading during the period of immobilization[1]. Immobilization reduces the water and proteoglycan content of tendons and increases the number of reducible collagen cross links[133,134]. Collagen fascicles from stress-shielded rabbit patellar tendons displayed lower tensile strength and strain at failure than control samples[135]. Additionally, as detailed above, lack of tension in the musculotendinous unit leads to structural damage of MTJ[18].

CONCLUSION

Perception of tendon biology and the biological processes that regulate tendon repair have progressed to a great extent; however, many challenges need to be addressed to bring about a successful treatment strategy. The simplicity of a surgical technique that is based on control of the mechanical loading at the suture line may reduce the requirement for demanding tissue engineering, particularly in simple circumstances. Moreover, this technique may open the way for earlier plaster removal and institution of more vigorous rehabilitation programs; thereby, the morbidity period can be reduced.

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MINIREVIEWS

Methods of predicting vertebral body fractures of the lumbar spine

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Abstract

Lumbar vertebral body (VB) fractures are increasingly common in an ageing population that is at greater risk of osteoporosis and metastasis. This review aims to identify different models, as alternatives to bone mineral density (BMD), which may be applied in order to predict VB failure load and fracture risk. The most representative models are those that take account of normal spinal kinetics and assess the contribution of the cortical shell to vertebral strength. Overall, predictive models for VB fracture risk should encompass a range of important parameters including BMD, geometric measures and patient-specific factors. As interventions like vertebroplasty increase in popularity for VB fracture treatment and prevention, such models are likely to play a significant role in the clinical decision-making process. More biomechanical research is required, however, to reduce the risks of post-operative adjacent VB fractures.

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Key words: Lumbar spine; Vertebral body; Fracture; Prediction; Model; Bone mineral density; Osteoporosis

Core tip: Lumbar vertebral body (VB) fractures are increasingly common in an ageing population that is at greater risk of osteoporosis and metastasis. This review aims to identify different models, as alternatives to bone mineral density (BMD), which may be applied in order to predict VB failure load and fracture risk. The most representative models are those that take account of normal spinal kinetics and assess the contribution of the cortical shell to vertebral strength. Overall, predictive models for VB fracture risk should encompass a range of important parameters including BMD, geometric measures and patient-specific factors.

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INTRODUCTION

Lumbar vertebral body (VB) fractures, particularly in the osteoporotic or otherwise diseased spine, are a frequent cause of pain and reduced function amongst an ever-aging population. The treatment and prevention of such fractures has therefore gained increasing importance in recent years given the potential impact on healthcare and quality-of-life amongst the elderly.

Despite their prevalence, the aetiology of VB fractures remains relatively poorly understood; partly because only a relative minority have radiographically evident vertebral deformity and fail to gain medical attention; and partly because of the protracted onset of such fractures compared to limb injuries[1]. By far the most widespread cause is regarded to be osteoporosis-a skeletal disorder characterised by a generalised reduction in bone mass and deterioration of bone microarchitecture[2]-with

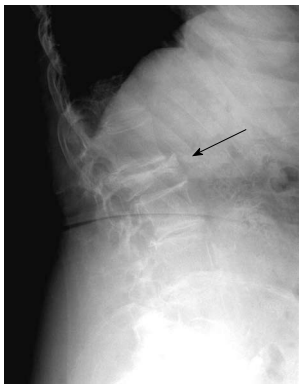

Figure 1 Wedge compression fracture of a lumbar vertebrae. The lateral radiograph of the lumbar spine with an arrow demonstrating an osteoporotic compression fracture of the L2 vertebral body with significant collapse, in an elderly woman.

VB compression fractures accounting for more than 45% of all osteoporotic fractures[3]. Consequently, the measure of bone mineral density (BMD) by techniques such as dual X-ray absorptiometry (DXA) and-to a lesser extent-quantitative computed tomography (QCT), has become the mainstay of clinical practice with regard to the diagnosis of osteoporosis and the prediction subsequent of VB fracture[4,5].

Fractures occur when the force applied to bone exceeds its load-bearing capacity. Hence, by causing a reduction in compressive strength of bone, osteoporosis typically increases the risk of VB fracture by way of either endplate failure and burst fracture, or more commonly by wedge compression fracture-as shown in Figure 1[1,6].

Forces acting on the lumbar spine can be substantial under physiological conditions with loads between 800 and 1200 N of axial compression being applied at L1 vertebra during upright standing[7]. Such compressive loads have been shown to increase vastly with forward bending particularly when combined with lifting-a5-fold increase has been observed with 45° of forward flexion whilst lifting 10 kg[1]. With their six degrees of freedom, functional spinal units (FSU) undergo motion other than just flexion under the action of a range of internal and external forces. However, as indicated, compressive forces associated with flexion and extension are the most important when considering the kinetics of the lumbar vertebrae. This arises from the observation that at static equilibrium the centre of mass of the upper torso, arms and head lies anterior to the axis of rotation found at L4/L5 or L5/S1 in the upright posture. The forward flexion moment generated is countered by the paraspinal muscles and subsequently the resultant vector acts to confer axial compression. Most biomechanical models, including both experimental and computational research, therefore aim to predict VB fracture by focussing on compressive forces.

Clearly, osteoporosis is not the only risk factor for VB failure. Pathological lesions produce discrete areas of vertebral weakness and subsequent fracture. In particular, the spine is the most frequent site of metastasis-such pathology has been reported in up to 80% of all cancer patients after death[7,8]. As is the case with osteoporosis, VB fractures associated with metastasis frequently produce vertebral collapse, deformity and subsequent pain. Deformity, be it within the (FSU) or the whole spinal segment, is believed to contribute to deleterious loading changes in the thoraco-lumbar spine. In the presence of VB wedge fracture(s) the loss of anterior vertebral height results in an increase in the flexion moment arm generated by the upper body, thereby increasing compressive loads and the propensity for further fracture[9]. More numerous fractures that produce a kyphotic segment of the spine can hasten abnormal biomechanics leading to a "vertebral fracture cascade"[9]. In recent years, there has been an increase in the rates of surgical intervention for such patients, both as preventative and therapeutic measures[3]. The injection of bone cement into the VB-known as vertebroplasty-to restore strength and reduce pain is the foremost treatment currently, in terms of popularity and cost-effectiveness[3]. In spite of its advantages, however, vertebroplasty has been linked with several drawbacks based on both clinical and biomechanical grounds-most notably, an increased risk of adjacent VB fracture.

This review article focuses on biomechanical models that aim to predict the risk of failure load and fracture in the VBs of healthy spines and in those that harbour disease. The challenges that exist in the implementation of such risk models and in the use of vertebroplasty, are also described.

BONE MINERAL DENSITY AND VB FRACTURE RISK

In principle, excessive loading and/or a reduction in VB strength result in fracture. Given that spinal loading is essentially an external driver and varies with different activities, it is necessary to determine VB strength in order that fracture risk can be assessed[10]. Although BMD has widespread clinical use and has been shown to predict vertebral fractures with a relative risk of 2.3 per standard deviation change[5], there exists much literature that expounds only a partial role of BMD in determining VB strength[10-12]. In engineering terms, the prediction of fracture risk is also dependent on vertebrae's complex geometry, their elastoplasticity and structural heterogeneity[10]. As BMD can vary widely between those with and without VB fractures, it is a test that may be regarded as having poor sensitivity with respect to fracture thresholds[6,11]. Additionally, the interpretation of scans used to determine BMD clinically can be distorted by aortic calcification along with other artefacts[5]. Perhaps the most compelling limitation of BMD measurement as the sole predictor of fracture risk, is the fact that imaging techniques such as QCT generally fail to take into account the cortical shell of VBs, analysing only the spongy bone portion[2]. This is in spite of evidence suggesting that the

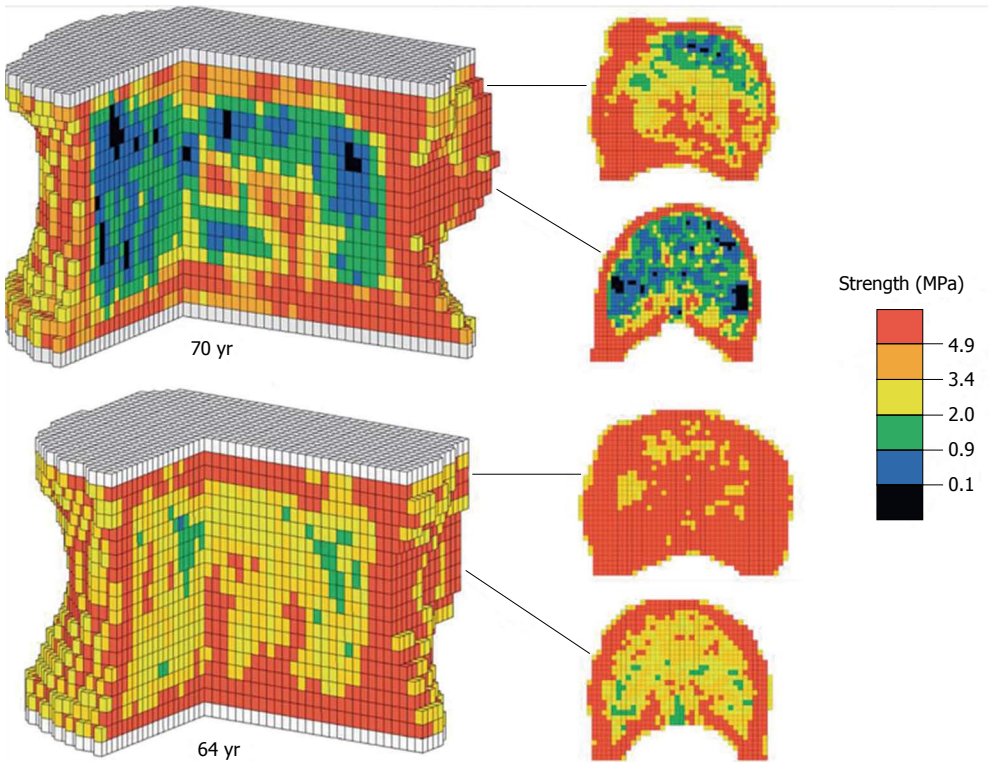

Figure 2 Three-dimensional quantitative computed tomography-based finite element modelling of the vertebral body. The L3 vertebra from two individuals (one aged 70 and the second 64 years) modelled using voxels from 3D quantitative computed tomography, allowing estimation of bone mineral density. The model has been used to predict vertebral strength under axial compression, as illustrated by the colour scale. Overall vertebral strength were predicted as 4656 N in the younger patient (64 years) *vs* 6095 N in the older patient (70 years). Reproduced from Melton *et al*[5].

best predictor of distal radius and proximal femur failure load is cortical bone geometry at the respective sites[4]. Hence, BMD estimation of both the spongiosa and the cortical shell is advocated, in addition to consideration of the cortical geometry when predicting VB strength[2,4].

The contribution of cortical bone to the overall mechanical properties of vertebrae is gaining increasing attention, as variation in cortical BMD has been seen to follow patterns according to age and sex-related differences. Relative reductions in cortical BMD have been associated with increasing age and with women, highlighting at least two areas of concern[2]. Firstly, the BMD, structure and therefore the contribution to overall VB strength of the spongiosa and cortical shell are distinct. Hence, those QCT-based models that assume uniformity between the two constituents of the VB may be underestimating vertebral strength and overestimating fracture risk. Secondly, the age and sex-related differences in cortical BMD and structure, suggest that cortical bone goes through a process of change during which heterogeneity within the shell may be exhibited. Models using computer tomography (CT) systems of lower resolutions may fail to identify areas of demineralisation and in doing so misrepresent failure load. In contrast, however, it is also argued that unlike the thick cortices of long bones in the body, the VB cortical bone is much too thin for significant load-bearing-a view supported by studies demonstrating that VB failure loads were the same as the mean crushing strength of decorticated specimens of VB spongiosa[2].

QUANTITATIVE CT

In noting some of the shortcomings in the use of BMD as a predictor of VB fracture risk, it is necessary to consider alternative methods by which this might be achieved with greater reliability. QCT imaging of cadaveric spines has been widely employed as a basis of computational modelling techniques of analysing VB structure-*e.g.*, finite element (FE) modelling which employs computer software programs to generate 3D representations of the VB, constituted from minute geometric shapes (Figures 2 and 3). In spite of such techniques, however, there is relatively little research predicting absolute VB failure loads. That which does exist has shown very strong correlations between predicted and observed yield loads (stress at which the bone begins to deform plastically) and fracture loads[10]. By evaluating more than just failure loads such analyses can be said to be more accurate, and findings suggest that QCT in this respect is a reliable technique of obtaining a geometric and architectural survey of VBs in order for fracture risk prediction. However, an important limitation of QCT is that it fails to take account of the material properties, *e.g.*, elastic modulus, of VB bone, which means that such a system would fail to incorporate variability in bone stiffness in its fracture risk prediction. Additionally, most QCT systems lack the relatively higher resolution needed

Figure 3 Pathological fracture of a lumbar vertebra. Sagittal magnetic resonance imaging image displaying a pathological fracture of L1 vertebral body with collapse, secondary to metastatic infiltration (shown by arrow). The T12 vertebra also has metastatic deposits but is not fractured.

Table 1 Relative risk of incident vertebral fracture according shape of prevalent deformity

	Shape	Relative risk[1]
McCloskey-Kanis deformity type	Biconcavity	3.7
	Wedge	3.4
	Crush	4.4

[1]Relative risk for an incident fracture of any shape according to the baseline deformity of a given shape-reference group consisted of subjects without prevalent deformity. Reproduced from Lunt *et al*[12].

to decipher the heterogeneous properties of the VB' s cortical bone[10]. This potential source of error may underestimate cortical shell density and thus predicted VB strength values, particularly since it has been demonstrated that as the BMD of VB spongiosa reduces, load is increasingly transferred to the cortex[2].

A further noteworthy limitation of QCT-based VB fracture prediction arises from removal of the posterior elements of the vertebrae during loading tests. The ligaments, laminae and facet joints that make up the posterior elements are known to be load sharing structures and therefore their exclusion, in an attempt to reduce interference during VB CT imaging, can introduce inaccuracies when predicting *in vivo* VB fracture risk[10]. This may account for its relative lack of popularity in clinical practice as compared to its use in research and modelling. Despite the limitations of using QCT-based analytical models, their use does still demonstrate very strong correlations between predicted and measured VB strength[1].

GEOMETRIC PARAMETERS AND VB FRACTURE PREDICTION

Anterior vertebral height

The measurement of anterior vertebral height (AVH) is another parameter that offers potential as an independent predictor of VB failure and the use of lateral spinal radiographs is the gold standard method by which this is achieved. AVH evaluation has been shown to be significantly more accurate in diagnosing and predicting VB fractures than DXA-based BMD values for the lumbar vertebrae and indeed for the femoral neck[11]. A much greater risk (95.2%) of VB fracture is observed when the AVH is ≤ -2.5 SD amongst female patients. Such research has further made the case against BMD as a valid predictor of VB fracture risk, given that a third of women presenting with VB fracture possess normal BMD values, whilst a substantial group of patients free of fracture demonstrate BMD values ≤ -2.5 SD. Though the use of AVH in this way does not employ numerical or experimental methods to calculate VB failure loads or strength values, it clearly demonstrates the relevance of VB geometry to vertebral strength and the prediction of fracture risk.

Reductions in AVH can generally be regarded as a representation of VB wedging frequently observed in osteoporotic patients. Such deformity even with single fractures has been linked to deterioration in the physiologic kinetics of the spine-significantly greater flexion moments (> 15%) and shear forces (> 250%) have been noted[9]. The increased forces result from the tilting of VB endplates, increased Cobb angle and subsequent anterior translation of the upper body centre of mass. Spinal curvature, as a form of pathology in its own right and not just a consequence of osteoporosis, has been intimately linked to loading in static conditions and therefore even subtle, yet clinically insignificant deformity, can give rise to adverse loading and increased fracture risk[9]. For instance, when baseline and follow-up lateral patient radiographs are prospectively evaluated for any prevalent vertebral deformities or incident VB fractures, those with a single vertebra deformity are six times more likely to suffer an incident VB fracture than those without deformity[12]. This figure rises to a greater than 20-fold increase in fracture risk for those with three or more deformed vertebrae.

Fractures can also be classified according to the McCloskey-Kanis algorithm-which describes deformity as either "biconcave", "wedged" or "crushed" -and then further subdivided with regard to detailed height measurements. Models that include such information acknowledge shape and severity of deformity as independent (of BMD) predictors of VB fracture-the former being of greater importance (Table 1)[12]. In addition, they also predict that the highest risk of fracture is present amongst individuals in whom the prevalent deformities occur at T5-T7 and L1-L3. Notably, the use of such predictive models serves to highlight several additional issues of relevance: firstly, that not all types of deformity confer the same risk; secondly that global factors, *e.g.*, age, and propensity to fall, must play a role as fracture determinants given that the whole spine is deemed to be at risk despite localized deformity; and lastly the importance of multi-level spinal segment studies which are

more representative of *in vivo* conditions[13].

Spinal deformity index

A widely used method of evaluating VB fracture risk in the clinical trial setting is that developed by Genant *et al*[14]. Like AVH, spinal deformity index (SDI) is a system that also involves a visual assessment of lateral spine radiographs but instead grades each vertebra between T4 and L4 as either normal, mild, moderate or severe depending on the percentage compression. This semi-quantitative index represents both the severity of VB compression and the number of levels affected. SDI has been shown to be significantly correlated with vertebral fracture risk in validation studies, which is in keeping with the widely-held view that previous VB fracture is one of the most important predictors of subsequent VB fracture[15]. An important issue that such systems do not address, however, is the risk of fracture in patients known to have osteoporosis but without a pre-existing fracture or associated deformity.

Combining BMD with geometric parameters

The key to reliable predictions of VB fracture load, it has been suggested, is in the combination of BMD and geometric parameters of the VB[6] -in particular vertebral strength being dependent on the product of bone density x endplate area. Thus, strength reduces with a decrease in either BMD or vertebral dimensions. Since vertebral geometry is known to vary between individuals, within an individual's spine and indeed with time-an age-related 14% increase in vertebral cross-sectional area has been observed in women[5] -vertebral failure load may too vary widely and less predictably than some models might suggest. For instance, a large VB endplate may compensate for a relatively low BMD and vice versa, which in turn suggests that the use of BMD to exclusively characterise vertebral strength may be somewhat inaccurate.

Vertebral fracture assessment (VFA) has in recent years gained recognition as a method of estimating fracture risk, particularly in the elderly female population[16]. Dual-energy X-ray absorptiometry is employed to provide low dose radiation imaging of the lateral spine which in turn allows for vertebral fracture(s) and associated deformity to be identified along with BMD measurements. The combined information generated from VFA has been shown to be comparable to spinal radiographs with regard to its ability to predict incident vertebral fractures in elderly women, but with the advantages of lower radiation exposure and less expense[16]. An important area of concern for VFA, however, is the adequacy of upper thoracic spine imaging[17].

QCT is an alternative investigation that can also exploit data pertaining to both BMD and the geometry of VBs. The authors of one particular study took measurements of both BMD and endplate area of the L3 vertebra of 75 patients and subsequently applied regression formulae to calculate compressive strength[6]. The presence or absence of VB insufficiency fractures amongst the same patients was determined by conventional radiographs from T10 to L5. By relating fracture prevalence to compressive strength, the researchers identified three stratified risk groups. Most notably, strength values of less than 3 kN were linked to a fracture risk of virtually 100%, whilst for values above 5 kN the risk was practically zero. Such data and others like it, demonstrate that compressive strength or failure loads of VB are better parameters by which to define fracture risk thresholds, than is BMD alone[6,18].

SPINAL PATHOLOGY AND VB FRACTURES

Metastasis arising from malignancy is another pathological process that afflicts the spine and impacts fracture risk. Fracture types frequently associated with such pathology are "burst" as well as wedge fractures and can occur under normal loading conditions[8]. Figure 3 demonstrates a lumbar burst fracture secondary to metastatic deposits. The proposed mechanism of burst fracture is believed to occur just prior or just subsequent to vertebral endplate failure. Experimentally validated FE modelling of metastatically involved motion segments (including the posterior arch) has suggested that patient-specific burst fracture risk is higher for those with increased tumour size, lower BMD, increased loads, and pedicle involvement[7]. Two further 'biomechanical parameters have also been put forward-namely "vertebral bulge" and "vertebral displacement", which refer to compression-induced changes in VB width and height, respectively (Figure 4). Both measures have been shown to linearly correlate with cortical fracture strain threshold values, when under compressive loading conditions-although, the vertebral bulge equation has performed as the most accurate predictor (predictive power 100%), producing a clear threshold value for burst fractures[7,8].

In addition to the positive determinants of fracture risk prediction as seen in metastasis, degenerative disc disease has been identified as a factor that acts to reduce the risk of VB burst fracture[7]. Analytical and experimental models have demonstrated potential for their applicability in VB fracture risk prediction in the diseased spine. However, limitations and challenges to the widespread implementation of such models exist such as their lack of clinical validation. Also, like most others, these models fail to predict neurological injury-a tangible risk associated with burst fractures-which may consequently influence clinical decision-making. Finally, further assessment of multi-level spinal segments is required in order to provide a more representative prediction for fracture risk.

VERTEBROPLASTY

The ultimate purpose of models that predict vertebral fracture risk is to provide a rationale on which clinicians may base their decisions for intervention. Traditional

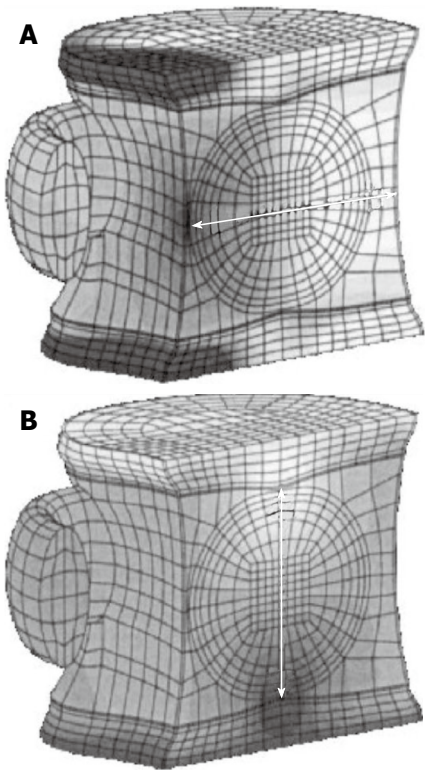

Figure 4 Finite element model of a metastatically-involved spinal motion segment. A: Vertebral "bulge" in the transverse plane determines the risk of burst fracture independent of endplate failure; B: Axial vertebral displacement denotes risk of endplate failure resulting in burst fracture. Reproduced from Whyne *et al*[7].

conservative therapies have included bed rest, analgesia and bracing, whilst instrumented spinal stabilization was, until recently, the mainstay of surgical intervention[3]. Vertebroplasty, however, has gained increasing popularity over the last two decades acting in both preventative and therapeutic capacities. Vertebral augmentation with bone cement-most commonly polymethylmethacrylate (PMMA)-has provided early clinical improvement in regard to pain relief in more than 90% of cases[13] (Figure 5). Biomechanically, it serves to retain the normal vertebral and spinal geometry by increasing the VB stiffness and strength. But the procedure is not without risk. PMMA goes through an exothermic reaction which can cause neurological damage, localized inflammation and osteonecrosis[13]. There are also concerns regarding cement leakage, which can encroach into the spinal canal with disastrous consequences[3]. From a biomechanical standpoint the most significant complication is that of subsequent fracture in adjacent VBs. Some studies have noted a significant increase in the odds ratio of adjacent vertebral fractures before (1.44) and after (2.27) vertebroplasty, whilst others report that two thirds of new VB fractures occurred within the first 30 days of surgery[3].

Several potential mechanisms, by which adjacent fractures might occur following vertebroplasty, have been acknowledged. The rapid pain relief afforded by the procedure can allow for higher levels of physical activities, which are associated with greater risks of VB fracture. Alternatively, the fractures may occur merely as a consequence of the normal progression of osteoporosis and the fracture cascade that has been observed after the initial VB fracture[3]. Vertebroplasty (unlike kyphoplasty) does not restore normal geometry, namely vertebral height, after fracture and therefore the risks of subsequent fracture still exist due to suboptimal spinal kinetics, including the increased flexion moment arm.

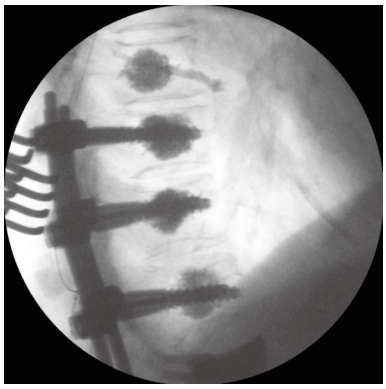

Figure 5 Vertebroplasty and stabilization surgery of lumbar spine. Intraoperative image intensifier lateral radiograph of the lumbar spine during vertebroplasty and posterior spinal instrumentation for osteoporotic compression fractures. polymethylmethacrylate bone cement is seen in the vertebral body and has been used to augment vertebral strength.

Based on both experimental and computational studies, the "pillar" effect has been hypothesized to play an important role, whereby the relatively stiff augmented VB reduces and resists endplate bulge into it during axial compressive loading. The resultant increase in adjacent intradiscal pressure is transferred to the adjacent vertebra, thereby raising the risk of fracture here[3]. Despite conferring increased VB strength, vertebroplasty appears to reduce the overall strength of the FSU. Further biomechanical modeling and data is needed which may allow for modification of the material properties of cement.

CONCLUSION

Lumbar VB fractures are occurring with increasing frequency amongst an ageing population that is at greater risk of osteoporosis and metastasis. This article has served to demonstrate a number of models, as alternatives to BMD, which may be applied in order to predict VB failure load and subsequent risk of fracture. The conventional use of BMD and QCT has its limitations, such as the failure to incorporate the contribution of the cortex to overall VB strength and not only that of the spongiosa. Overall, predictive models for VB fracture risk should encompass a range of important parameters including BMD, geometric measures and patient-specific factors. As interventions like vertebroplasty increase in popularity, such models are likely to play a significant role in the clinical decision-making process.

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ORIGINAL ARTICLE

Feasibility of progressive strength training shortly after hip fracture surgery

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Abstract

AIM: To investigate the feasibility of a 6-wk progressive strength-training programme commenced shortly after hip fracture surgery in community-dwelling patients.

METHODS: This prospective, single-blinded cohort study evaluated 31 community-dwelling patients from four outpatient geriatric health centres aged 60 years or older, who started a 6-wk programme at a mean of 17.5 ± 5.7 d after hip fracture surgery. The intervention consisted primarily of progressive fractured knee-extension and bilateral leg press strength training (twice weekly), with relative loads commencing at 15 and increasing to 10 repetitions maximum (RM), with three sets in each session. The main measurements included progression in weight loads, hip fracture-related pain during training, maximal isometric knee-extension strength, new mobility score, the timed up and go test, the 6-min walk test and the 10-meter fast speed walk test, assessed before and after the programme.

RESULTS: Weight loads in kilograms in the fractured limb knee-extension strength training increased from 3.3 ± 1.5 to 5.7 ± 1.7 and from 6.8 ± 2.4 to 7.7 ± 2.6, respectively, in the first and last 2 wk ($P < 0.001$). Correspondingly, the weight loads increased from 50.3 ± 1.9 to 90.8 ± 40 kg and from 108.9 ± 47.7 to 121.9 ± 54 kg in the bilateral leg press exercise ($P < 0.001$). Hip fracture-related pain was reduced, and large improvements were observed in the functional outcome measurements, *e.g.*, the 6-min walk test improved from 200.6 ± 79.5 to 322.8 ± 68.5 m ($P < 0.001$). The fractured limb knee-extension strength deficit was reduced from 40% to 17%, compared with the non-fractured limb. Ten patients reported knee pain as a minor restricting factor during the last 10 RM knee-extension strength-training sessions, but with no significant influences on performance.

CONCLUSION: Progressive strength training, initiated shortly after hip fracture surgery, seems feasible and does not increase hip fracture-related pain. Progressive strength training resulted in improvement, although a strength deficit of 17% persisted in the fractured limb compared with the non-fractured limb.

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Key words: Hip fracture; Resistance training; Feasibility; Repetition maximum; Pain

Core tip: The recovery of strength and function in patients with hip fractures is an on-going challenge. We aimed to evaluate the feasibility of a 6-wk progressive lower limb strength-training programme. To our knowledge, this was the first study to implement such a program successfully in an outpatient geriatric setting within 2-3 wk after hip fracture surgery. Training loads, muscle strength and functional performances improved without an increase in hip fracture-related pain, which

is considered new and important knowledge for all professionals aiming to improve the rehabilitation outcomes of patients with hip fractures.

Overgaard J, Kristensen MT. Feasibility of progressive strength training shortly after hip fracture surgery. *World J Orthop* 2013; 4(4): 248-258 Available from: URL: http://www.wjgnet.com/2218-5836/full/v4/i4/248.htm DOI: http://dx.doi.org/10.5312/wjo.v4.i4.248

INTRODUCTION

Hip fractures are associated with poorer survival[1], a greater than 50% loss of fractured lower limb strength within a few week after surgery[2-4] and the return of only poor functional mobility within 4 mo[5]. Knee extensor muscle strength is an independent predictor of falls within 6 mo of hip fracture[6]. Thus, reducing strength deficits should be a high priority in rehabilitation, as the incidence of falls is higher with asymmetrical lower extremity power[7]. Some trials have suggested the benefits of exercise after hip fracture[8], but studies have most often commenced as extended programmes after standard physical therapy has ceased, 6 to 8 wk after fracture at the earliest[9-16]. To our knowledge, only one study has evaluated the effects of early 6-wk (median of 15 d post-surgery) strength training after hip fracture as an in-patient rehabilitation programme[3]. However, no similar studies have been conducted in community-dwelling geriatric patients with hip fractures or have succeeded in promoting the regaining of symmetrical lower limb muscle strength. In addition, most strength intervention studies have based their training intensity on the one repetition maximum (RM) level[3,10-12,15-17], which requires further calculations before use in clinical practice, as well as new one-RM measurements for the subsequent adjustment of training intensity. Such one-RM-based programmes challenge progressive exercise in comparison with, *e.g.*, programmes that start with 12 repetitions and a 12-RM intensity, which in principal, allows physiotherapists to adjust weight loads after each set. That is, weight loads should be increased in the next set for a patient able to perform, *e.g.*, 14 repetitions for such a programme to be called progressive. In summary, there is only limited knowledge regarding the feasibility and effects of a non-one-RM-based progressive strength-training programme commenced within a few wk after hip fracture surgery.

The primary purpose of this prospective cohort study was to evaluate the feasibility of a 15- to 10-RM programme, based on a 6-wk early progressive strength-training programme, after hip fracture. Feasibility was indicated if the absolute strength-training loads increased progressively and if hip fracture-related pain during training remained the same or decreased over time. The secondary purpose was to report functional adaptations, the details of specific weight loads and whether hip fracture-related pain influenced strength and functional testing.

MATERIALS AND METHODS

Patients

Thirty-nine community-dwelling geriatric patients with hip fractures were included in this study (Table 1) and began the exercise programme at a mean of 17.5 ± 5.7 d after surgery. The types of surgery included hip pins (n = 3), screws (n = 10) and hemiarthroplasty (n = 10) for the 23 patients with intracapsular cervical femoral fractures, whereas the patients with extracapsular intertrochanteric fractures underwent surgery with dynamic hip screws (n = 8) or short intra-medullar hip screws (IMHS, n = 4). Four patients with subtrochanteric fractures all underwent surgery with long IMHS. All of the patients were cleared by the orthopaedic surgeon at the hospital for immediate weight bearing as tolerated on the operated limb, and with the exception of those with hemi-arthroplasty, the patients were under no other restrictions during rehabilitation. Patients with hemiarthroplasty were not allowed to perform > 90° flexion, adduction or internal rotation of the hip. Before inclusion, all of the patients followed a short in-hospital physical therapy programme without strength training, focused on the regaining of basic mobility activities[18,19], before being discharged to their own homes. Patients were recruited from four outpatient geriatric municipality health centres from September 2010 to August 2011. The inclusion criteria were as follows: age greater than or equal to 60 years; intra- or extracapsular hip fracture; no post-surgical restrictions for weight bearing; living in their own homes; and ability to walk independently, according to an indoor new mobility score[20,21] (NMS) ⩾ 2 points. The exclusion criterion was as follows: adverse medical conditions, such as neurological impairment (*e.g.*, history of stroke with residual hemiplegia) or uncontrolled cardiac diseases that could potentially influence the patient's ability to participate in the programme. The ethics committee of the Sealand region (study no. SJ-145) and the Danish data protection agency approved this study. All of the patients provided written informed consent, according to the Declaration of Helsinki Ⅱ.

Procedure

The patients were asked to follow a standardised 6-wk rehabilitation programme with sessions twice weekly (12 sessions in total), which included progressive lower limb strength training. Before the first training session and after the last training session, all of the patients performed the following objective examinations: the timed up-and-go (TUG) test[22]; the 10-m fast speed walk test (10mWT)[23]; the tandem balance test[24]; the 6-min walk test (6MWT)[25]; and the maximal isometric knee-extension strength test for each limb. The pre-fracture functional level was assessed using the questionnaire of the modified[26], functionally validated[27] and reliable[21] NMS (0-9 points, a score of 9 indicating a fully indepen-

Table 1 Baseline data of patients with hip fractures included in a 6-wk rehabilitation programme

	All	Dropout within 6 wk, *n* = 8	Followed 6-wk program, *n* = 31	*P* value
Age (yr)	77.7 ± 8.7	77.2 ± 8.3	77.9 ± 9.0	0.8
Women	33 (85)	7 (21)	26 (79)	1.0
Men	6 (15)	1 (17)	5 (83)	
Cervical femoral fracture	23 (59)	4 (17)	19 (83)	0.8
Intertrochanteric fracture	12 (31)	3 (25)	9 (75)	
Subtrochanteric fracture	4 (10)	1 (25)	3 (75)	
New mobility score (0-9):				
Pre-fracture functional level	9 (9-9)	9 (8.5-9)	9 (9-9)	0.8
Baseline functional level	4 (3-4)	4 (3-4)	4 (3-4)	0.9
Barthel-20 (0-20)	18 (17-20)	8 (17-19.5)	18 (17-20)	0.9
Balance, tandem test (0-30)	30 (23-30)	27 (24-30)	30 (22-30)	0.5
Timed up and go test, seconds	21.0 ± 7.2	22.4 ± 10	20.2 ± 6.0	0.4
Ten-meter fast speed walk, m/s	0.72 ± 0.22	0.65 ± 0.31	0.74 ± 0.19	0.3
Six min walk test, meters	198 ± 79	189 ± 80	201 ± 80	0.7
Fractured, knee-extension strength, Nm/kg	0.47 ± 0.16	0.39 ± 0.16	0.49 ± 0.16	0.1
Non-fractured, knee-extension strength, Nm/kg	0.79 ± 0.22	0.69 ± 0.29	0.81 ± 0.28	0.2

Data are presented as mean ± SD, as medians (25%-75% quartiles) or as *n* (%).

dent pre-fracture walk level)[20] and activities of daily living, using the Barthel-20[28]. Health-related quality of life was assessed using the 36-item short form health survey (SF-36) and was reported as SF-36P (physical) and SF-36M (mental)[29]. The patients were instructed to take their prescribed pain medication before the testing and training.

Physiotherapists involved in the testing of the patients before and after the rehabilitation were blinded to the patients' participation and progress during the 6-wk rehabilitation programme, and the physiotherapists did not supervise training the sessions.

Hip pain and restricting factors

Hip fracture-related pain was measured with a 5-point verbal ranking scale (VRS) (0 = none, 1 = light, 2 = moderate, 3 = severe, 4 = intolerable pain) during all of the strength and performance testing, as well as during all of the strength-training sessions (patients were asked immediately after). The VRS has proved most appropriate for measuring pain in patients with hip fractures[30] and has been used in previous hip fracture studies[2,31,32].

During each strength-training session, the patients were asked about any factors restricting their performance.

Walking aids and number of trials

The TUG, performed as fast as safely possible, has proved highly reliable in patients with hip fractures[33] when using a standardised four-wheeled rollator[34] and selecting the best of three timed trials[35]. Accordingly, as all of the patients used some kind of walking aid, a standardised four-wheeled rollator was used for all of the walk tests (TUG, 10mWT and 6MWT), both at baseline and at follow-up testing. The best of three timed trials was used for the TUG (performed as previously described)[34], the 10mWT and the tandem balance test (no walking aid used), whereas one timed trial was used for the 6MWT.

Gait speed

Fast speed walking was measured with the 10mWT[23]. Patients were instructed to "walk as fast as safely possible without running" from a standing position, starting behind a line drawn on floor. A stopwatch was started on the command "3-2-1-GO" and was then stopped when the patient's leading foot crossed a line 10 m away. The results are reported in meters walked per second (m/s).

Balance

Static balance was assessed with the tandem test[24] with a score from 0 to 30 points (a score of 30 points indicating no balance problems). The first position was standing with the feet together, the second was placing the feet in semi-tandem, and the last position was setting the feet in a full tandem position. The time was measured with a stopwatch, and up to 10 points (one per second) were assigned for maintaining balance in each of the three positions.

Isometric knee-extension strength

Maximal isometric knee-extension strength was assessed for both limbs with a fixated hand-held dynamometer[36] (Power Track Ⅱ Commander). The patients were seated on an examination couch with their arms crossed (as in a previous study[37], personnel communication with the first author), their knees at a 90° angle and their upper limb fixed with a strap to the examination couch during testing. The transducer (placed 5 cm above the lateral malleoli) was positioned under a fixation belt that was fastened to the examination couch. After familiarisation with the procedure, the patients performed five voluntary isometric knee extensions for each limb (non-fractured limb first) with strong verbal encouragement, separated by a minimum of a 30-s pause. Maximal isometric strength was expressed in Nm/kg and was derived from the units of force in newtons (N) multiplied by the corresponding lever arm (distance from lateral epicondyle of the femur to the transducer) measured in meters (m), divided by the weight (kg) of the patient[37].

Endurance

The 6MWT was performed according to recommendations of the American Thoracic Society[25], using a 30-m course with a cone marking each end. The patients were instructed to walk as far as possible, and Borg dyspnoea and fatigue levels[38] were recorded immediately after finishing. No practice trial was conducted, but the patients performed the other objective outcome measurements before the 6MWT.

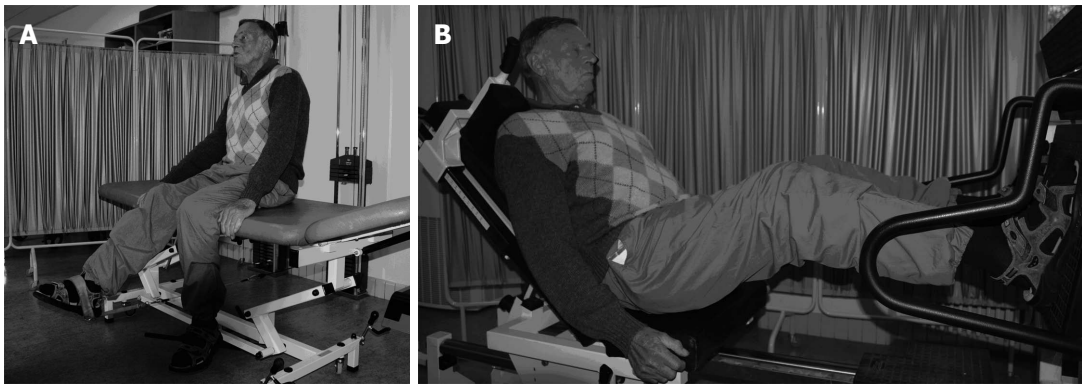

Figure 1 The progressive strength training included unilateral (fractured limb) knee-extension (A) and bilateral leg presses (B).

Rehabilitation programme

The patients who entered the programme were of different ages (range, 61-96 years) and pre-fracture functional levels (NMS, 6-9) and therefore exhibited different functional levels at start of the programme. Accordingly, walking and balance exercises were chosen and progressed on an individual level to ensure that each exercise was conducted with the same intensity for all of the patients. The exercises began with warm-up on a stationary bicycle (intensity according to the Borg 10) for 10 min and were followed by functional exercises focused on improving walking forward, backward and sideways and stair climbing with the maximal tolerable weight bearing on the operated limb, with or without the use of walking aids, for 15 min.

The balance training was conducted for approximately 10 min with the patient standing with both legs on the floor and on different surfaces, *e.g.*, an Airex pillow/mattress, an ankle disk or a trampoline, with or without support.

The progressive strength training included unilateral (fractured limb) knee extension (Figure 1A) and bilateral leg presses (Figure 1B). For each exercise, three sets of approximately 15 repetitions with a relative weight load of 15 RM were performed for 2 wk (four sessions). This period was followed by 2 wk with three sets of 12 repetitions (12 RM) and 2 wk with three sets of 10 repetitions (10 RM). To determine the relative weight load, the supervising physiotherapist adjusted the weight load, so the patient reached fatigue at the respective RM level. Accordingly, the weight loads were adjusted after each of the three training sets in each of the 12 sessions if the patient was able to perform more than the planned repetitions, to ensure training at the respective RM level. The reduction in the number of repetitions from 15 to 12 to 10 during the 6-wk strength-training programme was followed by a corresponding increase in intensity from 15 to 12 to 10 RM. The largest difference in kilograms between the starting point and endpoint was used in the final analysis. The total exercise programme lasted approximately 60 min per session.

The fractured limb knee-extension strength training was performed with the patient seated on an examination couch with a 90° hip and knee angle. In the seated position, the patient was instructed to grasp the edge of the examination couch with his or her hands to assure a standardised position. The patient was connected to a weight load system with a strap around the ankle, and a successful single repetition was defined as movement from the 90° knee angle to as close as possible to a maximal knee extension (Figure 1A).

The bilateral leg press strength training was started with maximum allowed flexion in the hip (90° for patients who underwent surgery with hemi- or total arthroplasty) and the knee to a full possible knee extension, and the patients were instructed to press equally with both limbs (Figure 1B).

Strong verbal encouragement was given during all of the strength exercises, and the patients were instructed to continue each set until failure/fatigue. The patients were instructed not to perform additional training during the 6-wk programme.

Statistical analysis

Descriptive statistics were utilised for baseline characteristics. We used Student's *t* test for normally distributed data, the Mann Whitney *U* test for non-normally distributed data and the χ^2 test or Fisher's exact test for categorical data to evaluate differences between patients and dropouts over the 6-wk programme. We used the paired *t* test and Wilcoxon's test to examine changes from baseline to 6 wk, whereas Pearson's product moment or Spearman's rho was used for correlation analyses of normally and non-normally distributed data, respectively. Additionally, intention-to-treat analysis was performed, including dropouts with baseline data. The data are presented as mean ± SD when normally distributed and are otherwise presented as medians (25%-75% quartiles) or as numbers with percentages. All of the data analyses were conducted using SPSS, version 19.0. The level of significance was set at *P* less than 0.05.

RESULTS

Eight of the 39 patients included in this study did not complete the 6-wk programme for the following reasons: back pain (n = 2, already present before study inclusion); second surgeries (n = 2); withdrawal of consent (n = 2); and death (n = 2). Both patients who underwent

Table 2 Changes in function, knee-extension strength, and weight loads within six week of rehabilitation (n = 31)

	Baseline	6 wk	Percentage change	*P* value
New mobility score (0-9)	3.7 ± 1.1	5.9 ± 1.6	59	< 0.001
Barthel (0-20)	18 (17-20)	20 (18-20)	11	< 0.001
Balance, tandem test (0-30)	30 (22-30)	30 (29-30)	0	< 0.001
Timed up and go test, seconds	20.2 ± 6.0	13.9 ± 3.2	-31	< 0.001
Ten-meter fast speed walk, m/s	0.74 ± 0.19	0.99 ± 0.2	34	< 0.001
Six-min walk, meters	200.6 ± 79.5	322.8 ± 68.5	61	< 0.001
Short-form 36, physical component summary	33.8 ± 9	37.1 ± 8	10	0.035
Short-form 36, mental component summary	45.5 ± 11.1	46.4 ± 9.6	2	0.639
Fractured knee-extension strength, Nm/kg	0.49 ± 0.16	0.82 ± 0.32	67	< 0.001
Non-fractured knee-extension strength, Nm/kg	0.82 ± 0.28	0.99 ± 0.34	21	< 0.001
Weight loads in kilograms (kg), fractured knee-extension:	First session	Last session		
15 RM sessions, *n*: 34	3.3 ± 1.5	5 ± 1.7	52	< 0.001
12 RM sessions, *n*: 32	5.3 ± 1.9	6.6 ± 2.3	25	< 0.001
10 RM sessions, *n*: 31	6.8 ± 2.4	7.7 ± 2.6	13	< 0.001
Weight loads (kg), bilateral leg press:				
15 RM training sessions	50.3 ± 13.4	90.8 ± 40.0	81	< 0.001
12 RM training sessions	91.2 ± 38.8	108.9 ± 47.7	19	< 0.001
10 RM training sessions	108.9 ± 47.7	121.9 ± 54.0	12	< 0.001

Data are presented as mean ± SD, as medians (25%-75% quartiles) or as percentages. RM: Repetition maximum.

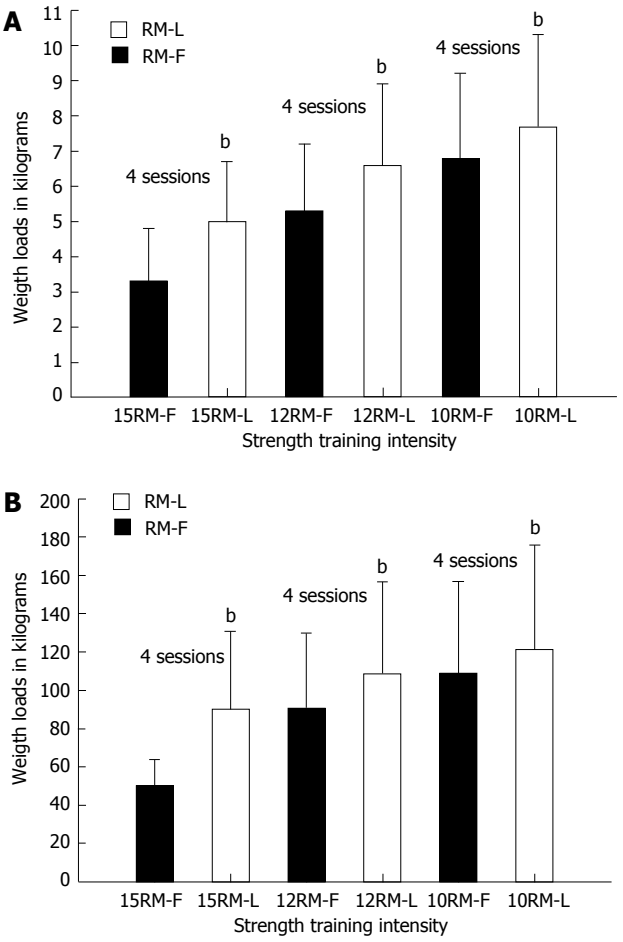

Figure 2 Feasibility of the programme. A: Absolute weight load over 12 fractured knee-extension strength-training sessions; B: Absolute weight load over 12 bilateral leg press strength-training sessions. $^{b}P < 0.001$ *vs* RM-F. RM: Repetition maximum; F: First session; L: Last session.

a second operation exhibited dislocated intracapsular fractures (classified as Garden 3 and 4, respectively). One of these patients did not start the program due to luxation of a hemi-arthroplasty in her own home, whereas the other patient, who underwent surgery with hip pins, participated in three training sessions. Only three out of the eight dropout patients commenced the training programme after baseline testing, of whom one underwent a second surgery (hip pins), one died within the first 2 wk, and one withdrew consent within 4 wk of beginning training due to an acute illness of the spouse. However, those who did not start (n = 5) or complete the training programme exhibited similar demographic and baseline data, compared with the 31 patients who completed the strength-training programme (Table 1), and none of the patients who dropped out cited reasons specific to the programme itself.

Feasibility of the programme

Weight loads for the 15, 12 and 10 RM strength training for fractured limb knee extension (Figure 2A) and bilateral leg press (Figure 2B) training increased progressively ($P < 0.001$) from 12% to 81% (Table 2). At the same time, hip fracture-related pain was reduced (Figure 3 A-B). Adherence to the programme was noteworthy, with 95% of possible sessions completed (352 out of 372 possible).

Of some concern, 10 patients reported knee pain as a minor restricting factor in the last 10 RM session of the fractured limb in the knee extension strength training. Nonetheless, these 10 patients exhibited similar improvements in all strength and functional performances ($P > 0.1$) and walked a greater distance ($P = 0.04$) in the 6MWT at follow-up compared with the 21 reporting no knee-pain. The number of patients who expressed knee pain as a minor restricting factor was unchanged (n = 4) during the first and last leg press training session.

Hip pain

Regarding hip pain, only six out of the 39 patients (15%) experienced more than light pain (VRS > 1) in the fractured hip during the baseline knee-extension strength test, but the performances of these patients did not differ from those reporting light or no pain ($P = 0.9$). Eight patients reported more than light hip pain during the first 15-RM strength-training session (Figure 3C), but their performances did not differ from those reporting none (n = 18) to light pain (n = 6). Hip fracture-related pain was in general very rare in the subsequent strength-training and testing sessions and appeared unrelated to performance (Figure 3D). In contrast, hip fracture-related pain was present in 26% of the TUG, 41% of the 10mWT and 63% of the 6MWT performances at baseline testing

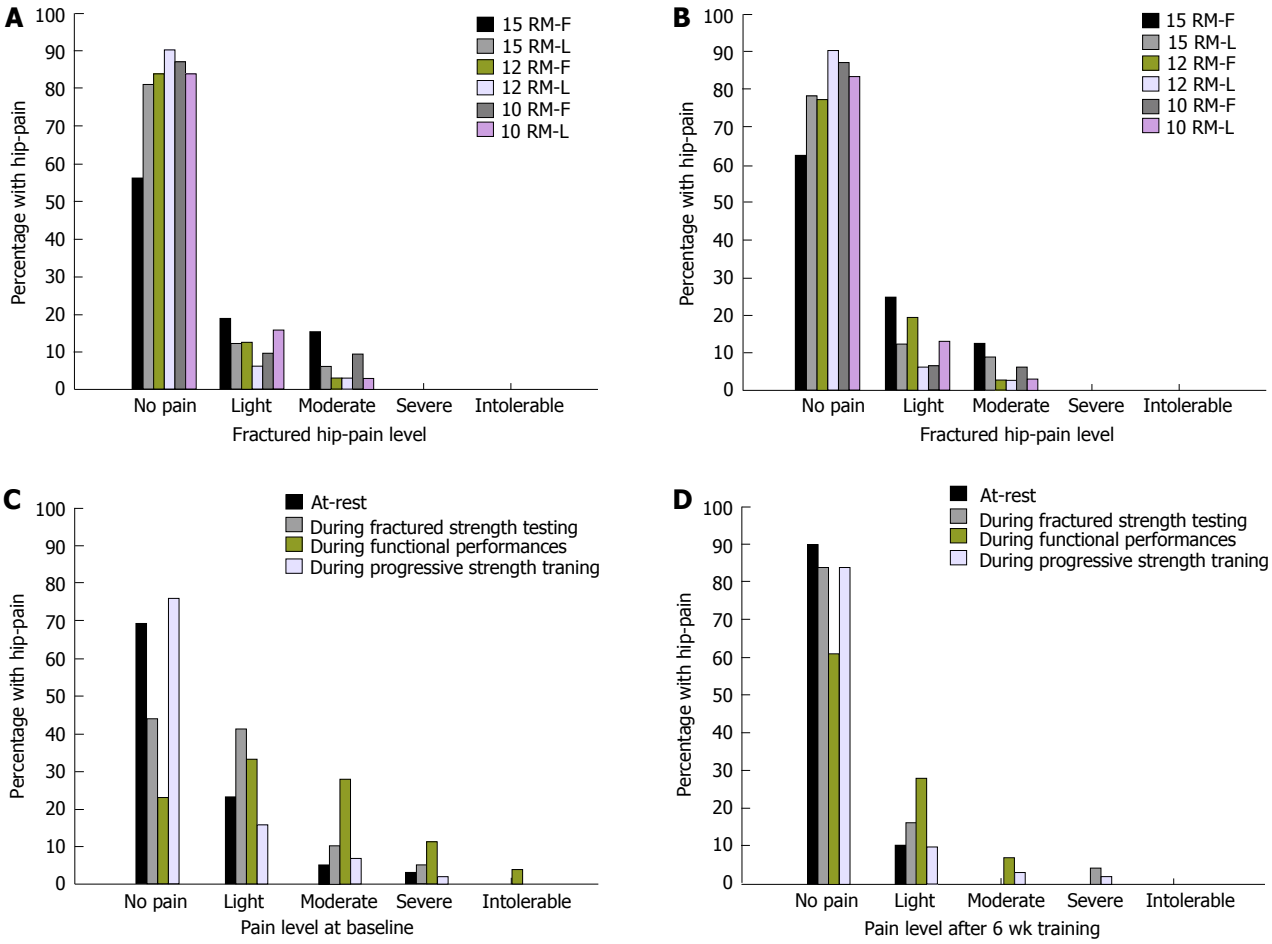

Figure 3 Hip pain. A: Hip pain over 12 fractured knee-extension strength-training sessions; B: Hip pain over 12 bilateral leg press sessions; C: Hip pain at rest and at the time of baseline functional testing or at the first strength-training session; D: Hip pain at rest and at the last testing or training session. RM: Repetition maximum; F: First session; L: Last session.

(Figure 3C). No significant influence was observed for the TUG or fast speed walking tests ($P > 0.1$), whereas patients reporting more than light hip fracture-related pain during the baseline 6MWT actually walked a significantly shorter distance of 174 m, compared with 233 m for those with less pain ($P = 0.02$), and very few reported more than light pain at the 6-wk follow-up testing (Figure 3D).

Follow-up

The patients who completed the 6-wk programme exhibited significant improvements ($P < 0.001$) in the objective walk measurements, ranging from -31% for the TUG to 61% for the 6MWT (Table 2, Figure 4A). Twenty-six of the 31 patients (84%) exhibited improvements of more than 50 m (range 60-278 m) for the 6MWT, while 81% improved by more than 0.1 m/s for the 10mWT. The maximal isometric knee-extension strength improved ($P < 0.001$) in both the fractured and non-fractured limbs, by 67% and 21%, respectively. The strength deficit in the fractured limb decreased after rehabilitation, from an average of 40% at baseline to 17% at the study's conclusion, compared with the non-fractured limb. In addition, the Barthel-20 and the NMS improved ($P < 0.001$) by 11% and 59%, respectively, whereas the SF-36P improved by 10% (Table 2, Figure 4A). Further analysis of the correlations among all of the different outcome variables after the 6-wk programme revealed that the maximal isometric fractured limb knee-extension strength was significantly correlated with all of the variables (except for the SF-36M) and was superior to that of the non-fractured limb (Figure 4B).

A conservative intention-to-treat analysis for all 39 patients, including baseline data carried forward for the eight dropouts, demonstrated similar 6-wk functional improvements, compared with those patients who completed the programme (Figure 4A).

DISCUSSION

To our knowledge, this was the first physiotherapy programme including progressive strength training for community-dwelling older patients that commenced within a few wk after hip fracture surgery in an outpatient geriatric health centre. We determined that 6 wk of lower limb strength training in general seems feasible (weight loads increased, and only three patients (9%) who started the programme were not able to complete it), and we

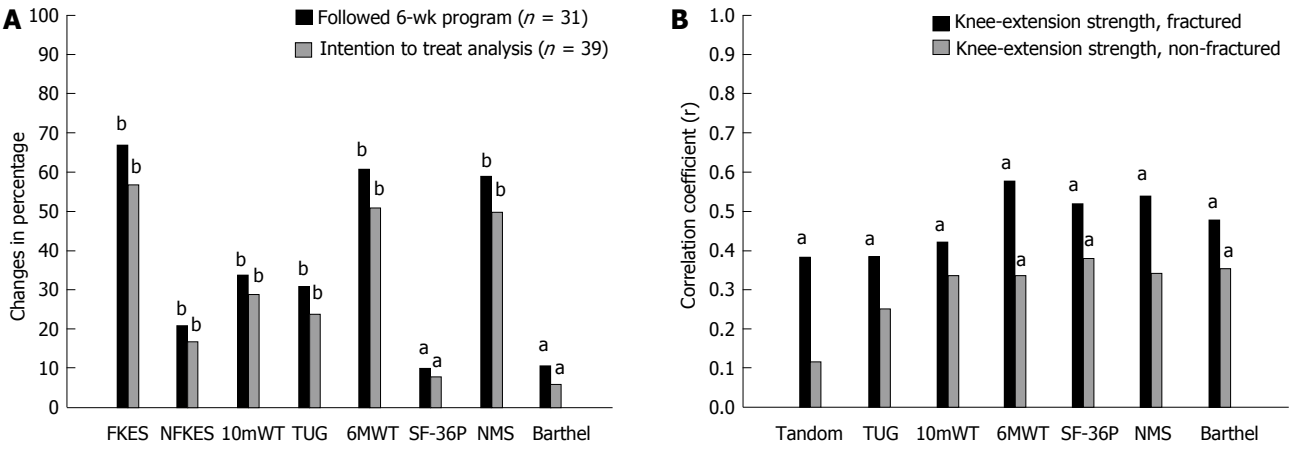

Figure 4 Follow up. A: Improvements in function and knee-extension strength after 6 wk of training, $^{b}P < 0.001$ *vs* Intention to treat analysis ($n = 39$); B: Correlations between knee-extension strength and function after 6 wk of training, $^{a}P < 0.05$ *vs* Knee-extension strength, non-fractured. FKES: Fractured knee extension strength; NFKES: Non-fractured knee extension strength; 10mWT: 10-m walk test; 6MWT: 6-min walk test; SF-36P: Short form-36 physical; NMS: New mobility score.

observed large improvements in objective and patient-reported outcome measurements, including a conservative intention-to-treat-analysis. Systematic registration of hip fracture-related pain revealed reduced pain levels during strength training, indicating that most of the patients could tolerate the progressive strength-training programme when commenced within 2-3 wk after hip fracture surgery, without hip pain interfering.

Nonetheless, an unexpected and increasing number of patients reported knee pain as a minor restricting factor during the fractured knee-extension strength training. Importantly, no dropouts and improvements similar to those not experiencing this problem were observed. Additionally, knee-extension strength training is recommended nationally for subjects with mild knee osteoarthritis in the study country. In addition, clinicians are provided with the details of specific weight loads used from the start to the end of the 15- to 10-RM sessions for fractured limb knee-extension and bilateral leg press training.

Weight load

The mean absolute weight load increased by ⩾ 52%, 19% and 12% within the 15, 12 and 10 RM knee-extension and leg press sessions, respectively, with an accompanying decrease in hip fracture-related pain. These increases emphasise the importance of adjusting weight loads on a set-to-set basis, as reported in previous studies of patients after knee arthroplasty[37], for the strength training to be progressive, compared to re-evaluation every 2-wk[3] or over a longer interval[15,16], using a one-RM estimation for the training.

Hip pain

Hip fracture-related pain is common and seems to compromise functioning in the short and long terms after hip fracture surgery[31,32,39,40]. Critics might therefore argue that it is not possible to implement our strength programme due to pain problems. We found that up to 25% of patients experienced moderate to severe hip pain during the first 15-RM knee-extension training sessions, but the percentage dropped to only 6% reporting moderate pain at the last 15-RM session and to 0% at the last 10-RM session after 6 wk. Similarly, only 4% of patients reported moderate hip pain as the highest score at the last leg press session. To complete the "pain" picture, up to 63% (6MWT) of patients experienced moderate to intolerable pain during the objective outcome measurements at baseline testing. Nonetheless, hip pain "only" influenced the baseline 6MWT performances and did not compromise performance after 6 wk of training. Thus, it seems possible to increase weight loads progressively; patients might experience a decrease in hip pain within an early 6-wk strength-training programme

Restricting factors

Positively, the pre-defined measurement of hip fracture-related pain was of minor influence, but we did find that a number of patients reported knee pain as a minor restricting factor in their fractured knee-extension strength training as intensity increased, which was likely related to patella femoral osteoarthritis. Although no dropouts and similar improvements were observed for these patients, these reports of knee pain should be noted. Unfortunately, we did not monitor whether these patients reduced their pain medications over the 6-wk programme, nor did we assess information about former or present knee problems, *e.g.*, knee osteoarthritis, which could potentially have explained these changes. We therefore recommend the leg press as a more appropriate exercise for patients who report knee pain, as fewer patients reported pain during this exercise, compared with the knee-extension exercise.

Objective outcome measures

The maximal isometric knee-extension strength of the fractured limb increased by a mean of 67%, compared with 21% for the non-fractured limb, but a mean frac-

tured strength deficit of 17% persisted at the 6-wk follow-up. It is possible that initiating a strength-training programme even earlier could have reduced this deficit further, which should be examined in the future. Nonetheless, these results were better than the previously reported leg extensor power deficit of 26% after another early 6-wk strength programme that, in addition, required standard physical therapy on all week days[3]. Furthermore, improvements in our study were much larger than those reported (11%) for fractured knee-extension torque in older patients with hip fractures following a late (mean of 1587 ± 736 d after fracture) 12-wk intensive strength-power programme[41]. In the present study, although not eliminated, the fractured limb strength deficit was reduced by 23% and reached the non-fractured baseline level. Thus, if fractured single-limb leg press training had been chosen, instead of bilateral training, this difference might have been even further diminished. This relationship should be given high priority, as the importance of reducing asymmetric strength deficits after hip fracture is further emphasised; the fractured knee-extension strength was correlated with all of the functional assessments at the follow-up testing and was superior to that of the non-fractured limb. Similar associations have been reported at earlier time points after hip fracture surgery[2].

Performance in the TUG, the 10mWT and the 6MWT improved by a mean of 31%-61%, whereas no improvement was observed for the median tandem balance values. The latter results were probably related to a ceiling effect already present at baseline, which indicates that the tandem test is probably not suitable for measuring progress in balance within this patient group.

Natural recovery and/or less hip pain during follow-up testing probably should be credited to some of the large improvements observed in our study, particularly with regard to knee-extension strength and the 6MWT. Moreover, our patient group walked a mean of 323 m, compared with a mean of 297 m in a Norwegian study that examined patients after ceasing standard rehabilitation and after an additional 3 mo of rehabilitation, including strength training twice weekly plus home training once weekly[15]. In addition, 84% of our patients improved by more than 50 m, which has been considered a meaningful change for the 6MWT in older adults[42] and in patients with hip fractures (> 54 m)[43].

Different opinions exist regarding what should be considered a meaningful improvement in gait speed after hip fracture, ranging from 0.1[44] to 0.26 m/s for a substantial meaningful improvement[45]. We have reported improved gait speed performances, although obtained at the same[3] or at a longer interval post-surgery compared with other studies[11,15], and we have demonstrated an average improvement of 0.25 m/s. More than 80% of the patients improved by more than 0.1 m/s. Nevertheless, the patients did not reach the maximum gait speed level considered "normal" for older people in their 70 s[46]. The improvements in the TUG exceeded the standard error of measurement (2.2 s), but only two patients took less than 10 s at follow-up - a time considered normal for older individuals[33].

Standardised walking aid

The influence of different walking aids on functional performance has been reported for walking velocity[47], the 2-min walk test[48] and for the TUG[34,49]. Thus, the effect of rehabilitation could be overestimated if the same walking aid were not used during pre- and post-rehabilitation testing[34]. All patients with hip fractures use some type of walking aid in the early period after the fracture[50,51], and they commonly change to a less supportive aid, or they eliminate walking aids altogether after rehabilitation[43,50].

Thus, functional improvements beyond natural recovery might more truly be related to the rehabilitation programme in the present study, using a standardised functional walking aid pre- and post-testing.

Patient-reported outcome measurements

Large average improvements were observed for the NMS (59%), compared with the Barthel-20 and the SF-36. However, only three patients reached their pre-fracture NMS functional levels. The ceiling effect seen for the Barthel-20 at baseline (median of 18, IQR 17-20) was even more obvious in the follow-up testing, as reported in two earlier studies[3,15]. Thus, as for the tandem balance test, the Barthel-20 index cannot be recommended for measuring progress in similar groups of patients with hip fractures.

Although significant and correlated with measures of knee-extension strength for both limbs upon follow-up, only small improvements (10%) in self-rated health (SF-36P) were reported, whereas no improvement was observed for the SF-36M. These results might be related to the patients, to some extent, basing their self-rated health on their daily lives and function pre-fracture - a level not attained after the 6-wk programme. Similarly, a "later" 3-mo hip fracture intervention programme reported no effect on self-rated health measurements[15].

Study weaknesses and strengths

Functional improvements should be considered in light of the non-randomised design, the level of hip fracture-related pain upon baseline testing and the natural recovery over this early time period after hip fracture surgery. Thus, although we eliminated the potential influence of walking aids on the observed functional improvements, we do not know the exact effect of the progressive strength-training programme. Additionally, the included patients exhibited high pre-fracture functional and cognitive levels, which thus restrict our findings to patients with these characteristics. This limitation is, however, a common problem for research in this patient group, and our expectation is that patients with lower levels of functioning and cognition would also benefit from the programme, which was seen when patients with dementia were provided with an appropriate rehabilitation

programme[52]. Another limitation was the consumption of pain medication before testing and training, as well as former knee problems, which were not monitored or recorded.

One strength of the study was the systematic recording of hip fracture-related pain, in addition to other factors that restricted the progressive strength training. Another strength regarding the large improvements seen for both objective and subjective measurements was the blinding of the physiotherapists who conducted all of the baseline and follow-up testing to the progress and participation in the training programme. Finally, although this trial was not randomised, we included a conservative intention-to-treat analysis, which also demonstrated significant improvements for all of the outcome measurements.

In conclusion, this study has demonstrated that progressive strength training, commenced early after hip fracture surgery in community-dwelling older patients, seems feasible; the weight loads increased throughout the study, and hip fracture-related pain during training decreased. Furthermore, the fractured limb strength deficit was reduced, and functional performances improved. That a growing number of patients reported knee pain, although such pain did not influence training or performance, should be considered in clinical practice and in future strength-training studies. Studies focused on the full recovery of function and strength should be conducted using a randomised, controlled design.

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COMMENTS

Background

Patients with hip fracture experience more than 50% knee-extension strength deficits in the fractured limb, compared with the non-fractured limb, shortly after surgery. To the authors' knowledge, no study has succeeded in eliminating this strength deficit with a rehabilitation programme.

Research frontiers

Early intervention after surgery is considered crucial for patients with hip fractures potentially to regain their pre-fracture functional levels.

Innovations and breakthroughs

The major difference of this strength training study, compared with previous studies, was the progressive "on a set-to-set" approach. That is, weight loads were adjusted in the next set in the same session if the patient performed more than the planned number of repetitions, compared with adjustments on a weekly or longer-interval basis.

Applications

The strength-training programme seems feasible, as weight loads increased and hip fracture-related pain decreased. The effects of the programme require confirmation in a randomised, controlled trial.

Terminology

The feasibility of a progressive strength-training programme: If the absolute strength training loads increased progressively and if, at the same time, hip fracture-related pain during training remained the same or if it decreased over time. Progressiveness of the strength-training programme: The reduction in the number of repetitions from 15 to 12 to 10 during the 6-wk strength-training programme is followed by a corresponding increase in the intensity from 15 to 12 to 10 repetitions maximum.

Peer review

The aim of authors is to investigate the feasibility of a 6-wk progressive strength-training programme commenced shortly after hip fracture.

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ORIGINAL ARTICLE

Collecting a comprehensive evidence base to monitor fracture rehabilitation: A case study

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Abstract

AIM: To determine the feasibility and potential role of combining radiostereometric analysis (RSA), gait analysis and activity monitoring in the follow-up of fracture patients.

METHODS: Two patients with similar 41B3 tibial plateau fractures were treated by open reduction internal fixation augmented with impaction bone grafting and were instructed to partial weight bear to 10 kg for the first six postoperative weeks. Fracture reduction and fixation were assessed by postoperative computer tomographic (CT) scanning. Both patients had tantalum markers inserted intra-operatively to monitor their fracture stability during healing using RSA and differentially loaded RSA (DLRSA) at 6 and 12 wk postoperatively. Gait analyses were performed at 1, 2, 6, and 12 wk postoperatively. Activity monitors were worn for 4 wk between the 2 and 6 wk appointments. In addition to gait analysis, knee function was assessed using the patient reported Lysholm scores, and doctor reported knee range of motion and stability, at 6 and 12 wk postoperatively.

RESULTS: There were no complications. CT demonstrated that both fractures were reduced anatomically. Gait analysis indicated that Patient 1 bore weight to 60% of body weight at 2 wk postoperative and 100% at 6 wk. Patient 2 bore weight at 10% of body weight to 6 wk and had very low joint contact forces to that time. At 12 wk however, there was no difference between the gait patterns in the two patients. Patient 1 increased activities of moderate-vigorous intensity from 20 to 60 min/d between 2 and 6 postoperative weeks, whereas Patient 2 remained more stable at 20-30 min/d. The Lysholm scores were similar for both patients and did not improve between 6 and 12 wk postoperatively. DLRSA examination at 12 wk showed that both patients were comfortable to weight bear to 80 kg and under this weight the fractures displaced less than 0.4 mm. RSA measurements demonstrated over time fracture migrations of less than 2 mm in both cases. However, Patient 2, who followed the postoperative weight bearing instructions most closely, displaced less (0.3 mm *vs* 1.6 mm).

CONCLUSION: This study demonstrates the potential of using a combination of RSA, gait analysis and activity monitoring to obtain a comprehensive evidence base for postoperative weight bearing schedules during fracture healing.

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Key words: Radiostereometric analysis; Gait analysis; Activity monitoring; Rehabilitation protocols; Lower

limb trauma

Core tip: The extent to which patients follow rehabilitation instructions, likely affects not only the early recovery, but also the long-term outcomes that are dependent on maintenance of fracture reduction. We have demonstrated the feasibility of using radiostereometric analysis, gait analysis and activity monitoring to assess early fracture healing. Future larger clinical studies using this novel combination of assessment tools may provide an evidence base for particular rehabilitation schedules following different fracture types and fixation techniques.

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INTRODUCTION

Outcomes of tibial plateau fractures (TPF) have been correlated with the degree of initial articular fragment reduction and the maintenance of reduction[1-3]. In the laboratory, articular steps of greater than 1.5 mm of the tibial condyles were shown to cause significantly increased pressure on the surrounding cartilage[4]. In clinical practice, reduction of the articular surface of the tibia with articular steps of less than 2 mm have been labeled as "anatomical"[5,6], while articular steps of more than 3 mm have been associated with worse outcomes and identified as a risk factor for post-traumatic knee osteoarthritis[2,3]. The problem with correlating outcomes of TPF, and for that matter of any articular fracture, with small articular steps measured on standard radiographs, is that the method is known to have a poor accuracy of ± 5 mm[7-10]. This has limited the previous reported results and outcome correlations considerably. In contrast to standard radiographs, radiostereometric analysis (RSA) has been shown to be a highly accurate and precise method to measure fracture displacement in clinical practice[11]. When applied to small TPF fragments, the method has been shown to have an accuracy of ± 0.037 mm and a precision of ± 0.016 mm[12]. The limitations of RSA are that it requires expensive equipment and software, is time consuming, requires experienced personnel and can only be used in prospective studies. However, imaging techniques with such a degree of accuracy are required to establish any objective correlations between the quality of reduction and maintenance of reduction and outcomes in these fractures.

To date, there is no consensus on how TPF patients should be rehabilitated after open reduction and internal fixation (ORIF), with current recommendations varying from non-weight bearing for up to 12 wk[13] to partial weight bearing in all cases[5,6]. It is reasonable to assume that most surgeons would recommend various postoperative weight bearing prescriptions for their patients, depending on the type of fracture and the "quality" of fixation achieved. Such prescriptions are largely empirical. In addition, it is well established that most patients cannot observe, or disregard, the postoperative weight bearing instructions set by their surgeon[14-16].

To our knowledge, we have performed the only study to investigate the stability of TPF in patients allowed to weight bear in the first six postoperative weeks[17]. We used RSA and differentially loaded RSA (DLRSA) performed under weight bearing load to assess fracture fragment stability[17]. Patients were recommended a postoperative partial weight-bearing regimen of 20 kg for the first six postoperative weeks, followed by progressive weight bearing as tolerated. However, during the DLRSA examinations performed under weight-bearing as tolerated at two and six postoperative weeks, two out of seven patients exceeded 20 kg at 2 wk and three were full weight bearing at 6 wk. Despite all fracture movements under load being reported to be elastic (the final position of the fracture returned to the preload position), the fractures were found to have migrated over time up to 2 mm in the cranio-caudal and medio-lateral directions[17]. These results suggest that during the first six postoperative weeks, the patients either loaded more than their body weight through their injured knee and/or the direction of the joint reaction forces during ambulation differed from that during standing for the DLRSA examinations. Monitoring patients' activity and investigating their joint reaction force through gait analysis combined with musculoskeletal modeling, may provide a better understanding of fracture migration during different rehabilitation protocols. In addition, combining the results provided by monitoring fracture stability during healing with an accurate technique, namely RSA, with objective snapshots of patient activity level and objective biomechanical data from gait analysis has the potential to provide an evidence base for particular rehabilitation schedules to be recommended following different fractures types and fixation techniques.

The aim of this study was therefore to investigate the feasibility of monitoring the healing of TPF patients with RSA, gait analysis and physical activity monitoring. Using these combined assessment tools in larger clinical studies may provide more comprehensive and objective data to confirm the appropriateness of current postoperative weight bearing regimes in lower limb articular fractures.

MATERIALS AND METHODS

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved by the Royal Adelaide Hospital Research Ethics Committee (Protocol Numbers 060621 and 080107). All patients provided informed written consent.

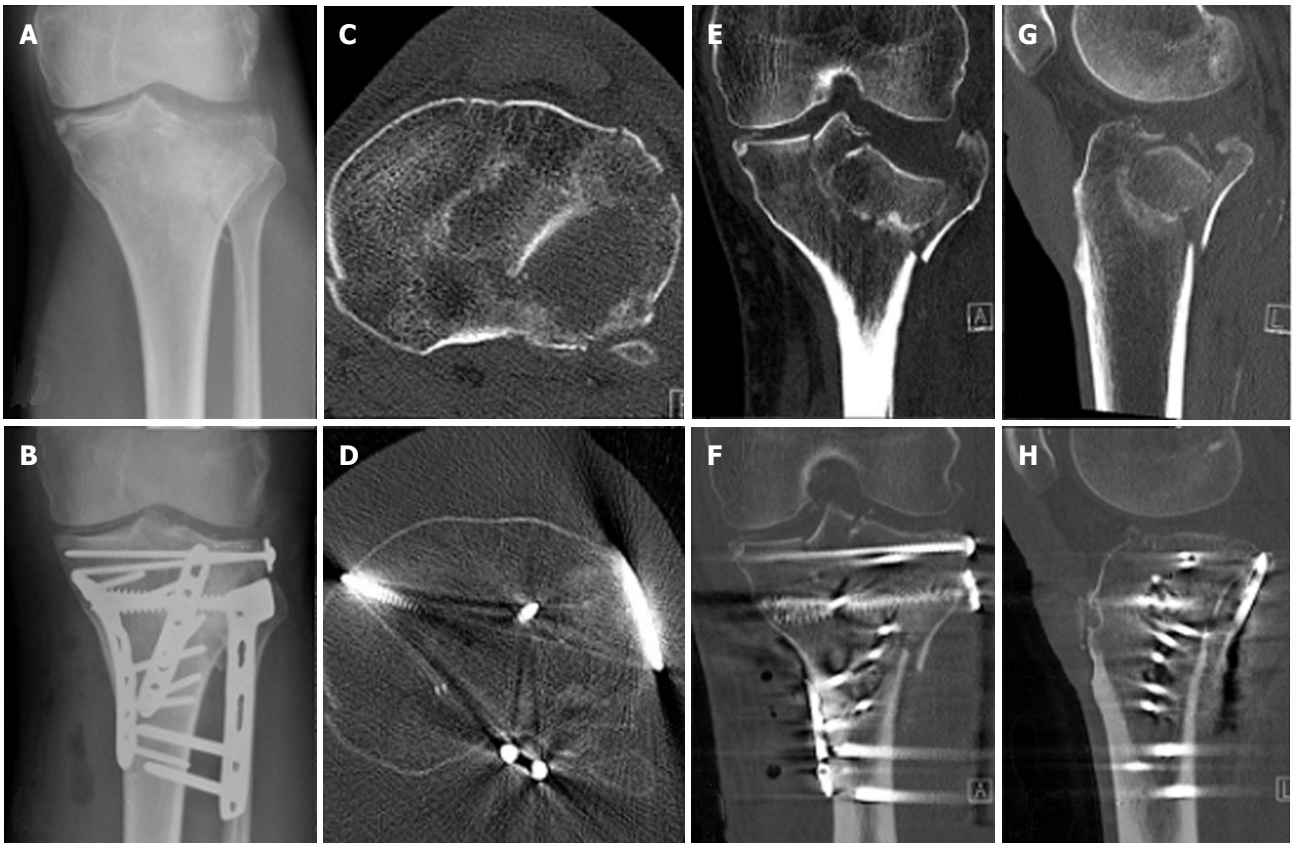

Figure 1 Radiographic imaging of the fracture of Patient 1 illustrating the initial displacement as well as the operative reduction and fixation achieved. A: Preoperative X-ray; B: Post operative X-ray; C: Preoperative transverse computed tomography (CT); D: Post operative transverse CT; E: Preoperative coronal CT; F: Post operative coronal CT; G: Preoperative sagittal CT; H: Post operative sagittal CT.

Two consecutive patients treated in our institution for a similar pattern 41B3 fracture, involving a split component of the posterior medial tibial condyle and a split depression of the lateral tibial condyle, who agreed to have their fracture healing monitored with RSA, activity monitoring and gait analysis were included in this study (Figures 1 and 2). Both patients were male of a similar age (56 and 60 years respectively) and both sustained their TPF as an isolated injury in a low speed motorbike accident. Both patients lived with supportive families. At the time of the accident, Patient 1 was on a long-standing disability support pension for a traumatic amputation of two fingers, while Patient 2 was self-employed as an electrician. Each fracture had multiple split and depressed fragments with the maximum depression on preoperative CT scans measured 19 and 22 mm respectively. Both patients had ORIF by the same surgeon within 24 h of their injury through a combined anterolateral and posteromedial approach to allow buttressing of the posteromedial, posterolateral and anterolateral cortical components of the fracture and to contain the lateral tibial condyle cancellous bone defect to allow impaction bone grafting. The internal fixation was completed by impaction bone grafting and a raft of subchondral screws (Figures 1 and 2). At the time of surgery, tantalum beads (1.0 mm, RSA Biomedical, Umea, Sweden) were inserted in the largest depressed fracture fragment as well as in the unfractured tibial metaphysis, to allow for RSA and DLRSA. Postoperatively, the patients were instructed and educated to partial weight bear to 10 kg on the injured limb for the first six postoperative weeks and to progress to full weight bearing as tolerated afterwards. Unrestricted knee range of motion was encouraged immediately after surgery.

In the first postoperative days, the patients had standard radiographs and a fine cut computer tomographic scan to assess the fracture reduction. An RSA radiographic examination was taken as a baseline for measurement of fracture displacement. Following radiographic imaging, each patient had gait analysis.

The patients were reviewed at 2, 6 and 12 postoperative weeks. Clinical examination, plain radiographs, RSA radiographs and gait analysis were repeated at each of these times. The patients were given a physical activity monitor to wear between their 2 and 6 wk outpatient appointments. Lysholm patient reported outcomes were completed at the 6 and 12 wk outpatient appointments. Knee range of motion and stability were recorded during the 6 and 12 wk outpatient appointments.

RSA and DLRSA

Baseline RSA radiographs were taken in the supine position, centering the patient's knee over the RSA calibration

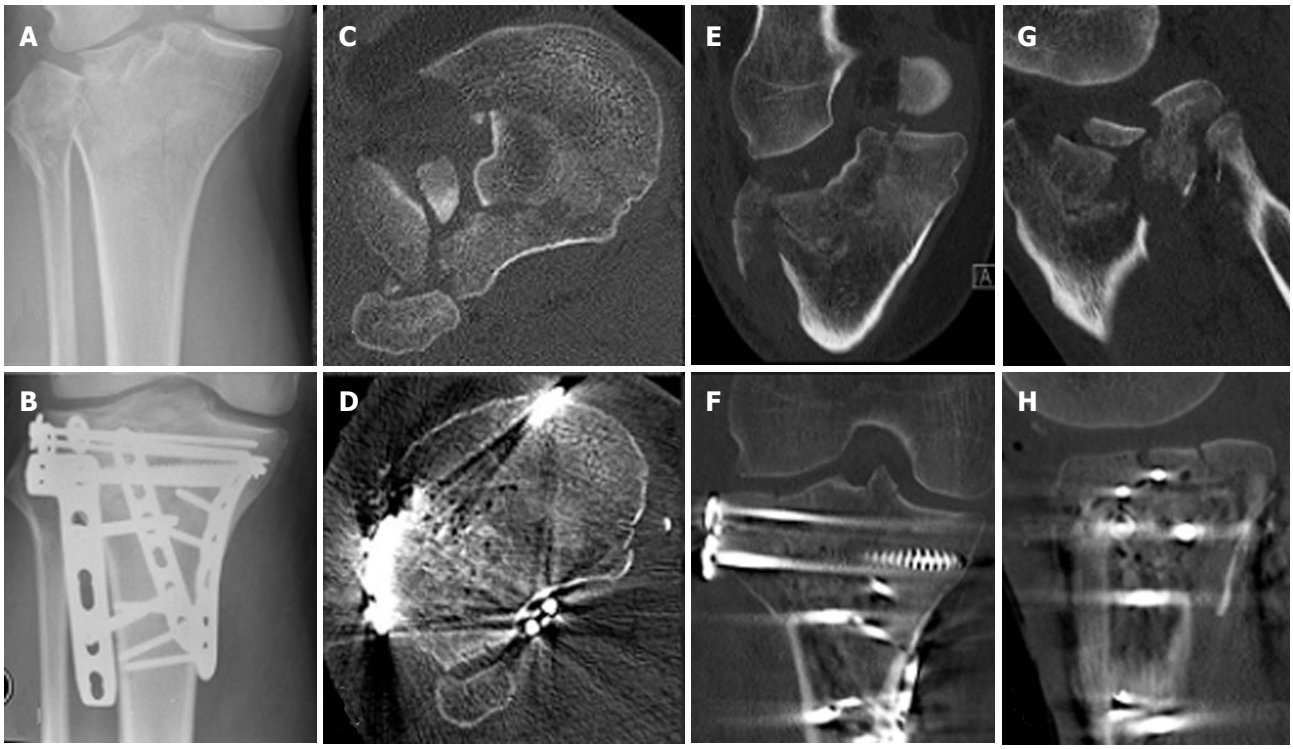

Figure 2 Radiographic imaging of the fracture of Patient 2 illustrating the initial displacement as well as the operative reduction and fixation achieved. A: Preoperative X-ray; B: Post operative X-ray; C: Preoperative transverse computed tomography (CT); D: Post operative transverse CT; E: Preoperative coronal CT; F: Post operative coronal CT; G: Preoperative sagittal CT; H: Post operative sagittal CT.

cage (Cage No. 43, RSA Biomedical, Umea, Sweden). Radiographs were analyzed using specialized software (UmRSA v6.0, RSA Biomedical, Umea, Sweden). The mean error of rigid body fitting accepted was less than 0.35 mm.

DLRSA examinations were performed at 6 and 12 wk with each patient standing on a custom built platform that allows centering of the patient's knee in front of the RSA calibration cage, as described previously[17]. During the RSA examination, a digital foot scale was used to measure the load applied whilst weight bearing. RSA radiographs were taken with the foot placed on the scale but applying 2-5 kg (pre-load), followed by radiographs with the patient applying a maximum weight bearing load on the scales, as tolerated without pain (loaded). A final pair of radiographs was taken while applying 2-5 kg load (post-load). Parallel bars were used by patients as support during examination to allow a "controlled static" weight bearing. Inducible displacement of fracture fragments was calculated as the difference in position of the fracture fragment relative to the proximal tibia using the pre-load radiographs as the reference examination. Two dimensional (2D) migration was calculated as the vectorial sum of proximal-distal and medio-lateral migrations. The subsequent apparent stiffness was calculated as the force (applied maximum tolerated load) divided by the displacement (2D migration).

Gait analysis

The gait analysis was undertaken with the patients walking at their self-selected pace along a 10-m walkway. A minimum of five successful trials were recorded at all assessments. Patients were allowed rest periods between trials, if required. Small reflective markers were attached to the lower limbs and pelvis of the patient[18]. The trajectories of the markers were recorded using a 12-camera Vicon MX-F20 motion capture system (Vicon Inc., Oxford, United Kingdom) at 100 Hz. Ground reaction forces were recorded simultaneously through Vicon Nexus 1.8 (Vicon Inc., Oxford, United Kingdom) with the motion data, using two AMTI (AMTI, Watertown, United States) and two Kistler (Kistler Inc., Switzerland) force platforms at 400 Hz. Data were exported to Visual3D (C-Motion, Inc., United States) where the motion was reconstructed[19] and the knee joint angles and loads (forces and moments) calculated. Joint angles were calculated using the joint coordinate system[20]. Joint loads were computed using inverse dynamics. From Visual 3D, further processing was performed in Matlab (Mathworks, United States). Using a musculoskeletal model[21], the joint reaction forces were calculated. From the gait analysis, the peak vertical ground reaction force, peak vertical knee joint reaction force, the peak knee flexion and extension moments, the peak knee adduction moment and the knee joint range of motion were extracted.

Patient activity monitoring

Each patient was asked to wear a GENEActiv accelerometer on their non-dominant wrist after their discharge from the hospital. These activity monitors are small,

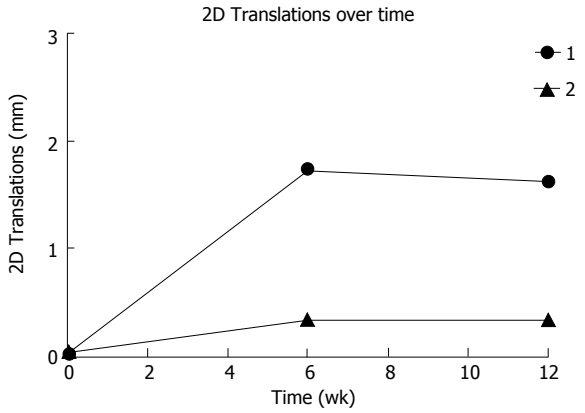

Figure 3 The distal migration of the fracture fragment for each patient over time. 2D: Two dimensional.

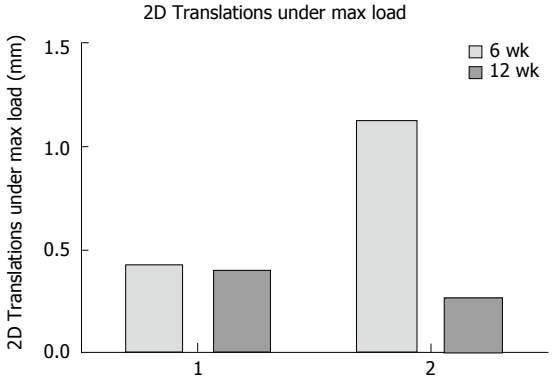

Figure 4 The two dimensional translations under the maximum load applied at each differentially loaded radiostereometric analysis examination for both cases. 2D: Two dimensional.

lightweight, wireless devices that provide a continuous record of activity patterns over extended periods of time. Data obtained were used to quantify the amount of time the patients spent in activity of light and moderate-to-vigorous intensity following their discharge.

The patients were instructed to wear the wrist monitor 24 h a day, including during water-based activities (showering/bathing) and sleeping. The GENEActiv is a triaxial accelerometry-based activity monitor with a dynamic range of +/- 8 g (www.geneactiv.co.uk, Gravity Estimator of Normal Everyday Activity, ActivInsights Ltd, Cambridgeshire, United Kingdom). GENEActiv PC software was used to configure the GENEActivs to collect data at 10 Hz, upload the data and convert the .bin files to 15 s epoch .csv files for data analysis. The sampling frequency of 10 Hz was selected to enable data collection for over one month.

Periods of non-wear were identified using an algorithm that identified minute-by-minute changes of position. No changes of position in a rolling 60-min window were classified as non-wear. Sixty-minute windows of no movement have been used previously to classify non-wear[22]. A minimum of 10-hour wear time during daytime was required for a valid day[22]. The sum and mean of the vector magnitude (VM) of the 15 s epochs were calculated for each valid day. Outcome variables for each valid day were: time in light and moderate-to-vigorous intensity physical activity (classified using published cut-points[23]). Light activity includes activity greater than one and a half times resting metabolic rate and moderate-to-vigorous activity includes activities with an intensity at and above that of a brisk walk. Data analysis was performed using Microsoft Excel 2010.

RESULTS

There were no complications. Both patients had an uneventful recovery with a continuous improvement in their knee symptoms and function. The postoperative CT scan demonstrated that both fractures were reduced anatomically (Figures 1 and 2). No measurable fracture displacement over time was identifiable on plain radiographs in any of the patients. At six weeks Patient 1 reported a Lysholm score of 51, his knee was stable and had a range of motion of 5°-100°. At 12 wk Patient 1 reported a Lysholm score of 48, his knee was stable and had a range of motion of 0°-110°. At 6 wk Patient 2 reported a Lysholm score of 49, his knee was stable and had a range of motion of 10°-90°. At 12 wk Patient 2 reported a Lysholm score of 47, his knee was stable and had a range of motion of 5°-100°.

RSA and DLRSA

RSA measurements demonstrated that the two-dimensional (2D) fracture migration over time was less than 2mm in both cases (Figure 3). There was a difference in size and pattern of fracture migration, with the fracture fragment of Patient 1 migrating almost 1.6 mm compared to 0.3 mm for Patient 2. The majority of the migration occurred within the first six postoperative weeks (Figure 3).

Fracture displacement during DLRSA examinations was elastic, with the post-load examinations demonstrating that that the fracture fragments returned to their pre-load position. During DLRSA examinations, Patients 1 and 2 applied 47 kg and 30 kg respectively, at 6 wk and both applied 80 kg at 12 wk. The 2D translations under the 80 kg loads at 12 wk were both below 0.4 mm (Figure 4). The calculated apparent stiffness value for the fracture construct of Patient 2 at 6 wk (261 N/mm) was lower compared to that of Patient 1 (1064 N/mm) (Figure 5). Conversely, Patient 2 had a higher apparent stiffness at 12 wk than Patient 1 (Figure 5). Both fractures showed increased stiffness over time, consistent with other measures of fracture healing.

Gait analysis

At one week postoperative, Patient 1 had a peak Fz of 0.7 times their total body weight (*bw*). In contrast, Patient 2 loaded to only 0.15 *bw*. Between 1 wk and 12 wk, increases of 0.49 and 1.05 *bw* were observed in the peak Fz for Patients 1 and 2, respectively (Figure 6A). At 1 wk

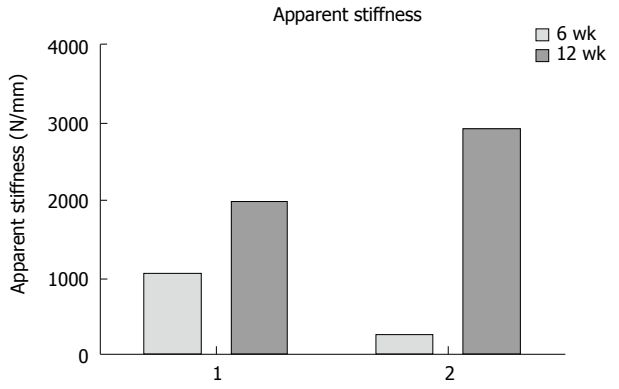

Figure 5 The apparent stiffness of each fracture at 6 and 12 wk calculated from the movement under each applied load.

postoperative, Patient 1 had a peak knee JRFz of 1.11 *bw*, which was comparable to that calculated for Patient 2 of 0.86 *bw*. Between 1 and 12 wk, increases of 1.45 and 2.04 *bw* were observed in the peak JRFz for Patient 1 and 2, respectively (Figure 6B). Besides a peak in the knee ROM at week 2 for Patient 2, no substantial changes were observed in the knee ROM (Figure 6C). Patient 1 showed an increase of both the knee flexion and adduction moment between 1 and 12 wk postoperative, with a magnitude of 0.25 and 0.11 Nm/kg, respectively. No change was observed in the knee extension moment. Patient 2 showed a similar percentage increase in the knee flexion moment to Patient 1, with the peak moment increasing by 0.12 Nm/kg between 1 and 12 wk (Figure 7A). The knee extension moment increased by 0.27 Nm/kg (Figure 7B); however, no change was noted in the knee adduction moment (Figure 7C).

Patient activity monitoring

Patient 1 did not wear the monitor for a period of 10 days in the middle of the investigated period. Between 2 and 6 wk post-surgery, light activity increased by approximately one hour per day in Patient 1 (from 270 min/d to 330 min/d) and stayed fairly constant in Patient 2 (approximately 300 min/d) (Figure 8A). Patient 1 also increased from approximately 20 min/d of moderate-vigorous intensity physical activity at 2 wk post-surgery to approximately 60 min/d of moderate-vigorous intensity physical activity 6 wk post-surgery (Figure 8B). In contrast, Patient 2 maintained fairly stable levels of 20-30 min/d moderate-vigorous intensity physical activity between 2 and 6 wk post-surgery.

DISCUSSION

The influence of rehabilitation instructions and the extent to which patients follow them likely affects not only the early recovery, but also the long-term outcomes that are dependent on maintenance of fracture reduction. This study investigated the feasibility of using a number of postoperative outcome tools to provide a better understanding of the stability of TPF during rehabilitation and healing. The highly accurate technique of RSA was used in conjunction with physical activity monitors, patient assessment forms and specific gait analyses.

This case study of two fracture patients was, to the best of the authors knowledge, the first time that RSA, activity monitors and gait analysis had all been used to monitor fracture healing and functional improvement during the early postoperative period. While the results suggest the feasibility of applying these particular analyses, clearly no conclusion can be drawn from this case study regarding the way patients follow rehabilitation instructions and their long-term outcomes. Larger scale studies using RSA, gait analysis and activity monitoring are required to obtain an evidence base for particular schedules following different fracture types and fixation techniques.

The postoperative rehabilitation of fractures is arguably as important for uncomplicated fracture healing as their surgical management. It is well known that lengthy periods of immobilization can have severe detrimental effects on wellbeing of patients, while over aggressive mobilization can equally lead to severe complications. Such complications have implications not only for the wellbeing of the patient but also on the direct and indirect costs of treatment to the health care providers. Conversely, significant improvements have been made in fracture care over time due partly to more aggressive rehabilitation of patients. Unfortunately, changes in fracture rehabilitation remain empirical and speculative. Such changes are compounded by most patients' inability to follow partial weight bearing instructions[14-16] and, until recently, by the absence of objective tools to assess fracture stability during healing.

Objective biomechanical data and activity monitoring reported in this study are examples of the different compliance of patients when following rehabilitation instructions. The amount of activity patients perform in the first few postoperative weeks can be extremely variable along with the amount of weight bearing. Interestingly in the cases investigated, the non-compliant weight bearing applied by Patient 1 did not lead to excessive displacement of the fracture according to current definitions of anatomical reduction (less than 2 mm of articular step)[5,6]. The results of Patient 1 also suggested that his fracture stabilization was adequate and in these cases weight bearing as tolerated after a TPF may lead to a quicker rehabilitation. Recovery of a gait pattern similar to the uninjured limb was observed as early as 6 wk after surgery for Patient 1 compared to 12 wk for Patient 2. Finally, Patient 2, who did adhere to postoperative weight bearing instructions, displayed larger elastic displacement under load at 6 wk, but did not displace as much over time. Larger scale clinical studies that apply the combination of technologies used in the current investigation may provide more information to suggest which postoperative weight bearing regimes are appropriate for different fracture types and internal fixation techniques. In addition, the accurate measurement of fracture stability, combined with objective activity monitoring and patient outcomes, could assist to better define terms such as "anatomical reduction"

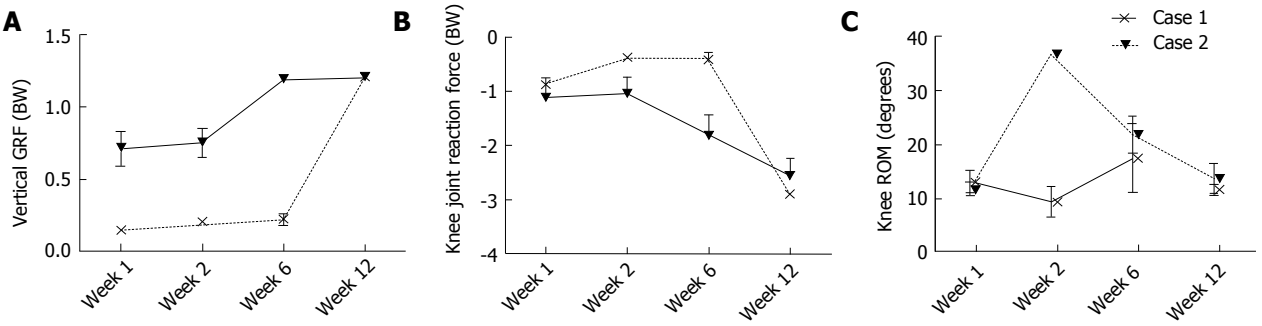

Figure 6 The mean and standard deviation over time. A: Vertical ground reaction force (GRF); B: Peak knee joint reaction force; C: Knee range of motion (ROM).

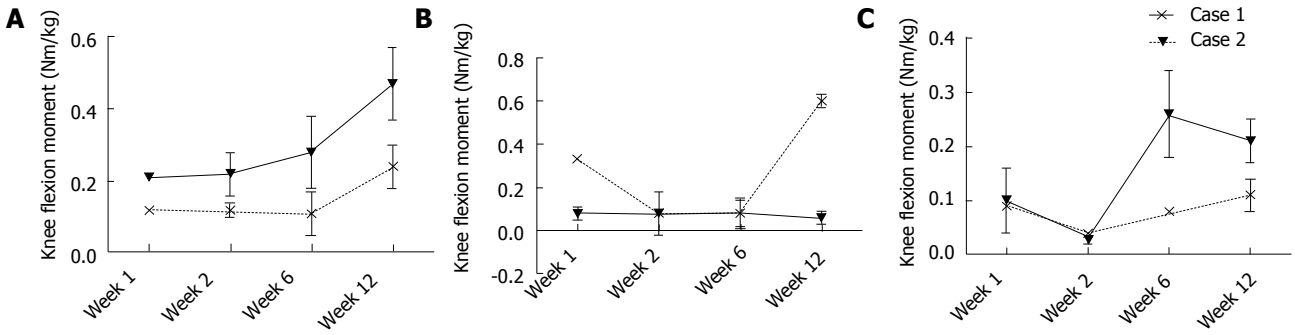

Figure 7 The mean and standard deviation over time. A: Peak knee flexion moment; B: Peak knee extensions moment; C: Peak knee adduction moment.

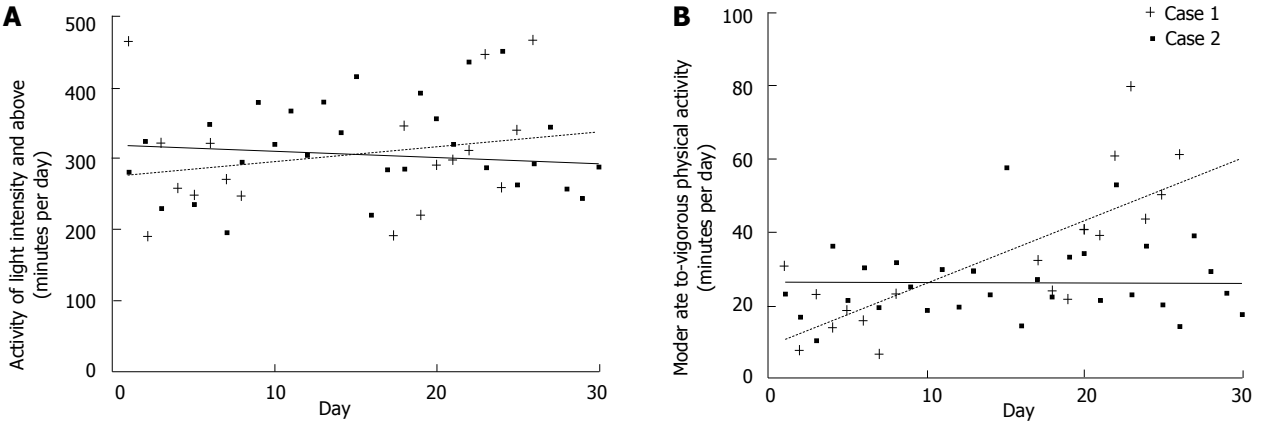

Figure 8 The physical activity of each patient over time. A: Light intensity; B: Moderate-to-vigorous intensity.

and objective correlations between articular fracture displacements and outcomes.

In conclusion, this case study demonstrates the potential of using a combination of RSA, gait analysis and activity monitoring to provide, for the first time, an evidence base for the application of particular rehabilitation schedules following fracture. Such large scale studies are required before rehabilitation protocols can be optimized by objective data.

COMMENTS

Background

There is no consensus on the recommended rehabilitation protocol after lower limb trauma, including tibial plateau fractures. The results of previous studies investigating different weight bearing regimes have been limited due to the lack of relevant assessment tools available to identify clinically significant differences in patient cohorts.

Research frontiers

Recent improvements in monitoring fracture stability with radiostereometric analysis, and monitoring patient movement with specific gait analysis and patient activity monitors may allow novel research to be undertaken.

Innovations and breakthroughs

Authors have demonstrated the feasibility of using radiostereometric analysis, gait analysis and activity monitoring to assess rehabilitation protocols after lower limb trauma.

Applications

Using this combination of assessment methods in larger clinical studies has the potential to provide, for the first time, an evidence base for the application of particular rehabilitation schedules following fracture.

Terminology

RSA: A very accurate measurement method that uses two simultaneous X-rays

to monitor the movement of a fracture fragment over time and under load.

Peer review

This case report presents a good concept of combining three assessment tools to monitor two patients after tibial plateau fracture. Using these methods in larger studies may allow novel improvements to clinical practice.

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ORIGINAL ARTICLE

Experimental and finite element analysis of tibial stress fractures using a rabbit model

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Author contributions: Franklyn M and Field BW designed the research, analysed the results and wrote the paper; Franklyn M conducted the experiments and developed the FE model; Field BW provided expert advice on the experiments and finite element model.
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Abstract

AIM: To determine if rabbit models can be used to quantify the mechanical behaviour involved in tibial stress fracture (TSF) development.

METHODS: Fresh rabbit tibiae were loaded under compression using a specifically-designed test apparatus. Weights were incrementally added up to a load of 30 kg and the mechanical behaviour of the tibia was analysed using tests for buckling, bone strain and hysteresis. Structural mechanics equations were subsequently employed to verify that the results were within the range of values predicted by theory. A finite element (FE) model was developed using cross-sectional computer tomography (CT) images scanned from one of the rabbit bones, and a static load of 6 kg (1.5 times the rabbit's body weight) was applied to represent running. The model was validated using the experimental strain gauge data, then geometric and elemental convergence tests were performed in order to find the minimum number of cross-sectional scans and elements respectively required for convergence. The analysis was then performed using both the model and the experimental results to investigate the mechanical behaviour of the rabbit tibia under compressive load and to examine crack initiation.

RESULTS: The experimental tests showed that under a compressive load of up to 12 kg, the rabbit tibia demonstrates linear behaviour with little hysteresis. Up to 30 kg, the bone does not fail by elastic buckling; however, there are low levels of tensile stress which predominately occur at and adjacent to the anterior border of the tibial midshaft: this suggests that fatigue failure occurs in these regions, since bone under cyclic loading initially fails in tension. The FE model predictions were consistent with both mechanics theory and the strain gauge results. The model was highly sensitive to small changes in the position of the applied load due to the high slenderness ratio of the rabbit's tibia. The modelling technique used in the current study could have applications in the development of human FE models of bone, where, unlike rabbit tibia, the model would be relatively insensitive to very small changes in load position. However, the rabbit model itself is less beneficial as a tool to understand the mechanical behaviour of TSFs in humans due to the small size of the rabbit bone and the limitations of human-scale CT scanning equipment.

CONCLUSION: The current modelling technique could be used to develop human FE models. However, the rabbit model itself has significant limitations in understanding human TSF mechanics.

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Key words: Rabbit; Stress fracture; Tibia; Finite element analysis; Finite element model; Mechanics

Core tip: In the current study, experimental and finite element (FE) analysis demonstrated that under compression, the rabbit tibia exhibits linear behaviour. The stresses in the rabbit tibia are sensitive to small changes in load position due to its high slenderness ratio. Low tensile stresses occur at the anterior border of the midshaft, suggesting that this region fails in fatigue, as

bone under cyclic loading initially fails in tension. The current modelling technique could be used to develop human FE models.

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INTRODUCTION

Stress fractures are fatigue fractures which occur in normal bone subjected to atypical cyclic loading. This altered stress state results in microcracks in the cortical bone tissue due to bone failure. Most commonly sustained in the tibia, stress fractures are debilitating injuries, often requiring weeks to months of rest and rehabilitation. Despite various interventions introduced in order to mitigate the risk of stress fractures, athletes[1-3] and military recruits[4,5] continue to be susceptible to these injuries due to their intense training regimes.

In previous research, tibial stress fractures (TSFs) have been analysed using rabbit bones as they are relatively inexpensive and easy to acquire. However, the rabbit and human tibia differ anatomically, with one of the primary distinctions being the distal articulation of the tibiofibula complex: in the human it is near the ankle joint whereas in the rabbit it is at the tibial midshaft.

In some earlier research where TSFs were produced in rabbit tibiae, 20 rabbits were trained to run and jump in response to electrical stimulation so the applied loads to the rabbit bones were equivalent to a human performing impact exercise[6]. By sacrificing the rabbits at various stages during the experiment, the radiographic and histological changes in the bone over a 60-d period could be analysed. Although this study provided invaluable data on the development of TSFs, the exact loads to the tibia were unknown as only the electrical stimulation could be controlled, and not the loading.

In order to overcome the above limitation, another research group later used a specifically-designed apparatus which could apply compressive cyclic loads to rabbit hind limbs[7]. The device was subsequently used to load the tibia of 31 rabbits by approximately 1.5 times their body weight on one limb, using the other unloaded side as a control. Scintigraphically-confirmed TSFs were successfully produced in 68% of the rabbits within six weeks of the loading regime. The same researchers later developed a finite element (FE) model of a rabbit's tibia[8,9]. However, there were significant limitations with both their experimental and modelling approach. For example, the rabbits were not under anaesthetic; hence, in addition to the applied compression, bending forces could be produced by involuntary muscle contraction. The results of the FE model were also anomalous.

In a more recent study, rabbit tibiae were fatigue tested under three-point bending with the aim of determining fatigue resistance due to age and sex differences[10]. The authors found there were differences in fatigue behaviour due to age but not sex; fatigue resistance increased with both greater skeletal maturity and increased bone mineral density. However, it is not possible to determine from this research where rabbit tibia may fail *in-vivo* due to normal physiological loading as three-point loading can only be used to evaluate fatigue in a localised area of the tibial mid-diaphysis, but not the fatigue behaviour of the remaining bone.

Using a combination of experimental analysis and FE modelling, the aim of the current research was to quantify the mechanical behaviour of the rabbit tibia and to determine the stresses in the bone when subjected to typical applied compressive loads representing the rabbit running. A secondary aim was to design a method which could be later used to develop FE models of human bone.

MATERIALS AND METHODS

Tibiae were harvested from rabbits obtained from the Monash University Department of Physiology in accordance with the Australian Code of Practise for the Use of Animals for Scientific Purposes (7th Edition, 2004). Experimental work was initially performed to determine the mechanical behaviour of the rabbit's tibia; one of these tests was also used for FE model validation. The experiments were performed first, thus enabling fresh wet specimens to be tested before the bone was imaged by computed tomography (CT) for the FE model geometry. Mechanical compression and beam theory analysis were also used to verify the results.

Rabbit experiments

Rabbit sample preparation: One English Cross-Breed and two New Zealand White Rabbits (NZWRs) were sacrificed with an overdose of pentobarbitone sodium (300 mg/kg) intravenously and the hind limbs were dissected from the rabbits with the musculature and tissues still intact. The limbs were separated, wrapped in gauze bathed in physiological saline to keep them moist, then frozen for later use. Prior to each experiment, the right limb (for consistency) was removed from frozen storage and saturated in tepid saline to thaw the tissues while keeping the tibia moist. After thawing, the limb was removed from the water bath and the tibia/fibula complex was dissected from the remaining tissue.

Rabbit tibial experiments: A purpose-built rig consisting of a vertical bar attached to a base and a pivoting lever on the bar was assembled (Figure 1A). Calibrated weights were applied to the loop at one end of the lever, thus loading the bone, which was located one third the distance between the pivot and the weight. The tibia was retained by a steel ball at each end; this enabled the bone to remain fixed during the test, and more importantly, fa-

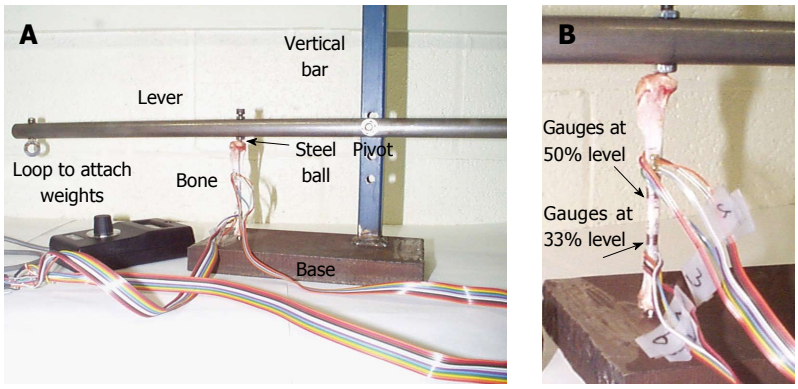

Figure 1 Testing apparatus used for the rabbit experiments. A: The full rig; B: The strain gauge positions.

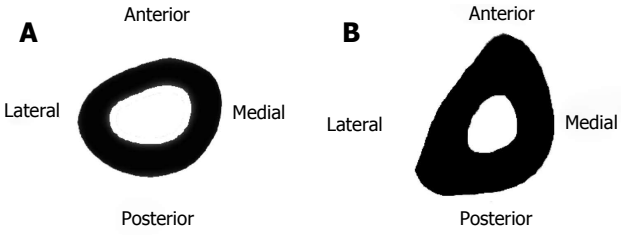

Figure 2 Rabbit cross-section of the right tibia showing the position of the gauges. A: At the 33% level; B: At the 50% level.

cilitated bone loading through a concentrated rather than a distributed load, which could then be easily replicated in the FE model. Three tests were conducted: (1) a buckling test, to quantify bone deflection and linear behaviour under axial load; (2) a strain gauge test, to obtain stresses for FE model validation; and (3) a hysteresis test, which in addition to measuring hysteresis, was used to verify that the strain gauges had adhered properly to the bone. The English Cross-Breed Rabbit tibia was used in the first experiment, while NZWR tibiae were used in the subsequent experiments. After the strain gauge test, the tibia was then CT scanned in order to obtain the geometry for the FE model.

In the first experiment, weights were incrementally added to the loop on the pivoting rod to compress the bone and a dial gauge was used to measure the deflection of the bone in the anteroposterior (AP) direction at the midshaft for each successive increase in load. In the second and third experiments, the strain gauges were bonded to the tibia in predetermined locations using M-Bond 200 cement. Although the positions chosen were somewhat arbitrary as the aim was to validate the FE model in different locations, the magnitude of the stresses in the areas where TSFs[2,4,8,11,12] and Medial Tibial Stress Syndrome[2,13] are sustained were of interest; hence the gauges were attached to those sites.

As shown in Figures 1B and 2, four strain gauges (anterior, posterior, medial and lateral) were attached at the junction of the mid and distal thirds of the tibia (33% of the tibial length from the distal end of the tibia) and four strain gauges were attached in the centre of the midshaft (50% of the tibial length from the distal of the end of the tibia), where the tibial length was defined to be the distance from the medial malleolus to the medial joint line. A hand-held strain gauge reader was used to record measurements from the gauges.

Development of the tibial FE model

Geometry: Using a Hitachi W1000GR scanner (Hitachi Medical Corporation, Tokyo, Japan), one scout film and 71 consecutive tibial cross-sectional CT images 1.55 mm apart were scanned; this was the maximum number of cross-sections which could be imaged due to the small size of the rabbit bone. These images were used to create a base, or reference, model. The cross-sections were automatically aligned by the CT scanner using the origin of each image, which was located at the top left corner. The images were digitised from DICOM format to TIFF format using eFilm (Merge Healthcare) software. In order to ensure the load position in the computer model was the same as the load position in the experiments, a point at each end of the bone was marked using a scalpel. These points, which approximately corresponded to the physiological load positions, could be later visualised on the CT scans.

The University of Texas Health Science Center at San Antonio ImageTool for Windows (Version 2.0, San Antonio) software was used to display the images and to generate data points for the geometry. To eliminate user variability, one person performed all measurements. To find the optimum number of data points required around a cross-section, convergence tests were performed using a Fortran program, where a number of cross-sectional properties were computed while varying the number of perimeter points. More details on these tests can be found in previous publications[2,14]. The third co-ordinate was based on the CT scan position along the longitudinal axis. As only the cortical bone was of interest, any regions of indistinct bone were not included in the data acquisition.

To create the solid model, two FE packages, Abaqus CAE (Version 5.0) and Hypermesh 3D (Altair, Versions 6.2 and 7.0), were used in conjunction with a specifically-written Python script. The Python code was executed in Abaqus, which then automatically generated a command

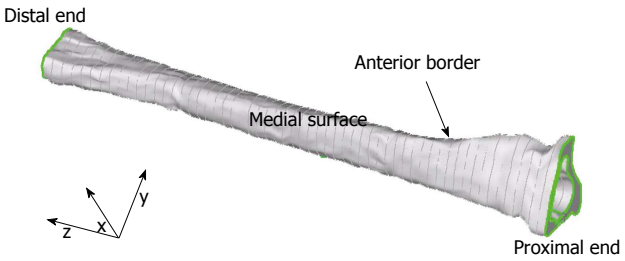

Figure 3 The full rabbit tibial finite element model illustrating the cross-sections and the surface geometry.

file and used the data points to produce a series of cross-sectional splines by cubic spline interpolation. The command file was subsequently executed within Hypermesh to create the wireframe model from the spline data. The solid model geometry and the remainder of the pre-processing were performed using Hypermesh.

Six slices were truncated from each end of the 71 CT images as the complex geometry at each end is laborious to model and not of interest in the current study. Thus, the final base model was 90 mm in length and was comprised of 59 equally-spaced CT slices 1.55 mm apart. The model was meshed with 28248 parabolic 10-nodded tetrahedral elements 0.77 mm apart. The tetrahedral element length was the smallest distance which could be meshed without the model developing numerical instabilities, for example, instabilities which resulted from the average distance between adjacent nodes falling below the computational accuracy of the program. The final base model (Figure 3) was used as a reference to which other, less detailed, models could be compared.

Material properties: The material properties of rabbit bone available in the literature are limited. However, as the experimental results (presented later) demonstrated, linear elastic isotropic material properties could be presumed for loads up to 12.5 kg; hence, this assumption was used in the FE model. The value used for the Young's Modulus (E) was the mean of the values from the rabbit femoral and humeral bone midshafts for wet cortical bone (since no Young's Modulus was available for the rabbit tibia), thus E = 10950 MPa. A Poisson's ratio of μ = 0.3 was used, which is the value of μ for both the rabbit femoral and humeral bone[15].

Boundary conditions: Using the Image Tool software, the scalpel marks at each end of the bone were identified on the CT scans and the 3D Cartesian co-ordinates were determined. With the neutral axis as a reference, the corresponding co-ordinates were found at the cross-sectional level where the model had been truncated (recalling that six CT scans were truncated at each end). A nodal point and a series of rigid beam elements were created at each end of the model in order to transfer load, with the number of beam elements controlled by the element density. A static axial load of 60 N, which represents approximately 1.5 times the body weight of the rabbit (*i.e.,* a typical load representing the rabbit running), was applied to each end of the model. For quasi-static loading such as running, which can be represented as a step-function and occurs over a fraction of a second, static loading is appropriate[16]. This is consistent with FE models in the literature where, for example, femoral fractures from falls in the elderly have been evaluated using static FE analysis[17,18]. Conversely, impulse loads which are dynamic and occur over a period of milliseconds, such as ballistic and automatic impacts, require dynamic FE models.

FE model analyses: The models were executed using the OptiStruct solver, and then the post-processing was performed using Hypermesh (Altair, Versions 6.2 and 7.0). In order to validate the model, the von Mises stresses were plotted for the base rabbit model and then compared to the experimental strain gauge results at eight locations. Due to the high mesh density, there were many nodes on the model corresponding to a particular strain gauge location on the rabbit; hence, the stresses at several nodes in the relevant region of the model were measured and the results averaged. A sensitivity analysis was then conducted by moving the axial load on the full model to four other positions so the change in stresses due to distance from the centroid could be investigated.

Geometric and elemental convergence tests were performed in order to establish the minimum number of cross-sections and elements respectively required in a reduced FE model to produce similar stresses to the base rabbit model with the 59 cross-sections. Geometric convergence tests were conducted by reducing the number of cross-sections while the tetrahedral element length was kept constant. After the optimal number of cross-sections was ascertained, the elemental convergence tests were performed using a constant number of cross-sections but reducing the number of elements.

RESULTS

Rabbit experimental results

Elastic buckling test: For lower axial loading levels, the rabbit tibia demonstrated linear behaviour, particularly for loads less than 12.5 kg (Figure 4A), or 122.5 N (throughout the paper, mass has been used as a convenient representation of force). There was non-linear behaviour at higher loads, although the non-linear region (> 12.5 kg) also demonstrated linear behaviour (20-25 kg). At a maximum load of 25 kg, the deflection was 0.1 mm anteriorly in the AP direction at the centre of the anterior midshaft (measured by the dial gauge). Using the CT images, the bone length was measured to be 100 mm and the width in the AP direction at the midshaft was 7.5 mm. Hence, the deflection of the bone was 1.33% of the AP width and 0.1% of the tibial length. These results demonstrated that not only did the bone not buckle, but the rabbit's tibia is not particularly flexible under load.

Using mechanics theory, the expected buckling load was calculated for a straight, uniform column having

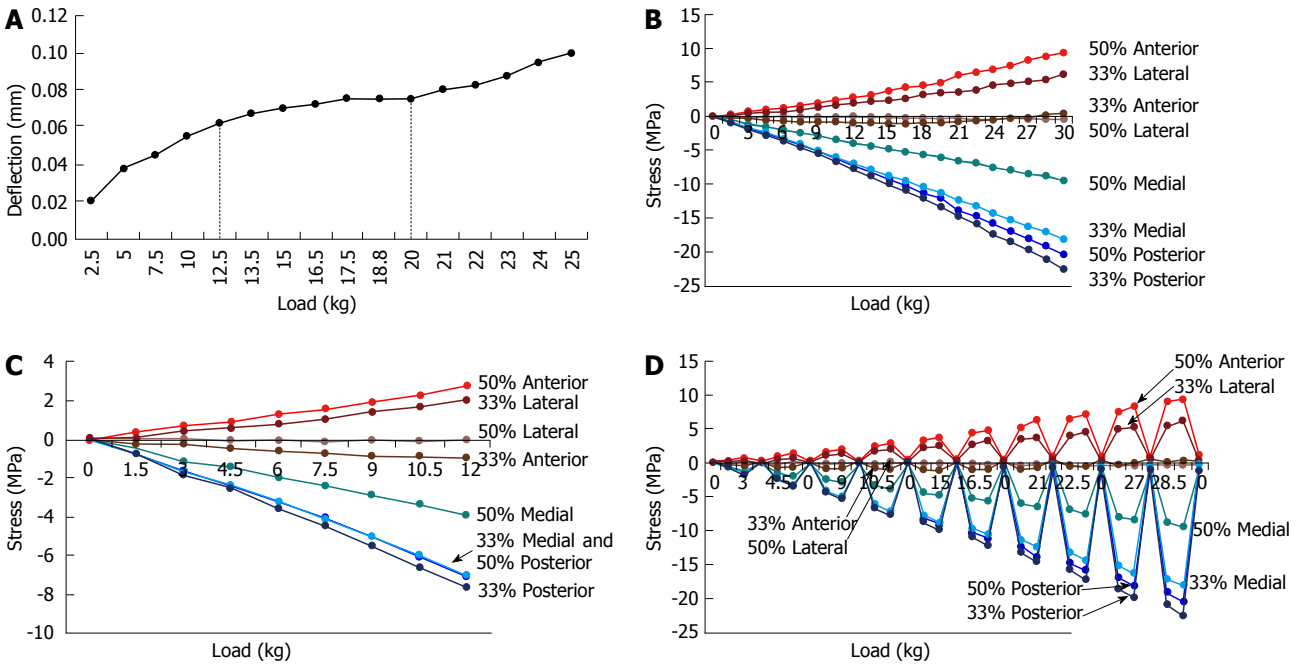

Figure 4 Results for the rabbit bone experiments. A: Elastic buckling test. Loads < 12.5 kg were linear, whereas there was non-linear behaviour for loads > 12.5 kg. However, the non-linear region also demonstrated some linear behaviour (*i.e.*, from 20-25 kg); B: Strain gauge test. Gauges were attached in eight locations on the bone. Tension is positive and compression is negative; C: The segment of the rabbit tibial strain gauge test from 0 to 12 kg; D: Hysteresis test. The results show that the bone exhibits predominately elastic behaviour.

the same midshaft AP dimension as the rabbit's bone. The slenderness ratio was 59 ($L_e/p \approx 100$ mm/1.7 mm), where L_e is the equivalent length of the column and p is the radius of gyration. Using the Fortran program, the value of p was numerically computed from the CT scan at the centre of the tibial midshaft. A slenderness ratio of 59 (*i.e.,* a slenderness ratio > 10) represents a long slender column. The critical loading limit, P_{cr}:

$$P_{cr} = \frac{\pi^2 E I_{min}}{L_e^2} = \frac{\pi^2(1095)(97.56)\text{kg/mm}^4}{100^2\text{mm}^2} \approx 105 \text{ kg}$$

where E, I_{min} and L_e are the Young's Modulus (kg/mm^2), the minimum second moment of area (mm^4) and the equivalent length (mm^2) respectively[19]; in an irregular bone such as the rabbit tibia, I_{min} is along the axis where I is minimised, although in the cylinder here I is the same in all directions. Since the rabbit tibia is bent (the line of loading does not pass through the centroid of the mid-point cross-section), it would be expected to buckle at less than 105 kg, but highly unlikely to buckle at 25 kg. This is consistent with the experimental results.

If the rabbit tibia was quite flexible, then the compressive load acting may cause the neutral axis (*i.e.,* the axis through the centroids of all cross-sections) to shift further away from the line of action of the compressive load. This increase in offset distance has the potential to produce additional tension in the bone due to the creation of bending stresses. The experiment demonstrated that bone was not particularly flexible; hence, under a compressive axial load, the stress in the bone is predominately compressive. Any tensile stress would be produced on the anterior border due to the forward curvature of the bone.

This is discussed further under the section Mechanical theory predictions.

Strain gauge test: Strains were measured from eight gauge locations in increasing 1.5 kg loads, then converted to stress using the Young's Modulus (defined earlier) for rabbit bone (Figure 4B). Two gauges, the 33% level anterior and the 50% level lateral, were unstable and remained close to zero as it was difficult to keep the device fixed at the precise loading point for very small loads. Examination of the output strains at near-zero loads demonstrated that the strains were sensitive to small changes in the point of load application. At higher loads, the strains were stable due to the compression applied through the loading device onto the bone.

The stress-strain graphs are slightly non-linear (Figure 4C), consisting of two linear curves (approximately 0-15 kg and 18-30 kg) joined by a non-linear segment (approximately 15-18 kg). Thus, linearity for loads up to approximately 12 kg can be assumed, and in particular, linearity for loads simulating a rabbit running (about 6 kg) can be used.

Hysteresis test: Although the rabbit tibia displayed some hysteresis (Figure 4D), it was not extensive, but gradually increased with increasing load. For example, for a load of 30 kg, the maximum compressive and tensile stresses were -22.6 MPa and +9.4 MPa respectively, representing a corresponding hysteresis of approximately -1.1 MPa and +1.0 MPa (*i.e.,* 5% hysteresis in compression and 10.5% hysteresis in tension). At a load of 6 kg, the hysteresis was approximately 0.5% (-0.12 MPa) in

compression and 2% (+0.19 MPa) in tension. Hence, there was no significant hysteresis. These results demonstrated that (1) the gauges had adhered to the bone and (2) the bone demonstrates elastic behaviour for loads up to 30 kg. When considered in conjunction with the results from Figure 4A, it can be concluded that for loads up to 12.5 kg, rabbit bone shows linear elastic behaviour, while for loads between 12.5 kg and 30 kg, rabbit bone is elastic but shows some non-linearity. Thus, for loading which represents a rabbit running (6 kg), linear elastic behaviour can be assumed.

Mechanical theory predictions

The minimum offset distance required to produce tension on the opposite side of a beam when a compressive force is applied can be calculated from mechanics theory. A net tension can occur in the section when the tensile bending stress caused by the offset is greater than the magnitude of the stress caused by the compressive load.

Assuming a hollow cylinder where $r_2 > r_1$, the bending moment stress (σ_{BM}) can be calculated by:

$$\sigma_{BM} = \frac{my}{I}$$

where m is the bending moment, y is the distance from the centroid to the point the stress is being calculated (equal to the maximum radius of the cylinder) and I is the second moment of area.

However, $m = Fx$ and $I = \frac{\pi}{4}(r_2^4 - r_1^4)$, where F is the compressive force, x is the offset distance of the load from the centroidal axis and r_2 and r_1 are the outer and inner radii mentioned above. Hence, substitution of the equations for m and I into the bending moment equation:

$$\sigma_{BM} = \frac{4Fxy}{\pi(r_2^4 - r_1^4)}$$

The compressive stress (σ_C) can be calculated by:

$$\sigma_C = \frac{F}{A}$$ where F is the applied force and A is the cross-sectional area. The area can be described in terms of the inner (r_1) and outer (r_2) radii of the section:

$$A = \frac{\pi}{4}[(2r_2)^2 - (2r_1)^2]$$

Substitution of the area equation into the compressive stress equation:

$$\sigma_C = \frac{4F}{\pi[(2r_2)^2 - (2r_1)^2]}$$

$$\text{Hence } \sigma_C = \frac{4F}{\pi(4r_2^2 - 4r_1^2)}$$

$$\therefore \sigma_C = \frac{F}{\pi(r_2^2 - r_1^2)}$$

If $\sigma_{BM} > \sigma_C$, then tension can be produced on the opposite side of the beam.

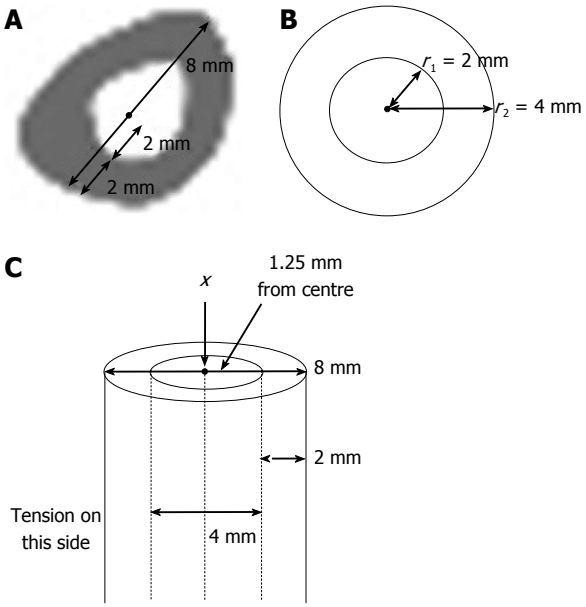

Figure 5 For tension to be produced in a typical beam a similar size to the rabbit tibia, a compressive load needs to be offset from the centroid in the opposite direction by only 1.25 mm. A: Dimensions from the midshaft of a rabbit's tibial cross-section: AP width (8 mm), cortical width (2 mm) and medullary half-width (2 mm); B: The rabbit midshaft cross-section represented as a section from a beam; C: The beam showing an axial load through the centroid (x) and the offset.

This is satisfied when:

$$\frac{4Fxy}{\pi(r_2^4 - r_1^4)} > \frac{F}{\pi(r_2^2 - r_1^2)}$$

$$\text{Simplifying } \frac{4Fxy}{(r_2^4 - r_1^4)} > \frac{F}{(r_2^2 - r_1^2)}$$

Solving for x, the distance between the centroid and the load position:

$$x > \frac{r_2^4 - r_1^4}{4y(r_2^2 - r_1^2)} \text{ but } y = r_2 \text{ (maximum)}$$

$$\text{Hence: } x > \frac{r_2^4 - r_1^4}{4r_2(r_2^2 - r_1^2)}$$

If the dimensions of the rabbit tibia at the centre of the midshaft are 8 mm in width, where 4 mm is the medullary region and 2 mm each end is comprised of cortical bone (approximate measurements from CT images, as shown in Figure 5A, and shown on a beam cross-section in Figure 5B), then the equation is satisfied when:

$$x > \frac{4^4 - 2^4}{4(4)(16 - 4)} > \frac{240}{192} \text{ mm}$$

Hence $x > 1.25$ mm

Thus, a load applied at one end of the bone would only need to move 1.25 mm away from the centroid (less than half the medullary width) in the x - y plane to produce tension in the midshaft on the opposite side of the bone. This is demonstrated in Figure 5C. Tension can

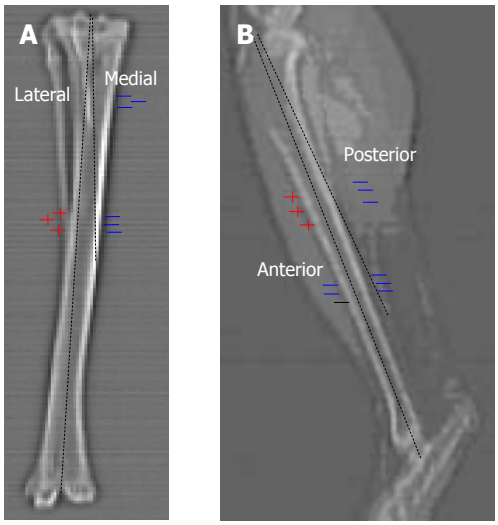

Figure 6 As demonstrated by these radiographs, a compressive load through the centroidal axis of the rabbit tibia will result in a similar stress pattern as when applying an offset axial load to a straight bone. A: Anterior view; B: Lateral view.

also arise from a slight curvature of the tibia (*i.e.,* when it is bent by 1.25 mm or more), such as *via* the natural curvature which already exists in the bone (Figure 6).

Validation, sensitivity and convergence tests on the rabbit FE model

Convergence tests on the FE model: The base model, which was used as a reference, was 90 mm in length and contained 59 equally-spaced CT slices 1.55 mm apart (Figure 3**,** shown earlier). As mentioned previously, the mesh was comprised of 28248 parabolic 10-nodded tetrahedral elements 0.77 mm apart. The von Mises stresses were computed since sites of high stress intensity were of interest because these would indicate where local yielding may occur and hence initiate microfractures.

The geometric convergence test results are shown in Figure 7A and B (at the mid-distal junction and midshaft respectively). At the mid-distal junction, the results have clearly converged when the model has 22 cross-sections, as demonstrated by the fluctuating stresses for the results of the last three cross-sections (*i.e.,* the 13, 22 and 59 cross-sections). Similarly, at the midshaft, the stresses have converged by 22 cross-sections for all regions except the posterior surface, which is on the point of convergence. Hence, a model with 22 cross-sections is sufficient for the analysis, *i.e.,* will give comparable stresses to the full model with 59 cross-sections.

The mesh convergence test results demonstrate that all regions have converged or almost converged (Figure 7C and D). When the model was meshed with elements of tetrahedral element lengths of 0.4 mm, and then 0.58 mm, the simulation aborted due to numerical instabilities as adjacent nodes were too close. Hence, a tetrahedral element length of 0.77 mm was the finest mesh which could be achieved in the rabbit model due to the small dimensions of the bone (this would not be an issue in a larger structure, such as a model of the human tibia). A comparison of the convergence data shows that the variation in stress is considerably greater for the geometric convergence test than the mesh convergence test, indicating that it is more critical to have a greater number of cross-sections than a more refined mesh in the rabbit model.

Beam theory and experimental results: Results from the beam theory predictions and the strain gauge experiments were plotted on the same graphs for comparison (Figure 8). For the beam theory analysis, an axial compressive load between the two condyles of the tibia was used in conjunction with standard engineering equations for a hollow non-circular cylinder.

Under an axial load of 6 kg, the predicted stresses were all compressive at the mid-distal tibial junction. At the midshaft, the stresses were all compressive, except at and adjacent to the anterior border. The experimental results were reasonably consistent with the calculated values, excluding the lateral gauge, where there was some disparity.

FE model results and sensitivity tests: The von Mises stress contours from the FE model were plotted in conjunction with the stress moduli (since von Mises is a positive entity) from the beam theory and experimental results at the mid-distal junction and the midshaft (Figure 9A). At the mid-distal junction, there was good agreement between the FE model, the beam theory results and the experimental values for the posterior and lateral surfaces; however, at the medial surface and anterior border, there was some disparity between the FE model and the other results. The FE results for the midshaft were fairly close to both beam theory and experimental results in all four locations.

Figure 9A demonstrates a colour contour plot of the von Mises stress distribution in the rabbit model. There were high stresses along a large region of the posterior surface of the model; this was reflected in the experimental results where the highest (compressive) stresses at the 33% and 50% levels were on the posterior strain gauge (shown earlier in Figure 8). Figure 9B demonstrates a view of the model truncated at the 50% level; these stresses were consistent with the strain gauge results shown in earlier in Figure 8B (note that exact numbers cannot be compared as the gauges in the experiments cover a region, where the stresses are then averaged). The model also showed that highest stresses were not at the 33% and 50% (where the strain gauges were located in the experiments), but around the 23% level of the tibia (Figure 9A). In order to explore this further, the principal moments and cross-sectional area for the rabbit cross-sections were numerically calculated using the Fortran program and plotted (Figure 10).

The illustration of the sensitivity test, where the applied load was moved to a number of positions near the original load and the centroid of the cross-section,

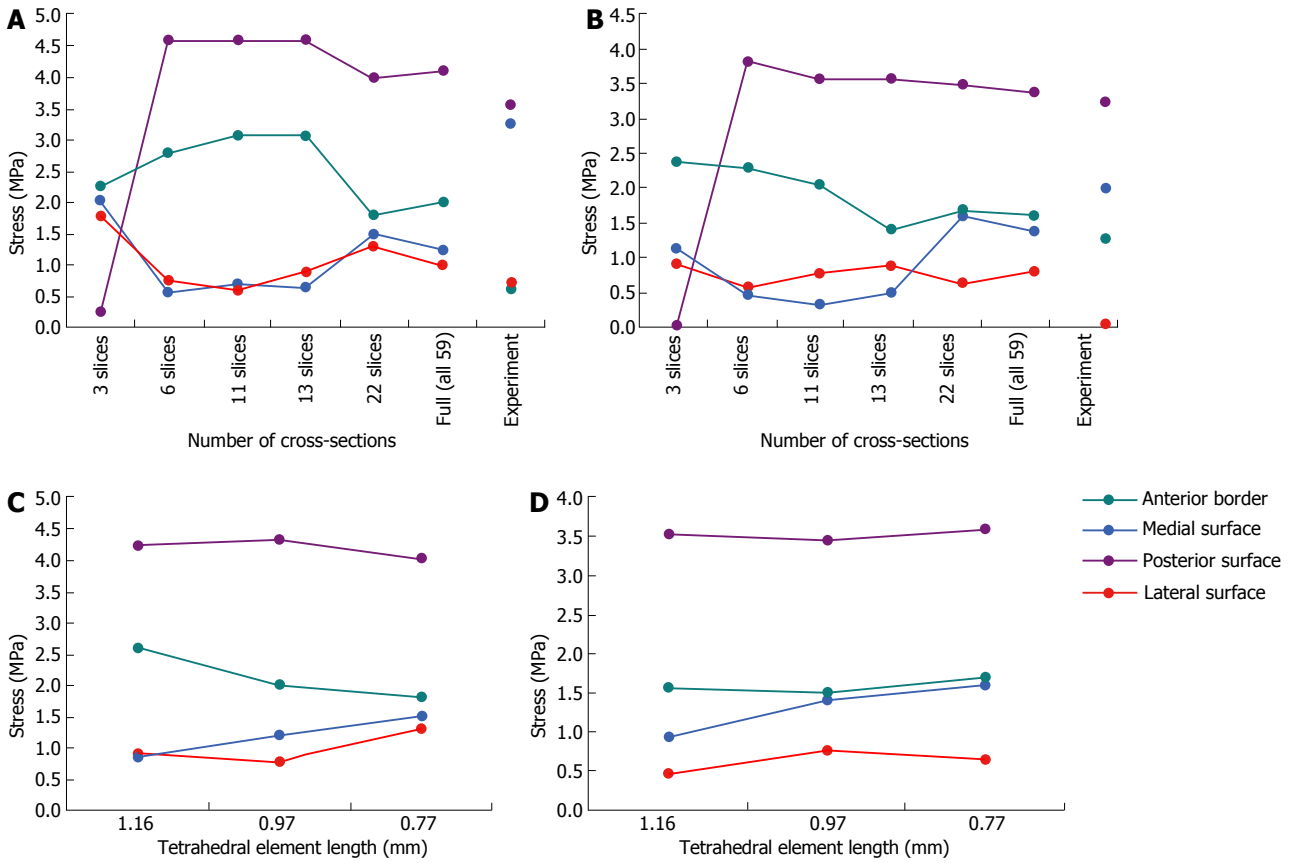

Figure 7 Convergence test results on the finite element model. A: Geometric convergence tests at the 33% level; B: Geometric convergence tests at the 50% level; C: Mesh convergence tests at the 33% level; D: Mesh convergence tests at the 50% level.

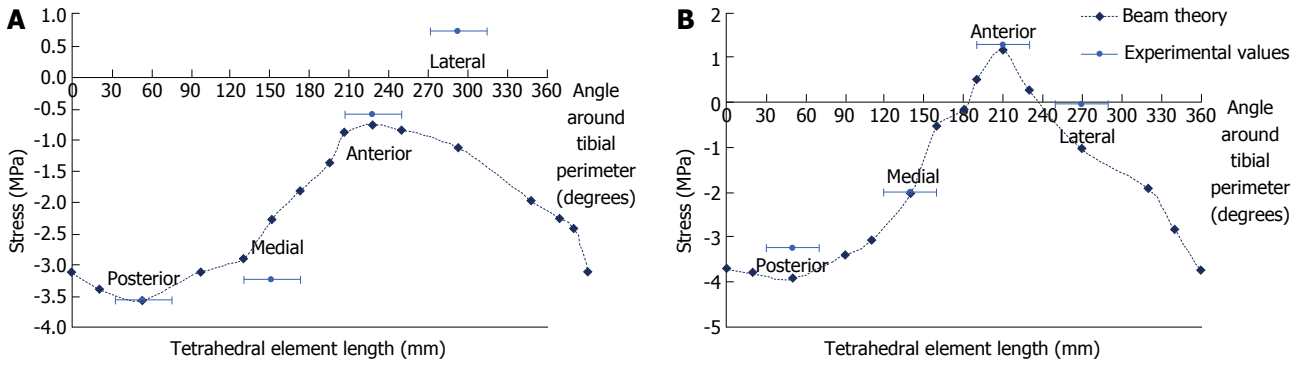

Figure 8 Theoretical and experimental stresses in the rabbit tibiae. A: The 33% level; B: The 50% level.

is shown in Figure 11. The results of the sensitivity test and comparison with the beam theory and experimental results are shown in Figure 12.

The results demonstrated that it was probable that the load position was in fact posteromedial to Load 1 (*i.e.,* posterior to Load 2, Figure 11), which is 1-2 pixels from the original load, based on measurements made using the imaging software. Moving the load position one pixel (*i.e.,* about 0.4 mm) resulted in a significant change in the stress output, particularly in the anterior and medial positions (up to 27% on the anterior border); hence, the rabbit FE model stresses are highly sensitive to load position, which is consistent with the large slenderness ratio of the rabbit tibia.

DISCUSSION

As shown by predictions using engineering mechanics, experimental data and FE analysis, a compressive point load between the two condyles of the rabbit tibia will predominately result in compressive stresses throughout the bone. The highest compressive stress is on the posterior surface, around the 24%-28% level of the bone, which also corresponds to the regions which have the lowest cross-sectional areas and principal moments. Tension is produced predominately on the anterior border

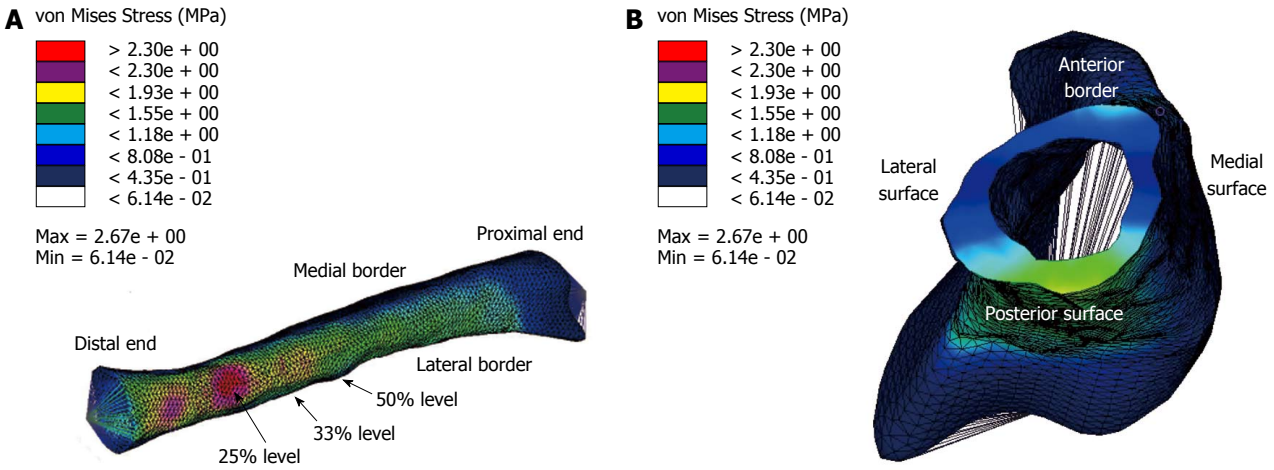

Figure 9 Rabbit finite element model showing the von Mises stresses. A: Posterior view: High stresses were found along the posterior surface; these were most prominent around 25% level, which is shown in red; B: A section through the 50% level. The highest stress (which is compressive) is on the posterior surface, which is consistent with the stress results presented in Figure 8B.

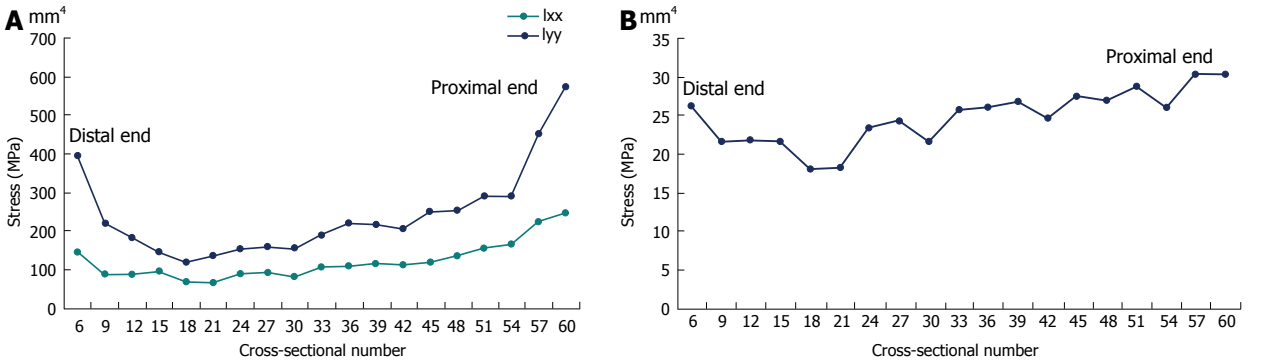

Figure 10 Geometric properties of the rabbit cross-sections: every third section is calculated numerically using a Fortran computer program. NB: Not all sections are shown, there are 71 sections in total. A: The principal moments: the lowest moments are between cross-sections 18 and 21, which represent the 25% to 29% of the model and correspond to the high stress region in the finite element model; B: The cross-sectional areas: the lowest areas are for cross-sections 18 and 21, which correspond to the 25% to 29% levels respectively.

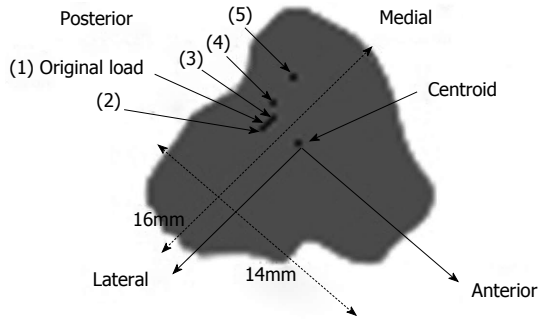

Figure 11 Load positions for the sensitivity tests.

of the midshaft, but also on the anterolateral region at the midshaft and distal thirds. The magnitude of tension is not high, and since the rabbit bone is not particularly flexible under load and does not buckle, this tension is likely to remain low. Bone generally fails in tension from static loading[20], while under cyclic loading, cortical bone fails in tension before compressive failure later occurs after repeated loading[21,22]. Hence, the results suggest that TSFs in the rabbit model are produced in the anterior midshaft by low levels of tensile stress *i.e.*, the region of least compressive stress.

In the current study, the stresses in the rabbit bone primarily demonstrated linear behaviour (for up to three times the rabbit's body weight) with little hysteresis. Previous work has shown that stress-strain curves of a number of different animal bones are similar to those of human bones, with the only difference being the Young's modulus[15]. Hence, linearity can be assumed for the human tibia for static loading up to three times body weight. The FE model of the rabbit tibia also demonstrated that the stresses were exceptionally sensitive to small changes in loading position (to the level of one pixel, or 0.4 mm), which is not surprising, because the rabbit tibia has a large slenderness ratio. This differs to the human tibia, which is considerably wider relative to its length; hence, the same sensitivity to small changes in load position would not be expected in a human tibia.

In previous studies, rabbit models have been used to study TSFs. In some earlier research by Li and colleagues[6], rabbits were trained to run and jump when

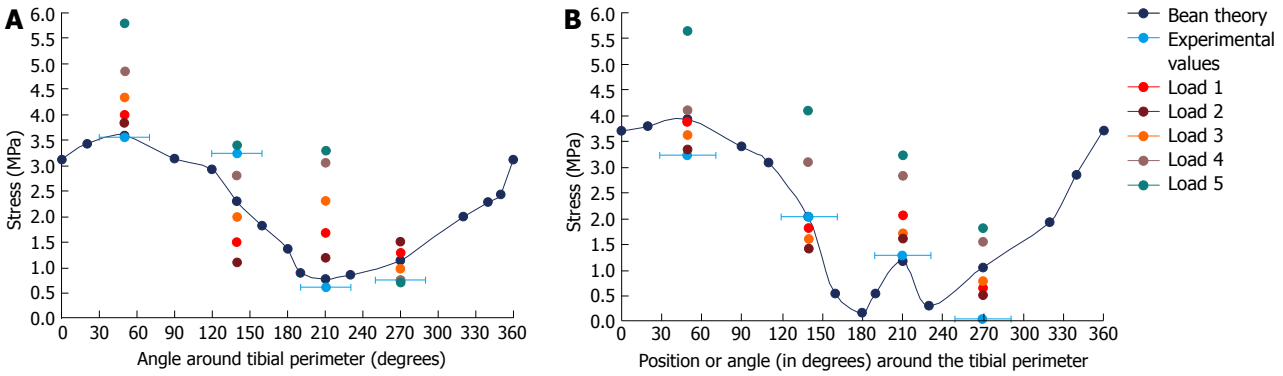

Figure 12 Beam theory results against strain gauge (experimental) and finite element model (Loads 1-5). The load positions applied to the model were previously shown in Figure 11 (Load 1 is the original load position on the model). A: Results for the 33% level; B: Results for the 50% level.

subjected to electrical stimuli. The histological analysis from these experiments demonstrated that cracks developed on the cement lines of the Haversian systems, most frequently in the midshaft of the tibia (16 tibiae), followed by the distal third (3 tibiae) and lastly the upper third (1 tibia). These cracks predominately developed on the anterior and medial aspects of the tibia. Fracture lines were then formed by convergence of adjacent cracks from the Haversian systems. This rabbit experiment provided *in-vivo* verification of the early cortical bone specimen tests in the literature, where it was found that tensile failure occurs first under cyclic loading, and this tensile failure resulted in osteon debonding at the cement lines[21,22]. Li *et al*[6] did not specify which types of cracks (longitudinal, transverse or oblique) occurred in the various locations of the tibiae. However, they did observe that most cracks occurred in the anterior and medial aspects of the midshaft, which was consistent with other research to date on tensile stresses and tensile failure at this site. The main limitation with their study was that the exact magnitude of loading to the bone was unknown and could not be controlled.

In a subsequent study by Burr and colleagues, this limitation was overcome by loading rabbits using a specifically designed apparatus which could apply compressive cyclic loads, where the magnitude was known and could be controlled, to the hindlimbs of 31 rabbits[7].TSFs were successfully produced in 68% of the rabbits within six weeks of loading and were verified by scintigraphy. Of these TSFs, 89% were in the midshaft (implying that 11% were distal) and 74% were anteromedial, although it was not clear how many of the midshaft TSFs were anteromedial. The authors later stated that the rabbit model frequently shows TSFs distally[23], although the 89% in the midshaft was not mentioned, suggesting that it is, in fact, difficult to determine the exact location of TSFs in the rabbit. This is not surprising, as scintigraphy only shows a region of increased radionuclide uptake and the exact location would be difficult to visualise in a small bone such as the rabbit tibia. Although the study by Burr and colleagues[7] demonstrated that TSFs could be produced using a controlled load, the main limitation was that the rabbits were not under anesthetic during loading; hence their muscles could involuntary contract. Hence, the loading applied to the tibia was not purely compressive, as the involuntary muscle contractions apply other loads to the bone such as bending (which is then accentuated by the natural bend in the tibia), resulting in tensile stresses on the anterior border of the tibia. Furthermore, if the knee of the rabbit was flexed significantly in the experiment, the load line may be outside the cross-sectional area of the bone, which would produce further tension on the anterior side of the bone.

Using the Patran FE package (MSC Software), the same researchers who designed the controlled loading apparatus (discussed above) later developed a FE model of the rabbit's tibia where compressive loading only was applied[8,9]; the model was based on some earlier work by the same researchers[24]. However, there were a number of discrepancies with their FE model. For example, the model did not have any loads from the musculature applied other than compression, yet, as mentioned above, it is probable that the tibia was subjected to other loads, such as bending, in the rabbit experiments. More significantly, the results of the FE model showed that high compressive stresses occurred on the anterior border of the tibia, yet from clinical research and knowledge of fracture types at this site, TSFs on the anterior border are a result of tensile failure due to tensile or bending forces[13,25,26]. In order to produce large compressive stresses on the anterior border (and tensile stress on the posterior surface), the load line would need to be significantly forward of the centroid, particularly as the tibia is bent anteriorly and the rabbit leg is partially flexed (Figure 12). However, this is not consistent with the load position in the experiments, as the load was applied to the rabbit's heel; hence the load line would be posterior to the centroid.

While supporting body weight, the tibia is under compression; however, the tibia experiences both compressive and tensile stresses. Tension can arise from elastic buckling, from compressive loading, and from applied bending moments from the musculature. As demonstrated in the present research, the rabbit tibia does not fail by buckling with the loads normally experienced while running. Additionally, in the current rabbit model, muscle loads were not factored; hence, applied bending

moments do not cause failure. However, in this experiment, low levels of tension were produced around the anterior border of the midshaft as a result of the applied compressive load. If the rabbit bone was a hollow beam, an applied compressive load needs to be moved only 1.25 mm posteriorly from the centroid to produce tension on the anterior aspect of the rabbit midshaft due to its large slenderness ratio. Since the tibia is curved, however, this condition is satisfied at the midshaft for a distance less than 1.25 mm. *In-vivo*, the musculature also applies bending to the rabbit tibia; hence, this increases the magnitude of tension on the anterior border.

The current study has a number of limitations, the primary one being that only one set of data was collected for each type of experiment. However, the experimental results were consistent with both the FE model and the beam theory predictions; hence, the test results are unlikely to be outside the range of stresses expected for the loads applied. The second limitation is that the stresses measured in the rabbit experiment are likely to have a larger error than the error involved if a larger bone, such as the human, had been used. As the rabbit tibia is quite small and the gauges are relatively large, the gauges measured the stress over a considerable region of the tibia rather than at one precise point. In addition, at each level (midshaft and mid-distal junction), there were four strain gauges attached to three anatomical surfaces; hence, the gauges were mounted to curved surfaces, which may have affected their accuracy. However, this would not be a significant issue in a large bone, such as the human tibia.

Previous research has demonstrated that a rabbit model has been highly beneficial in understanding the bone failure mechanisms involved in the development of TSFs. In the current study, it was found that the rabbit tibia does not fail from elastic buckling when a representative compressive load is applied; instead, low levels of tensile stress are produced, predominately around the anterior border of the midshaft, but also on the anterolateral region at the midshaft and distal thirds of the bone. It is known that bone fails under tension; hence, TSFs are most likely to be sustained on the anterior midshaft in this model.

The stresses in the rabbit bone primarily demonstrated linear behaviour (linear for up to three times body weight) with little hysteresis. Despite the precision used in the current study to match the position of the load in the experiment and the FE model, the large slenderness ratio of the rabbit tibia means that the stresses in the bone are highly sensitive to exceptionally small changes in position of the applied load (one pixel in a scanned image, or 0.4 mm), making it difficult to study the mechanics of TSFs in the rabbit tibia. Hence, although the rabbit model has been invaluable in understanding the biological mechanisms involved TSF development, it is less beneficial as a model to study the mechanical behaviour of TSFs in humans due to the small size of the rabbit bone and the limitations of human-scale CT scanning equipment.

The results of FE model developed in this research were shown to be consistent with both predictions from mechanics theory and the experimental strain gauge results. The number of cross-sections required and the optimum number of elements for convergence of the results were determined. Hence, the modelling technique used in the current study could have applications in the development of human FE models of bone, where, unlike rabbit tibia, the model would be relatively insensitive to very small changes in load position.

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COMMENTS

Background

Stress fractures are fatigue fractures which occur in normal bone subjected to atypical cyclic loading. This altered stress state results in microcracks in the cortical bone tissue due to bone failure. Most commonly sustained in the tibia, stress fractures are debilitating injuries, often requiring weeks to months of rest and rehabilitation.

Research frontiers

In previous research, tibial stress fractures have been analysed using rabbit bones as they are relatively inexpensive and easy to acquire.

Innovations and breakthroughs

In the current study, the stresses in the rabbit bone primarily demonstrated linear behaviour (for up to three times the rabbit's body weight) with little hysteresis. Previous work has shown that stress-strain curves of a number of different animal bones are similar to those of human bones, with the only difference being the Young's moduli.

Applications

The modelling technique used in the current study could have applications in the development of human finite element (FE) models of bone, where, unlike rabbit tibiae, the model would be relatively insensitive to very small changes in load position.

Peer review

In the current study, experimental and FE analysis demonstrated that under compression, the rabbit tibia exhibits linear behaviour. This is a good paper which merits publication.

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BRIEF ARTICLE

Percutaneous pelvic osteotomy in cerebral palsy patients: Surgical technique and indications

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Abstract

AIM: To describe the surgical technique of and indications for percutaneous pelvic osteotomy in patients with severe cerebral palsy.

METHODS: Twenty-one non-ambulatory children and adolescents (22 hips) were consecutively treated with percutaneous pelvic osteotomy, which was used in conjunction with varus, derotational, shortening femoral osteotomy and soft tissue release, to correct progressive hip subluxation and acetabular dysplasia. The age, gender, Gross Motor Function Classification System level, side(s) of operated hip, total time of follow-up, immediate post-operative immobilization, complications, and the need for revision surgery were recorded for all patients.

RESULTS: Seventeen patients (81%) were classified as GMFCS level Ⅳ, and 4 (19%) patients were classified as GMFCS level Ⅴ. At the time of surgery, the mean age was 10.3 years (range: 4-15 years). The mean Reimers' migration percentage improved from 63% (range: 3%-100%) pre-operatively to 6.5% (range: 0%-70%) at the final follow-up ($P < 0.05$). The mean acetabular angle (AA) improved from 34.1° (range: 19°-50°) pre-operatively to 14.1° (range: 5°-27°) ($P < 0.05$). Surgical correction of MP and AA was comparable in hips with open ($n = 14$) or closed ($n = 8$) triradiate cartilage ($P < 0.05$). All operated hips were pain-free at the time of the final follow-up visit, although one patient had pain for 6 mo after surgery. We did not observe any cases of bone graft dislodgement or avascular necrosis of the femoral head.

CONCLUSION: Pelvic osteotomy through a less invasive surgical approach appears to be a valid alternative with similar outcomes to those of standard techniques. This method allows for less muscle stripping and blood loss and a shorter operating time.

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Key words: Percutaneous pelvic osteotomy; Cerebral palsy; Hip; Acetabular dysplasia; Children; Non-ambulatory

Core tip: In severe non-ambulatory, Gross Motor Function Classification System Ⅳ and Ⅴ cerebral palsy patients with acetabular dysplasia and progressive hip subluxation or dislocation, most patients can achieve a painless and stable hip when a pelvic osteotomy through a minimally invasive surgical approach is performed in conjunction with a varus, derotational, shortening femoral osteotomy and soft tissue release surgery. Pelvic osteotomy through a less invasive surgical approach appears to be a valid alternative with an outcome similar to that of standard techniques and allows for less muscle stripping and blood loss and a shorter operating time.

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INTRODUCTION

Hip subluxation and dislocation are common in children with cerebral palsy (CP) and have been reported in up to 45% of these patients[1-4]. The risk of hip displacement is related to the gross motor functional level as graded by the Gross Motor Function Classification System (GMFCS)[5-8]. In this system, children can be divided into five groups (Level I through V). Level I and II children have good walking abilities. Level III children can walk with the help of an assistive device. Level IV and V children are unable to walk[6]. The risk of progressive hip subluxation and/or dislocation is higher in patients with GMFCS IV and V ratings[5]. In 50%-70% of CP patients, hip displacement can make perineal care difficult[2,3,9-13], alter sitting balance[13-15], and be a source of pain[2,3,14-18]. Most clinicians agree that surgical treatment is indicated for progressive hip subluxation in this patient population[3,4,18-21].

The goal of any treatment is to create a reduced, stable, mobile hip with reduction of existing pain. Once a hip develops significant subluxation, reduction and stabilization can be achieved with a varus, derotational, shortening femoral osteotomy (VDRSO), which decreases anteversion and the tension on the surrounding hip musculature, including the hamstrings[14]. If acetabular dysplasia is present, acetabular osteotomy may also be needed. Acetabular dysplasia can be addressed with surgical procedures redirecting (*e.g.,* Salter osteotomy), reshaping (*e.g.,* Albee, Dega, Pemberton, or San Diego osteotomy) and salvaging/augmenting the depth of the acetabulum, such as with the shelf and Chiari osteotomies. The Dega osteotomy is an incomplete transiliac osteotomy and takes advantage of the inherent flexibility of the posterior column of bone in the pelvises of young children to reshape the acetabulum[22]. The Pemberton osteotomy extends directly to the triradiate cartilage[16]. In 1915, Albee described a semicircular osteotomy of the lateral part of the acetabular rim that is directed from lateral to medial into the ilium; the osteotomy is just cephalad to the attachment of the hip capsule to the ilium[23]. The San Diego osteotomy hinges symmetrically on or slightly above the triradiate cartilage, with care taken to use bone grafts that provide posterior coverage equal to the anterior coverage[10].

The Albee, Dega, Pemberton, and San Diego osteotomies reduce the volume and shape of the acetabulum by increasing its lateral coverage without a significant reduction in the posterior coverage[8-10,24-26]. Using a standard technique to reshape the acetabulum, Roposch *et al*[25], Robb *et al*[26], and Inan *et al*[27] showed that a stable, painless, and concentric reduction of the hip could be achieved in the majority of their patients. All the authors reported good results, with improvements in migration percentage and acetabular angle[28-30].

More recently, Canavese *et al*[24] described a minimally invasive, Albee-like percutaneous technique, *i.e.,* percutaneous pelvic osteotomy, to correct acetabular dysplasia in non-ambulatory GMFCS IV and V patients with severe cerebral palsy. In their pilot study, approximately 28 hips treated with this minimally invasive technique, Canavese *et al*[24] reported similar radiological and clinical results with less muscle stripping and less bleeding and a shorter operating time compared to traditional surgical techniques[26,27,29].

The aim of this project is to describe the minimally invasive surgical technique, *i.e.*, percutaneous pelvic osteotomy, used in conjunction with VDRSO and soft tissue release to correct hip subluxation or dislocation and acetabular dysplasia in non-ambulatory, GMFCS IV and V cerebral palsy patients. A clinical and radiological analysis of all the patients treated surgically with this technique is provided.

MATERIAL AND METHODS

Patients and methods

Twenty-one non-ambulatory children and adolescents (12 boys and 9 girls) with CP, GMFCS level IV and V, were consecutively treated, regardless of the age at presentation, with the percutaneous pelvic osteotomy technique in conjunction with VDRSO and soft tissue release.

Of these, 17 (81%) patients were classified as GMFCS level IV, and 4 (19%) patients were classified as GMFCS level V. All the patients were available for follow-up (Table 1). The mean age at the time of surgery was 10.3 years (range: 4-15), and the mean follow-up period was 16 mo (range: 9-28). The demographics, orthopedic manifestations, and age at surgery are shown in Table 1. The age, gender, GMFCS level, side(s) of operated hip, total time of follow-up, immediate post-operative immobilization, complications, and the need for revision surgery were recorded for all patients. Overall, 22 consecutive hips (9 right and 13 left) of non-ambulatory patients with severe CP were treated by this technique. All surgical procedures were performed by the first author of this work (FC) at one institution. The data collection and analysis were performed by a confirmed pediatric orthopedic surgeon not involved in the surgery (MR).

Surgical technique

The percutaneous pelvic osteotomy is performed as part of a combined procedure that includes femoral VDRSO and soft-tissue release.

Position of the patient: The patient was placed in a supine position on the operating table. A small sand bag must be placed under the gluteal area of the operated side to push the affected hemipelvis forward. First, the VDRSO is carried out through a standard lateral approach to the proximal femur. Subsequently, without changing the position of the patient, the reference points for the percutaneous pelvic osteotomy are identified under an image intensifier. The image

Table 1 Patient characteristics

Pt.	Sex	GMFCS	Triradiate cartilage	Age at surgery (yr)	Percutaneous pelvic osteotomy (Side)	VDRSO	Soft tissue release	Post-operative immobilization (Spica cast)
1	M	Ⅳ	Open	8	Right	Unilateral (Right)		
2	M	Ⅳ	Closed	15	Left	Bilateral		
3	M	Ⅴ	Open	12	Right	Unilateral (Right)		
4	M	Ⅴ	Open	6	Left	Bilateral	No	
5	F	Ⅳ	Open	10	Left	Bilateral		Yes
6	F	Ⅴ	Open	8	Right	Unilateral (Right)		
7	M	Ⅳ	Open	11	Left	Bilateral		
8	M	Ⅳ	Open	7	Left	Bilateral		
9	M	Ⅳ	Open	15	Right	Bilateral		
10	M	Ⅳ	Closed	15	Bilateral	Bilateral		Yes
11	F	Ⅳ	Open	8	Left	Bilateral		
12	F	Ⅳ	Open	4	Left	Bilateral		Yes
13	M	Ⅳ	Open	15	Left	Bilateral	No	
14	M	Ⅳ	Open	6	Left	Bilateral	No	Yes
15	F	Ⅳ	Closed	12	Left	Bilateral		
16[1]	F	Ⅴ	Closed	14	Left	Bilateral		
17	M	Ⅳ	Closed	14	Left	Bilateral		
18	F	Ⅳ	Closed	12	Right	Bilateral		Yes
19	F	Ⅳ	Open	10	Right	Bilateral	No	Yes
20	M	Ⅳ	Open	5	Right	Bilateral		Yes
21	M	Ⅳ	Open	8	Right	Bilateral	No	Yes

All patients were available for follow-up. The mean age at surgery is 10.3 years (range 4 to 15) and the mean follow-up period is 16 mo (range 9-28). [1]One patient died approximately 3 mo post-surgery following a severe respiratory tract infection (pneumonia ab ingestis). GMFCS: Gross Motor Function Classification System; VDRSO: Varus, derotational, shortening femoral osteotomy; M: Male; F: Female.

intensifier is placed in front of the surgeon

Landmarks and skin incision: Two lines must be drawn on the patient's skin to identify the correct site of incision. Under an image intensifier, a straight vertical line, corresponding to the axis of the acetabular roof, is drawn 5-10 mm proximal to the roof of the acetabulum. A second horizontal line starting at the tip of the greater trochanter is traced between the anterior superior iliac spine (ASIS) and the posterior iliac spine. The intersection between the first and the second line indicates where to make the skin incision. The skin incision should measure approximately 2 to 3.5 centimeters in length and be parallel to the femoral shaft.

Superficial and deep surgical dissection: After the skin incision is made, dissection down through the subcutaneous fat can be performed with scissors; electrocautery can be used if needed. During dissection, the proximal portion of the tensor fascia latae muscle must be opened to reach the gluteus medius and the gluteus minimus muscles. The gluteus minimus muscle must be dissected bluntly to reach the outer table of the iliac bone. At this stage, an image intensifier must be used to verify that the instrument used for the dissection has reached the planned point for the osteotomy. Using a Cobb dissector, the muscle tissue is scraped off the outer table of the iliac bone from the sciatic notch to the ASIS. By sliding the index finger under the muscles, it is possible to feel the smooth surface of the outer table of the iliac crest, the prominence of the ASIS anteriorly, and the curved most lateral portion of the sciatic notch posteriorly. At this point, a smooth dissector can be slid under the periosteum to reach the sciatic notch and used to protect the nervous structures when performing the osteotomy.

Pelvic osteotomy: The pelvic osteotomy should be performed between 5 and 10 mm proximal to the acetabular roof[10]. The pelvic osteotomy must be performed under an image intensifier, and the osteotome should always appear as a straight line during the entire procedure, indicating that the osteotome is perpendicular to the bone and parallel to the source of radiation. Only the outer table of the iliac bone from the ASIS to the sciatic notch must be cut (Figure 1).

The osteotomy is first performed with a straight osteotome, and then, a curved osteotome is used to complete the osteotomy. The osteotomes must always be directed towards the triradiate cartilage. The skin incision must be wide enough to allow the straight and curved osteotomes to perform the pelvic osteotomy without damaging the skin and the subcutaneous tissues. The osteotome can be displaced upwards and downwards toward the ASIS and the sciatic notch, respectively. In patients with closed triradiate cartilage, the osteotomy must be extended to the original site of the cartilage and takes advantage of the reduced resistance of the porous iliac bone[24]. In this subgroup of patients, broader osteotomes should be used to open the osteotomy to avoid collapse of the porotic iliac bone under the pressure exerted by the osteotome during the opening maneuver[22,24].

Bone graft: Once the pelvic osteotomy is completed, two straight osteotomes are inserted and used to lever

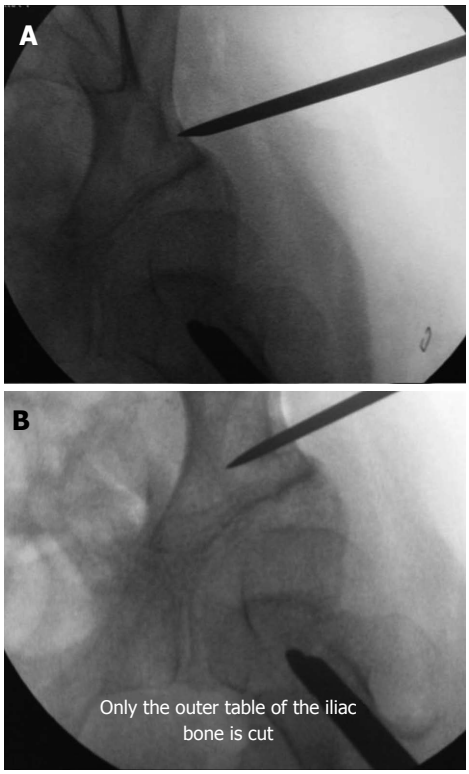

Figure 1 Percutaneous osteotomy. A: The skin incision is wide enough to allow the osteotome to perform the osteotomy. The osteotome can be displaced upwards and downwards towards the anterior iliac spine and the sciatic notch, respectively. The osteotomy should be performed between 5 and 10 mm proximally to the acetabular roof; B: The pelvic osteotomy must be performed under an image intensifier, and the osteotome should appear as a straight line during the entire procedure, meaning that it is perpendicular to the bone and parallel to the source of radiation. Only the outer table is cut.

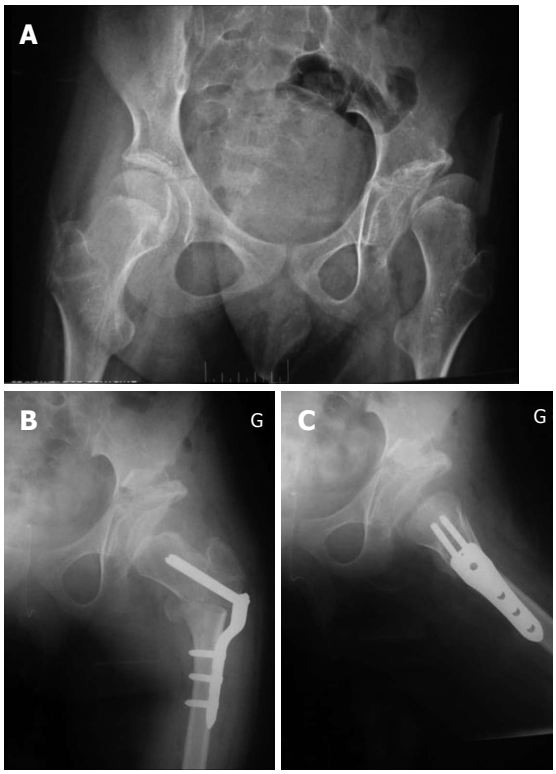

Figure 2 Pre (A) and post-operative operative antero-posterior (B) and lateral (C) radiographs of the pelvis (male patient, open triradiate cartilage).

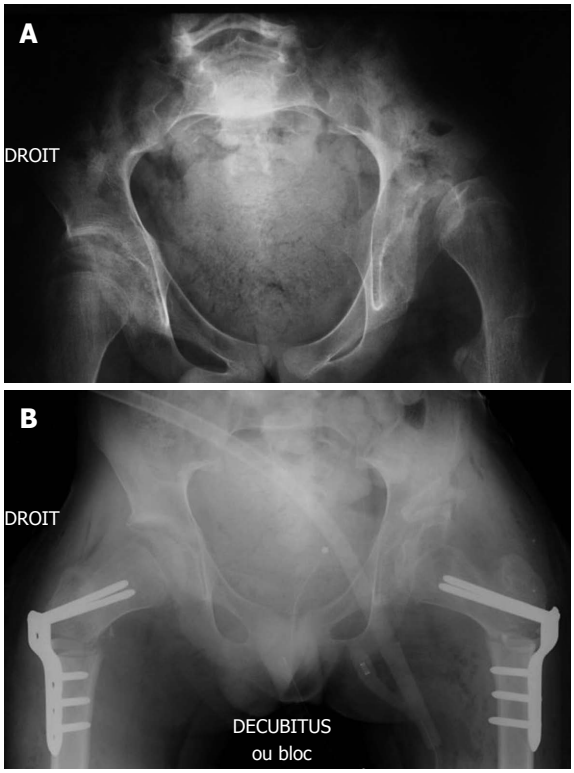

Figure 3 Pre (A) and post-operative operative antero-posterior (B) radiographs of the pelvis (male patient, closed triradiate cartilage).

open the osteotomy. The maximum opening of the osteotomy is assessed under an image intensifier. The graft obtained from the femoral shortening must be wedged on the basis of this measurement. A 2 mm Kirschner wire is inserted into the graft to help push it into the opened space. Spreading the two osteotomes, or, using a bone distractor, opens the space created by the osteotomy and allows the bone graft to slide into it, without having the graft rotate around the wire. As soon as approximately 40% of the length of the graft passes the outer table, the upper osteotome can be removed. At this point, the graft can be advanced further by hitting the tip of the Kirschener wire with an adequately sized hammer. Counter pressure must be applied on the Kirschener wire when removing the second osteotome. At this stage, the Kirschener wire can be removed and, if needed, a bone impactor can be used to impact the graft further. There is no need to fix the bone graft with metal hardware because soft tissues contribute toward keeping the bone graft in place by pushing it against the iliac bone, as the surgical dissection is reduced compared with standard techniques[24].

Radiographic assessment: An anterior-posterior radiograph of the pelvis and a lateral radiograph of the operated hip must be performed to assess the coverage of the femoral head and verify good positioning of the bone graft (Figures 2 and 3).

Length of surgery: Surgical time is reduced with this procedure compared with standard techniques. The procedure lasts between 15 and 25 min, from skin incision to skin closure. Longer operating times (from 30 to 40 min) were observed at the beginning of our experience.

Radiation exposure: Because the osteotomy is performed under image intensifier guidance, the amount of exposure may be higher compared with standard open techniques.

Dangers: vessels and nerves

One possible complication, although not yet encountered by the authors of this study, is a lesion of the superior gluteal artery and/or the superior gluteal nerve, which run close to each other approximately 3-4 cm proximal to the skin incision. We recommend ensuring that the skin incision is not excessively proximal and that the incision is made only after the identification of adequate reference points. In order not to damage the sciatic nerve, a smooth dissector can be placed under the periosteum to reach the sciatic notch. The osteotome can be used safely above the dissector, which protects the nerve running below it. No cases of sciatic nerve damage or transection have been reported[24].

Surgical indications

This procedure is indicated for non-ambulatory, GMFCS Ⅳ and Ⅴ, patients with severe CP who have unilateral or bilateral hip subluxation or dislocation and acetabular dysplasia. If the hip does not reduce after soft-tissue release and VDRSO, an open reduction should be considered. Hips that have been displaced for several years are most likely to be associated with capsular retraction, and percutaneous pelvic osteotomy should not be performed. This surgical procedure should not be performed in ambulatory patients because the effect of cutting through the abductor muscle mass is not known.

Ethics

Study ethics approval was obtained (CECIC Rhône-Alpes-Auvergne, Grenoble, France IRB 5921).

Statistical analysis

The results were analyzed using a paired Student's *t* test to assess the pre- and post-operative differences. The level of significance was set at $P < 0.05$.

RESULTS

Radiological assessment

The mean Reimers' migration percentage (MP) improved from 63% (range: 33%-100%) pre-operatively to 6.5% (range: 0%-70%) at the final follow-up ($P < 0.05$). The MP remained stable during the follow-up period; it was 14%, 15%, 13.6% and 12.4% at 3, 6, 12 and 18 mo after surgery, respectively.

The mean acetabular angle (AA) improved from 34.1° (range: 19-50°) pre-operatively to 14.1° (range: 5-27°) ($P < 0.05$). The AA remained stable during the follow up period; it was 8.0°, 6.9°, 6.4° and 8.0° at 3, 6, 12 and 18 mo after surgery, respectively.

Table 2 Post-operative rate of complications (n = 21)

Complication	n (%)
Avascular necrosis (femoral head)	0 (0.0)
Bone graft dislodgement	0 (0.0)
Hip dislocation	0 (0.0)
Premature triradiate cartilage closure	0 (0.0)
Pathological fracture	2 (9.5)[1]
Post-operative pain	1 (4.7)
Pain at last follow-up	0 (0.0)
Post-operative infection	0 (0.0)
Death	1 (4.7)[2]

[1]One femur fracture occurred at the distal metaphysis and was not directly related to the surgical procedure (osteoporosis). The other fracture occurred 18 mo after surgery at the distal end of the metal hardware (trauma); [2]One Gross Motor Function Classification System Ⅴ patient died approximately 3 mo post-surgery due to a severe respiratory tract infection.

Follow-up

At 18 mo average follow-up (range: 9-28), all hips remained located and the MP and AA improved from 63% to 6.5% and from 34.1° to 14.1°, respectively ($P < 0.05$). The MP and AA remained stable between the index surgery and the last follow up visit. We did not detect radiographic evidence of premature closure of the triradiate cartilage in any patient with open triradiate cartilage in our series. The surgical correction of the MP and AA was comparable in hips with open (n = 14) or closed (n = 8) triradiate cartilage ($P < 0.05$). All operated hips were pain-free at the time of the last follow-up visit, although one patient had pain for 6 months after surgery. We did not observe any cases of bone graft dislodgement or avascular necrosis of the femoral head.

Post-operative immobilization

Immobilization was accomplished postoperatively with a spica cast for 10 wk in 9 out of 21 patients (42.8%) because of abnormal and/or dystonic movements.

Post-operative complications

One GMFCS Ⅴ patient died approximately three months after surgery because of a severe respiratory tract infection. Two patients had unilateral femur fractures. One femur fracture occurred at the distal metaphysis and was not directly related to the surgical procedure (osteoporosis). The other fracture occurred 18 mo after surgery at the distal end of the metal hardware (trauma). No cases of avascular necrosis of the femoral head, bone graft dislodgment, hip dislocation and premature closure of triradiate cartilage were recorded (Table 2).

DISCUSSION

Most non-ambulatory, GMFCS Ⅳ and Ⅴ patients with

severe CP that present with progressive hip subluxation or dislocation and acetabular dysplasia can achieve a painless and stable hip when a pelvic osteotomy is performed through a minimally invasive surgical approach in conjunction with VDRSO and soft tissue release surgery.

The skin incision, 2-3 cm in length, is wide enough to allow the straight and curved osteotomes to perform the osteotomy. One to two and a half centimeter osteotomes can be used without damaging the skin and subcutaneous soft tissues. The osteotomes can be displaced easily upwards and downwards towards the anterior iliac spine and the sciatic notch, respectively. Using a standard technique to reshape the acetabulum, Roposch *et al*[25], Robb *et al*[26], and Inan *et al*[27] demonstrated that a stable, painless, and concentric reduction of the hip could be achieved in most of their patients. All authors reported good results with improvement of the MP and AA[25-30].

More recently, Canavese *et al*[24] described a minimally invasive, pelvic osteotomy technique to correct acetabular dysplasia in severely involved CP patients. Canavese *et al*[24] undertook a retrospective review of 28 patients (17 boys and 11 girls) with the diagnoses of CP, GMFCS level Ⅳ and Ⅴ, progressive hip subluxation and acetabular dysplasia who were treated surgically by simultaneous percutaneous pelvic osteotomy, VDRSO and soft tissue release. The authors reported favorable mid to long term results and concluded that similar radiological and clinical results with less muscle stripping, less bleeding and a shorter operating time compared to traditional surgical techniques can be achieved with a percutaneous pelvic osteotomy in conjunction with VDRSO and soft tissue release[24].

We did not detect radiographic evidence of premature closure of the triradiate cartilage in any patients with open triradiate cartilage in our series. Image intensifier guidance and adequate osteotomes are needed to prevent physeal damage and avoid this complication. The osteotomy extends down to the triradiate cartilage, but does not cross it (Figure 2). Bucholz *et al*[31] found that premature closure of the triradiate cartilage did not affect the stability of the hip if the closure occurred after 10 years of age. Twelve patients (5%) in our group were 10 years or older at the time of surgery.

We found that this technique could also be successfully performed in patients with severe CP that have closed triradiate cartilage (Figure 3). Surgical correction of the MP and AA was comparable in hips with open or closed triradiate cartilage. This is most likely related to the porous bone quality of non-ambulatory CP patients, which allows the surgeon to open the osteotomy site and pack in the graft. Osteoporosis is a common finding in patients with severe neuromuscular conditions and in non-ambulatory CP patients[32]. In particular, patients with severe CP suffer from osteoporosis, which contributes to poor bone condition, pathological fractures, and discomfort[32-35].

In skeletally mature patients, the osteotomy must be extended to the original site of the triradiate cartilage to take advantage of the reduced resistance of the porous iliac bone. In this subgroup of patients, broader osteotomes should be used to open the osteotomy. We believe that this procedure is necessary to avoid collapse of the porotic iliac bone under the pressure exerted by the osteotome during the opening maneuver.

We did not observe any cases of bone graft dislodgement. The bone graft comes from the femoral shortening and is reshaped immediately before insertion. Our hypothesis is that soft tissues play an important role in keeping the graft in place, as the surgical dissection is reduced compared to classic techniques. Soft tissue may contribute to keeping the bone graft in place by pushing it against the iliac bone. This hypothesis is further supported by the findings that approximately one-half of our patients did not require cast immobilization, regardless of the age at surgery. In our series, all hips remained located, and no one developed avascular necrosis.

Blood loss is reduced with this technique compared to standard techniques, and the surgical time is shorter. Because the osteotomy is performed under image intensifier guidance, the amount of exposure may be higher compared to standard open techniques.

There is some evidence that VDROs are highly effective in younger patients, before significant acetabular dysplasia develops, but are less effective in older patients[14,29,31,36]. In their long-term follow-up study, Song and Carroll reported hip dislocation or subluxation rates of 26% after VDRSO alone and 12% after VDRSO and pelvic osteotomy[29]. Khalife *et al*[30] reported a 13.5% redislocation rate after VDRSO. They concluded that the major risk factors for secondary dislocation appear to be insufficient correction of preexisting valgus and uncorrected acetabular dysplasia. In their group of patients with severe CP that underwent unilateral hip surgery, Canavese *et al*[14] found that greater than 50% had an MP over 50%, or had redislocation of the operated hip or displacement of the contralateral hip at skeletal maturity. Mid- and long-term follow-up studies are required to assess redislocation and/or revision surgery rates and to draw a definitive conclusion. During the follow-up period, none of the patients required additional surgery because all hips remained located.

Although longer follow-up studies are required to draw definitive conclusions, our findings indicate that a combined approach of percutaneous pelvic osteotomy, VDRSO and soft-tissue release is an effective, reliable, and minimally invasive method for the treatment of spastic dislocated hips in patients with severe CP. Patients with relative incongruity, closed triradiate cartilage, and some deformity of the femoral head can benefit from this combined approach. If the hip does not reduce after soft-tissue release and VDRSO, an open reduction should be considered. Pelvic osteotomy through a less invasive surgical approach appears to be a valid alternative with outcomes similar to standard techniques. This method allows for less muscle stripping and blood loss and a shorter operating time. Recent studies suggest that soft-tissue procedures for the management of hip displacement in

children at GMFCS levels Ⅳ and Ⅴ have a high failure rate, but the best form of bony reconstruction is yet to be determined.

COMMENTS

Background

Acetabular dysplasia and hip subluxation and dislocation are common findings in children with cerebral palsy. The risk of hip displacement is related to the gross motor functional level as graded by the Gross Motor Function Classification System (GMFCS). The risk of progressive hip subluxation and/or dislocation is higher in GMFCS Ⅳ and Ⅴ patients.

Research frontiers

The goal of any treatment is to create a reduced, stable, mobile hip with reduction of existing pain. Once a hip develops significant subluxation, reduction and stabilization can be achieved with a varus, derotational shortening femoral osteotomy (VDRSO) to decrease anteversion and the tension on the surrounding hip musculature, including the hamstrings. If acetabular dysplasia is present, acetabular osteotomy may be needed.In this study, authors demonstrate that the correction of hip dysplasia can be safely achieved with a minimally invasive technique, *i.e.*, percutaneous pelvic osteotomy.

Innovations and breakthroughs

Although longer follow-up studies are required to draw definitive conclusions, a combined approach of percutaneous pelvic osteotomy, VDRSO and soft-tissue release is an effective, reliable, and minimally invasive method for the treatment of spastic dislocated hips in patients with severe cerebral palsy. Patients with relative incongruity, closed triradiate cartilage, and some deformity of the femoral head can also benefit from this combined approach.

Applications

This procedure is indicated for non-ambulatory, GMFCS Ⅳ and Ⅴ, severe cerebral palsy patients with unilateral or bilateral hip subluxation or dislocation and acetabular dysplasia. If the hip does not reduce after soft-tissue release and VDRSO, an open reduction should be considered. This surgical procedure should not be performed in ambulatory patients because the effect of cutting through the abductor muscle mass is not known.

Terminology

Cerebral palsy indicates a group of non-progressive disorders of movement and posture caused by abnormal development of, or damage to, the motor control centers of the brain. The condition can be caused by events before, during, or after birth. Acetabular dysplasia, hip subluxation and dislocation, lower limb abnormalities, tendon contractures and scoliosis are common orthopedic disorders in cerebral palsy patients.

Peer review

The authors presented a new surgical technique. The pelvic osteotomy can be performed through a 2 to 3 cm skin incision. The clinical and radiological outcomes are good. The results are interesting, and this approach can be used in patients with open and closed triradiate cartilage. The percutaneous pelvic osteotomy seems to be an effective, reliable, and minimally invasive method for the treatment of acetabular dysplasia in patients with severe cerebral palsy.

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BRIEF ARTICLE

Reliability of preoperative measurement with standardized templating in Total Knee Arthroplasty

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Abstract

AIM: To investigate the correlation between preoperative measurement in total knee arthroplasty and the prosthetic size implanted.

METHODS: A prospective double-blind study of 50 arthroplasties was performed. Firstly, the reliability and correspondence between the size of said measurement and the actual implant utilized was determined. Secondly, the existing correlation between the intra- and interobserver determinations with the intraclass correlation coefficient was analyzed.

RESULTS: An overall correspondence of 54%, improving up to 92% when the measured size admitted a difference of one size, was found. Good intra- and interobserver reliability with an intraclass correlation coefficient greater than 0.90 ($P < 0.001$) was also discovered.

CONCLUSION: Agreement between the preoperative measurement with standardized acetate templates and the prosthetic size implanted can be considered satisfactory. We thus conclude it is a reproducible technique.

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Key words: Total knee arthroplasty; Templating; Preoperative measurement; Prosthetic size; Correlation coefficient

Core tip: Choosing the correct size in total knee arthroplasty is one of the factors known to the good evolution of this procedure. Preoperative evaluation using templates is a recommended step in achieving this goal. There are controversies in the literature on the correlation between this measurement and the size of the prosthesis finally implanted.

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INTRODUCTION

Preoperative planning in total knee replacement helps in making decisions and anticipating potentially severe problems that may arise during surgery[1,2]. X-rays in two projections that include the hip and ankle allow for the localization of the mechanical axis and the appropriate planning of the femoral angulation, the thickness of the polyethylene, the height of the joint line, and the ideal size of the prosthetic components.

Oversized components may cause tissue irritation or affect the lower extremity joints during articular stress. On the other hand, undersized components may lead to the exposure of the damaged bone, a greater peri-prosthetic osteolysis, and the overload of the articular contact zone with accentuated wearing down of the polyethylene insert[3].

Measurement with standardized templates on the preoperative X-ray is a commonly used practice in this type of surgery and some authors have proclaimed its advantages[4-9]. However, authors like Knight *et al*[10] or Heal *et al*[11] have pointed out its limitations. Schiffers *et al*[12] have even suggested using differing diagnostic methods such as computerized axial tomography.

The aim of this investigation was to ascertain the suitability of preoperative measurement of a prosthetic knee implant. Our hypothesis was that preoperative measurement would be reproducible, and thus help the surgeon in choosing the most suitable implant.

MATERIALS AND METHODS

A prospective double-blind study to assess the suitability of preoperative measurement of a prosthetic implant by evaluating 50 primary TKA's consecutively implanted was carried out. The first diagnosis was primary osteoarthritis in all cases.

The series was made up of 37 females (74%) and 13 males (26%). The average age and weight were 73.40 years (ranging from 57 to 84) and 76.45 kg (55 to 95) in the female subgroup. In the male subgroup, the average age was 73.38 years (63 to 88), and the average weight was 81.92 kg (68 to 98). The right side was involved in 30 cases and the left in twenty. There were no bilateral cases. Minimally invasive surgery (MIS), *via* mid-vastus approach, was carried out in 9 cases (18%).

Preoperative anteroposterior and lateral weight-bearing X-rays and a 30º patellar axial view were taken; a long standing radiograph that included the hip and the ankle was also done according to the specific protocol for this work. In order to make all the measurements reproducible, a constant and uniform distance between the X-ray tube and the knee was maintained.

The measuring was done by superimposing the acetate templates on the X-ray images. Two observer groups were formed (observer 1 and 2), as well as the implanting surgeon (neither of them knew the measurement of the other). The size implanted by the surgeon, who did not have knowledge of the measurement carried out previously, was considered the standard with which to compare. The TKA implanted was always the Triathlo® Knee System (Stryker, Mahwah, New Jersey, United States) with tibial, femoral, and patellar components cemented. The thickness of the polyethylene was decided by the surgeon during surgery according to the final mobility and stability obtained with the trial implants.

All data were analyzed with the statistical SPSS (V 15.9) software package. A tool for assessing reliability (Cronbach's Alpha > 0.95) was used throughout the process. All the variables were described by inputting the percentage and the number of cases as categorical variables. The quantitative variables were described as an average and a standard deviation. The suitability study was done by calculating the intraclass correlation coefficient (ICC), also denominated the "internal correlation coefficient" or "reliability coefficient", with a confidence interval of 95%. The relationship between the variables was described with contingency tables for the study of two categorical variables. The inference was studied with the χ^2 test or Fisher's exact test, as required. The inference was carried out with the *t* test. Finally, by applying logistic regression, a multivariant approximation was obtained by selecting the variables that previously showed a slight slide towards significance ($P < 0.20$). The level of significance was set at $P < 0.05$.

Table 1 Suitability of the implant size

		Frequency	Percentage
Femur	Yes	29	58%
	No	21	42%
Tibia	Yes	25	50%
	No	25	50%

Yes: Same exact size; No: Size different than the measured one.

Table 2 Differences between the measured size and the size implanted in the femur and tibia

	Frequency	Percentage
Femur		
-2 (2 sizes smaller)	2	4%
-1 (1 size smaller)	11	22%
0 (same size)	27	54%
1 (1 size larger)	8	16%
2 (2 sizes larger)	2	4%
Tibia		
-2 (2 sizes smaller)	0	0%
-1 (1 size smaller)	11	22%
0 (same size)	24	48%
1 (1 size larger)	13	26%
2 (2 sizes larger)	2	4%

RESULTS

The correlation between the femoral component measured and the one implanted was 55%, and 50% for the tibial component (Table 1). The overall value was 54%. In light of a variability of more or less a correlative size, the percentage increases up to 90% for the femur and 94% for the tibia (Table 2). There was a tendency to underestimate the size of the tibia for which the cause was unknown. The measured size was right for 58.2% of the women and 42.4% of the men. With reference to the side operated on, there seems to be a greater percentage adequate for the right-side at 60% while for the right-side it was 45%. When the MIS technique was used, the suitability percentage was 66.7% with a clear decrease of effectiveness in the measurement of the tibial component.

Intraobserver reliability was clearly correct in all cases; the lower limit of the CI was 95% of the ICC, which was greater than 0.90. It was statistically significant in all of them ($P < 0.001$). There was a tendency towards a slightly lower ICC in the case of the tibia compared to the femur, and the same tendency relative to the second observer in comparison to the first (Table 3). The study of the intraobserver results was carried out by comparing the measurements of observer 1 before and after the

Table 3 Intraclass correlation coefficient inter- and intraobserver values

	Femur	Tibia
Observer 1	0.989	0.974
Observer 2	0.960	0.944
Before operation	0.994	0.942
After operation	0.943	0.863
ICC	0.735	0.806

Intraclass correlation coefficient (ICC) for intraobserver study. $P < 0.001$ (before *vs* after, observer 1 *vs* observer 2, measured *vs* implanted).

operation with those of observer 2. Thus, it was possible to confirm the reproducibility of the measuring process on the same person by taking the readings at different times. The ICC was > 0.9 for observer 1, the same as for observer 2, and the same was true for both the femur and the tibia. That being the case, the measurement was considered valid and reproducible. The reading of the femur turned out to be slightly more reliable and reproducible than that of the tibial plate.

The interobserver study makes it possible to know whether different people can carry out the preoperative measurements and obtain the same or similar results. The first readings by observer 1 were compared with those of observer 2 and subsequently the second readings of those very same observers were also compared. Intra- and interobserver reliability was high in all of the cases (both groups of observers for both bones); the lower limit of the IC was 95% of the ICC, which was greater than 0.77. It was statistically significant in all of them ($P < 0.001$). Therefore, it can be said that the study with standardized templates can be reproduced with different observers. The reading of the femoral component is still better than the reading of the tibia, just like in the intraobserver study.

DISCUSSION

The measurement with templates should be a part of the systematic preoperative evaluation in TKA. It allows for finding the most adequate size of the implant (as exactly as possible) and the prevention of possible errors or technical difficulties at the time of surgery[13]. However, the aforementioned opinion is not uniform. Some studies[14] suggest that preoperative measuring is not currently substantially beneficial for the surgeon, since the correlation percentage stands at around 50%. Our study obtained a 54% reliability percentage for the measurement of the implanted prostheses. Although this figure is not very high, the percentage increases to 92% if one larger or smaller size is added. There are few works that assess intra- and interobserver reliability in the preoperative measuring of implants. Bothra *et al*[15] observed greater intraobserver than interobserver agreement. However, the differences between both readings were insignificant in terms of clinical practice. Good inter- and intraobserver agreement was demonstrated for both femoral and tibial templating in a recent work. The correct size of the implant was predicted in only 48% of the femoral and 55% of the tibial components[16]. Those figures are very similar to the results in the current study.

Preoperative measuring, if accompanied by checking/verification of the results after the operation also initiates a dynamic learning process as useful for the expert surgeon as for the resident in training. Therefore, this planning makes for a reduction in the learning curve of the surgeon[17]. It also shortens surgery duration, and facilitates the job of the surgical nurse and the adequate programming of the surgical theatre.

Howcroft *et al*[14] found greater agreement in the measurements of the tibia in comparison to the femur. The measurement was very similar for both components in this study when the average of the measurements was taken. It was slightly greater for the tibia, but the difference was not statistically significant. The slight difference seen might be influenced by the different anatomical characteristics of the tibia and the femur[18] as well as the projection of the bone segment in the radiography.

The measurement with standardized templates might not end up being very exact for different reasons, such as the incorrect superimposition of the templates on the part of the observer. The collaboration of the Radiology department is essential, as defects in the positioning of the member upon doing the X-rays or a deficient quality of the same can make the measure useless, or even lead to errors in the surgical procedure[19-21]. The acceptance of a uniform protocol agreed between surgeons and radiologists should avoid these errors.

As diverse authors indicate[22,23], the acquisition of digitalized X-rays may permit greater ease in the preoperative measuring of orthopedic implants. With this method, it is possible to select the magnification, and the superimposition of the digital templates is more exact and less subject to personal variables. Trickett *et al*[16] studied the correlation of measurements with digitalized templates from 40 TKA patients. The results were similar to those obtained with standardized acetate templates. The same findings were published by The *et al*[24] upon comparing analogical and digital templates in hip arthroplasties. Other authors[25,26] even find a greater frequency of errors with the latter compared to the acetate templates. Manual measurement may disappear with time, especially in certain countries, but measurement with standardized templates will still be the rule for many years to come. The profound change in hospital equipment required and the cost-benefit it yields will not be feasible in underdeveloped healthcare systems.

The utility of this preoperative practice can be confirmed with the results obtained herein. Measurement with standardized templates allows for finding the closest suitable implant size, facilitates the surgical technique, is a reproducible technique and can presumably improve the clinical outcomes of knee arthroplasties.

COMMENTS

Background

The measurement with templates should be a part of the systematic preoperative evaluation in total knee arthroplasty. It allows for finding the most adequate

size of the implant (as exactly as possible) and the prevention of possible errors or technical difficulties at the time of surgery.

Research frontiers

Measurement with standardized templates on the preoperative X-ray is a commonly used practice in this type of surgery and some authors have proclaimed its advantages. However, other authors have pointed out its limitations.

Innovations and breakthroughs

The study obtained a 54% reliability percentage for the measurement of the implanted prostheses. Although this figure is not very high, the percentage increases to 92% if one larger or smaller size is added. Good inter- and intraobserver agreement was demonstrated for both femoral and tibial templating.

Applications

Preoperative measuring, if accompanied by checking/verification of the results after the operation also initiates a dynamic learning process as useful for the expert surgeon as for the resident in training. Therefore, this planning makes for a reduction in the learning curve of the surgeon. It also shortens surgery duration, and facilitates the job of the surgical nurse and the adequate programming of the surgical theatre.

Terminology

Preoperative measuring (templating) was done by superimposing the acetate templates on the X-ray images of the knee.

Peer review

The utility of this preoperative practice can be confirmed with the results obtained herein. Measurement with standardized templates allows for finding the closest suitable implant size, facilitates the surgical technique, is a reproducible technique and can presumably improve the clinical outcomes of knee arthroplasties. Manual measurement may disappear with time, especially in certain countries, but measurement with standardized templates will still be the rule for many years to come.

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BRIEF ARTICLE

Acute effects of stochastic resonance whole body vibration

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Abstract

AIM: To investigate the acute effects of stochastic resonance whole body vibration (SR-WBV) training to identify possible explanations for preventive effects against musculoskeletal disorders.

METHODS: Twenty-three healthy, female students participated in this quasi-experimental pilot study. Acute physiological and psychological effects of SR-WBV training were examined using electromyography of descending trapezius (TD) muscle, heart rate variability (HRV), different skin parameters (temperature, redness and blood flow) and self-report questionnaires. All subjects conducted a sham SR-WBV training at a low intensity (2 Hz with noise level 0) and a verum SR-WBV training at a higher intensity (6 Hz with noise level 4). They were tested before, during and after the training. Conclusions were drawn on the basis of analysis of variance.

RESULTS: Twenty-three healthy, female students participated in this study (age = 22.4 ± 2.1 years; body mass index = 21.6 ± 2.2 kg/m^2). Muscular activity of the TD and energy expenditure rose during verum SR-WBV compared to baseline and sham SR-WBV (all $P < 0.05$). Muscular relaxation after verum SR-WBV was higher than at baseline and after sham SR-WBV (all $P < 0.05$). During verum SR-WBV the levels of HRV were similar to those observed during sham SR-WBV. The same applies for most of the skin characteristics, while microcirculation of the skin of the middle back was higher during verum compared to sham SR-WBV ($P < 0.001$). Skin redness showed significant changes over the three measurement points only in the middle back area ($P = 0.022$). There was a significant rise from baseline to verum SR-WBV (0.86 ± 0.25 perfusion units; $P = 0.008$). The self-reported chronic pain grade indicators of pain, stiffness, well-being, and muscle relaxation showed a mixed pattern across conditions. Muscle and joint stiffness ($P = 0.018$) and muscular relaxation did significantly change from baseline to different conditions of SR-WBV ($P < 0.001$). Moreover, muscle relaxation after verum SR-WBV was higher than after sham SR-WBV ($P < 0.05$).

CONCLUSION: Verum SR-WBV stimulated musculoskeletal activity in young healthy individuals while cardiovascular activation was low. Training of musculoskeletal capacity and immediate increase in musculoskeletal relaxation are potential mediators of pain reduction in preventive trials.

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Key words: Musculoskeletal system; Electromyography; Quasi-experimental study; Prevention; Relaxation

Core tip: Musculoskeletal function improves after application of stochastic whole body vibration (SR-WBV). The pathway of the beneficial effect, however, is unclear. This study shows SR-WBV to increase muscle activity of descending trapezius muscle, the muscle that is often associated with reported pain in computer work. Participants report improved muscular relaxation after SR-WBV while the cardiovascular activation was very low. In addition to ergonomic interventions SR-WBV may help to prevent trapezius muscle related pain at work.

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INTRODUCTION

Stochastic resonance whole body vibration training (SR-WBV) is still rather new and to date, only few studies have been conducted with this kind of vibration[1,2]. Nevertheless, there is increasing evidence that SR-WBV improves musculoskeletal function in patients with neurodegenerative disorders[3-5] and paraplegia[6]. The application of SR-WBV in stroke patients has been approved and found to not be physically demanding[7]. SR-WBV is a practical and well-accepted method to prevent musculoskeletal disorders (*e.g.,* neck, shoulder or low back pain)[8] while the exact physiological working mechanisms are still unclear[9]. Bosco *et al*[10] found metabolic changes after sinusoidal WBV, although these findings could not be reproduced by other researchers[9]. By using electromyography (EMG) an enhancement of the muscle activity was shown after sinusoidal WBV[11]. Studies on the activity of back muscles are still lacking. Therefore, the aim of this study was to assess the immediate effects of SR-WBV on back muscles, especially the descending trapezius muscle. A recent study showed that sustained trapezius muscle activity is associated with neck and shoulder pain in young adults[12]. It was hypothesized that SR-WBV would increase muscle activity during SR-WBV while the expected cardiovascular activation would remain low. In addition increased muscle relaxation is expected after SR-WBV.

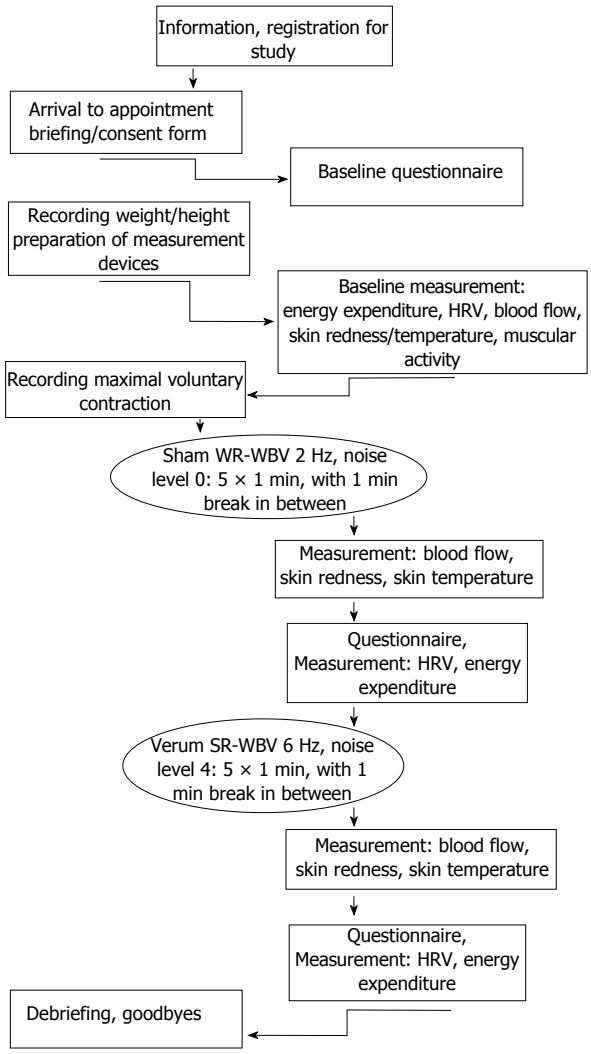

Figure 1 Flow chart of the study procedure. HRV: Heart rate variability; SR-WBV: Stochastic resonance whole body vibration.

MATERIALS AND METHODS

Ethics

All participants gave informed consent prior to study inclusion. The study was performed in accordance with the requirements defined by the Swiss Society of Psychology. Every participant was able exit the study at any time. The study has been approved by the Ethical Committee of the Faculty of Human Sciences of the University of Bern.

Subjects

Healthy participants between 18 and 30 years with a body mass index (BMI) between 17 and 26 kg/m^2 being able to cope physically with the load of a SR-WBV training were included in the study. Potential participants with any kind of metallic or synthetic implants such as a cardiac pacemaker were excluded. Due to gender specific variations in heart rate variability (HRV)[13] male participants were excluded as well. In addition, athletes and individuals performing more than three training units per week were also excluded. All of these restrictions assured homogeneity of the fitness level and the age range within the sample as they could possibly interfere with the measurements[14] and hence, confound the outcome data.

Design

The present study can be considered as a quasi-experimental pilot study using repeated measurements. The participants performed two training sessions: a sham SR-WBV at a frequency where no effects were expected[1] followed by training at a vibration frequency high enough to expect effects (Figure 1). Thus, changes from sham SR-WBV to verum SR-WBV levels were considered as acute training effects.

SR-WBV

Ward *et al*[15] defined stochastic resonance as "a nonlinear cooperative effect wherein the addition of a random process, or 'noise' to a weak signal, or stimulus results in improved detectability or enhanced information content in some response". SR-WBV is a whole body vibration training based on stochastic oscillation with the benefit that the sensorimotor system does not adapt to the stim-

ulus and therefore reacts continuously[3]. SR-WBV training in this study lasted for one minute. SR-WBV training was followed by a break of one minute where the person on the device was able to rest. For SR-WBV the srt Zeptor® medical plus noise device (FreiSwiss AG, Zurich, Switzerland)[1] was used.

For the sham SR-WBV a frequency of 2 Hz with noise level 0 was used as no increased muscle activity effects can be expected under such conditions[1]. For the verum SR-WBV intervention a 6 Hz frequency with noise level 4 was used as this condition is applied most often when subjects have a free choice. Moreover, these SR-WBV training characteristics have been shown to activate muscles[8,16].

Muscle activity

The activity of the descending trapezius (TD) muscle was measured by EMG following the application recommendations of SENIAM (Seniam project)[17] and Perreto[18]. EMG signals were taken by single-use surface electrodes (Nicolet Disposable Center Snap Rectangular Silver/Silver Chloride Electrode, REF: 019-767700, Warwick, United Kingdom). All myoelectric signals were filtered by a pre-amplifier (Input impedance > 100 MOhm, common mode rejection ratio > 100 dB, Base gain = 500, Bandpass 10-500 Hz), then transferred to a transmitter (TeleMyo™ 2400T G2 Transmitter, Noraxon Inc. United States, Velamed medical technics and biomedical concepts GmbH, Cologne, Germany) and finally transduced to a receiver (TeleMyo™ 2400T G2 Receiver, Noraxon Inc. United States, Velamed medical technics and biomedical concepts GmbH, Cologne, Germany). The EMG signals were sampled with a frequency of 2 kHz. Obtained data were displayed and analyzed with the "Analog Signal Caption and Analysis" software (ADS, uklabs, Kempen, Germany). The root-mean-square (RMS) values of the EMG-signal parts of maximal voluntary contraction (MVC) and SR-WBV were calculated and all SR-WBV signals normalized to the RMS values of the MVC signal part (%MVC).

Energy expenditure

Total energy expenditure (EE) during one training session was assessed using a SenseWear Armband (SWA) motion sensor (HealthWear Bodymedia, Pittsburgh, Penn., United States) placed on the back of the upper right arm just above the triceps muscle. The SWA measures heat flux, galvanic skin response, skin temperature and near-body temperature including also a 2-axis accelerometer[19,20]. Based on additional personal data such as gender, age, body height and weight, EE was calculated by the SWA system[21]. Validity and reliability of the SWA has been shown for different situations, activities and populations[22].

Heart rate variability

Heart rate variability (HRV) was assessed following the guidelines of the Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology (1996) (furthermore referred as the task force). According to this task force, a power spectral analysis is especially suitable for short-term measurements. As such, the square root of the mean of the sum of the squares of the differences (RMSSD) between adjacent intervals was analyzed[23]. The RMSSD reacts sensitively to fast variations of the HRV and can be seen as a marker for parasympathetic activity[13]. Therefore, RMSSD can be used as a proxy for the degree of body relaxation. For HRV measurements the telemetric Polar RSX 800 system (Polar Electro Europe BV, Zug, Switzerland) was used. This procedure has been shown to be accurate for short-term measurements[24].

Skin measurements

The skin microperfusion was measured using the Periflux laser-Doppler device (Periflux 4001, perimed AB, Järfälla, Sweden). The Periflux device "counts" by laser technology the movement of blood cells at the moment of measurement and provides an average value of the blood flow in arbitrary perfusion units (AU). The reliability of the instrument has been demonstrated in previous studies[25].

Skin redness was measured using the Chroma Meter CR-300 Camera (Minolta Camera Co., Ltd., Osaka, Japan). This device is specially designed to analyze reflecting colors of surfaces and can therefore be used to analyze the degree of redness of the skin surface (Minolta, n.d). This technique is based on pulsed xenon light illuminating the surface and feedback systems recording the incident and reflected light and thus calculating the color of the surface. The device is often used in medical studies and its reliability has been approved by Van den Kerckhove *et al*[26]. In addition, skin temperature was measured using an infrared thermometer (ScanTemp 380, TFA Dostmann, Wertheim-Reicholzheim, Germay). Several skin characteristics were measured at standardized anatomical landmarks on the upper, middle and lower back as proposed by Perreto[18].

Questionnaire assessment

Muscular well-being and relaxation were assessed by a short version of the Burger *et al*[8] self-administered questionnaire and completed before and after the sham SR-WBV and after the verum SR-WBV.

This questionnaire was based on items of the chronic pain grade questionnaire (CPG)[27], but has some changes due to time specification. Four items being relevant for the study question were used. The first item assessed pain in muscle and joints, the second muscle and joints stiffness while the third and fourth item assessed muscular and joint well-being, as well as muscular relaxation. The participants were asked to rate themselves on a 10-point Likert scale. In its original version the CPG showed a high internal consistency and reliability (Cronbach alpha > 0.9)[28]. Other studies showed good correlations between the CPG and other pain related proxies[29].

Procedure

University students were the main recruitment source.

Eligible participants were contacted and informed about this study and their potential participation in early February 2012. The participants could apply *via* email or telephone, then received further information about the procedure of the study and were asked to inform the authors prior to the appointment about any acute health issues such as a major flu, headaches, feeling unwell, back or muscle pains. In such a case, the potential participants were ineligible and excluded from the study. All measurements were conducted at the Movement Laboratory of the Bern University of Applied Sciences. After their arrival at the laboratory, participants were informed about the procedure and signed the consent form. Then, the self-administered baseline questionnaires were completed. Body weight and height were recorded. Skin of the participant was prepared, the EMG device as well as the polar belt and the SWA were placed. The anatomical landmarks were palpated and electrodes then attached by the same trained research assistant at all times. The resistance of the electrodes was tested and a resistance beneath 10 κΩ was accepted[17]. If the resistance was higher the electrodes were removed and the preparation procedure of the skin repeated. The cables connecting the electrodes with the EMG device were attached to the body of the participants to avoid motion artifacts. The participants were then given a large T-shirt to wear over these instruments.

The EMG, EE, HRV and skin characteristics baseline data were measured while standing still. To normalize the EMG data, measurement of the maximal voluntary muscles force (maximal voluntary contractions, MVC) were taken by the same trained research assistant at all times. To compare muscle activities of different subjects, an isometric MVC had to be performed prior to the test trials for data normalization (%MVC). MVC testings (3-5 s per muscle, break of 15 s between two series) were based on muscle tests[30].

Once the participants had been prepared, the training started. For the first intervention, the sham SR-WBV was chosen. The subjects were barefoot and asked to stand still during 15 s on the srt Zeptor® medical vibration platform with loose-hanging arms at their sides and slightly bent knees looking at a fixed point on the wall as a preparation before the vibration of one minute took place, which was followed by a recovery of 60 s where the participants could relax and move on the platform. This procedure was repeated 5 times. The participants completed the intervention training on the srt Zeptor® medical with the verum SR-WBV. Hence, both SR-WBV training sessions were very similar varying only in vibration frequency and noise level. Skin characteristics were measured immediately after the SR-WBV training. Five minutes after the training the participants were asked to sit down to complete the questionnaire. In the meantime the HRV and the SWA measurements were taken.

Statistical analysis

The HRV data, initially recorded by the Polar System, were exported to the Kubios HRV Version 2.0 software (University of Kuopio, Biosignal Analysis and medical Imaging Group, Kuopio, Finland) to calculate the RMSSD for the specific time intercepts. These time intercepts used for the RMSSD calculations were the 5 times 1 min of vibration training (for the HRV). In addition, the minimal RMSSD reached as well as the average RMSSD over the whole training were taken into account for HRV analysis. Further RMSSD for the baseline (T0), after the sham SR-WBV (T1) and the verum SR-WBV (T2) were calculated. The RMSSD for these measurement points were calculated for 1 min each.

The mean muscle activation of the 1 min vibration blocks in each of the two SR-WBV conditions was calculated based on the EMG data and presented as percent of the (%MVC). For all statistical analyses the SPSS software (version 19, SPSS, IBM Inc., United States) was used and the level of significance was set at $P < 0.05$. Pearson's product-moment correlations between study variables at each time point were calculated. Repeated measures analyses of variance were calculated to test differences between sham and verum SR-WBV. Post hoc tests using the Bonferroni correction were applied. If the assumption of sphericity was violated the degrees of freedom were corrected by the Greenhouse-Geisser correction as proposed by Field[31]. The effect sizes were calculated by the partial eta-squared (η^2).

RESULTS

Twenty-three healthy, female students participated in this study (age = 22.4 ± 2.1 years; BMI = 21.6 ± 2.2 kg/m^2). Table 1 depicts the descriptive study results while the repeated measures analysis of variance results for all measurements are shown in Table 2. Analyses indicated that the activity of the back muscles differed between time points of measurement. Post hoc tests with Bonferroni correction showed that muscle activity increased significantly during sham SR-WBV (2.24 ± 0.48 %MVC) and during verum SR-WBV (5.71 ± 1.14 %MVC) (both $P < 0.0005$). The observed muscle activity increased between sham and verum SR-WBV training condition (3.47 ± 0.97 %MVC) and also reached statistical significance ($P = 0.006$). The effect size for muscle activity change was large ($\eta^2 = 0.50$).

Further analyses showed that HRV dropped during sham and verum SR-WBV training compared to baseline when mean HRV was analyzed and also when minimal HRV reached during SR-WBV was considered (all $P \leqslant 0.0005$). EE rose significantly under verum SR-WBV conditions ($P < 0.0005$). Post hoc tests showed, that increased EE was significant for sham and verum training (4.86 ± 0.81 calories and 21.81 ± 1.36 calories, respectively) as well as the difference between sham and verum training (16.95 ± 1.19 calories) (all $P < 0.0005$). Effect size of change in EE was $\eta^2 = 0.91$.

Among the indicators of microperfusion of the skin, only the flow of the middle back regions showed a significant rise over the three measurement time points (P

Table 1 Descriptive study results (mean ± SD)

	Baseline	Sham SR-WBV (2 Hz, noise level 0)	Verum SR-WBV (6 Hz, noise level 4)
EMG TD (%MVC)	3.43 ± 2.08	5.68 ± 2.78	9.14 ± 5.81
HRV (mean RMSSD, ms)	38.28 ± 19.76	28.07 ± 26.81	26.14 ± 17.38
Energy expenditure (kcal)	13.67 ± 3.41	18.52 ± 2.96	35.48 ± 5.69
Blood flow (perfusion units)			
Neck	27.83 ± 9.22	27.86 ± 11.05	30.81 ± 20.62
Middle back	22.25 ± 6.04	26.33 ± 7.82	27.13 ± 12.45
Lower back	15.40 ± 5.15	14.92 ± 6.22	15.87 ± 6.04
Skin temp (℃)			
Neck	34.48 ± 0.85	35.27 ± 1.04	35.65 ± 0.81
Middle back	33.95 ± 0.99	34.85 ± 1.30	35.19 ± 0.91
Lower back	33.90 ± 1.34	34.19 ± 1.35	34.25 ± 1.32
Skin redness (colour unit)			
Neck	8.56 ± 2.37	8.83 ± 2.75	8.91 ± 2.58
Middle back	6.39 ± 1.63	7.20 ± 2.03	7.25 ± 2.27
Lower back	6.55 ± 1.74	6.34 ± 1.61	6.41 ± 1.94
CPG pain	1.52 ± 0.75	1.33 ± 0.58	1.33 ± 0.91
Stiffness	2.52 ± 2.16	1.95 ± 1.72	1.76 ± 1.67
Well-being	8.10 ± 1.34	8.24 ± 1.04	8.14 ± 1.71
Muscle relaxation	6.67 ± 1.74	7.24 ± 1.95	8.38 ± 0.97

EMG: Electromyography, activation expressed as percentage of activation measured at maximal voluntary contraction (%MVC) of the decending part of the trapezius muscle (TD); RMSSD: Root of the mean of the sum of the squares of the differences; HRV: Heart rate variability; CPG: Chronic pain grade; SR-WBV: Stochastic resonance whole body vibration.

< 0.0005; $\eta^2 = 0.49$) with significant changes between baseline and verum SR-WBV (7.33 ± 1.58 AU, $P < 0.0005$) and sham and verum SR-WBV noise 4 (11.41 ± 2.11 AU, $P < 0.0005$). Skin temperature of neck and middle back differed significantly between baseline and follow-up ($P \leqslant 0.0005$). On average the overall skin temperature raised from baseline to sham SR-WBV by 0.66 ± 0.12℃ ($P \leqslant 0.0005$) and between baseline and verum SR-WBV with 0.92 ± 0.13℃ ($P \leqslant 0.0005$).

Skin redness showed significant changes over the three measurement points only in the middle back area ($P = 0.022$). There was a significant rise from baseline to verum SR-WBV (0.86 ± 0.25 AU, $P = 0.008$).

The self-reported CPG indicators of pain, stiffness, well-being and muscle relaxation showed a mixed pattern across conditions. Muscle and joint stiffness ($P = 0.018$) and muscular relaxation did significantly change from baseline to different conditions of SR-WBV ($P < 0.001$). Moreover, muscle relaxation after verum SR-WBV was higher than after sham SR-WBV ($P < 0.05$).

DISCUSSION

Stochastic whole body vibration training activates the musculoskeletal system[9] while the metabolic and cardiovascular strain is low[7]. The EMG, HRV and EE data of the present study showed significant differences over the different SR-WBV modalities, suggesting SR-WBV related acute psychological and physiological effects[1]. As hypothesized, verum SR-WBV training effect showed a pattern of enhanced muscle activity, decreased HRV and increased EE. With this observed substantial increase of EE and muscle activity, this verum SR-WBV training at a frequency of 6 Hz and noise level 4 fulfills the requirements of a physical activity or an exercise to prevent diseases according to the definition by the United Sates Surgeon General's Report[32]. The latter defined physical activity as "bodily movement that is produced by the contraction of skeletal muscle and that substantially increases energy expenditure" and exercise as "planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness".

However, the 9.14 %MVC muscle activity during verum SR-WBV remains fairly limited compared to more classic strength training such as push-up or press-up exercises which increase the trapezius muscle activity between 22 and 33 %MVC[33]. Similarly, the effects on EE during verum SR-WBV were low to moderate compared to classic resistance exercise. The EE during classical resistance training varies widely[34] from 2.2 to 35 calories per minute adding up to 22 to 350 calories for a 10-min session. Hence, the mean energy consumption of 35.5 calories per 10 min is low but in line with other findings on resistance training related EE[35]. These results support previous findings concerning the moderately increased oxygen absorption during WBV training[3]. Furthermore, these findings suggest that verum SR-WBV training may be an effective prevention tool for musculoskeletal diseases in work environments. SR-WBV training sessions can easily be done before, during or after work without having to change clothes or take a shower afterwards.

HRV measurements during training showed that both sham and verum SR-WBV training conditions may have similar effects on the parasympathetic system. No differences between sham and verum training conditions were found. Thus, cardiovascular training demands in verum SR-WBV are low. The effects of verum SR-WBV on the musculoskeletal system and proxies of microperfusion of the skin (blood flow, temperature and redness) could explain the self-reported musculoskeletal well-being experiences of the participants. The measurements of skin characteristics showed an unusual pattern over all performed analyses. Though the measurements of temperature and skin redness of the three different anatomical locations of the back were correlated with each other only the middle back showed significant differences throughout the means of elicitation. This study demonstrated that there is only a significant rise of blood flow, skin temperature and redness of the skin under verum training conditions, while these changes do not occur under sham training conditions. These findings corroborate those of Elfering *et al*[1] who did not find any significant long-term effects on the prevention of musculoskeletal diseases at very low vibration frequencies. Musculoskeletal relaxation rose significantly after verum SR-WBV training ($P < 0.001$) but not after sham training ($P = 0.657$) while well-being and pain did not show any significant differences after verum SR-WBV. As a healthy young sample was addressed a possible explanation could be a floor effect.

Table 2 Results of repeated measurement analyses of variance

	df[1]	*F*	*P*	η^2	BL *vs* Sham		BL *vs* Verum		Sham *vs* Verum	
						P[3]		*P*[3]		*P*[3]
EMG TD (%MVC)	1.26	20.19	< 0.001	0.50	2.24 ± 0.48	< 0.001	5.71 ± 1.14	< 0.001	3.37 ± 0.97	0.006
HRV (mean RMSSD, msec)	1.54	6.73	< 0.001	0.25	-10.21 ± 4.41	0.094	12.14 ± 3.25	0.004	1.93 ± 2.83	1.000
Energy expenditure (kcal)	1.56	199.90	< 0.001	0.91	4.86 ± 0.81	< 0.001	21.81 ± 1.30	< 0.001	16.95 ± 1.19	< 0.001
Blood flow (AU)	1.42	0.42	0.591	0.02	0.03 ± 2.31	1.000	2.98 ± 4.04	1.000	2.95 ± 4.48	1.000
Middle back	2.00	18.93	< 0.001	0.49	-4.08 ± 1.91	0.136	7.33 ± 1.58	< 0.001	11.41 ± 2.11	< 0.001
Lower back	1.56	0.35	0.655	0.02	-0.48 ± 0.92	1.000	0.48 ± 1.04	1.000	0.95 ± 1.41	1.000
Skin temperature (℃)	2.00	23.79	< 0.001	0.54	0.79 ± 0.18	< 0.001	1.17 ± 0.18	< 0.001	0.38 ± 0.16	0.075
Middle back	1.36	27.98	< 0.001	0.58	0.90 ± 0.19	< 0.001	1.24 ± 0.10	< 0.001	0.34 ± 0.21	0.348
Lower back	1.55	1.74	0.197	0.08	0.29 ± 0.18	0.390	0.35 ± 0.25	0.515	0.07 ± 0.16	1.000
Skin redness (colour unit)	2.00	0.58	0.565	0.03	0.27 ± 0.30	1.000	0.35 ± 0.32	0.889	0.08 ± 0.38	1.000
Middle back	2.00	4.19	0.022	0.17	0.81 ± 0.38	0.130	0.86 ± 0.25	0.008	0.05 ± 0.36	1.000
Lower back	2.00	0.93	0.404	0.04	-0.20 ± 0.11	0.257	-0.14 ± 0.17	1.000	0.07 ± 0.16	1.000
CPG pain	1.55	1.49	0.240	0.07	0.19 ± 0.09	0.127	0.19 ± 0.15	0.641	0.00 ± 0.14	1.000
CPG stiffness	1.33	5.65	0.018	0.22	0.57 ± 0.29	0.187	0.76 ± 0.30	0.023	0.19 ± 0.13	1.000
CPG well-being	1.31	0.09	0.828	0.01	0.14 ± 0.19	1.000	0.05 ± 0.41	1.000	0.10 ± 0.42	1.000
CPG muscle relaxation	2.00	10.32	< 0.001	0.34	0.57 ± 0.45	0.657	1.71 ± 0.33	< 0.001	1.14 ± 0.36	0.014

[1]If the sphericity is not given the Greenhouse-Geisser correction was applied; [3]Bonferroni correction applied for *post hoc* tests. EMG: Electromyography, activation expressed as percentage of activation measured at maximal voluntary contraction ± %MVC) of the decending part of the trapezius muscle ± TD); HRV: Heart rate variability; CPG: Chronic pain grade; RMSSD: The square root of the mean of the sum of the squares of the differences.

The significant rise of mean skin temperature has to be viewed critically. It could be hypothesized that SR-WBV leads to the release of vaso-active substances from connective tissue cells, increasing the local blood flow and the microperfusion of the skin. However, it cannot be excluded that the observed change in skin temperature is related to the procedure of the experiment. For example, baseline values were assessed shortly after the electrodes had been placed, hence, after the participants had spent some time without clothes. This could have caused a cool down of the skin temperature at baseline. Significant changes of the skin measurements were found only in the middle back region. In addition, verum SR-WBV increased musculoskeletal relaxation. The middle back includes the trapezius muscle and according to Blangsted *et al*[36] office workers often report muscle problems of this region. Therefore, the observed increase in blood flow and activity of the trapezius muscles can lead to musculoskeletal relaxation. Relaxation is deeper after muscles have been forced. Many relaxation techniques include this technique, *e.g.,* progressive relaxation technique after Jacobson[37] So, to improve muscle relaxation in clerical workers with excessive stable tension in low back and upper limb musculature SR-WBV appears to be a promising technique that induces relaxation after activation. Also more appropriate postures and better office furniture should be addressed to avoid excessive muscle tension during work.

Limitations

This pilot study had a quasi-experimental design and thus has to face criticism[36]. There are confounders which are difficult to control in quasi-experimental designs and as such they jeopardize the internal validity[38] with respect to alternative explanations of effects that cannot be ruled out. Because of the convenience sampling method, aimed at recruiting healthy, young and physically active participants external validity of the study may be questioned. Potential selection bias has been attempted to control with the limitation of women exercising not more three times a week. With an average activity level of 2.4 training units per week the study participants are comparable to the activity level in the Swiss population[39]. A blinding of the primary investigator was not possible but the blinding of participants was guaranteed by sham training sessions. The participants were told in the beginning that they would go through two identical training programmes and that they would have to complete questionnaires afterwards. The participants stood on the vibration device with their back to the remote control where the vibration frequency was set and the setting-screen was additionally covered by a piece of paper so that the participants never knew the exact vibration frequency. Griffin[40] wrote in his Handbook of Human Vibration: "The shaking of the human body - a complex, active, intelligent, dynamic structure - should not be expected to have a single, simple or easily predictable consequence." This may apply as well to SR-WBV training. As difficult as it is to predict the effects of SR-WBV so complicated it is to show all training effects that contribute to SR-WBV effectiveness in prevention. Nevertheless, this study sheds some light on this complex matter.

Verum SR-WBV induced acute changes in the musculoskeletal system that are eligible to cause the known positive effects on back pain[1,8]. These findings make a contribution to the explanation of back pain prevention through SR-WBV. Verum SR-WBV stimulated musculoskeletal activity in young healthy females while the cardiovascular activation was low. Therefore, verum SR-WBV served as short, specific exercise stimulus (likely followed by muscle relaxation), but was not a stressful, constant load, *e.g.,* like sitting in front of a computer. So, to improve muscle relaxation in office workers with excessive

stable tension in the lower back and upper limb musculature SR-WBV appears to be a promising technique.

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COMMENTS

Background

Musculoskeletal pain is common and so far no tests of acute musculoskeletal and cardiovascular changes due to stochastic resonance whole-body vibration training (SR-WBV) as intervention have been reported.

Research frontiers

There is need for research on short, economic, and effective training interventions. In this pilot study SR-WBV is shown to specifically activate back muscles while cardiovascular demands are low.

Innovations and breakthroughs

The study demonstrates acute SR-WBV training effects in physiological and self-perceived musculoskeletal function.

Applications

SR-WBV at work appears to be a promising tool in the prevention of occupational musculoskeletal problems.

Terminology

SR-WBV constantly challenges the neuro-musculoskeletal coordination to adapt to unforeseeable changes.

Peer review

The present manuscript investigated the influence of a technique termed SR-WBV on various physiological and psychological parameters. Young healthy participants underwent a "sham" (2 Hz with noise level 0) then a "verum" (6 Hz with noise level 4) SR-WBV training. Main results showed that electromyography activity of descending trapezius and energy expenditure were both larger during verum training as compared to baseline and sham training. This study is globally interesting, the experiments well-conducted and the topic chosen by the authors.

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BRIEF ARTICLE

Should aspirin be stopped before carpal tunnel surgery? A prospective study

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Abstract

AIM: To determine whether patients taking aspirin during carpal tunnel release had an increase of complications.

METHODS: Between January 2008 and January 2010, 150 patients underwent standard open carpal tunnel release (CTR) under intravenous regional anaesthesia. They were divided into three groups: groups 1 and 2 were made of 50 patients each, on aspirin 100 mg/d for at least a year. In group 1 the aspirin was never stopped. In group 2 it was stopped at least 5 d before surgery and resumed 3 d after. Group 3 acted as a control, with 50 patients who did not take aspirin. The incidence of clinically significant per- or post-operative complications was recorded and divided into local and cardio-cerebro-vascular complications. Local complications were then divided into minor and major according to Page and Stern. Local haematomas were assessed at 2 d (before resuming aspirin in group 2) and 14 d (after resuming aspirin in group 2) postoperatively. Patients were reviewed at 2, 14 and 90 d after surgery.

RESULTS: There was no significant difference in the incidence of complications in the three groups. A total of 3 complications (2 major and 1 minor) and 27 visible haematomas were recorded. Two major complications were observed respectively in group 1 (non stop aspirin) and in group 3 (never antiaggregated). The minor complication, observed in one patient of group 2 (stop aspirin), consisted of a wound dehiscence, which only led to delayed healing. All haematomas were observed in the first 48 h, no haematoma lasted for more than 2 wk and all resolved spontaneously. A major haematoma (score > 20 cm^2) was observed in 8 patients. A minor haematoma (score < 20 cm^2) was recorded in 19 patients. All patients at 90 d after surgery were satisfied with the result in terms of relief of their preoperative symptoms. Major and minor haematomas did not impair hand function or require any specific therapy.

CONCLUSION: Our study demonstrates that continuation of aspirin did not increase the risk of complications. It is unnecessary to stop aspirin before CTR with good surgical techniques.

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Key words: Carpal tunnel syndrome; Aspirin; Antiaggregation therapy; Hand surgery; Carpal tunnel release

Core tip: Our study demonstrates that continuation of aspirin did not increase the risk of local or general complications. Continuation of aspirin did not influence the subjective scar assessment. It is concluded that it is unnecessary to stop aspirin before carpal tunnel release when good meticulous surgical techniques are used.

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INTRODUCTION

Antiplatelet agents, such as aspirin and thienopyridines (clopidogrel and ticlopidin), reduce the risk of vascular death by about one sixth and the risk of non-fatal myocardial infarction and stroke by about one third in patients with unstable angina or a past history of myocardial disease, according to a meta analysis of several randomized studies[1-5]. Low-dose aspirin may however increase bleeding complications when taken peroperatively or during certain diagnostic procedures such as gastroscopy and bronchoscopy, especially in conjunction with biopsies[1,6]. Therefore, there is a need to balance the risk of haemorrhagic complications when continuing anti-aggregation therapy against the risk of thrombotic complications when interrupting it[7-12]. The aim of this prospective study was to determine the effect of interrupting or continuing antiplatelet therapy in open carpal tunnel.

MATERIALS AND METHODS

We carried out carpal tunnel release (CTR) on 150 patients between January 2008 and January 2010 with a 90-day follow-up. They were divided into three groups: (1) group 1: 50 patients taking 100 mg of aspirin/d for at least one year. These patients did not interrupt the anti-aggregation; (2) group 2: 50 patients taking 100 mg of aspirin/d for at least one year. In this group, aspirin was withdrawn in agreement with the cardiologist for at least 5 d before surgery and was resumed 3 d post-operatively, as described in several studies[7,13-16]; and (3) group 3: 50 patients who were not anti-aggregated.

Inclusion criteria were: age between 50 and 75, symptomatic, unilateral and electrophysiologically confirmed carpal tunnel syndrome. We excluded patients undergoing simultaneous surgical procedures (*e.g.,* trigger finger), those with known haematological disorders (*e.g.,* haemophilia) or with severe heart disease. No routine pre-operative blood tests were performed. The standard surgical management in all cases consisted of intravenous regional anaesthesia (IVRA) with a tourniquet applied at mid-arm level inflated at 250 mmHg. No post-operative splints or drains were used and 90 mg of acemetacin were administered twice a day during 48 h. All patients were followed-up in our outpatient clinic on day 2, 14 and 90 after surgery, for a subjective and objective wound assessment and neurological examination. Scar massage was recommended after suture removal at day 14. No physiotherapy was prescribed. The incidence of clinically significant pre or post operative complications was recorded and these were divided into local and systemic (cardio-cerebro-vascular). They were then divided into minor and major complications according to an adaptation of the Page and Stern Classification[17]. Major local complications included those requiring additional surgery and significantly compromised function like Complex Regional Pain Syndrome. The onset of haematoma was assessed locally at day 2 post-surgery (before resuming antiplatelet treatment in group 2) and at day 14 (after resuming antiplatelet treatment in group 2). In the absence of an objective method of assessing the haematoma, we decided to quantify its extent by calculating an arbitrary score of visible extension based on its area (maximal length along the proximal-distal axis x maximal length along the medio-lateral axis, measured in centimetres). A score of more than 20 in one of the two measurements was considered a "major" haematoma.

Table 1 A major haematoma was observed in 8 patients and a minor haematoma was recorded in 19 patients *n* (%)

	Group 1 (non stop aspirin)	Group 2 (stop aspirin)	Group 3 (never antiaggregated)	Total
Complications				
Major	1 (heart)		1 (acute haematoma)	2
Minor		1 (wound)		1
Total complications	1	1	1	3 (2)
Haematoma				
Major (> 20)	3	2	3	8
Minor (< 20)	7	7	5	19
Total haematoma	10	9	8	27 (18)

RESULTS

There were no significant differences in the incidence of complications in the three groups. A total of 3 complications (2 major and 1 minor) and 27 visible haematomas was recorded. The two major complications were observed respectively in group 1 (non stop aspirin) and in group 3 (never antiaggregated). In group 1, one patient with pre-existing known coronary disease experienced peroperative atypical chest pains with non diagnostic electrocardiogram and serum enzymes. She was admitted to the intensive care unit during 24 h and discharged without specific treatment after a negative cardiac scintigraphy. In group 3, one patient suffered an acute compressive intracanalar haematoma two hours after surgery due to uncontrolled arterial bleeding followed by immediate return to theatre. The minor complication, observed in one patient of group 2, consisted of a wound dehiscence, which only led to delayed would healing. All haematomas were observed in the first 48 h, and none lasted for more then 2 wk. All resolved spontaneously. A major haematoma (score > 20) was observed in 8 patients: 3 in group 1, 2 in group 2 and 3 in group 3. A minor haematoma (score < 20) was recorded in 19 patients: 7 in group 1, 7 in group 2 and 5 in group 3 (Table 1). All patients at 90 d post-surgery (last follow up) were satisfied with the result in relation to the degree of the initial compression. Major and minor haematomas did not impair hand function or require physiotherapy.

DISCUSSION

Our study shows that there were no significant differ-

ences between the 3 groups. There were no major complications in patients in whom aspirin was suspended, as described in other studies[2,7]. The occurrence of a complication did does not affect the final outcome as assessed subjectively or objectively.

In our experience, the presence of post-operative local haematoma is a source of anxiety in patients. Sometimes, their anxiety justifies an urgent consultation to reassure them and their family doctor. We arbitrarily measured the external appearance of the local haematoma, but we could not say whether it was superficial or deep. However, this is irrelevant because each haematoma was asymptomatic and resolved spontaneously. Many studies have emphasized that aspirin withdrawal in patients with heart disease may lead to serious complications, including death[1,2,7,18,19]. Other studies recommend continuing antiplatelet therapy provided an adequate haemostasis is carried out[20]. On the other hand, because of IVRA, it is impossible to ensure a perfectly visible haemostasis, as in local anaesthesia and, therefore, postoperative compression bandaging is applied. There are no studies showing that a postoperative immobilization with a plaster decreases the risk of local bleeding[21]. Aspirin should only be discontinued peroperatively if the risk of bleeding and its consequences are expected to be similar or more severe than the cardiovascular risks after aspirin withdrawal (myocardial infarction, stroke, peripheral vascular occlusion or death)[1]. This type of surgery, in close proximity to peripheral nerves, exposes to the risk of developing an acute post-operative intracanalar haematoma. The current literature advises to avoid antiplatelet agents only in eye surgery, neurosurgery and in surgery of the prostate[6,14,16,22-25], where bleeding-related fatalities after aspirin ingestion have been reported. In carpal tunnel surgery, the onset of acute intracanalar haematoma is always possible, in spite of complete opening of the transverse carpal ligament. In our study, we observed only one case of acute intracanalar haematoma needing urgent re-operation, in a never anti-aggregated patient. Other similar studies[20,26,27] on the use of anticoagulant therapy rather than antiaggregant, in open CTR, also conclude that its continuation does not increase bleeding complications[9,28-32]. We used an arbitrary score for haematoma measurement, in the absence of a specific scoring system. The aim was to match the visible extension of the haematoma with the neurological impairment. No haematoma in our study had ill effects on the clinical recovery, compared to patients without haematoma. It is important to reassure patients and to avoid needless ultrasound examinations.

Continuation of anti-aggregation therapy does not influence the final outcome. The decision to operate and whether to discontinue aspirin must be individualized considering the nature of the procedure and the patient's medical condition. It may be appropriate to continue aspirin in certain patients at increased risk for a vascular event, ensuring adequate haemostasis throughout the procedure[11,21,33]. The decision to operate and whether to discontinue aspirin must be weighed against the risks related to indication for which antiaggregation is being used. Decisions must be adapted case by case. In the case of patients taking dual antiplatelet therapy (aspirin and clopidogrel), we follow the cardiologist's recommendations[34,35]. As a result of this study, we have changed our protocol for open carpal tunnel release and now continue aspirin treatment perioperatively.

COMMENTS

Background

There are not many studies on intra- and post-operative complications of hand surgery in patients who take aspirin peroperatively. Bleeding complications can occur continuing antiplatelet therapy and stopping aspirin can lead to serious thromboembolic events.

Research frontiers

In the case of patients taking dual antiplatelet therapy (aspirin and clopidogrel), authors follow the cardiologist's recommendations. As a result of this study, authors have changed the protocol for open carpal tunnel release and now continue aspirin treatment perioperatively.

Applications

To investigate the effects of aspirin in patients undergoing hand surgery, authors performed a prospective study to determine whether patients who continued to take aspirin during carpal tunnel surgery had an increased incidence of clinically significant complications.

Peer review

This is a prospective study evaluating the implications of antiplatelet therapy in open carpal tunnel surgery. The authors concluded that continuation of antiplatelet therapy does not influence post operative subjective and clinically objective final outcome. This is a well written manuscript that may add to the existing literature.

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BRIEF ARTICLE

Cemented Müller straight stem total hip replacement: 18 year survival, clinical and radiological outcomes

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Abstract

AIM: To present the 18 year survival and the clinical and radiological outcomes of the Müller straight stem, cemented, total hip arthroplasty (THA).

METHODS: Between 1989 and 2007, 176 primary total hip arthroplasties in 164 consecutive patients were performed in our institution by the senior author. All patients received a Müller cemented straight stem and a cemented polyethylene liner. The mean age of the patients was 62 years (45-78). The diagnosis was primary osteoarthritis in 151 hips, dysplasia of the hip in 12 and subcapital fracture of the femur in 13. Following discharge, serial follow-up consisted of clinical evaluation based on the Harris Hip Score and radiological assessment. The survival of the prosthesis using revision for any reason as an end-point was calculated by Kaplan-Meier analysis.

RESULTS: Twenty-four (15%) patients died during the follow-up study, 6 (4%) patients were lost, while the remaining 134 patients (141 hips) were followed-up for a mean of 10 years (3-18 years). HSS score at the latest follow-up revealed that 84 hips (59.5%) had excellent results, 30 (22.2%) good, 11 (7.8%) fair and 9 (6.3%) poor. There were 3 acetabular revisions due to aseptic loosening. Six (4.2%) stems were diagnosed as having radiographic definitive loosening; however, only 1 was revised. 30% of the surviving stems showed no radiological changes of radiolucency, while 70% showed some changes. Survival of the prosthesis for any reason was 96% at 10 years and 81% at 18 years.

CONCLUSION: The 18 year survival of the Müller straight stem, cemented THA is comparable to those of other successful cemented systems.

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Key words: Total hip; Replacement; Muller; Straight stem; Cemented; Survivorship

Core tip: There are few cemented implants that have made history and are still used today. The original Müller straight stem prosthesis falls into this category. In this study, 176 primary cemented total hip replacements in 164 consecutive patients were followed-up for a mean of 10 years (3-18) years. Survival of the prosthesis, as calculated by Kaplan-Meier analysis, was 96% at 10 years and 81% at 18 years. The 18 year survivorship of the Müller straight stem, cemented total hip arthroplasty is comparable with that of other successful cemented or uncemented systems.

Nikolaou VS, Korres D, Lallos S, Mavrogenis A, Lazarettos I, Sourlas I, Efstathopoulos N. Cemented Müller straight stem total hip replacement: 18 year survival, clinical and radiological outcomes. *World J Orthop* 2013; 4(4): 303-308 Available from:

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INTRODUCTION

There are few implants that have made history and are still used today. The original Müller straight stem prosthesis falls into this category. The original Müller straight stem prosthesis has shown excellent results at 10 to 15 years[1-4]. The 10 year survival rate for the stem ranges from 91.2% to 98.3%[3,5]. Good results after 10 years of using a third generation cementing technique, with a survival rate of 93.2%, are also presented in the Swedish National Hip Arthroplasty Register[6].

The original forged Müller cemented straight stem (Zimmer, Winterthur, Switzerland), manufactured from Protasul-10 (CoCrNiMo alloy) with a matte, fine-blasted surface, was introduced in 1977. Müller[7] developed a cemented stem based on the principle of achieving fixation in the bowed femur by inserting the largest possible stem. So for a particular femur, a press-fit is achieved between the medial and lateral walls of the femur and the prosthesis and this leads to an incomplete cement mantle with bone-metal contact. The fluted structure of the stem, with the two particularly marked longitudinal grooves anteroposterior in the stem axis, enables very good cement adhesion. The small proximal collar serves to compress the cement, prevents the stem from sinking into the cement and, together with the fine-blasted surface of the straight stem, achieves a very stable anchorage of the implant. The design of the stem achieves optimum adaptation because it increases rigidity, decreases stress peaks and supports less micromotion. Moreover, there is positive contact in the frontal plane and additional interlocking is often achieved in the sagittal plane by the curvature of the femur.

Long term survival data are only available from Scandinavian hip registries[3,4,6] which lack detail on the clinical or radiological outcome. The aim of this study is to present the 18 year survival, clinical and radiological outcomes of the Müller straight stem, cemented total hip arthroplasty (THA) in our institution. This was a retrospective study of prospectively collected data.

MATERIALS AND METHODS

Between July 1989 and June 2007, a total of 176 Müller straight stem primary THAs were performed in our hospital. The mean age of the patients was 62 years (45 to 78). There were 136 women and 28 men. The primary diagnosis was osteoarthritis in 151 patients, dysplasia of the hip in 12 and subcapital fracture in 13 patients.

All operations were undertaken by one single surgeon (N.E.). The patients were operated on in a standardized way, in a supine position through an anterolateral transgluteal approach (Watson Jones). After reaming the acetabulum, the corresponding size polyethylene cup was cemented with the finger-packing technique. The femoral canal was prepared with rasps and the femoral component was introduced with a cement gun. In contrast to other canal-filling implants, no spongious bone was removed in the sagittal plane. All stems were cemented with a second-generation cementing technique. During the first ten years of the study, Palacos bone cement was used, while Gentafix (Teknimed SAS) was used later on in the study. The size of the femoral stem for all patients was 7.5. In all patients, a 28 mm diameter, cobalt-chromium femoral head and a drain that was removed on the second postoperative day was used. All patients received prophylactic antibiosis and anticoagulation therapy. The patients were mobilized after the second postoperative day and full weight bearing was permitted as tolerated.

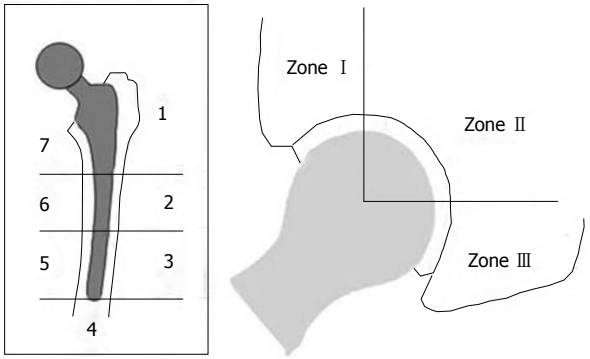

Figure 1 The radiological assessment of loosening was done according to the Gruen zones for the femoral component (Left) and according to Delee *et al*[27] for the acetabular component (right).

Table 1 Definition of loosening of cemented femoral stem

Potential loosening	radiolucency (linear-focal) < 2 mm
Probable loosening	linear radiolucenc > 2 mm or focal radiolucency > 5 mm
Definitive loosening	linear radiolucency > 2 mm all around

Clinical and radiological follow-up was at 1, 3, 6 and 12 mo and thereafter every year. Clinical follow-up included a standardized examination using the Harris Hip Score (HHS)[8]. At the latest follow-up, a postoperative score of 90-100 points was considered an excellent result; 80-89 points as good; 70-79 as fair; and less than 70 points as poor. Radiological assessment was based on a standardized anteroposterior radiograph of the pelvis centered on the pubic symphysis, showing the entire prosthesis, and a second radiograph with the false profile view. The films were rated according to the Gruen zone system for the femoral component and according to De Lee and Charnley for the acetabular component (Figure 1)[9]. Loosening was defined as follows: potential loosening: radiolucency (linear/focal) < 2 mm; probable loosening: linear radiolucency > 2 mm; focal radiolucency > 5 mm; definitive loosening: linear radiolucency > 2 mm all around[1,9] (Table 1). Subsidence of the stem was measured as the difference between the highest point of the prosthesis shoulder and the horizontal sclerotic line above the shoulder.

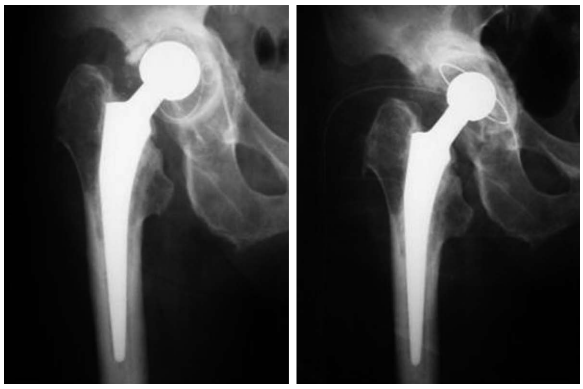

Figure 2 A case of acetabular cup loosening and migration, 9 years post surgery (left). This hip was revised and a new cemented acetabular component was implanted with good results. The femoral component was left *in situ*.

The indication for revision was persistent patient, pain and/or radiological evidence indicating loosening of the acetabular or femoral component. The 18 year cumulative survival was calculated by a Kaplan-Meier analysis.

This study is conducted in accordance with the World Medical Association Declaration of Helsinki. Institutional review board approval has been obtained.

RESULTS

From the 164 patients (176 hips), 24 patients (15%) died, while 6 patients (4%) were lost to follow-up, both without revision at their last review. That left us with 134 patients (141 hips) that they were followed up for a mean of 10 years (range 3-18 years). No patient died during the early postoperative period. In 5 patients (3.5% of hips), the greater trochanter was fractured during the intraoperative manipulations. In all cases, osteosynthesis of the greater trochanter was done by wiring and the patients were kept in bed for prolonged time. This fracture rate can be attributed to the manipulations that are necessary during the anterolateral transgluteal approach (Watson Jones) as the patient lies supine on the OR table (figure of four leg position). Early hip dislocation occurred in 3 patients. Closed reduction under general anesthesia and C-arm control was successfully done and these patients were kept in bed for three weeks with no further complications. No cases of deep infection or pulmonary embolism were noted. Superficial wound infection occurred in 3 patients. In 3 patients, revision of the acetabular component was done 9, 11 and 13 years postoperatively respectively, due to aseptic loosening (Figure 2). One femoral stem was revised due to aseptic loosening.

Clinical results

The mean HHS was 87 (34 to 100), of which 84 (59.5%) of the hips showed excellent (90 to 100 points), 30 (22.2%) good (80 to 89 points), 11 (7.8%) fair (70 to 79 points) and 9 (6.3%) poor results (< 70 points) at the latest follow-up.

Table 2 Radiological results (radiolucencies) around the femoral stem *n* (%)

Type of radiolucency	No. of hips
Overall	104 (73)
Linear-focal < 2 mm	65 (46)
Linear > 2 mm or focal > 5 mm	33 (23.4)
Linear > 2 mm all around	6 (4.2)

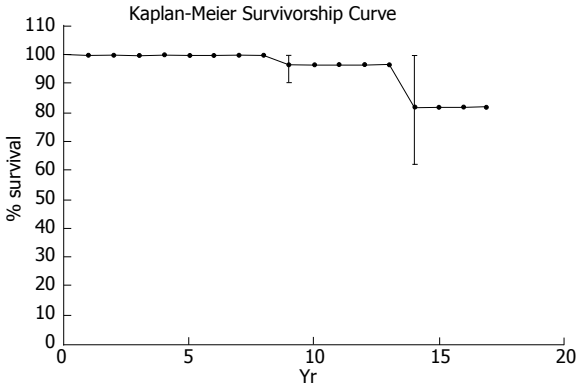

Figure 3 Kaplan-Meier survivorship of the Müller straight stem cemented total hip arthroplasty at 10 and 18 years was 96% and 81% respectively.

Radiological results

All radiographs were evaluated by an experienced hip arthroplasty surgeon. A total of 99 (70%) of all 141 hips had linear or focal osteolysis in one or more zones of the stem but only 6 hips (4.2%) of the 134 analyzed patients had evidence of definitive loosening, while 30 (21%) had no radiographic changes. However, from the 6 (4.2%) hips with radiographic aseptic loosening, only 1 stem was revised because the radiographic findings were not always combined with hip pain (in 2 patients), while the other 2 patients refused to be operated on. Radiographic changes were noticed mainly on the proximal-medial side of the stem (Gruen zones 7 and 6) and rarely laterally (Gruen zones 1 to 3). We found radiolucency of any type in 104 hips (73%). According to the above mentioned definition of loosening: 65 hips (46%) were potentially loose; 33 hips (23.4%) were probably loose; and 6 hips (4.2%) were definitely loose (Table 2)[9]. Stem subsidence was present in 21 hips (15%). 1 mm in 17 stems, 2mm in 3 and 3mm in one stem. We could not identify any correlation between the stem subsidence and the clinical results of these patients.

With revision for any reason, survival was 96% for 10 years and 81% for 18 years (Figure 3).

DISCUSSION

The limited survival data published for the Müller straight stem shows great variation in outcome: at six to eight years, 20.1% of the stems were judged to be at risk for later aseptic loosening[10] in a series for which further follow-up has not been presented. For stems implanted with

a first-generation cementing technique[11], a ten year revision rate of 8% and a revision rate of 19.7% at 17 years was observed, whereas when using a second generation cementing technique[11], the revision rate was reduced to 4% at ten years[6].

The Müller straight stem was designed to achieve a press fit fixation in the anteroposterior radiological view with a self-centering effect (shape-closed). A close stem-bone contact is established in the coronal plane, resulting in a thin or even incomplete cement mantle[1,12,13] which has been described in the literature as the "French paradox"[13]. It is well known that it is desirable to have a complete cement mantle around the stem[14]. The optimum thickness of the cement mantle is thought to be 2-4 mm. However, this conventional teaching has been challenged by the success of French-designed cemented stems, such as the Charnley Kerboull and the Ceraver Osteal. In France, the philosophy had been to insert the largest stem possible, which fully occupies the medullary canal, resulting in a thin or even deficient mantle. The rectangular cross-section provides intrinsic stability in torsion even in the absence of cement[15]. This is the concept for the Muller straight stem. Moreover, the stem design and implantation technique make gross errors in varus-valgus orientation almost impossible as the prosthesis almost fills the femoral canal in the AP plane.

The stem had a satin surface finish (Ra 1.0 μm), exceeding a postulated roughness of 0.4 μm defined as maximum roughness for polished stems. Thus, abrasive wear of the surface and a high volume of metal debris might be expected[16]. Later versions of the stem had an even higher surface roughness and survival decreased[17]. The combination of the soft metal titanium with a rough surface had the worst results[18]. Polished stems have a better survival with force-closed cementing technique (shape-closed implants)[19-21]. However, the biological effect of the abrasive wear of the rough stem might be equally important[21]. This cannot be overcome by modifications to the cementing technique[16] and can only be overcome by polishing the stem.

The Swedish Hip Registry[6] showed improved long term survival for the Müller straight stem using a second-generation cementing technique compared with a series with a first-generation cementing technique. There are no data for third-generation techniques (jet lavage, vacuum-mixed cement) and it must be questioned whether these techniques can further improve the cement penetration for an implant with high introduction forces. The use of ceramic heads was associated with a decreased wear rate and the use of modern bearing surfaces might further improve survival[10,12,13]. The use of a femoral seal or finger-packing might improve the proximal sealing and reduce access of polyethylene particles at the interface, thus reducing the risk of osteolysis for the Müller straight stem.

In the present study, the femoral component was divided into 7 zones, as described by Gruen *et al*[9]. The development of radiolucent lines around these zones in a progressive fashion suggests loosening. We distinguish progressive radiolucent lines in the femur from the typical age-related expansion of the femoral canal and cortical thinning, which may give the appearance of a progressively widening radiolucency. Age-related radiolucent zones generally do not have the associated sclerotic line seen about loose femoral stems. In addition, radiolucent lines associated with osteolysis tend to be more irregular, with variable areas of cortical thinning and ectasia. Smith *et al*[22] described an age-related expansion of the human proximal femur in a series of 2300 healthy female femora and postulated that endosteal resorption would result in an expansion of the medullary canal, which might even occur after insertion of a THA[23]. A time and gender-related widening of the medullary canal with consecutive thinning of the cortex has also been reported in female cadaver femora of various ages[24]. Radiologically, an obvious loss of mineralization of the cortex and cancellous bone has been observed in older women[25].

Räber *et al*[1] reported a 15 year survival rate for aseptic loosening of 88.1% with the Müller straight stem when using a first generation cementing technique, but found that about 70% of the remaining stems exhibited osteolysis or longitudinal lucencies. The incidence of osteolysis was not reported but the longitudinal lucencies might have been due to cortical atrophy. In our series, the incidence of any radiological lucency lines was frequent. A total of 99 (70%) of all 141 hips had radiological changes of lucency, but only 6 hips (4%) had evidence of definitive loosening, while 30 (21%) had no radiographic changes. The high rate of radiolucency without definitive loosening may be explained by the fact that the incomplete cement mantle leaves places with a thin cement mantle and zones with direct metal-bone contact and this allows the particles access to the bone, leading to bone resorption. Consciousness of the natural process of cortical atrophy is necessary in order not to overestimate the number of cases at risk, as cortical atrophy did not compromise the clinical and radiological results. Clauss *et al*[26] stated that cortical atrophy appears to be an effect of ageing and not a sign of loosening of the femoral component.

Krismer *et al*[10] found an increased rate for aseptic loosening for Müller straight stems with an incomplete cement mantle at the tip of the stem. In our series, cement defects at the tip of the stem were uncommon (5 hips) and not associated with an increased incidence of revision.

With aseptic loosening as the endpoint, the survivorship according to Kaplan-Meier of the Müller straight stem at 10 and 18 years was 96% and 81% respectively. This survival rate and clinical results are comparable to that of other well known and successful cemented systems in larger multi-surgeon series[4,6].

COMMENTS

Background

Total hip replacement is one of the most common surgical procedures. Cementless prostheses, although the most expensive, have become the most common type of prosthesis used for total hip replacement worldwide. However,

long term follow-up studies have failed to prove the superiority of cementless hip arthroplasties over the well time-tested cemented designs. There are few implants that have made history and are still used today. The original Müller straight stem prosthesis falls into this category. A long term follow-up of patients with primary total hip replacements that were treated with the cemented Müller straight stem prosthesis is presented in this study.

Research frontiers

A long term follow-up of patients with primary total hip replacements that were treated with the cemented Müller straight stem prosthesis is presented in this study. Currently, there is a relative paucity of evidence regarding the survivorship of patients with primary total hip arthroplasties treated with this cemented prosthesis.

Innovations and breakthroughs

This study confirms that cemented Müller straight stem total hip arthroplasty displayed satisfactory survivorship in a long term follow-up. These results are comparable with that reported in other larger series of cemented and uncemented prostheses. The authors should note that the majority of components were implanted using second generation cementing techniques. The polyethylene cup was cemented with the finger-packing technique and the femoral stem was implanted without distal cement plug and without pressurization.

Applications

Surgeons should consider using this cemented total hip arthroplasty, taking in to account that uncemented total hip replacements are much more expensive and that the findings of this study and other similar studies confirm that results of cemented hip arthroplasties are at least as good as those reported in uncemented designs.

Terminology

Total hip replacement can be done using bone cement to stabilize the acetabular and femoral components. This kind of total hip replacement is known as cemented. Alternatively, porous coated materials can be used and the bonding of the implants with the patient's host bone occurs without the usage of bone cement. This kind of hip arthroplasty is known as cementless.

Peer review

The paper shows a good follow-up of their patients and leaves few comments to be added.

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BRIEF ARTICLE

Current practice variations in the management of anterior cruciate ligament injuries in Croatia

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Abstract

AIM: To investigate current preferences and opinions on the diagnosis, treatment and rehabilitation of patients with anterior cruciate ligament (ACL) injury in Croatia.

METHODS: The survey was conducted using a questionnaire which was sent by e-mail to all 189 members of the Croatian Orthopaedic and Traumatology Association. Only respondents who had performed at least one ACL reconstruction during 2011 were asked to fill out the questionnaire.

RESULTS: Thirty nine surgeons responded to the survey. Nearly all participants (95%) used semitendinosus/gracilis tendon autograft for reconstruction and only 5% used bone-patellar tendon-bone autograft. No other graft type had been used. The accessory anteromedial portal was preferred over the transtibial approach (67% *vs* 33%). Suspensory fixation was the most common graft fixation method (62%) for the femoral side, followed by the cross-pin (33%) and bioabsorbable interference screw (5%). Almost all respondents (97%) used a bioabsorbable interference screw for tibial side graft fixation.

CONCLUSION: The results show that ACL reconstruction surgery in Croatia is in step with the recommendations from latest world literature.

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Key words: Anterior cruciate ligament; Survey; Knee; Surgery; Reconstruction

Core tip: The anterior cruciate ligament (ACL) is the prime static stabilizer against anterior translation of the tibia on the femur. We conducted a survey of members of the Croatian Orthopaedics and Traumatology Association to gain an understanding of preferences and opinions regarding the treatment of ACL injuries. Our findings are compared with those of previous surveys found in the literature to highlight temporal shifts and geographic differences in opinion.

Mahnik A, Mahnik S, Dimnjakovic D, Curic S, Smoljanovic T, Bojanic I. Current practice variations in the management of anterior cruciate ligament injuries in Croatia. *World J Orthop* 2013; 4(4): 309-315 Available from: URL: http://www.wjgnet.com/2218-5836/full/v4/i4/309.htm DOI: http://dx.doi.org/10.5312/wjo.v4.i4.309

INTRODUCTION

It has been 105 years since Hey Groves[1] made the first

anterior cruciate ligament (ACL) reconstruction using a patient's iliotibial band as autograft. Since then, a large number of surgical techniques, graft types, and rehabilitation protocols have been described in the literature. Today, ACL reconstruction is the sixth most common surgical procedure in orthopaedics with over 300000 reconstructions performed every year in the United States[2]. Despite the large-scale use of ACL reconstructions, questions still remain regarding indications, surgical techniques, graft selection, fixation method, and postoperative rehabilitation protocol, causing controversy regarding both nonsurgical and surgical treatment of ACL injury[3-5]. However, not all practicing surgeons may be aware of recent trends in the management of these injuries. Until now there has been no study conducted on the graft type, surgical method, preoperative prerequisites, postoperative applications required, and rehabilitation approach in ACL reconstruction preferred by orthopaedic and traumatology surgeons in Croatia. There are several similar studies in other countries described in the literature[3,6-11].

The primary goal of this study was to conduct a survey of members of the Croatian Orthopaedics and Traumatology Association (COTA) to gain an understanding of preferences and opinions regarding the treatment of ACL injuries. The secondary goal was to compare our findings with those of previous surveys found in the literature and to highlight temporal shifts and geographic differences in opinion.

MATERIALS AND METHODS

A questionnaire was sent by e-mail to members of COTA. An e-mail invitation was distributed *via* kwiksurveys.com with a link to the survey. Reminder e-mails were sent out 1 and 4 mo after the initial e-mail. Surgeons were asked if had they performed ACL reconstructive surgery within the past 12 mo. If so, they were asked to complete the remaining survey questions. Responses were identified using study numbers and were kept separate from the names/e-mails of the respondents.

The survey comprised 45 questions that were divided into three groups: 21 multiple-choice questions, 6 questions with yes/no answers and 18 questions containing a series of statements for which respondents indicated agreement or disagreement on a 5-point Likert scale[3]. The questionnaire included questions regarding the natural history of ACL-injured knees, indications for ACL reconstruction, surgical technique, graft type used, postoperative rehabilitation, starting time for specific exercises and for return to sports.

Results from this study were analyzed by descriptive statistics (mean, standard deviation, minimum-maximum values, frequency values, percentages). Results are displayed numerically and graphically, thus simplifying their interpretation. In accordance with the study of Marx *et al*[3], a minimum of 80% in matching responses was required to achieve a clinical agreement.

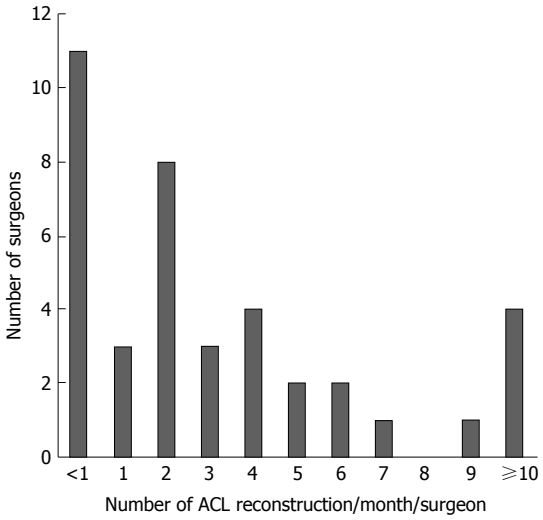

Figure 1 Frequency distribution of the number of surgeons performing anterior cruciate ligament reconstructions per month.

RESULTS

Thirty nine surgeons responded that they had performed at least one ACL reconstruction in 2011. A frequency distribution of surgeons by the number of ACL reconstructions performed per month is presented in Figure 1. Almost 75% of respondents performed four or less ACL reconstructions per month, meaning less than fifty ACL reconstructions per year. Also, among the members of COTA, ACL reconstruction is performed mostly by younger surgeons, supported by data that about 56% of respondents had spent less than ten years in surgical practice.

Ratings, from "strongly disagree" to "strongly agree", of a series of statements regarding natural history and related clinical recommendations are presented in Table 1. The criterion of "clinical agreement" was met for only 2 statements: (1) "hamstrings and quadriceps strength affects function in ACL-deficient knees" (94.9% agreement); and (2) "ACL disruption is associated with increased rate of arthrosis"(87.2% agreement). Attitudes regarding the indications for ACL reconstruction are shown in Table 2. Surgeons agreed or strongly agreed that giving up activities of daily living (94.8%), giving up sporting events (89.7%), high-demand activity (94.8%) and patients with repairable meniscal tear (92.3%) were positive factors and that advanced degenerative changes on X-ray (87.1%) was a negative factor influencing the decision to perform an ACL reconstruction.

Most of the surgeons start ACL reconstruction by performing diagnostic arthroscopy (82%). Among the members of COTA, no one uses allograft, while a staggering 95% of participants use semitendinosus/gracilis tendon autograft for reconstruction and only 5% use bone-patellar tendon-bone (BPTB) autograft. The accessory anteromedial portal was preferred over the transtibial approach (67% *vs* 33%). Furthermore, 80% of surgeons who performed more than fifty ACL recon-

Table 1 Percentage (number) of surgeons choosing each response on a 5-Point Likert Scale regarding statements on the natural history of anterior cruciate ligament tear and related clinical recommendations *n* (%)

Statement	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Clinical agreement					
Hamstrings and quadriceps strength affects function in ACL-deficient knees	2 (5.1)	0 (0)	0 (0)	17 (43.6)	20 (51.3)
ACL disruption is associated with increased rate of arthrosis	0 (0)	2 (5.1)	3 (7.7)	14 (35.9)	20 (51.3)
No clinical agreement					
ACL reconstruction reduces the rate of arthrosis in ACL-deficient knees	0 (0)	4 (10.3)	7 (17.9)	15 (38.5)	13 (33.3)
ACL-deficient, ligamentously lax individuals are more symptomatic	0 (0)	6 (15.4)	5 (12.8)	22 (56.4)	6 (15.4)
Patients with ACL-deficient knees who have not had surgery are able to participate in recreational sporting activities	9 (23.1)	15 (38.5)	6 (15.4)	7 (17.9)	2 (5.1)
Patients awaiting surgery are able to participate in recreational sporting activities	10 (25.6)	17 (43.6)	9 (23.1)	3 (7.7)	0 (0)
Bracing is useful for the ACL-deficient knee treated nonoperatively	10 (25.7)	13 (33.3)	8 (20.5)	8 (20.5)	0 (0)

ACL: Anterior cruciate ligament.

Table 2 Percentage (number) of surgeons choosing each response on a 5-Point Likert Scale regarding statements on positive factors influencing the decision to proceed with anterior cruciate ligament reconstruction *n* (%)

Statement	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Clinical agreement					
Giving up activities of daily living	1 (2.6)	1 (2.6)	0 (0)	11 (28.2)	26 (66.6)
Giving up sporting activities only	1 (2.6)	1 (2.6)	2 (5.1)	22 (56.4)	13 (33.3)
High-demand activity	1 (2.6)	0 (0)	1 (2.6)	14 (35.9)	23 (58.9)
Advanced degenerative changes on the X-ray	8 (20.5)	26 (66.6)	4 (10.3)	0 (0)	1 (2.6)
Repairable meniscal tear	1 (2.6)	2 (5.1)	0 (0)	17 (43.6)	19 (48.7)
No clinical agreement					
Complaining of severe pain	0 (0)	12 (30.8)	14 (35.9)	7 (17.9)	6 (15.4)
Female sex	7 (17.9)	12 (30.8)	15 (38.5)	5 (12.8)	0 (0)
Older than 40 yr	1 (2.6)	17 (43.6)	16 (40.9)	4 (10.3)	1 (2.6)
Open growth plates	5 (12.8)	19 (48.7)	8 (20.5)	4 (10.3)	3 (7.7)
Non-repairable meniscal tear	2 (5.1)	6 (15.4)	8 (20.5)	19 (48.7)	4 (10.3)
Recurrent swelling of the knee	1 (2.6)	10 (25.6)	8 (20.5)	15 (38.5)	5 (12.8)

ACL: Anterior cruciate ligament.

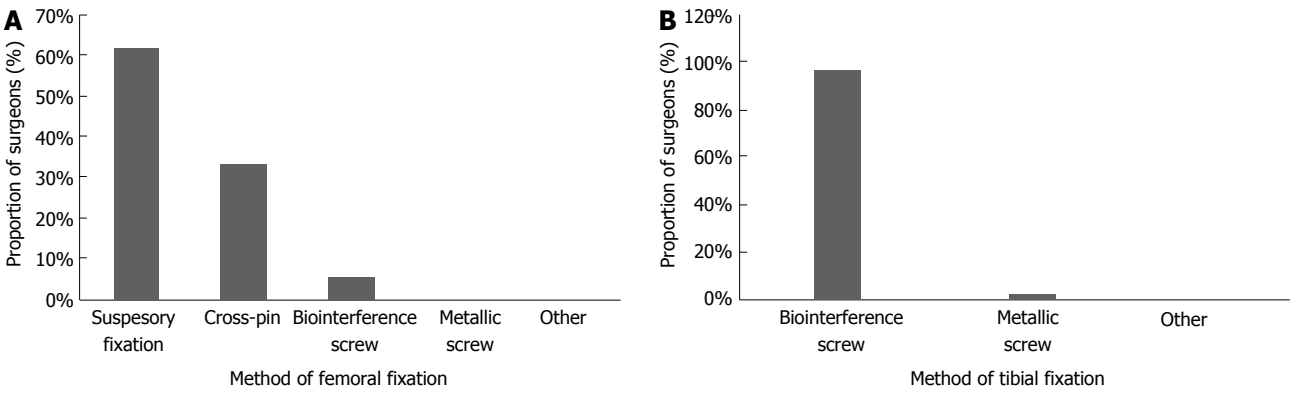

Figure 2 Method of graft fixation on femoral (A) and tibial (B) sides.

structions per year use an accessory anteromedial portal. Suspensory fixation was the most common graft fixation method for the femoral side (62%), followed by the cross-pin (33%) and bioabsorbable interference screw (IS) (5%). Astonishingly, 97% of our respondents use bioabsorbable IS for tibial side graft fixation (Figure 2). All patients received perioperative prophylactic antibiotics.

There is a large diversity of opinions regarding recommendations for the use of knee braces in patients after ACL reconstruction (Figure 3A). Some surgeons (17.95%) did not use knee braces at all. However, most surgeons (66.67%) routinely prescribed some sort of knee brace post-surgery. Of those who prescribe knee braces, most (43.59%) used post-operative functional braces and others (23.08%) used knee immobilizers. In relation to allowing full weight-bearing after surgery,

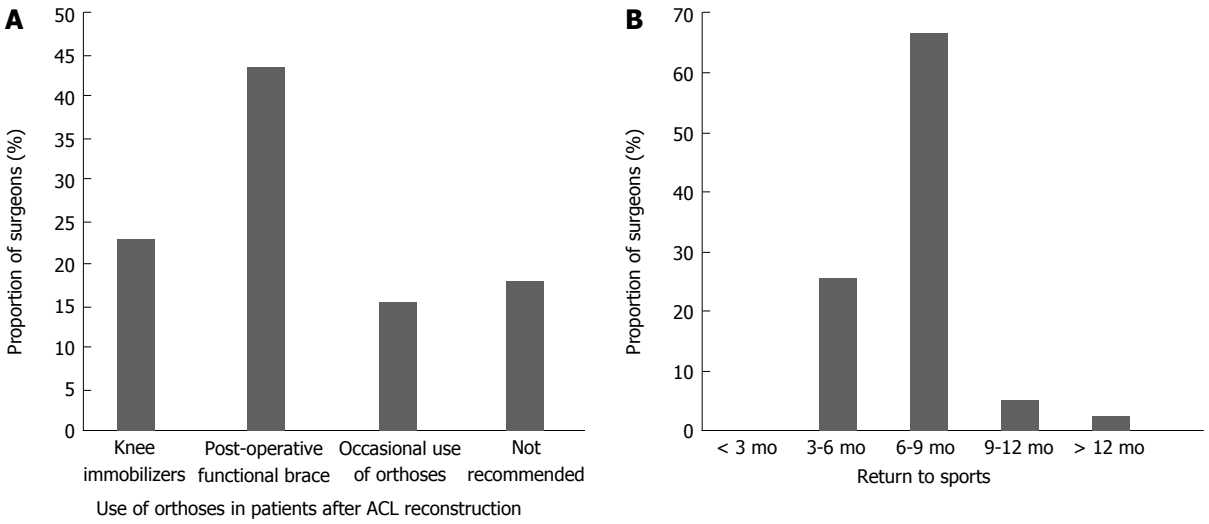

Figure 3 Recommendations. A: For the use of orthoses in patients after anterior cruciate ligament (ACL) reconstruction; B: Time until return to full sporting activity after ACL reconstruction.

25.64% surgeons initiate the full weight-bearing immediately after surgery, 33.34% prefered to wait three weeks after surgery, 38.46% allowed their patients to weight-bear on the operated knee six weeks after surgery and the remaining 2.56% waited two month before initiating complete weight-bearing. The recommended duration of physiotherapy by 66.67% surgeons was 6-12 wk. For most surgeons (66.67%) time for a complete return to sports activities after ACL reconstruction was 6 to 9 mo, 25.64% considered 3-6 mo to be sufficient for returning to sport activities, and others waited longer than 9 mo (Figure 3B).

DISCUSSION

This survey shows the diversity of opinions and approaches in ACL reconstruction surgery among orthopaedic and traumatology surgeons in Croatia. Consensus among surgeons was achieved on the decision to perform ACL reconstruction surgery if a patient has knee instability during everyday tasks or sport activities, if a patient has a physically demanding job, or if a patient has a meniscus tear that can be treated by suturing. Also, agreement was achieved on the statement that ACL injury increases degenerative changes in knee and on the statement that the strength of quadriceps and hamstrings muscles affects the knee function after ACL injury. General informed consent has to be signed in every hospital in Croatia in which surgical reconstruction of ACL is performed, yet only one third of participants claim that their institution has a specific informed consent on surgical reconstruction of ACL. Therefore, quality of patient information related to ACL reconstruction and postoperative rehabilitation might be deficient, and this should be improved in future[12].

An ideal graft for use in ACL reconstruction is one that is easily harvested, results in little or no harvest site morbidity, has structural and biomechanical properties similar to those of the native ligament, can be secured predictably and rapidly incorporates to the bones[13]. Historically, ACL reconstructions were performed using BPTB autografts fixed with metal IS. That has been considered the gold standard to which other technologies are compared. Although, semitendinosus/gracilis tendon autograft was introduced at roughly the same time as BPTB autograft it was only recently that it gained popularity. Typically, semitendinosus/gracilis tendon autograft is associated with less anterior knee pain and also allows separation of the graft for performing double-bundle reconstruction, which BPTB grafting does not[14-17]. On the other hand, a BPTB autograft has an excellent initial fixation and improved graft incorporation related to bone-to-bone healing, but its use may also be associated with patellofemoral pain and, occasionally, patellar fractures[13,15,18-21]. Examination of data found in the literature indicates a shift in opinion regarding graft choice from BPTB autograft to semitendinosus/gracilis tendon autograft. For example, in the United States in the late nineties, BPTB autograft was commonly preferred (79%) followed by semitendinosus/gracilis tendon autograft (12%) and allografts (8%)[3,10]. In 2006, however, in United States, BPTB autograft was preferred by 46% of surgeons, semitendinosus/gracilis tendon autograft by 32%, and allografts by 22%. Furthermore, a more recent study Chechiak *et al*[6] showed that among North American surgeons BPTB autograft was preferred by only 39%, semitendinosus/gracilis tendon autograft by 42%, and allografts by 19%. A much stronger temporal shift can be seen among members of the Canadian Orthopaedic Association (COA). McRae *et al*[7] conducted a study and found that in 2011 there is preference for using semitendinosus/gracilis tendon autograft over BPTB autograft (70% *vs* 28.5%). This demonstrates a shift from an earlier survey conducted in 1995 in which COA surgeons indicated a preference for BPTB autograft (63%) over semitendinosus/gracilis tendon autograft (32%)[22]. The use

of allograft for ACL reconstruction has gained increasing popularity and is now estimated to be used in about 20% of primary reconstructions in the United States[23,24]. Although they are associated with no harvest site morbidity, and provide predictable graft size, shorter operative time and easier recovery in the postoperative period, allografts are considered more likely to fail because of decreased mechanical properties due to the sterilization process and the possibility of triggering an inflammatory foreign body response. Chechiak *et al*[6] conducted their research among 261 American Academy of Orthopaedic Surgeons (AAOS) and European Federation of National Associations of Orthopaedics and Traumatology (EFORT) members worldwide and found that 63% of surgeons use semitendinosus/gracilis tendon autograft, 26% use BPTB autograft and 11% use allograft. More interestingly, they found a significant difference in graft choice by geographic regions. Surgeons in Europe prefer semitendinosus/gracilis tendon autograft (72%) while 19% of surgeons use BPTB autograft. In addition, Granan *et al*[25] published Scandinavian ACL registries and found that semitendinosus/gracilis tendon autograft was the most frequently used graft in all of Scandinavia (61% in Norway, 71% in Denmark, and 86% in Sweden), followed by BPTB autograft (38% in Norway, 22% in Denmark, and 14% in Sweden) and allografts (< 1% in Norway, 7% in Denmark, and < 1% in Sweden). Our results show extreme popularity of semitendinosus/gracilis tendon autograft among members of COTA.

Throughout history there have been two concepts to ACL reconstruction: isometric and anatomic. The biomechanical concept of graft isometry was developed in the 1960s and was based on the notion that the ideal ACL graft should be "isometric", which means that the distance between the femoral and tibial attachment sites does not change as the knee flexes[26,27]. By the 1990s, surgeons started to recognize that the goal to achieve isometry within a single or double tubular graft had proved an elusive one which, if achievable, would create unphysiological conditions, as none of the identifiable native ACL bundles are isometric in their own right. Thus it was realized that any reconstructive effort must restore any injured anatomic structure to its normal functional position and tension. The use of an arthroscopic accessory anteromedial portal for femoral drilling allows a more accurate placement of the femoral tunnel, thus allowing anatomic reconstruction[28-32]. McRae *et al*[7] divided surgeons into two groups: a "high-volume" and a "low-volume" group based on the number of ACL reconstructions performed per month and found statistically significant differences in implementation of the accessory anteromedial portal to create the femoral tunnel. Results showed that the "high-volume"group preferred creating a new, accessory anteromedial portal for femoral drilling. A survey conducted in the United States in 2006 found that 90% of surgeons perform a single-incision arthroscopic ACL reconstruction and, of those, 85% still prefered the transtibial approach, while only 15% performed an accessory anteromedial portal[10]. In contrast, Chechik *et al*[6] found that 68% prefered the accessory anteromedial portal over a transtibial approach in their worldwide survey in 2011. Our study showed the same results, 67% of surgeons used an accessory anteromedial portal and that the percentage was higher among surgeons who performed more than 50 ACL reconstructions per year.

Graft fixation methods can be divided into suspensory, cross-pin and metal or bioabsorbable IS. Today, the most commonly used suspensory fixation is the endobutton and the most commonly used cross-pin fixation is rigid-fix system. The fixation device must provide strong enough fixation to allow early rehabilitation with minimal movement of the graft until biological fixation is complete. While some biomechanical studies suggested that suspensory fixation is strongest in terms of load to failure[33], others showed that the further the fixation point from the joint line, the more it allows the graft to elongate under cyclic loading[34]. Metallic IS is the longtime gold standard[35,36] of graft fixation and it was the preferred choice of most surgeons until 1999[37]. Bioabsorbable and biocomposite materials were introduced, which allowed magnetic resonance imaging with fewer artifacts and image distortion and were also better handled during revision surgery[13]. On the other hand, bioabsorbable IS have been reported to break intraoperatively. They can contribute to tunnel widening and in some cases provoke an inflammatory response and pain which requires their surgical removal[36,38]. Chechik *et al*[6] reported that they found no consensus among 261 AAOS and EFORT members worldwide on the choice of fixation device. Metal or bioabsorbable IS and suspensory fixation were almost equally used (40% *vs* 46%), and bioabsorbable were preferred over metallic IS (34% *vs* 12%). However, surgeons in North America use screws more often than suspensory fixation (58% *vs* 35%), while in Europe surgeons use screws and suspensory fixation equally(41% *vs* 41%). A study conducted by Sandhu[8] reported that in 2008 the two main fixation methods used for stabilizing the graft in the Indian subcontinent were bioabsorbable IS (50%) and the metallic IS (25.50%). Among COA surgeons, McRae *et al*[7] reported that suspensory fixation was the preferred method for fixation on the femoral side (51.5%) and bioabsorbable IS for graft fixation on the tibial side (63.2%). Our study also showed a preference among members of the COTA towards suspensory fixation, used by 62% of surgeons.

Bracing after ACL reconstruction is still a controversial subject[39-45]. Many clinicians believe that braces improve the outcome of ACL reconstruction by improving extension, decreasing pain and graft strain, and providing protection from excessive force. However, a systematic review conducted by Wright *et al*[39] found that there is no evidence that pain, range of motion, graft stability, or protection from subsequent injury were affected by brace use after ACL reconstruction. Our study showed the same diversity of opinions regarding use of knee braces after ACL reconstruction among the members of COTA.

This study does carry some notable limitations. It is a retrospective study that relies on the accuracy of the reporting surgeon, and this could be a source of bias. The study is also limited by the lack of comparison between surgical techniques used and patients' functional outcomes. These limitations could be solved by prospective design of future studies related to this topic. Despite its limitations, this is the first study conducted in Croatia into opinions and agreements among orthopaedic and traumatology surgeons concerning the diagnosis, treatment and rehabilitation of patients with ACL injury. The results show that ACL reconstruction surgery in Croatia follows the trend of the recommendations from the latest world literature.

COMMENTS

Background

The anterior cruciate ligament (ACL) is the prime static stabilizer against anterior translation of the tibia on the femur. Injury to the ACL is the most common ligament injury in the knee and ACL reconstruction is the sixth most common surgical procedure in orthopaedics. Despite the large-scale use of ACL reconstructions, questions still remain regarding indications, surgical techniques, graft selection, fixation method, and postoperative rehabilitation protocol, causing controversy regarding both nonsurgical and surgical treatment of ACL injury.

Research frontiers

The research aim was to investigate current preferences and opinions on the diagnosis, treatment and rehabilitation of patients with a ACL injury in Croatia and to compare the findings with those of previous surveys found in the literature and to highlight geographic differences in opinion.

Innovations and breakthroughs

The research showed that nearly all participants use semitendinosus/gracilis tendon autograft for reconstruction and only 5% use bone-patellar tendon-bone autograft. The accessory anteromedial portal was preferred over the transtibial approach (67% *vs* 33%). Suspensory fixation was the most common graft fixation method (62%) for the femoral side, followed by the cross-pin (33%) and bioabsorbable interference screw (5%). Almost all respondents (97%) use a bioabsorbable interference screw for tibial side graft fixation.

Applications

The research showed that ACL reconstruction surgery in Croatia is in line with the recommendations from latest world literature.

Peer review

The paper shows a common opinion of anterior cruciate ligament repair for Croatian doctors in comparison to the western countries. It is well written.

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BRIEF ARTICLE

Effect of risedronate on speed of sound in postmenopausal women with osteoporosis

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Abstract

AIM: To examine the effects of treatment with risedronate for 1 year on speed of sound (SOS) of the calcaneus and bone turnover markers in postmenopausal women with osteoporosis.

METHODS: Thirty-eight postmenopausal women with osteoporosis who had been treated with risedronate for > 1 year were enrolled in the study. The SOS and bone turnover markers were monitored during treatment with risedronate for 1 year.

RESULTS: The urinary levels of cross-linked N-terminal telopeptides of type I collagen and serum levels of alkaline phosphatase were significantly decreased at 3 mo (-34.7%) and 12 mo (-21.2%), respectively, compared with the baseline values. The SOS increased modestly, but significantly by 0.65% at 12 mo compared with the baseline value. Treatment with risedronate elicited an increase in the SOS of the calcaneus exceeding the coefficient of variation *in vivo* (0.27%).

CONCLUSION: The present study confirmed that risedronate suppressed bone turnover and elicited a clinically significant increase in the SOS of the calcaneus in postmenopausal women with osteoporosis.

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Key words: Risedronate; Postmenopausal women; Quantitative ultrasound; Speed of sound; Bone turnover

Core tip: The effects of risedronate treatment on quantitative ultrasound parameters of the calcaneus remain to be established in patients with osteoporosis. The aim of the present clinical practice-based observational study was to examine the effects of treatment with risedronate for 1 year on speed of sound (SOS) of the calcaneus and bone turnover markers in postmenopausal women with osteoporosis. The present study confirmed that risedronate suppressed bone turnover and elicited a clinically significant increase in the SOS of the calcaneus in postmenopausal women with osteoporosis.

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INTRODUCTION

Osteoporosis mostly affects postmenopausal women and substantially increases their risk of fracture. Risedronate is widely used as the first-line drug for treating postmenopausal osteoporosis because of its efficacy, demonstrated

in the Vertebral Efficacy with Risedronate Therapy Study, the Hip Intervention Program Study, and a systematic review of 11 randomized controlled trials (RCTs), in which it reduced the incidence of vertebral, non-vertebral, and hip fractures[1-4].

Because risedronate increases the bone mineral density (BMD) of the lumbar spine, femoral neck, and total hip in postmenopausal women with osteoporosis[1,2], the BMD measured by dual-energy X-ray absorptiometry (DXA) remains the optimal method for monitoring the response to risedronate treatment. Quantitative ultrasound (QUS) is a more recently developed non-invasive method to determine bone density and structure *in vivo*. QUS parameters, including speed of sound (SOS), broadband ultrasound attenuation, and stiffness index, can predict the risk of hip, wrist, and total non-vertebral fractures up to 10 years later[5]. QUS may also provide a better assessment of the structural changes of bone compared with DXA[6].

The SOS of the calcaneus can be measured using a QUS device (CM-200; Elk Corp., Osaka, Japan). Recently, we reported the effects of 1 year of treatment with alendronate treatment on the SOS as well as bone turnover markers in Japanese postmenopausal women with osteoporosis[7]. In that study, alendronate reduced the urinary levels of cross-linked N-terminal telopeptides of type I collagen (NTX) and serum levels of alkaline phosphatase (ALP), and modestly increased the SOS. To date, however, very few studies have examined the effects of risedronate on QUS parameters in postmenopausal women with osteoporosis. We hypothesized that risedronate, similar to alendronate, would increase the SOS at the calcaneus in postmenopausal women with osteoporosis. Therefore, the aim of the present clinical practice-based observational study was to examine the effects of 1 year of treatment with risedronate on the SOS and bone turnover markers in Japanese postmenopausal women with osteoporosis. We also discuss the differential effects of risedronate and alendronate on the SOS and bone turnover markers in Japanese postmenopausal women with osteoporosis.

MATERIALS AND METHODS

Subjects

Thirty-eight Japanese postmenopausal women with osteoporosis who had been treated with risedronate (17.5 mg weekly) for more than 1 year were recruited at the outpatient clinic of Hiyoshi Medical Clinic (Kanagawa, Japan) during the 6-month period between July 1 and December 31, 2012. This dose of risedronate is the dose used in Japan to treat osteoporosis in postmenopausal women, and has shown safety and efficacy[8-11]. Patients were eligible if they had postmenopausal osteoporosis defined according to the Japanese diagnostic criteria[12,13] as: (1) BMD < 70% of the young adult mean (YAM) or the "presence" of osteopenia on X-ray images of the spine; and (2) BMD of 70%-80% of the YAM or "possible" osteopenia on X-ray images of the spine together with a history of osteoporotic fractures. Because DXA of the spine is useful for monitoring osteoporosis in Japanese women, and QUS appears to be less useful[14], the diagnosis of osteoporosis was made using both the SOS (< 70% of the YAM or 70%-80% of the YAM together with a history of osteoporotic fractures) and X-ray findings of the spine (*i.e.*, presence of osteopenia or possible osteopenia along with a history of osteoporotic fractures). Patients were excluded if they had a history of reflux esophagitis, gastric or duodenal ulcer, gastrectomy, renal failure, and bone diseases, including cancer-induced bone loss because of aromatase inhibitors, primary hyperparathyroidism, hyperthyroidism, Cushing's syndrome, multiple myeloma, Paget's disease of the bone, rheumatoid arthritis, or osteogenesis imperfecta.

The assessment performed before starting risedronate treatment included a medical history, physical examination, plain radiography of the thoracic and lumbar spine, measurement of the SOS of the calcaneus, and blood (*e.g.,* serum calcium, phosphorus, and ALP) and urinary (*e.g.,* NTX) biochemical tests. The urinary NTX levels were measured at 3 mo after starting treatment. The serum levels of calcium, phosphorus and ALP, and the SOS of the calcaneus were measured every 6 mo after starting treatment. Plain X-rays of the thoracic and lumbar spine were taken after 1 year of treatment. We evaluated the outcome of risedronate treatment for 1 year.

Assessment of morphometric vertebral fractures

Plain lateral X-ray films of the thoracic and lumbar spine were obtained at the start of treatment to detect evidence of morphometric vertebral fractures. According to the Japanese criteria, a vertebral fracture is defined according to the vertebral height on lateral X-ray films[12,13]. Briefly, the vertebral height is measured at the anterior (A), central (C), and posterior (P) parts of the vertebral body. The presence of a vertebral fracture was defined as: (1) a reduction in the vertebral height of > 20% (A, C, and P) as compared with the height of the adjacent vertebrae; (2) the C/A or C/P ratio is < 0.8; or (3) the A/P ratio is < 0.75. Vertebral fractures were assessed at the T4-L4 level.

Assessment of clinical vertebral and non-vertebral fractures

Low-traumatic osteoporotic clinical fractures were assessed. Clinical vertebral fractures were determined based on the clinical symptoms and findings of radiographic or magnetic resonance images of the lumbar and thoracic spine. Non-vertebral fractures, including major osteoporotic fractures of the distal radius, proximal humerus, and hip, were determined based on the clinical symptoms and radiographic images of the wrist, shoulder and hip joints, respectively.

Measurement of serum calcium, phosphorus and ALP, and urinary NTX

Serum and urine samples were sent to Kotobiken Medi-

Table 1 Baseline anthropometry, speed of sound and biochemical markers of the study subjects

	mean ± SD	Range
Age (yr)	71.1 ± 9.7	49-88
Height (m)	1.54 ± 0.06	1.40-1.70
Body weight (kg)	53.2 ± 7.6	40-80
Body mass index (kg/m^2)	22.4 ± 3.1	18.7-35.0
SOS (m/s)	1473 ± 13	1442-1500
SOS as % of YAM	68.9 ± 5.9	53-79
Calcium (mg/dL)	9.2 ± 0.4	8.6-10.2
Phosphorus (mg/dL)	3.5 ± 0.3	2.9-4.5
ALP (IU/L)	229 ± 63	142-365
Urinary NTX (nmol BCE /mmol Cr)	56.2 ± 17.8	35.2-99.9

The normal ranges of serum calcium, phosphorus, and alkaline phosphatase (ALP) were 8.4-10.2 mg/dL, 2.5-4.5 mg/dL, and 100-340 IU/L, respectively. The standard range of urinary cross-linked N-terminal telopeptides of type I collagen (NTX) was 9.3-54.3 nmol bone collagen equivalent (BCE)/mmol Creatinine (Cr), and the cutoff values for bone loss and vertebral fracture risk were 35.3 and 54.3 nmol BCE/mmol Cr, respectively. SOS: Speed of sound; YAM: young adult mean.

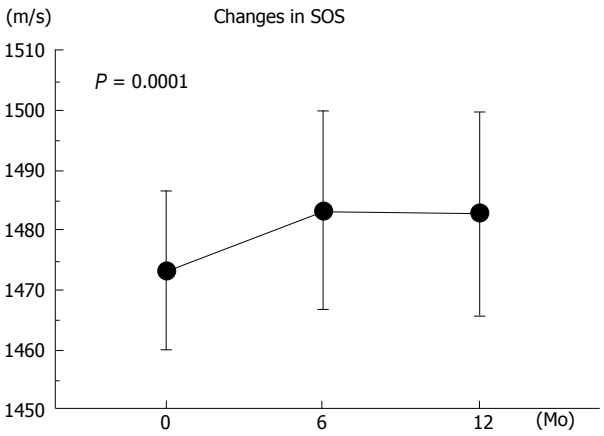

Figure 1 Changes in speed of sound. Data are expressed as mean ± SD. One-way analysis of variance with repeated measurements was used to analyze the longitudinal changes in the speed of sound (SOS). The longitudinal change in SOS was statistically significant (P = 0.0001 *vs* the baseline).

cal Laboratories, Inc. (Yokohama, Kanagawa, Japan) for the following biochemical analyses. Serum calcium and phosphorus levels were measured using standard laboratory techniques. Serum ALP levels were measured using the JSCC reference methods. The coefficient of variation (CV = 100 × standard deviation/mean) of two consecutive measurements made within 1 d was < 1.15% for 20 people. The CV of two measurements at the same time on two consecutive days was < 4.08% for 6 people. Urinary NTX levels were measured using an enzyme-linked immunosorbent assay. The CV of two consecutive measurements made within 1 d was < 7.4% for 10 people. The CV of two measurements made at the same time on two consecutive days was < 15.0% for 24 people.

Measurement of SOS of the calcaneus

The SOS of the left calcaneus was measured using a QUS device (CM-200; Elk Corp., Osaka, Japan). The reliability and reproducibility of this QUS device have already been reported, and the CV was 0.15% using the phantom technique and 0.27% *in vivo*[15].

Statistical analysis

Data are expressed as mean ± SD. One-way analysis of variance (ANOVA) with repeated measurements was used to determine the significance of the longitudinal changes in the SOS and biochemical markers. Univariate regression analysis was used to determine associations between the change in urinary NTX at 3 mo and the changes in the SOS at 6 and 12 mo. All statistical analyses were performed using StatView-J5.0 software (SAS Institute, Cary, NC, United States) on a Windows computer. A significance level of $P < 0.05$ was used in all comparisons.

RESULTS

Characteristics of the study subjects at the start of treatment

Table 1 shows the anthropometry, SOS, and biochemical markers of the study subjects at the start of treatment. The mean age of the subjects was 71.1 years (range: 49-88 years). The mean SOS was 1473 m/s, which corresponds to 68.9% of the YAM. The mean serum calcium, phosphorus, and ALP levels were 9.2 mg/dL, 3.5 mg/dL, and 229 IU/L, respectively, which were within the normal ranges (8.4-10.2 mg/dL, 2.5-4.5 mg/dL, and 100-340 IU/L, respectively). However, the mean urinary NTX level was 56.2 nmol bone collagen equivalent (BCE)/mmol Cr, which was higher than the normal range for Japanese women (9.3-54.3 nmol BCE/mmol Cr)[16], indicating a high bone turnover in these women, a characteristic of osteoporosis.

Changes in the SOS of the calcaneus

Figure 1 shows the changes in the SOS of the calcaneus. One-way ANOVA with repeated measurements showed a significant longitudinal increase in the SOS at 1 year (P = 0.0001). The mean percent changes in the SOS from the baseline after 6 and 12 mo of treatment were +0.68% and +0.65%, respectively (Table 2), which were beyond the coefficient of variation *in vivo* (0.27%)[15].

Changes in biochemical markers

Figure 2 shows the changes in the biochemical markers. The mean urinary NTX levels decreased to the normal range for Japanese women (9.3-54.3 nmol BCE/mmol Cr)[16] after 3 mo of treatment. The mean serum ALP levels also decreased and remained within the normal range (135-340 IU/L) during the 1-year treatment period. One-way ANOVA with repeated measurements showed significant longitudinal decreases in the serum ALP and urinary NTX levels (both, $P < 0.0001$). There were no significant longitudinal changes in the serum calcium or phosphorus levels. The mean percent change in the urinary NTX level from the baseline after 3 mo of treatment was -34.7% (Table 2), while those for serum ALP

Table 2 Changes in speed of sound and biochemical markers

	Baseline	3 mo	6 mo	12 mo
SOS (m/s)	1473 ± 13		1483 ± 16	1483 ± 17
Percent changes from baseline			0.68% ± 1.10%	0.65% ± 1.24%
Calcium (mg/dL)	9.2 ± 0.4		9.2 ± 0.5	9.2 ± 0.4
Percent changes from baseline			−0.43% ± 3.36%	0.30% ± 3.68%
Phosphorus (mg/dL)	3.5 ± 0.3		3.5 ± 0.6	3.5 ± 0.4
Percent changes from baseline			2.48% ± 17.6%	1.17% ± 9.85%
ALP (IU/L)	229 ± 63		187 ± 57	177 ± 48
Percent changes from baseline			−17.2% ± 16.7%	− 21.2% ± 16.7%
Urinary NTX (nmol BCE/mmol Cr)	56.2 ± 17.8	35.9 ± 11.3		
Percent changes from baseline		−34.7% ± 15.0%		

Data are expressed as mean ± SD. The normal ranges of serum calcium, phosphorus, and alkaline phosphatase (ALP) were 8.4-10.2 mg/dL, 2.5-4.5 mg/dL, and 100-340 IU/L, respectively. The standard range of urinary cross-linked N-terminal telopeptides of type I collagen (NTX) was 9.3-54.3 nmol bone collagen equivalent (BCE)/mmol creatinine (Cr), and the cutoff values for bone loss and vertebral fracture risk were 35.3 and 54.3 nmol BCE/mmol Cr, respectively. SOS: Speed of sound.

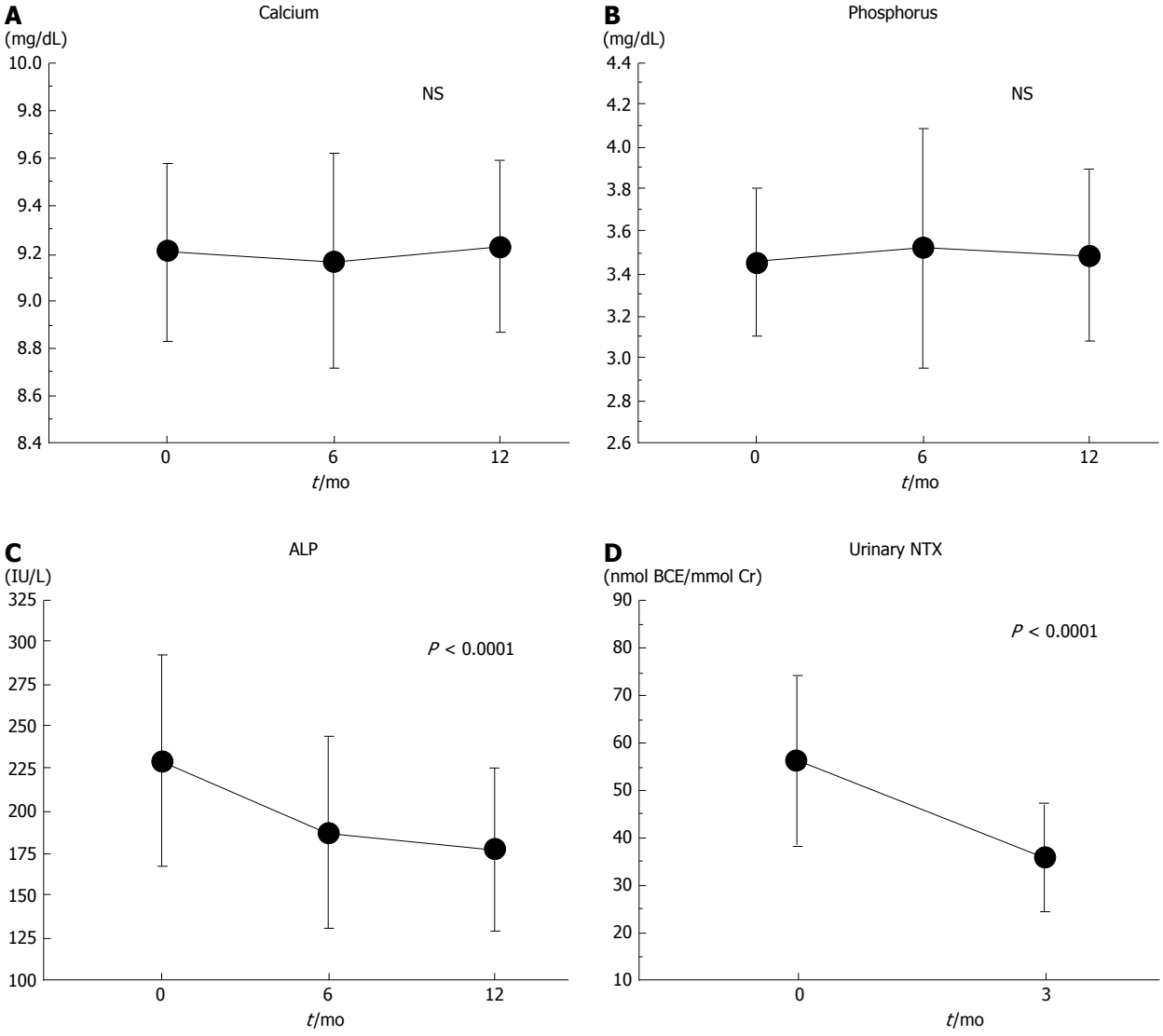

Figure 2 Changes in biochemical markers. Data are expressed as mean ± SD. One-way analysis of variance (ANOVA) with repeated measurements was used to analyze the longitudinal changes in biochemical markers. The longitudinal changes in serum alkaline phosphatase (ALP) and urinary cross-linked N-terminal telopeptides of type I collagen (NTX) were statistically significant (both, $P < 0.0001$ *vs* the baseline). NS: Not significant; BCE: Bone collagen equivalent.

levels after 6 and 12 mo of treatment were -17.2% and -21.2%, respectively (Table 2).

Associations between changes in urinary NTX levels and changes in the SOS of the calcaneus

Univariate regression analysis showed no significant associations between the percent decrease in urinary NTX at 3 mo and the percent increase in the SOS at either 6 or 12 mo.

Fractures

During the 1-year treatment period, one patient experienced a rib fracture and one patient experienced a morphometric vertebral fracture.

Adverse events

One patient underwent a tooth extraction during the 1-year treatment period. There were no serious adverse events in this study, such as osteonecrosis of the jaw, femoral diaphysis atypical fractures, or atrial fibrillation, which have been reported in other studies[17-19].

DISCUSSION

The present study confirmed that treatment with risedronate decreased the urinary NTX and serum ALP levels (by -34.7% at 3 mo and -21.2% at 12 mo, respectively), and elicited a modest increase in the SOS of the calcaneus (by +0.68% at 6 mo and +0.65% at 12 mo) in Japanese postmenopausal women with osteoporosis. The objectives of this study were to determine: (1) whether decreases in bone turnover markers would be similar to those reported in our previous studies; and (2) whether the increase in the SOS of the calcaneus would be significant and greater than the range of reproducibility. We also compared the effects of risedronate and alendronate on the changes in these parameters.

Urinary NTX levels were measured at 3 mo after starting treatment, because measurement of urinary NTX levels at this time helps to assess whether the antiresorptive effects of risedronate (2.5 mg daily and 17.5 mg weekly) are sufficient or clinically significant[8,11]. Previous RCTs showed that risedronate together with calcium supplementation decreased urinary NTX (by about -38% to -40% at 3 mo) and serum ALP (by about -28% to -30% at 1 year) in Japanese postmenopausal women with osteoporosis[8,9,11]. The decreases in urinary NTX and serum ALP levels in the present study were slightly smaller than those in the previous RCTs. One reason for this discrepancy is that calcium supplementation was not used in the present study unlike in the previous RCTs. Nevertheless, this clinical practice-based observational study confirmed that treatment with risedronate for 1 year suppressed bone turnover in postmenopausal women with osteoporosis. Optimal vitamin D repletion is thought to be necessary to maximize the response to antiresorbers in terms of BMD changes and reducing the risk of fracture in postmenopausal women with osteoporosis[20]. Thus, improvements in vitamin D status may be necessary for greater response of the SOS and bone turnover markers to risedronate.

The mean age of the study subjects at the start of treatment was 71.1 years. The reference values of the SOS of the calcaneus in healthy Japanese women aged 65-69, 70-74, and 75-79 years are 1487, 1481, and 1475 m/s, respectively[21]. Treatment with risedronate for 1 year increased the SOS of the calcaneus from 1473 m/s at the start of treatment to 1483 m/s at 12 mo. Therefore, it seems that risedronate might help to increase the SOS of the calcaneus in postmenopausal women with osteoporosis. The percent increase in SOS from the baseline was +0.65% at 12 mo. Although this increase appeared to be modest, it was likely to exceed the CV of the SOS of the calcaneus *in vivo* (0.27%)[15].

We previously reported the effects of 1 year of treatment with alendronate (35 mg weekly) on the SOS and bone turnover markers in postmenopausal women with osteoporosis (mean age: 69.0 years)[7], In that study, alendronate reduced urinary NTX levels (by -44.9% at 3 mo) and increased the SOS (by +0.6% at 12 mo). In the present study, 1 year of treatment with risedronate (17.5 mg weekly) decreased the urinary NTX levels (by -34.7% at 3 mo) and increased the SOS of the calcaneus (by +0.65% at 12 mo) in postmenopausal women with osteoporosis (mean age: 71.1 years). In prior Japanese RCTs in postmenopausal women with osteoporosis, 1 year of treatment with alendronate (5 mg daily and 35 mg weekly) increased BMD of the lumbar spine by 5.8%-6.4% from baseline[22-24], while risedronate (2.5 mg daily and 17.5 mg weekly) increased it by 4.9%-5.9%[8-11]. The reductions in levels of bone turnover markers were also greater with alendronate than with risedronate[8-11,22-24]. Thus, alendronate may be elicit greater reductions in bone turnover and greater increases in BMD of the lumbar spine in postmenopausal Japanese women with osteoporosis compared with risedronate. However, the increase in the SOS was very similar with both treatments, suggesting that risedronate and alendronate have similar effects on bone structure and quality.

Dufresne *et al*[25] investigated the effect of 1 year of treatment with risedronate on bone structure by analyzing iliac crest bone biopsy specimens from women enrolled in a double-blind, placebo-controlled study of risedronate for the prevention of early postmenopausal bone loss using three-dimensional microcomputed tomography. The placebo group experienced decreases in bone volume (placebo: -5.1%, risedronate: +3.5%), trabecular thickness (placebo: -20 μm, risedronate: +23 μm), and trabecular number (placebo: -0.223 mm^{-1}, risedronate: +0.099 mm^{-1}), and increases in percent plate (placebo: +2.79%, risedronate: -3.23%), trabecular separation (placebo: +79 μm, risedronate: -46 μm) and marrow star volume (placebo: +2.80 mm^3, risedronate: -2.08 mm^3) as compared with the risedronate group. These changes in the trabecular structure appeared to partly reflect changes in the SOS.

There was no further increase in the SOS after 6 mo of treatment with risedronate, although serum ALP levels continued to decrease. However, the reduction in the serum ALP levels were blunted after 6 mo (229 IU/L at the baseline, 187 IU/L at 6 mo, and 177 IU/L at 12 mo). It has been reported that the anti-fracture effect of risedronate against clinical vertebral fractures is recognized as early as 6 mo after the start of treatment in postmenopausal women with osteoporosis[26], suggesting the rapid skeletal effects of risedronate. It was likely that risedronate rapidly improved the trabecular architecture by suppressing bone turnover, thereby increased the SOS from the baseline, and maintained the trabecular structure thereafter.

There are several limitations of the present study. In particular, the statistical quality of the present analyses may be relatively poor because of the small sample size, the absence of statistical power for the fracture incidence, and the retrospective nature of the analyses. Further studies are needed to confirm our results.

In conclusion, the present study confirmed that risedronate suppresses bone turnover, producing a modest but significant increase in the SOS of the calcaneus in Japanese postmenopausal women with osteoporosis. The results of this study and our previous studies suggest risedronate and alendronate have similar beneficial effects on the SOS of the calcaneus.

COMMENTS

Background

The effects of risedronate treatment on quantitative ultrasound (QUS) parameters of the calcaneus remain to be established in patients with osteoporosis.

Research frontiers

The aim of the present clinical practice-based observational study was to examine the effects of treatment with risedronate for 1 year on speed of sound (SOS) of the calcaneus and bone turnover markers in postmenopausal women with osteoporosis.

Innovations and breakthroughs

The urinary levels of cross-linked N-terminal telopeptides of type I collagen (NTX) and serum levels of alkaline phosphatase were significantly decreased at 3 mo (-34.7%) and 12 mo (-21.2%), respectively, compared with the baseline values. The SOS increased modestly, but significantly by 0.65% at 12 mo compared with the baseline value. Treatment with risedronate elicited an increase in the SOS of the calcaneus exceeding the coefficient of variation *in vivo* (0.27%).

Applications

The present study confirmed that risedronate suppressed bone turnover and elicited a clinically significant increase in the SOS of the calcaneus in postmenopausal women with osteoporosis.

Peer review

This study convincingly demonstrates that risedronate slightly increases the speed of sound in the calcaneous, as well as reduce the rate of bone turnover based on lower concentrations of circulating collagen and alkaline phosphatase. The methodology is sound and sufficiently detailed, the results are clearly presented, and the conclusions are supported by the results.

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CASE REPORT

Treatment of C2 body fracture with unusual distractive and rotational components resulting in gross instability

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Abstract

Cervical fractures can result in severe neurological compromise and even death. One of the most commonly injured segments is the C2 vertebrae, which most frequently involves the odontoid process. In this report, we present the unusual case of a 28-year-old female who sustained a C2 vertebral body fracture (comminuted transverse fracture through the body and both transverse processes) that had both a significant distractive and rotational component, causing the fracture to be highly unstable. Application of halo bracing was unsuccessful. The patient subsequently required a C1-C4 posterior spinal fusion. Follow-up computer tomography imaging confirmed fusion and the patient did well clinically thereafter.

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Key words: C2; Distractive; Odontoid fracture; Rotational; Spine; Type Ⅲ; Unstable

Core tip: Patients with a transverse fracture through the C2 body can have significant distractive and rotational components leading to significant instability. In such cases, external bracing may not be the best method of treatment. Rather, surgical stabilization is needed in order to promote optimal outcome.

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INTRODUCTION

Cervical fractures are potentially devastating injuries due to the potential deleterious neurological sequelae that can result. In general, the more superior the injury, the greater the chance for morbidity and mortality; craniocervical junction injuries can be the deadliest[1]. One of the most vulnerable cervical vertebrae in trauma is the C2 segment. It is estimated that C2 fractures occur in 10%-20% of all cervical injuries[2-5]. The incidence of C2 fractures is on the rise[6], and it is now the most commonly fractured vertebra in the elderly[7,8]. Fractures that involve the odontoid process of C2 are commonly categorized according to the Anderson and D'Alonzo system[4]. Type Ⅱ odontoid fractures are not infrequently deemed unstable and surgical stabilization is warranted. In contrast, type Ⅰ odontoid fractures are rarely unstable, and type Ⅲ odontoid fractures are most often stable enough to be treated with an external orthosis such as halo bracing. Rarely, patients with type Ⅲ odontoid fractures can present with additional instability in the form of a distractive com-

ponent with significant vertical displacement and even spinal cord injury[9,10]. In this case report, we present the uncommon case of a transverse C2 body fracture with a distractive and rotational component. We discuss the diagnosis and management of patients with this pathology.

CASE REPORT

A 28-year-old female presented to the emergency department with a catalogue of injuries following a roll-over motor vehicle accident (MVA). She had been riding without seatbelt restraints and was ejected from the vehicle. Most notably, she had significant pain and subjective weakness of her left shoulder. On neurological examination she had full strength throughout her right upper extremity. Examination of her left upper extremity found weakness in the biceps, triceps, wrist flexion, wrist extension, and finger grip: Motor Research Council (MRC) strength score 4+ out of possible 5. Her left deltoid strength was the weakest of all muscle groups, scoring 0 out of 5.

Computer tomography (CT) of the cervical spine revealed an acute comminuted transverse fracture through the body and both transverse processes of the C2 vertebrae, involving the foramina transversaria bilaterally (Figure 1). The C2 body involved a significant rotational component (Figure 2) such that the left portion of the body was within the vertebral canal causing stenosis (Figure 3). Epidural hemorrhage was also noted within the spinal canal at levels C1-C2. As this was deemed a highly unstable fracture, the patient was immediately fixated in a halo and steroids were administered for potential cord injury.

The patient was neurologically stable on post-halo day 1, but on post-halo day 2, her neurological examination began to worsen. She now demonstrated MRC strength of 0 out of 5 in the left deltoid, 0 out of 5 in the left biceps, 3 out of 5 in the left triceps, and 2 out of 5 in left hand grip. MRI did not show significant spinal cord compression. Consequently, the etiology of her weakness was not clear, although a brachial plexus injury was considered. However, surgical stabilization of her C2 fracture was recommended given that the fracture did not appear stable, even with halo bracing (Figure 4). A C1 to C4 posterior spinal fusion with placement of lateral mass screws at C1, C3, and C4 was performed. Significant improvement in the distractive and rotational mal-alignment was achieved. There were no intraoperative complications.

Postoperatively the patient demonstrated MRC strength of 3 out of 5 in left hand grip and left triceps. Left deltoid and biceps strength were still trace out of 5. She remained neurologically stable throughout the rest of her hospital stay and was discharged to a subacute rehabilitation facility. At 2-year follow-up, the patient had made a remarkable recovery of motor function. On examination, she had full strength throughout both her left and right upper extremities (5 out of 5 for deltoids, biceps, triceps, wrist extension, wrist flexion, and finger grip). She did report moderate residual neck pain. Cervical X-ray demonstrated proper placement of instrumentation without evidence of hardware failure and CT confirmed fusion (Figure 5).

Figure 1 Reformatted coronal computer tomography images showing the transverse body fracture extending through the transverse processes (A, B).

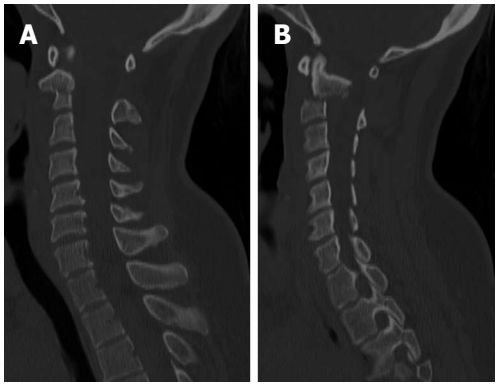

Figure 2 Reformatted sagittal computer tomography images right of midline (A), and left of midline (B).

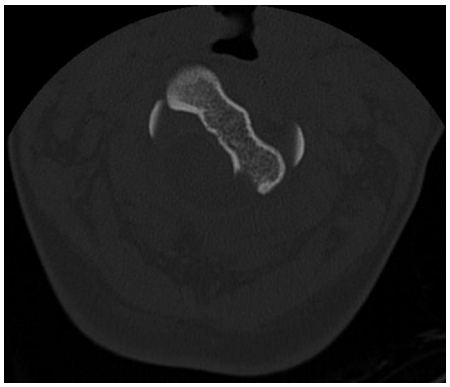

Figure 3 Axial computer tomography showing left rotational component of upper C2 body.

DISCUSSION

Cervical spine injuries can be associated with significant morbidity and even mortality when the spinal cord is

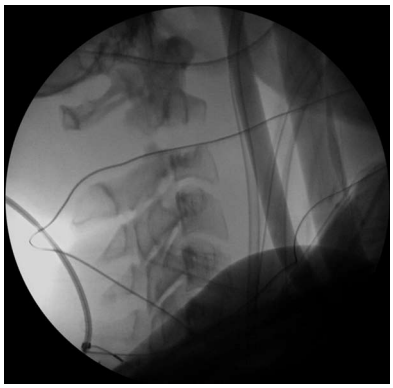

Figure 4 Lateral X-ray image showing persistent distraction in halo brace.

Figure 5 Reformatted sagittal computer tomography image obtained at 2-year follow-up showing anatomic alignment and fused segments.

injured[11]. One of the most vulnerable cervical levels following trauma is the C2 level[2]. There are a variety of fractures and injuries that can occur at this level. The most common C2 fractures include lateral mass fractures, extension teardrop fractures, traumatic spondylolisthesis (hangman fractures), and odontoid (or dens) fractures[12]. It is estimated that odontoid fractures occur in 10%-20% of all cervical spine injuries[2-5] and its incidence has been reported to be on the rise[6].

Odontoid fractures most commonly occur following trauma after a mechanical fall or motor vehicle collision[13]. The mechanism of injury is a dorsal blow to the head[14]. Its presentation can range from asymptomatic to severe neurological deficits such as quadriparesis. There are also rare reports of patients who present with specific spinal cord syndromes such as Brown-Sequard syndrome[15]. Diagnosis of odontoid fractures relies heavily on imaging, typically plain films (with anteroposterior, lateral, and odontoid views) and cervical CT imaging[16,17]. On initial evaluation for odontoid fractures, plain films have been the first diagnostic test performed. However, CT imaging should be performed when there is suspicion of an odontoid fracture. CT imaging is generally much more sensitive for detecting fractures, defining the extent of pathology, and evaluating the surrounding soft tissue than plain films.

Decisions on the course of treatment for an odontoid fracture depend primarily on two factors: radiologic appearance/characteristics (type of odontoid fracture) and clinical status (presence or absence of neurological deficit)[18,19]. The most widely used classification system currently in practice was described by Anderson and D' Alonzo in which fractures were classified into three main types and can be further subcategorized as displaced or non-displaced[4]. A type 1 odontoid fracture involves an oblique fracture through the odontoid itself and is thought to be a manifestation of an avulsion of the attached alar ligament. This type is the least common of all odontoid fractures and is typically considered a stable fracture with a good rate of successful union because the fracture is located high enough that it does not cause instability[4]. A type Ⅱ odontoid fracture involves the junction of odontoid process and the vertebral body of C2. These fractures make up the majority of all odontoid fractures. They are generally considered unstable with a high rate of non-union and are the most difficult to treat[4]. A type Ⅲ odontoid fracture involves a fracture through the cancellous portion of the C2 body. These types of fractures are the second most common of the three odontoid fracture types, and are considered stable enough that external bracing is sufficient to achieve a high rate of union given the presence of large cancellous surfaces[4,18].

Rarely, however, type Ⅲ odontoid fractures may require surgical attention when deemed unstable. Although displacement and/or dislocation of an odontoid fracture has been described in terms of translation or angulation, vertical displacement (distractive component) or even rotation as a factor in determining stability or adequacy of reduction has received little attention. It is known that the presence of atlantoaxial dislocation in type Ⅲ odontoid fracture is unstable[20,21], and when there is complete disruption of the anterior atlantoaxial ligament, these injuries appear to be vertically unstable type Ⅲ odontoid fractures, similar to the injury described in this report[22].

There are only a few reports of isolated unstable type Ⅲ fractures where a distractive component was present and external traction bracing was deemed inapt warranting surgical management[9,10]. Jea *et al*[9] described the case of a 73-year-old female with a type Ⅲ odontoid fracture associated with a significant distractive component following a MVA. On presentation, the patient was quadriplegic and had bilateral cranial nerve XI palsies. This patient underwent a C1-C2 fusion. Despite this treatment, the patient remained quadriplegic and ventilator-dependent. In a case series of three patients reported by Kirkpatrick *et al*[10], a 65-year-old female, 39-year-old female, and 29-year-old female all sustained type Ⅲ odontoid fractures associated with unstable distractive components (at least 5 mm of vertical displacement was present) following a MVA. In the 39-year-old female, halo immobilization was attempted but, despite this, motion at the fracture site was noted; the distractive component was severe enough that the C1-C2 facet space oscillated with ventilation when viewed under fluoroscopy. All

three patients underwent C1-C2 arthrodesis with transarticular screws and iliac crest bone graft. Two patients had permanent neurological deficits: at 27-mo follow-up, the 65-year-old patient had incomplete C1-C5 level quadriparesis, and at 10 mo, the 39-year-old patient had a C5 tetraplegia. The last patient regained full neurological function at 18 mo post-procedure.

To our knowledge, there are no reports of a C2 body fracture that possess both significant rotational and distractive components as was seen in our patient. These components likely resulted from the atypical fracture pattern seen in this patient; the fracture traversed the C2 vertebral body in a transverse manner. The rotational component in our patient was quite significant, as the left portion of the body caused some degree of narrowing of the spinal canal. Complications from purposely or inadvertently applying traction axially have not been readily described because longitudinal instability associated with odontoid fractures is rare[23]. But in fractures associated with a distractive component, halo traction is not ideal as there is instability secondary to circumferential injury so that traction could cause or worsen neurologic symptoms. Therefore, fractures with distractive and/or rotational components warrant surgical stabilization.

Transverse C2 body fractures with rotational and distractive components are unusual and highly unstable. Surgical stabilization should be considered for these types of fractures.

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CASE REPORT

Low-grade central osteosarcoma of distal femur, resembling fibrous dysplasia

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Abstract

We report a case of a 32 year-old male, admitted for a lytic lesion of the distal femur. One month after the first X-ray, clinical and imaging deterioration was evident. Open biopsy revealed fibrous dysplasia. Three months later, the lytic lesion had spread to the whole distal third of the femur reaching the articular cartilage. The malignant clinical and imaging features necessitated excision of the lesion and reconstruction with a custom-made total knee arthroplasty. Intraoperatively, no obvious soft tissue infiltration was evident. Nevertheless, an excision of the distal 15.5 cm of the femur including 3.0 cm of the surrounding muscles was finally performed. The histological examination of the excised specimen revealed central low-grade osteosarcoma. Based on the morphological features of the excised tumor, allied to the clinical findings, the diagnosis of low-grade central osteosarcoma was finally made although characters of a fibrous dysplasia were apparent. Central low-grade osteosarcoma is a rare, well-differentiated sub-type of osteosarcoma, with clinical, imaging, and histological features similar to benign tumours. Thus, initial misdiagnosis is usual with the condition commonly mistaken for fibrous dysplasia. Central low-grade osteosarcoma is usually treated with surgery alone, with rare cases of distal metastases. However, regional recurrence is quite frequent after close margin excision.

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Key words: Osteosarcoma; Fibrous dysplasia of bone; Distal femur; Custom-made total knee arthroplasty; Tumour

Core tip: We report a case of a 32 year-old male, admitted for a lytic lesion of the distal femur. Although open biopsy suggested fibrous dysplasia, clinical and radiological evaluation indicated malignancy. Histological examination of the excised specimen revealed central low-grade osteosarcoma. Central low-grade osteosarcoma is a rare, well-differentiated, sub-type of osteosarcoma, with clinical, imaging, and histological features in keeping with benign tumours. Thus, initial misdiagnosis is common, typically being mistaken for fibrous dysplasia. Central low-grade osteosarcoma is usually treated with surgery in isolation, with rare cases of distal metastases. However, regional recurrence is quite frequent after close margin excision.

Vasiliadis HS, Arnaoutoglou C, Plakoutsis S, Doukas M, Batistatou A, Xenakis TA. Low-grade central osteosarcoma of distal femur, resembling fibrous dysplasia. *World J Orthop* 2013; 4(4): 327-332 Available from: URL: http://www.wjgnet.com/2218-5836/full/v4/i4/327.htm DOI: http://dx.doi.org/10.5312/wjo.v4.i4.327

INTRODUCTION

Low-grade central osteosarcoma (LGCO) is a rare well-differentiated sub-type of osteosarcoma[1]. It is first described by Unni *et al*[2] who reported 27 patients with an "Intraosseous well-differentiated osteosarcoma". Since then, only a few cases of LGCO have been reported being variously described as "well-differentiated intramedullary osteosarcoma", "low grade intraosseous osteosarcoma", "central osteosarcoma of low-grade malignancy", or " low-grade endosteal osteosarcoma"[2-5].

LGCO usually presents in the third decade of life, with an almost equal male to female ratio[2,3,6,7]. It represents less than 2% of all osteosarcomas[8]. Metaphyseal region of the long bones is usually affected, while distal femur and proximal tibia are involved in more than half of the cases and long bones in over 80%[2,3,6]. Its high differentiation and relatively low malignancy contribute to an extremely high rate of initial misdiagnoses, typically masquerading as fibrous dysplasia.

CASE REPORT

A 32 year-old male attended our institute complaining of pain and swelling of his left knee over a period of 3 to 4 mo. Clinical examination revealed a solid expansion of the distal femur with no signs of effusion or inflammation. Plain X-rays showed a lytic lesion occupying the distal third of the femur including the medial and lateral condyle, reaching the subchondral area of the knee joint (Figure 1A). Computed tomography (CT) and magnetic resonance imaging (MRI) (Figure 1B and C) confirmed the lytic characters of the lesion which was found to spread mainly intramedullary, without expansion beyond the joint. Low signal was seen in T1-weight images and intermediate in STIR with areas of cortical interruption and periosteal reaction. Soft tissue infiltration was also evident focally. The patient was initially discharged and advised to avoid weight bearing with close observation.

One month later, X-ray images revealed deterioration of the characteristics of the lesion, with more obvious lysis of the distal femur (Figure 2). Thick and coarse trabeculation had become apparent, while cortical perforation was found especially to the anterior cortex. Meanwhile, an methylene diphosphonate bone scan was performed, showing an increased uptake at the distal femur at the lesion area, with no further cephalic or distal expansion. No other spots of increased uptake were apparent in the rest of the skeleton. CT scan of the thoracic cavity and abdomen was also negative for metastasis.

Open biopsy was performed obtaining bone specimens from the outer lateral condyle with 3 cm × 2 cm × 1 cm total dimensions. The tissue specimen consisted of multiple tan-grey fragments with a bony texture. Microscopic examination revealed a lesion consisting of fibrous and osseous components, in variable amounts in all sections. The fibrous stroma was composed of spindle-shaped cells without features of malignancy. Non-stress oriented trabeculae of immature bone without osteoblastic rimming, as well as haphazardly shaped trabeculae ("alphabet soup") were also observed. The morphologic features were consistent with fibrous dysplasia.

Figure 1 Imaging of the lesion at the patient admission. A: Lytic lesion of the distal femur is seen on radiographs; B: Computed tomography scan of distal femur showing the erosion of the bone with focal cortical destruction; C: T1-weighted magnetic resonance imaging demonstrating the extent of the lesion with areas of cortical destruction and periostic reaction.

Figure 2 Radiograph at 1 mo follow up. More obvious lysis of the distal femur comparatively to the initial image. Thick and coarse trabeculation is obviously apparent. Cortical breech is clearly found especially to the anterior cortex.

However, the wide extent of the tumour and the involvement of both the femoral condyles and the subchondral area were considered to increase the risk of a pathological fracture or total joint surface depression. Moreover, the clear evidence of deterioration on the images allied to the signs of cortical perforation with focal soft tissue infiltration increased the clinical suspicion of malignancy. Therefore, despite the benign histological

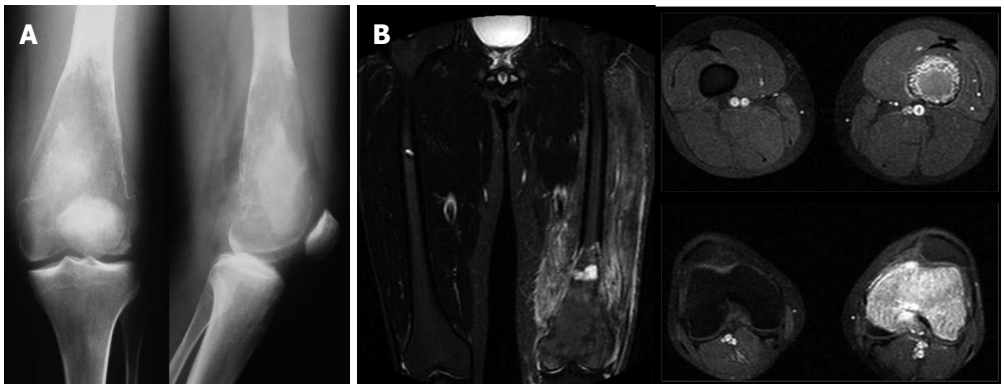

Figure 3 Imaging at three months after the first admission. A: Elimination of the bone trabeculation is accompanied by a compressive fracture of the metaphysic; B: Magnetic resonance imaging shows no signs of wider extension of the lesion. STIR-weight images reveal an increased oedema of the surrounding muscles.

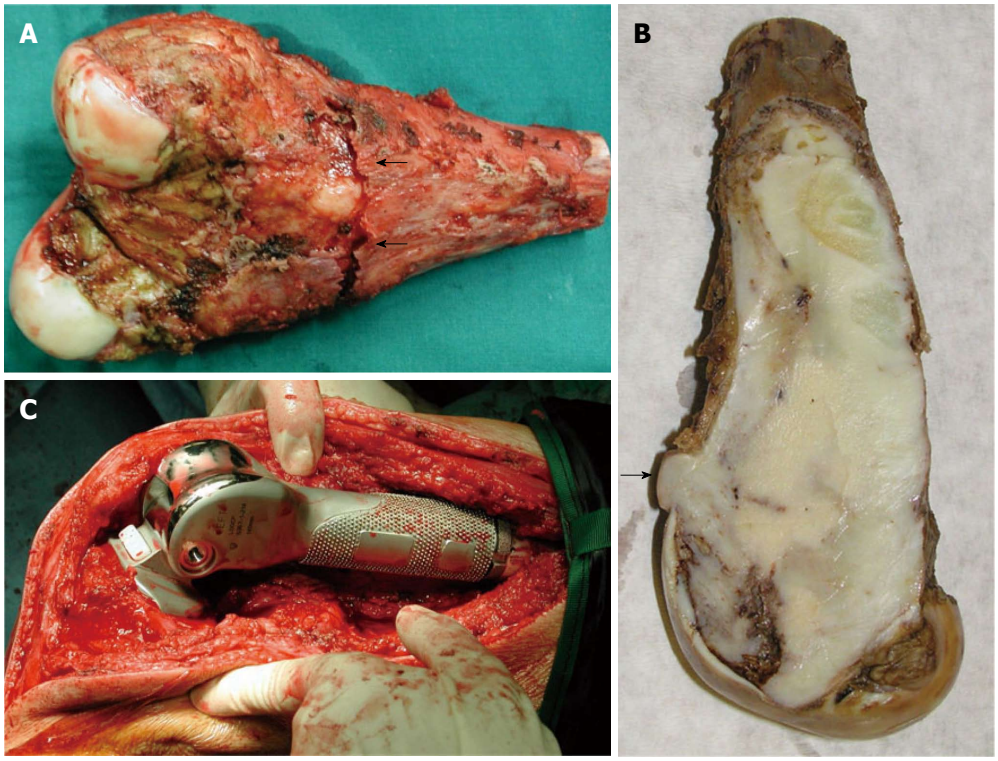

Figure 4 Open biopsy was performed obtaining bone specimens from the outer lateral condyle with 3 cm × 2 cm × 1 cm total dimensions. A: Excised specimen of the distal 15.5 cm of the femur. Compressive fracture of the posterior cortex (arrows); B: The tumor arose within the medullary cavity and extended from the cartilage surface to 3 cm distance from the excision line. The mass clearly breaches the cortex (arrow); C: Hinged custom made total knee arthroplasty (Howmedica Modular Resection System, Stryker Howmedica Osteonics, Inc).

diagnosis, a wide excision of the upper femur (involving tumor removal with a margin of at least 3 cm of normal tissue) was undertaken followed by a hinged custom-made total knee arthroplasty (Howmedica Modular Resection System, Stryker Howmedica Osteonics, Inc).

Readmission of the patient for the arthroplasty procedure three months after the first admission, revealed a severely affected bone radiographically (Figure 3). Lysis of the distal femur with elimination of the bone trabeculation was accompanied by a compressive fracture of the metaphysis (Figures 3A, 4A). Severe pain was provoked even with partial weight bearing, while clinical examination revealed paradox mobility of the distal femur. A new MRI was performed. In contrast to the plain X-rays, the MRI showed similar findings to the previous image, with no evidence of wider extension of the lesion. However, a high signal to the STIR-weight images revealed an increased oedema of the surrounding muscles, probably due to a haematoma secondary to the fracture (Figure 3B).

Intra-operatively, no obvious soft tissue infiltration was evident. Nevertheless, an excision of the distal 15.5 cm of the femur including 3.0 cm of the surrounding muscles was finally performed (Figure 4A and B). Macroscopically, a large well-demarcated, grey-white mass with a firm and gritty texture, measuring 15.5 cm × 5.0 cm was excised and sent for histological evaluation. The

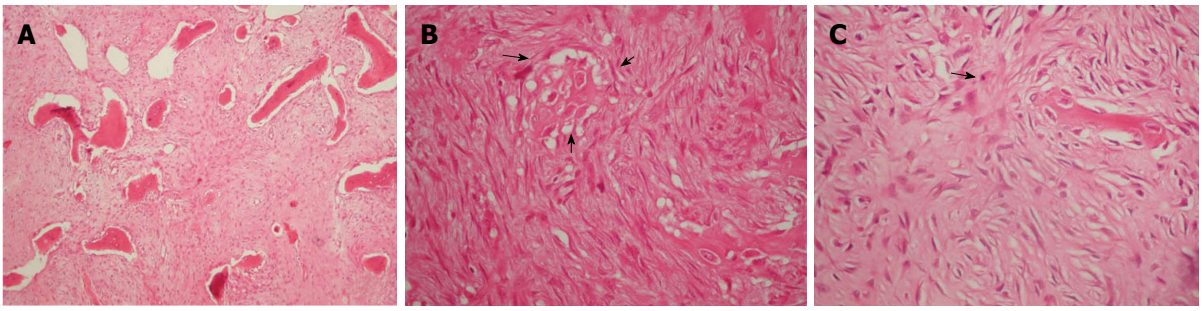

Figure 5 Microscopic features throughout the tumor. A: Areas with characteristic irregularly shaped bony spicules, surrounded by hypocellular spindle cell stroma, resembling fibrous dysplasia (HE × 200); B: Focal osteoid production (arrow) within the moderately cellular fibroblastic stroma (HE × 400); C: Occasional mitotic figures were identified (arrow), (HE × 400).

tumor arose within the medullary cavity and extended from the cartilage surface to within 3 cm distance from the excision line (Figure 4A and B). The cartilage had a chondral lesion (Outerbridge grade I) with no signs of infiltration. The mass breached the cortex without infiltrating the overlying soft tissue. Microscopically, a hypocellular neoplasm with an infiltrative pattern of growth was observed. The stroma consisted of collagen-producing spindle cells with slight cytologic atypia and occasional mitotic figures. MIB-1 was expressed in less than 10% of the tumor cells. Upon careful microscopic examination of multiple sections, focal osteoid production was noted. The latter was eosinophilic, curvilinear, with small nubs, abortive lacunae formation and atypical neoplastic cells. There was no osteoblastic rimming. Based on the morphological features described allied to the clinical findings, the diagnosis of low-grade central osteosarcoma was made although characters of a fibrous dysplasia were apparent (Figure 5). Postoperatively, although the lesion was excised with healthy margin, preventive radiation of 60 Gy was finally delivered to the site.

After 7 years follow-up, the patient was apparently disease-free with no signs of implant mobility. Bone-scan imaging was performed annually following the surgery, with no signs of metastasis. The patient's overall condition is very good with no ambulatory problems. However, there are frequent recurrences of subcutaneous and skin infection at the distal femur (a potential side-effect of radiotherapy secondary to the operation). This responded to antibiotics, requiring intravenous administration on two occasions. Limited range of motion to full extension and 40 degrees of flexion has developed postoperatively. This has responded well to physiotherapy including continuous passive motion assistance.

DISCUSSION

Since the first description of the low-grade central osteosarcoma, only a few case reports and fewer case series have been published in the literature[2,3,8-10]. The very low incidence of LGCO means that identifying the condition based on either the clinical, imaging or histological features of this tumour is complex. Moreover, the minimal cytological atypia, with the very low mitotic activity usually resembles more benign tumours. Differentiation from other conditions particularly fibrous dysplasia is complicated. Other conditions resembling this LGCO include ossifying or non-ossifying fibroma, aneurysmal bone cyst, or chondromyxoid fibroma or even malignant tumours such as parosteal osteosarcoma[3-5,10-23].

The clinical presentation on LGCO is heterogeneous usually manifesting as long-standing pain ranging from months to even several years before medical consultation is sought[8,24-26]. Mass, swelling or pathological fractures are rarely observed at the first admission[15].

There is also a highly variable radiographic appearance in LGCO[2,3,8,15,20]. The condition usually appears as a large medullary tumour often with trabeculation and sclerosis, with no periosteal new bone formation or soft tissue extension; it is thus easily mistaken for a benign lesion[8,10]. However, a potential cortical interruption due to localized destruction and soft tissue mass are the most typical radiographic findings leading to diagnosis[3,4,11]. It is believed that careful evaluation usually reveals at least a small region showing with cortical perforation, soft tissue shadows, or calcification, as well as periosteal reaction that should strengthen a suspicion of malignancy[6-8,15]. Nevertheless, 27 of the 90 patients in the Andresen *et al*[3] series show no aggressive features on the x-ray that could lead to a diagnosis of malignancy.

Andresen *et al*[3] described four radiographic patterns; a lytic with varying amounts of thick and coarse trabeculation, a predominantly lytic with few thin and incomplete trabecula, a densely sclerotic, and a mixed lytic and sclerotic subtype. It seems that radiographic appearance of a LGCO may evolve over a period of time. Our patient first appeared with a lytic lesion with varying trabeculation (Figure 1), while one month later it had altered into a mixed lytic and sclerotic lesion (Figure 2). The final image three months after the initial diagnosis was, however, clearly suggestive of the predominantly lytic pattern (Figure 3).

LGCO with sclerosis and lysis juxtaposed on the X-ray predisposes to a high incidence of misdiagnosis as this pattern is considered to radiographically mimic fibrous dysplasia in its morphology and matrix pattern[3]. The lesion usually extends to the end of the affected long bone, as found in 25 of 59 cases of Andersen series[3]. It usually reaches the subchondral bone without affecting the ar-

ticular cartilage, as was also seen in the present case.

Although biopsy usually leads to the diagnosis, in the case of LGCO histology may be misleading, as arose in the present case. Inwards describes three main histological patterns of bone production, classifying the LGCO into three types: the fibrous dysplasia-like, the parosteal osteosarcoma-like and the desmoid-like[15]. In the fibrous dysplasia-like pattern, irregularly shaped spicules of woven bone are found even mimicking the classic "Chinese letters" pattern of fibrous dysplasia[10]. In that case misdiagnosis is likely and only further biopsy or radiographic findings may prevent it. The other two patterns also have histological features typically resembling parosteal osteosarcoma or desmoids tumour.

Seemingly benign features from either the clinical examination or the imaging or histological evaluation commonly lead to a misdiagnosis of LGCO. Choong *et al*[8] report a series of 20 cases of LGCO, 9 of each were initially misdiagnosed; one as chondrosarcoma while the other eight as benign lesions including fibrous dysplasia (3), nonossifying fibroma (2), fibroma (1), chondromyxoid fibroma (1) and simple bone cyst. Other tumours have also been diagnosed instead of LGCO, such as giant cell tumours, aneurysmal bone cysts, chondromyxoid fibromas, parosteal osteosarcomas or a malignant lymphoma[2,6,7,11,25].

There is agreement in the literature that wide excision is the only accepted treatment of LGCO, providing a very good prognosis. Wide excision is almost never followed by recurrence[6-8]. On the other hand, there is high incidence of local recurrence after inadequate surgical margins as with local excision of the tumour; this situation is highly likely to present with greater soft tissue and bony involvement. Recurrences are very often found to exhibit a higher histologic grade or dedifferentiation with the potential for metastases[14,15,27]. In the Mayo clinic series a 15% of the recurrences appeared as conventional osteosarcoma with poor prognosis[6]. Unni *et al*[2] report a high risk of transformation to conventional osteosarcoma if the lesion is initially treated only with curettage.

Choong *et al*[8] also report that an intralesional resection in 12 patients was associated with local recurrence to all of them. Four of the 12 recurrences were of a higher grade (25%), and 3 of these patients died of their disease. One was histologically undifferentiated. The time of the recurrence varies with a median period of 3 years, ranging from 3 months to even 14 years as found in one patient. Kurt *et al*[6] report two patients with initial diagnosis of fibrous dysplasia and long term recurrence following initial treatment with curettage. Both these patients eventually developed high-grade osteosarcoma 15 and 20 years after their initial curettage.

Distal metastases are rarely found from a LGCO but are more in keeping with a high-grade conventional osteosarcoma. Time of appearance varies with reported recurrence ranging from some months to several years after diagnosis[6,8]. Metastases can be pulmonary, osseous or to the lymph nodes[8]. It is the metastatic tumour from the higher-grade recurrence that can lead to death in patients with a low-grade central osteosarcoma[6,8,15].

A local recurrence with a higher clinical grade or signs of dedifferentiation, even if no metastases are apparent, is the only indication for adjuvant chemotherapy[6,8,11]. More aggressive forms of treatment such as amputation should not be required nowadays, with rare exceptions such as in the case of a diffuse tumor dedifferentiated to a high grade conventional osteosarcoma[8]. Radiotherapy is not generally mentioned in the literature as a treatment option for LGCO. However, in our case it was used due to the wide extension of the tumor in order to ensure the sterilization of the excision borders. It is nonetheless agreed that the treatment of low-grade central osteosarcoma is en-bloc resection with wide surgical margins, supported by the few published reports of prolonged follow-up.

LGCO is a rarely-encountered malignant tumour of the bones. Histologically it is a subtype of osteosarcoma, though with a much more favourable clinical outcome if treated appropriately. The typically late first diagnosis and the increased size of the initially found tumour, apparent with the low rate of recurrence or metastases, indicate its relatively benign progression. Nevertheless, its similarity to benign tumours and especially to fibrous dysplasia makes LGCO an insidious tumour, very often misdiagnosed and thus undertreated. The fibrous dysplasia-like histological pattern and the mixed lytic and sclerotic radiological pattern of LGCO are more likely to resemble fibrous dysplasia leading to misdiagnosis. An in-depth understanding of the histological features and its correlation to radiological and also clinical findings is instrumental in correct diagnosis.

Despite the extremely high incidence of misdiagnosis of a LGCO, very few specific diagnostic features have been described. However, lasting recent years there has been significant progress in identifying tools that will help the attending physician to correctly diagnose the type of lesion raising suspicion of its potential malignancy. Heat shock proteins (HSPs) for instance are known to overexpress in several tumours, and the HSP27 and HSP70 subtypes seem to allow discrimination between conventional and low-grade central osteosarcoma[28]. More interestingly, advances in immunohistochemistry and the understanding of chromosomal expression in sarcomas through the CDK4 and MDM2 proteins can facilitate safe differential diagnosis of a benign fibrous or fibro-osseous lesion rather than a low-grade osteosarcoma with its attendant requirement for appropriate surgical treatment[29,30]. Yoshida *et al*[29] report a very high percentage of sensitivity and specificity for the determination of low-grade osteosarcoma.

Nevertheless, detailed knowledge of the behaviour of this tumour remains the cornerstone of early diagnosis and appropriate treatment. A high level of suspicion should be held for any lesion in the metaepiphyseal region of a long bone with radiological findings suggesting malignancy, even in the presence of a benign histological diagnosis. In this instance LGCO should still be definitively excluded[3].

Additionally, the incidence of late recurrence or metastases, even up to 20 years after the excision of the tumour, makes long-term follow up important in order to

ensure a long-term survival.

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