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DIAGNOSTIC ADVANCES

Nuclear medicine imaging in osteonecrosis of hip: Old and current concepts

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Abstract

Osteonecrosis (ON) is caused by inadequate blood supply leading to bone death, which results in the collapse of the architectural bony structure. Femoral head is the most common site involved in ON. Magnetic resonance imaging (MRI) is a commonly used imaging modality to detect early ON. When MRI is inconclusive, bone scan is helpful in detecting ON during early phase of the disease. As newer nuclear medicine equipment, like single photon emission computed tomography/computed tomography (CT) and positron emission tomography/CT, are emerging in medical science, we review the role of these imaging modalities in ON of femoral head.

Key words: Osteonecrosis; Avascular necrosis; Bone scan; Magnetic resonance imaging; Photon emission computed tomography scan; Single photon emission computed tomography/computed tomography

Core tip: Early diagnosis and treatment remains the key to hip preservation in osteonecrosis (ON). Till date magnetic resonance imaging (MRI) is considered as the gold standard diagnostic modality for ON. However with the improvement in nuclear imaging technique, the disease can be diagnosed even at a very early stage. Available literature suggests that single photon emission computed tomography/computed tomography (CT) bone scan and

^{18}F-fluoride photon emission computed tomography/CT have similar or better results in comparison to MRI in ON of the femoral head. They also provide both morphological and metabolic information in the disease part and hence can indicate whether the disease is active or healed.

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INTRODUCTION

Osteonecrosis (ON) is caused by inadequate blood supply leading to bone death, which results in the collapse of the architectural bony structure. ON can be due to interruption of the vascular supply as a result of local trauma or non-traumatic systemic conditions[1]. In general, symptomatic patients present with pain and reduced range of motion. Initially, pain is due to increase in intramedullary pressure resulting from medullary bone marrow edema. However, clinical diagnosis is often difficult due to lack of specific symptoms during the initial period. Common sites for ON include the femoral head, humeral head, knee, femoral and tibial metadiaphysis, scaphoid, lunate and talus[2]. Femoral head is the most common site involved in ON[1]. In the femoral head, site of necrosis is immediately below the weight bearing articular surface of the bone, *i.e*., the anterolateral aspect of the femoral head. Early recognition of the disease is essential for better patient management.

RADIOLOGICAL IMAGING IN ON

The clinical findings and imaging studies are the primary modalities used to diagnose and stage ON. In radiology, the imaging modalities to detect ON are conventional radiographs, computed tomography (CT) and magnetic resonance imaging (MRI). In nuclear medicine imaging, the imaging modalities are planar bone scintigraphy, single photon emission computed tomography (SPECT) only bone scintigraphy, SPECT/CT bone scintigraphy and ^{18}F-fluoride positron emission tomography/CT (PET/CT) bone scan. Different staging systems have been developed based on the severity of symptoms and imaging findings. Knowledge of degree of involvement in ON of femoral head helps in selecting the optimal treatment and also predicting the prognosis. In general, the most important feature of the staging system is the initial collapse of the cortex of femoral head. Before collapse, the necrotic lesion in the cortex can undergo repair and the damage may be reversible; after collapse, the damage is irreversible[1].

Conventional radiographs

Being the least expensive and most widely available method, imaging evaluation of ON usually begins with conventional radiography. Ideally, both frontal and frog-leg lateral projections should be obtained. The typical radiographic appearance shows patchy areas of lucency with surrounding sclerosis[2]. The surrounding sclerotic margin correlates with the host bone response to wall off the areas of necrosis. X-rays may also show early articular collapse (Figure 1). However, radiography has low sensitivity during early stages.

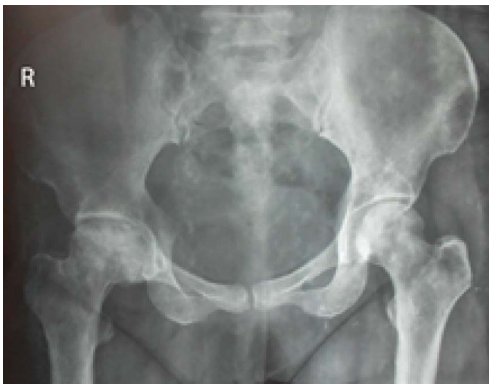

Figure 1 X-ray pelvis anteroposterior view shows collapsed right femoral head with sclerosis and subchondral lucencies, suggestive of osteonecrosis of right femoral head.

CT

In early femoral head ON, a CT scan may shows alteration of the normal "asterisk" that is formed due to condensation of the compressive and tensile trabeculae. Although, CT has lower sensitivity in detection of early changes than scintigraphy or MR imaging, it is helpful for detecting articular collapse location and extent in epiphyseal ON[3-5].

MRI

MRI is considered the most sensitive and specific imaging modality in detection of ON[6,7]. Generally, early fatty marrow necrosis is not associated with changes in signal intensity on MR studies. Death of cellular marrow components initiates tissue reaction, which results in appearance of a reactive interface between live and necrotic marrow areas. The hallmark of early avascular necrosis lesions is clear delineation of normal-appearing epiphyseal area with either a low-signal-intensity band on T1-weighted images or a rim of sclerosis on radiographs[2]. The rim of sclerosis is often crescentic or wedge shaped. The interface appears as a low-signal-intensity band with a sharp inner face and a blurred outer face on MRI[8]. A "double-line" sign on T2 weighted MRI has been demonstrated in 65%-85% of cases of early ON[8]. This double-line sign consists of an outer low signal intensity rim of sclerosis and a second inner high signal intensity representing the reparative granulation tissue of the reactive interface. However, some authors have attributed the outer low signal intensity rim to a potential chemical-shift artifact[9].

In a minority of patients, the area of ON may also show intrinsic characteristics such as hemorrhage

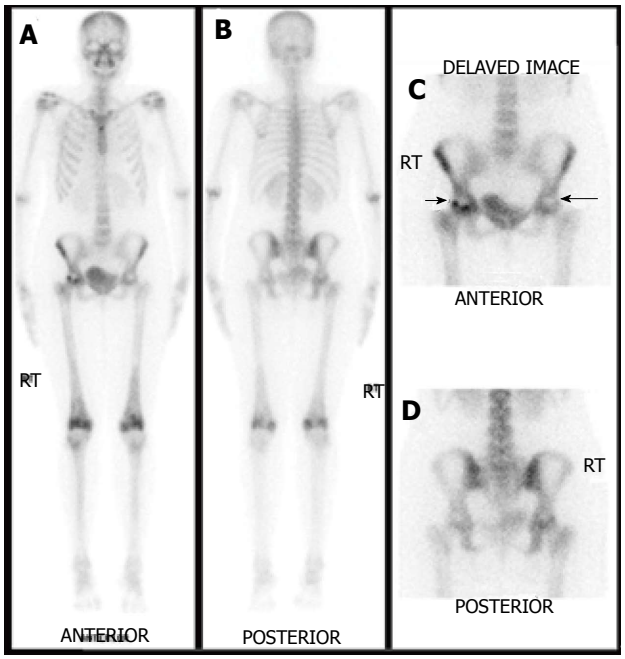

Figure 2 A 30-year-old female treated with chemotherapy for breast cancer was referred for ^{99m}Tc-MDP bone scan to evaluate cause of disabling hip pain. Whole body (A and B) and delayed images (C and D) demonstrate photopenic areas in bilateral femoral heads (arrows) with increased osteoblastic activity surrounding the photopenic region in the right femoral head, suggestive of bilateral avascular necrosis. Increased osteoblastic activity in bilateral distal femora is likely due to biomechanical stress reaction due to altered gait.

(high signal intensity on T1- and T2-weighted), cystic changes (low signal intensity on T1-weighted and high signal intensity on T2-weighted images), and fibrous tissue (low signal intensity with all pulse sequences). Non-specific diffuse marrow signal abnormality may be seen in patients with sickle cell anemia and Gaucher's disease. On a contrast enhanced MR study, typically, there is lack of enhancement of the necrosed area. A peripheral rim of enhancement corresponding to the zone of creeping substitution granulation tissue is generally seen[2]. In advanced disease, lesions show low signal intensity on T1 weighted and variable signal intensity on T2 weighted images. However, previous studies have demonstrated that signal changes on MR imaging may not be evident despite histologic evidence of ON[10-12]. It has been shown that signal changes caused by the death of marrow cells from ischemia on T1- and T2-weighted images may not occur until 5 d after interruption in the blood supply[10]. Hence, MRI may be false negative in the early phase of ON.

NUCLEAR MEDICINE IMAGING IN ON

Planar technetium-99m methylene diphosphonate bone scintigraphy

Technetium-99m methylene diphosphonate (^{99m}Tc-MDP) bone scintigraphy is one of the most commonly performed nuclear medicine studies. It is highly sensitive in detection of different benign and malignant bone pathologies[13]. The skeleton is made up of inorganic calcium hydroxyapatite crystals. The tracer uptake in a bone scan primarily identifies areas of osteoblastic activity. ^{99m}Tc-MDP binding occurs by chemisorption in the hydroxyapatite component of the osseous matrix. However, blood flow is the other most important factor influencing uptake of the radiotracer. As low as 5% change in bone turnover can be detected on bone imaging, whereas 40%-50% of mineral must be lost to detect lucency within the bone on radiographs and CT[14].

Three phase bone scan is usually performed in patients with suspected ON. In the three phase study, a bolus of ^{99m}Tc-MDP is injected intravenously with the concerned body parts under the gamma camera. The first phase of the study includes immediate dynamic images after radiotracer injection acquired for 60 s. The second phase or blood pool or soft tissue phase is acquired after approximately 5-10 min of radiotracer administration and delayed phase after 2-3 h.

As ON is an evolving process, the appearance on bone scan depends on the stage of the disease. In the acute phase of ON, no radiotracer is delivered to the bone tissue. Therefore, initially for 7-10 d after the event, ON generally appears on bone imaging as a photopenic area (Figures 2 and 3). After 1-3 wk, increased radiotracer uptake is seen in a subchondral distribution due to osteoblastic activity at the reactive interface around the necrotic segment[15]. Imaging with pinhole collimator is useful as it increases the resolution. Overall sensitivity of bone scintigraphy for diagnosis of ON of femoral head is from 78% to 91%[16-18]. This variation in sensitivity is probably due to different etiology of ON of femoral head. For example, sensitivity is high in ON following femoral neck fracture due to sudden and nearly complete cut off of blood supply resulting in large, well defined cold lesion on bone scintigraphy. However, in chronic processes like steroid induced ON, typical cold lesion may not be identified and scintigraphy usually demonstrates increased tracer localization due to microcollapse and repair. Some studies have shown that bone scan is superior to conventional MRI in early detection of ON[19]. However, a planar bone scan has its own limitations of low specificity due to difficulty in distinguishing ON from fractures, transient osteoporosis or other conditions[1]. Although MRI is considered the diagnostic modality of choice in patients with femoral head ON, bone scan remains a valid alternative with fractured femoral neck with a metallic fixation device. Moreover, it is also helpful when involvement of multiple sites is suspected in patients with risk factors such as sickle cell disease.

SPECT bone scintigraphy

SPECT imaging is a nuclear medicine modality which produces cross-sectional images similar in presentation to CT and MRI in radiology. On planar bone scintigraphy, earliest and most evident finding of ON, *i.e.*, photopenic region in the femoral head may be obscured by the superimposed acetabular and other surrounding bone activity[20]. This overlying increased activity could be

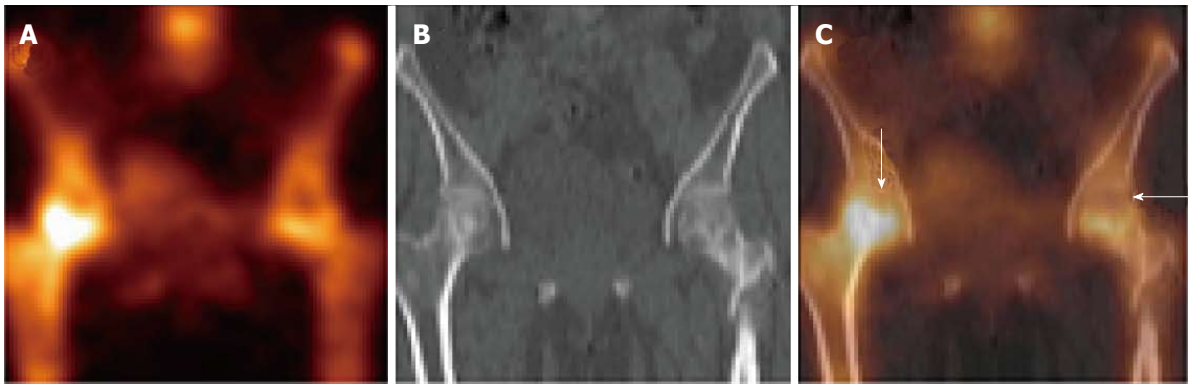

Figure 3 Coronal single photon emission computed tomography (A), coronal computed tomography (B) and coronal fused single photon emission computed tomography/computed tomography images (C) of the patient mentioned in Figure 2 localizes the photopenic defects to head of bilateral femora. The lucent areas with surrounding sclerosis in both femoral heads on low dose computed tomography (CT) component of single photon emission computed tomography/CT (B) increase the diagnostic confidence and specificity.

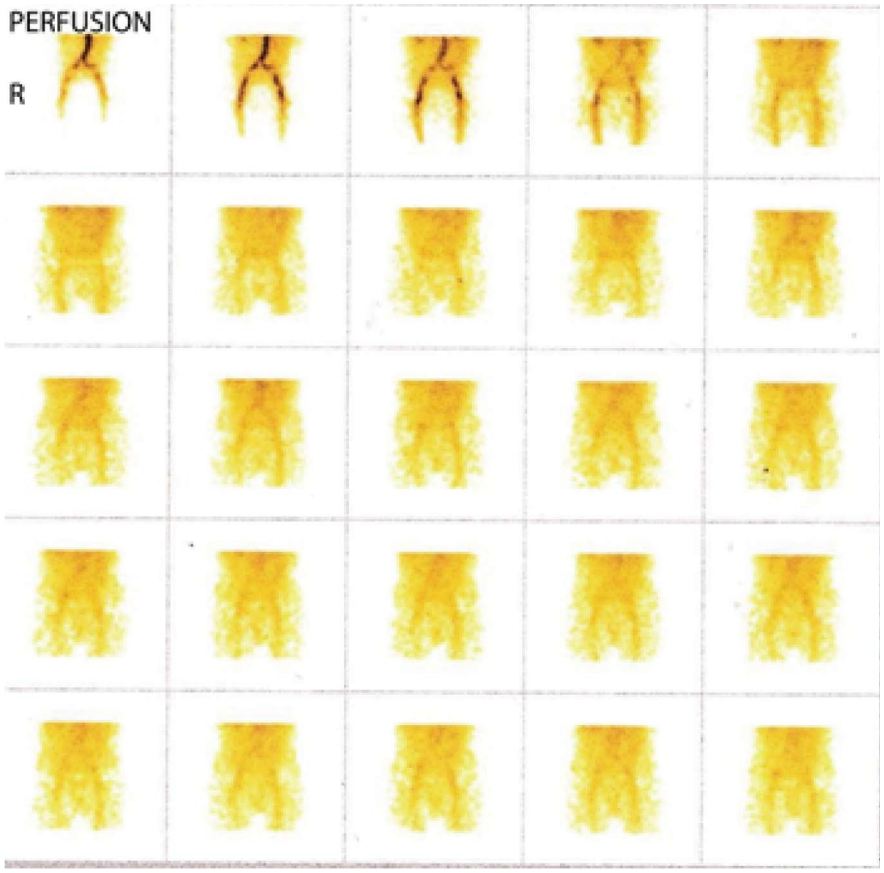

Figure 4 Perfusion phase of three-phase ^{99m}Tc-MDP bone scan of a patient with right side hip pain shows symmetrical flow of tracer in bilateral hips.

due to osteoarthritis, fracture, inflammatory arthritis, *etc*., and results in false negative test results. As SPECT provides three-dimensional images, it is possible to separate the femoral head from other overlying bony structures (Figures 4-6). Siddiqui *et al*[21] demonstrated that both MRI and bone SPECT are complementary to each other in detecting subclinical avascular necrosis in asymptomatic renal allograft recipients. Ryu *et al*[20] showed that bone SPECT imaging is more sensitive than MRI in early detection of femoral head ON in renal transplant recipients. Their study revealed 100% sensitivity of SPECT in detection of ON of the femoral head, compared to 66% for MRI. Several other studies have shown that in ON of the femoral head, the sensitivity of MRI ranges from 85% to 100% and that of SPECT bone imaging ranges from 85% to 97%[22-24]. Hence, SPECT bone scan could be equally informative in patients with suspicion of ON of the femoral head.

SPECT/CT bone scintigraphy

Hybrid SPECT/CT provides both anatomical and metabolic information (Figures 2 and 3)[13]. CT component is helpful

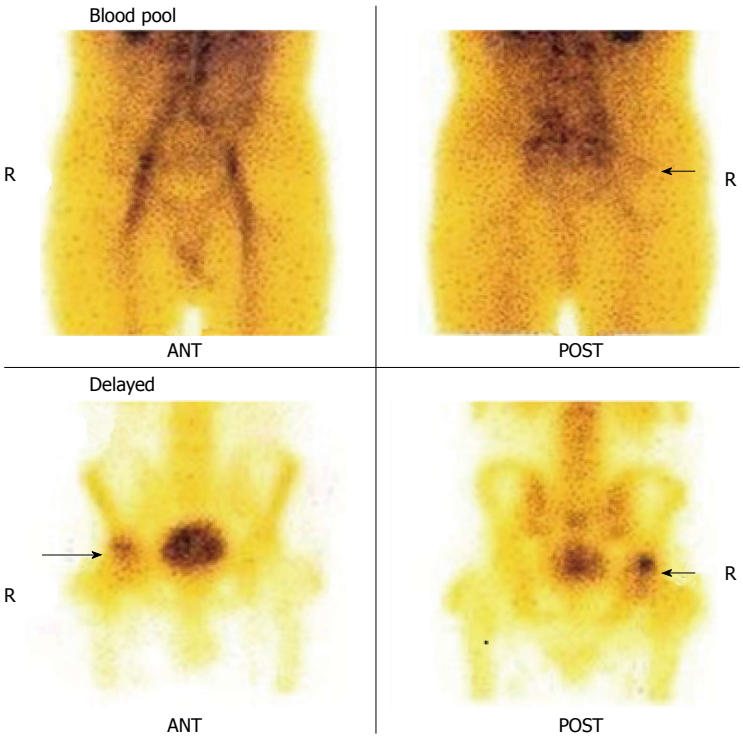

Figure 5 Blood pool images of the patient (as mentioned Figure 4) show minimally increased tracer uptake in the region of right hip. The delayed images show increased tracer uptake in the right hip region with no definite photopenic area.

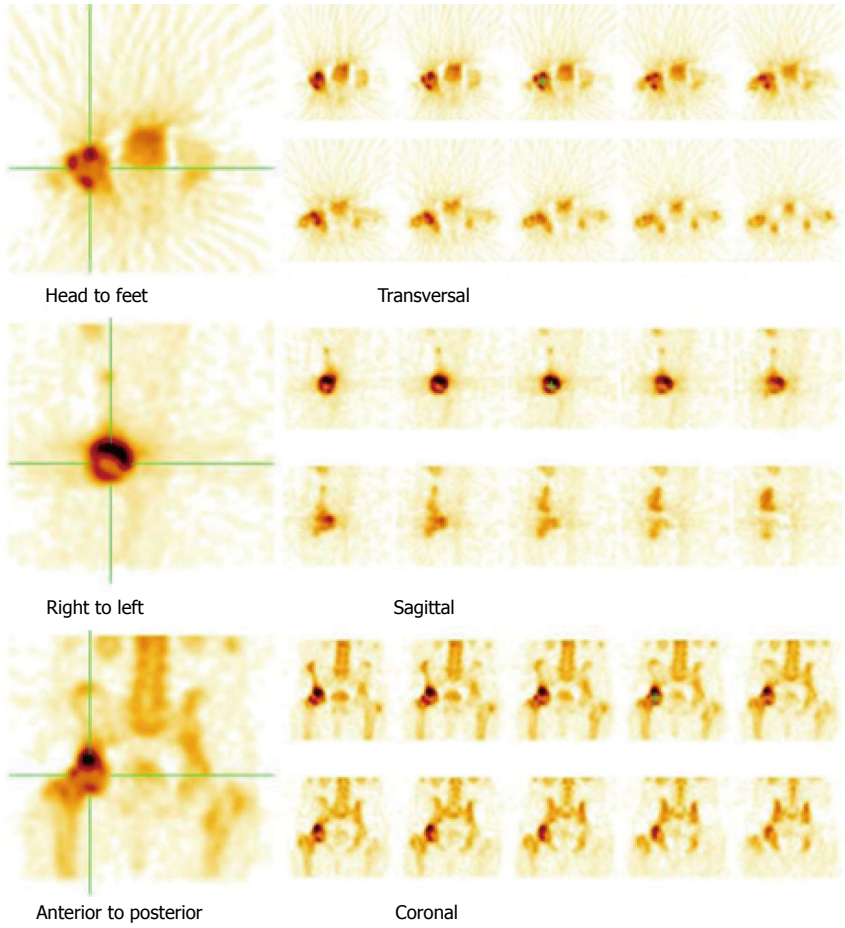

Figure 6 The single photon emission computed tomography images of the patient (as mentioned in Figure 4) show definite central photopenia with surrounding increased tracer uptake in the right femoral head (not evident on planar delayed images), suggestive of osteonecrosis of the right femoral head.

in localization and characterization of increased osteoblastic activity seen on planar or SPECT only images. CT scan added to SPECT can detect subtle collapse of the femoral head, which may not be easily visible on plain radiographs. In addition, morphological imaging may detect other underlying pain generators, which may explain the symptoms. Although SPECT-only bone scintigraphy has high sensitivity, its specificity is low. Luk *et al*[25] showed that SPECT/CT has similar sensitivity (100%) as SPECT bone scintigraphy, but better specificity compared to SPECT imaging alone (88% *vs* 82%) for the diagnosis of ON of the femoral head. In another study, SPECT/CT was found superior to planar and SPECT only bone scan for the diagnosis of ON. SPECT/CT demonstrated diagnostic accuracy of 95%, sensitivity of 98% and specificity of 87% compared to diagnostic accuracy of 67%, sensitivity of 75% and specificity of 40% for planar bone scan[26].

^{18}F-fluoride PET bone scan

With wider use of PET/CT and reintroduction of the ^{18}F-fluoride bone scan, its role in ON has been evaluated by researchers. ^{18}F-fluoride is a positron-emitting radiotracer[13]. After diffusion through capillaries into bone extracellular fluid, ^{18}F-ions exchange with hydroxyl groups in hydroxyapatite crystals to form fluorapatite[13]. ^{18}F-fluoride PET has several advantages over ^{99m}Tc-MDP bone scan. ^{18}F-fluoride has approximately 100% first-pass extraction in bone, allowing the estimation of bone blood flow. Further, its uptake in bone is two-fold higher than that of ^{99m}Tc-MDP. Moreover, it is not protein bound, which leads to faster blood clearance and better target-to-background ratio. In addition, PET/CT imaging has higher resolution compared to SPECT/CT leading to better appreciation of the characteristic photopenic region on PET/CT. Hence, ^{18}F-fluoride bone scan has high sensitivity compared to ^{99m}Tc-MDP bone scan[13]. Quantification is another technical advantage of PET/CT imaging. Additional CT features theoretically results in high specificity of ^{18}F-fluoride PET/CT in ON of femoral head.

Typically, a ring sign, *i.e.*, circular pattern uptake surrounding a photopenic region is noted on ^{18}F-fluoride PET/CT studies[27]. The central photopenia represents the necrotic area, whereas the surrounding uptake area probably reflects reactive bone formation around the necrotic area or microcollapse. A study by Gayana *et al*[28] revealed higher sensitivity and accuracy of ^{18}F-fluoride PET/CT compared to MRI in ON of the femoral head. Recently, one group showed that metabolic information obtained from ^{18}F-fluoride PET/CT is useful to predict femoral head collapse in ON[27]. A semi-quantitative parameter like SUVmax is used for quantifying bone metabolism. They concluded that SUVmax increases with stage progression and collapse of femoral head was observed within 12 mo after ^{18}F-fluoride PET in patients with SUVmax more than 6.45. This finding could be very useful in predicting femoral head collapse in ON and may lead to early management change.

CONCLUSION

Imaging plays a crucial role in early diagnosis of ON of the femoral head. Although MRI is a commonly used modality in detecting ON, nuclear medicine imaging technology has improved tremendously in recent years. Although there is scarcity of literature, new imaging modalities like SPECT/CT bone scan and ^{18}F-fluoride PET/CT have similar or better results in comparison to MRI in ON of the femoral head. In addition, they provide both morphological and metabolic information.

REFERENCES

1 **Assouline-Dayan Y**, Chang C, Greenspan A, Shoenfeld Y, Gershwin ME. Pathogenesis and natural history of osteonecrosis. *Semin Arthritis Rheum* 2002; **32**: 94-124 [PMID: 12430099]

2 **Murphey MD**, Foreman KL, Klassen-Fischer MK, Fox MG, Chung EM, Kransdorf MJ. From the radiologic pathology archives imaging of osteonecrosis: radiologic-pathologic correlation. *Radiographics* 2014; **34**: 1003-1028 [PMID: 25019438 DOI: 10.1148/rg.344140019]

3 **Hauzeur JP**, Pasteels JL, Orloff S. Bilateral non-traumatic aseptic osteonecrosis in the femoral head. An experimental study of incidence. *J Bone Joint Surg Am* 1987; **69**: 1221-1225 [PMID: 2822722]

4 **Stevens K**, Tao C, Lee SU, Salem N, Vandevenne J, Cheng C, Neumann G, Valentin-Opran A, Lang P. Subchondral fractures in osteonecrosis of the femoral head: comparison of radiography, CT, and MR imaging. *AJR Am J Roentgenol* 2003; **180**: 363-368 [PMID: 12540435 DOI: 10.2214/ajr.180.2.1800363]

5 **Yeh LR**, Chen CK, Huang YL, Pan HB, Yang CF. Diagnostic performance of MR imaging in the assessment of subchondral fractures in avascular necrosis of the femoral head. *Skeletal Radiol* 2009; **38**: 559-564 [PMID: 19234700 DOI: 10.1007/s00256-009-0659-0]

6 **Glickstein MF**, Burk DL Jr, Schiebler ML, Cohen EK, Dalinka MK, Steinberg ME, Kressel HY. Avascular necrosis versus other diseases of the hip: sensitivity of MR imaging. *Radiology* 1988; **169**: 213-215 [PMID: 3420260 DOI: 10.1148/radiology.169.1.3420260]

7 **Kamata N**, Oshitani N, Sogawa M, Yamagami H, Watanabe K, Fujiwara Y, Arakawa T. Usefulness of magnetic resonance imaging for detection of asymptomatic osteonecrosis of the femoral head in patients with inflammatory bowel disease on long-term corticosteroid treatment. *Scand J Gastroenterol* 2008; **43**: 308-313 [PMID: 18938768]

8 **Vande Berg BE**, Malghem JJ, Labaisse MA, Noel HM, Maldague BE. MR imaging of avascular necrosis and transient marrow edema of the femoral head. *Radiographics* 1993; **13**: 501-520 [PMID: 8316660 DOI: 10.1148/radiographics.13.3.8316660]

9 **Duda SH**, Laniado M, Schick F, Claussen CD. The double-line sign of osteonecrosis: evaluation on chemical shift MR images. *Eur J Radiol* 1993; **16**: 233-238 [PMID: 8508844]

10 **Brody AS**, Strong M, Babikian G, Sweet DE, Seidel FG, Kuhn JP. John Caffey Award paper. Avascular necrosis: early MR imaging and histologic findings in a canine model. *AJR Am J Roentgenol* 1991; **157**: 341-345 [PMID: 1853819 DOI: 10.2214/ajr.157.2.1853819]

11 **Genez BM**, Wilson MR, Houk RW, Weiland FL, Unger HR Jr, Shields NN, Rugh KS. Early osteonecrosis of the femoral head: detection in high-risk patients with MR imaging. *Radiology* 1988; **168**: 521-524 [PMID: 3393675 DOI: 10.1148/radiology.168.2.3393675]

12 **Koo KH**, Jeong ST, Jones JP Jr. Borderline necrosis of the femoral head. *Clin Orthop Relat Res* 1999; **358**: 158-165 [PMID: 9973987]

13 **Agrawal K**, Marafi F, Gnanasegaran G, Van der Wall H, Fogelman I. Pitfalls and Limitations of Radionuclide Planar and Hybrid Bone Imaging. *Semin Nucl Med* 2015; **45**: 347-372 [PMID: 26278850 DOI: 10.1053/j.semnuclmed.2015.02.002]

14 **Brenner AI**, Koshy J, Morey J, Lin C, DiPoce J. The bone scan. *Semin Nucl Med* 2012; **42**: 11-26 [PMID: 22117809 DOI: 10.1053/j.semnuclmed.2011.07.005]

15 **Fernandez-Ulloa M**, Klostermeier TT, Lancaster KT. Orthopaedic nuclear medicine: the pelvis and hip. *Semin Nucl Med* 1998; **28**: 25-40 [PMID: 9467191]

16 **Lucie RS**, Fuller S, Burdick DC, Johnston RM. Early prediction of avascular necrosis of the femoral head following femoral neck fractures. *Clin Orthop Relat Res* 1981; **161**: 207-214 [PMID: 6273037]

17 **Markisz JA**, Knowles RJ, Altchek DW, Schneider R, Whalen JP, Cahill PT. Segmental patterns of avascular necrosis of the femoral heads: early detection with MR imaging. *Radiology* 1987; **162**: 717-720 [PMID: 3809485 DOI: 10.1148/radiology.162.3.3809485]

18 **Beltran J**, Herman LJ, Burk JM, Zuelzer WA, Clark RN, Lucas JG, Weiss LD, Yang A. Femoral head avascular necrosis: MR imaging with clinical-pathologic and radionuclide correlation. *Radiology* 1988; **166**: 215-220 [PMID: 3336682 DOI: 10.1148/radiology.166.1.3336682]

19 **Koo KH**, Kim R, Cho SH, Song HR, Lee G, Ko GH. Angiography, scintigraphy, intraosseous pressure, and histologic findings in high-risk osteonecrotic femoral heads with negative magnetic resonance images. *Clin Orthop Relat Res* 1994; **308**: 127-138 [PMID: 7955674]

20 **Ryu JS**, Kim JS, Moon DH, Kim SM, Shin MJ, Chang JS, Park SK, Han DJ, Lee HK. Bone SPECT is more sensitive than MRI in the detection of early osteonecrosis of the femoral head after renal transplantation. *J Nucl Med* 2002; **43**: 1006-1011 [PMID: 12163624]

21 **Siddiqui AR**, Kopecky KK, Wellman HN, Park HM, Braunstein EM, Brandt KD, Klatte EC, Capello WN, Leapman SB, Filo RS. Prospective study of magnetic resonance imaging and SPECT bone scans in renal allograft recipients: evidence for a self-limited subclinical abnormality of the hip. *J Nucl Med* 1993; **34**: 381-386 [PMID: 8441027]

22 **Collier BD**, Carrera GF, Johnson RP, Isitman AT, Hellman RS, Knobel J, Finger WA, Gonyo JE, Malloy PJ. Detection of femoral head avascular necrosis in adults by SPECT. *J Nucl Med* 1985; **26**: 979-987 [PMID: 3875700]

23 **Kim KY**, Lee SH, Moon DH, Nah HY. The diagnostic value of triple head single photon emission computed tomography (3H-SPECT) in avascular necrosis of the femoral head. *Int Orthop* 1993; **17**: 132-138 [PMID: 8340165]

24 **Sarikaya I**, Sarikaya A, Holder LE. The role of single photon emission computed tomography in bone imaging. *Semin Nucl Med* 2001; **31**: 3-16 [PMID: 11200204]

25 **Luk WH**, Au-Yeung AW, Yang MK. Diagnostic value of SPECT versus SPECT/CT in femoral avascular necrosis: preliminary results. *Nucl Med Commun* 2010; **31**: 958-961 [PMID: 20717063 DOI: 10.1097/MNM.0b013e32833e7732]

26 **Agarwal KK**, Mukherjee A, Sharma P, Bal C, Kumar R. Incremental value of 99mTc-MDP hybrid SPECT/CT over planar scintigraphy and SPECT in avascular necrosis of the femoral head. *Nucl Med Commun* 2015; **36**: 1055-1062 [PMID: 26308940 DOI: 10.1097/MNM.0000000000000357]

27 **Kubota S**, Inaba Y, Kobayashi N, Tateishi U, Ike H, Inoue T, Saito T. Prediction of femoral head collapse in osteonecrosis using 18F-fluoride positron emission tomography. *Nucl Med Commun* 2015; **36**: 596-603 [PMID: 25714808 DOI: 10.1097/MNM.0000000000000284]

28 **Gayana S**, Bhattacharya A, Sen RK, Singh P, Prakash M, Mittal BR. F-18 fluoride positron emission tomography/computed tomography in the diagnosis of avascular necrosis of the femoral head: Comparison with magnetic resonance imaging. *Indian J Nucl Med* 2016; **31**: 3-8 [PMID: 26917886 DOI: 10.4103/0972-3919.172337]

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ORIGINAL ARTICLE

Basic Study

Bone regeneration with osteogenic matrix cell sheet and tricalcium phosphate: An experimental study in sheep

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Author contributions: Kira T designed the study and conducted the animal experiments; Akahane M and Shimizu T conducted biological analysis; Omokawa S designed the study and interpreted the results; Kawate K and Onishi T conducted the data analysis; Tanaka Y interpreted the results.

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Abstract

AIM

To determine the effects of a cell sheet created from sheep bone marrow and tricalcium phosphate (TCP) on osteogenesis.

METHODS

Bone marrow cells were harvested from a sheep and cultured in a minimal essential medium (MEM) containing ascorbic acid phosphate (AscP) and dexamethasone (Dex). After 2 wk, the formed osteogenic matrix cell sheet was lifted from the culture dish using a scraper. Additionally, harvested bone marrow cells were cultured in MEM only as a negative control group, and in MEM with AscP, Dex, and β-glycerophosphate as a positive control group. For *in vitro* evaluation, we measured the alkaline phosphatase (ALP) activity and osteocalcin (OC) content in the media of the cultured cells from each group. For *in vivo* analysis, a porous TCP ceramic was used as a scaffold. We prepared an experimental group comprising TCP scaffolds wrapped with the osteogenic matrix cell sheets and a control group consisting of the TCP scaffold only. The constructs were

implanted subcutaneously into athymic rats and the cell donor sheep, and bone formation was confirmed by histology after 4 wk.

RESULTS

In the *in vitro* part, the mean ALP activity was 0.39 ± 0.03 mg/well in the negative control group, 0.67 ± 0.04 mg/well in the sheet group, and 0.65 ± 0.07 mg/well in the positive control group. The mean OC levels were 1.46 ± 0.33 ng/well in the negative control group, 3.92 ± 0.16 ng/well in the sheet group, and 4.4 ± 0.47 ng/well in the positive control group, respectively. The ALP activity and OC levels were significantly higher in the cell sheet and positive control groups than in the negative control group ($P < 0.05$). There was no significant difference in ALP activity or OC levels between the cell sheet group and the positive control group ($P > 0.05$). TCP constructs wrapped with cell sheets prior to implantation showed bone formation, in contrast to TCP scaffolds alone, which exhibited poor bone formation when implanted, in the subcutaneous layer both in athymic rats and in the sheep.

CONCLUSION

This technique for preparing highly osteoinductive TCP may promote regeneration in large bone defects.

Key words: Cell sheet; Osteogenesis; Sheep; Bone marrow; Mesenchymal stromal cell

Core tip: An osteogenic matrix cell sheet derived from sheep bone marrow enhances osteogenic differentiation. We found that the osteogenic matrix cell sheets on tricalcium phosphate discs efficiently promotes bone formation.

Kira T, Akahane M, Omokawa S, Shimizu T, Kawate K, Onishi T, Tanaka Y. Bone regeneration with osteogenic matrix cell sheet and tricalcium phosphate: An experimental study in sheep. *World J Orthop* 2017; 8(10): 754-760 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i10/754.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i10.754

INTRODUCTION

Massive bone defects that result from trauma or tumor resection, osteomyelitis, or osteonecrosis require bone grafting and represent a great burden in clinical practice. Although an autologous bone graft transferred as either vascularized or non-vascularized tissue remains the gold standard to treat bone defects, the graft procedure is associated with complications at donor sites[1,2]. Allografts carry high risks of infections, immunological rejection, and poor rate of bone-healing[3]. Although artificial bone material possesses some osteoinductive and osteoconductive activities, its osteogenic potential is limited[4].

Bone marrow mesenchymal stromal/stem cells (BMSCs) are capable of differentiating into osteoblasts, chondrocytes, or adipocytes *in vitro* and are widely applied in bone tissue engineering[5]. They are preferably combined with scaffolds to prevent the BMSCs from flowing out of the target site[6].

We previously developed a new technique of BMSC transplantation using osteogenic matrix cell sheets (OMCSs) derived from rat BMSCs to induce osteogenesis[7]. Because these OMCSs do not require a scaffold and maintain intercellular networks with the extracellular matrix that they produce, these sheets can be used in various graft sites in animal models[8,9]. Furthermore, these OMCSs produce growth factors, such as bone morphogenetic protein and vascular endothelial growth factor. Therefore the OMCSs represent an ideal candidate for promoting new bone formation. However, no studies have investigated *in vivo* osteogenesis of OMCSs in a large animal model.

This study aimed to investigate whether OMCSs could promote *in vivo* osteogenesis in a sheep model. The sheep is a frequently used model for orthopedic research for several reasons: The bone size is large enough to allow complex orthopedic procedures to be performed and for medical devices and biomaterials to be tested; the lifespan of the animal is short enough for age-related studies in diseases such as osteoarthritis and osteoporosis to be performed; and bone remodeling in sheep is comparable to that in humans[10,11].

MATERIALS AND METHODS

BMSC preparation

BMSCs were obtained from the humeral head of a 2-year-old male Corriedale sheep (40.0 kg body weight; Japan Lamb, Hiroshima, Japan) by bone marrow aspiration under general anesthesia with intravenous atipamezole (20 μg/kg *IV*, ZENOAQ, Fukushima, Japan) and induction with intravenous ketamine (2 mg/kg IV, Daiichi Sankyo Propharma, Tokyo. Japan). The aspirated cells were collected in two 75-cm^2 culture flasks (Falcon; BD Biosciences, Franklin Lakes, NJ, United States) containing 15 mL of regular medium comprising minimal essential medium (Nacalai Tesque, Kyoto, Japan) supplemented with 15% fetal bovine serum (Gibco Life Technologies, Carlsbad, CA, United States) and antibiotics (100 U/mL penicillin and 100 μg/mL streptomycin; Nacalai Tesque). Cells were cultured in a humidified atmosphere of 95% air and 5% carbon dioxide at 37 ℃. After reaching confluence (at approximately day 14), the primary cultured cells were released from the culture substratum using trypsin-EDTA (Nacalai Tesque).

OMCS preparation and cell culture

To create OMCSs, the cells released from the primary culture were seeded at 2 × 10^3 cells/cm^2 in culture dishes

Figure 1 Macroscopic appearance of a sheep osteogenic matrix cell sheet (A), the cell sheet was easily detached from the culture surface using a scraper (B and C). Macroscopic appearance of β-tricalcium phosphate (TCP) wrapped with a bone marrow cell sheet.

for subculture in regular medium containing 10 nmol/L dexamethasone (Dex, Sigma, St. Louis, MO, United States) and 0.28 mmol/L l-ascorbic acid phosphate magnesium salt n-hydrate (AscP, Wako Pure Chemical Industrials, Kyoto, Japan) until they reached confluence (at approximately day 14). After two rinses with PBS (Gibco), the cell sheet was lifted using a scraper. The cell sheet was easily detached from the culture dish by gentle scraping in PBS, starting from the periphery of the sheet (Figure 1A). As positive and negative controls for osteoblastic differentiation, respectively, released cells were also seeded at the same cell density and cultured in osteoinductive medium (containing 10 nmol/L Dex, 0.28 mmol/L AscP, and 10 mmol/L β-glycerophosphate) or in regular medium (without Dex, AscP or β-glycerophosphate) until they reached confluence.

In vitro study

Alkaline phosphatase activity measurement: Alkaline phosphatase (ALP) activity was measured in cells cultured in 12-well plates (Falcon), as reported previously[12]. For each condition, six wells were evaluated. ALP activity is represented as the amount of *p*-nitrophenol released after 30 min of incubation at 37 ℃. The measurements were repeated twice.

Osteocalcin measurement: The Osteocalcin (OC) content of the culture medium was measured by an ELISA developed in a previous study[13]. Briefly, conditioned medium was collected at day 12 and an aliquot (100 μL) of 1:10 diluted medium was analyzed. The OC measurements evaluated four wells for each group, and the measurements were repeated twice.

In vivo study

Construction of tricalcium phosphate scaffold wrapped with a OMCS: Sterilized porous beta tricalcium phosphate (TCP) ceramics (Superpore; discs: 5 mm in diameter and 2 mm thick; 60% porosity) were purchased from Pentax (Tokyo, Japan). Constructs with OMCSs were prepared by wrapping the OMCS around the TCP immediately previous to transplantation (Figure 1B and C).

Construct implantation in the subcutaneous layer of athymic rats and the cell donor sheep: TCP constructs were implanted into the subcutaneous layer on the backs of athymic 7-wk-old male F344/NJcl-rnu/rnu rats (CLEA Japan Inc., Tokyo, Japan) as described previously[7,14]. Additionally, constructs were implanted subcutaneously into the abdomen of the cell donor sheep under the general anesthesia conditions described above. We also prepared control groups in which TCP discs were implanted subcutaneously into athymic rats and at a different site in the sheep. For each group, six constructs were implanted into one recipient rat to produce the subcutaneous implantation model, and all constructs were implanted into the cell donor sheep. After 4 wk, the implanted constructs were harvested and bone formation was histologically evaluated. The harvested discs were fixed in buffered formalin (Wako Pure Chemical Industries). Each disc was embedded in paraffin after decalcification, cut through the middle of the disk, and then stained with hematoxylin and eosin for histological evaluation.

Animal care and use statement

The care and handling of the rats and the sheep used in this study was approved by the animal care committee of our institute and met the standards of the National Institutes of Health.

Statistical analysis

The ALP activity values and OC levels are presented as mean and SD. One-way analysis of variance with *post-hoc* multiple comparisons using Tukey's test was conducted to determine statistical significance. Values of $P < 0.05$ were considered statistically significant.

RESULTS

In vitro study

In the *in vitro* study, the mean ALP activity was 0.39 ± 0.03 mg/well in the negative control group, 0.67 ± 0.04 mg/well in the sheet group, and 0.65 ± 0.07 mg/well in the positive control group (Figure 2). The mean OC levels were 1.46 ± 0.33 ng/well in the negative control group, 3.92 ±

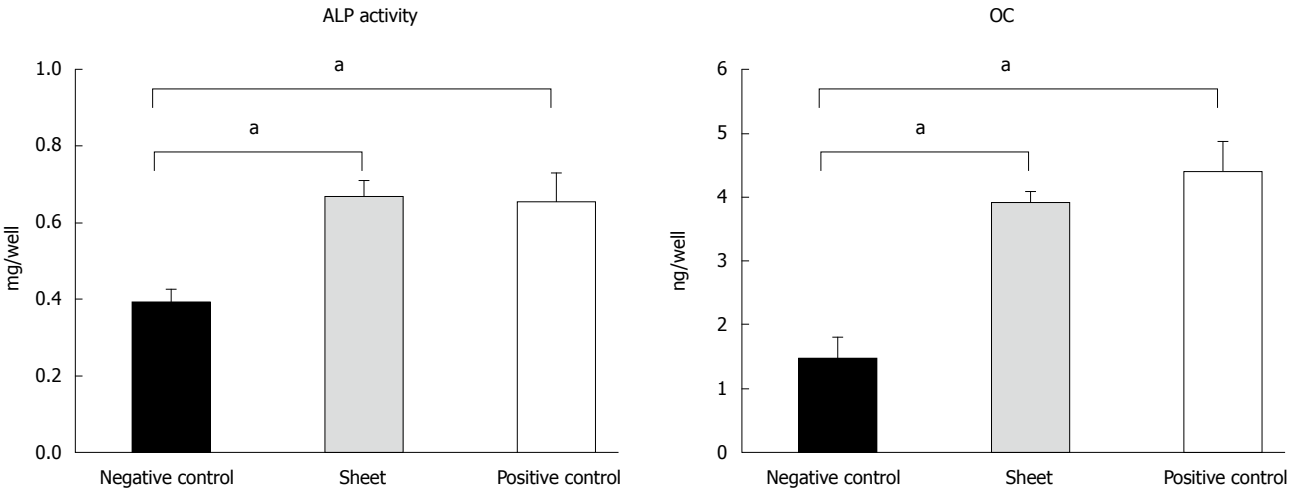

Figure 2 Alkaline phosphatase activity (A) and osteocalcin levels (B) in the culture medium of the bone marrow cell sheet, positive control and negative control groups in the *in vitro* study. [a]The alkaline phosphatase (ALP) activity and osteocalcin (OC) levels in the cell sheet and positive control groups were significantly higher than those in the negative control group.

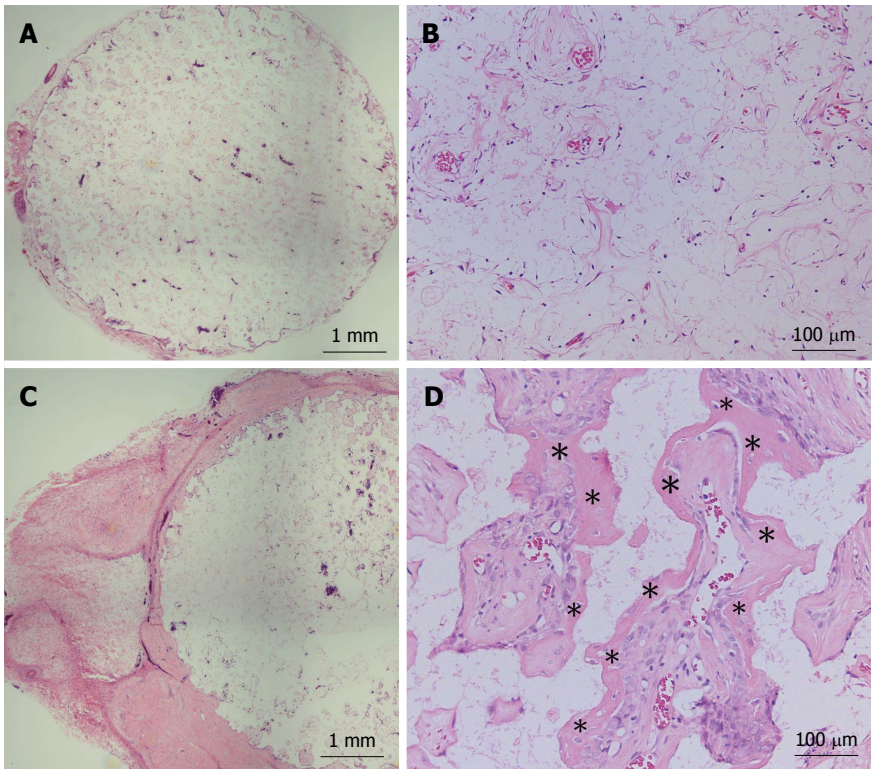

Figure 3 Hematoxylin and eosin-stained sections at 4 wk after implantation into the subcutaneous layer of athymic rats. A low-magnification image of a β-tricalcium phosphate (TCP) disc without the cell sheet shows poor bone formation (A and B). Conversely, a high level of bone formation is visible in and around TCP wrapped with an osteogenic matrix cell sheet cultured in minimum essential medium containing ascorbic acid and dexamethasone (C and D). Asterisks indicate bone tissue.

0.16 ng/well in the sheet group, and 4.4 ± 0.47 ng/well in the positive control group, respectively. The ALP activity and OC levels were significantly higher in the cell sheet and positive control groups than in the negative control group ($P < 0.05$). There was no significant difference in ALP activity or OC levels between the cell sheet group and the positive control group ($P > 0.05$).

In vivo study

Figures 3 and 4 show representative histological sections of constructs subcutaneously implanted at 4 wk into athymic rats and the cell donor sheep, respectively. The low-magnification images show higher levels of bone formation in the TCP-cell sheet construct sections than in sections of TCP discs without the cell sheet, in

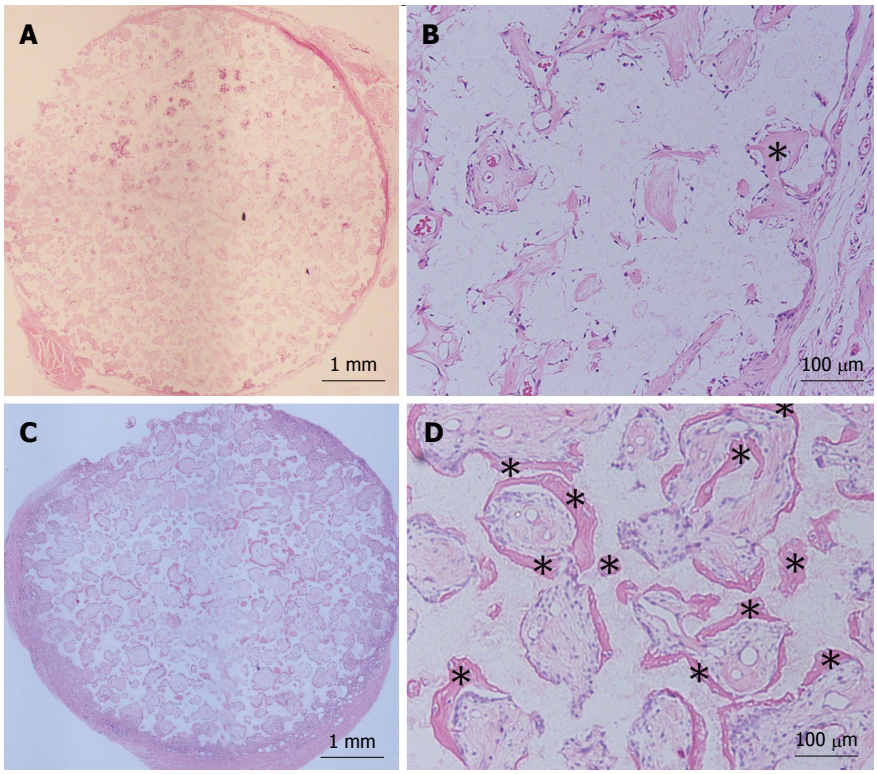

Figure 4 Hematoxylin and eosin-stained sections at 4 wk after implantation into the subcutaneous layer of the donor sheep. A low-magnification image of a β-tricalcium phosphate (TCP) disc without the cell sheet shows poor bone formation (A and B) whereas relatively high level of bone formation is visible in and around TCP wrapped with an osteogenic matrix cell sheet cultured in minimum essential medium containing ascorbic acid and dexamethasone (C and D). Asterisks indicate bone tissue.

the subcutaneous layer of both athymic rats and sheep.

DISCUSSION

Our study demonstrates that we can successfully use large animal models to derive and culture OMCS, and that TCP constructs wrapped with sheep OMCSs lead to bone formation after implantation. This is important, as sheep bone healing is more comparable to that of humans than rodents used in previous models.

Even though BMSCs alone have osteogenic potential, their implantation as a cell suspensions leads to an uneven distribution and weak adhesion of cells to the bone surface, potentially leading to cell defluvium from the target site[15]. In contrast, cell sheets bear intact cell-cell junctions and an extracellular matrix, which provide mechanical support to the cell and thereby maintain the viability of the cells at the transplanted site[16]. Furthermore, prior culture with medium that includes agents that potentiate bone formation, such as Dex and AscP, allows for already pre-determined cells to be implanted[17], which have a better chance of laying down additional matrix and integrating with the transplant site than cells that are still actively engaged in proliferation.

BMSCs including osteoblasts and osteoprogenitor cells are bone-forming cells that express various osteoblastic markers such as OC, and exhibit ALP activity[18,19]. ALP is considered a relevant biochemical marker in osteoblast differentiation. The activity and correct localization of ALP are necessary for bone development and differentiation[20,21]. OC is considered a late marker of osteogenic differentiation and its expression at high levels indicates maturation and terminal differentiation of osteoblasts[22]. Others have suggested that Dex may inhibit OC expression through direct binding of the Dex-activated glucocorticoid receptor to negative glucocorticoid response elements in the OC promoter[23]. However, we observed enhanced OC expression in OMCSs compared with the negative control group[23]. The effect of Dex is dependent on its concentration and on the stage of cellular differentiation. The Dex concentration used in this study (10 nmol/L) is considered an appropriate concentration for the differentiation of BMSCs committed to the osteogenic lineage. The ALP activity and OC levels observed in the OMCS suggest that the osteogenic differentiation ability of the BMSCs was enhanced by AscP and Dex.

OMCSs can be easily detached from the plastic dish and transplanted subcutaneously with or without a scaffold, and has osteogenic potential to form new bone tissue. The TCP scaffold also has osteoinductive properties in bone; however, minimal osteogenesis was observed inside the TCP without the cell sheet in athymic rats, presumably because of the small number of osteoprogenitor cells available for integration into the disc in the subcutaneous layer. Conversely, substantial amounts of new bone was found inside the TCP that had

been wrapped with an OMCS. We suggest that these transplanted sheep cells from the OMCSs migrated into the TCP disc, proliferated, differentiated into osteoblasts, and mineralized, and thus induced bone formation.

Results similar to those for athymic rats were obtained for implantation in the cell donor sheep. We have previously investigated cell sheets derived from rodent bone marrow and reported their efficacy for osteogenesis, angiogenesis and reconstructive surgery[8,9,24,25]. We found that severe fracture and nonunion could be united by the implantation of OMCSs[9,24] and that OMCSs can enhance early bone tunnel healing in a tendon graft model[8]. Furthermore, we show that a vascularized tissue-engineered bone scaffold composed of OMCSs wrapped around vascular bundles within a TCP mediates abundant vascularization and osteogenesis[25]. Although these studies reported that OMCS transplantation is useful for bone reconstruction, large animal studies are required to further support the potential of OMSC transplantation for clinical application. Guo *et al*[26] created cell sheets using canine cells, and showed that cell sheets exhibited normal activity and a preserved extracellular matrix and multi-layer cell structure, and displayed osteogenic induction. They used AscP (vitamin C) to create cell sheets from bone marrow mesenchymal stem cells, whereas we used a combination of AscP and Dex to create our cell sheets. Culturing cell in the medium containing AscP and Dex can stimulate osteogenic differentiation and complete cell sheet formation; therefore, using induction medium containing AscP and Dex may be more suitable for creating cell sheets for application in bone reconstruction surgery[17].

We chose a sheep model because sheep have bone properties similar to those of humans, with similar bone turnover and remodeling activities[27-29]. Furthermore, their size allows for the simultaneous implantation of many TCP constructs[30-33], and the subcutaneous implantation approach used in this study permitted the implantation of multiple TCP constructs in one sheep. Thus, the results of these *in vivo* studies suggest that human OMCSs can induce high levels of osteogenesis in TCP.

There were a few limitations in our study. First, we only used 2-mm-thick TCP. In future studies, we aim to use thicker TCP discs to assess their osteogenic ability when transplanted with OMCSs. Second, the experimental period in the present study was relatively short. Therefore, a longer follow-up study is required to investigate whether the implanted TCP remains in the sheep or is broken down and resorbed by the newly formed tissue. Third, we did not confirm whether the bone that formed in the TCP construct was derived from host cells or donor cells. Finally, we need to verify osteoinductive and osteoconductive ability of human OMCSs. Concerning these points, further study will be necessary.

COMMENTS

Background

Osteogenic matrix cell sheets (OMCSs) created from bone marrow mesenchymal stromal/stem cells (BMSCs) can be used to aid fracture nonunion, delayed bone union, or bone defects in rodent models. However, there has been no report as to whether OMCSs can also successfully induce bone formation in a large animal model. Here, the authors investigated whether OMCSs could promote *in vivo* osteogenesis in a sheep model.

Research frontiers

OMCSs are easily created from BMSCs and can be transplanted without the requirement for a scaffold. OMCSs have a high osteogenic potential, because the cells are supported by a rich extracellular matrix and various growth factors required for bone formation. As such, OMCSs are thought to be an ideal graft material for bone regenerative medicine.

Innovations and breakthroughs

Over the past decade, the utility of OMCSs for bone reconstruction has been verified in rat models of bone repair. However, rat bone does not contain Haversian canals, and thus the mode of remodeling differs to that of humans. In the current study, the authors used a sheep model to explore the osteoconductive and osteoinductive potential of sheep-drived OMCSs as sheep bone formation and repair is similar to that of human bone.

Applications

The authors suggest that OMCSs in combination with bone prostheses could be manipulated to intricately shape bony defects, and will be particularly relevant in areas where the osteogenic potential for regeneration is poor, such as in older patients or patients with bone disorders.

Terminology

TCP: Tricalcium phosphate is a calcium salt of phosphoric acid with the chemical formula $Ca_3(PO_4)_2$. TCP is grafted into the bone defect, but has lowered osteogenic potential; BMSCs: Bone marrow mesenchymal stromal/stem cells. BMSCs can be induced to differentiate into osteogenic, chondrogenic, adipogenic or other cell lineages with the appropriate media conditions. Furthermore, BMSCs secrete various growth factors, such as bone morphogenetic protein, basic fibroblast growth factor, transforming growth factor, vascular endothelial growth factor, as well as matrix proteins, including osteocalcin, and alkaline phosphatase. These cells are routinely used as a cell source for musculoskeletal tissue engineering purposes; OMCSs: Osteogenic Matrix Cell Sheets are BMSCs cultured with dexamethasone and ascorbic acid phosphate. The cells undergo differentiation and matrix production, producing a cell sheet structure that can be collected as a single cell sheet. These sheets offer *in vitro* osteogenic potential and *in vivo* bone formation with/without the aid of an additional scaffold.

Peer-review

The manuscript is an interesting biotechnological application of bone marrow-derived cell sheets to induce subcutaneous osteogenesis in a rat and a sheep model. The manuscript is of interest in its field and has novelty since it explores the use of these cell sheets in a large animal model, the sheep, which outcomes are fairly more comparable to humans than the usual rodent models.

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REFERENCES

1 **Colen SR**, Shaw WW, McCarthy JG. Review of the morbidity of 300 free-flap donor sites. *Plast Reconstr Surg* 1986; **77**: 948-953 [PMID: 2940612]

2 **Laurie SW**, Kaban LB, Mulliken JB, Murray JE. Donor-site morbidity after harvesting rib and iliac bone. *Plast Reconstr Surg* 1984; **73**: 933-938 [PMID: 6374708]

3 **Agarwal R**, García AJ. Biomaterial strategies for engineering implants for enhanced osseointegration and bone repair. *Adv Drug Deliv Rev* 2015; **94**: 53-62 [PMID: 25861724 DOI: 10.1016/j.addr.2015.03.013]

4 **Liu B**, Lun DX. Current application of β-tricalcium phosphate composites in orthopaedics. *Orthop Surg* 2012; **4**: 139-144 [PMID: 22927147 DOI: 10.1111/j.1757-7861.2012.00189.x]
5 **Jiang X**, Zou S, Ye B, Zhu S, Liu Y, Hu J. bFGF-Modified BMMSCs enhance bone regeneration following distraction osteogenesis in rabbits. *Bone* 2010; **46**: 1156-1161 [PMID: 20036345 DOI: 10.1016/j.bone.2009.12.017]
6 **Pneumaticos SG**, Triantafyllopoulos GK, Chatziioannou S, Basdra EK, Papavassiliou AG. Biomolecular strategies of bone augmentation in spinal surgery. *Trends Mol Med* 2011; **17**: 215-222 [PMID: 21195666 DOI: 10.1016/j.molmed.2010.12.002]
7 **Akahane M**, Nakamura A, Ohgushi H, Shigematsu H, Dohi Y, Takakura Y. Osteogenic matrix sheet-cell transplantation using osteoblastic cell sheet resulted in bone formation without scaffold at an ectopic site. *J Tissue Eng Regen Med* 2008; **2**: 196-201 [PMID: 18493911 DOI: 10.1002/term.81]
8 **Inagaki Y**, Uematsu K, Akahane M, Morita Y, Ogawa M, Ueha T, Shimizu T, Kura T, Kawate K, Tanaka Y. Osteogenic matrix cell sheet transplantation enhances early tendon graft to bone tunnel healing in rabbits. *Biomed Res Int* 2013; **2013**: 842192 [PMID: 24106718 DOI: 10.1155/2013/842192]
9 **Shimizu T**, Akahane M, Morita Y, Omokawa S, Nakano K, Kira T, Onishi T, Inagaki Y, Okuda A, Kawate K, Tanaka Y. The regeneration and augmentation of bone with injectable osteogenic cell sheet in a rat critical fracture healing model. *Injury* 2015; **46**: 1457-1464 [PMID: 26021664 DOI: 10.1016/j.injury.2015.04.031]
10 **Pearce AI**, Richards RG, Milz S, Schneider E, Pearce SG. Animal models for implant biomaterial research in bone: a review. *Eur Cell Mater* 2007; **13**: 1-10 [PMID: 17334975]
11 **Andreasen CM**, Ding M, Overgaard S, Bollen P, Andersen TL. A reversal phase arrest uncoupling the bone formation and resorption contributes to the bone loss in glucocorticoid treated ovariectomised aged sheep. *Bone* 2015; **75**: 32-39 [PMID: 25689083 DOI: 10.1016/j.bone.2015.02.014]
12 **Ohgushi H**, Dohi Y, Katuda T, Tamai S, Tabata S, Suwa Y. In vitro bone formation by rat marrow cell culture. *J Biomed Mater Res* 1996; **32**: 333-340 [PMID: 8897137 DOI: 10.1002/(SICI)1097-4636(199611)32: 3< 333: : AID-JBM5> 3.0.CO; 2-T]
13 **Nakamura A**, Dohi Y, Akahane M, Ohgushi H, Nakajima H, Funaoka H, Takakura Y. Osteocalcin secretion as an early marker of in vitro osteogenic differentiation of rat mesenchymal stem cells. *Tissue Eng Part C Methods* 2009; **15**: 169-180 [PMID: 19191495 DOI: 10.1089/ten.tec.2007.0334]
14 **Tohma Y**, Ohgushi H, Morishita T, Dohi Y, Tadokoro M, Tanaka Y, Takakura Y. Bone marrow-derived mesenchymal cells can rescue osteogenic capacity of devitalized autologous bone. *J Tissue Eng Regen Med* 2008; **2**: 61-68 [PMID: 18361480 DOI: 10.1002/term.67]
15 **Yamato M**, Okano T. Cell sheet engineering. *Materials Today* 2004; **7**: 42-47
16 **Xie Q**, Wang Z, Huang Y, Bi X, Zhou H, Lin M, Yu Z, Wang Y, Ni N, Sun J, Wu S, You Z, Guo C, Sun H, Wang Y, Gu P, Fan X. Characterization of human ethmoid sinus mucosa derived mesenchymal stem cells (hESMSCs) and the application of hESMSCs cell sheets in bone regeneration. *Biomaterials* 2015; **66**: 67-82 [PMID: 26196534 DOI: 10.1016/j.biomaterials.2015.07.013]
17 **Akahane M**, Shimizu T, Kira T, Onishi T, Uchihara Y, Imamura T, Tanaka Y. Culturing bone marrow cells with dexamethasone and ascorbic acid improves osteogenic cell sheet structure. *Bone Joint Res* 2016; **5**: 569-576 [PMID: 27881440 DOI: 10.1302/2046-3758.511.BJR-2016-0013.R1]
18 **Yamaguchi A**, Komori T, Suda T. Regulation of osteoblast differentiation mediated by bone morphogenetic proteins, hedgehogs, and Cbfa1. *Endocr Rev* 2000; **21**: 393-411 [PMID: 10950158 DOI: 10.1210/edrv.21.4.0403]
19 **Young MF**. Bone matrix proteins: their function, regulation, and relationship to osteoporosis. *Osteoporos Int* 2003; **14** Suppl 3: S35-S42 [PMID: 12730768 DOI: 10.1007/s00198-002-1342-7]
20 **Miao D**, Scutt A. Histochemical localization of alkaline phosphatase activity in decalcified bone and cartilage. *J Histochem Cytochem* 2002; **50**: 333-340 [PMID: 11850436 DOI: 10.1177/002215540205000305]
21 **Sabokbar A**, Millett PJ, Myer B, Rushton N. A rapid, quantitative assay for measuring alkaline phosphatase activity in osteoblastic cells in vitro. *Bone Miner* 1994; **27**: 57-67 [PMID: 7849547]
22 **Karsenty G**. Minireview: transcriptional control of osteoblast differentiation. *Endocrinology* 2001; **142**: 2731-2733 [PMID: 11415989 DOI: 10.1210/endo.142.7.8306]
23 **Choo MK**, Yeo H, Zayzafoon M. NFATc1 mediates HDAC-dependent transcriptional repression of osteocalcin expression during osteoblast differentiation. *Bone* 2009; **45**: 579-589 [PMID: 19463978 DOI: 10.1016/j.bone.2009.05.009]
24 **Nakamura A**, Akahane M, Shigematsu H, Tadokoro M, Morita Y, Ohgushi H, Dohi Y, Imamura T, Tanaka Y. Cell sheet transplantation of cultured mesenchymal stem cells enhances bone formation in a rat nonunion model. *Bone* 2010; **46**: 418-424 [PMID: 19716454 DOI: 10.1016/j.bone.2009.08.048]
25 **Nakano K**, Murata K, Omokawa S, Akahane M, Shimizu T, Kawamura K, Kawate K, Tanaka Y. Promotion of Osteogenesis and Angiogenesis in Vascularized Tissue-Engineered Bone Using Osteogenic Matrix Cell Sheets. *Plast Reconstr Surg* 2016; **137**: 1476-1484 [PMID: 27119922 DOI: 10.1097/PRS.0000000000002079]
26 **Guo P**, Zeng JJ, Zhou N. A novel experimental study on the fabrication and biological characteristics of canine bone marrow mesenchymal stem cells sheet using vitamin C. *Scanning* 2015; **37**: 42-48 [PMID: 25588682 DOI: 10.1002/sca.21177]
27 **Martini L**, Fini M, Giavaresi G, Giardino R. Sheep model in orthopedic research: a literature review. *Comp Med* 2001; **51**: 292-299 [PMID: 11924786]
28 **Gardel LS**, Serra LA, Reis RL, Gomes ME. Use of perfusion bioreactors and large animal models for long bone tissue engineering. *Tissue Eng Part B Rev* 2014; **20**: 126-146 [PMID: 23924374 DOI: 10.1089/ten.TEB.2013.0010]
29 **Timmins NE**, Scherberich A, Früh JA, Heberer M, Martin I, Jakob M. Three-dimensional cell culture and tissue engineering in a T-CUP (tissue culture under perfusion). *Tissue Eng* 2007; **13**: 2021-2028 [PMID: 17590148 DOI: 10.1089/ten.2006.0158]
30 **Reichert JC**, Woodruff MA, Friis T, Quent VM, Gronthos S, Duda GN, Schütz MA, Hutmacher DW. Ovine bone- and marrow-derived progenitor cells and their potential for scaffold-based bone tissue engineering applications in vitro and in vivo. *J Tissue Eng Regen Med* 2010; **4**: 565-576 [PMID: 20568083 DOI: 10.1002/term.276]
31 **Braccini A**, Wendt D, Jaquiery C, Jakob M, Heberer M, Kenins L, Wodnar-Filipowicz A, Quarto R, Martin I. Three-dimensional perfusion culture of human bone marrow cells and generation of osteoinductive grafts. *Stem Cells* 2005; **23**: 1066-1072 [PMID: 16002780 DOI: 10.1634/stemcells.2005-0002]
32 **Cheng M**, Moretti M, Engelmayr GC, Freed LE. Insulin-like growth factor-I and slow, bi-directional perfusion enhance the formation of tissue-engineered cardiac grafts. *Tissue Eng Part A* 2009; **15**: 645-653 [PMID: 18759675 DOI: 10.1089/ten.tea.2008.0077]
33 **Valonen PK**, Moutos FT, Kusanagi A, Moretti MG, Diekman BO, Welter JF, Caplan AI, Guilak F, Freed LE. In vitro generation of mechanically functional cartilage grafts based on adult human stem cells and 3D-woven poly(epsilon-caprolactone) scaffolds. *Biomaterials* 2010; **31**: 2193-2200 [PMID: 20034665 DOI: 10.1016/j.biomaterials.2009.11.092]

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ORIGINAL ARTICLE

Case Control Study

Neuropathic pain-like symptoms and pre-surgery radiographic severity contribute to patient satisfaction 4.8 years post-total joint replacement

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Abstract

AIM

To investigate a comprehensive range of factors that contribute to long-term patient satisfaction post-total joint replacement (TJR) in people who had undergone knee or hip replacement for osteoarthritis.

METHODS

Participants (n = 1151) were recruited from Nottinghamshire post-total hip or knee replacement. Questionnaire assessment included medication use, the pain-DETECT questionnaire (PDQ) to assess neuropathic pain-like symptoms (NP) and TJR satisfaction measured on average 4.8 years post-TJR. Individual factors were tested for an association with post-TJR satisfaction, before incorporating all factors into a full model. Data reduction was carried out using LASSO and receiver

operator characteristic (ROC) curve analysis was used to quantify the contribution of variables to post-TJR satisfaction.

RESULTS

After data reduction, the best fitting model for post-TJR satisfaction included various measures of pain, history of revision surgery, smoking, pre-surgical X-ray severity, WOMAC function scores and various comorbidities. ROC analysis of this model gave AUC = 0.83 (95%CI: 0.80-0.85). PDQ scores were found to capture much of the variation in post-TJR satisfaction outcomes: AUC = 0.79 (0.75-0.82). Pre-surgical radiographic severity was associated with higher post-TJR satisfaction: $OR_{satisfied}$ = 2.06 (95%CI: 1.15-3.69), P = 0.015.

CONCLUSION

These results highlight the importance of pre-surgical radiographic severity, post-TJR function, analgesic medication use and NP in terms of post-TJR satisfaction. The PDQ appears to be a useful tool in capturing factors that contribute to post-TJR satisfaction.

Key words: Osteoarthritis; Patient satisfaction; Total joint arthroplasty; Neuropathic pain; Surgery outcomes

Core tip: The growing number of total joint replacement (TJR) surgeries performed worldwide every year means that research in this area has the potential to impact millions of people. These results highlight the importance of a number of factors with regards to post-TJR satisfaction. The painDETECT questionnaire for neuropathic pain-like symptoms (NP) appears to be a useful tool in capturing factors that contribute to post-TJR satisfaction. Individuals with NP pre- or post-TJR could be indicated using this short questionnaire and referred for further testing and treatment to improve outcomes at every stage of their osteoarthritis treatment process.

Warner SC, Richardson H, Jenkins W, Kurien T, Doherty M, Valdes AM. Neuropathic pain-like symptoms and pre-surgery radiographic severity contribute to patient satisfaction 4.8 years post-total joint replacement. *World J Orthop* 2017; 8(10): 761-769 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i10/761.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i10.761

INTRODUCTION

A total joint replacement (TJR) is the only treatment for clinically severe osteoarthritis (OA). A TJR should be considered in individuals with marked symptoms of OA which significantly limit activity and participation and reduce quality of life if conservative treatments (*e.g.*, exercise, weight loss if overweight, analgesic medication) are insufficient[1]. In the United Kingdom alone 160000 TJR are performed every year[2]. Generally very good outcomes are reported post-TJR[3] but pain can remain a concern for some individuals. According to one study, 27% of people who had undergone total hip replacement (THR) and 44% of people who had undergone a total knee replacement (TKR) had joint pain 3-4 years after surgery[4]. This pain can be inflammatory, nociceptive or neuropathic in nature[5].

Patient satisfaction post-TJR has been the subject of some studies[6-10] which have focused only on pain and function post-TJR[11]. Pre-operative radiographic severity, co-occurrence of painful conditions, a history of revision surgery, other comorbidities, and pain catastrophizing have also been linked to post-TJR outcomes in the literature but not all in the same cohort[7,12-15].

Neuropathic pain-like symptoms (NP) are caused by changes or damage to the nervous system, which can result from chronic nociceptive input (as seen in chronic pain states) and nerve damage during surgery[5,16,17]. NP has been reported in people with OA and post-TJR[4,18]. However, to our knowledge, currently no studies have investigated the role of NP on patient satisfaction post-TJR.

As TJR is currently the only long-term treatment for OA, if its effectiveness can be improved with better understanding of the individual differences in post-operative outcomes, this must be addressed. Due to the high number of TJR carried out in the United Kingdom and worldwide, research in this area has the potential to impact many individuals.

The aim of the present study was to investigate a comprehensive range of factors that contribute to long-term patient satisfaction post-TJR in people who had undergone knee or hip replacement for OA.

MATERIALS AND METHODS

Participants

The North Nottinghamshire Research Ethics Committee approved the study protocol (REC number: 07/Q2501/22). Participants who had undergone a TJR for OA were recruited from secondary care in Nottinghamshire (n = 1151) and gave written, informed consent. All participants had symptomatic and radiographic OA prior to TJR surgery. Between 2008 and 2011, nurse-administered questionnaires were completed by participants (n = 1219) on average 18 mo after surgery. These questionnaires included information on demographic variables, pain scores, TJR satisfaction and medication use. A subsequent follow-up postal questionnaire was sent to those who consented to further involvement in the study. This questionnaire was very similar in design to the baseline questionnaire. There was an average of 3.3 years between the first and second questionnaires. When the baseline and follow-up responses of participants who completed both questionnaires were compared there were no significant differences in age (P < 0.38), sex (P < 0.89), BMI (P < 0.07) or WOMAC pain scores (P < 0.51). There was not a significant difference in satisfaction levels (P =

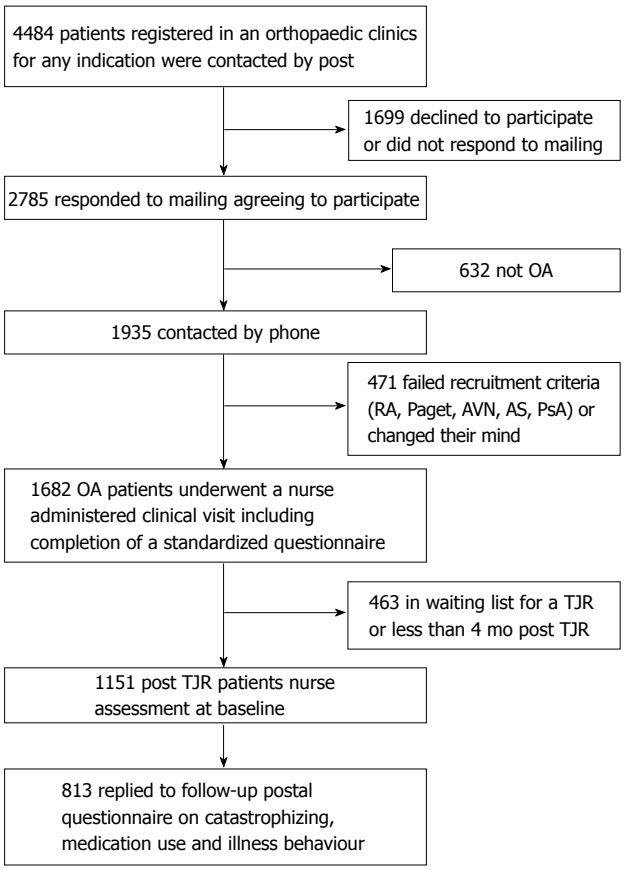

Figure 1 Flow-chart of participant recruitment for the current study.

0.22). Individuals had not been not phenotyped for pain pre-surgery but pre-operative radiographic severity grade has been linked previously to TJR outcomes[12]. The study design is presented in Figure 1.

Statistical analysis

Statistical review of this study was performed by a biomedical statistician. The statistics package R (version 3.0.2) was used to run logistic regression analyses to measure associations between TJR satisfaction and potential risk factors.

To select the risk factors contributing to post-TJR satisfaction, the least absolute shrinkage and selection operator method (LASSO) was used. LASSO is a feature selection method which, given a set of input measurements and an outcome measurement (in this case post-TJR satisfaction), fits a linear model[19]. We employed a LASSO-regularised regression model as implemented by the R package "glmnet"[20] (http://cran.r-project.org/web/packages/glmnet/index.html) using a logistic link function and the fitted LASSO coefficients derived were used.

Receiver operating characteristic (ROC) analysis was used to quantify the contribution of variables in the above models. The discrimination ability of the models was examined using the "PredictABEL" package for R (http://cran.r-project.org/web/packages/PredictABEL/index.html).

Trait definitions for statistical analysis

Neuropathic pain-like symptoms at the operated joints (knees or hips): The PDQ is a validated instrument for assessing NP. Scores range from 0-35, with > 12 indicating possible NP and ⩾ 19 indicating likely NP[21].

Pain severity: A visual analogue scale (VAS) was used to categorise individuals with high or low pain intensity at the operated joint (knee or hip). Scores range from 0-10, with ⩾ 6 used to categorise high pain intensity.

TJR satisfaction: Individuals were asked to state how satisfied they felt with their TJR using an ordinal scale of "very satisfied", "not very satisfied" and "dissatisfied". For logistic regression analysis, individuals were dichotomised between: (1) "very satisfied"; and (2) "not very satisfied" and "dissatisfied".

Radiographic severity: The extent of joint damage evident by X-rays was categorised by assessment of pre-surgery knee and hip radiographs by a single observer. For knees, the Kellgren-Lawrence (K/L) grading system was used. Scores range from 0-4, with ⩾ 3 classified as severe and 2 classified as not severe (K/L < 2 no OA)[22]. An association with minimum joint space width (JSW) pre-surgery and pain post-surgery has been reported in a separate cohort[12]. The minimum JSW was therefore used to classify hip OA, with minimum JSW ⩽ 2.5 mm (which is a standard cut-off)[23] being classified as radiographically severe. For bilateral surgery the joint with the most severe radiographic score was used.

Pain catastrophizing: The 13-item Pain Catastrophizing Scale (PCS) is a measure of the tendency to exaggerate the threat of a perceived harmful stimulus[24]. Scores range from 0-52 and the highest tertile was used as a cut-off point to classify individuals as high catastrophizers, as previously described[25].

WOMAC pain, stiffness and function: The OA-specific Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire includes questions about pain (scored from 0-20), stiffness (scored from 0-8) and function (scored from 0-76)[26]. WOMAC function scores were categorised according to an OMERACT-defined PASS score of "acceptable function" (a score of ⩽ 22) to allow a clinical guideline to be used in this study to put the importance of post-TJR satisfaction into a clinical context[27,28].

Medication use

Questionnaire responses were used to classify participants as taking over-the-counter analgesics (OTC), opioids, non-steroidal anti-inflammatory drugs (NSAIDs) or other prescription medications which can be used to treat pain, as previously described[25].

Table 1 Descriptive statistics categorised by total joint replacement satisfaction status and their contribution to the risk of dissatisfaction post-total joint replacement

	Trait	Very satisfied (n = 861)	Not very satisfied (n = 227)	Dissatisfied (n = 63)	OR not very satisfied/ dissatisfied (95%CI)[1]
Demographic and morphometric	Age ± SD (yr)	73.2 ± 8.6	73.0 ± 8.8	72.2 ± 9.1	1.00 (0.98-1.01)
	% female	57.4	56.8	47.6	0.85 (0.65-1.12)
	BMI ± SD (kg/m^2)	29 ± 5.2	29.4 ± 5.1	30.7 ± 5.9	1.03 (1.00-1.06)[a]
Type of surgery	THR (n = 494)	407 (82.4%)	74 (15.0%)	13 (2.6%)	0.58 (0.44-0.77)[e]
	TKR (n = 591)	410 (69.4%)	136 (23.0%)	45 (7.6%)	2.02 (1.50-2.71)[e]
	THR + TKR (n = 66)	44 (66.7%)	17 (25.8%)	5 (7.6%)	1.63 (0.95-2.78)
	Years since most recent surgery	4.26	3.96	4.58	0.99 (0.96-1.03)
Pre-operative X-ray	Radiographically severe OA	92.10%	93.40%	96.50%	0.49 (0.27-0.87)[a]
History of surgery	Previous arthroscopic knee surgery[3]	20.00%	26.40%	34.90%	1.65 (1.21-2.25)[c]
	Revision surgery	5.70%	9.30%	14.30%	2.36 (1.44-3.86)[e]
Psychological	% depression	15.9	22.0	28.6	1.64 (1.17-2.30)[c]
	PCS score (0-52)	8.2	12.8	19.7	1.06 (1.05-1.08)[e]
	Top tertile of PCS[2]	20.80%	37.00%	55.60%	3.40 (2.52-4.59)[e]
Use of medication	% opioid	21.7	39.5	41.3	2.37 (1.77-3.18)[e]
	% OTC	49.0	64.5	61.9	1.33 (0.84-2.12)
	% NSAIDs	7.8	12.3	3.2	1.83 (1.38-2.42)[e]
	% other prescription analgesics	12.2	20.0	23.8	1.85 (1.29-2.66)[e]
Measures of pain	PDQ score (0-35)	4.8	10.1	14.3	1.15 (1.13-1.18)[e]
	Possible Neuropathic Pain (PDQ > 12)	10.00%	33.90%	57.10%	5.91 (4.22-8.29)[e]
	Likely Neuropathic Pain (PDQ ⩾ 19)	6.50%	18.10%	34.90%	7.66 (4.80-12.22)[e]
	VAS (0-10)	3.1	5.8	7.0	1.35 (1.29-1.41)[e]
	HighVAS (> 5)	30.80%	61.20%	76.20%	6.47 (4.80-8.73)[e]
	WOMAC pain (0-20)	5.2	8.5	10.9	1.28 (1.23-1.33)[e]
	WOMAC stiffness (0-8)	2.9	4.1	4.4	1.62 (1.49-1.76)[e]
	WOMAC function (0-76)	25.7	38.0	47.8	1.07 (1.06-1.08)[e]
Comorbidities	% heart disease/angina	16.7	19.4	27.0	1.34 (0.95-1.89)
	% stroke	5.1	9.3	12.7	2.09 (1.26-3.44)[c]
	% hypertension	52.3	50.2	57.1	0.95 (0.72-1.25)
	% asthma/COPD	13.8	15.4	14.3	1.07 (0.73-1.57)
	% irritable bowel syndrome	10.2	14.5	11.1	1.44 (0.96-2.17)
	% diabetes	11.8	15.0	19.0	1.28 (0.86-1.90)
	% gout	7.5	11.9	11.1	1.50 (0.95-2.37)
	% osteoporosis	11.0	10.1	19.0	1.23 (0.80-1.88)
	% cancer	15.9	19.8	17.5	1.29 (0.91-1.83)
	% current smoker	6.5	11.0	14.3	1.93 (1.22-3.07)[c]

[1]All ORs are adjusted for age, sex and BMI; [2]Individuals in the top tertile of scores for the PCS questionnaire were classified as high catastrophizing; [3]This classification includes any previous arthroscopic knee surgery. [a]$P < 0.05$, [c]$P < 0.01$, [e]$P < 0.001$. PCS: Pain Catastrophizing Scale; BMI: Body mass index.

Comorbidities

Comorbid conditions are commonly seen in people with OA, and people with OA are more likely to develop comorbid conditions such as cardiovascular disease and diabetes[29]. A list of comorbidities was included in the questionnaire. Participants were asked to indicate which of these conditions they had been previously diagnosed with by a doctor.

RESULTS

The descriptive characteristics, stratified by TJR satisfaction status, are shown in Table 1. One fourth of study participants (290) were dissatisfied or not very satisfied with the outcome of their surgery. The study was thus powered (80%, $P < 0.05$) to detect associations with odds ratios of 1.75 or higher for binary traits with a prevalence of 10% or higher in the satisfied group, such as neuropathic pain (Table 1).

On univariate analysis, the majority of the variables tested were found to be significantly associated with satisfaction post-TJR. This includes a higher BMI, various measures of pain (such as PDQ scores, high pain intensity and WOMAC pain scores), WOMAC function scores and pain catastrophizing (Table 1). Additionally, THR participants reported higher levels of being very satisfied (82.4%) than TKR patients (69.4%) (Table 1). Some factors were highly correlated with each other, such as PDQ scores and high pain intensity, PDQ scores and WOMAC pain scores and WOMAC pain scores and high pain intensity ($P < 0.001$ for all).

Given the large number of factors associated, many of them correlated with each other, we performed data reduction, using LASSO to identify which factors remain important contributors to post-TJR, post-THR and post-TKR satisfaction. After data reduction, the factors that remained in all three groups were: BMI, WOMAC function scores, PDQ scores, high pain intensity, severe pre-surgery radiographic OA and a past stroke. The full results of these analyses are shown in Table 2. Some

Table 2 The best fitting and pain-DETECT questionnaire models showing the contribution of factors to post-total joint replacement, post-total hip replacement and post-total knee replacement satisfaction

	Full/best fitting model	pain-DETECT questionnaire scores
Total joint replacement satisfaction	2.207 + (-0.013·PCS) + (0.189·sex) + (-0.398·TKR) + (0.016·BMI) + (-0.027·WOMAC function) + (-0.042·WOMAC stiffness) + (-0.012·past knee surgery) + (-0.056·PDQ) + (-0.483·highVAS) + (-0.380·revision surgery) + (0.352·severe pre-surgical radiographic OA) + (-0.066·OTC) + (-0.113·opioid) + (-0.010·current smoker) + (-0.218·stroke) + (0.051·hypertension) + (0.062·IBS) + (-0.055·gout) + (-0.123·depression)	2.796 + (-0.142·PDQ) + (-0.015·age) + (0.382·sex) + (0.004·BMI)
Total hip replacement satisfaction	2.985 + (0.014·years since surgery) + (-0.018·age) + (0.036·BMI) + (-0.036·WOMAC function) + (0.599·past knee surgery) + (-0.018·PDQ) + (-0.725·high VAS) + (-0.723·revision surgery) + (0.779·severe pre-surgical radiographic OA) + (-0.248·OTC) + (-0.119·opioid) + (-0.429·other medications for pain relief) + (-0.442·current smoker) + (-0.014·stroke) + (-0.514·depression) + (-0.022·cancer)	4.788 + (-0.121·PDQ) + (-0.038·age) + (0.036·sex) + (0.008·BMI)
Total knee replacement satisfaction	2.425 + (-0.018·PCS) + (0.190·sex) + (0.00045·BMI) + (-0.015·WOMAC function) + (-0.130·WOMAC stiffness) + (-0.076·PDQ) + (-0.313·high VAS) + (0.009·severe pre-surgical radiographic OA) + (-0.143·stroke) + (0.072·hypertension) + (0.334·IBS) + (-0.120·gout)	1.072 + (-0.146·PDQ) + (0.003·age) + (0.467·sex) + (0.011·BMI)

differences were observed in the factors that contribute to satisfaction post-THR and post-TKR, most notably a history of a revision surgery for THR and the WOMAC stiffness score for TKR. In both cases PDQ and VAS scores contribute significantly after adjustment for all other factors.

Higher pre-operative radiographic severity was also significantly associated with increased odds of TJR satisfaction: $OR_{satisfied}$ = 2.06 (1.15-3.69), P = 0.015.

It was investigated whether patient satisfaction was related to measures of healthcare usage, specifically the use of analgesic medication. Strong associations were found between dissatisfaction and an increased likelihood of the use of some prescription analgesics (opioids and other prescription medications which can be used to treat pain) and OTC analgesics, but not prescription NSAIDs (Table 1). After adjustment for possible NP, high pain catastrophizing and high pain intensity (VAS) these associations become non-significant except in the case of opioids and OTC analgesics [$OR_{dissatisfied}$ = 1.68 (1.21-2.34), P = 0.002; $OR_{dissatisfied}$ = 1.44 (1.06-1.97), P = 0.020, respectively].

Post-TJR satisfaction is strongly associated with a measure of acceptable function post-TJR, according to OMERACT-defined PASS scores in the literature[27,28]. This definition of acceptable function, according to a clinical guideline, was a very strong contributor to post-TJR satisfaction in this study after adjusting for age, sex and BMI: $OR_{satisfied}$ = 9.88 (95%CI: 6.58-14.85), P < 0.001. This association remained significant after further adjustment for possible NP, high pain catastrophizing and high pain intensity: $OR_{satisfied}$ = 4.82 (95%CI: 3.08-7.55), P < 0.001.

With regards to comorbidities, a history of stroke was associated with an increased risk of dissatisfaction post-TJR, as was being a current smoker (*vs* ex-smokers and people who have never smoked); P < 0.01 for both, see Table 1.

It was quantified how much these models contribute to satisfaction. The results of ROC analysis of the best-fitting model for each surgery group are shown in Table 2 and Figure 2. The results show that the list of identified factors explains an AUC of 0.83 of patient satisfaction for post-TJR, 0.84 for post-THR and 0.83 for post-TKR. This, however, includes a large number of factors and it was investigated whether one of the factors may capture the effects of most of the other factors.

Possible NP, classified using PDQ scores, was seen in 17.3% of participants in this study. However, in the dissatisfied group the prevalence of possible NP was 3.8 times higher than in the very satisfied group OR_{possNP} = 5.91 (4.22-8.29), P < 0.001 and the prevalence of likely NP was 5.4 times higher: OR_{likNP} = 7.66 (4.80-12.22), P < 0.001 (see Table 1). Possible NP was less common in THR than TKR participants (11.9% and 22.3%, respectively) (Table 1). Likely NP has been reported previously to be present only in a small proportion of individuals post-TJR[4] using as a definition a PDQ > 19. However strong differences exist in satisfaction at various lower cut-offs which explains why pain-DETECT scores capture such a large proportion of patient satisfaction in these data (Figure 3).

Given this strong effect we hypothesised that PDQ scores, being strongly correlated with pre-surgery X-ray scores (Spearman's rho = -0.13, P < 0.001) and associated with post-TJR pain intensity [$OR_{highpainintensity}$ = 1.35 (1.30-1.40), P < 0.001], may capture much of the variation in post-TJR satisfaction outcomes, and indeed we find that this is the case. According to ROC analysis of PDQ scores (adjusted for age, sex and BMI), there is a significant contribution to post-TJR, post-THR and post-TKR satisfaction when this model is used (Table 2 and Figure 2). AUC values of 0.75 and over were reached in all three groups, even without the inclusion of any of the other available measures.

DISCUSSION

This study incorporated a comprehensive range of factors and shows that a number of factors including pain, comorbidities, smoking, history of revision surgery

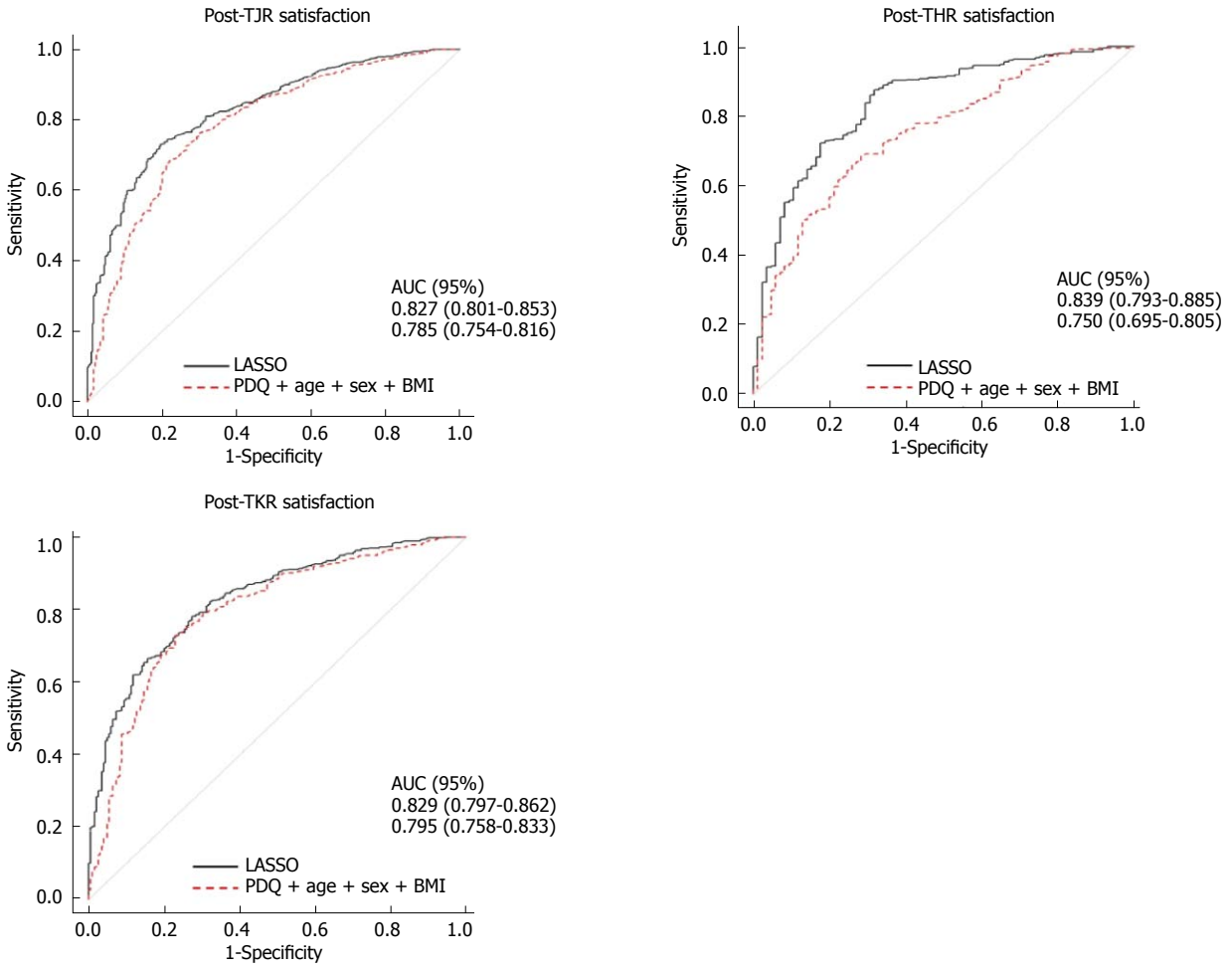

Figure 2 Receiver operator characteristic curves adjusted for age, sex and body mass index to show the amount of post-surgery satisfaction predicted by preoperative radiographic severity, pain-DETECT questionnaire scores and the best fit model. A: Post-TJR (THR and TKR combined); B: Post-TKR; C: Post-THR. TJR: Total joint replacement; THR: Total hip replacement; TKR: Total knee replacement.

and pre-surgical radiographic severity contribute to post-TJR satisfaction 4.8 years after surgery. Scores measuring the presence of NP appear to capture a large proportion of the variation seen.

Patient satisfaction is an outcome measure which is simple to use and accounts for the complex aspects of TJR[30]. It has been recommended that patient satisfaction should be incorporated into assessments of post-TJR outcomes[30]. Our results suggest that although post-TJR satisfaction is influenced by a large number of factors, it is well summarised by one single instrument, namely PDQ scores.

The proportion of possible NP identified in this study falls within the range reported by previous studies on NP post-TJR (reviewed in[31]) particularly when differences in methodology and sample composition are taken into consideration[4,15,32-37]. At first sight the importance of NP post-TJR detailed here appears to contrast with the report by Wylde *et al*[4] who suggested that NP is a minor component of post-TJR pain.

The current data indicate that people who undergo TJR with only modest radiographic structural damage are more likely to report NP post-surgery. Although this might suggest that the NP was also present pre-surgery, we lack the pre-operative pain assessments necessary to confirm if that is the case. In addition, pain may derive from other sources, such as bone marrow lesions, that are not evident on radiographs and may still be present post-surgery[38]. Central nervous system involvement in OA, such as seen in NP, seems likely when the inconsistent correlation between pain and radiographic severity and the non-linear relationship between nociception and pain experienced are considered[17] supporting the findings in this study.

In this study we fitted prediction models for patient dissatisfaction using all the contributing risk factors selected by LASSO. These models are fairly complicated in terms of the number of variables and therefore may not be applicable in clinical practice. However, we also show that PDQ scores have almost as much predictive value as the best fitting models. Therefore, in terms of clinical application our data suggest that assessing NP symptoms using the PDQ will help identify patients at highest risk of surgery dissatisfaction.

One key limitation to this study is the lack of pre-surgical pain data. However, Phillips *et al*[39] found

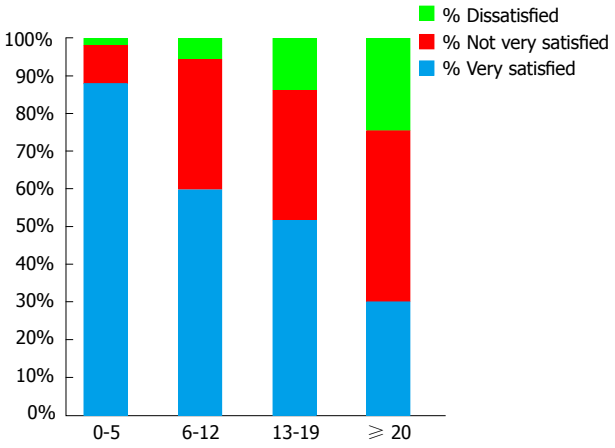

Figure 3 Proportion of post-total joint replacement patients reporting to be dissatisfied, not very satisfied or very satisfied depending on their pain-DETECT score.

that it was not possible to reliably predict post-TKR outcomes from pre-operative pain intensity and PDQ scores[39], whereas Dualé *et al*[16] have reported a higher risk of NP post-surgery if peripheral NP is present pre-surgery. Although the self-administered PDQ allows data collection from a large number of individuals it does not provide definitive evidence of NP[40]. Nonetheless, one study showed a correlation between PDQ scores and periaqueductal grey matter activation (which is involved in central sensitisation) in people with OA in areas of referred pain in response to punctate stimuli[41].

Although in this study we did not use the widely accepted National Joint Registry agreed Patient Reported Outcomes (PROMS) data[42], 92% of the questions in the Oxford hip and knee score (OXHS and OXKS, respectively) questionnaires are accounted for by the questionnaire used in this study, as was 83% of the content in the EQ-5D questionnaire. The questionnaire measured used in this study therefore reflects a large majority of the material covered in the PROMS. On the other hand we have examined other factors that are not usually included as part of post TJR PROMS, such as comorbidities, use of analgesic medication and pre-surgery X-ray severity all of which contribute to patient self-reported satisfaction in our data. To our knowledge this is one of the few studies to date which has looked at pain assessment integrated with comorbidities and use of medication.

Some of the factors identified as contributing to satisfaction could be addressed pre-surgery or considered when assessing outcomes post-surgery. The presence of comorbid conditions appears also to have a considerable effect on patient satisfaction, and this information may be use to manage patient expectations pre-surgery.

In conclusion, the PDQ appears to be particularly useful in capturing factors that contribute to post-TJR outcomes and may be considered as an important post-surgical assessment. These results also highlight the importance of understanding the mechanisms behind NP symptoms post-TJR, as it is a significant factor contributing to post-TJR satisfaction and, importantly, affects a considerable proportion of individuals post-TJR.

COMMENTS

Background

Total joint replacement is a very common type of surgery. Understanding the determinants of patient satisfaction is necessary to address the increasing need for this type of surgery with population aging.

Research frontiers

The authors investigated for the first time the relationship between pre-operative radiographic severity and neuropathic pain symptoms and satisfaction post total joint replacement.

Innovations and breakthroughs

The authors show that neuropathic pain symptoms are the most important contributor to post-total joint replacement satisfaction. Other contributors are smoking and low pre-operative radiographic severity.

Applications

The prediction models used in this work can be applied to patients undergoing total joint replacement surgery for osteoarthritis.

Terminology

Neuropathic pain symptoms, caused by changes or damage to the nervous system. Pre-operative radiographic severity, refers to the extent of large joint (hip or knee) damage detected in X-rays prior to surgery.

Peer-review

This manuscript aims to evaluate factors predict satisfaction post total joint replacement. It is a vary serious paper dealing with the results of joints replacement. A well written paper and well organized study.

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REFERENCES

1 National Institute for Health and Care Excellence. NICE Pathways: Management of osteoarthritis. [accessed 2016 May 1]. Available from: URL: http://pathways.nice.org.uk/pathways/osteoarthritis#path=view%3A/pathways/osteoarthritis/management-of-osteoarthritis.xml&content=view-index

2 National Joint Registry for England and Wales. 7th Annual Report. Hemel Hempstead: National Joint Registry for England and Wales; 2010. [accessed 2016 Jun 20]. Available from: URL: http://www.njrcentre.org.uk/njrcentre/Portals/0/NJR%207th%20Annual%20Report%202010.pdf

3 **Losina E**, Walensky RP, Kessler CL, Emrani PS, Reichmann WM, Wright EA, Holt HL, Solomon DH, Yelin E, Paltiel AD, Katz JN. Cost-effectiveness of total knee arthroplasty in the United States: patient risk and hospital volume. *Arch Intern Med* 2009; **169**: 1113-1121; discussion 1121-1122 [PMID: 19546411 DOI: 10.1001/archinternmed.2009.136]

4 **Wylde V**, Hewlett S, Learmonth ID, Dieppe P. Persistent pain after joint replacement: prevalence, sensory qualities, and postoperative determinants. *Pain* 2011; **152**: 566-572 [PMID: 21239114 DOI: 10.1016/j.pain.2010.11.023]

5 **Kehlet H**, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006; **367**: 1618-1625 [PMID: 16698416 DOI: 10.1016/S0140-6736(06)68700-X]

6 **Dunbar MJ**, Haddad FS. Patient satisfaction after total knee replacement: new inroads. *Bone Joint J* 2014; **96-B**: 1285-1286 [PMID: 25274909 DOI: 10.1302/0301-620X.96B10.34981]

7 **Dunbar MJ**, Richardson G, Robertsson O. I can't get no satisfaction after my total knee replacement: rhymes and reasons. *Bone Joint J* 2013; **95-B**: 148-152 [PMID: 24187375 DOI: 10.1302/0301-620X.95B11.32767]

8 **Robertsson O**, Dunbar M, Pehrsson T, Knutson K, Lidgren L. Patient satisfaction after knee arthroplasty: a report on 27,372 knees operated on between 1981 and 1995 in Sweden. *Acta Orthop Scand* 2000; **71**: 262-267 [PMID: 10919297 DOI: 10.1080/000164700317411852]

9 **Ross CK**, Steward CA, Sinacore JM. A comparative study of seven measures of patient satisfaction. *Med Care* 1995; **33**: 392-406 [PMID: 7731280 DOI: 10.1097/00005650-199504000-00006]

10 **Carr AJ**, Robertsson O, Graves S, Price AJ, Arden NK, Judge A, Beard DJ. Knee replacement. *Lancet* 2012; **379**: 1331-1340 [PMID: 22398175 DOI: 10.1016/S0140-6736(11)60752-6]

11 **Clement N**. Patient factors that influence the outcome of total knee replacement: a critical review of the literature. *OA Orthopaedics* 2013; **1**: 11 [DOI: 10.13172/2052-9627-1-2-697]

12 **Valdes AM**, Doherty SA, Zhang W, Muir KR, Maciewicz RA, Doherty M. Inverse relationship between preoperative radiographic severity and postoperative pain in patients with osteoarthritis who have undergone total joint arthroplasty. *Semin Arthritis Rheum* 2012; **41**: 568-575 [PMID: 21868060 DOI: 10.1016/j.semarthrit.2011.07.002]

13 **Peter WF**, Dekker J, Nelissen RG, Fiocco M, van der Linden-van der Zwaag HM, Vermeulen EM, Tilbury C, Vliet Vlieland TP. Comorbidity in osteoarthritis patients following hip and knee joint replacement surgery. *Osteoarthr Cartil* 2014; **22**: S185-S6 [DOI: 10.1016/j.joca.2014.02.351]

14 **Edwards RR**, Haythornthwaite JA, Smith MT, Klick B, Katz JN. Catastrophizing and depressive symptoms as prospective predictors of outcomes following total knee replacement. *Pain Res Manag* 2009; **14**: 307-311 [PMID: 19714271 DOI: 10.1155/2009/273783]

15 **Nikolajsen L**, Brandsborg B, Lucht U, Jensen TS, Kehlet H. Chronic pain following total hip arthroplasty: a nationwide questionnaire study. *Acta Anaesthesiol Scand* 2006; **50**: 495-500 [PMID: 16548863 DOI: 10.1111/j.1399-6576.2006.00976.x]

16 **Dualé C**, Ouchchane L, Schoeffler P; EDONIS Investigating Group, Dubray C. Neuropathic aspects of persistent postsurgical pain: a French multicenter survey with a 6-month prospective follow-up. *J Pain* 2014; **15**: 24.e1-24.e20 [PMID: 24373573 DOI: 10.1016/j.jpain.2013.08.014]

17 **Graven-Nielsen T**, Wodehouse T, Langford RM, Arendt-Nielsen L, Kidd BL. Normalization of widespread hyperesthesia and facilitated spatial summation of deep-tissue pain in knee osteoarthritis patients after knee replacement. *Arthritis Rheum* 2012; **64**: 2907-2916 [PMID: 22421811 DOI: 10.1002/art.34466]

18 **Hochman JR**, Gagliese L, Davis AM, Hawker GA. Neuropathic pain symptoms in a community knee OA cohort. *Osteoarthritis Cartilage* 2011; **19**: 647-654 [PMID: 21440077 DOI: 10.1016/j.joca.2011.03.007]

19 **Tibshirani R**. Regression shrinkage and selection via the lasso: a retrospective. *J R Stat Soc: Series B* (Stat Methodol) 2011; **73**: 273-282 [DOI: 10.1111/j.1467-9868.2011.00771.x]

20 **Friedman J**, Hastie T, Tibshirani R. Regularization Paths for Generalized Linear Models via Coordinate Descent. *J Stat Softw* 2010; **33**: 1-22 [PMID: 20808728 DOI: 10.18637/jss.v033.i01]

21 **Freynhagen R**, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin* 2006; **22**: 1911-1920 [PMID: 17022849 DOI: 10.1185/030079906X132488]

22 **Kellgren JH**, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957; **16**: 494-502 [PMID: 13498604]

23 **Croft P**, Cooper C, Wickham C, Coggon D. Defining osteoarthritis of the hip for epidemiologic studies. *Am J Epidemiol* 1990; **132**: 514-522 [PMID: 2389755 DOI: 10.1093/oxfordjournals.aje.a115687]

24 **Sullivan MJL**, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. *Physchol Assessment* 1995; **7**: 524-532 [DOI: 10.1037/1040-3590.7.4.524]

25 **Valdes AM**, Warner SC, Harvey HL, Fernandes GS, Doherty S, Jenkins W, Wheeler M, Doherty M. Use of prescription analgesic medication and pain catastrophizing after total joint replacement surgery. *Semin Arthritis Rheum* 2015; **45**: 150-155 [PMID: 26092331 DOI: 10.1016/j.semarthrit.2015.05.004]

26 **Bellamy N**, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988; **15**: 1833-1840 [PMID: 3068365]

27 **Escobar A**, Gonzalez M, Quintana JM, Vrotsou K, Bilbao A, Herrera-Espiñeira C, Garcia-Perez L, Aizpuru F, Sarasqueta C. Patient acceptable symptom state and OMERACT-OARSI set of responder criteria in joint replacement. Identification of cut-off values. *Osteoarthritis Cartilage* 2012; **20**: 87-92 [PMID: 22155074 DOI: 10.1016/j.joca.2011.11.007]

28 **Maxwell JL**, Felson DT, Niu J, Wise B, Nevitt MC, Singh JA, Frey-Law L, Neogi T. Does clinically important change in function after knee replacement guarantee good absolute function? The multicenter osteoarthritis study. *J Rheumatol* 2014; **41**: 60-64 [PMID: 24293582 DOI: 10.3899/jrheum.130313]

29 **Stang PE**, Brandenburg NA, Lane MC, Merikangas KR, Von Korff MR, Kessler RC. Mental and physical comorbid conditions and days in role among persons with arthritis. *Psychosom Med* 2006; **68**: 152-158 [PMID: 16449426 DOI: 10.1097/01.psy.0000195821.25811.b4]

30 **Halawi MJ**. Outcome Measures in Total Joint Arthroplasty: Current Status, Challenges, and Future Directions. *Orthopedics* 2015; **38**: e685-e689 [PMID: 26270754 DOI: 10.3928/01477447-20150804-55]

31 **Haroutiunian S**, Nikolajsen L, Finnerup NB, Jensen TS. The neuropathic component in persistent postsurgical pain: a systematic literature review. *Pain* 2013; **154**: 95-102 [PMID: 23273105 DOI: 10.1016/j.pain.2012.09.010]

32 **Baker PN**, van der Meulen JH, Lewsey J, Gregg PJ; National Joint Registry for England and Wales. The role of pain and function in determining patient satisfaction after total knee replacement. Data from the National Joint Registry for England and Wales. *J Bone Joint Surg Br* 2007; **89**: 893-900 [PMID: 17673581 DOI: 10.1302/0301-620X.89B7.19091]

33 **Clarke H**, Kay J, Mitsakakis N, Katz J. Acute pain after total hip arthroplasty does not predict the development of chronic postsurgical pain 6 months later. *J Anesth* 2010; **24**: 537-543 [PMID: 20490573 DOI: 10.1007/s00540-010-0960-z]

34 **Martinez V**, Fletcher D, Bouhassira D, Sessler DI, Chauvin M. The evolution of primary hyperalgesia in orthopedic surgery: quantitative sensory testing and clinical evaluation before and after total knee arthroplasty. *Anesth Analg* 2007; **105**: 815-821 [PMID: 17717244 DOI: 10.1213/01.ane.0000278091.29062.63]

35 **Remérand F**, Le Tendre C, Baud A, Couvret C, Pourrat X, Favard L, Laffon M, Fusciardi J. The early and delayed analgesic effects of ketamine after total hip arthroplasty: a prospective, randomized, controlled, double-blind study. *Anesth Analg* 2009; **109**: 1963-1971 [PMID: 19923527 DOI: 10.1213/ANE.0b013e3181bdc8a0]

36 **Sanders JC**, Gerstein N, Torgeson E, Abram S. Intrathecal baclofen for postoperative analgesia after total knee arthroplasty. *J Clin Anesth* 2009; **21**: 486-492 [PMID: 20006256 DOI: 10.1016/j.jclinane.2008.12.019]

37 **Singh JA**, Lewallen D. Predictors of pain and use of pain medications following primary Total Hip Arthroplasty (THA): 5,707 THAs at 2-years and 3,289 THAs at 5-years. *BMC Musculoskelet Disord* 2010; **11**: 90 [PMID: 20462458 DOI: 10.1186/1471-2474-11-90]

38 **Kurien T**, Kerslake R, Haywood B, Pearson RG, Scammell BE. Resection and resorption of bone marrow lesions is associated with improvement of pain after knee replacement surgery. Liverpool, UK: British Orthopaedic Research Society, 2015

39 **Phillips JR**, Hopwood B, Arthur C, Stroud R, Toms AD. The natural history of pain and neuropathic pain after knee replacement: a prospective cohort study of the point prevalence of pain and neuropathic pain to a minimum three-year follow-up. *Bone Joint J* 2014; **96-B**: 1227-1233 [PMID: 25183595 DOI: 10.1302/0301-620X.

96B9.33756]
40 **Bouhassira D**, Attal N. Diagnosis and assessment of neuropathic pain: the saga of clinical tools. *Pain* 2011; **152**: S74-S83 [PMID: 21185120 DOI: 10.1016/j.pain.2010.11.027]
41 **Gwilym SE**, Keltner JR, Warnaby CE, Carr AJ, Chizh B, Chessell I, Tracey I. Psychophysical and functional imaging evidence supporting the presence of central sensitization in a cohort of osteoarthritis patients. *Arthritis Rheum* 2009; **61**: 1226-1234 [PMID: 19714588 DOI: 10.1002/art.24837]
42 **Health and Social Care Information Centre**. Monthly Patient Reported Outcome Measures (PROMs) in England. [accessed 2016 May 1]. Available from: URL: http://www.hscic.gov.uk/proms

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ORIGINAL ARTICLE

Retrospective Cohort Study

Soft tissue swelling incidence using demineralized bone matrix in the outpatient setting

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Author contributions: All authors contributed with drafting writing and final revision of manuscript; Pencle FJR performed statistical analysis; Valdivia JM provided independent assessment of pre and post op radiographs; Chin KR performed supervision and important critical revision.

Institutional review board statement: IRB approval was granted for patients involved in study from George Washington University as part of a cohort of patients who had anterior cervical surgery.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: We did not seek or receive any funding from the National Institutes of Health (NIH), Wellcome Trust, Howard Hughes Medical Institute (HHMI), or others for this work. Chin KR is a shareholder in and receives other benefits from SpineFrontier Inc.; none of the other authors (Pencle FJR, Valdivia JM and Seale JA) have any potential conflicts of interest to declare for this work.

Data sharing statement: This dataset available from the corresponding author at Dryad repository, who will provide a permanent, citable and open-access home for the dataset.

Manuscript source: Unsolicited manuscript

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Abstract

AIM

To assess use of demineralized bone matrix (DBM) use in anterior cervical discectomy and fusion (ACDF) in outpatient setting.

METHODS

One hundred and forty-five patients with prospectively collected data undergoing single and two level ACDF with DBM packed within and anterior to polyetheretherketone (PEEK) cages. Two groups created, Group 1 (75) outpatients and control Group 2 (70) hospital patients. Prevertebral soft tissue swelling (PVSTS) was measured anterior to C2 and C6 on plain lateral cervical radiographs preoperatively and one week postoperatively and fusion assessed at two years.

RESULTS

There was no intergroup significance between preoperative and postoperative visual analogue scales (VAS)

and neck disability index (NDI) scores between Group 1 and 2. Mean preoperative PVSTS in Group 1 was 4.7 ± 0.2 mm at C2 level and 11.1 ± 0.5 at C6 level compared to Group 2 mean PVSTS of 4.5 ± 0.5 mm and 12.8 ± 0.5, P = 0.172 and 0.127 respectively. There was no radiographic or clinical evidence of adverse reaction noted. In Group 1 mean postoperative PVSTS was 5.5 ± 0.4 mm at C2 and 14.9 ± 0.6 mm at C6 compared Group 2 mean PVSTS was 4.9 ± 0.3 mm at C2 and 14.8 ± 0.5 mm at C6, P = 0.212 and 0.946 respectively. No significant increase in prevertebral soft tissue space at C2 and C6 level demonstrated.

CONCLUSION

ACDF with adjunct DBM packed PEEK cages showed a statistical significant intragroup improvement in VAS neck pain scores and NDI scores (P = 0.001). There were no reported serious patient complications; post-operative radiographs demonstrated no significant difference in prevertebral space. We conclude that ACDF with DBM-packed PEEK cages can be safely done in an ASC with satisfactory outcomes.

Key words: Ambulatory surgery center; Anterior cervical discectomy and fusion; Demineralized bone matrix; Less Exposure Surgery; Packed polyetheretherketone cages

Core tip: This manuscript scientifically assesses prevertebral swelling with the use of demineralized bone matrix (DBM) anterior to cervical cage. The use of clinical and radiographic outcomes demonstrates the safety of DBM in the outpatient setting. There are no studies showing safety or outcomes of DBM anterior to the cage and directly exposed to the pre vertebral soft tissues therefore we wanted to document this study.

Chin KR, Pencle FJR, Seale JA, Valdivia JM. Soft tissue swelling incidence using demineralized bone matrix in the outpatient setting. *World J Orthop* 2017; 8(10): 770-776 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i10/770.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i10.770

INTRODUCTION

Instrumented anterior cervical discectomy and fusion (ACDF) introduced in 1952[1] has remained the gold standard in the treatment of cervical spondylosis. Complications ranging from relatively minor and transient dysphagia, hoarseness, post-operative neck pain and wound infection to potentially catastrophic hematoma and airway compromise, vertebral artery and neurologic injury as well as esophageal perforation[2] have reduced over the years. This can be attributed to better technology and less exposure surgery techniques.

The outcome of ACDF is based on adequate decompression and osseous radiographic fusion[3,4]. Autogenous bone grafts have demonstrated high fusion rates however; the immediate and long-term morbidity associated with iliac crest harvest is well recognized[5-7]. The use of demineralized bone matrix (DBM) to aid in fusion has been demonstrated to be safe and effective[8-10]. A review conducted by Aghdashi *et al*[9], DBM has similar outcome to autogenous bone graft[11]. Studies also revealed good outcomes compared to recombinant bone morphogenic proteins (rh-BMP)[12]. Rh-BMP has been shown to cause life threatening airway edema and compromise[13-15].

Several studies over recent years have looked at the feasibility of ACDF being done on an outpatient basis with promising results and low complication rates[2,16-18]. Additionally, there are studies which have found that it is clinically safe to use DBM during ACDF within cages in a hospital setting[4,11,19]. A study by Suk *et al*[20] demonstrated peak onset of prevertebral soft tissue swelling (PVSTS) at 3 d post op. There were no studies assessing prevertebral soft tissue swelling and DBM in the outpatient setting found. The authors aim to demonstrate the safety of DBM in the outpatient setting.

MATERIALS AND METHODS

This was a non-randomized, single-center, prospective study of a total of 145 patients. We reviewed the charts retrospectively of 75 consecutive patients who single and two-level instrumented ACDF in the ASC (Outpatient ACDF), in which polyetheretherketone (PEEK) cages (Arena-C®, SpineFrontier Inc. Malden, MA, United States) with DBM (DBM pure®, SpineFrontier Inc., Malden, MA, United States) packed within and anterior to the cage and assigned them to Group 1. Fusion was reinforced with an anterior cervical plate (Inset®, SpineFrontier Inc. Malden, MA, United States). Our control group, Group 2 included 70 patients who had single and two levels ACDF in the hospital setting (Inpatient ACDF), all implants and DBM was from the same company and design. IRB approval was granted for patients involved in study as part of a cohort of patients who had anterior cervical surgery.

Operations were performed by a single surgeon, who was experienced in performing procedures in academic and private hospitals, prior to commencing in an outpatient setting. Patients were only considered for surgery after failed conservative management for at least six weeks. Indications for surgery included but not limited to patients with cervical degenerative disc degeneration (DDD) and herniated nucleus pulposus. Decision on type of surgery was based on severity of pathology. Exclusion criteria for surgery included acute severe trauma, fractures, malignancy, infection, unstable chronic medical illnesses, prior anterior cervical fusions and BMI > 42[21-23]. All patients were assessed preoperatively and narcotics were recommended to be discontinued

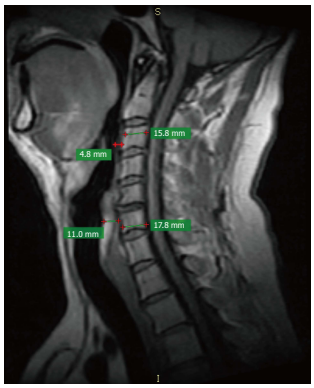

Figure 1 Preoperative radiograph showing retropharyngeal/prevertebral soft tissue at the level of C2 vertebral body and at the level of C6 vertebral body.

in patients with chronic use[24]. Patients with chronic but stable medical conditions, including hypertension, diabetes mellitus, asthma, hypercholesterolemia and heart disease were medically cleared by their family practitioner and/or cardiologist where applicable. All preoperative radiographs were reviewed by the chief surgeon, as well as two additional researchers, to rule out pre-existing abnormal widening of the prevertebral soft tissue space. This was standardized by ensuring that the prevertebral soft tissue space (PVSTS) at the level of C2 was less than 50% of the C2 vertebral body and at the level of C6 measurements were approximately less than 22 mm or the prevertebral measurement should not be greater than the width of the vertebral body of C6[25] (Figure 1). Post-operative radiographs were assessed at one week, 3 mo and at the end of follow up. Prevertebral soft tissue space (PVSTS) was compared between pre-op and 1 wk post-op films[20,26,27].

Surgical technique

Signed consent was obtained for the procedure and under general anesthesia; patients were prepped and draped under sterile conditions. Surgical exposure of the desired vertebral level was achieved through a midline anterior cervical incision. Following discectomy, the posterior longitudinal ligament was retained *in situ*[28] and the appropriately sized PEEK cage was inserted. DBM was packed within and anterior to the cage prior to an anterior cervical plate (ACP) being placed (Figure 2). The smallest sized ACP was placed, hemostasis confirmed and a Penrose drain was placed in all patients for wound drainage for 24 h to prevent postoperative hematoma development at home.

Discharge and follow up

Outpatients were discharged within hours of completing surgery after being deemed oriented and neurologically intact by the anesthesiologist and operating surgeon[22,23]. Outpatient postoperative instructions were discussed with patients and caregivers with written copies provided. An assigned member of the outpatient team was responsible for educating patients prior to consent on the risks and benefits of outpatient ACDF, as well as potential complications such as transient to persistent dysphagia, postoperative hematoma, infection and soft tissue edema with possible airway compromise. A team member called patients postoperatively on the night of surgery as well as the following morning to ensure a normal and comfortable postoperative recovery period, as well as to identify any evolving complications, which may require hospital admission. In the event of a complication, a prearranged agreement with a nearby local hospital was established before surgery. Patient reported outcomes included visual analogue scales (VAS) for neck pain, neck disability index (NDI) score and Nurick grade for those with myelopathy. Clinical outcomes were assessed based on the presence of soft tissue swelling and airway compromise. Postoperative potential DBM-related side effects were assessed clinically in all patients by palpating for soft tissue edema or swelling along the medial aspect of the sternocleidomastoid muscle. Postoperative radiological assessment was conducted with the use of anteroposterior (AP) and lateral plain radiographs looking for soft tissue emphysema, airway narrowing, tracheal deviation and PVSTS measurement in the first week postoperatively[25-27]. Evidence of interbody fusion was assessed by radiographs at the patient's final follow up. Follow up visits occurred within the first week, one month, three months, six months, twelve months and at final two year follow up. Additional postoperative complications were also recorded.

Statistical analysis

Statistical analysis was performed using SPSS v22 (IBM corporation, New York, United States). An independent sample student *T*-test was used to compare groups for continuous data and χ^2 used for categorical data. Continuous data comparisons were expressed as means with standard error. Tests were considered significant if $P < 0.05$.

RESULTS

Comparing group 1 (75 patients outpatient ACDF) to group 2 (70 patients inpatient ACDF) no statistical differences in age, BMI and gender were found between groups, $P = 0.591$, 0.484 and 0.631 respectively. Demographics and initial diagnosis are illustrated in Table 1.

There was no significance between preoperative VAS and NDI scores between Group 1 and 2, $P = 0.75$, $P = 0.289$ respectively as shown in Table 2. After two years follow up intragroup significant improvement was demonstrated in both groups for VAS and NDI scores demonstrated in Table 2. Statistical comparison of postoperative outcomes between Group 1 and 2 shows no statistical difference in VAS and NDI scores $P = 0.62$, $P = 0.34$ respectively (Table 2). The surgical operative time in Group 1 was 92 ± 15 min as compared to Group 2 which was 140 ± 3 min. This difference of 48 min did

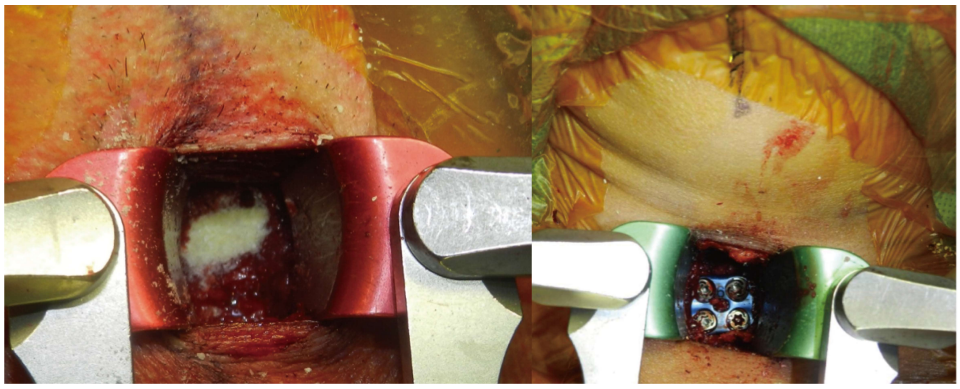

Figure 2 Photograph showing demineralized bone matrix packed within cage after insertion into disc space and anterior cervical discectomy and fusion plate.

Table 1 Cohort demographics with chief complaint

Variable	ACDF + DBM outpatient	ACDF + DBM inpatient	*P* value
Sample size (*n*)	75	70	
Age (yr)	53 ± 1.0	53.4 ± 1.6	0.591
BMI (kg/m^2)	27.9 ± 0.8	25.4 ± 1.0	0.484
Male	33	34	0.631
Female	42	36	
Diagnosis			
Herniated disc	28	23	
Degenerative disc disease	26	24	
Spondylosis (chronic pain)	7	12	
Myelopathy	3	4	
Radiculopathy	11	7	

ACDF: Anterior cervical discectomy and fusion; DBM: Demineralized bone matrix; BMI: Body mass index.

Table 2 Showing preoperative and postoperative visual analogue scales and neck disability index scores

	Preoperative VAS	Postoperative VAS	Intragroup *P* value	Preoperative NDI	Postoperative NDI	Intragroup *P* value
Group 1	7.4 ± 0.2	4.0 ± 0.2	0.001	46.9 ± 1.9	26.1 ± 1.2	0.001
Group 2	8.9 ± 1.5	5.3 ± 0.3	0.03	46.2 ± 2.6	33.4 ± 2.4	0.002
Intergroup *P* value	0.75	0.62		0.289	0.34	

VAS: Visual analogue scales; NDI: Neck disability index.

achieve statistical significance, $P = 0.001$. Estimated blood loss of 42 ± 6 mL in group 1 compared to 77 ± 9 mL in Group 2 showed no intergroup significance, $P = 0.131$.

Preoperative dimensions of airway diameter were all within normal limits[29]. No intergroup significance demonstrated (Table 3) preoperatively at C2 and C6, $P = 0.172$ and 0.127 respectively. None of our patients complained of difficulty breathing within the first 24 h postoperatively. There was no radiographic[30] or clinical evidence of adverse reaction in the patients who had ACDF to DBM (airway edema or neck swelling) within the first week postoperatively, Figure 3. Postoperative PVSTS dimension increased in both groups; however this was not a significant intragroup increase or intergroup difference as shown in Table 3. Additionally, all our patients achieved solid bony fusion[31] as evidenced by clinical and radiological (confirmed by report from independent radiologist) by the final follow up visit.

Three patients (4%) in Group 1 diagnosed with myelopathy without radiculopathy had a preoperative Nurick grade of 2, 1 and 1 respectively, which improved to 1 and 0 for the first two patients and remained unchanged for the third patient by the final follow up visit.

During the study period from 2011-2014, no major complications were reported in our series and there were no unplanned postoperative admissions for pain, nausea or any other complaints, all complaints are listed in Table 4. The main postoperative complaint of postoperative dysphagia was defined as any discomfort or difficulty with swallowing which was not historically present prior to surgery[32]. The severity was assessed using the Bazaz-Yoo dysphagia severity scale

Table 3 Showing preoperative and postoperative prevertebral soft tissue swelling at C2 and C6 vertebrae

	C2 preop PVSTS (mm)	C2 postop PVSTS (mm)	C2 intragroup *P* value	C6 preop PVSTS (mm)	C6 postop PVSTS (mm)	C6 intragroup *P* value
Group 1	4.7 ± 0.2	5.5 ± 0.4	0.08	11.1 ± 0.5	14.9 ± 0.6	0.285
Group 2	4.5 ± 0.5	4.9 ± 0.3	0.107	12.8 ± 0.5	14.8 ± 0.5	0.873
Intergroup *P* value	0.172	0.212		0.127	0.946	

PVSTS: Prevertebral soft tissue swelling.

Table 4 Demonstrating complications after surgery in each group

Complication	Outpatient	Inpatient
Dysphagia	4	5
Visited ER (not admitted)	3	0
Pain not relieved by TTH medications	2	0
Dressing completely soaked	1	0
Intractable pain	0	1

TTH: To take home.

of mild, moderate and severe, over the initial 3 mo postoperative period[33].

DISCUSSION

The authors aimed to demonstrate the safety of the use of DBM within and anterior to an ACDF PEEK cage in the outpatient setting. This study shows significant improvement in postoperative outcomes in both groups; however no intergroup significance was noted. Analysis of postoperative PVSTS demonstrated no clinical or statistically significant intragroup increase as well as no significant difference between groups.

The literature has copious studies endorsing ACDF as the gold standard treatment for failed conservative management of numerous cervical pathologies[34-37]. More recently, patients and spine surgeons are turning their attention toward the potential benefits of ACDF in an ambulatory surgery center, based on promising results of preliminary reports[2,16,17,38]. While the feasibility and safety of outpatient ACDF has been established for up to three cervical levels[39], there is a lack of consensus regarding the safety of DBM in the anterior cervical spine as an adjunct to fusion. Studies have looked at the effectiveness, safety of its use in a hospital setting[4,11,19] as well as normal prevertebral soft tissue swelling post ACDF[30]; however, the paucity of data on the clinical outcomes of DBM use during ACDF in an ASC, prompted the authors to report the results of a single-center local experience.

In this series there were no adverse graft related complications noted. There was no clinical or radiologic evidence of edema one week post-operative and therefore no further evaluation for this finding performed beyond this point. The creation of DBM involves a process of allograft bone acid extraction[40] which exposes type Ⅰ collagen, growth factors and BMPs. Although lacking in structural integrity, DBM contains osteoconductive agents, which render it a viable alternative biologic agent for bony fusion. This study has demonstrated the effective use of DBM within and anterior to PEEK cages therefore, the authors conclude that the exposed BMPs within DBM is not significant in concentration to cause a clinical or radiographic response.

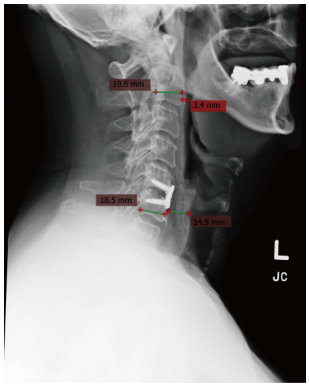

Figure 3 Plain lateral radiograph of the cervical spine, taken one week postoperatively, which shows the normal dimensions of the prevertebral space being less than 50% of the vertebral body at C2 and less than the body width of C6 respectively.

The adherence to our local, standardized outpatient criteria[21-23], comprehensive patient education and postoperative protocol were instrumental in providing self-assurance to both patients and the surgeon when proceeding with this operation[4,11,19]. Included in all preoperative counseling and consent sessions, were the potential risks for postoperative dysphagia, airway irritation and soft tissue swelling. Additional comfort was added by calling our patients the night of, and the morning after surgery in order to act in a timely manner should any complications occur, requiring immediate admission to hospital, which is always within 30 min of the patients' location.

As the literature expands on the safety and effectiveness of anterior cervical fusions in ambulatory surgery centers, this paper reinforces the conclusion that it is safe, with excellent patient satisfaction. The authors do acknowledge the limitations of this study: Its retrospective nature and the lack of CT scan to assess post-op soft tissue swelling. However, despite these limitations, we are confident that adherence to our strict patient selection criteria, preoperative education, consistent operating team, and systematic postoperative protocol can safely produce excellent outcomes. Our findings show that the

use of DBM within and anterior to cervical PEEK cages in the outpatient setting is safe with similar outcomes in the inpatient setting.

ACDF with adjunct DBM packed PEEK cages showed a statistical significant intragroup improvement in VAS neck pain scores and NDI scores. There were no reported serious patient complications; post-operative radiographs demonstrated no statistically significant difference in prevertebral space. We conclude that ACDF with DBM-packed PEEK cages can be safely done in an ASC with satisfactory outcomes.

COMMENTS

Background

Demineralized bone matrix (DBM) has been demonstrated to be safe in the hospital setting; however concerns may be heightened with use anterior to the cage in the outpatient setting. The authors hypothesize that clinical outcomes and safety should be similar or improved in the outpatient setting.

Research frontiers

Outpatient spine surgery continues to evolve with the introduction of minimally invasive and less exposure surgery. This study adds to the body of knowledge for outpatient surgery.

Innovations and breakthroughs

Based on literature no other study has assessed clinically DBM being placed anterior to the cage as well as within the cages looking specifically at soft tissue swelling.

Applications

This study demonstrates the safety of DBM being used anterior to polyetheretherketone interbody cage with no additional complications.

Terminology

Standard terminology used throughout text.

Peer-review

It is a well written paper.

REFERENCES

1 **Bailey RW**, Badgley CE. Stabilization of the cervical spine by anterior fusion. *J Bone Joint Surg Am* 1960; **42-A**: 565-594 [PMID: 13848906 DOI: 10.2106/00004623-196042040-00001]

2 **Erickson M**, Fites BS, Thieken MT, McGee AW. Outpatient anterior cervical discectomy and fusion. *Am J Orthop* (Belle Mead NJ) 2007; **36**: 429-432 [PMID: 17849028]

3 **Lied B**, Roenning PA, Sundseth J, Helseth E. Anterior cervical discectomy with fusion in patients with cervical disc degeneration: a prospective outcome study of 258 patients (181 fused with autologous bone graft and 77 fused with a PEEK cage). *BMC Surg* 2010; **10**: 10 [PMID: 20302673 DOI: 10.1186/1471-2482-10-10]

4 **Park HW**, Lee JK, Moon SJ, Seo SK, Lee JH, Kim SH. The efficacy of the synthetic interbody cage and Grafton for anterior cervical fusion. *Spine* (Phila Pa 1976) 2009; **34**: E591-E595 [PMID: 19644317 DOI: 10.1097/BRS.0b013e3181ab8b9a]

5 **Silber JS**, Anderson DG, Daffner SD, Brislin BT, Leland JM, Hilibrand AS, Vaccaro AR, Albert TJ. Donor site morbidity after anterior iliac crest bone harvest for single-level anterior cervical discectomy and fusion. *Spine* (Phila Pa 1976) 2003; **28**: 134-139 [PMID: 12544929 DOI: 10.1097/00007632-200301150-00008]

6 **Summers BN**, Eisenstein SM. Donor site pain from the ilium. A complication of lumbar spine fusion. *J Bone Joint Surg Br* 1989; **71**: 677-680 [PMID: 2768321]

7 **Castro FP Jr**, Holt RT, Majd M, Whitecloud TS 3rd. A cost analysis of two anterior cervical fusion procedures. *J Spinal Disord* 2000; **13**: 511-514 [PMID: 11132982 DOI: 10.1097/00002517-200012000-00008]

8 **Tilkeridis K**, Touzopoulos P, Ververidis A, Christodoulou S, Kazakos K, Drosos GI. Use of demineralized bone matrix in spinal fusion. *World J Orthop* 2014; **5**: 30-37 [PMID: 24649412 DOI: 10.5312/wjo.v5.i1.30]

9 **Aghdasi B**, Montgomery SR, Daubs MD, Wang JC. A review of demineralized bone matrices for spinal fusion: the evidence for efficacy. *Surgeon* 2013; **11**: 39-48 [PMID: 23040457 DOI: 10.1016/j.surge.2012.08.001]

10 **Bruce C**, Chin KR, Cumming V, Crawford NR. Stabilizing Effects of a Particulate Demineralized Bone Matrix in the L4 Interbody Space with and without PEEK Cage - A Literature Review and Preliminary Results of a Cadaveric Biomechanical Study. *West Indian Med J* 2013; **62**: 748-751 [PMID: 25014862]

11 **An HS**, Simpson JM, Glover JM, Stephany J. Comparison between allograft plus demineralized bone matrix versus autograft in anterior cervical fusion. A prospective multicenter study. *Spine* (Phila Pa 1976) 1995; **20**: 2211-2216 [PMID: 8545714 DOI: 10.1097/00007632-199510001-00006]

12 **Vaidya R**, Carp J, Sethi A, Bartol S, Craig J, Les CM. Complications of anterior cervical discectomy and fusion using recombinant human bone morphogenetic protein-2. *Eur Spine J* 2007; **16**: 1257-1265 [PMID: 17387522]

13 **Carragee EJ**, Hurwitz EL, Weiner BK. A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. *Spine J* 2011; **11**: 471-491 [PMID: 21729796 DOI: 10.1016/j.spinee.2011.04.023]

14 **Lebl DR**. Bone morphogenetic protein in complex cervical spine surgery: A safe biologic adjunct? *World J Orthop* 2013; **4**: 53-57 [PMID: 23610751 DOI: 10.5312/wjo.v4.i2.53]

15 **Mroz TE**, Wang JC, Hashimoto R, Norvell DC. Complications related to osteobiologics use in spine surgery: a systematic review. *Spine* (Phila Pa 1976) 2010; **35**: S86-104 [PMID: 20407355 DOI: 10.1097/BRS.0b013e3181d81ef2]

16 **Garringer SM**, Sasso RC. Safety of anterior cervical discectomy and fusion performed as outpatient surgery. *J Spinal Disord Tech* 2010; **23**: 439-443 [PMID: 20087224 DOI: 10.1097/BSD.0b013e3181bd0419]

17 **Lied B**, Rønning PA, Halvorsen CM, Ekseth K, Helseth E. Outpatient anterior cervical discectomy and fusion for cervical disk disease: a prospective consecutive series of 96 patients. *Acta Neurol Scand* 2013; **127**: 31-37 [PMID: 22571345 DOI: 10.1111/j.1600-0404.2012.01674.x]

18 **Liu JT**, Briner RP, Friedman JA. Comparison of inpatient vs. outpatient anterior cervical discectomy and fusion: a retrospective case series. *BMC Surg* 2009; **9**: 3 [PMID: 19265540 DOI: 10.1186/1471-2482-9-3]

19 **Topuz K**, Colak A, Kaya S, Simşek H, Kutlay M, Demircan MN, Velioğlu M. Two-level contiguous cervical disc disease treated with peek cages packed with demineralized bone matrix: results of 3-year follow-up. *Eur Spine J* 2009; **18**: 238-243 [PMID: 19130094]

20 **Suk KS**, Kim KT, Lee SH, Park SW. Prevertebral soft tissue swelling after anterior cervical discectomy and fusion with plate fixation. *Int Orthop* 2006; **30**: 290-294 [PMID: 16521012 DOI: 10.1007/s00264-005-0072-9]

21 **Chin KR**, Coombs AV, Seale JA. Feasibility and patient-reported outcomes after outpatient single-level instrumented posterior lumbar interbody fusion in a surgery center: preliminary results in 16 patients. *Spine* (Phila Pa 1976) 2015; **40**: E36-E42 [PMID: 25271488 DOI: 10.1097/BRS.0000000000000604]

22 **Chin KR**, Pencle FJ, Coombs AV, Packer CF, Hothem EA, Seale JA. Eligibility of Outpatient Spine Surgery Candidates in a Single Private Practice. *Clin Spine Surg* 2016; Epub ahead of print [PMID: 26992175]

23 **Chin KR**, Pencle FJR, Seale JA, Pencle FK. Clinical Outcomes of Outpatient Cervical Total Disc Replacement Compared With Outpatient Anterior Cervical Discectomy and Fusion. *Spine* (Phila Pa

1976) 2017; **42**: E567-E574 [PMID: 27755491]
24 **Lawrence JT**, London N, Bohlman HH, Chin KR. Preoperative narcotic use as a predictor of clinical outcome: results following anterior cervical arthrodesis. *Spine* (Phila Pa 1976) 2008; **33**: 2074-2078 [PMID: 18758363 DOI: 10.1097/BRS.0b013e3181809f07]
25 **Song KJ**, Choi BW, Kim HY, Jeon TS, Chang H. Efficacy of postoperative radiograph for evaluating the prevertebral soft tissue swelling after anterior cervical discectomy and fusion. *Clin Orthop Surg* 2012; **4**: 77-82 [PMID: 22379559 DOI: 10.4055/cios.2012.4.1.77]
26 **Kepler CK**, Rihn JA, Bennett JD, Anderson DG, Vaccaro AR, Albert TJ, Hilibrand AS. Dysphagia and soft-tissue swelling after anterior cervical surgery: a radiographic analysis. *Spine J* 2012; **12**: 639-644 [PMID: 22561176 DOI: 10.1016/j.spinee.2012.03.024]
27 **Khaki F**, Zusman NL, Nemecek AN, Ching AC, Hart RA, Yoo JU. Postoperative prevertebral soft tissue swelling does not affect the development of chronic dysphagia following anterior cervical spine surgery. *Spine* (Phila Pa 1976) 2013; **38**: E528-E532 [PMID: 23380821 DOI: 10.1097/BRS.0b013e31828a2992]
28 **Chin KR**, Ghiselli G, Cumming V, Furey CG, Yoo JU, Emery SE. Postoperative magnetic resonance imaging assessment for potential compressive effects of retained posterior longitudinal ligament after anterior cervical fusions: a cross-sectional study. *Spine* (Phila Pa 1976) 2013; **38**: 253-256 [PMID: 23104194 DOI: 10.1097/BRS.0b013e3182796e9c]
29 **Dai LY**, Jia LS. Radiographic measurement of the prevertebral soft tissue of cervical vertebrae. *Chin Med J* (Engl) 1994; **107**: 471-473 [PMID: 7956490]
30 **Sanfilippo JA Jr**, Lim MR, Jacoby SM, Laterra R, Harrop JS, Vaccaro AR, Hilibrand AS, Anderson DG, Albert TJ. "Normal" prevertebral soft tissue swelling following elective anterior cervical decompression and fusion. *J Spinal Disord Tech* 2006; **19**: 399-401 [PMID: 16891973 DOI: 10.1097/00024720-200608000-00004]
31 **Rhee JM**, Chapman JR, Norvell DC, Smith J, Sherry NA, Riew KD. Radiological Determination of Postoperative Cervical Fusion: A Systematic Review. *Spine* (Phila Pa 1976) 2015; **40**: 974-991 [PMID: 25893344 DOI: 10.1097/BRS.0000000000000940]
32 **Webster-Kerr KR**, Christie C, Grant A, Chin D, Burrowes H, Clarke K, Wellington I, Shaw K, De La Haye W. Emergence of Zika Virus Epidemic and the National Response in Jamaica. *West Indian Med J* 2016; **65**: 243-249 [PMID: 28375542]
33 **Bazaz R**, Lee MJ, Yoo JU. Incidence of dysphagia after anterior cervical spine surgery: a prospective study. *Spine* (Phila Pa 1976) 2002; **27**: 2453-2458 [PMID: 12435974 DOI: 10.1097/00007632-200211150-00007]
34 **Hacker RJ**. A randomized prospective study of an anterior cervical interbody fusion device with a minimum of 2 years of follow-up results. *J Neurosurg* 2000; **93**: 222-226 [PMID: 11012052 DOI: 10.3171/spi.2000.93.2.0222]
35 **Martin GJ Jr**, Haid RW Jr, MacMillan M, Rodts GE Jr, Berkman R. Anterior cervical discectomy with freeze-dried fibula allograft. Overview of 317 cases and literature review. *Spine* (Phila Pa 1976) 1999; **24**: 852-858; discussion 858-859 [PMID: 10327505 DOI: 10.1097/00007632-199905010-00004]
36 **Daentzer D**, Floerkemeier T, Bartsch I, Masalha W, Welke B, Hurschler C, Kauth T, Kaltbeitzel D, Hopmann C, Kujat B, Kalla K. Preliminary results in anterior cervical discectomy and fusion with an experimental bioabsorbable cage - clinical and radiological findings in an ovine animal model. *Springerplus* 2013; **2**: 418 [PMID: 24024102 DOI: 10.1186/2193-1801-2-418]
37 **Korinth MC**. Treatment of cervical degenerative disc disease - current status and trends. *Zentralbl Neurochir* 2008; **69**: 113-124 [PMID: 18666050 DOI: 10.1055/s-2008-1081201]
38 **Sheperd CS**, Young WF. Instrumented outpatient anterior cervical discectomy and fusion: is it safe? *Int Surg* 2012; **97**: 86-89 [PMID: 23102004 DOI: 10.9738/CC35.1]
39 **Villavicencio AT**, Pushchak E, Burneikiene S, Thramann JJ. The safety of instrumented outpatient anterior cervical discectomy and fusion. *Spine J* 2007; **7**: 148-153 [PMID: 17321962 DOI: 10.1016/j.spinee.2006.04.009]
40 **Miyazaki M**, Tsumura H, Wang JC, Alanay A. An update on bone substitutes for spinal fusion. *Eur Spine J* 2009; **18**: 783-799 [PMID: 19280232]

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ORIGINAL ARTICLE

Retrospective Study

Total joint replacement in inhibitor-positive haemophilia: Long-term outcome analysis in fifteen patients

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Abstract

AIM

To collect data from joint replacement in inhibitor patients, evaluate haemostatic and patient outcomes, and analyse the costs.

METHODS

We report our 21-year, single-centre cumulative experience of 15 joint arthroplasties in six inhibitor patients.

RESULTS

Two low responder inhibitor patients were in the early days treated with FVIII, whereas bypassing agents were used in the rest of the high responder patients. The primary haemostatic outcome was good in 8/15, fair in 4/15 and poor in 3/15 operations. The overall patient outcome, including joint health and patient satisfaction, was good in 10/15, fair 4/15 and poor in 1/15. No deep infections were observed. Cost analysis was most beneficial in low responders and in two immune-tolerized, high responder patients. In all cases, factor replacement comprised the main treatment costs.

CONCLUSION

Our experience supports the initial use of bypassing agents as well as preoperative immune-tolerance induction when possible. Despite the challenges of haemostasis and severe joint disease, total joint arthroplasty can reach a good outcome, even in inhibitor patients. The risk for deep infection might be smaller than previously reported. Individual planning, intense multidisciplinary teamwork

and execution of operations should be centralised in a professional unit.

Key words: Haemophilia; Joint replacement; Inhibitor; Cost analysis; Arthroplasty

Core tip: There are only few reports including joint arthroplasties on inhibitor-positive haemophilia patients. Generally the focus is mainly on immediate haemostatic outcome leaving the long-term orthopaedic results unreported. Our study brings out the importance of long-term and overall outcome when performing elective life-quality surgery. Management of inhibitor patients is especially challenging regarding not only the operative treatment but also the costs. As the health economic analysis of the topic is lacking, we provide new data. According to our cost analysis, preoperative immune-tolerance induction for high responder patients will bring cost- and outcome benefit both in surgery and preventing postoperative bleeds.

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INTRODUCTION

Total joint arthroplasty covered with coagulation factor replacement therapy is the treatment of choice in severe haemophilic arthropathy when conservative treatment has failed. The failure to stabilize the joint disease is usually due to the late initiation of secondary prophylaxis with replacement therapy. Patients may develop inhibitors to their factor replacement therapy due to the foreign protein and have thus often missed the prophylactic replacement therapy and surgical treatment because of the fear of bleeds and the high costs of the treatment. In the literature, the inhibitor prevalence is around 10% among the adult patient population, mainly affected by the earlier treatment and availability of immune-tolerance induction (ITI) therapy[1-3].

The appropriate replacement therapy depends on the patient's individualized response, which is not always similar - nor predictable - at each haemostatic challenge or management strategy. The introduction of bypassing agents has enabled total joint replacements also for high responder inhibitor patients[4]. However, the use of these products is costly.

The reports on joint arthroplasties in inhibitor patients are mainly case-based, and established standards of the management of these operations are scanty[5-7]. At Orton Orthopaedic Hospital of Invalid Foundation, centralised operative treatment of haemophilic joint disease has been carried out already since the 1970s. The haematological and laboratory support has been available by Red Cross Transfusion Central from 1957, and from 2002 also by the Helsinki University Hospital Coagulation Disorders unit. The first total hip replacement (THR) for a haemophilia patient in Finland was performed in 1982, and the first knee replacement (TKR) in 1984. The first TKR on a patient with recognized inhibitors was performed in 1991. We report our cumulative experience of 21 years of 15 joint arthroplasties in six haemophilia inhibitor patients.

MATERIALS AND METHODS

From 1991 to 2012, six haemophilia patients with inhibitors (two low; inhibitor titre < or equal to 5 BU/mL) and four high responders; inhibitor titre > 5 IU/mL) were operated on (Tables 1 and 2). The 15 surgical procedures consisted of seven primary TKRs (in two patients, bilateral), one unicondylar knee arthroplasty, one glenohumeral replacement, two ankle arthroplasties, one THR and three knee revision arthroplasties.

Two patients were low responders (inhibitor titre < 5 BU/mL). Four patients who had a history of high inhibitor titre (> 5 BU/mL) were classified as high responders, but the titre immediately prior to surgery was < 5 BU/mL. Two high-titre inhibitor patients underwent successful ITI as a part of the ObsITI protocol at a later stage (from 2010 onwards) of the follow-up. Five patients (83%) had a history of hepatitis C. One patient also was antibody-positive for hepatitis B. None of the patients was HIV positive.

To manage surgery during the early 1990s, the historical peak inhibitor titre, whether low or high (< or > 5 BU/mL), dictated the strategy. Traditionally, immediately preoperatively in the absence of FVIII inhibitory antibodies (*i.e.*, confirmed normal recovery and half-life of FVIII), either recombinant or plasma-derived FVIII is infused intravenously to secure haemostasis by reaching normal FVIII levels (usually 80%-100%). In contrast, the presence of inhibitors neutralise FVIII, and for the surgery FVIII bypassing agents, either activated prothrombin complex concentrate (aPCC, FeibaR) or recombinant activated Factor VII (rFVIIa, NovoSeven), are the current effective options to maintain surgical haemostasis of blood. The specific agent is chosen according to the individual bleeding phenotype, history and patient weight. Initially, either cryoprecipate or a plasma-derived FVIII (pdFVIII) was used in all low responders and initially in high responders having a preoperative low inhibitor titre, with the objective to switch to a bypassing agent once the inhibitor titre inclined. Low responders (Patients A and B) were initially treated with their standard replacement therapy: Cryoprecipitate (AHF-20®, *n* = 1/8) or coagulation factor VIII (pdFVIII, Amofil®, *n* = 7/8). For the high responder patients (C-F), the treatment was either activated prothrombin complex concentrate (aPCC, FEIBA®) or

Table 1 Main surgical operations in patients (A and B) with the low historical inhibitor titre (< 5 BU/mL)

Patient and operations (model)	Haemophilia therapy	Primary haemostatic outcome	Surgical outcome
A			
TKR (cruciate retaining)	Cryo (AHF-20) → pdFVIII	Good	Good
TKR (cruciate retaining)	pdFVIII	Good	Good
Ankle arthroplasty	pdfVIII	Good	Good
Ankle arthroplasty	pdFVIII	Good	Good
Knee revision arthroplasty (reconstructive)	rFVIII	Fair	Good
Knee revision arthroplasty (reconstructive)	rFVIII	Good	Good
B			
Knee hemiarthroplasty (unicondylar)	pdFVIII	Good	Poor
Revision arthroplasty (cruciate retaining)	pdFVIII → rFVIIa	Fair	Good

In A, six operations and in B, two operations were performed. TKR: Total knee replacement; pdFVIII: Plasma-derived factor VIII; rFVIII: Recombinant FVIII.

Table 2 Main surgical operations in the patients (C-F) with the high historical inhibitor titre

Patient and operations (model)	Replacement therapy	Primary haemostatic outcome	Surgical outcome ROM/pain
C			
TKR bilateral (hinge + posterior stabilised)	pdFVIII → aPCC	Poor	Fair
THR (uncemented)	rFVIII	Good	Good
D			
TKR bilateral (reconstructive)	aPCC→ rFVIIa	Fair	Fair
E			
TKR (posterior stabilized)	aPCC → rFVIIa	Poor	Good
F			
Glenohumeral hemiarthroplasty	rFVIII	Good	Good

ROM: Range of motion; TKR: Total knee replacement; THR: Total hip replacement; aPCC: Activated prothrombinase complex concentrate.

recombinant activated factor VIIa (rFVIIa, NovoSeven®). In one case, the treatment was started with pdFVIII, but changed to aPCC when the inhibitor titre arose.

The routine blood coagulation tests were monitored daily during the FVIII replacement period to capture FVIII: C clotting activity or during bypassing therapy to capture the possible development of disseminated intravascular coagulation (DIC), anaemia or thrombocytopenia. Cefuroxime was used as standard antibiotic prophylaxis (or clindamycin, in case of allergy).

After TKR, continuous passive motion (CPM) treatment was started at the 2nd-7th postoperative day. After THR, immediate full body weight bearing was allowed, if the blood and haemostatic status supported the decision. After ankle arthroplasties, half-weight bearing with walker orthosis was recommended for 6-8 wk. After glenohumeral arthroplasty, the upper arm was immobilized in an arm sling for 4 wk and only passive mobilization for 6 wk was allowed.

Primary haemostatic outcome was considered good if the postoperative bleeding did not differ from the normal arthroplasty, fair if there were additional bleeds and poor if there were massive or repetitive additional bleeds that were difficult to manage.

The statistical analysis was carried out using the SPSS 20.0, Lead Technologies, Inc. statistical software system. For analysis, a paired-samples *T*-test was used. In this study, a *P*-value < 0.05 (two-sided probability) was considered significant.

RESULTS

Low responders (A and B). Two low inhibitor titre patients underwent several operations, the details of which are captured in Table 1.

In Patient A, TKR was carried out under cryoprecipitate coverage. At three days, the treatment had to be changed to pdFVIII when the FVIII: C response started to decline. The haemostatic outcome was good.

Three years later, a second primary TKR with pdFVIII replacement therapy was performed. The inhibitor titre remained low, and the haemostatic and surgical outcomes were good. Two years later, the patient experienced recurrent knee bleeds at the recent TKR site. Three arthroscopical synovectomies were performed under pdFVIII replacement, while any vascular anomaly was excluded by popliteal angiography[8,9]. After each synovectomy, the bleeding tendency decreased temporarily for a few months. Finally, the bleeds ceased with Holmium isotope radiosynoviorthesis. Additionally, two total ankle arthroplasties were performed successfully under pdFVIII coverage with good haemostatic and primary outcomes.

Later, the patient underwent revision knee arthroplasties due to aseptic loosening of the components. Both arthroplasties were performed using rFVIII. After

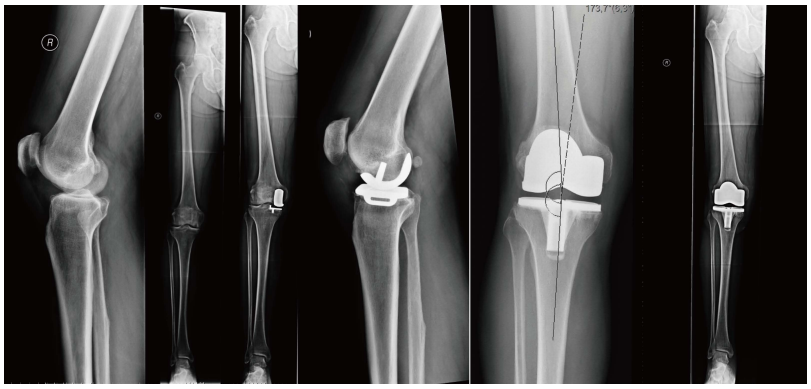

Figure 1 Unicondylar knee replacement and revision arthroplasty.

the first operation, the patient experienced a knee bleed at 8 d while on continuous replacement therapy, which was treated with higher dosing of rFVIII. There was a temporary rise in the FVIII antibody, but the final outcome was good. The second knee operation resulted in good haemostatic and overall outcome.

Patient B had experienced only occasional spontaneous bleeding episodes. Before the primary operation, he was devoid of inhibitor history. He suffered from posttraumatic medial knee arthrosis, and unicondylar knee replacement was performed with a good haemostatic outcome using pdFVIII. However, the patient needed revision arthroplasty 9 mo after the primary operation. Next, the replacement therapy was started with pdFVIII, and at 12 d postoperatively, the inhibitor titre raised the replacement therapy was switched to rFVIIa with good haemostatic outcome (Figure 1).

In conclusion, the two low responder inhibitor patients were managed successfully with FVIII concentrate, while the inhibitor titre remained low. Individually and according to the type of surgery, the FVIII was switched to bypassing agents when the inhibitor titre rose. One postoperative bleed in association with 8 operations occurred without long-term consequences.

High-responders, patients C-F

The surgical details of Patients C-F are presented in Table 2. In Patient C with bilateral primary knee arthroplasty, the preoperative inhibitor titre was < 5 BU/mL, and the operation was carried out without complications using pdFVIII. At five days when the inhibitor titre rose, however, the patient experienced bilateral knee bleeds and aPCC was started. The dose (up to 200-250 U/kg) had to be increased for several days due to a fair haemostatic response. DIC or deep venous thrombosis did not develop. After 5.5 years, the patient underwent a successful ITI therapy with rFVIII, and a primary THR could be performed with rFVIII 6 mo later with good haemostatic and surgical outcome. The recovery and half-life of rFVIII were appropriate, and the inhibitor did not reoccur throughout the early and later follow-up.

Patient D had bilateral TKR with aPCC as replacement therapy. At 8 d the patient experienced a severe knee bleed, which ceased with rFVIIa [two doses of 5 mg (90 μg/kg *iv*) at 2 h interval]. Next, aPCC was re-administered (at 200 IU/kg) but the patient bled with regard to the operated knee twice, at days 11 and 14. After the third bleed, the replacement therapy was carried out with rFVIIa for four days and thereafter with sequential aPCC and rFVIIa for two weeks.

Patient E underwent TKR with aPCC as replacement therapy pre- and perioperatively. At two days, he suddenly bled a lot (800 mL/30 min) with regard to his operated knee. A bolus of 12 mg of rFVIIa (220 μg/kg) stopped the bleed immediately. The replacement therapy was continued with rFVIIa (6 mg every 2 h) for several days, and the haemostatic outcome was finally optimal.

Patient F had a history of high inhibitor titre and successful ITI with rFVIII one year preoperatively. He underwent glenohumeral hemiarthroplasty with good haemostatic outcome and without an increase of the inhibitor titre during the follow-up.

Overall, in 5 operations out of 12, the patients experienced major bleeds at 2-8 d postoperatively. Albeit this initial haemostatic response was either fair or even poor in two patients, the joint outcome was good. One patient had bilateral knee operation initially managed with pdFVIII, during which there was the reactivation of the inhibitor and both-sided bleeds occurred. He had the poor haemostatic response. However, the complication was controlled by switching the therapy to bypassing agents. A single bypassing therapy did not necessarily manage to control haemostasis, but the switch between aPCC and rFVIIa or their sequential use finally secured the haemostatic outcome.

Primary arthroplasties

The mean follow-up for patients with primary TKR (eight arthroplasties) was 7.3 years (0.3-20.3, SD 7.6). The median age of the patients at the time of the operation was 48.4 years (35.4-66.1, SD 10.9). The median hospital stay was 19.6 d (10-25, SD 6.1). The range of motion (ROM) improved from mean 81.9° flexion to 96.9° (SD 17.1 and 11.9, $P = 0.07$) and from mean 21.3° extension deficiency to 7.5° (SD 12.7 and 8.4, $P = 0.09$). One high

responder patient (Patient D) with severe knee flexion contracture with bilateral knee arthroplasty had a patellar fracture. It was observed at the two-month control and treated conservatively with orthosis. No deep infections were observed.

The two ankle arthroplasties were performed without complications to the same low responder Patient A. The patient had severe haemophilic arthropathy without significant deformation or bone loss in both ankles, and the preoperative walking distance had diminished below 500 m. Preoperative ROM in both ankles was from neutral position to 20° plantar flexion and primary outcome was from 5° dorsiflexion to 30° of plantar flexion, respectively. In 6.1 and 7.0 years follow-up 0°-20° ROM in plantar flexion of both ankles was observed. The patient could stand on his toes, walking ability was improved to 2 km and both ankles were pain-free. Radiologically, the components were in good position without signs of loosening or other complications.

The total hip arthroplasty for the high responder Patient C with a preoperative successful ITI was performed with an excellent haemostatic and primary outcome. At the 2-mo follow-up, the patient had a pain-free joint and ROM 0°-90° extension-flexion, 20° rotation and 40° abduction. The radiographic control showed a good position of the prosthesis.

The high responder Patient F with glenohumeral hemiarthroplasty had also undergone recent preoperative ITI. The patient had a painful haemophilic arthropathy with restricted ROM (abduction 45°, flexion 60° and outer rotation -10°), severe prolonged pain problems and an addiction to opiates. The surgery succeeded well under rFVIII coverage. The pain significantly diminished, and at the 7-mo follow-up, ROM substantially improved (abduction 80°/110° using scapulae, flexion 90°/130° using scapulae and outer rotation 45°) with pain-free peripheral movements. The X-rays showed a good position of the prosthesis.

Revision arthroplasties

Two revision knee arthroplasties using reconstructive prostheses for Patient A were performed at 17.7 and 15.7 years after primary operations because of loosening of the components. The hospital stay was 16 and 11 d, and CPM treatment was started three and five days after the operation, respectively. The postoperative mobility was 0°-100° and 0°-110° at 2.1 years and 1.8 years follow-up. After the first operation there was an initial bleed, but the joint outcome was good. The second operation and primary rehabilitation were successful with both good haemostatic and primary outcome. Five months postoperatively, a bacterial prepatellar bursitis was treated with peroral antibiotics. No deep infection was detected and the patient recovered well.

The third knee revision arthroplasty was performed at 9 mo after a primary operation for Patient B because of loosening of the components. The patient had suffered from posttraumatic medial knee arthrosis, and the joint problem was considered primarily posttraumatic rather than haemophilic arthropathy. For these reasons, unicondylar knee replacement was performed. The loosening was thought to result from mechanical factors, but the compromised haemostasis by haemophilia may also play a role. Neither bacteria nor the signs of infection were detected. In spite of the fair haemostatic outcome, the joint outcome was good with 0°-110° ROM and freedom from pain at the 3.5-year follow-up. Radiologically, the components were in good position, and the walking ability had improved from 100 m to over one kilometre.

Cost analysis

Since 2005 in Orton Orthopaedic Hospital, 11 major orthopaedic procedures (13 arthroplasties) on inhibitor patients were performed (Table 3). Among the high responder patients when aPCC and/or rFVIIa were needed, the total costs varied between 350900-500400 Euros. In these cases, the replacement therapy covered the great majority, *i.e.*, 87%-94%, of the total costs, even though two of the three operations were bilateral. Of the two low responders and in two cases among high responder patients after ITI, the replacement therapy costs were lower, being 59%-81% of the total costs. The total costs of these operations were also clearly lower compared to the high responders with an active inhibitor: About 1/5 - 1/3, *i.e.*, 47200-103200 Euros, in the low responders and about 1/10, *i.e.*, 43300-49800 Euros, in the two high responders having undergone ITI.

High responder patients with postoperative inhibitor formation had also a longer hospital stay (15-24 d) compared with the low responder patients (8-18 d) or the high responders with preoperative ITI (8-9 d). However, two of the three operations in high responder patients were also bilateral.

DISCUSSION

According to the guidelines of World Federation of Haemophilia[10], joint replacement surgery for haemophilia patients requires multidisciplinary teamwork. Despite the demanding surgery, good results among haemophilia patients with inhibitors have been previously reported[5-7,11-16]. However, there are only a few reports including joint arthroplasties on inhibitor patients[7,11,12,16-19] with scant follow-up data. As this is a rare patient group, randomised controlled trials are not - and are not likely - to become available.

In our report, the primary haemostatic outcome was good in half of the patients and poor in 20% of the high responder patients, and improved only with switching between the bypassing agents. However, the primary surgical outcome turned out fairly well, even in those patients who initially had a poor haemostatic outcome. Along prolonged rehabilitation, postoperative bleeding complications increase costs and reduce the patient's

Table 3 Cost analysis of arthroplasties on inhibitor patients since 2005

Resp	Operation		Component	TOT eur	HT[2] eur	HT (%)[3]	Product®	Hospital stay(d)
Low	Knee revision arthroplasty	Unilateral	Reconstructive	103200	75700	73	Kogenate Bayer	18
Low	Knee revision arthroplasty	Unilateral	Reconstructive	95400	66900	70	Kogenate Bayer	11
Low	Ankle arthroplasty	Unilateral	Primary ankle	47200	35600	75	Kogenate Bayer	10
Low	Ankle arthroplasty	Unilateral	Primary ankle	60200	48800	81	Kogenate Bayer	12
Low	Knee hemiarthroplasty	Unilateral	Unicondylar	51500	41600	81	Amofil	9
Low	Knee revision arthroplasty	Unilateral	Cruciate retaining	50200	36300	72	Amofil	8
High	Knee arthroplasty	Bilateral	Ps[4] + hinge	350900	305500	87	Amofil FEIBA	24
High	Hip arthroplasty	Unilateral	Primary uncemented	43300	27800	64	ReFacto AF[1]	8
High	Knee arthroplasty	Bilateral	Reconstructive	500400	445100	89	FEIBA NovoSeven	24
High	Knee arthroplasty	Unilateral	Ps[4]	409900	386100	94	FEIBA NovoSeven	15
High	Glenohumeral arthroplasty	Unilateral	Primary glenohumeral	49800	29300	59	ReFacto AF[1]	9

[1]Successful preoperative ITI; [2]HT haemophilia therapy (costs of replacement therapy); [3]Procentual costs of replacement therapy; [4]Ps posterior stabilized; Resp: Inhibitor responder (low = historical inhibitor titre < 5 BU/mL, high = historical inhibitor titre > 6 BU/mL).

quality of life by increasing pain and disability. Every effort should focus on the avoidance of postoperative bleeds. Point of care monitoring with thromboelastography or a calibrated automated thrombogram may help in treatment decisions as the therapy unexpectedly may fail[20]. The therapy should be started preferentially with the bypassing agents, and the team should work intimately together with bedside visits to secure the haemostasis when the patient is to be mobilized. According to our experience, the use of cold to reduce swelling and pain may not be optimal, as cooling in the knee may impair the early haemostatic response. Finally, the tailored use of tranexamic acid, not only with rFVIIa but also with aPCC, may turn beneficial[21-23].

Radiosynovectomy has been shown to be an effective treatment in chronic haemophilic synovitis, diminishing pain and bleeding occurrence[24-26]. One of our patients had joint bleeds after TKR with only a temporary help from arthroscopical synovectomies. Even angiography was performed to exclude vascular anomalies, which have been reported in the form of pseudoaneurysms and their rupture after joint surgery or even natively[8]. Radiosynoviorthesis with Holmium isotope finally ended the bleeding episodes. The case is similar to Papavasiliou's report[27] of successful radiosynovectomy after TKR, although that patient was not reported to have inhibitors. In our experience, radiosynoviorthesis seems to be effective also for patients who have undergone joint arthroplasty.

The risk of infection (early- and late-onset) is known to be greater in haemophilia patients undergoing arthroplasty compared with the non-haemophilia population[21,28]. In our report there was one prepatellar bursitis, but deep infections were absent. However, the follow-up times were partly short.

In one case, a unicondylar knee replacement was performed to a patient devoid of previous inhibitor history. The patient suffered from posttraumatic medial arthrosis and the primary hemostatic outcome was good. However, a rapid revision (9 mo postoperatively) was performed because of aseptic loosening of components. The loosening was thought to result from mechanical factors, but the compromised haemostasis by haemophilia may also play a role. In our experience, we do not recommend unicondylar arthroplasty to a patient with haemophilia.

Surgery for patients with inhibitors is expensive and highly demanding. In our report, in 3/8 primary TKRs, revision-type (constrained or reconstructive) prostheses were used because of severe bone defects and soft tissue degeneration. According to our cost analysis, the operation itself including the components, surveillance, medication and hospital stay was less significant, whereas the major cost comprised of the haemostatic replacement therapy. This was especially evident among the high responder patients and when bypassing agents were needed, thus constituting ca. 90% of total costs. Instead, in high responder cases that had undergone preoperative ITI, the cost of replacement therapy was similar to the low responder patients' cases and those of regular haemophilia management. The hospital stay was prolonged for the high responder patients, albeit two of the three operations were bilateral arthroplasties. In our opinion, preoperative ITI for high responder patients will bring cost and outcome benefits, both in surgery and the prevention of postoperative bleeds[29-31]. The disadvantages of ITI are its partial success rates and time constraints, under conditions where there is an urgent need for surgery.

When determining the optimal timing for arthroplasty one must consider the grade of arthrosis, the patient's age, the supposed survival of the chosen prosthesis, as well as the risk of complications. Also, working ability, the status of other joints, osteoporosis and the estimated overall prognosis are to be taken into account. For optimal prognosis, the operation should be performed before permanent joint contractures. From the haematological point of view, the patient

characteristics, plan for replacement therapy for surgery and rehabilitation must be meticulously evaluated preoperatively. An appropriate rehabilitation program prior to and after surgery takes into account other joints and their functionality during recovery in order not to induce other joint problems. In the surgery of haemophilia patients, especially with inhibitors, the comprehensive medical team has to observe the patient for early haemostatic symptoms and signs. Therefore, it is essential that these operations are centralized in a professional unit with the availability of skilled surgeons and haematologists having access to the bypassing agents and optimal laboratory tools.

COMMENTS

Background

Total joint arthroplasty covered with coagulation factor replacement is the treatment of choice in severe haemophilic arthropathy. Inhibitor patients are especially challenging regarding not only the operation and haemostasis management but also the costs since the treatment can be very expensive. The aim was to collect data from joint replacement in inhibitor patients, evaluate haemostatic and patient outcomes, and analyse the costs.

Research frontiers

Despite the demanding surgery, good results among haemophilia patients with inhibitors have been previously reported. However, there are only a few reports including joint arthroplasties on inhibitor patients with scant follow-up data.

Innovations and breakthroughs

In this report, the primary haemostatic outcome was good in half of the patients and poor in 20% of the high responder patients, and improved only with switching between the bypassing agents. However, the primary surgical outcome turned out fairly well, even in those patients who initially had a poor haemostatic outcome. In the authors' opinion, preoperative immune-tolerance induction (ITI) for high responder patients will bring cost and outcome benefits, both in surgery and the prevention of postoperative bleeds. Also, in the authors' experience, radiosynoviorthesis seems to be effective also for patients who have undergone joint arthroplasty.

Applications

In the authors' opinion, preoperative ITI for high responder patients will bring cost and outcome benefits, both in surgery and the prevention of postoperative bleeds. Also, in the authors' experience, radiosynoviorthesis seems to be effective also for patients who have undergone joint arthroplasty. Surgery of haemophilia patients should be centralized in a professional unit with the availability of skilled surgeons and haematologists having access to the bypassing agents and optimal laboratory tools.

Terminology

ITI: With ITI therapy, factor concentrate is given regularly over a period of time until the body is trained to recognize the treatment product without reacting to it.

Peer-review

The manuscript is written well.

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REFERENCES

1 **Webert KE**, Rivard GE, Teitel J, Carcao M, Lillicrap D, St-Louis J, Walker IR. Low prevalence of inhibitor antibodies in the Canadian haemophilia population. *Haemophilia* 2012; **18**: e254-e259 [PMID: 22077390 DOI: 10.1111/j.1365-2516.2011.02694.x]
2 **Wight J**, Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. *Haemophilia* 2003; **9**: 418-435 [PMID: 12828678]
3 **Hay CR**. The epidemiology of factor VIII inhibitors. *Haemophilia* 2006; **12** Suppl 6: 23-28; discussion 28-29 [PMID: 17123390 DOI: 10.1111/j.1365-2516.2006.01362.x]
4 **Astermark J**, Donfield SM, DiMichele DM, Gringeri A, Gilbert SA, Waters J, Berntorp E; FENOC Study Group. A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven Comparative (FENOC) Study. *Blood* 2007; **109**: 546-551 [PMID: 16990605 DOI: 10.1182/blood-2006-04-017988]
5 **Rodriguez-Merchan EC**, Rocino A. Literature review of surgery management in inhibitor patients. *Haemophilia* 2004; **10** Suppl 2: 22-29 [PMID: 15385043 DOI: 10.1111/j.1365-2516.2004.00937.x]
6 **Quintana-Molina M**, Martínez-Bahamonde F, González-García E, Romero-Garrido J, Villar-Camacho A, Jiménez-Yuste V, Fernández-Bello I, Hernández-Navarro F. Surgery in haemophilic patients with inhibitor: 20 years of experience. *Haemophilia* 2004; **10** Suppl 2: 30-40 [PMID: 15385044 DOI: 10.1111/j.1365-2516.2004.00938.x]
7 **Goudemand J**, Tagariello G, Lopaciuk F. Cases of surgery in high-responder haemophilia patients. *Haemophilia* 2004; **10** Suppl 2: 46-49 [PMID: 15385046 DOI: 10.1111/j.1365-2516.2004.00940.x]
8 **Saarela MS**, Tiitola M, Lappalainen K, Vikatmaa P, Pinomäki A, Alberty A, Lassila R. Pseudoaneurysm in association with a knee endoprothesis operation in an inhibitor-positive haemophilia A patient - treatment with local thrombin. *Haemophilia* 2010; **16**: 686-688 [PMID: 20201962 DOI: 10.1111/j.1365-2516.2010.02205.x]
9 **Mauser-Bunschoten EP**, Zijl JA, Mali W, van Rinsum AC, van den Berg HM, Roosendaal G. Successful treatment of severe bleeding in hemophilic target joints by selective angiographic embolization. *Blood* 2005; **105**: 2654-2657 [PMID: 15613551 DOI: 10.1182/blood-2004-06-2063]
10 **Wiedel J**, Stabler S, Geraghty S, Funk S. Joint replacement surgery in haemophilia. *World Federation Haemophilia* 2010; **50**: 1-17
11 **Rodriguez-Merchan EC**, Jimenez-Yuste V, Gomez-Cardero P, Alvarez-Roman M, Martin-Salces M, Rodriguez de la Rua A. Surgery in haemophilia patients with inhibitors, with special emphasis on orthopaedics: Madrid experience. *Haemophilia* 2010; **16**: 84-88 [PMID: 20536990 DOI: 10.1111/j.1365-2516.2010.02223.x]
12 **Rangarajan S**, Yee TT, Wilde J. Experience of four UK comprehensive care centres using FEIBA® for surgeries in patients with inhibitors. *Haemophilia* 2011; **17**: 28-34 [PMID: 20642787 DOI: 10.1111/j.1365-2516.2010.02360.x]
13 **Caviglia H**, Candela M, Galatro G, Neme D, Moretti N, Bianco RP. Elective orthopaedic surgery for haemophilia patients with inhibitors: single centre experience of 40 procedures and review of the literature. *Haemophilia* 2011; **17**: 910-919 [PMID: 21342367 DOI: 10.1111/j.1365-2516.2011.02504.x]
14 **Balkan C**, Karapinar D, Aydogdu S, Ozcan C, Ay Y, Akin M, Kavakli K. Surgery in patients with haemophilia and high responding inhibitors: Izmir experience. *Haemophilia* 2010; **16**: 902-909 [PMID: 20518817 DOI: 10.1111/j.1365-2516.2010.02329.x]
15 **Boadas A**, Fernández-Palazzi F, De Bosch NB, Cedeño M, Ruiz-Sáez A. Elective surgery in patients with congenital coagulopathies and inhibitors: experience of the National Haemophilia Centre of Venezuela. *Haemophilia* 2011; **17**: 422-427 [PMID: 21118333 DOI: 10.1111/j.1365-2516.2010.02427.x]
16 **Jenkins PJ**, Ekrol I, Lawson GM. Total knee replacement in patients with haemophilia: the Scottish experience. *Scott Med J* 2013; **58**: 223-227 [PMID: 24215041 DOI: 10.1177/0036933013507870]
17 **Faradji A**, Bonnomet F, Lecocq J, Grunebaum L, Desprez D, Kern

O, Barbier L, Sibilia J. Knee joint arthroplasty in a patient with haemophilia A and high inhibitor titre using recombinant factor VIIa (NovoSeven): a new case report and review of the literature. *Haemophilia* 2001; **7**: 321-326 [PMID: 11380637]

18 **Hvid I**, Rodriguez-Merchan EC. Orthopaedic surgery in haemophilic patients with inhibitors: an overview. *Haemophilia* 2002; **8**: 288-291 [PMID: 12010425]

19 **Rodriguez-Merchan EC**, Wiedel JD, Wallny T, Hvid I, Berntorp E, Rivard GE, Goddard NJ, Querol F, Caviglia H. Elective orthopaedic surgery for inhibitor patients. *Haemophilia* 2003; **9**: 625-631 [PMID: 14511305]

20 **Dargaud Y**, Lienhart A, Negrier C. Prospective assessment of thrombin generation test for dose monitoring of bypassing therapy in hemophilia patients with inhibitors undergoing elective surgery. *Blood* 2010; **116**: 5734-5737 [PMID: 20810929 DOI: 10.1182/blood-2010-06-291906]

21 **Westberg M**, Paus AC, Holme PA, Tjønnfjord GE. Haemophilic arthropathy: long-term outcomes in 107 primary total knee arthroplasties. *Knee* 2014; **21**: 147-150 [PMID: 24156923 DOI: 10.1016/j.knee.2013.09.010]

22 **Holmström M**, Tran HT, Holme PA. Combined treatment with APCC (FEIBA®) and tranexamic acid in patients with haemophilia A with inhibitors and in patients with acquired haemophilia A--a two-centre experience. *Haemophilia* 2012; **18**: 544-549 [PMID: 22348384 DOI: 10.1111/j.1365-2516.2012.02748.x]

23 **Tran HT**, Sørensen B, Rea CJ, Bjørnsen S, Ueland T, Pripp AH, Tjønnfjord GE, Holme PA. Tranexamic acid as adjunct therapy to bypassing agents in haemophilia A patients with inhibitors. *Haemophilia* 2014; **20**: 369-375 [PMID: 24251535 DOI: 10.1111/hae.12318]

24 **Rampersad AG**, Shapiro AD, Rodriguez-Merchan EC, Maahs JA, Akins S, Jimenez-Yuste V. Radiosynovectomy: review of the literature and report from two haemophilia treatment centers. *Blood Coagul Fibrinolysis* 2013; **24**: 465-470 [PMID: 23492910 DOI: 10.1097/MBC.0b013e3283602a28]

25 **De la Corte-Rodriguez H**, Rodriguez-Merchan EC, Jimenez-Yuste V. Radiosynovectomy in hemophilia: quantification of its effectiveness through the assessment of 10 articular parameters. *J Thromb Haemost* 2011; **9**: 928-935 [PMID: 21352468 DOI: 10.1111/j.1538-7836.2011.04246.x]

26 **Cho YJ**, Kim KI, Chun YS, Rhyu KH, Kwon BK, Kim DY, Yoo MC. Radioisotope synoviorthesis with Holmium-166-chitosan complex in haemophilic arthropathy. *Haemophilia* 2010; **16**: 640-646 [PMID: 20148979 DOI: 10.1111/j.1365-2516.2009.02192.x]

27 **Kapetanos GA**, Papavasiliou KA, Makris V, Nikolaides AP, Kirkos JM, Symeonides PP. Recurrent spontaneous hemarthrosis after total knee arthroplasty successfully treated with synoviorthesis. *J Arthroplasty* 2008; **23**: 931-933 [PMID: 18534524 DOI: 10.1016/j.arth.2007.07.012]

28 **Hirose J**, Takedani H, Koibuchi T. The risk of elective orthopaedic surgery for haemophilia patients: Japanese single-centre experience. *Haemophilia* 2013; **19**: 951-955 [PMID: 23746133 DOI: 10.1111/hae.12209]

29 **Ettingshausen CE**, Kreuz W. The immune tolerance induction (ITI) dose debate: does the International ITI Study provide a clearer picture? *Haemophilia* 2013; **19** Suppl 1: 12-17 [PMID: 23278995 DOI: 10.1111/hae.12051]

30 **Scharf R**, Kucharski W, Nowak T. Surgery in hemophilia A patients with factor VIII inhibitor: 10-year experience. *World J Surg* 1996; **20**: 1171-1181 [PMID: 8864078]

31 **Gringeri A**. VWF/FVIII concentrates in high-risk immunotolerance: the RESIST study. *Haemophilia* 2007; **13** Suppl 5: 73-77 [PMID: 18078402 DOI: 10.1111/j.1365-2516.2007.01579.x]

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ORIGINAL ARTICLE

Observational Study

Digital blinding of radiographs to mask allocation in a randomized control trial

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Abstract

AIM

To demonstrate the effectiveness of a digital radiographic altering technique in concealing treatment allocation to blind outcome assessment of distal femur fracture fixation.

METHODS

Digital postoperative anteroposterior and lateral radiographs from a sample of 33 randomly-selected patients with extra-articular distal femur fractures treated by surgical fixation at a Level 1 trauma center were included. Using commercially available digital altering software, we devised a technique to blind the radiographs by overlaying black boxes over the implant hardware while preserving an exposed fracture site for assessment of fracture healing. Three fellowship-trained surgeons evaluated a set of blinded radiographs twice and a control set of unblinded radiographs once. Each set of radiographs were reviewed independently and in a randomly-assigned order. The degrees of agreement and disagreement among evaluators in identifying implant type while reviewing both blinded and unblinded radiographs were assessed using the Bang Blinding Index and James Blinding Index. The degree of agreement in fracture union was assessed using kappa statistics.

RESULTS

The assessment of blinded radiographs with both the Bang Blinding Index (BBI) and James Blinding Index (JBI) demonstrated a low degree of evaluator success at identifying implant type (Mean BBI, far cortical locking: -0.03, SD: 0.04; Mean BBI, standard screw: 0, SD: 0; JBI: 0.98, SD: 0), suggesting near perfect blinding. The assessment of unblinded radiographs with both blinding indices demonstrated a high degree of evaluator success at identifying implant type (Mean BBI, far cortical locking: 0.89, SD: 0.19; Mean BBI, standard screw: 0.87, SD: 0.04; JBI: 0.26, SD: 0.12), as expected. There was moderate agreement with regard to assessment of fracture union among the evaluators in both the blinded (Kappa: 0.38, 95%CI: 0.25-0.52) and unblinded (Kappa: 0.35, 95%CI: 0.25-0.45) arms of the study. There was no statistically significant difference in fracture union agreement between the blinded and unblinded groups.

CONCLUSION

The digital blinding technique successfully masked the surgeons to the type of implant used for surgical treatment of distal femur fractures but did not interfere with the surgeons' ability to reliably evaluate radiographic healing at the fracture site.

Key words: Methods; Randomized controlled trials; Patient outcome assessment; Fracture healing; Femoral fractures

Core tip: The purpose of this study was to demonstrate the effectiveness of a digital blinding protocol to conceal treatment allocation and permit blinded assessment of radiographic healing of various distal femur fractures. Digital postoperative radiographs from a randomly-selected sample were blinded using digital altering software and evaluated by three fellowship-trained surgeons. This study demonstrates the success with which an uncomplicated and reproducible technique can blind radiographs of distal femur fractures. The blinding protocol successfully masked the surgeons to the type of fixation devices implanted but did not interfere with reliable evaluation of radiographic union.

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INTRODUCTION

Locking plates with standard locking screws are currently used as the gold standard of treatment to stabilize displaced extra-articular distal femur fractures. These plate and screw constructs provide excellent strength to withstand early joint motion and rehabilitation. However, emerging evidence suggests that the rigidity of these constructs may cause complications such as delayed union, nonunion, implant failure, late loss of alignment, and subsequent need for an additional surgical procedure[1-7]. In response to the increasing clinical concern that plates with standard locking screws are too stiff, "far cortical locking" (FCL) screw technology has been introduced to permit controlled micro-motion within a locked construct, which in theory leads to earlier and more predictable healing[8,9]. While initial reports in animal studies and small retrospective clinical series have examined the efficacy of FCL screw technology in treating femur fractures, with more uniform callus formation[6,9], prospective clinical trials comparing standard locking and FCL technologies are necessary to guide treatment recommendations.

The comparison of standard locking screws *vs* FCL screws is currently being conducted in a multi-center randomized control trial (RCT). One of the challenges of surgical RCT's is blinding to reduce bias, since surgeons cannot be blinded to treatment allocation. However, blinding independent outcome assessors can be and effective way to reduce bias[10]. The purpose of this study is to demonstrate the effectiveness of a digital blinding protocol to conceal treatment allocation and permit blinded assessment of radiographic healing of distal femur fractures treated with standard locking screws and FCL screws.

MATERIALS AND METHODS

Blinding

Digital postoperative anteroposterior and lateral radiographs from a sample of 33 randomly-selected patients with extra-articular distal femur fractures (OTA 33-A) were included. All patients were treated with a pre-contoured distal femur plate. Twelve subjects had been treated with standard locking screws, while the other 21 had been managed with FCL screws. Radiographs from the 6 wk, 12 wk, and 24 wk postoperative follow-up visits were acquired for each patient. Week 6 images were not always available, and when this was the case, week 2 postoperative images were substituted. All available radiographs from each patient were of adequate quality for use in the study.

Using commercially available digital altering software (Acorn 1.5.5, Flying Meat, Inc., Everett, WA, United States), we devised a technique to blind the radiographs by overlaying black boxes over the hardware while preserving an exposed fracture site for assessment of healing. The radiographs of standard locking screw constructs contained an average of 6 shaft screws, while those of FCL screw constructs contained an average of 4. To deal with this discrepancy, we standardized each radiograph by placing a minimum of 6 blinding boxes on the shaft portion of the distal femur (Figure 1). A single investigator (L.S.) digitally modified the entire series of images. This investigator had minimal experience with

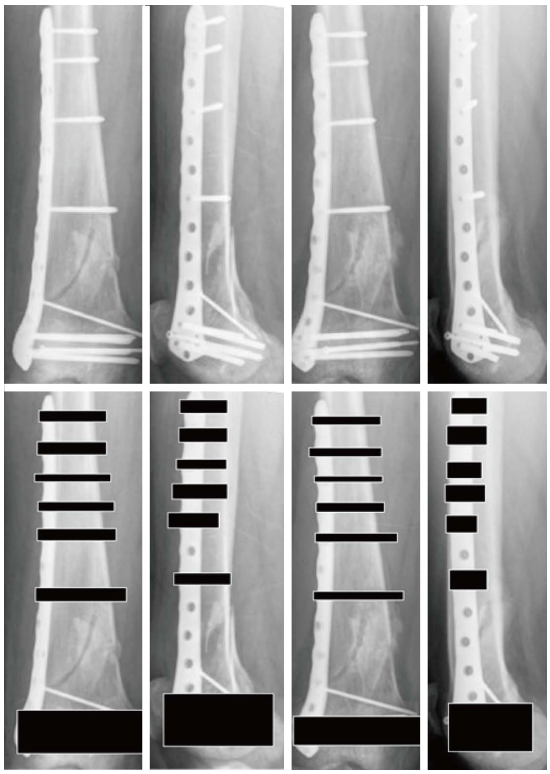

Figure 1 Examples of radiographs before (top) and after (bottom) blinding. Images were taken at 12- (left) and 24-wk (right) post-operation.

digital photo alteration and no previous experience with the digital altering software.

Study design

Three attending physicians with fellowship training in orthopaedic traumatology evaluated the images. All of the evaluators had experience operating with both types of locking screws and interpreting postoperative radiographs. All were aware of, and one was directly involved with, the development of the blinding protocol.

The 33 patients were each assigned a subject number, and random number generating software was used to order the radiographs corresponding to each patient into two PowerPoint (Microsoft, Redmond, WA) presentations, one with unblinded images and the other with blinded images. Each PowerPoint slide contained orthogonal views of four radiographs corresponding to each patient. One set of anteroposterior and lateral views from the time point of healing assessment-either the 12-wk or 24-wk postoperative follow-up visit-and another set of views from a previous time point was used for comparison. Specifically, week 24 images were paired with week 12 images, and week 12 images were paired with week 6 images.

The blinded set of radiographs was assessed twice and the unblinded control once. The evaluations were performed independently and in a randomly-assigned order. A minimum of 2 wk elapsed between evaluations.

For each PowerPoint slide (unblinded and blinded radiographs), the surgeons assessed: (1) the type of hardware used (standard locking screws, FCL screws, or unsure); and (2) status of bony union (healed, not healed, or unsure). Although radiographic fracture healing is subjective and without a clear gold standard[11], in this study radiographic healing was defined as evidence of minimum bridging of 2 cortices. For the blinded images, the evaluators were also asked whether or not the blinding interfered with his or her ability to assess fracture healing (yes, no). If the blinding did interfere, the evaluators were asked to specify which area of the image was problematic (proximal, distal, or both).

Statistical analysis

Statistical analysis was performed using Stata 10.0 (Stata Corp LP, College Station, TX) to calculate the Bang Blinding Index[12,13] and the James Blinding Index[14]. The Bang Blinding Index is commonly used to measure the degree of agreement between evaluators beyond the degree expected by chance. Scores range from -1 to 1, with 1 representing a complete lack of blinding, 0 representing perfect blinding, and -1 representing opposite guessing, which may be related to unblinding[12]. The James Blinding Index measures the degree of disagreement between evaluators. Scores range from 0 to 1, with 0 representing a complete lack of blinding, 0.5 representing completely random blinding, and 1 representing perfect blinding[15].

The kappa statistic is related to the James Blinding Index and was calculated to measure the degree of fracture union agreement between evaluators. The kappa statistic was interpreted using the methods of Landis and Koch, commonly used for interpreting inter-evaluator agreement for qualitative or categorical outcome measures[16].

RESULTS

Evaluation of blinding

The assessment of blinded radiographs with both the Bang Blinding Index and James Blinding Index demonstrated a low degree of evaluator success at identifying implant type, suggesting near perfect blinding (Table 1). The mean Bang Blinding Index was 0 ± 0 for the images with standard locking screws and -0.03 ± 0.04 for those with FCL screws. The mean James Blinding Index was 0.98 ± 0.

The assessment of unblinded radiographs with both indices demonstrated a high degree of evaluator success at identifying implant type (Table 2), as expected. The mean Bang Blinding Index was 0.92 ± 0.87 for the images with standard locking screws and 0.89 ± 0.19 for those with FCL screws. The mean James Blinding Index was 0.26 ± 0.12.

Evaluation of fracture healing

There was moderate agreement with regard to assessment of fracture healing among the evaluators in

Table 1 Blinding assessment with blinded radiographs

	BBI-FCL screw	BBI-standard screws	James Blinding Index
Observer 1	0	0	0.99
Observer 2	0	0	0.99
Observer 3	-0.08	0	0.98
Mean	-0.03	0	0.98
SD	0.04	0	0

BBI: Bang Blinding Index; FCL: Far cortical locking; SD: Standard deviation.

Table 2 Blinding assessment with unblinded radiographs

	BBI-FCL screw	BBI-standard screws	James blinding index
Observer 1	1	0.85	0.32
Observer 2	1	0.85	0.32
Observer 3	0.67	0.92	0.12
Mean	0.89	0.87	0.26
SD	0.19	0.04	0.12

BBI: Bang Blinding Index; FCL: Far cortical locking; SD: Standard deviation.

both the blinded and unblinded arms of the study (Table 3). There was no difference in agreement between the blinded and unblinded groups.

DISCUSSION

This study demonstrates the success with which an uncomplicated and reproducible technique can blind radiographs of distal femur fractures. The blinding protocol successfully masked the surgeons to the type of locking screws implanted in the distal femur. Statistical analysis with the Bang Blinding Index and James Index scores confirmed the success of the blinding protocol: The interval estimates were all close to 0 and 1, respectively, representing near perfect blinding. The blinding protocol did not interfere with the surgeons' ability to evaluate radiographic healing at the fracture site. There was no difference in agreement for assessment of fracture union between the blinded and unblinded radiographs. Furthermore, moderate agreement of fracture healing using radiographs is consistent with previously published literature[17].

The protocol used to blind the type of hardware placed in the distal femur is based upon the previously published work by Karanicolas *et al*[18]. Karanicolas *et al*[18] identified three different methods of digitally concealing radiographic hardware in the femoral neck: The "blackout" technique involves the placement of an opaque polygon over the hardware, the "subtraction" technique involves digitally copying bone from another region and passing it over the hardware, and the "overlay" technique involves digitally copying one implant and passing it over a radiograph consisting of the other implant. Although all three techniques successfully

Table 3 Agreement scores for the assessment of fracture healing

Type of review	Kappa	95%CI
Blinded	0.376	0.253-0.515
Unblinded	0.353	0.252-0.453

blinded evaluators to the type of hardware implanted, the "blackout" technique resulted in the most difficulty in identifying hardware and required the least amount of time per radiograph. Although our study differs in the anatomic location of implanted hardware, focusing on the distal femur, our digital blinding protocol is similar to their most easily reproducible and effective method, the "blackout" technique.

Our results must be interpreted within the limitations of the study design. The number of fractures included in this study was limited, with radiographs from only 33 subjects being assessed. Furthermore, the quality and profile of the radiographs were not uniformly standardized, potentially affecting the radiographic assessment. Finally, we blinded the distal articular portion of the plate to mask subtle differences in the plate design of the various manufacturers. This may have impeded some assessments of fracture healing; however, this will not be necessary in the current RCT because all enrolled patients will receive the same locking plate.

Our study design has a number of strengths, including the separation of a randomized order of independent images into two PowerPoint presentation modules (unblinded and blinded) for individual surgeon assessment a minimum of 2 wk apart. All radiographs were evaluated for distal femur fracture union by the overall impression of trauma surgeons, which has been reported to be a moderately reliable method of assessing the quality of radiographic healing of femur fractures[19]. Additionally, our blinding protocol was successfully utilized without negative consequence on fracture healing assessment. A gathering of results and thorough statistical analysis was performed independently to test the criteria for effective blinding, further limiting detection bias. The James and Bang Blinding Indices were both used to limit the effect of "correct guessing"[5-7]. Finally, our blinding method is effective, efficient, and easily reproducible for future study designs.

Distal femur fractures are commonly treated by plate and screw constructs, but comparative efficacy research in this field is difficult to perform due to the practical limitation of blinding outcome assessments. This study provides not only a simple blinding technique for outcome evaluation but also a method to assess the success of blinding, both of which increase the validity of future trials which compare standard locking screws and FCL screws in the treatment of distal femur fractures. These techniques may be applied to investigations in other fields of orthopaedic surgery which involve evaluation of radiographs containing opaque implants.

COMMENTS

Background

Surgical fixation of distal femur fractures with locking plates and far cortical locking screw (FCL) technology may cause controlled, micro-motion at the fracture site to allow more reliable and uniform callus formation for predictable healing. However, no comprehensive studies comparing the effectiveness of FCL technology to standard locking screws in the treatment of distal femur fractures exist. The aim of this study was to devise and analyze a digital radiographic altering technique to conceal treatment allocation and blind outcome assessment of distal femur fracture fixation. This would allow unbiased comparison of distal femur fixation methods.

Research frontiers

Locking screws are necessary for surgical fixation of displaced extra-articular distal femur fractures. Standard locking or FCL screws may be used. However, there are few studies which directly compare, without bias, standard locking and FCL screws in effectively healing distal femur fractures.

Innovations and breakthroughs

The authors created and analyzed a digital blinding technique to objectively assess radiographic union of distal femur fractures treated with two types on plate-and-screw constructs. Statistical analysis with the Bang Blinding Index and James Index scores confirmed the success of the blinding protocol. There was no statistically significant difference in agreement for assessment of fracture union between the blinded and unblinded radiographs.

Applications

The results of this study suggest that a simple digital radiographic blinding technique may be a reliable method for objective, unbiased outcome evaluation in trials comparing the efficacy of standard locking screws and FCL screws in the treatment of distal femur fractures. These techniques may be applied to investigations in other fields of orthopaedic surgery which involve evaluation of radiographs containing opaque implants.

Terminology

Digitally altering radiographs with black boxes overlaying hardware, while preserving an exposed fracture site, is a technique to blind outcome assessors in evaluating distal femur fracture fixation.

Peer-review

This is an interesting study on the use of a digital protocol to blind outcome assessors in evaluating radiographic union of bone fractures after surgical fixation.

REFERENCES

1 **Henderson CE**, Kuhl LL, Fitzpatrick DC, Marsh JL. Locking plates for distal femur fractures: is there a problem with fracture healing? *J Orthop Trauma* 2011; **25** Suppl 1: S8-14 [PMID: 21248560 DOI: 10.1097/BOT.0b013e3182070127]

2 **Button G**, Wolinsky P, Hak D. Failure of less invasive stabilization system plates in the distal femur: a report of four cases. *J Orthop Trauma* 2004; **18**: 565-570 [PMID: 15475855 DOI: 10.1097/00005131-200409000-00015]

3 **Sommer C**, Babst R, Müller M, Hanson B. Locking compression plate loosening and plate breakage: a report of four cases. *J Orthop Trauma* 2004; **18**: 571-577 [PMID: 15475856 DOI: 10.1097/00005131-200409000-00016]

4 **Vallier HA**, Hennessey TA, Sontich JK, Patterson BM. Failure of LCP condylar plate fixation in the distal part of the femur. A report of six cases. *J Bone Joint Surg Am* 2006; **88**: 846-853 [PMID: 16595476 DOI: 10.2106/JBJS.E.00543]

5 **Henderson CE**, Lujan TJ, Kuhl LL, Bottlang M, Fitzpatrick DC, Marsh JL. 2010 mid-America Orthopaedic Association Physician in Training Award: healing complications are common after locked plating for distal femur fractures. *Clin Orthop Relat Res* 2011; **469**: 1757-1765 [PMID: 21424831 DOI: 10.1007/s11999-011-1870-6]

6 **Bottlang M**, Lesser M, Koerber J, Doornink J, von Rechenberg B, Augat P, Fitzpatrick DC, Madey SM, Marsh JL. Far cortical locking can improve healing of fractures stabilized with locking plates. *J Bone Joint Surg Am* 2010; **92**: 1652-1660 [PMID: 20595573 DOI: 10.2106/JBJS.I.01111]

7 **Gardner MJ**, Nork SE, Huber P, Krieg JC. Less rigid stable fracture fixation in osteoporotic bone using locked plates with near cortical slots. *Injury* 2010; **41**: 652-656 [PMID: 20236642 DOI: 10.1016/j.injury.2010.02.022]

8 **Doornink J**, Fitzpatrick DC, Madey SM, Bottlang M. Far cortical locking enables flexible fixation with periarticular locking plates. *J Orthop Trauma* 2011; **25** Suppl 1: S29-S34 [PMID: 21248557 DOI: 10.1097/BOT.0b013e3182070cda]

9 **Ries Z**, Hansen K, Bottlang M, Madey S, Fitzpatrick D, Marsh JL. Healing results of periprosthetic distal femur fractures treated with far cortical locking technology: a preliminary retrospective study. *Iowa Orthop J* 2013; **33**: 7-11 [PMID: 24027454]

10 **Poolman RW**, Struijs PA, Krips R, Sierevelt IN, Marti RK, Farrokhyar F, Bhandari M. Reporting of outcomes in orthopaedic randomized trials: does blinding of outcome assessors matter? *J Bone Joint Surg Am* 2007; **89**: 550-558 [PMID: 17332104 DOI: 10.2106/JBJS.F.00683]

11 **Dijkman BG**, Sprague S, Schemitsch EH, Bhandari M. When is a fracture healed? Radiographic and clinical criteria revisited. *J Orthop Trauma* 2010; **24** Suppl 1: S76-S80 [PMID: 20182242 DOI: 10.1097/BOT.0b013e3181ca3f97]

12 **Bang H**, Ni L, Davis CE. Assessment of blinding in clinical trials. *Control Clin Trials* 2004; **25**: 143-156 [PMID: 15020033 DOI: 10.1016/j.cct.2003.10.016]

13 A web-based repository of blinding data from controlled trials. [accessed 2015 Oct 24]. Available from: URL: http//www.blindi ngindex.org

14 **James KE**, Bloch DA, Lee KK, Kraemer HC, Fuller RK. An index for assessing blindness in a multi-centre clinical trial: disulfiram for alcohol cessation--a VA cooperative study. *Stat Med* 1996; **15**: 1421-1434 [PMID: 8841652 DOI: 10.1002/(SICI)1097-0258(19960715)15:13<1421::AID-SIM266>3.0.CO;2-H]

15 **Kolahi J**, Bang H, Park J. Towards a proposal for assessment of blinding success in clinical trials: up-to-date review. *Community Dent Oral Epidemiol* 2009; **37**: 477-484 [PMID: 19758415 DOI: 10.1111/j.1600-0528.2009.00494.x]

16 **Landis JR**, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; **33**: 159-174 [PMID: 843571 DOI: 10.2307/2529310]

17 **Bhandari M**, Guyatt GH, Swiontkowski MF, Tornetta P, Sprague S, Schemitsch EH. A lack of consensus in the assessment of fracture healing among orthopaedic surgeons. *J Orthop Trauma* 2002; **16**: 562-566 [PMID: 12352564 DOI: 10.1097/00005131-200209000-00004]

18 **Karanicolas PJ**, Bhandari M, Walter SD, Heels-Ansdell D, Guyatt GH. Radiographs of hip fractures were digitally altered to mask surgeons to the type of implant without compromising the reliability of quality ratings or making the rating process more difficult. *J Clin Epidemiol* 2009; **62**: 214-223.e1 [PMID: 18778914 DOI: 10.1016/j.jclinepi.2008.05.006]

19 **Karanicolas PJ**, Bhandari M, Walter SD, Heels-Ansdell D, Sanders D, Schemitsch E, Guyatt GH. Interobserver reliability of classification systems to rate the quality of femoral neck fracture reduction. *J Orthop Trauma* 2009; **23**: 408-412 [PMID: 19550226 DOI: 10.1097/BOT.0b013e31815ea017]

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ORIGINAL ARTICLE

Observational Study

Restoration of the joint geometry and outcome after stemless TESS shoulder arthroplasty

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Abstract

AIM

To evaluate the joint geometry and the clinical outcome of stemless, anatomical shoulder arthroplasty with the TESS system.

METHODS

Twenty-one shoulders with a mean follow-up 18 of months were included. On scaled digital radiographs the premorbid center of rotation (CoR) was assessed and compared to the CoR of the prosthesis by using the MediCAD® software. Additionally, the pre- and post-operative geometry of the CoR was assessed in relation to the glenoid, the acromion as well as to the proximal humerus. Radiological changes, such as radiolucencies, were also assessed. Clinical outcome was assessed with the Constant and DASH score.

RESULTS

Both, the Constant and DASH scores improved signifi-

cantly from 11% to 75% and from 70 to 30 points, $P < 0.01$ respectively. There were no significant differences regarding age, etiology, cemented or metal-backed glenoids, *etc*. ($P > 0.05$). The pre- and postoperative humeral offset, the lateral glenohumeral offset, the height of the CoR, the acromiohumeral distance as well as neck-shaft angle showed no significant changes ($P > 0.05$). The mean deviation of the CoR of the prosthesis from the anatomic center was 1.0 ± 2.8 mm. Three cases showed a medial deviation of more than 3 mm. These deviations of 5.1, 5.7 and 7.6 mm and were caused by an inaccurate humeral neck cut. These 3 patients showed a relatively poor outcome scoring.

CONCLUSION

TESS arthroplasty allows an anatomical joint reconstruction with a very good outcome. Outliers described in this study sensitize the surgeon for an accurate humeral neck cut.

Key words: Anatomical shoulder arthroplasty; Stemless; Omarthrosis; Total shoulder replacement; Joint geometry

Core tip: By using bony landmarks that are not altered by osteoarthritic changes, the premorbid center of rotation (CoR) was assessed in comparison to the postoperative one after TESS arthroplasty. Furthermore, joint geometry changes were assessed in relation to the glenoid, the acromion and the proximal humerus. Our data demonstrate a precise restoration of the joint and a very good clinical outcome. This study also describes outliers with a clinically relevant medialized CoR. Being caused by a slightly inaccurate humeral neck cut, this study might sensitize us that this osteotomy is a crucial step to ensure a good clinical outcome.

von Engelhardt LV, Manzke M, Breil-Wirth A, Filler TJ, Jerosch J. Restoration of the joint geometry and outcome after stemless TESS shoulder arthroplasty. *World J Orthop* 2017; 8(10): 790-797 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i10/790.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i10.790

INTRODUCTION

The traditional stemmed design of anatomical total shoulder arthroplasties is based on the principles of total hip replacement. Similarly to hip arthroplasty, stem-related complications, such as a bone loss secondary to stress shielding, humeral fractures, *etc*., are not so infrequent[1-4]. A further difficulty of a stemmed shoulder arthroplasty is that the restoration of the individual anatomy with its offset and center of rotation (CoR) is not always reached even with newer modular designs[5,6]. Another aspect is the revision surgery, where severe difficulties may arise during and after stem revision. A recent report describes complications such as a canal perforation, bone destructions and humerus fractures in around 50% of the cases[7]. Thus, avoiding stem-related complications, improved options to gain an anatomic reconstruction of the proximal humerus and preserving the bone stock for easier revisions are practical reasons why stemless designs have been introduced as an alternative to traditional designs. However, both patients and surgeons have high expectations regarding activity levels and return to sports following shoulder replacement surgery[8]. In regard to these data, the ongoing development of shoulder arthroplasty is a logical consequence.

The Total Evolutive Shoulder System (TESS, Biomet-Zimmer, Warsaw, IN, United States) uses different sizes of an impaction-implanted 6-armed corolla for a peripheral metaphyseal anchoring close to the cortical bone. This method of fixation is different to those with a much more central anchoring within the metaphysis, *e.g.*, the threaded central cage of the Arthrex Eclipse (Arthrex, Karlsfeld, Germany) or the Simpliciti system with a nucleus and 3 fins for central impaction (Wright Medical, formerly Tornier, Montbonnot, France)[9]. The principle of a peripheral metaphyseal anchoring might influence the reconstruction of the individual anatomy of the proximal humerus. The purpose of this study was to evaluate the restoration of the joint geometry as well as the clinical and radiographic outcome of the TESS system for anatomical shoulder arthroplasty.

MATERIALS AND METHODS

This study has been approved by the Ethical Committee of the University of Duesseldorf (Study No. 4426). All patients were operated at the Department of Orthopedics, Trauma Surgery and Sports Medicine of the Johanna-Etienne Hospital Neuss. Patients included in this study had an anatomical shoulder arthroplasty with the TESS system (TESS, Biomet-Zimmer, Warsaw, IN, United States). Pre-operative planning of the prosthesis components was performed in all cases on scaled anteroposterior digital radiographs using the MediCAD® software. After a deltopectoral approach, the elevation of the subscapularis tendon and the dislocation of the humeral head, the rotator cuff insertions, the humeral head and the anatomical neck were visualized. The cutting guide was held parallel to the anatomical neck and the inclination, retroversion and the height of the cut were adjusted by using these landmarks. After the saw cut, the size of the corolla broach was measured using the humeral sizing templates. Then the glenoid was prepared. A cemented all-polyethylene component or a metal-backed glenoid which allows a conversion to a reversed version were available. After broaching and impaction of the corolla into the metaphysis, different trial heads with a diameter of 41, 43, 45, 48, 50 and 52 mm with or without an offset were available. The subscapularis tendon was reattached to its origin by using transosseus Ethibond sutures. A biceps tenodesis was performed in patients with slender

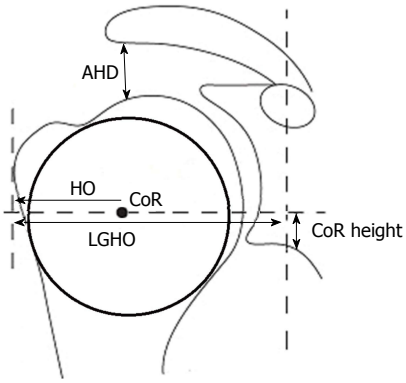

Figure 1 Assessment of the pre- and postoperative joint geometry. The best-fit circle with the premorbid center of rotation (CoR) is generated with bony landmarks which are not altered by osteoarthritic deformities: The lateral major tubercle border, the medial calcar at the inflection point and the medial edge of the greater tuberosity at the medial supraspinatus insertion. Further parameters were the acromiohumeral distance (AHD), the humeral offset (HO) as the distance between the CoR and the lateral major tubercle border, the lateral glenohumeral offset (LGHO) as the distance between the coracoid and the lateral major tubercle border, and the height of the center of rotation (height CoR) as the distance to the inferior glenoid.

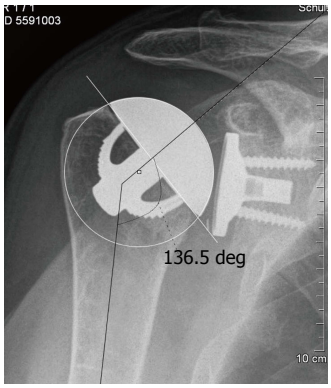

Figure 2 The postoperative center of rotation of the prosthesis shows no deviation compared to the the native one. The neck shaft angle is defined as the medial angle between the shaft axis and a perpendicular line to the preoperative anatomic neck or the base of the humeral head component.

overarms. Physiotherapy with restricted external rotation was started directly after the operation. Besides the exclusion of patients with rotator cuff tears or a defect arthropathy, there were no further exclusion criteria for the implantation of an anatomical TESS prosthesis. All patients received a non-stemmed version. The decision whether to use a stemmed or non-stemmed design was made intraoperatively depending on the metaphyseal bone quality. One patient with a humeral head necrosis had an incorrect positioning of the humeral component leading to an extensively elevated humeral offset. In this patient, a revision to a stemmed version was performed immediately. This case was considered a surgical failure. Another patient suffered a fall with a traumatic rotator cuff tear before the follow-up appointment. Both patients were excluded from this study. Finally, 21 shoulders in 19 patients (m/f = 10/9) with anatomic TESS shoulder prostheses were evaluated regarding their clinical and radiological outcome. The mean follow-up was 18 ± 9 mo. The average age at surgery was 66 years (range 32-79 years). In 10 cases, the dominant side was involved. 15 shoulders received a total arthroplasty with a metal-backed glenoid, four a cemented PE glenoid and three received a hemiarthroplasty. Indications were an osteoarthritis (n = 19) and a humeral head necrosis (n = 2). One necrosis was caused by a thalassaemia and one was posttraumatic after plate fixation of a proximal humeral fracture.

As recommended by Booker *et al*[10], the clinical outcome of the patients was assessed with the combination of two outcome scoring tools. The Disabilities of the Arm, Shoulder, Hand (DASH) score was used as a patient self-assessment measurement tool and the constant score (CS) as a clinically-based outcome measuring.

A standardized anterior-posterior- and an axillary view were performed preoperatively and at the follow-up appointment. Preoperative X-rays were scaled by using a 25 mm diameter ball marker. Postoperative X-rays were scaled using the size of the glenosphere. Measurements were performed with the MediCAD® software. The premorbid CoR was assessed with the best-fit circle method generated with three bony landmarks which are not altered by the osteoarthritic articular surface (Figures 1 and 2): The lateral cortex of the greater tuberosity, the medial calcar at the inflection point where the calcar meets the articular surface, and the medial edge of the greater tuberosity at the medial supraspinatus insertion[11]. This way, the deviation of the CoR of the implanted humeral head can be assessed in comparison to the native anatomic one. As described by Alolabio *et al*[12], a deviation of more than 3 mm was considered as being clinically significant. A medial deviation compared to the premorbid CoR was defined as an overstuffing (Figure 3), whereas a lateral deviation was defined as an understuffing (Figure 4). To further assess the geometry of the pre- and postoperative CoR in relation to the glenoid, the acromion as well as to the proximal humerus, further parameters were measured as described by Thomas *et al*[13] (Figure 1). Because some preoperative X-rays showed a poor positioning quality, four cases had to be excluded from the assessment of these pre- to postoperative geometry changes. The following differences of the pre- and postoperative values were calculated: The acromiohumeral distance (AHD) is defined as the shortest distance between the humerus and the acromion, the humeral offset (HO) as the distance between the CoR and the lateral border of the greater tuberosity, the lateral glenohumeral offset (LGHO) as the distance between the basis of the coracoid and the lateral border of the greater tuberosity and the height of the CoR regarding to the inferior border of the glenoid (CoR height)[13]. Pre- to post-operative neck shaft angles, defined as the medial angle between the shaft axis and a perpendicular line to the anatomic neck, were also

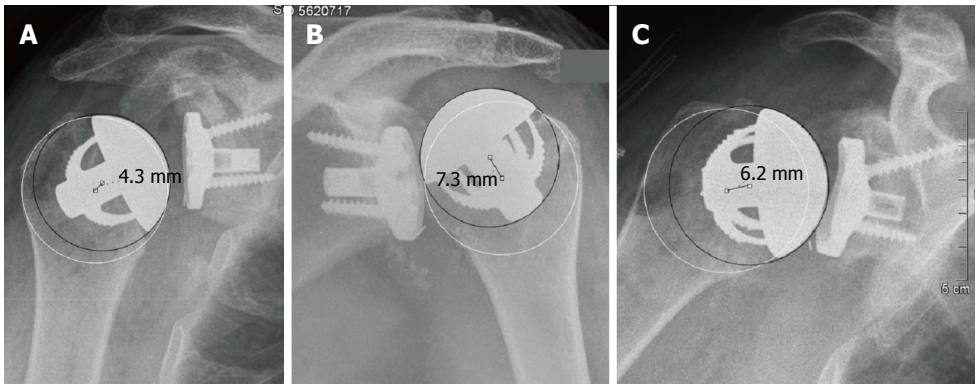

Figure 3 In three cases, a medial deviation of 4.3 (A), 7.3 (B) and 6.2 (C) mm was caused by an inaccurate humeral neck cut with a resection level which was to high in all cases. These findings were defined as an overstuffing: These patients showed a relatively poor outcome scoring.

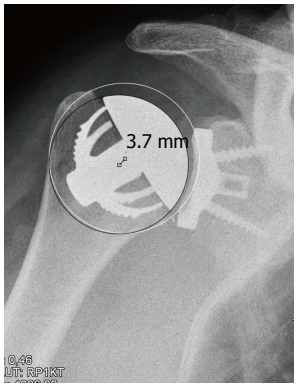

Figure 4 The center of rotation of the prosthesis was 3.7 mm lateral to the anatomical one and caused by a slightly too small humeral head size. This patient showed a relatively high postoperative constant score.

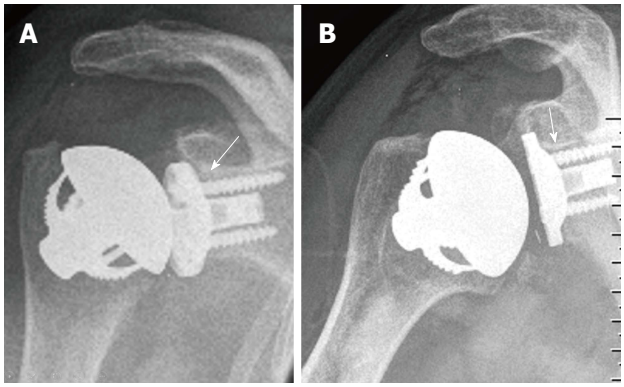

Figure 5 In two cases small radiolucent lines of a maximal thickness of 2 mm were noticed at the upper screw and behind the superior third of the baseplate (white arrows).

measured (Figure 2).

Statistical analysis

Statistical analysis were performed with SPSS Statistics software 22.0 (SPSS Inc., Chicago, Illinois, United States). The Wilcoxon test was used for the comparison between the pre- and postoperative data of the clinical scores, the Mann-Whitney-*U* test to compare the clinical scores between two different groups of the population and the Kruskal-Walis test to compare the clinical scores between several groups. The parametric Students *t*-test was used to compare pre- and post-operative geometrical measurements. The level of significance was set to alpha < 0.05. A statistical review was conducted by a biomedical statistician.

RESULTS

Functional outcome

The relative CS and DASH score improved significantly from a median of 11% ± 19% to 75% ± 26% and from 70 ± 22 points to 30 ± 19 points, $P < 0.01$, respectively. In the symptoms section of the DASH score, the patients improved from 24 ± 7 points to 12 ± 5 points ($P < 0.01$). In the function section, the score improved from 82 ± 19 points to 53 ± 18 points. There were no significant differences regarding age, sex, etiology groups, side of surgery, cemented or metal back glenoids treatment with a hemi- or total arthroplasty ($P > 0.05$).

Radiological results

With the best-fit circle method, the mean deviation of the CoR of the prosthesis from the anatomic CoR was 1.0 ± 2.8 mm. Of the 21 cases, four (19%) exhibited a deviation of more than 3 mm. Three cases (14%) showed an overstuffing with a medial deviation of 4.9, 6.2 and 7.6 mm. These patients showed a relatively poor outcome with a CS of 39, 41 and 51 points. The reasons for these deviations were a too high resection level (Figure 3A and C) and an inaccurate inclination of the humeral neck cut (Figure 3B). In the fourth case, the CoR of the humeral component was 3.7 mm lateral to the anatomical CoR. This deviation with an understuffing was caused by a slight undersizing of the humeral head (Figure 4). This patient showed a relatively high postoperative CS of 77 points.

The geometry of the CoR in relation to the glenoid, the acromion as well as to the proximal humerus, described by the AHD, HO, LGHO, the CoR height and the neck-shaft

Table 1 Pre- to post-operative geometrical joint parameters

	Mean	Median	SD	Minimum	Maximum
Pre-OP neck shaft angle	135.4°	135.3°	3.0°	131.6°	139.7°
Post-OP neck shaft angle	136.6°	133.8°	9.4°	119.3°	158.9°
Pre-OP AHD (mm)	6	6.5	3.1	2	13
Post-OP AHD (mm)	9.6	7	6.8	2	25
Pre-OP HO (mm)	25.3	25	2.8	22	32
Post-OP HO (mm)	25.2	25.5	4.2	18	36
Pre-OP LGHO (mm)	63.9	63	6	52	74
Post-OP LGHO (mm)	60.9	62.5	6.5	49	74
Pre-OP CoR height (mm)	17.2	17	6.3	8	28
Post-OP CoR height (mm)	17.7	17.5	6.5	5	29

All changes depicted were statistically not significant ($P > 0.05$). CoR: Center of rotation; AHD: Acromiohumeral distance; LGHO: Lateral glenohumeral offset.

angle, showed only slight differences between the pre- and post-operative measurements. By using the Students *t*-test all these minor changes of the geometry presented in Table 1 were not significant ($P > 0.05$).

Small radiolucent lines were seen in two of 15 cases with a metal-backed glenoid (13%) (Figure 5). In both cases it was above the superior part of the upper screw and behind the superior third of the baseplate. Both radiolucencies measured a maximal thickness of 2 mm. Further signs of a loosening were not noticed. At the last follow-up, both patients were pain-free and showed a CS of 75 and 52 points. At the cemented all-polyethylene glenoid radiolucent lines and/or osteolyses were not noticed. Radiolucent lines were also not detected around the 21 humeral components.

Complications

We observed three (14%) complications. One patient with a posttraumatic humeral head necrosis developed a frozen shoulder which was treated with an arthroscopic capsular release. The CS at the last follow-up was 48 points. One patient showed a partial brachial plexus lesion. He underwent an intensive rehabilitation. At the follow-up appointment, he recovered partially but still showed a CS of only 15 points. One of the patients with an overstuffed positioning of the humeral component (Figure 3B) suffered a cuff failure three months after the last follow-up appointment nine months postoperatively. This patient showed a CS of only 51 points. A revision to a reversed prosthesis was performed.

DISCUSSION

In this study, we had to document three complications which lead to an overall complication rate of 14%. Looking closer, one partial brachial plexus lesion was treated with an intensive rehabilitation, one shoulder arthrofibrosis was treated with an arthroscopic capsular release and one cuff failure needed a revision to a reversed prosthesis. In recent review articles, the overall complication rate lies between 4.2% and 15.2%[14,15]. In the literature, an arthrofibrosis after shoulder arthroplasty is rarely documented[15,16], whereas a rotator cuff failure is reported with incidences between 1.3% and 14%[17-19] and a *plexus* lesion with incidences up to 15%[20,21]. Taken together, our complication rate is high and lies in the upper range compared to the literature. In our opinion, these results are poor and interfere with the outcome scorings. This should be highlighted at the beginning of this discussion.

The humeral head varies individually in its retroversion, inclination as well as its medial and posterior offset[22,23]. Therefore, first and second generation stemmed arthroplasties did not meet the requirements to reach an exact restoration of the anatomy[22]. Even if newer modular stemmed designs have improved the adaptation to the individual anatomy, an exact anatomic match is not always achieved[5,6]. In a finite element analysis, Büchler and Farron[24] demonstrated the importance of an anatomically reconstructed humeral head to avoid an eccentric glenoid loading. In a study on patients with dissatisfaction after shoulder arthroplasty, main findings were substantially malpositioned components with or without loosened glenoids, stiffness and instabilities[25]. These clinical and biomechanical studies demonstrate the importance of an exact reconstruction of the joint geometry to achieve a good clinical outcome.

The impacted corolla of the TESS prosthesis provides a peripheral metaphyseal anchoring[9]. This relatively stable fixation close to the cortical bone might explain why findings indicating a loosening were not noticed. This is in accordance to previous studies where no radiolucent lines were noticed around the corolla of the TESS implant[26,27]. On the other hand, the peripheral metaphyseal anchoring with different sizes might influence the reconstruction of the joint geometry. Our hypothesis was that the stemless TESS system provides a reliable reconstruction of the individual anatomy with a good clinical outcome. In our series, the relative CS and DASH scores improved significantly with results that are in a similar range to previous reports on the anatomic TESS prosthesis[26-28]. Youderian *et al*[11] demonstrated that the premorbid CoR can be accurately predicted by a circle fitted from preserved nonarticular bony landmarks. We used this best-fit circle to measure the deviation of the center of the prosthesis to the premorbid CoR. Previous studies demonstrated that a malpositioning of 3 to 4 mm can affect the clinical outcome[5,12,29-31]. According to Alolabi *et al*[12] and Kadum *et al*[31], we defined a deviation of 3 mm as clinically relevant. In our series, 81% showed no deviation or a deviation of less than 3 mm. Another study also used the best-fit circle method to assess the restoration of the CoR with different anatomical prosthesis types. This study demonstrated no deviation or a deviation of less than 3 mm with lower rates lying between 34.9% and 68.8%. The mean deviation between the premorbid CoR and the center of the prosthesis measured between 2.5 and 3.8 mm which is two to four times higher compared to our study[12]. However, even if

our results are relatively good, we have to notice that we were not able to demonstrate a 100% rate of an exact restoration of the CoR. Thus, four patients (19%) showed a deviation of more than 3 mm. We hypothesized that a significant deviation might lead to a relatively poor clinical outcome. One patient showed an understuffing with a lateral deviation of the implant CoR which was caused by a relatively small humeral component. Showing a relatively high CS of 77 points, this deviation did not lead to a poor clinical outcome. Three patients showed an overstuffing caused by an inaccurate resection level for the humeral neck cut. With 51, 39 and 41 points, these patients showed a relatively poor CS. Because the inaccurate humeral neck cut lead to a clinically relevant overstuffing, these cases have to be characterized as avoidable failures during surgery. Besides a poor clinical outcome, one of these three patients suffered a cuff failure after the last follow-up, requiring a revision to a reversed arthroplasty. Showing an incidence of 11%, a recent systematic review suggests that these cuff tears following total shoulder arthroplasty may be more common than previously thought[19]. Maybe these data should sensitize the surgeon to be aware of an exact identification of anatomical landmarks for a correct humeral neck cut. Besides a digital scaled preoperative planning, the use of the best-fit circle method might support the surgeon's ability to find the right resection level and to choose the correct head size. In some cases, osteophytes as bony landmarks might be helpful to mark the correct resection level and angle during surgery. In some cases, an intraoperative fluoroscopy, where the best-fit circle method can be used again, might provide an increased security to achieve an exact humeral head position and size. Especially in cases with advanced deformities or in cases where the achievement of an optimal soft tissue balancing of the implant is not completely satisfactory, such additional intraoperative X-rays might be helpful.

The pre- and post-operative AHD, HO, LGHO and the CoR height were measured as described by Thomas *et al*[13]. Table 1 depicts that these measurements, including the pre- and postoperative neck shaft angles, showed only minimal changes. Thus, the geometry of the CoR in relation to the glenoid, the proximal humerus and the acromion does not seem to be altered. Regarding these data, the TESS system allows a reliable restoration of the individual joint geometry. This might explain the relatively good clinical outcome of the TESS prosthesis described in our series as well as in previous studies with follow-up times ranging from 6 to 45 mo[26-28,32-34].

At the cemented all-polyethylene glenoid components, radiolucent lines were not noticed. This is similar to previous studies on pegged designs, where radiolucent lines were not detected[35,36]. At the metal-backed glenoids, small radiolucent lines were seen in two cases (2/15, 13%) behind the superior third of the baseplate and above the upper screw (Figure 5). Further signs of a loosening were not noticed. In previous studies with newer metal-backed glenoids, radiolucencies were also noticed in 7%[37], 10%[38,39] and 23%[40] of the cases. The TESS system has a central convex section in both the polyethylene and the metal-backed component. Compared to those with a flat-backed glenoid, this design showed lower distraction forces in biomechanical testings[41] as well as a lower presence and progression of radiolucencies[40]. Moreover, the metal-backed glenoid baseplate of the TESS system has a double coating with porous titanium and hydroxyapatite. Besides the design chracteristics, these material features have also been shown not to be as critical as those with older flat shaped, uncoated metal-backed glenoid components[40,42,43]. These features of the TESS system might explain why radiolucencies were noticed in our series in only two cases of metal-backed components and in none of the cases with a polyethylene glenoid component.

We acknowledge that our study has several limitations. There was no randomized control group treated with a conventional stemmed prosthesis to compare our results. Further limitations of this study are the short mean follow-up of 18 mo and the small number of 21 shoulders being evaluated. The study presented here was a necessary first step in exploring our first experiences with the TESS system, which seems to provide reasonable advantages. Therefore, the outcome scorings and the assessment of complications should be regarded cautiously. Larger studies with longer follow-up intervals are needed to assess the sustainability of the clinical outcome as well as long-term changes of the joint geometry. For this reason we recently applied for ethical approval of a long term study on the TESS prosthesis.

In conclusion, the stemless shoulder arthroplasty using the TESS system allows a reliable reconstruction of the individual anatomy with an excellent clinical outcome. On the other hand, we noticed three cases with a slight but clinically relevant overstuffed reconstruction of the CoR caused by an inaccurate humeral neck cut. This should increase our awareness. An optimized bone cut is a crucial step to ensure a good clinical outcome during surgery.

COMMENTS

Background

An exact reconstruction of the individual anatomy of the shoulder joint is vital to reach a good clinical outcome of anatomical shoulder replacement. The restoration of the joint geometry as well as the clinical and radiographic outcome of stemless, peripheral metaphyseal anchored shoulder arthroplasty by using the TESS system is evaluated.

Research frontiers

Besides modular prosthesis designs, current developments in shoulder arthroplasty include smaller, bone sparing components. Research is needed to interpret advantages, pitfalls and the clinical efficacy.

Innovations and breakthroughs

Stemless TESS shoulder arthroplasty allows an exact reconstruction of the premorbid center of rotation (CoR). Additional parameters, such as the relation between the pre- and postoperative CoR and the glenoid, the acromion as

well as the proximal humerus are reconstructed. Thus, the data demonstrate a precise restoration of the joint geometry with a good clinical outcome. A loosening of the metaphyseal anchoring was not detected. Similarly to previous studies, this article also demonstrates that even a slightly inaccurate humeral neck cut can cause a clinically relevant medialized CoR.

Application

Surgical precision work and a highly modular prosthesis system with variable sizes is needed to ensure a good clinical outcome. The use of the best-fit circle method during the preoperative planning might be helpful to find the right resection level and to choose the correct head size. During surgery, an exact identification of anatomical landmarks is vital to find the correct level and angle for the humeral neck cut. In some cases, intraoperative fluoroscopy might be an additional support.

Terminology

TESS: Total Evolutive Shoulder System; DASH score: Disabilities of the Arm, Shoulder and Hand score; CS: Constant score; CoR: Center of rotation; AHD: Acromiohumeral distance; HO: Humeral offset; LGHO: Lateral glenohumeral offset.

Peer-review

It is a well-written manuscript with information useful to the readers of the journal.

REFERENCES

1 **Nagels J**, Stokdijk M, Rozing PM. Stress shielding and bone resorption in shoulder arthroplasty. *J Shoulder Elbow Surg* 2003; **12**: 35-39 [PMID: 12610484 DOI: 10.1067/mse.2003.22]

2 **Raiss P**, Edwards TB, Deutsch A, Shah A, Bruckner T, Loew M, Boileau P, Walch G. Radiographic changes around humeral components in shoulder arthroplasty. *J Bone Joint Surg Am* 2014; **96**: e54 [PMID: 24695931 DOI: 10.2106/JBJS.M.00378]

3 **Rockwood CA Jr**, Wirth MA. Observation on retrieved Hylamer glenoids in shoulder arthroplasty: problems associated with sterilization by gamma irradiation in air. *J Shoulder Elbow Surg* 2002; **11**: 191-197 [PMID: 11988733 DOI: 10.1067/mse.2002.121480]

4 **Aldinger PR**, Raiss P, Rickert M, Loew M. Complications in shoulder arthroplasty: an analysis of 485 cases. *Int Orthop* 2010; **34**: 517-524 [PMID: 19396634 DOI: 10.1007/s00264-009-0780-7]

5 **Nyffeler RW**, Sheikh R, Jacob HA, Gerber C. Influence of humeral prosthesis height on biomechanics of glenohumeral abduction. An in vitro study. *J Bone Joint Surg Am* 2004; **86-A**: 575-580 [PMID: 14996885 DOI: 10.2106/00004623-200403000-00017]

6 **Pearl ML**, Kurutz S. Geometric analysis of commonly used prosthetic systems for proximal humeral replacement. *J Bone Joint Surg Am* 1999; **81**: 660-671 [PMID: 10360694 DOI: 10.2106/00004623-199905000-00007]

7 **Antoni M**, Barthoulot M, Kempf JF, Clavert P. Revisions of total shoulder arthroplasty: Clinical results and complications of various modalities. *Orthop Traumatol Surg Res* 2016; **102**: 297-303 [PMID: 26969208 DOI: 10.1016/j.otsr.2016.01.009]

8 **Johnson CC**, Johnson DJ, Liu JN, Dines JS, Dines DM, Gulotta LV, Garcia GH. Return to sports after shoulder arthroplasty. *World J Orthop* 2016; **7**: 519-526 [PMID: 27672564 DOI: 10.5312/wjo.v7.i9.519]

9 **Churchill RS**, Athwal GS. Stemless shoulder arthroplasty-current results and designs. *Curr Rev Musculoskelet Med* 2016; **9**: 10-16 [PMID: 26809955 DOI: 10.1007/s12178-016-9320-4]

10 **Booker S**, Alfahad N, Scott M, Gooding B, Wallace WA. Use of scoring systems for assessing and reporting the outcome results from shoulder surgery and arthroplasty. *World J Orthop* 2015; **6**: 244-251 [PMID: 25793164 DOI: 10.5312/wjo.v6.i2.244]

11 **Youderian AR**, Ricchetti ET, Drews M, Iannotti JP. Determination of humeral head size in anatomic shoulder replacement for glenohumeral osteoarthritis. *J Shoulder Elbow Surg* 2014; **23**: 955-963 [PMID: 24321169 DOI: 10.1016/j.jse.2013.09.005]

12 **Alolabi B**, Youderian AR, Napolitano L, Szerlip BW, Evans PJ, Nowinski RJ, Ricchetti ET, Iannotti JP. Radiographic assessment of prosthetic humeral head size after anatomic shoulder arthroplasty. *J Shoulder Elbow Surg* 2014; **23**: 1740-1746 [PMID: 24856628 DOI: 10.1016/j.jse.2014.02.013]

13 **Thomas SR**, Sforza G, Levy O, Copeland SA. Geometrical analysis of Copeland surface replacement shoulder arthroplasty in relation to normal anatomy. *J Shoulder Elbow Surg* 2005; **14**: 186-192 [PMID: 15789013 DOI: 10.1016/j.jse.2004.06.013]

14 **Bohsali KI**, Bois AJ, Wirth MA. Complications of Shoulder Arthroplasty. *J Bone Joint Surg Am* 2017; **99**: 256-269 [PMID: 28145957 DOI: 10.2106/JBJS.16.00935]

15 **Roberson TA**, Bentley JC, Griscom JT, Kissenberth MJ, Tolan SJ, Hawkins RJ, Tokish JM. Outcomes of total shoulder arthroplasty in patients younger than 65 years: a systematic review. *J Shoulder Elbow Surg* 2017; **26**: 1298-1306 [PMID: 28209327 DOI: 10.1016/j.jse.2016.12.069]

16 **Harmer L**, Throckmorton T, Sperling JW. Total shoulder arthroplasty: are the humeral components getting shorter? *Curr Rev Musculoskelet Med* 2016; **9**: 17-22 [PMID: 26801933 DOI: 10.1007/s12178-016-9313-3]

17 **Norris TR**, Iannotti JP. Functional outcome after shoulder arthroplasty for primary osteoarthritis: a multicenter study. *J Shoulder Elbow Surg* 2002; **11**: 130-135 [PMID: 11988723 DOI: 10.1067/mse.2002.121146]

18 **Bohsali KI**, Wirth MA, Rockwood CA Jr. Complications of total shoulder arthroplasty. *J Bone Joint Surg Am* 2006; **88**: 2279-2292 [PMID: 17015609 DOI: 10.2106/JBJS.F.00125]

19 **Levy DM**, Abrams GD, Harris JD, Bach BR Jr, Nicholson GP, Romeo AA. Rotator cuff tears after total shoulder arthroplasty in primary osteoarthritis: A systematic review. *Int J Shoulder Surg* 2016; **10**: 78-84 [PMID: 27186060 DOI: 10.4103/0973-6042.180720]

20 **Lynch NM**, Cofield RH, Silbert PL, Hermann RC. Neurologic complications after total shoulder arthroplasty. *J Shoulder Elbow Surg* 1996; **5**: 53-61 [PMID: 8919443 DOI: 10.1016/S1058-2746(96)80031-0]

21 **Pape G**, Raiss P, Aldinger PR, Loew M. [Comparison of short-term results after CUP prosthesis with cemented glenoid components and total shoulder arthroplasty: a matched-pair analysis]. *Z Orthop Unfall* 2010; **148**: 674-679 [PMID: 20135592 DOI: 10.1055/s-0029-1186202]

22 **Roberts SN**, Foley AP, Swallow HM, Wallace WA, Coughlan DP. The geometry of the humeral head and the design of prostheses. *J Bone Joint Surg Br* 1991; **73**: 647-650 [PMID: 2071652 DOI: 10.1016/j.jse.2012.01.027]

23 **Boileau P**, Walch G. The three-dimensional geometry of the proximal humerus. Implications for surgical technique and prosthetic design. *J Bone Joint Surg Br* 1997; **79**: 857-865 [PMID: 9331050 DOI: 10.1007/978-3-642-58365-0_8]

24 **Büchler P**, Farron A. Benefits of an anatomical reconstruction of the humeral head during shoulder arthroplasty: a finite element analysis. *Clin Biomech* (Bristol, Avon) 2004; **19**: 16-23 [PMID: 14659925 DOI: 10.1016/j.clinbiomech.2003.09.009]

25 **Hasan SS**, Leith JM, Campbell B, Kapil R, Smith KL, Matsen FA 3rd. Characteristics of unsatisfactory shoulder arthroplasties. *J Shoulder Elbow Surg* 2002; **11**: 431-441 [PMID: 12378161 DOI: 10.1067/mse.2002.125806]

26 **Berth A**, Pap G. Stemless shoulder prosthesis versus conventional anatomic shoulder prosthesis in patients with osteoarthritis: a comparison of the functional outcome after a minimum of two years follow-up. *J Orthop Traumatol* 2013; **14**: 31-37 [PMID: 23138538 DOI: 10.1007/s10195-012-0216-9]

27 **Huguet D**, DeClercq G, Rio B, Teissier J, Zipoli B; TESS Group. Results of a new stemless shoulder prosthesis: radiologic proof of maintained fixation and stability after a minimum of three years' follow-up. *J Shoulder Elbow Surg* 2010; **19**: 847-852 [PMID: 20303799 DOI: 10.1016/j.jse.2009.12.009]

28 **Razmjou H**, Holtby R, Christakis M, Axelrod T, Richards R. Impact of prosthetic design on clinical and radiologic outcomes of total shoulder arthroplasty: a prospective study. *J Shoulder Elbow Surg* 2013; **22**: 206-214 [PMID: 22819578 DOI: 10.1016/j.jse.2012.04.016]

29 **Williams GR Jr**, Wong KL, Pepe MD, Tan V, Silverberg D, Ramsey

ML, Karduna A, Iannotti JP. The effect of articular malposition after total shoulder arthroplasty on glenohumeral translations, range of motion, and subacromial impingement. *J Shoulder Elbow Surg* 2001; **10**: 399-409 [PMID: 11641695 DOI: 10.1067/mse.2001.116871]

30 **Harryman DT**, Sidles JA, Harris SL, Lippitt SB, Matsen FA 3rd. The effect of articular conformity and the size of the humeral head component on laxity and motion after glenohumeral arthroplasty. A study in cadavera. *J Bone Joint Surg Am* 1995; **77**: 555-563 [PMID: 7713972 DOI: 10.2106/00004623-199504000-00008]

31 **Kadum B**, Hassany H, Wadsten M, Sayed-Noor A, Sjödén G. Geometrical analysis of stemless shoulder arthroplasty: a radiological study of seventy TESS total shoulder prostheses. *Int Orthop* 2016; **40**: 751-758 [PMID: 26257276 DOI: 10.1007/s00264-015-2935-z]

32 **Kadum B**, Mukka S, Englund E, Sayed-Noor A, Sjödén G. Clinical and radiological outcome of the Total Evolutive Shoulder System (TESS®) reverse shoulder arthroplasty: a prospective comparative non-randomised study. *Int Orthop* 2014; **38**: 1001-1006 [PMID: 24458592 DOI: 10.1007/s00264-013-2277-7]

33 **Castricini R**, De Benedetto M, Pirani P, Panfoli N, Pace N. Shoulder hemiarthroplasty for fractures of the proximal humerus. *Musculoskelet Surg* 2011; **95** Suppl 1: S49-S54 [PMID: 21503723 DOI: 10.1007/s12306-011-0112-0]

34 **Hawi N**, Tauber M, Messina MJ, Habermeyer P, Martetschläger F. Anatomic stemless shoulder arthroplasty and related outcomes: a systematic review. *BMC Musculoskelet Disord* 2016; **17**: 376 [PMID: 27577859 DOI: 10.1186/s12891-016-1235-0]

35 **Everding NG**, Levy JC, Formaini NT, Blum S, Gil CC, Verde K. Observation of initial postoperative radiolucent lines using a modern pegged-glenoid design. *Int J Shoulder Surg* 2016; **10**: 67-71 [PMID: 27186058 DOI: 10.4103/0973-6042.180718]

36 **Edwards TB**, Labriola JE, Stanley RJ, O'Connor DP, Elkousy HA, Gartsman GM. Radiographic comparison of pegged and keeled glenoid components using modern cementing techniques: a prospective randomized study. *J Shoulder Elbow Surg* 2010; **19**: 251-257 [PMID: 20185072 DOI: 10.1016/j.jse.2009.10.013]

37 **Panti JP**, Tan S, Kuo W, Fung S, Walker K, Duff J. Clinical and radiologic outcomes of the second-generation Trabecular Metal™ glenoid for total shoulder replacements after 2-6 years follow-up. *Arch Orthop Trauma Surg* 2016; **136**: 1637-1645 [PMID: 27566616 DOI: 10.1007/s00402-016-2562-1]

38 **Uschok S**, Magosch P, Moe M, Lichtenberg S, Habermeyer P. Is the stemless humeral head replacement clinically and radiographically a secure equivalent to standard stem humeral head replacement in the long-term follow-up? A prospective randomized trial. *J Shoulder Elbow Surg* 2017; **26**: 225-232 [PMID: 27856267 DOI: 10.1016/j.jse.2016.09.001]

39 **Budge MD**, Nolan EM, Heisey MH, Baker K, Wiater JM. Results of total shoulder arthroplasty with a monoblock porous tantalum glenoid component: a prospective minimum 2-year follow-up study. *J Shoulder Elbow Surg* 2013; **22**: 535-541 [PMID: 22959525 DOI: 10.1016/j.jse.2012.06.001]

40 **Castagna A**, Randelli M, Garofalo R, Maradei L, Giardella A, Borroni M. Mid-term results of a metal-backed glenoid component in total shoulder replacement. *J Bone Joint Surg Br* 2010; **92**: 1410-1415 [PMID: 20884980 DOI: 10.1302/0301-620X.92B10.23578]

41 **Anglin C**, Wyss UP, Pichora DR. Mechanical testing of shoulder prostheses and recommendations for glenoid design. *J Shoulder Elbow Surg* 2000; **9**: 323-331 [PMID: 10979530 DOI: 10.1067/mse.2000.105451]

42 **Boileau P**, Avidor C, Krishnan SG, Walch G, Kempf JF, Molé D. Cemented polyethylene versus uncemented metal-backed glenoid components in total shoulder arthroplasty: a prospective, double-blind, randomized study. *J Shoulder Elbow Surg* 2002; **11**: 351-359 [PMID: 12195253 DOI: 10.1067/mse.2002.125807]

43 **Taunton MJ**, McIntosh AL, Sperling JW, Cofield RH. Total shoulder arthroplasty with a metal-backed, bone-ingrowth glenoid component. Medium to long-term results. *J Bone Joint Surg Am* 2008; **90**: 2180-2188 [PMID: 18829916 DOI: 10.2106/JBJS.G.00966]

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SYSTEMATIC REVIEWS

Scaffolds based therapy for osteochondral lesions of the talus: A systematic review

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Abstract

AIM

To clarify the effectiveness of scaffold-based therapy for osteochondral lesions of the talus (OLT).

METHODS

A systematic search of MEDLINE and EMBASE databases was performed during August 2016 and updated in January 2017. Included studies were evaluated with regard to the level of evidence (LOE) and quality of evidence (QOE) using the Modified Coleman Methodology Score. Variable reporting outcome data, clinical outcomes, and the percentage of patients who returned to sport at previous level were also evaluated.

RESULTS

Twenty-eight studies for a total of 897 ankles were included; 96% were either LOE Ⅲ or Ⅳ. Studies were designated as either of poor or fair quality. There were 30 treatment groups reporting six different scaffold repair techniques: 13 matrix-induced autologous chondrocyte transplantation (MACT), nine bone marrow derived cell transplantation (BMDCT), four autologous matrix-induced chondrogeneis (AMIC), and four studies of other techniques. The categories of general demographics (93%) and patient-reported outcome data (85%) were well reported. Study design (73%), imaging data (73%), clinical variables (49%), and patient history (30%) were also included. The weighted mean American Orthopaedic Foot and Ankle Society (AOFAS) score at final follow-up was: 86.7 in MACT, 88.2 in BMDCT, and 82.3 in AMIC. Eight studies reported that a weighted mean of 68.3% of

patients returned to a previous level of sport activity.

CONCLUSION

Scaffold-based therapy for OLT may produce favorable clinical outcomes, but low LOE, poor QOE, and variability of the data have confounded the effectiveness of this treatment.

Key words: Scaffold; Ankle; Talar osteochondral lesion; Systematic review; Cartilage

Core tip: This systematic review demonstrated that scaffold-based therapy for lesions of the talus (OLT) may produce favorable clinical outcomes. However, 96% of included studies were classified into the category of poor level of evidence and no papers were of good methodological quality. Therefore, careful attention should be paid when evaluating scaffold-based therapy for OLT. In addition, large variability and underreporting of clinical data between studies made it difficult to reliably compare the results. Further well-designed studies are necessary to determine the effectiveness of scaffold-based therapy for OLT, especially when compared to the available traditional treatments.

Shimozono Y, Yasui Y, Ross AW, Miyamoto W, Kennedy JG. Scaffolds based therapy for osteochondral lesions of the talus: A systematic review. *World J Orthop* 2017; 8(10): 798-808 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i10/798.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i10.798

INTRODUCTION

Numerous surgical treatment strategies for osteochondral lesions of the talus (OLT) have been proposed, but a universally ideal treatment has yet to be established[1,2]. The operative treatment for OLT can be divided into two broad categories: Reparative and replacement procedures. Reparative procedures aim to regenerate tissue with biomechanical properties similar to normal hyaline cartilage. Bone marrow stimulation (BMS) is the most common reparative procedure, which stimulates mesenchymal stem cell proliferation and promotes fibrous cartilage repair tissue at the defect site. However, the fibrous cartilage repair tissue has different biological and mechanical properties compared to native hyaline cartilage and is likely to degenerate over time[3]. Autologous chondrocyte implantation (ACI) is another reparative procedure that attempts to regenerate damaged cartilage with more hyaline-like repair tissue, but this procedure has the disadvantage of the need for a two-staged intervention, which increases both cost and the potential for morbidity[4].

Recently, tissue-engineering approaches using various types of bioavailable scaffolds has emerged with greater potential for cellular differentiation and maturation. The templates are typically seeded with elements selected to improve the quality of reparative cartilage and include stem cells and growth factors. Matrix-induced autologous chondrocyte transplantation (MACT) is a second-generation ACI technique, which uses a type Ⅰ/Ⅲ bilayer collagen membrane seeded with cultured autologous chondrocytes. However, MACT also requires a two stage procedure[5,6]. Autologous matrix-induced chondrogenesis (AMIC) is a one-step scaffold-based therapy that combines bone marrow stimulation (BMS) with the use of a porcine collagen Ⅰ/Ⅲ matrix scaffold[7]. Bone marrow-derived cell transplantation (BMDCT) is also a one-step procedure and is a combination of concentrated bone marrow aspirate and scaffold material[8].

Scaffold-based therapy for OLT offers alternative reparative procedures and is quickly becoming more popular as data supporting clinical efficacy increases[9]. However, no consensus has been reached regarding the effectiveness of scaffold-based therapy on OLT to date.

The purpose of the current systematic review was to clarify the effectiveness of scaffold-based therapy for OLT based on available clinical evidence.

MATERIALS AND METHODS

Search strategy

Two independent reviewers performed a systematic review of the databases PubMed/MEDLINE and EMBASE in January 2017 based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[10].

The combination of search terms were: (cartilage OR cartilage injury OR cartilage damage OR cartilage repair OR cartilage defect OR osteochondral lesion OR osteochondral dissecans OR osteochondral defect OR osteochondral injury OR osteochondral fracture OR osteochondritis dissecans) AND (ankle OR talus OR tibia OR talocrural joint) AND (scaffold OR scaffold-based repair OR matrix-assisted chondrocyte implantation OR cartilage regeneration OR osteochondral repair). The reference list of all articles and relevant studies were also scanned for additional articles potentially not identified through our electronic search alone.

The inclusion and exclusion criteria are shown in the Table 1. No time limit was given to publication date.

The titles and abstracts were reviewed by applying the aforementioned criteria, and the full text of potentially relevant studies was then selected. Scaffold-based therapy for OLT was defined as operative treatment using any scaffolds for OLT.

Differences between reviewers were discussed until agreement was achieved, and the senior author was consulted in the event of persistent disagreement.

Assessment of level of evidence

Two independent investigators reviewed each study and the LOE was determined using previously published

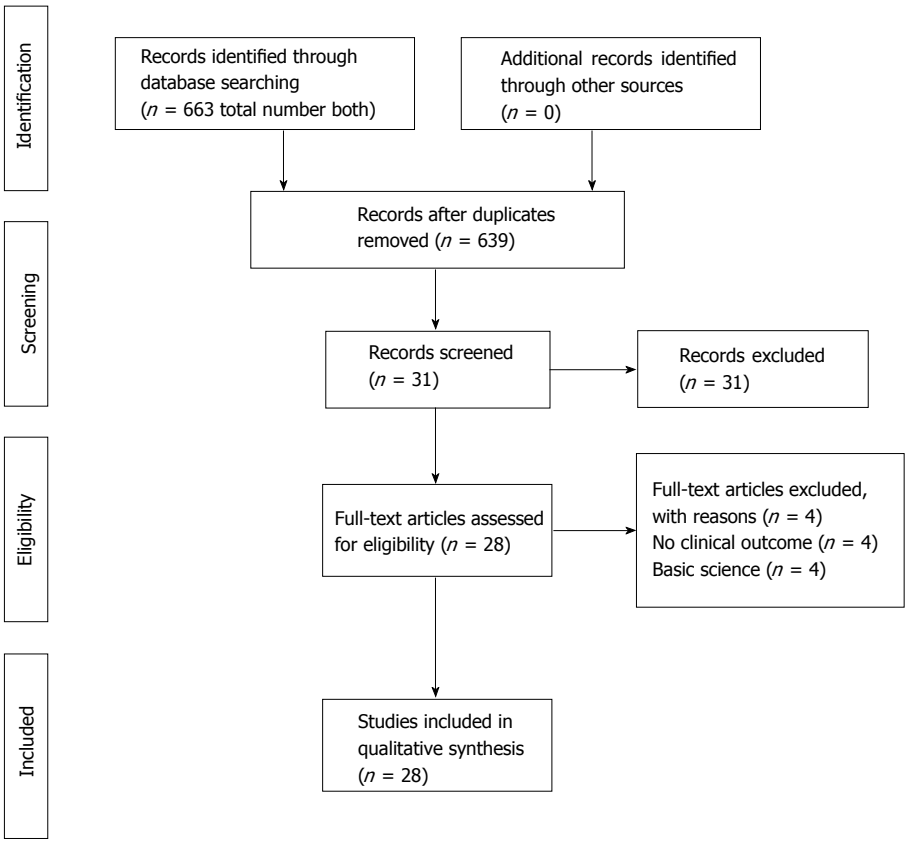

Figure 1 PRISMA flowchart outlining the systematic review.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	
	Therapeutic clinical studies evaluating the effect of scaffolds for ankle cartilage repair
	All patients included had > 6-mo follow-up
	Published in a peer-reviewed journal
	Published in English
	Full-text version available
Exclusion criteria	
	Review articles
	Case reports
	Technique articles
	Cadaveric studies
	Animal studies
	In vivo studies

criteria[11].

Assessment of methodological quality of evidence

Two independent investigators evaluated the methodological quality of evidence (QOE) of the included studies using the Modified Coleman Methodology Score (MCMS) (Table 2)[12,13]. Instances of discrepancy were resolved by consensus and if any disagreement persisted, a senior author was consulted and a consensus was reached. Excellent studies were considered those that scored 85 to 100 points; good studies scored 70 to 84 points; fair studies scored 55 to 69 points, and poor studies scored less than 55 points[14].

Data extraction and analysis

Two reviewers independently extracted data from each study and assessed variable reporting of outcome data using parameters of previously published criteria[15]. In addition, clinical outcomes and the percentage of patients who returned to sport at previous level were evaluated.

Statistical analysis

All statistical analysis was performed using a commercially available statistical software package (SAS 9.3; SAS Institute, Inc., Cary, NC, United States). Descriptive statistics were calculated for each study and parameters analyzed. For each variable, the number and percentage of studies that reported the variable was calculated. Variables were reported as weighted average ± weighted standard deviation where applicable.

RESULTS

After full text review, 28 clinical studies for a total of 897 ankles were identified for inclusion in the current study (Figure 1)[4-8,16-38]. The weighted mean follow-up was 37.7 (range 6-87) mo, with only three studies reporting a follow-up time of greater than five years[20,22,24].

Of the 28 clinical studies, there were 30 treatment groups, including six different scaffold-based therapies: 13 MACT[5,6,16-26], nine BMDCT[4,8,26-31], four AMIC[7,32-34], two cartilage extracellular matrix[35,36], one autologous

Table 2 Modified Coleman Methodology Score

		Score
Part A: Only 1 score to be given for each section		
Number of study patients		
	> 60	10
	41-60	7
	20-40	4
	< 20, not stated	0
Mean follow-up (mo)		
	> 24	5
	12-24	2
	< 12, not stated or unclear	0
Number of different surgical procedures included in each reported outcome		
	1	10
	> 1, but > 90% of patients undergoing the 1 procedure	7
	Not stated, unclear, or < 90% of subjects undergoing the 1 procedure	0
Type of study		
	Randomized controlled trial	15
	Prospective cohort study	10
	Retrospective cohort study	0
Diagnostic certainty (MRI)		
	In all	5
	In > 80%	3
	In < 80%	0
Description of surgical procedure given		
	Adequate (technique stated and necessary details of that type of procedure provided)	5
	Fair (technique only stated without elaboration)	3
	Inadequate, not stated, or unclear	0
Description of postoperative rehabilitation		
	Well described (ROM, WB, and sport)	10
	Not adequately described (2 items between ROM, WB, and sport)	5
	Protocol not reported	0
Part B: Scores may be given for each option in each of the 3 sections if applicable		
Outcome criteria		
	Outcome measures clearly defined	2
	Timing of outcome assessment clearly stated (*e.g.*, at best outcome after surgery or follow-up)	2
	Objective, subjective, and imaging criteria	6
	2 items between objective, subjective, and imaging criteria	4
	Objective, subjective, or radiological criteria	2
Procedure for assessing outcomes		
	Patients recruited (results not taken from surgeons' files)	5
	Investigator independent of surgeon	4
	Written assessment	3
	Completion of assessment by patinets themselves with minimal investigator assistance	3
Description of patient selection process		
	Selection criteria reported and unbiased	5
	Recruitment rate reported	
	> 80%	5
	< 80%	3
	Eligible patients not included in study satisfactorily accounted for or 100% recruitment	5

collagen-induced chondrogenesis (ACIC)[37], and one cell free scaffold therapy[38]. All included studies of scaffold-based therapy were summarized in Table 3. Patient demographics and clinical characteristics of each procedure are shown in Table 4.

LOE

There was one (3.6%) study of LOE Ⅱ[30], three studies (10.7%) of LOE Ⅲ[4,24,26], and 24 studies (85.7%) of LOE Ⅳ[5-8,16-23,25,27-29,31-38] (Table 5) according to established criteria[11]. No study of LOE I was reported. The further data of LOE in each procedure group was shown in Table 5.

QOE

The weighted mean MCMS of the overall population of studies was 49.3 ± 10.0 out of a possible 100 points. There were seven studies (25%) of fair

Table 3 Studies of two-step and one-step procedures for ankle scaffold-based repair

Procedure	Product	Scientific publication	Type of study	LOE	No. of patients	Lesion size (cm^2)	Follow-up (mo)	Results
Two-step MACT	MACI	Schneider *et al*[6], 2009	Case series	Ⅳ	20	2.3	21	Significant improvement in functional score Pain improved in 70% of patients
		Giza *et al*[5], 2010	Case series	Ⅳ	10	1.3	24	Significant clinical improvement at 1 yr and maintained at 2 yr
		Aurich *et al*[16], 2011	Case series	Ⅳ	18	-	25	Significant improvement in all clinical scores 64% were excellent or good Age and symptoms duration were correlated with results
		Dixon *et al*[17], 2011	Case series	Ⅳ	25	1.3	44	72% improved symptoms 78% patients over 40 yr reported restricted recreational activity
		Lee *et al*[18], 2013	Case series	Ⅳ	38	1.9	24	Functional outcomes improved significantly at 2 yr 68% were excellent or good outcome 75% ICRS grade I or II in 2nd look arthroscopy at 1 yr
		Johnson *et al*[19], 2013	Case series	Ⅳ	18	1.9	82	Functional outcomes improved at final follow-up
		Giannini *et al*[20], 2014	Case series	Ⅳ	46	1.6	87	Significant clinical improvement at 1 yr and maintained at 3 yr; 3 failures
	Hyalograft C	Giannini *et al*[21], 2008	Case series	Ⅳ	46	1.6	36	Significant clinical improvement at 1 yr and 3 yr Results correlated with age and previous surgery Hyaline-like cartilage regeneration in histological evaluation
		Battaglia *et al*[22], 2011	Case series	Ⅳ	20	2.7	60	Significant clinical improvement T2 mapping MRI showed 69% of lesion are covered with repair tissue
		Nehrer *et al*[23], 2011	Case series	Ⅳ	13	-	47	Significant clinical improvement in all cases
		Domayer *et al*[24], 2012	Comparative study	Ⅲ	18	1.2	65	Significant clinical improvement but no significant difference compared to MFX group No difference between MFX and MACT on T2 maps
		Apprich *et al*[25], 2012	Case series	Ⅳ	10	1.2	48	Significant clinical improvement No differences in functional outcome and MOCART score between MFX and MACT
Two-step BMDCT	Spontostan Powder HYAFF-11	Giannini *et al*[8], 2009	Case series	Ⅳ	48 (25 HA membrane, 23 collagen powder)	2.1	29	Significant clinical improvement at 1 yr maintained at 2 yr Similar results with two scaffolds Correlation between clinical outcome and lesion size
	Spontostan Powder HYAFF-11	Giannini *et al*[26], 2010	Comparative study	Ⅲ	25 BMDCT 46 two-step MACI	2.2 1.6	39 57	Significant clinical improvement at 1 yr and further improvement at 3 yr 76% complete intergration with surrounding cartilage on MRI Hyaline-like cartilage tissue on histological evaluation
	HYAFF-11	Battaglia *et al*[27], 2011	Case series	Ⅳ	20	1.5	24	85% excellent or good clinical results at 2 yr 78% of lesion are covered with repair tissue comparable to hyaline cartilage
	Spontostan Powder HYAFF-11	Giannini *et al*[28], 2013	Case series	Ⅳ	49	2.1	29	Significant clinical improvement at 1 yr with subsequent significant decrease at 2 and 3 yr 78% of repaired tissue similar to hyaline cartilage on T2 maps
	Spongostan Powder	Buda *et al*[29], 2014	Case series	Ⅳ	64	5.3	53	Clinical results peaked at 2 yr, declining gradually at follow-up of 6 yr

	Biopad	Cadossi *et al*[30], 2014	Comparative study	Ⅲ	15 BMDCT 15 BMDCT with PEMF	2 1.9	12 12	Significant clinical improvement in both groups
	HYAFF-11	Buda *et al*[4], 2015	Case series	Ⅳ	40	1.8	48	Significant clinical improvement Higher presence of hyaline-like cartilage in BMDCT than ACI on MRI T2 mapping
	HYAFF-11 Spongostan Powder Biopad	Vannini *et al*[31], 2017	Case series	Ⅳ	140	2	26	Significant clinical improvement at 2 yr maintained at 4 yr Return to sports at preinjury level; 32.1% at 12 mo, 72.8% at 48 mo
AMIC	Unclear	Wiewiorski *et al*[7], 2013	Case series	Ⅳ	23	-	23	Significant clinical improvement
	Chondro-Gide	Valderrabano *et al*[32], 2013	Case series	Ⅳ	26	-	31	Significant clinical improvement Normal signal intensity of repair tissue was seen in 15% on MRI
	Chondro-Gide	Kubosch *et al*[33], 2016	Case series	Ⅳ	17	2.4	39	Significant clinical improvement MOCART score correlated with AOFAS score
	Chondro-Gide	Wiewiorski *et al*[34], 2016	Case series	Ⅳ	60	-	47	Calcaneal osteotomy was performed in 63% of patients Low rate for return to sports; postoperative sports activity levels remain stable when compared with preoperative levels
Cartilage ECM	BioCartilage	Desai S[35], 2016	Case series	Ⅳ	9	1.3	12	78% excellent, 22% good clinical outcomes
		Clanton *et al*[36], 2014	Case series	Ⅳ	7	-	8	Significant clinical improvement
ACIC	Cartifill	Volpi P *et al*[37], 2014	Case series	Ⅳ	5	3.1	6	Significant clinical improvement at 6 mo
Cell-free scaffold	MaioRegen®	Christensen *et al*[38], 2015	Case series	Ⅳ	4	-	30	No clinical scores improvement No improvement in MOCART score and 3 patients had 0%-10% bone formation in defect at 1 yr on CT

Table 4 Patient demographics and clinical characteristics

	Procedure						
	Total	MACT	BMDCT	AMIC	Cartilage ECM	ACIC	Cell-free scaffold
Treatment groups, *n*	30	13	9	4	2	1	1
Ankles, *n*	897	330	416	126	16	5	4
Sex, male/female/unknown, *n*	501/322/72	174/111/45	238/153/22	79/47/0	7/9/0	3/2/0	-
Age, yr, weighted mean (range)	30.9 (19-61)	30.1	30.2	34.9	42.7	25.6	-
Duration of symptoms, mo, weighted mean (range)	34.3 (6-216)	34.5	36.5	23	-	-	-
Lesion size, mm^2, weighted mean (range)	215 (116-527)	171	248	240	130	-	-
Follow-up, mo, weighted mean (range)	37.7 (6-87)	45.8	32.7	38.2	10.4	6	30

Table 5 Level and quality of evidence of included studies *n* (%)

		Total Studies	Procedure groups					
			MACT	BMDCT	AMIC	Cartilage ECM	ACIC	Cell-free scaffold
Level of evidence								
	1	0	0	0	0	0	0	0
	2	1 (3.6)	0	2 (22.2)	0	0	0	0
	3	3 (10.7)	2 (15.4)	2 (22.2)	0	0	0	0
	4	24 (85.7)	11 (84.6)	5 (55.6)	4 (100)	2 (100)	1 (100)	1 (100)
Quality of evidence								
	Excellent (MCMS ⩾ 85)	0	0	0	0	0	0	0
	Good (MCMS 70-84)	0	0	0	0	0	0	0
	Fair (MCMS 55-69)	7 (25.0)	3 (23.1)	4 (44.4)	0	0	0	0
	Poor (MCMS < 55)	21 (75.0)	10 (76.9)	5 (55.6)	4 (100)	2 (100)	1 (100)	1 (100)

quality [8,18,20,21,30,31,38] and the remainder (75%) were of poor quality[4-7,16,17,19,22-29,32-37] (Table 5). Further QOE

Table 6 Data reported (in percentage)

			Procedure					
		Total	MACT	BMDCT	AMIC	Cartilage ECM	ACIC	Cell-free scaffold
Procedure groups, *n*		30	13	9	4	2	1	1
Demographic information		93	92	94	100	100	100	0
	Sex	90	85	89	100	100	100	0
	Mean age + range	97	100	100	100	100	100	0
Patient history		30	35	31	44	13	0	0
	Body mass index	33	31	33	50	50	0	0
	Mean duration of symptoms	23	38	22	25	0	0	0
	Previous traumatic experience(s)	33	38	44	50	0	0	0
	Activities of daily living/athletic participation	30	31	22	50	0	0	0
Study design		73	71	78	72	56	63	38
	Type of study	50	23	56	25	0	0	100
	Number of patients	97	100	100	100	100	100	0
	Percentage of patients in follow-up	97	100	100	100	100	100	0
	Consecutive patients	23	23	22	50	0	0	0
	Follow-up time + range/standard deviation	100	100	100	100	100	100	100
	Method of lesion size measurement	43	54	44	50	0	0	0
	Lesion classification system utilized	77	77	100	50	50	100	0
	Surgical approach used to access lesion	97	92	100	100	100	100	100
Clinical variables		49	53	50	58	33	33	33
	Lesion size	93	100	100	75	50	100	100
	Lesion location	77	77	100	75	50	0	0
	Presence of cyst	13	23	0	25	50	0	0
	Associated pathology	13	23	0	25	0	0	0
	Concomitant procedures	20	15	22	50	0	0	0
	Description of rehabilitation	80	77	78	100	50	100	100
Imaging data		73	81	83	75	50	0	100
	Imaging used to identify lesion	80	92	89	75	50	0	100
	Imaging used at follow-up	67	69	78	75	50	0	100
Patient-reported outcomes		85	85	100	88	0	100	100
	Pain, function, and activity scale, pre-operative	80	77	100	75	0	100	100
	Pain, function, and activity scale, at follow-up	90	92	100	100	0	100	100

data is shown in Table 5.

Variable reporting of outcome data

The defined data that were reported in the studies included in this review are listed and the each data according to procedure group is shown in Table 6. General demographic information including age and gender were reported in 93% of the studies. While the study design, imaging data, and patient-reported outcomes were well-reported variables with 73%, 73% and 85% respectively, patient history was the least reported variable of all with 30% of the data being reported. Clinical variables were reported in only 49% of studies.

Clinical outcomes were evaluated using a number of different scoring systems for scaffolds-based therapy for OLT (Table 7). The American Orthopaedic Foot and Ankle Society (AOFAS) score was the most frequently utilized in 25 studies of the included[4-8,16-18,20-34,37,38]. Of the 25 studies that used AOFAS, 22 studies investigated both pre- and post-operative scores[4-8,16,18,20-23,25-32,34,37,38].

Twelve of 13 MACT groups reported pre and post-operative AOFAS scores and of the 310 patients who underwent MACT[5,6,16-18,20-26], the mean AOFAS score improved from 59.1 to 86.7 at a mean follow-up of 47.9 mo. Of the 416 patients from the nine BMDCT groups[4,8,26-31], the mean AOFAS score improved from 61.1 to 88.2 at a mean of 32.7 mo of follow-up. Of the 126 patients from the four AMIC groups[7,32-34], the mean AOFAS score improved from 50.7 to 82.3 at a mean follow-up of 38.2 mo. Of the two cartilage ECM studies included, one publication reported outcomes at less than one year follow-up[36], and the other one did not describe clinical outcomes[35]. There was only one publication reporting ACIC data but clinical evaluation was insufficient due to a follow-up of only six mo[37]. In the cell-free scaffold group, only one study was published, which showed no clinical improvement in AOFAS score at a mean 30 mo (from 48.7 to 52.7) follow-up. However, these results only included four studies[38].

In this systematic review, 12 procedure groups reported sequential clinical outcomes at two or more post-operative time points[4,5,8,18,20,21,26,28-31]. Four groups, which were all BMDCT studies, found temporal improvement in AOFAS scores over the first 2-3 years of post-operative follow-up with a mean decrease in AOFAS score of 87.1 reported at a mean 41.8 mo follow-up[4,28,29,31]. In contrast, eight groups, including four MACT and four BMDCT groups, demonstrated that there were no deteriorations during a weighted mean 38-mo follow-up[5,8,18,20,21,26,30].

Return to sport activity at previous level

Overall, eight studies (MACT: One study, AMIC: Two

Table 7 Clinical outcome scores utilized in included studies *n* (%)

Score	Studies, total	Procedure group					
		MACT	BMDCT	AMIC	Cartilage ECM	ACIC	Cell-free scaffold
AOFAS	25 (89)	12 (92)	9 (100)	4 (100)	0 (0)	1 (100)	1 (100)
VAS	7 (25)	1 (8)	2 (22)	4 (100)	0 (0)	1 (100)	0 (0)
Tegner activity score	3 (11)	1 (8)	0 (0)	1 (25)	0 (0)	0 (0)	1 (100)
SF-36	2 (7)	1 (8)	2 (22)	0 (0)	0 (0)	0 (0)	0 (0)
FFI	2 (7)	1 (8)	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)
FADI	1 (4)	0 (0)	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)
HSS	1 (4)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LEAS	1 (4)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AHS	1 (4)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AAOS	1 (4)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ARS	1 (4)	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)
Halasi score	1 (4)	0 (0)	1 (11)	0 (0)	0 (0)	0 (0)	0 (0)
Mazur ankle score	1 (4)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cincinnati score	1 (4)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

AAOS: American Academy of Orthopaedic Surgeons; AHS: Ankle-Hindfoot Score; AOFAS: American Orthopaedic Foot and Ankle Society; ARS: Activity Rating Scale; FADI: Foot and Ankle Disability Index; FFI: Foot Function Index; HSS: Hannover Scoring System; LEAS: University of California Lower Extremity Activity Scale; SF-36: Short Form-36 Health Survey; VAS: Visual analog scale.

studies, BMDCT: five studies) reported that a mean 68.3% of patients receiving scaffold-based therapy with mean lesion size of 250 mm^2 returned to previous sport activity at previous level[4,8,21,28,29,31,32,34]. Of the MACT procedures, Giannini *et al*[21] showed that 20 of 29 patients (69%) returned to sport at previous levels. In patients treated with AMIC procedures, Valderrabano *et al*[32] reported only nine of 20 patients (45%) returned to previous sport activity level, and Wiewiorski *et al*[34] also showed no significant difference when comparing preoperative and postoperative activity scores (ARS, Tegner). BMDCT was the most reported in five studies, and of these studies, 74.5% of patients were able to resume sports at preinjury level, with a range of 69% to 78%[4,8,28,29,31].

DISCUSSION

The results from this systematic review demonstrate that recommendations for scaffold-based therapy based solely on evidence is not yet conclusive. In the current evaluation, 96% of included studies in which scaffold-based therapy was performed for the treatment of OLT were classified into the category of poor LOE. In addition, of 28 included articles, no papers were of good or better methodological quality. According to the principles of evidence-based medicine[39], a high level of clinical evidence and good methodological quality are fundamentally warranted to treat patients because low LOE and QOE studies are more likely to show overestimated outcomes compared to higher LOE and QOE studies[40,41]. Careful attention therefore should be paid when evaluating outcomes following the studies of scaffold-based therapy for OLT.

The results from the current systematic review demonstrate large variability and underreporting of clinical data between studies reflecting and inability to compare the results across studies. These inconsistencies and general underreporting of data make it difficult to pool data, which furthermore makes it difficult to draw conclusions about effectiveness of the use of scaffold in the treatment for OLT. As Hannon *et al*[15] described, adequate reporting of data in the studies of the treatment for OLT should be required to perform high quality studies, and investigators should be encouraged to implement data collection both before and after surgery according to recommended list described by Hannon *et al*[15] in this review, the categories of imaging data were reported in 73% of included studies. Compared with reporting of outcome data on microfracture for OLT in the systematic review by Hannon *et al*[15], imaging data was reported in only 39% among the studies. However, this review showed a higher percentage of reporting of imaging data (73%). Nevertheless, only 67% of studies used MRI for patient follow-up evaluation, although MRI evaluation for scaffold-based treatment of OLT is crucial because the aim of the use of scaffolds and is generally believed to promote the subchondral bone and cartilage repair. In addition, the categories of clinical variables and patient history were reported only with 49% and 30% respectively. As these data including BMI, lesion location, presence of cyst, associated pathology, and concomitant procedures can have significant effect on patient outcome, what is alarming is that appropriate information is not enough taken in the current studies.

Lesion size has been widely accepted as the most commonly used predictor of clinical outcomes after BMS for OLT[42,43]. Choi *et al*[42] demonstrated that BMS should be indicated for lesions less than 150 mm^2 and lesions greater than this value resulted in poor outcomes. More recently, Ramponi *et al*[13] suggested that BMS could be best reserved for lesion size of less than 107.4 mm^2 rather than 150 mm^2. In the current review, however, the mean lesion size treated with scaffolds was 215 mm^2, which is much larger than traditional indication

size for BMS or the most current new indication size of 107 mm^2[13]. This suggests that the use of scaffolds may further improve the potential of reparative techniques. However, further well-designed studies are necessary to determine the effectiveness of scaffold-based therapy on OLT because of low LOE and QOE and the large variability in the data.

Despite of high frequency of OLT in the athletic population, little is reported regarding return to sport following surgical treatment of OLT in this population. In the current review, weighted mean 68.3% of patients receiving scaffold therapy with weighted mean 250 mm^2 of lesion size returned to previous sport activity at previous level in eight studies. There are no studies investigating the effectiveness of BMS alone for athletic populations who have large lesion as described above, but Choi *et al*[42] reported clinical failure rate in patients with lesion area $\geqslant$ 150 mm^2 was 80%. Furthermore, Chuckpaiwong *et al*[43] reported a 97% of failure rate in 32 patients with a lesion area $\geqslant$ 150 mm^2. This suggests that the use of scaffolds may provide better outcomes than BMS alone for larger lesions but high quality studies are warranted. On the other hand, in replacement procedures, including autologous osteochondral transplantation, which is generally indicated for larger lesions, several studies reported that more than 90% of patients returned to play sport at previous levels[44,45]. Although there is inconsistency in indications for the treatment strategy, the rate of return to sport following scaffold-based therapy appears to be relatively lower than AOT procedures. The highest rate of return to sport after scaffold-based therapy was only 78.0% in athletes treated with BMDCT[31]. However, there was variability of sport type, postoperative rehabilitation protocol, and time to return to sport, which makes it difficult to assess these results appropriately.

Our review found that there were 12 different scoring systems used to assess clinical outcomes, with AOFAS score being the most commonly used (89%). However, there remains no validated scoring system for the clinical follow-up for the treatment of OLT[13]. Moreover, four BMDCT groups have shown that clinical outcomes deteriorate after peaking at 2-3 year postoperatively[4,28,29,31], whereas four MACT and four BMDCT groups have no deterioration during follow-up[5,8,18,20,21,26,30]. A potential reason for these lags in clinical outcome data may be the invalid clinical evaluation methods after OLT surgery in addition to the use of the different kinds of scaffolds. A novel validated scoring system for the clinical follow-up of the treatment for OLT are currently warranted.

The appropriate treatment for OLT is still controversial. While the ideal procedure would regenerate a tissue with biomechanical properties similar to normal hyaline cartilage, reparative techniques can offer the replacement of the articular cartilage with a hyaline-like repair tissue. Scaffolds have been introduced to improve the requirements of the cartilage regeneration process, as ACI, the first generation approach for cartilage treatment, has evident biological and surgical limitations[46]. In fact, the use of scaffolds has overcome the drawbacks and simplified the procedure. However, any available substitute materials have not yet matched the properties of the normal cartilage, and there is no consensus about the superior effectiveness of these procedures over the other procedures, including replacement procedures. While the scaffold-based treatment has shown promising clinical results in numerous studies of case series, the current systematic review showed low LOE and poor methodological quality of the use of scaffolds for OLT. Further long-term comparative studies are warranted to investigate the potential of a bioengineered approach compared to other treatments. Furthermore, the definitive indications for this technique, including lesion size and character of the lesion, still remains controversial[13].

This systematic review has several inherent limitations and/or potential biases. The criterion was limited to MEDLINE, EMBASE and Cochrane Library Database articles published exclusively in English. The variables may not be all inclusive of data in each study, but they should be a representative summary of the most commonly used data. Another inherent concern was the overlapping of cohorts or subgroups of several cohorts studies in longitudinal follow-up studies. Finally, the data extraction was not performed blindly, but was performed by two independent reviewers and later confirmed by the lead author.

In conclusion, this systematic review demonstrated that the scaffold-based therapy for the treatment of OLT may produce favorable clinical outcomes, but low level of evidence, poor quality of evidence, and the variability of the data have confounded the effectiveness of scaffold-based therapy for OLT. Further, well-designed studies, are necessary to determine the effectiveness of the use of scaffold for the treatment of OLT, especially when compared to available traditional treatments.

COMMENTS

Background

Recently scaffold-based therapy for osteochondral lesions of the talus (OLT) has become more popular as an alternative reparative procedure. However, no consensus has been reached regarding the effectiveness of scaffold-based therapy in the treatment of OLT to date. In this study, the effectiveness of scaffold-based therapy was systematically reviewed based on available clinical evidence.

Research frontiers

Scaffolds have been introduced to improve the requirements of the cartilage regeneration process, as autologous chondrocyte implantation (ACI), the first generation approach for cartilage treatment, has evident biological and surgical limitations. Recently, the use of scaffolds has overcome the drawbacks and simplified the procedure.

Innovations and breakthroughs

The scaffold-based treatment has shown promising clinical results in numerous studies of case series and the use of scaffolds may further improve the potential of reparative techniques. Retrieved manuscripts were reviewed by the authors, and the data were extracted.

Applications

This systematic review suggests that the scaffold-based therapy for the

treatment of OLT may produce favorable clinical outcomes, but low level of evidence, poor quality of evidence, and the variability of the data have confounded the effectiveness of scaffold-based therapy for OLT.

Terminology

Matrix-induced autologous chondrocyte transplantation is a second-generation ACI technique, which uses a type Ⅰ/Ⅲ bilayer collagen membrane seeded with cultured autologous chondrocytes. Autologous matrix-induced chondrogenesis is a one-step scaffold-based therapy that combines bone marrow stimulation with the use of a porcine collagen Ⅰ/Ⅲ matrix scaffold. Bone marrow-derived cell transplantation is also a one-step procedure and is a combination of concentrated bone marrow aspirate and scaffold material.

Peer-review

The paper adequately concludes what is already suspected in that variable quality, small studies with limited outcome data serve to confuse the authors' knowledge. It's a useful review.

REFERENCES

1 **Wodicka R**, Ferkel E, Ferkel R. Osteochondral Lesions of the Ankle. *Foot Ankle Int* 2016; **37**: 1023-1034 [PMID: 27480500 DOI: 10.1177/1071100716654691]

2 **Zengerink M**, Struijs PA, Tol JL, van Dijk CN. Treatment of osteochondral lesions of the talus: a systematic review. *Knee Surg Sports Traumatol Arthrosc* 2010; **18**: 238-246 [PMID: 19859695 DOI: 10.1007/s00167-009-0942-6]

3 **Hannon CP**, Smyth NA, Murawski CD, Savage-Elliott I, Deyer TW, Calder JD, Kennedy JG. Osteochondral lesions of the talus: aspects of current management. *Bone Joint J* 2014; **96-B**: 164-171 [PMID: 24493179 DOI: 10.1302/0301-620X.96B2.31637]

4 **Buda R**, Vannini F, Castagnini F, Cavallo M, Ruffilli A, Ramponi L, Pagliazzi G, Giannini S. Regenerative treatment in osteochondral lesions of the talus: autologous chondrocyte implantation versus one-step bone marrow derived cells transplantation. *Int Orthop* 2015; **39**: 893-900 [PMID: 25662594 DOI: 10.1007/s00264-015-2685-y]

5 **Giza E**, Sullivan M, Ocel D, Lundeen G, Mitchell ME, Veris L, Walton J. Matrix-induced autologous chondrocyte implantation of talus articular defects. *Foot Ankle Int* 2010; **31**: 747-753 [PMID: 20880476 DOI: 10.3113/FAI.2010.074]

6 **Schneider TE**, Karaikudi S. Matrix-Induced Autologous Chondrocyte Implantation (MACI) grafting for osteochondral lesions of the talus. *Foot Ankle Int* 2009; **30**: 810-814 [PMID: 19755063 DOI: 10.3113/FAI.2009.0810]

7 **Wiewiorski M**, Miska M, Kretzschmar M, Studler U, Bieri O, Valderrabano V. Delayed gadolinium-enhanced MRI of cartilage of the ankle joint: results after autologous matrix-induced chondrogenesis (AMIC)-aided reconstruction of osteochondral lesions of the talus. *Clin Radiol* 2013; **68**: 1031-1038 [PMID: 23809267 DOI: 10.1016/j.crad.2013.04.016]

8 **Giannini S**, Buda R, Vannini F, Cavallo M, Grigolo B. One-step bone marrow-derived cell transplantation in talar osteochondral lesions. *Clin Orthop Relat Res* 2009; **467**: 3307-3320 [PMID: 19449082 DOI: 10.1007/s11999-009-0885-8]

9 **Vannini F**, Filardo G, Kon E, Roffi A, Marcacci M, Giannini S. Scaffolds for cartilage repair of the ankle joint: The impact on surgical practice. *Foot Ankle Surg* 2013; **19**: 2-8 [PMID: 23337268 DOI: 10.1016/j.fas.2012.07.001]

10 **Liberati A**, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009; **151**: W65-W94 [PMID: 19622512 DOI: 10.7326/0003-4819-151-4-200908180-00136]

11 **Marx RG**, Wilson SM, Swiontkowski MF. Updating the assignment of levels of evidence. *J Bone Joint Surg Am* 2015; **97**: 1-2 [PMID: 25568387 DOI: 10.2106/JBJS.N.01112]

12 **Coleman BD**, Khan KM, Maffulli N, Cook JL, Wark JD. Studies of surgical outcome after patellar tendinopathy: clinical significance of methodological deficiencies and guidelines for future studies. Victorian Institute of Sport Tendon Study Group. *Scand J Med Sci Sports* 2000; **10**: 2-11 [PMID: 10693606 DOI: 10.1034/j.1600-0838.2000.010001002.x]

13 **Ramponi L**, Yasui Y, Murawski CD, Ferkel RD, DiGiovanni CW, Kerkhoffs GMMJ, Calder JDF, Takao M, Vannini F, Choi WJ, Lee JW, Stone J, Kennedy JG. Lesion Size Is a Predictor of Clinical Outcomes After Bone Marrow Stimulation for Osteochondral Lesions of the Talus: A Systematic Review. *Am J Sports Med* 2017; **45**: 1698-1705 [PMID: 27852595 DOI: 10.1177/0363546516668292]

14 **Jakobsen RB**, Engebretsen L, Slauterbeck JR. An analysis of the quality of cartilage repair studies. *J Bone Joint Surg Am* 2005; **87**: 2232-2239 [PMID: 16203888 DOI: 10.2106/JBJS.D.02904]

15 **Hannon CP**, Murawski CD, Fansa AM, Smyth NA, Do H, Kennedy JG. Microfracture for osteochondral lesions of the talus: a systematic review of reporting of outcome data. *Am J Sports Med* 2013; **41**: 689-695 [PMID: 22967827 DOI: 10.1177/0363546512458218]

16 **Aurich M**, Bedi HS, Smith PJ, Rolauffs B, Mückley T, Clayton J, Blackney M. Arthroscopic treatment of osteochondral lesions of the ankle with matrix-associated chondrocyte implantation: early clinical and magnetic resonance imaging results. *Am J Sports Med* 2011; **39**: 311-319 [PMID: 21068444 DOI: 10.1177/036354651038157]

17 **Dixon S**, Harvey L, Baddour E, Janes G, Hardisty G. Functional outcome of matrix-associated autologous chondrocyte implantation in the ankle. *Foot Ankle Int* 2011; **32**: 368-374 [PMID: 21733438 DOI: 10.3113/FAI.2011.0368]

18 **Lee KT**, Kim JS, Young KW, Lee YK, Park YU, Kim YH, Cho HK. The use of fibrin matrix-mixed gel-type autologous chondrocyte implantation in the treatment for osteochondral lesions of the talus. *Knee Surg Sports Traumatol Arthrosc* 2013; **21**: 1251-1260 [PMID: 22752415 DOI: 10.1007/s00167-012-2096-1]

19 **Johnson B**, Lever C, Roberts S, Richardson J, McCarthy H, Harrison P, Laing P, Makwana N. Cell cultured chondrocyte implantation and scaffold techniques for osteochondral talar lesions. *Foot Ankle Clin* 2013; **18**: 135-150 [PMID: 23465953 DOI: 10.1016/j.fcl.2012.12.008]

20 **Giannini S**, Buda R, Ruffilli A, Cavallo M, Pagliazzi G, Bulzamini MC, Desando G, Luciani D, Vannini F. Arthroscopic autologous chondrocyte implantation in the ankle joint. *Knee Surg Sports Traumatol Arthrosc* 2014; **22**: 1311-1319 [PMID: 23996105 DOI: 10.1007/s00167-013-2640-7]

21 **Giannini S**, Buda R, Vannini F, Di Caprio F, Grigolo B. Arthroscopic autologous chondrocyte implantation in osteochondral lesions of the talus: surgical technique and results. *Am J Sports Med* 2008; **36**: 873-880 [PMID: 18227232 DOI: 10.1177/0363546507312644]

22 **Battaglia M**, Vannini F, Buda R, Cavallo M, Ruffilli A, Monti C, Galletti S, Giannini S. Arthroscopic autologous chondrocyte implantation in osteochondral lesions of the talus: mid-term T2-mapping MRI evaluation. *Knee Surg Sports Traumatol Arthrosc* 2011; **19**: 1376-1384 [PMID: 21503808 DOI: 10.1007/s00167-011-1509-x]

23 **Nehrer S**, Domayer SE, Hirschfeld C, Stelzeneder D, Trattnig S, Dorotka R. Matrix-Associated and Autologous Chondrocyte Transplantation in the Ankle: Clinical and MRI Follow-up after 2 to 11 Years. *Cartilage* 2011; **2**: 81-91 [PMID: 26069572 DOI: 10.1177/1947603510381095]

24 **Domayer SE**, Apprich S, Stelzeneder D, Hirschfeld C, Sokolowski M, Kronnerwetter C, Chiari C, Windhager R, Trattnig S. Cartilage repair of the ankle: first results of T2 mapping at 7.0 T after microfracture and matrix associated autologous cartilage transplantation. *Osteoarthritis Cartilage* 2012; **20**: 829-836 [PMID: 22542632 DOI: 10.1016/j.joca.2012.04.015]

25 **Apprich S**, Trattnig S, Welsch GH, Noebauer-Huhmann IM, Sokolowski M, Hirschfeld C, Stelzeneder D, Domayer S. Assessment of articular cartilage repair tissue after matrix-associated autologous chondrocyte transplantation or the microfracture technique in the ankle joint using diffusion-weighted imaging at 3 Tesla. *Osteoarthritis Cartilage* 2012; **20**: 703-711 [PMID: 22445916 DOI: 10.1016/j.joca.2012.03.00]

26 **Giannini S**, Buda R, Cavallo M, Ruffilli A, Cenacchi A, Cavallo C, Vannini F. Cartilage repair evolution in post-traumatic osteochondral lesions of the talus: from open field autologous chondrocyte to bone-marrow-derived cells transplantation. *Injury* 2010; **41**: 1196-1203

[PMID: 20934692 DOI: 10.1016/j.injury.2010.09.028]
27 **Battaglia M**, Rimondi E, Monti C, Guaraldi F, Sant'Andrea A, Buda R, Cavallo M, Giannini S, Vannini F. Validity of T2 mapping in characterization of the regeneration tissue by bone marrow derived cell transplantation in osteochondral lesions of the ankle. *Eur J Radiol* 2011; **80**: e132-e139 [PMID: 20801594 DOI: 10.1016/j.ejrad.2010.08.008]
28 **Giannini S**, Buda R, Battaglia M, Cavallo M, Ruffilli A, Ramponi L, Pagliazzi G, Vannini F. One-step repair in talar osteochondral lesions: 4-year clinical results and t2-mapping capability in outcome prediction. *Am J Sports Med* 2013; **41**: 511-518 [PMID: 23221772 DOI: 10.1177/0363546512467622]
29 **Buda R**, Vannini F, Cavallo M, Baldassarri M, Natali S, Castagnini F, Giannini S. One-step bone marrow-derived cell transplantation in talarosteochondral lesions: mid-term results. *Joints* 2014; **1**: 102-107 [PMID: 25606518]
30 **Cadossi M**, Buda RE, Ramponi L, Sambri A, Natali S, Giannini S. Bone marrow-derived cells and biophysical stimulation for talar osteochondral lesions: a randomized controlled study. *Foot Ankle Int* 2014; **35**: 981-987 [PMID: 24917648 DOI: 10.1177/1071100714539966]
31 **Vannini F**, Cavallo M, Ramponi L, Castagnini F, Massimi S, Giannini S, Buda RE. Return to Sports After Bone Marrow-Derived Cell Transplantation for Osteochondral Lesions of the Talus. *Cartilage* 2017; **8**: 80-87 [PMID: 27994723 DOI: 10.1177/1947603516642574]
32 **Valderrabano V**, Miska M, Leumann A, Wiewiorski M. Reconstruction of osteochondral lesions of the talus with autologous spongiosa grafts and autologous matrix-induced chondrogenesis. *Am J Sports Med* 2013; **41**: 519-527 [PMID: 23393079 DOI: 10.1177/0363546513476671]
33 **Kubosch EJ**, Erdle B, Izadpanah K, Kubosch D, Uhl M, Südkamp NP, Niemeyer P. Clinical outcome and T2 assessment following autologous matrix-induced chondrogenesis in osteochondral lesions of the talus. *Int Orthop* 2016; **40**: 65-71 [PMID: 26346373 DOI: 10.1007/s00264-015-2988-z]
34 **Wiewiorski M**, Werner L, Paul J, Anderson AE, Barg A, Valderrabano V. Sports Activity After Reconstruction of Osteochondral Lesions of the Talus With Autologous Spongiosa Grafts and Autologous Matrix-Induced Chondrogenesis. *Am J Sports Med* 2016; **44**: 2651-2658 [PMID: 27587743 DOI: 10.1177/0363546516659643]
35 **Desai S**. Surgical Treatment of a Tibial Osteochondral Defect With Debridement, Marrow Stimulation, and Micronized Allograft Cartilage Matrix: Report of an All-Arthroscopic Technique. *J Foot Ankle Surg* 2016; **55**: 279-282 [PMID: 25201233 DOI: 10.1053/j.jfas.2014.07.01]
36 **Clanton TO**, Jhonson NS, Matheny LM. Use of cartilage extracellular matrix and bone marrow aspirate concentrate in treatment of osteochondral lesions of the talus. *Tech Foot and Ankle* 2014; **13**: 212220 [DOI: 10.1097/BTF.0000000000000054]
37 **Volpi P**, Bait C, Quaglia A, Redaelli A, Prospero E, Cervellin M, Stanco D, de Girolamo L. Autologous collagen-induced chondrogenesis technique (ACIC) for the treatment of chondral lesions of the talus. *Knee Surg Sports Traumatol Arthrosc* 2014; **22**: 1320-1326 [PMID: 24414378 DOI: 10.1007/s00167-013-2830-3]
38 **Christensen BB**, Foldager CB, Jensen J, Jensen NC, Lind M. Poor osteochondral repair by a biomimetic collagen scaffold: 1- to 3-year clinical and radiological follow-up. *Knee Surg Sports Traumatol Arthrosc* 2016; **24**: 2380-2387 [PMID: 25691368 DOI: 10.1007/s00167-015-3538-3]
39 **Sackett DL**, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ* 1996; **312**: 71-72 [PMID: 8555924 DOI: 10.1136/bmj.312.7023.71]
40 **Moher D**, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A, Pham B, Klassen TP. Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses. *Health Technol Assess* 1999; **3**: i-iv, 1-98 [PMID: 10374081]
41 **Moher D**, Jadad AR, Klassen TP. Guides for reading and interpreting systematic reviews: III. How did the authors synthesize the data and make their conclusions? *Arch Pediatr Adolesc Med* 1998; **152**: 915-920 [PMID: 9743039 DOI: 10.1001/archpedi.152.9.915]
42 **Choi WJ**, Park KK, Kim BS, Lee JW. Osteochondral lesion of the talus: is there a critical defect size for poor outcome? *Am J Sports Med* 2009; **37**: 1974-1980 [PMID: 19654429 DOI: 10.1177/0363546509335765]
43 **Chuckpaiwong B**, Berkson EM, Theodore GH. Microfracture for osteochondral lesions of the ankle: outcome analysis and outcome predictors of 105 cases. *Arthroscopy* 2008; **24**: 106-112 [PMID: 18182210 DOI: 10.1016/j.arthro.2007.07.022]
44 **Fraser EJ**, Harris MC, Prado MP, Kennedy JG. Autologous osteochondral transplantation for osteochondral lesions of the talus in an athletic population. *Knee Surg Sports Traumatol Arthrosc* 2016; **24**: 1272-1279 [PMID: 25962962 DOI: 10.1007/s00167-015-3606-8]
45 **Kennedy JG**, Murawski CD. The Treatment of Osteochondral Lesions of the Talus with Autologous Osteochondral Transplantation and Bone Marrow Aspirate Concentrate: Surgical Technique. *Cartilage* 2011; **2**: 327-336 [PMID: 26069591 DOI: 10.1177/1947603511400726]
46 **Filardo G**, Kon E, Roffi A, Di Martino A, Marcacci M. Scaffold-based repair for cartilage healing: a systematic review and technical note. *Arthroscopy* 2013; **29**: 174-186 [PMID: 23159494 DOI: 10.1016/j.arthro.2012.05.891]

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CASE REPORT

Managing extremely distal periprosthetic femoral supracondylar fractures of total knee replacements - a new PHILOS-ophy

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Author contributions: Donnelly KJ and Tucker A contributed equally to the paper in terms of literature review and writing of the paper; Ruiz A and Thompson NW developed operative technique and performed the surgery; Ruiz A and Thompson NW were also involved in the writing of the paper.

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Abstract

We report two cases where a proximal humeral locking plate was used for the fixation of an extremely distal, type Ⅲ peri-prosthetic femoral fractures in relation to a total knee replacement (TKR). In each case there was concern regarding the fixation that could be achieved using the available anatomic distal femoral plates due to the size and bone quality of distal fragment. The design of the Proximal Humeral Internal Locking System (PHILOS) allows nine 3.5-mm locking screws to be placed over a small area in multiple directions. This allowed a greater number of fixation points to be achieved in the distal fragment. Clinical and radiological short-term follow-up (6-12 mo) has been satisfactory in both cases with no complications. We suggest the use of this implant for extremely distal femoral fractures arising in relation to the femoral component of a TKR.

Key words: Distal; Femoral; Periprosthetic; Fracture; PHILOS; Open reduction and internal fixation

Core tip: When dealing with periprosthetic fractures around a total knee replacement it is essential to consider the fracture site and configuration to allow selection of an implant that provides optimal fixation. When managing extremely distal femoral fractures a non-anatomic locking plate, such as Proximal Humeral Internal Locking System, may provide an option for fixation other than the available site-specific plates.

Donnelly KJ, Tucker A, Ruiz A, Thompson NW. Managing extremely distal periprosthetic femoral supracondylar fractures of total knee replacements - a new PHILOS-ophy. *World J Orthop* 2017; 8(10): 809-813 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i10/809.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i10.809

INTRODUCTION

Supracondylar periprosthetic femoral fractures around total knee replacement (TKR) are uncommon injuries with a reported prevalence in the literature of between 0.3% and 2.5%[1]. It is expected that these injuries will become more common as the population ages and an increasing number of TKRs are performed. Non-operative treatment of these fractures results in poorer outcomes and hence is reserved for minimally displaced fractures in low demand patients with significant co-morbidities[2,3].

A variety of operative treatment options exist, including retrograde femoral nailing, open reduction and internal fixation and revision arthroplasty. Perhaps the most challenging fracture patterns are the extremely distal peri-prosthetic femoral fractures. In these cases internal fixation or revision arthroplasty may be required as retrograde nailing may not be possible due to implant design or the inability to insert a locking screw in the distal fragment. Outcomes in treating these extreme distal fractures using femoral locking plates have been comparable with more proximal fractures treated in the same way[4]. One potential problem with anatomically designed distal femoral locking plates is the location and orientation of the screws, which may not allow adequate fixation in the distal fragment in these extremely distal peri-prosthetic femoral fractures.

Locking plates have been used successfully in proximal humeral fractures. The Proximal Humeral Internal Locking System (PHILOS) (DePuy Synthes, Switzerland) allows placement of 9 multi-directional locking screws over a small area. We discuss the use of the PHILOS in two elderly patients with very distal periprosthetic supracondylar fractures with satisfactory outcomes at short-term follow-up.

CASE REPORTS

Patient A

An 85-year-old female presented following a fall at home with pain and deformity around her left knee. She had undergone a left TKR four years previously. An ipsilateral long-stem revision total hip replacement was also noted. There was no other significant past medical history. She lived in sheltered accommodation and was independently mobile with the use of a single walking stick. Radiographs of her left femur revealed a very distal peri-prosthetic femoral fracture (Figure 1A).

Patient B

An 85-year-old female presented with pain and deformity around her left knee following a fall at home. She had undergone bilateral TKR's 19 years previously. Significant medical comorbidities were noted which included atrial fibrillation and previous transient ischaemic attack, anticoagulation with warfarin, hypothyroid disease and polymyalgia rheumatica. She lived at home alone, with input from her family twice daily. She was independently mobile with the use of a rollator. Radiographs of her left femur revealed a very distal periprosthetic femoral fracture (Figure 2A).

Operative techniques

Both senior authors reviewed each case and the injury radiographs. Pre-operative planning and templating was performed using the Northern Ireland Picture Archive and Communication System (Sectra AB, Sweden) (Figure 1B and Figure 2B). For both cases, surgery was performed under spinal anaesthesia and femoral nerve block. A single dose of 2 g *IV* Flucloxacillin and 160 mg *IV* Gentamicin were administered at induction of anaesthesia. A tourniquet was not used in either case. A direct lateral approach to the distal femur was performed in both cases. The fracture patterns extended very distally in each case and also narrow femoral shafts were noted. Taking these factors into consideration, a 6-hole PHILOS plate was used allowing optimal locking screw placement in the distal fragment and placement of the plate on the lateral aspect of the femur. Locking screws were placed in the distal fragment in both patients. To avoid a stress riser in Patient A the plate overlapped the distal aspect of the hip replacement stem by at least two cortical diameters. Three non-locking screws were inserted below the tip of the stem and two cables passed at the area of overlap (Dall-Miles, Stryker, Switzerland). Patient B had five diaphyseal screws inserted.

Both patients had uneventful peri-operative periods and were discharged day 8 post-operatively to rehabilitation units for on-going physiotherapy and social care. Immobilisation was achieved using a locked cast brace and both patients were kept non-weightbearing for six weeks followed by a period of partial weight bearing with the brace unlocked. At 3 mo both patients were allowed to mobilise bearing full-weight on the injured side albeit with the use of a walking aid.

Outcomes

Patient A: At 6 mo follow-up, the patient was fully weight bearing with the use of one crutch, with a range of movement of 10-70 degrees. Radiographs demonstrated bridging callus on both the AP and lateral views (Figure 1D). At 19 mo, the range of movement had improved to 5-95 degrees and remained independently mobile. Radiographs confirmed radiological union (Figure 1E).

Patient B: At 5 mo follow-up position has been main-

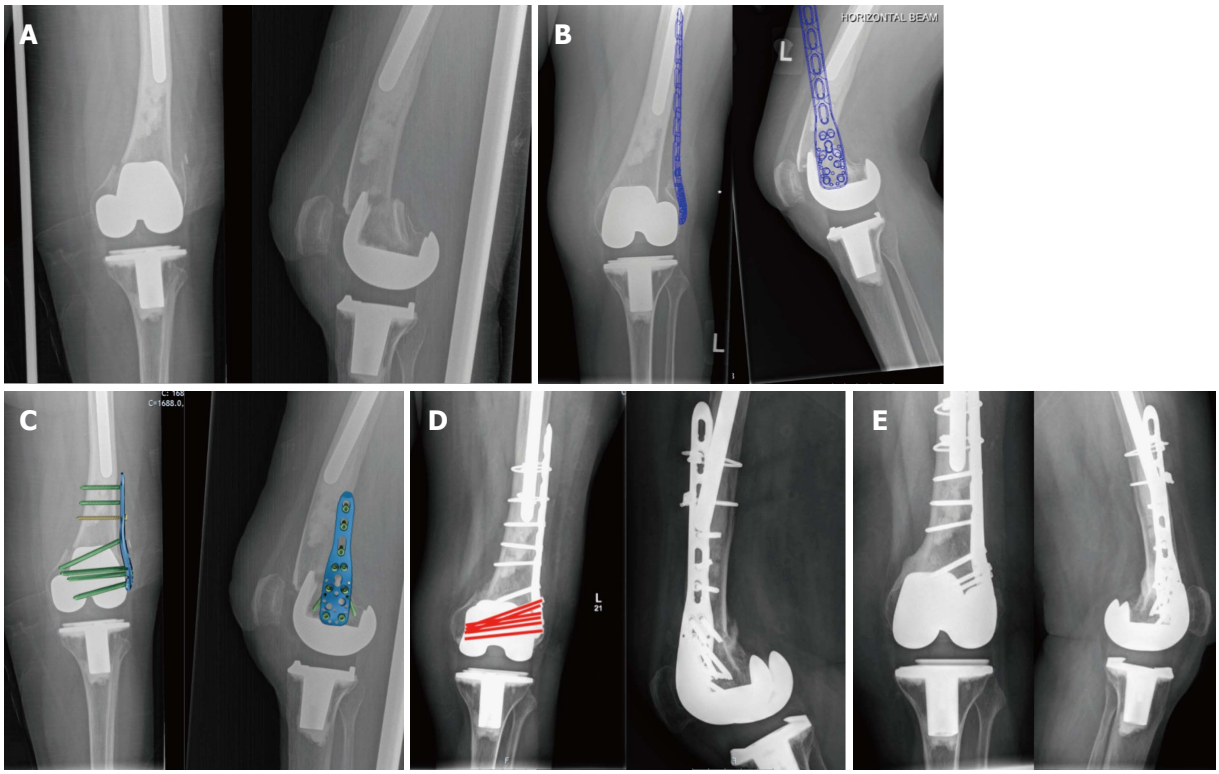

Figure 1 Radiograph series of patient A. A: Anteroposterior and lateral injury radiographs; B: Templated anteroposterior radiograph showing proposed position of implant; C: Anteroposterior and lateral radiographs with PHILOS plate image superimposed to show orientation of screws; D: Post-operative radiographs at 6 mo with orientation of screws behind the femoral component shown in red; E: Anteroposterior and lateral radiographs at 19 mo post-op.

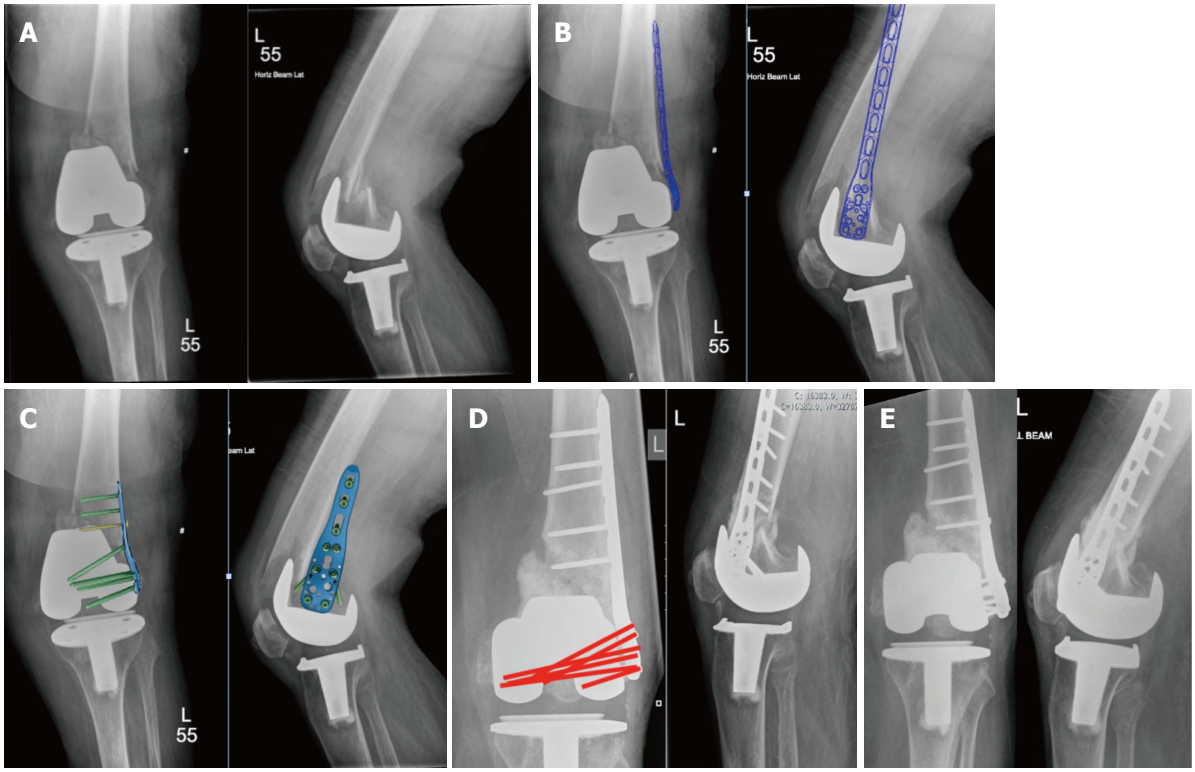

Figure 2 Radiograph series of patient B. A: Anteroposterior and lateral injury radiographs; B: Templated anteroposterior radiograph showing proposed position of implant; C: Anteroposterior and lateral radiographs with PHILOS plate image superimposed to show orientation of screws; D: Post-operative radiographs at 5 mo with orientation of screws behind the femoral component shown in red; E: Anteroposterior and lateral radiographs at 16 mo post-op.

tained. Callus is present posteriorly (Figure 2D). Range of movement 10-90 degrees. Has started progressive weightbearing. At 16 mo, range of movement was 5-90 degrees and the patient mobilised independently with the assistance of a walking frame. Radiographs confirmed radiological union (Figure 2E).

DISCUSSION

Fractures within 15 cm of the joint line or 5 cm of the proximal end of the femoral component of a TKR are considered peri-prosthetic femoral fractures. These fractures often occur in the setting of osteoporotic bone with rheumatoid arthritis, chronic steroid use and neurological disorders being established risk factors[1].

Su *et al*[1] suggested a classification system for these injuries based on fracture site and the available surgical options. Type Ⅰ fractures are proximal to the femoral component. Type Ⅱ fractures originate at the proximal aspect of the femoral component. These types were considered amenable to retrograde femoral nailing or fixation with a fixed angle device. In Type Ⅲ fractures all parts of the fracture line is distal to the anterior flange of the femoral component. Revision arthroplasty is one possible treatment, especially in the presence of a loose femoral component. Fixation may also be possible if the distal fragment allows placement of screws. Each of the patients we have discussed had Type Ⅲ fracture patterns.

A review performed by Ristevski *et al*[3] found favourable results with the use of retrograde intramedullary nailing and locked plating over conservatively managed fractures and those treated with conventional plating. However, in many cases the choice of fixation technique is influenced by factors such as the presence of a box in the femoral component to facilitate retrograde nailing[5], distal extent of the fracture, availability of existing bone stock and fix of the components. Good results have been reported with the use of site-specific locking plates[6-8], such as the Less Invasive Stabilization System (DePuy Synthes, Switzerland).

Biomechanically, locking plates create a fixed-angle single-beam construct[9]. This provides relative stability, allowing for secondary bone healing. Their use has been shown to possess superior resistance to rotational strain over both static and dynamically locked intramedullary nails -3.8° for locking plates, *vs* 14.2° and 15.7° for static and dynamic locking respectively[10]. Locking plate systems allow for even stress distribution along the implant length, and the plates function to convert shear forces into compressive forces at the screw bone interface[11].

The PHILOS has been used successfully in proximal humeral fractures where similar problems with osteoporotic bone and small fracture fragments can exist[12]. Again, it has been shown to resist torsional and bending forces more so than intramedullary nailing under cyclical loading, which is comparative to normal *in vivo* physiological functionality[13,14]. Periprosthetic fracture resulting in primary implant failure is rare complication, with rates quoted at 0.7%. The mechanical benefits of a PHILOS locking plate in managing this injury pattern make it an attractive implant option where longevity is required[15]. However, the PHILOS has not been studied for its use in lower limb fracture management.

A study by Stein *et al*[16] demonstrated that at any age, women have smaller femora, with less cortical bone and higher bone stresses than men. The PHILOS is narrower than many of the specific distal femoral locking plates and therefore may be a more appropriate fit for smaller females, such as the cases discussed. The major benefit we found of using the PHILOS was the design of the plate, which allowed the placement of a maximum of nine polyaxial divergent screws over a small area. This allowed us to maximise our fixation in the distal fragment.

In conclusion, we have shown that a PHILOS can be considered as a viable treatment option for very distal Type Ⅲ fracture patterns with good short-term results in low demand patients. Each case highlights the need for careful consideration of the fracture configuration to allow the treating surgeon to select an appropriate means of fixation.

COMMENTS

Case characteristics

Two cases of 85-year-old females who both presented with pain and deformity of their lower limb following a fall at home.

Clinical diagnosis

Pain and deformity about the knee was apparent, with localised swelling and the inability to weight bear. Midline anterior scars in keeping with a previous knee arthroplasty were evident.

Differential diagnosis

Periprosthetic fractures involving the distal femur or proximal tibia, fracture of femoral diaphysis.

Laboratory diagnosis

All laboratory tests were within normal limits.

Imaging diagnosis

A periprosthetic fracture about the femoral component of a total knee arthroplasty was evident on plain film radiographs. No additional 3D imaging (*i.e.*, computed tomography) was required.

Pathological diagnosis

A very distal periprosthetic femoral fracture.

Treatment

Open reduction and internal fixation of the fracture using a PHILOS locking plate, using the ability to place polyaxial locking screws into the small distal fragment, thereby maximising construct stability.

Related reports

Periprosthetic femoral fracture about a total knee arthroplasty are rare, and several methods for managing these are reported in the literature. This case is unique in that the distal fragment was too small to allow for a lateral LISS femoral plate, nor did the implants allow for a retrograde intramedullary device

to be used.

Term explanation

PHILOS is an acronym for Proximal Humeral Internal Locking Osteo-Synthesis, and describes the locking screw nature of the internal implant.

Experiences and lessons

The use of the PHILOS for this particular fracture configuration is novel. The authors have managed to use this in a rare, and challenging circumstance, with success both in terms of radiological union and restoration of mobility and function. Careful pre-operative planning, knowledge of available implants and appreciation of fracture configuration is crucial in managing the very distal femoral periprosthetic fracture about a total knee arthroplasty.

Peer-review

This is a nice paper. The idea for using PHILOS plate is very unique. This manuscript presents a novel technique for the management of periprosthetic supracondylar femoral fractures which deserves attention from the orthopaedic community in order to be fairly judged.

REFERENCES

1 **Su ET**, DeWal H, Di Cesare PE. Periprosthetic femoral fractures above total knee replacements. *J Am Acad Orthop Surg* 2004; **12**: 12-20 [PMID: 14753793 DOI: 10.5435/00124635-200401000-00003]

2 **McAlinden MG**, Masri BA, Garbuz DS, Duncan CP. Periprosthetic Fractures About Total Knee Arthroplasty. In: Callaghan JJ, Rosenberg AG, Rubash HE, Simonian PT, Wickiewicz PT. The Adult Knee

3 **Ristevski B**, Nauth A, Williams DS, Hall JA, Whelan DB, Bhandari M, Schemitsch EH. Systematic review of the treatment of periprosthetic distal femur fractures. *J Orthop Trauma* 2014; **28**: 307-312 [PMID: 24149447 DOI: 10.1097/BOT.0000000000000002]

4 **Streubel PN**, Gardner MJ, Morshed S, Collinge CA, Gallagher B, Ricci WM. Are extreme distal periprosthetic supracondylar fractures of the femur too distal to fix using a lateral locked plate? *J Bone Joint Surg Br* 2010; **92**: 527-534 [PMID: 20357329 DOI: 10.1302/0301-620X.92B3.22996]

5 **Thompson SM**, Lindisfarne EA, Bradley N, Solan M. Periprosthetic supracondylar femoral fractures above a total knee replacement: compatibility guide for fixation with a retrograde intramedullary nail. *J Arthroplasty* 2014; **29**: 1639-1641 [PMID: 24929282 DOI: 10.1016/j.arth.2013.07.027]

6 **Althausen PL**, Lee MA, Finkemeier CG, Meehan JP, Rodrigo JJ. Operative stabilization of supracondylar femur fractures above total knee arthroplasty: a comparison of four treatment methods. *J Arthroplasty* 2003; **18**: 834-839 [PMID: 14566736]

7 **Kääb MJ**, Stöckle U, Schütz M, Stefansky J, Perka C, Haas NP. Stabilisation of periprosthetic fractures with angular stable internal fixation: a report of 13 cases. *Arch Orthop Trauma Surg* 2006; **126**: 105-110 [PMID: 16374643 DOI: 10.1007/s00402-005-0075-4]

8 **Anakwe RE**, Aitken SA, Khan LA. Osteoporotic periprosthetic fractures of the femur in elderly patients: outcome after fixation with the LISS plate. *Injury* 2008; **39**: 1191-1197 [PMID: 18495125 DOI: 10.1016/j.injury.2008.02.003]

9 **Strauss EJ**, Schwarzkopf R, Kummer F, Egol KA. The current status of locked plating: the good, the bad, and the ugly. *J Orthop Trauma* 2008; **22**: 479-486 [PMID: 18670289 DOI: 10.1097/BOT.0b013e31817996d6]

10 **Citak M**, Kendoff D, Gardner MJ, Oszwald M, O'Loughlin PF, Olivier LC, Krettek C, Hüfner T, Citak M. Rotational stability of femoral osteosynthesis in femoral fractures - navigated measurements. *Technol Health Care* 2009; **17**: 25-32 [PMID: 19478402 DOI: 10.3233/THC-2009-0529]

11 **Egol KA**, Kubiak EN, Fulkerson E, Kummer FJ, Koval KJ. Biomechanics of locked plates and screws. *J Orthop Trauma* 2004; **18**: 488-493 [PMID: 15475843 DOI: 10.1097/00005131-200409000-00003]

12 **Erasmo R**, Guerra G, Guerra L. Fractures and fracture-dislocations of the proximal humerus: A retrospective analysis of 82 cases treated with the Philos(®) locking plate. *Injury* 2014; **45** Suppl 6: S43-S48 [PMID: 25457318 DOI: 10.1016/j.injury.2014.10.022]

13 **Edwards SL**, Wilson NA, Zhang LQ, Flores S, Merk BR. Two-part surgical neck fractures of the proximal part of the humerus. A biomechanical evaluation of two fixation techniques. *J Bone Joint Surg Am* 2006; **88**: 2258-2264 [PMID: 17015605]

14 **Kralinger F**, Gschwentner M, Wambacher M, Smekal V, Haid C. Proximal humeral fractures: what is semi-rigid? Biomechanical properties of semi-rigid implants, a biomechanical cadaver based evaluation. *Arch Orthop Trauma Surg* 2008; **128**: 205-210 [PMID: 18040704 DOI: 10.1007/s00402-007-0512-7]

15 **Thanasas C**, Kontakis G, Angoules A, Limb D, Giannoudis P. Treatment of proximal humerus fractures with locking plates: a systematic review. *J Shoulder Elbow Surg* 2009; **18**: 837-844 [PMID: 19748802 DOI: 10.1016/j.jse.2009.06.004]

16 **Stein MS**, Thomas CD, Feik SA, Wark JD, Clement JG. Bone size and mechanics at the femoral diaphysis across age and sex. *J Biomech* 1998; **31**: 1101-1110 [PMID: 9882042 DOI: 10.1016/S0021-9290(98)00127-4]

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RETRACTION NOTE

Retraction note to: Strategy for prevention of hip fractures in patients with Parkinson's disease

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RETRACTION NOTE

Retraction note to: Iwamoto J, Sato Y, Takeda T, Matsumoto H. Strategy for prevention of hip fractures in patients with Parkinson's disease. *World J Orthop* 2012; 3(9):137-141 PMID: 23173109 DOI: 10.5312/wjo.v3.i9.137. The online version of the original article can be found at https://www.wjgnet.com/2218-5836/full/v3/i9/137.htm.

This meta-analysis article[1] has been retracted at the request of the Co-Editors-in-Chief, as a substantial portion of the primary studies on which the review was based [References 12, 14, 15] have subsequently been retracted.

The Editors-in-Chief recently received communications indicating that 3 of the 5 articles on which the study was based upon were retracted, raising concerns about the integrity of the meta-analysis and its findings. The Editorial Office has conducted an investigation and has contacted the authors concerning the allegation. The authors declare that at the time the article was written, none-except for Dr. Yoshihiro Sato were aware of the fact that the studies subject to the analysis had been fraudulently conducted. The authors have agreed to retract the article from the Journal.

REFERENCES

1 **Iwamoto J**, Sato Y, Takeda T, Matsumoto H. Strategy for prevention of hip fractures in patients with Parkinson's disease. *World J Orthop* 2012; **3**: 137-141 [PMID: 23173109 DOI: 10.5312/wjo.v3.i9.137]

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