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MINIREVIEWS

Use of topical vancomycin powder in total joint arthroplasty: Why the current literature is inconsistent?

Fabio Mancino, Piers J Yates, Benjamin Clark, Christopher W Jones

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Abstract

Periprosthetic joint infection (PJI) is a rare but terrible complication in hip and knee arthroplasty, and the use of topical vancomycin powder (VP) has been investigated as a tool to potentially reduce its incidence. However, there remains no consensus on its efficacy. Therefore, the aim of this review is to provide an overview on the application of topical vancomycin in orthopaedic surgery focusing on the recent evidence and results in total joint arthroplasty. Several systematic reviews and meta-analyses on topical VP in hip and knee arthroplasty have been recently published reporting sometimes conflicting results. Apart from all being limited by the quality of the included studies (mostly level III and IV), confounding variables are often included potentially leading to biased conclusions. If taken into consideration the exclusive use of VP in isolation, the available data, although very limited, suggest that it does not reduce the infection rate in routine primary hip and knee arthroplasty. Therefore, we still cannot advise for a routinary application. A properly powered randomized-controlled trial would be necessary to clarify the role of VP in hip and knee arthroplasty. Based on the analysis of the current evidence, the use of topical VP appears to be safe when used locally in terms of systemic adverse reactions, hence, if proven to be effective, it could bring great benefits due to its low cost and accessibility.

Key Words: Periprosthetic joint infection; Vancomycin powder; Total knee arthroplasty;

Total hip arthroplasty; Infection; antibiotic

Core Tip: Vancomycin powder is widely used in orthopaedic surgery and it has been recently investigated in total joint arthroplasty (TJA), however, results are often conflicting. The aim of this study was to report on the use of vancomycin powder in orthopaedic surgery focusing on its application in TJA.

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INTRODUCTION

Periprosthetic joint infection (PJI) is one of the leading causes of revision in total joint arthroplasty (TJA) and its incidence has been reported between 1% to 4% after primary total knee arthroplasty (TKA) and 1% to 2% after primary total hip arthroplasty (THA) [1,2]. According to the available projections, the number of revisions is expected to grow proportionally to the number of primary implants performed every year[3] showing and increase of revision for PJI by 176% between 2014 and 2030 in THA, and by 170% in TKA[4]. Economic-based studies have reported that the yearly cost associated with PJI in the United States was approximately one billion United States dollars in 2017, and projected to reach almost two billion United States dollars by 2030[5].

Multiple strategies have been pursued to try to reduce the PJI rate in TJA, including preoperative screening, patient optimization, modified intraoperative techniques, and enhanced postoperative surveillance[6]. Vancomycin is a widely adopted and effective antibiotic in orthopaedic surgery, and its topical application has been investigated in different fields including spine surgery, trauma, and sport medicine to reduce the incidence of infection by providing a high concentration of antibiotic in a specific surgical site. Therefore, it has also been studied to reduce the PJI rate in TJA, reporting however conflicting conclusions.

The aim of this review is to provide an overview on the applications of topical vancomycin in orthopaedic surgery focusing on the use in TJA summarizing the results reported in the literature in order to clarify the current evidence for the use of topical VP.

The United States National Library of Medicine (PubMed/MEDLINE), EMBASE, and the Cochrane Database of Systematic Reviews were queried for publications utilizing various combinations of the search terms "VP", "vancomycin powder", "orthopaedic surgery", "orthopedic surgery" "arthroplasty", in combination with the Boolean operators (AND, OR, *) since January 2020 to December 2022. Two authors (Fabio Mancino and Christopher W Jones) independently conducted all the searches and screened the titles and abstracts to identify relevant studies. Differences were resolved by consulting a third senior reviewer (Piers J Yates). Only abstracts that evaluated the outcomes of VP in orthopaedic surgery were reviewed. If the title and abstract of each study contained insufficient information, the full manuscript was reviewed. An additional search was conducted by screening the references list of each selected article. Inclusion criteria were any systematic review and/or meta-analysis that pooled the results on the application of VP in orthopaedic surgery and TJA, analyzing the outcomes in terms of infection rate. Exclusion criteria were cohort studies, clinical trials, case reports, surgical technique reports, expert opinions, letters to editors, biomechanical reports, instructional course lectures, studies on animals, cadaver or *in vitro* investigations, book chapters, abstracts from scientific meetings, unpublished reports, and studies written in a non-English language. Two independent reviewers (Fabio Mancino and Christopher W Jones) separately examined all the identified studies and extracted data. During the initial review of the data, the following information was collected for each study: Title, first author, year of publication, study design, number of studies included, number of patients included, type of surgery, methods of application of VP, complications related to VP, superficial and deep infection rates.

BURDEN OF PERIPROSTHETIC JOINT INFECTION

PJI is a relatively rare complication. However, it is associated with a significantly greater morality when compared with patients undergoing aseptic revisions, up to five times higher at one year[7,8,9]. In addition, after the first case of PJI, the reinfection rate is up to 8.5% in THA and up to 16% in TKA[9], showing that the long-term consequences can be devastating. Kapadia *et al*[10], reported that patients with PJI had a significantly higher number of readmissions (3.6 *vs* 1.2; $P < 0.001$), length of hospitalization, clinic visits and sum-total episode cost than patients who had a non-infected primary implant (US$96,166 *vs* US$21,654; $P < 0.001$). When considering the economic burden, the cost of a revision for PJI is up to five times higher than a primary TJA ($116,382 *vs* $28,249)[11]. Moreover, managing this complication often requires a two-stage revision strategy, costing approximately US$60,000 more than revisions for mechanical failure and/ or aseptic loosening[12].

Currently, the only consensus recommendation for the use of antibiotics in TJA by international authorities is systemic perioperative administration[13].

VANCOMYCIN POWDER IN ORTHOPAEDIC SURGERY AND TJA

Gram-positive bacteria, particularly staphylococcal species, are the most common pathogenic organisms involved in post-operative orthopaedic infections[14]. Vancomycin is a tricyclic glycopeptide antibiotic with activity against gram-positive bacteria initially derived in 1953 from a compound produced by *Amycolatopsis orientalis*, a soil bacterium discovered within mud collected from a Borneo forest. The compound nicknamed "*Mississippi mud*" because of its appearance prior to purification became vancomycin (after the word "*vanquish*") and nearly 70 years later still retains antimicrobial activity against the majority of gram-positive organisms and remains the most commonly used antibiotic in the United States for the treatment of serious gram-positive infections, including those caused by methicillin-resistant Staphylococcus aureus (MRSA)[15].

The topical application of this antibiotic has been widely adopted in different fields of orthopaedic surgery with promising results. Sweet *et al*[16], demonstrated a significant reduction in postoperative deep wound infection rates (0.2% *vs* 2.6%; P < 0.0001) in posterior instrumented thoracolumbar spinal fusions with the adjunctive application of 2 g of VP before wound closure. Similar findings were reported by O'Neill *et al*[17], when analyzing 110 patients that underwent posterior spinal stabilization of traumatic injuries. The authors noted that the infection rate was significantly reduced (13% *vs* 0%; P = 0.02) when 1 g of vancomycin was applied before wound closure. Moreover, similarly reduced infection rates were reported both by Molinari *et al*[18] and by Bakhsheshian *et al*[19] when studying the effect of topical VP in instrumented and uninstrumented spine surgery.

The use of VP has been also investigated in tibial fractures, considered to be at high risk of infection, in an open-label multicentre randomized clinical trial reporting that the application of 1 g of VP was associated with a reduced risk of deep surgical site infection due to gram-positive organisms (risk difference, -3.7%; 95%CI, -6.7% to -0.8%; P = 0.02), in line with the activity of the antibiotic[20].

In addition, when VP was used in 422 shoulder arthroplasty, it has been associated with a significant reduction in PJI with no increased rate of aseptic wound complications, however, literature on shoulder surgery is limited and results are mostly based on retrospective analysis[21].

Similarly, studies on the application of topical VP in foot and ankle surgery and in total ankle arthroplasty (TAA) are limited, however, the economic viability has been investigated by Nam *et al*[22]. At their institutional cost of UD$3.06 per gram and a TAA PJI rate of 3%, VP would be cost-effective for TAA revision costs with an absolute risk reduction of 0.02% (number needed to treat = 5304). In addition, the authors showed that VP, when considered at their institutional price, would remain cost-effective even if the initial PJI rate was as low as 0.05%, and that if the PJI rate was held constant at 4%, VP would remain cost effective even within a range of price from US$2.50 to US$100.00 per gram. Nevertheless, the power analysis performed by the authors to confirm such results in a clinical trial shows the main limit of the investigations on VP.

Moreover, topical vancomycin is frequently used in anterior cruciate ligament reconstruction (ACLR) by wrapping the graft in a swab saturated with 5mg/mL vancomycin solution[23] and it has been associated with reduced incidence of postoperative septic arthritis[24]. In fact, Xiao *et al*[25], reported in a survey on the ACL Study Group members that 37.9% of the members pre-soak their ACL graft in vancomycin prior to implantation. In addition, Naendrup *et al*[24], pooled the results on 5075 ACLR showing a significant reduction in septic arthritis with no differences in clinical outcomes, biomechanical tendon properties, or cartilage integrity. Despite having many clinicians concerns regarding the potential toxicity on chondroblasts and osteoblasts, it has been proven *in-vitro* that when used at concentrations up to 5mg/mL, the vancomycin levels reached within the first 24-hours remain below the toxicity threshold for chondroblasts and osteoblasts [26].

Recently, vancomycin application has also been investigated in intraosseous (IO) infusion in THA at the concentration of 500mg/100cc of normal saline showing increased local tissue and decreased systemic concentrations when compared with standard prophylactic intravenous (IV) administration[27]. Similar findings have also been reported in a high body mass index (BMI) population that underwent TKA showing local concentrations up to 9-times higher than systemic administration[28].

Considering these promising results, VP is used in TJA with the hope of significantly reducing the risk of PJI (Figure 1). Weight-based (15 mg/Kg) IV vancomycin is already widely adopted as a second-line prophylaxis instead of first- or second-generation cephalosporin in case of allergies to penicillin, history of MRSA, or positive preoperative MRSA nasal-swab colture[29]. However, considering the better results associated with cephalosporins, the International Consensus on PJI recommended that these antibiotics can be safely used in case of non-anaphylactic penicillin allergy[30] since the cross-reactivity risk has been proven to be as low as 1%[31].

Topical application of VP allows higher concentrations in the surgical area while minimizing the systemic adverse effects[32]. In a rat model, the use of intra-articular VP combined with IV antibiotics resulted in the complete eradication of MRSA bacteria from contaminated implants[33]. Johnson *et al*[32] studied vancomycin concentration both locally and systemically after the administration of 1 g of intra-articular VP and 1 g after closure of the fascia in the superficial tissues in 34 THA reporting the different serum levels at 90 min, 3 h, 12 h, and 24 h, and the local levels at 3 h, 12 h, and 24 h. The authors reported that the mean serum concentration peaked at 12 h (4.7 mcg/mL; max observed 12.7 mcg/mL at 3 h)

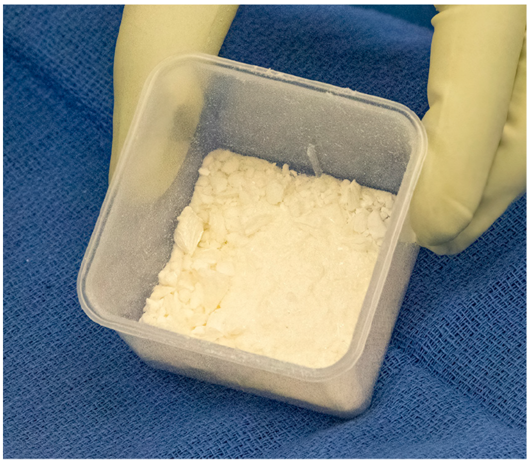

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Figure 1 Vancomycin powder used in 1-st stage revision total knee arthroplasty.

while the systemic therapeutic levels of 15-20 mcg/mL were never reached in any of the time-points. In addition, the intra-wound half-life was estimated to be 7.2 h with mean wound levels > 900 mcg/mL at 3 h while maintaining the local concentration over 200 mcg/mL for 24 h. Finally, the authors estimated that it would take up to 64 h for intrawound levels to drop below the minimum inhibitory concentration for *S. aureus* of 2 mcg/mL (Table 1).

Despite the potential benefits, there are also theoretical drawbacks. Firstly, the low systemic concentration of vancomycin may induce the development of resistant species of gram-positive bacteria colonizing the body. The Infectious Disease Society of America recommended serum levels > 10 mcg/mL to avoid the potential development of resistance[34]. Given the short half-life of the antibiotic when administered parenterally (4-6 h), this is not problematic when administered as a single dose of prophylactic IV antibiotic providing coverage for the first 24 h, but maybe a factor during ongoing and prolonged systemic absorption of intra-articular antibiotics. Secondly, a potential third body wear mechanism has been hypothesized between crystalline vancomycin and implant components since the solubility of vancomycin may vary in an intra-articular environment compared to saline solution. Nevertheless, Qadir *et al*[35] reported no appreciable difference in wear rates after 10 million simulated cycles between ultra-high-molecular-weight-polyethylene and Cobalt-Chrome alloy with the addition of VP. Lastly, vancomycin may have negative effects on the proliferation of viable cells including osteoblasts. Braun *et al*[36], reported the *in-vitro* effect of vancomycin on osteoblasts, endothelial cells, fibroblasts and skeletal muscle cells showing that the toxic effects were time (from day-3) and concentration-dependent (> 0.01 mg/mL). However, such results are yet to be proven *in-vivo*, and as shown by Johnson, no such concentrations have been reported at the 3-d mark. Therefore, based on the aforementioned studies, topical administration of VP can reasonably be considered clinically safe when used in TJA. Finally, if proven to significantly impact the PJI rate, VP would be highly cost-effective as its price has been reported from $2.50 to the highest of $44.00 per gram[37].

CURRENT LITERATURE FOR VP IN TKA AND THA

Overall, seven systematic reviews and/or meta-analyses were identified and analyzed[38-44] (Table 2).

Movassaghi *et al*[38], reported that intrawound VP may reduce the risk of PJI in primary and revision TJA while not leading to systemic complications. The authors included in their analysis 16 studies and 17164 TJA that received intrawound VP reporting an overall decreased rate of PJI (OR 0.46, $P < 0.05$), a decreased rate when considering TKA and THA separately (OR 0.41, $P < 0.05$ and OR 0.45, $P < 0.05$, respectively), and a decreased rate when considering primary implants only (OR 0.44, $P < 0.05$). Most of their results came from the outcomes of 14262 primary TKA (of 17164 joints, 83%) and that among them, 9884 cases (69% of primary knees) came from a study[44] where the so-called "VIP protocol" was used by mixing VP and 0.35% povidone-iodine (PI) solution (17.5 mL in 500 mL saline).

Regarding PI lavage, Kim *et al*[46], reported in a systematic review on 7 studies and 8861 TJA no difference between PI and saline in reducing the PJI rate. However, more recent studies showed efficacy in revision TJA reducing the PJI rate from 3.4% to 0.4% ($P = 0.038$, 478 revisions)[47], and efficacy in reducing the rate of any infection over 3232 TJA (OR 0.45, $P < 0.05$) or superficial site infections (SSI, OR 0.3, $P < 0.05$)[47]. Finally, Shohat *et al*[49] recently reported on the outcomes of 31331 cases showing a 2.34 times lower rate of PJI when comparing PI lavage with saline in TJA (0.6% *vs* 1.3%) with an absolute risk reduction of 0.73% and a number needed to treat of 137 patients. Therefore, the positive outcomes reported by Movassaghi *et al*[38] may have been influenced by the inclusion of iodine lavage.

Similarly, Liao *et al*[43], published in strong favor of VP suggesting that VP has a clear effect on preventing PJI in primary TKA. The authors reported on 11292 TKA where VP was used with a Risk Ratio (RR) of 0.41 (95%CI 0.29 to 0.58, $P < 0.001$) when compared to cases where VP was not used. However, as previously mentioned, 46.7% of of the cases analyzed came from studies[45,50] where VP was used in combination with a PI solution, potentially having once again a significant effect on the final results.

Table 1 Serum and local levels of vancomycin at different post-wound closure collection times

Procedure	Serum levels after wound closure of VP intrawound administration (g/mL)				
	1.5 h (mean ± SD; max)	3 h (mean ± SD; max)	12 h (mean ± SD; max)	24 h (mean ± SD; max)	Highest level observed across the 24-h period
THA (*n* = 15)	3.8 ± 3.9; 9.5	4.9 ± 4.5; 12.7	5.1 ± 3.3; 8.4	3.5 ± 3.5; 8.0	6.6 ± 3.8; 12.7
TKA (*n* = 19)	1.0 ± 2.5; 8.7	1.8 ± 3.2; 9.8	4.4 ± 3.1; 7.3	3.5 ± 3.6; 10.4	5.2 ± 3.4; 10.4
THA + TKA (*n* = 34)	2.2 ± 3.4; 9.5	3.2 ± 4.1; 12.7	4.7 ± 3.2; 8.4	3.5 ± 3.5; 10.4	5.8 ± 3.6; 12.7
	Local levels after wound closure of VP intrawound administration, *n* (g/mL)				
	-	**3 h (mean ± SD)**	**12 h (mean ± SD)**	**24 h (mean ± SD)**	**-**
THA	-	988 ± 628 (12)	769 ± 1059 (11)	280 ± 436 (11)	-
TKA	-	877 ± 455 (18)	288 ± 203 (16)	163 ± 220 (18)	-
THA + TKA	-	922 ± 523 (30)	484 ± 716 (27)	207 ± 317 (29)	-

VP: Vancomycin powder; THA: Total hip arthroplasty; TKA: Total knee arthroplasty. Adapted from: Johnson JD, Nessler JM, Horazdovsky RD, Vang S, Thomas AJ, Marston SB. Serum and Wound Vancomycin Levels After Intrawound Administration in Primary Total Joint Arthroplasty. *J Arthroplasty* 2017 Mar; 32(3): 924-928. Copyright © 2015 Elsevier Inc. All rights reserved.

Table 2 Main characteristics and results of the recent literature on the topic vancomycin powder

Ref.	Type of study	No. of studies	No. of cases (control/intervention)	PJI Rate/RR (control *vs* intervention)	SSI/Aseptic wound complications (control *vs* intervention)	Authors' conclusions
Martin *et al* [36], 2022	Systematic review and meta-analysis	7/7	144724/8029	RR 0.39 (95%CI 0.27-0.56, *P* < 0.001)	6.48% *vs* 3.79%	VP ± PI lavage reduced PJI rate in primary and revision THA/TKA. Associated with reduced aseptic wound complications
Liao *et al*[35], 2022	Systematic review and meta-analysis	14	7720/1292	RR 0.41 (95%CI 0.29-0.58, *P* < 0.001)	-	VP recommended in primary TKA
Movassaghi *et al*[30], 2022	Systematic review and meta-analysis	16	3731/17164	1.65% *vs* 0.87% (*P* < 0.05)	-	Local VP may reduce the risk of PJI in primary and revision TJA
Wong *et al* [31], 2021	Systematic review	9	6255/3371	-	No difference	Recommend the surgeons not to use VP in routine THA and TKA
Peng *et al*[32], 2021	Systematic review and meta-analysis	9	4512/2354	RR 0.37 (95%CI 0.23-0.60, *P* < 0.001)	RR = 0.40, 95%CI 0.27-0.61 (*P* < 0.001)	Local VP could significantly decrease the rate of SSI and PJI in primary TJA
Saidahmed *et al*[33], 2021	Systematic review and meta-analysis	9	3714/1985	3.5% *vs* 1.6%, RR 0.53 (95%CI 0.35-0.79, *P* = 0.002, I^2 = 0.0%)	No difference 1.6% *vs* 0.7%, RR = 0.61, 95%CI 0.17-2.12, (*P* = 0.43, I^2 = 0.0%)	Local antibiotic application results in a moderate reduction in deep infection rates in primary TJA, with no significant impact on SSI rate
Xu *et al*[34], 2020	Systematic review and meta-analysis	9	4607/2497	2.75% *vs* 1.20% (OR 0.44, 95%CI 0.28-0.69, I^2 = 0.0%)	No difference 1.60% *vs* 0.67% (OR 0.60, 95%CI 0.17-2.12, I^2 = 0.0%)	VP used in primary hip and knee arthroplasty may reduce the incidence of PJI but it may increase the risk of aseptic wound complications

RR: Relative risk; SSI: Superficial site infection; VP: Vancomycin powder; PI: Povidone iodine; PJI: Periprosthetic joint infection; THA: Total hip arthroplasty; TKA: Total knee arthroplasty; TJA: Total joint arthroplasty; OR: Odds ratio.

Moreover, Peng *et al*[40], stated that "the local application of VP could significantly decrease the rate of SSI and PJI in primary TJA" recommending its topical administration before wound closure. The meta-analysis included nine studies and three of those[49,51,52], representing a weight on the result of 44%, did not involve only the application of topical VP, therefore, their inclusion could be misleading. One of these[50], reported on the combined application of PI lavage and

VP showing that administration of local antibiotics was preventative for PJI only in the primary TKA (OR 0.28, 95%CI 0.09–0.89). The other two[51,53], reported on the application of VP on the surface of cementless implants in THA and TKA and not in the soft tissue deep or superficial to the fascia/capsule, therefore, a completely different way of using VP.

Xu *et al*[42], reported that "the current literature suggests that intrawound vancomycin used in primary hip and knee arthroplasty may reduce the incidence of PJI, but it may also increase risk of aseptic wound complications". Nine studies were included in their final analysis with 4605 TJA, 2497 of which were treated with VP. The authors reported a reduced PJI rate in the VP group (1.20% *vs* 2.75%) with an OR of 0.44 (95%CI 0.28 to 0.69, I^2 = 0.0%), a comparable risk of SSI (OR 0.60, 95%CI 0.17 to 2.12), and a higher incidence of aseptic wound complications (2.15% *vs* 0.96%, OR 2.39, 95%CI 1.09 to 5.23). However, when considering the aseptic wound complications, only four of the nine studies reported on such events (1069 treated cases), and all of them had different methodology protocols in terms of the amount of VP used, placement of the VP (deep to the fascia, superficial, or both), and the application of a drain for up to 48 h post-operative. Therefore, the conclusion that VP is associated with an increased risk of aseptic wound complications, based on such results, may require stronger evidence.

Saidahmed *et al*[41], stated that topical antibiotics led to a moderate reduction in PJI in primary TJA, with no significant impact on SSI rates but that it may be associated with a moderate increase in aseptic wound complication. However, once again, four of the nine studies reported mixed results considering the combined activity of PI lavage and VP[50], the application on cementless implants[52,53], or did not consider only the application of VP in TJA but more generally the use of topical antibiotics[54].

On the other hand, Wong *et al*[39] discouraged the application of VP in primary TJA after systematically analysing the outcomes of 9 studies and 3371 TJA in which VP was used compared with 2884 in which it was not. Only studies with similar procedures and those limited to the application of VP were included. The authors reported that only one of the studies included[51] was associated with significant improvement while the remaining eight had OR that broadly bracketed the line of no difference (range, 0.09 to 1.97). In addition, the authors noted insufficient evidence on the question of safety, therefore, their final statement was against the use of topical VP in routine THA and TKA unless adequately powered, multicentre, prospective trials demonstrate clear evidence. However, despite the methodology and the inclusion criteria being well defined to include only studies using topical VP in isolation, no statistical analysis was performed to verify the results.

Lastly, Martin *et al*[44] recently pooled together the studies using VP alone (7 studies) and in combination with PI lavage (7 studies) reporting a significant reduction of PJI rate (RR 0.39, 95%CI 0.27 to 0.56, P < 0.001) in primary and revision THA and TKA when compared with a control group. However, there remain doubts on the contribution of the PI lavage as we are still missing clear results on the VP alone used with standardized methods and compared with a control group. Interestingly, the authors reported a reduced aseptic wound complication rate in the treatment pool (110/2903, 3.79% *vs* 98/1512, 6.48%), though, still considering the combined effect of VP and PI lavage.

CONCLUSION

PJI in TJA is certainly one of the biggest challenges that the orthopaedic community is now facing with tremendous impact on the patient, the treating multi-disciplinary team, and the health care system. Despite the topical application of VP appears to be safe in terms of systemic complications, there are potential risks regarding the development of antimicrobial resistance following the administration of VP and most importantly, from the available data, we cannot conclude that when used in isolation it is effective in reducing the PJI rate. Evidence remains lacking with varying methodologies and important technical differences (amount of VP, placement deep or superficial to the fascia, use of drain). In fact, positive outcomes appear only to have been reported when the additional application of PI is considered together with VP. It must also be noted that the use of intraoperative antimicrobial irrigation (*e.g.* deep or subcutaneous tissues), or the application of antimicrobial agents (*e.g.* ointments, solutions, or powders) to the surgical incision for the prevention of SSI are not currently recommended by The Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection[55]. Moreover, evidence supports the perceived increased risk of aseptic wound complications, which should be further investigated.

Therefore, despite the multiple studies recently published, the efficacy of VP in TJA for reducing PJI is still essentially unknown. To overcome this issue, a randomized controlled trial with homogeneous methodology and exclusion of additional confounding variables (such as PI lavage) would be necessary.

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MINIREVIEWS

In vitro laboratory infection research in orthopaedics: Why, when, and how

Konstantinos Tsikopoulos, Lorenzo Drago, Gabriele Meroni, Dimitrios Kitridis, Byron Chalidis, Fotios Papageorgiou, Paraskevi Papaioannidou

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Abstract

The musculoskeletal system involves multiple tissues which are constantly exposed to being exposed to various biological and mechanical stimuli. As such, isolating and studying a particular system from a complex human clinical environment is not always a realistic expectation. On top of that, recruitment limitations, in addition to the nature of orthopaedic interventions and their associated cost, sometimes preclude consideration of human trials to answer a clinical question. Therefore, in this mini review, we sought to rationalize the rapid evolution of biomedical research at a basic scientific level and explain why the perception of orthopaedic conditions has fundamentally changed over the last decades. In more detail, we highlight that the number of orthopaedic *in vitro* publications has soared since 1990. Last but not least, we elaborated on the minimum requirements for conducting a scientifically sound infection-related laboratory experiment to offer valuable information to clinical practitioners. We also explained the rationale behind implementing molecular biology techniques,

ex vivo experiments, and artificial intelligence in this type of laboratory research.

Key Words: Biofilm; *In vitro*; Laboratory research; Methodology

Core Tip: This paper highlights some major orthopaedic research advances at a basic science level. On top of that, it is highlighted that the perception of orthopaedic conditions has fundamentally changed recently, reflecting on clinical practice. We also described the basic aspects of a successful *in vitro* infection laboratory experiment and expanded on recent evidence relating to molecular biology, *ex vivo* investigations, and artificial intelligence in orthopaedics.

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INTRODUCTION

Why and when to proceed with basic science orthopaedic research?

Barriers to orthopaedic research: It is widely recognized that high-quality randomized evidence is lacking in orthopaedics. The main reasons behind that include the increased cost of conducting a trial, the lack of funding and resources, the limited availability of time from the clinicians[1], and the overall recruitment limitations. Although significant musculoskeletal concerns are fraught with ambiguity in the scientific community, it has been demonstrated that many surgeons are insufficiently motivated to discuss trial participation with their patients[2]. On top of that, orthopaedic trainees may show limited interest in conducting research, feel unsupported, and lack mentorship and/or opportunities to get involved in experimental projects[3]. According to the above, when assessing the feasibility of orthopaedic projects, researchers should have realistic expectations and carefully select the appropriate study design.

Is *in vitro* research the appropriate remedy? It should be noted that *in vitro* models are laboratory-based experiments that imitate biological processes outside a real organism. *In vitro* models are frequently utilized in orthopaedic research to investigate many aspects of musculoskeletal diseases, tissue engineering, and medication development[4]. Conducting *in vitro* laboratory research enables researchers to overcome the complexity of multiple organ interactions in human beings [4]. Furthermore, funding for clinical and translational animal research is usually insufficient to address the unanswered orthopaedic research questions. Therefore, opting for basic science projects appears beneficial, particularly when investigating topics that have not been dealt with before. Nevertheless, we should underline that although basic science orthopaedic research intends to bridge the gap between the absence of knowledge on a given topic and clinical practice, we advocate that the results of *in vitro* trials must be interpreted cautiously and should not be exclusively extrapolated in human setting.

How to properly conduct infection orthopeadic research at a basic science level?

Infection outcomes and administration/training requirements: First, it must be pointed out that the standard strain of a given microorganism is investigated for reproducibility and transparency reasons. Initial testing should include planktonic growth evaluation not only in the presence of antimicrobial agents as well as untreated control, in order for the researcher to reliably evaluate the antimicrobial capacity of a potential antimicrobial agent. Subsequently, biofilm studies should include intervention(s) group(s) and an untreated biofilm control.

When assessing the results of the exposure of microorganisms to potential anti-bacterial agents, there are plenty of options to investigate their effectiveness in the lab. The most common method features a colorimetric evaluation of cell viability with the 2-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide reduction assay, which is a highly reliable method and particularly useful for investigating multiple technical replications in the lab[5,6].

Regarding the infection prevention experiments, attention should be paid to the difference in cell viability between the intervention and control groups. The minimum inhibition threshold of 80% must be surpassed for this difference to be clinically meaningful[7].

From an administrative perspective, attaining Institutional Review Board Approval before performing a formal microbiological experiment is advisable to ensure Good Laboratory Practice. According to our experience and literature, substantial up-front investment in infrastructure and lab consumables is suggested to ensure an uninterrupted flow of experiments. From a scientific point of view, collaboration with well-established infection labs as well as ongoing lab training of the personnel are essential steps for the successful execution of experiments.

Guidelines, statistical considerations, pictorial presentations and extrapolation of results: Similar to other types of research, reporting guidelines should be provided along with the experimental studies[8]. More specifically, the primary and secondary outcomes of a given *in vitro* experiment should be clearly reported in the methods sections.

From a statistical point of view, researchers should bear in mind that achieving sufficient study power applies to clinical papers and basic science research. In other words, implementing a sufficient sample size based on the primary outcomes of an *in vitro* study enables the authors to reach consistent and clinically meaningful conclusions. Moreover, authors are encouraged to comment on any potential biases which may compromise the reliability of their findings[8].

Pictorial and graphical presentation of the results is essential: Regarding infection-related *in vitro* pre-clinical research, it is proposed that the authors produce a graphical representation of microbial development that will serve as the basis for their future tests[9] (Figure 1).

In doing so, the credibility of the work and the establishment of future, more advanced and sophisticated investigations can be improved. Furthermore, in case of comparisons with control groups, implementation of a dedicated piece of software such as Prism (GraphPad Software, Inc, La Jolla, CA, United States) is advocated to generate scientifically sound figures[9] (Figure 2).

Furthermore, considering that *in vitro* research is the first step of the evidence-based procedure, researchers and clinicians alike should adopt a stepwise approach when validating the results of an *in vitro* laboratory experiment. More specifically, a proper animal model study should be generated following a successful *in vitro* experiment[10], so that the authors can assess their primary findings against *in vivo* conditions. As a last step, human testing should be performed for confirmation purposes[4].

Recently introduced techniques: Do they merit consideration?

Molecular biology techniques: Molecular-biology-based techniques have rapidly evolved in the last years in orthopedic infections and other fields, such as in diagnosing severe acute respiratory syndrome coronavirus 2[11] and water surveillance industry. In particular, more sophisticated molecular methods, including but not limited to clustered regularly interspaced short palindromic repeats, next-generation sequencing and droplet-digital polymerase chain reaction (PCR) are currently being investigated to contribute to the detection of the above mentioned virus. Moreover, rapid detection of harmful bacteria in wastewater is achievable when utilising DNA microarray and sequencing-based methods[12].

Similar progression has been recorded over the past years in orthopedic infections, not only in experimental laboratory settings but also in clinical practice. To illustrate, utilisation of PCR-based techniques, including but not limited to DNA microarrays and multiplex PCR, has been one of the most important advances in periprosthetic joint infections (PJI) diagnosis during the last decades[13]. The readily available multiplex polymerase chain reaction techniques (*i.e.*, commercial and bespoke ones) feature satisfactory diagnostic accuracy, with a specificity approaching 100% and sensitivity varying between 70% to 80%[13]. In addition, newer diagnostic modalities such as metagenomic next-generation sequencing enable DNA sequencing directly from synovial fluid[14]. It has been claimed that metagenomic next-generation sequencing may revolutionise PJI diagnosis as it demonstrates increased sensitivity relative to PCR, while maintaining specificity at the same ultimate levels[13].

Is artificial intelligence applicable to *in vitro* models? Artificial intelligence (AI) may be implemented into orthopaedic *in vitro* models. For example, AI may aid in evaluating massive volumes of information from *in vitro* studies, such as gene expression data, protein profiles, and biomechanical data, to detect trends and make predictions. Another example would be application of AI to tumor models to monitor tumorigenesis progression in addition to real-time modelling[15]. Furthermore, AI could also aid in controlling the quality of organoids in the field of organogenesis and bioprinting technology[16]. In general, *in vitro* models frequently generate enormous volumes of data, including pictures and signals from several imaging modalities such as microscopy, radiography, and biomechanical sensors. AI enables assessing those data, extracting relevant information, and spotting small changes that human eyes may miss. This can facilitate measuring cellular activity, tissue shape, and mechanical characteristics, thus resulting in a more complete knowledge of the underlying biology[17,18]. Therefore, researchers may better understand the underlying process of orthopaedic illness, predict disease development, and consider prospective therapy efficacy[19]. In addition, AI can optimize experimental research designs by finetuning experimental settings, addressing sample size issues, and recommending the most important experiment variables that should be prioritised during analysis. Therefore, researchers may become more effective and productive, eliminate trial-and-error and save time and money at the same time[17]. Another example of AI application is referred to personalized/individualised medicine. AI may utilise patient-specific data, such as genetic information and medical history and construct tailored *in vitro* models that simulate the patient's clinical condition. Researchers can monitor illness development and explore individualized treatment strategies, leading to more effective and targeted therapeutic approaches.

Additionally, AI can enhance the potential of medication research by evaluating enormous databases of chemical substances and predicting their possible effects on orthopaedic diseases. This can further identify interesting drug candidates and optimize their chemical structures, improving effectiveness and safety. Moreover, AI can generate virtual simulations of *in vitro* models, thus allowing researchers to test various scenarios and treatments in a controlled and cost-effective setting[20]. As a result, it could potentially refine experimental methods, minimise the requirement for physical experiments, and reduce the need to implement animal models.

Overall, AI has the potential to significantly improve orthopaedic *in vitro* models by enhancing predictive modeling, optimizing experimental design, assisting in image and signal analysis. Therefore, it improves customized therapy, expedites drug development, and facilitates virtual simulations. According to the above, orthopaedic researchers may obtain deeper insights into disease causes, devise more effective therapies, and ultimately enhance patient outcomes by utilizing the potential of AI.

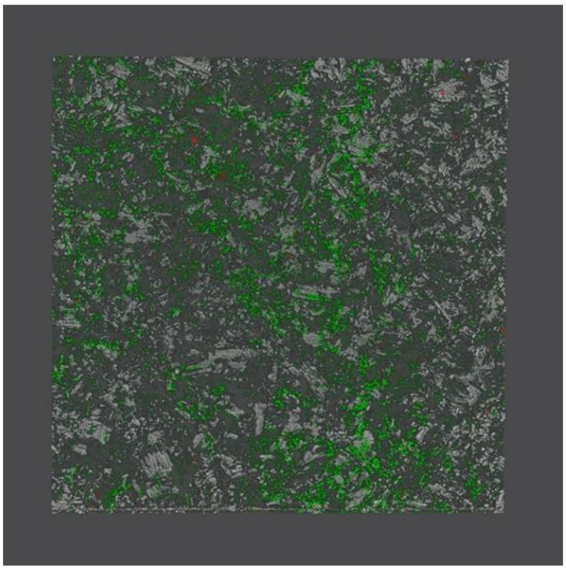

Figure 1 Image of a two-dimensional representation of *Cutibacterium acnes* growth on titanium alloy (Ti6Al4V) disk using Confocal laser microscopy (Leica model TCS SP5; Leica Microsystems CMS GmbH, Mannheim, Germany) following 72 h of anaerobic incubation. Live bacteria are represented in green and dead cells are in red.

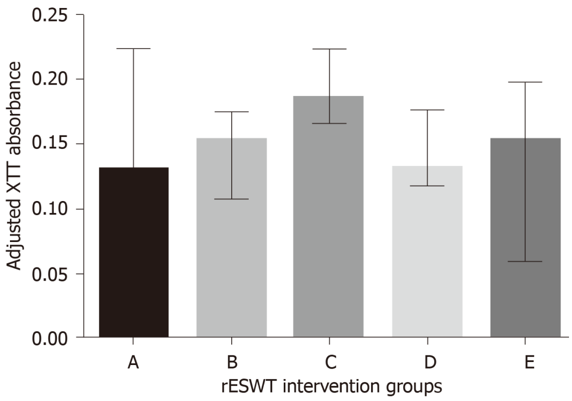

Figure 2 Graphical illustration enables visual comparison between the intervention groups. Variant absorption among the included radial extracorporeal shock wave treatment study groups following spectrophotometric evaluation is depicted. rESWT: Radial extracorporeal shock wave treatment; XTT: 2-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide.

Are *in vitro* "*ex-vivo*" infection models viable options? *Ex vivo* orthopaedic models allow using bone or muscle tissue as a substrate to form biofilm infections such as osteomyelitis[21]. These models appear particularly advantageous relative to their *in vitro* counterparts as they maintain important biological factors from the hosts[22]. *Ex vivo* experiments are cheaper than animal models and can spare animal lives[23]. However, careful consideration prior to selecting this type of laboratory research is advisable since no immune system interactions occur, and therefore the results may be suboptimal compared to *in vivo* settings[24].

CONCLUSION

Over the last years, the perception of orthopaedic conditions has shifted towards a more basic science-oriented approach. Therefore, the value of conducting high-quality basic science research tends to be increasingly appreciated by the orthopaedic community. In addition, when appropriate, favouring basic science over clinical investigations could mitigate the clinical research obstacles to some extent. However, it is important to highlight that unwarranted extrapolations of basic science research to human biology should be avoided.

FOOTNOTES

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MINIREVIEWS

Fractures around the shoulder in the skeletally immature: A scoping review

Tim Kraal, Peter AA Struijs, Lisette C Langenberg, Christiaan JA van Bergen

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Abstract

Fractures around the shoulder girdle in children are mainly caused by sports accidents. The clavicle and the proximal humerus are most commonly involved. Both the clavicle and the proximal humerus have a remarkable potential for remodeling, which is why most of these fractures in children can be treated conservatively. However, the key is to understand when a child benefits from surgical management. Clear indications for surgery of these fractures are lacking. This review focuses on the available evidence on the management of clavicle and proximal humerus fractures in children. The only strict indications for surgery for diaphyseal clavicle fractures in children are open fractures, tenting of the skin with necrosis, associated neurovascular injury, or a floating shoulder. There is no evidence to argue for surgery of displaced clavicle fractures to prevent malunion since most malunions are asymptomatic. In the rare case of a symptomatic malunion of the clavicle in children, corrective osteosynthesis is a viable treatment option. For proximal humerus fractures in children, treatment is dictated by the patient's age (and thus remodeling potential) and the amount of fracture displacement. Under ten years of age, even severely displaced fractures can be treated conservatively. From the age of 13 and onwards, surgery has better outcomes for severely displaced (Neer types III and IV) fractures. Between 10 and 13 years of age, the indications for surgical treatment are less clear, with varying cut-off values of angulation (30-60 degrees) or displacement (1/3 – 2/3 shaft width) in the current literature.

Key Words: Clavicle fracture; Proximal humerus fracture; Pediatric; Skeletally immature; Children; Shoulder

Core Tip: Fractures of the clavicle and proximal humerus in children can be treated conservatively in most patients because of their large remodeling potential. The difficulty is to understand when a child is better off with surgical treatment of his/her clavicle or proximal humerus fracture. This review aims to provide a better understanding of the indications for surgical management of these fractures in the skeletally immature based on the latest literature.

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INTRODUCTION

Fractures of the shoulder girdle in the skeletally immature are relatively rare, and most fractures can be treated conservatively. However, precisely this situation makes deciding which pediatric shoulder fracture needs surgical treatment difficult. Of the pediatric shoulder girdle injuries, fractures of the clavicle and proximal humerus are the most common. This review article updates treatment recommendations for these fractures in the skeletally immature.

DIAPHYSEAL CLAVICLE FRACTURES

Epidemiology

The clavicle is the most commonly fractured shoulder girdle bone in children. It accounts for 10%-15% of all pediatric fractures, more common in boys compared to girls[1]. Most clavicle fractures occur during sports activities like bike accidents or horse riding. About 90% of clavicle fractures are diaphyseal, and most are Allman type 1 fractures, in the middle third of the shaft[2]. More than 50% of clavicle shaft fractures in children and adolescents are completely displaced with substantial shortening[3]. Clavicle fractures due to obstetrical injury are beyond the scope of this review.

Anatomy

The clavicle has a medial and lateral ossification center which usually fuse around the seventh week of gestation. A congenital pseudoarthrosis can develop if this fusion does not occur, leading to a painless protuberance[4]. Eighty percent of clavicular longitudinal growth occurs from the medial physis. The lateral physis closes around 18-19 years of age, and the medial physis is the last of the human body to close around 23 to 25 years of age. The clavicle is surrounded by a thick periosteum around both ends. Sternoclavicular (SC) injuries and, to a lesser extent, acromioclavicular (AC) injuries, are often trans-physeal fractures rather than true AC or SC joint dislocations[5,6].

Treatment

There are few clear indications for surgical treatment of clavicle fractures in children; open fractures, irreducible fractures with significant tenting of the skin with impending skin necrosis, acute neurovascular injury, or concomitant fractures of the scapula (floating shoulder). In adults, substantial dislocation of a clavicular shaft fracture often indicates osteosynthesis to avoid non-union or symptomatic malunion. In children, however, these fractures can usually be treated non-operatively with a sling or figure-of-eight bandage. Your mentor might have told you the adage: “If the two ends of the child’s clavicle are in the same room, they will heal and remodel adequately”. There are several articles with typical radiographs showing consolidation and remodeling after displaced clavicle fractures[7,8]. Even an initial displacement of more than 2cm will most likely lead to union without clinically meaningful loss of shoulder motion or strength[9,10]. The degree of dislocation will most likely improve during the initial healing phase, and substantial remodeling can occur since clavicle growth continues up to 25 years of age[11,12]. However, there seems to be a tendency towards more surgical procedures for clavicle fractures in teenagers[13]. This is most likely the result of a similar trend toward surgical treatment of clavicle fractures in adults. In contrast to the situation in adults, however, little evidence supports this trend in the skeletally immature.

The potential advantages of surgical management are a quicker return to sports and avoiding non- and malunion. A recent review showed a quicker return to sports of 4-6 wk in the surgically treated group[14,15]. However, other studies do not show a significantly shorter return to sports[16]. The gain in weeks for return to sports is relatively minimal, but might be a consideration for young athletes who wish to return to high-level sports as soon as possible. Surgery is associated with higher healthcare costs and a higher complication rate. The most common complications are sensory loss at the chest region and implant prominence. Secondary surgery because of implant prominence is reported in 10%-20% of cases[8,17]. The pros and cons for young athletes should be used in shared decision-making if surgical treatment is considered, which is also highlighted in a current concepts review on this topic[18].

Nonunion, malunion, and re-fracture risk

Whether surgery should be performed to prevent non- and symptomatic malunion in children is highly questionable. Clavicular non-unions in children do exist, but are exceedingly rare. Figure 1 shows a rare case of a 15 year old boy with scapular dyskinesia caused by shortening of his clavicle due to a nonunion. A large randomized trial comparing surgical treatment with conservative treatment for displaced clavicular fractures found a non-union rate of 0.4%[19]. With such low numbers of non-union, the incidence of non-union is difficult to establish, but is estimated to be less than 1%[20]. Although most non-unions occur in completely displaced fractures, they can even happen in minimally displaced fractures[20]. The primary risk factor for non-union is a re-fracture[20,21]. Non-unions are usually treated successfully with plate fixation. Bone grafting from the locally available non-union fracture site is usually enough, and iliac crest bone graft is not necessary in most cases[20,22].

Historically, symptomatic malunion has been a concern, potentially leading to decreased function or strength of the affected shoulder. This hypothesis was mainly based on anatomical and biomechanical studies[23]. In clinical reports, it is assumed that malunion can cause a wide variety of symptoms, such as functional limitations of the arm with or without pain, weakness of the arm, scapular dyskinesia, thoracic outlet syndrome or compression on the brachial plexus, and cosmetic dissatisfaction[24].

There is good quality evidence on this topic available at the moment, with a recent large multicenter cohort study comparing operative *vs* non-operative treatment for displaced clavicle fractures in adolescents[19]. Multiple upper limb functional outcome scores showed no significant differences between both groups. Only two out of 291 patients in this cohort developed a symptomatic malunion after non-operative treatment. For the rare patient who develops a symptomatic malunion, delayed (corrective) osteosynthesis is a good option. Adequate pre-operative 3D planning and patient-specific cutting guides can aid in correcting the three-dimensional deformity of the clavicle. However, no reports could be found explicitly aimed at children concerning malunion corrections[25].

The re-fracture risk of the clavicle in pediatric patients is around 2% to 6%. Interestingly, the re-fracture risk is higher after angulation only for completely displaced fractures[7]. It is hypothesized that this can be caused by more callus formation in completely displaced fractures compared to angulation-only fractures. Re-fractures occur in both surgically and non-operatively treated patients, perhaps even more frequently in surgically treated patients[14,19]. Just like initial diaphyseal clavicle fractures, most re-fractures can be treated non-operatively.

To conclude, the standard of care for all diaphyseal clavicle fractures in the skeletally immature is non-operative treatment. A quicker return to sport is a relative argument to opt for surgery in the adolescent (professional) athlete. Non-union is very rare in the skeletally immature and can be treated with osteosynthesis. Most cases of initial shortening will remodel, and even most malunions will recover without functional limitations in the long term. Osteosynthesis of the clavicle should not be chosen to prevent non-union, shortening, or malunion in the skeletally immature. Corrective osteosynthesis should be reserved for rare cases with symptomatic malunion.

PROXIMAL HUMERUS FRACTURES

Epidemiology

Proximal humerus fractures in the pediatric population are quite rare and relatively uncommon compared to other upper limb fractures in children. This fracture accounts for approximately 0.5 to 3% of all pediatric fractures[26,27]. Pediatric proximal humerus fractures are more common in boys compared to girls in most geographical areas[28].

The trauma mechanism can be a backward fall on an extended and externally rotated arm. These injuries can result from sports, horse- or bike riding, and motor vehicle accidents. In the very young, especially under 18 mo of age, one must be aware of the possibility of child abuse[29].

Radiographs should be carefully screened for intra-osseous pathologic lesions or cysts if a proximal humerus fracture is diagnosed after minimal trauma. Of all pathologic fractures, the proximal humerus and the proximal femur are the most common locations for a pathologic fracture to occur[30]. Unicameral or solitary bone cysts are the leading cause of these pathologic fractures. Also, the presence of pain preceding the fracture should raise the suspicion of a pathologic fracture.

Little League Shoulder is an entity on its own. This is a stress- or insufficiency fracture of the proximal humeral physis due to overuse, most commonly repetitive throwing, such as in young baseball players. Patients typically report pain while throwing. In addition, radiographs can show widening of the physis and lateral physeal fragmentation, calcification, and/or sclerosis.

Anatomy

The proximal humerus develops from three ossification centers (head, greater and lesser tuberosity). The ossification center of the head appears between birth and six months, followed by the ossification center of the greater tuberosity around the age of 6-18 mo. Lastly, the ossification center of the minor tuberosity appears around the age of five. These ossification centers merge into one single proximal humerus physis between the 4^{th} and 7^{th} year of age[31].

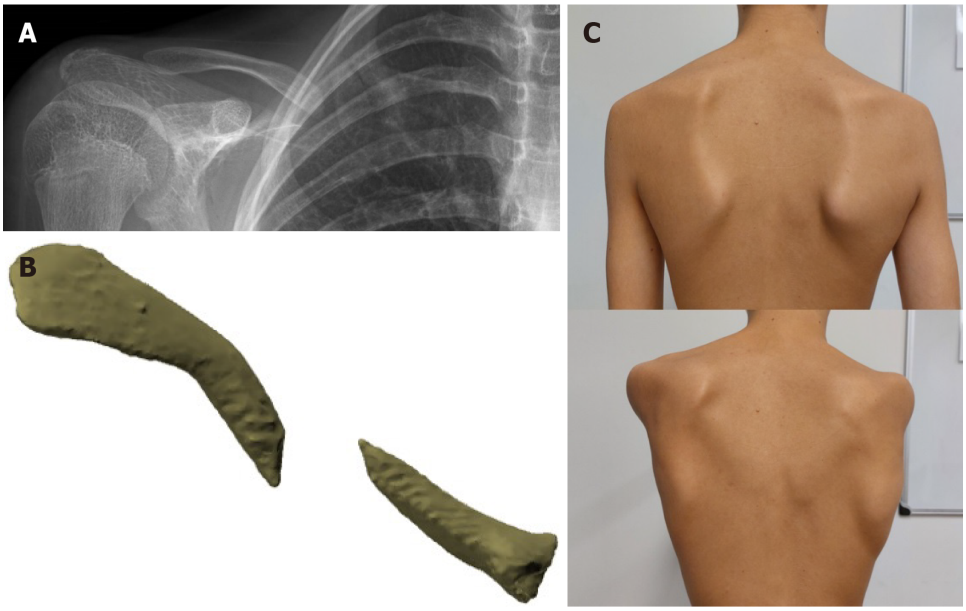

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Figure 1 A rare case of a 15-year-old boy with scapular dyskinesia caused by shortening of his clavicle due to a nonunion. A: Anteroposterior radiograph showing the clavicle nonunion; B: Three dimensional computed tomography reconstruction of the same clavicle nonunion; C: Scapular dyskinesia (right sided) caused by shortening of the clavicle due to nonunion.

During growth, the shape of the physis changes from a rounded shape to a more V-shape or pyramidal shape, which is responsible for the double contour on an AP radiograph (Figure 2).

The physis of the proximal humerus is responsible for 80% of the longitudinal growth of the humerus and therefore has tremendous potential for remodeling. The blood supply of the humeral head is abundant and arises from the anterior and posterior humeral circumflex arteries with their anastomoses; both are branches of the axillary artery. Hence, in contrast to proximal humerus fractures in the elderly population, the risk of posttraumatic avascular necrosis is very low in the pediatric population.

Diagnosis and classification

Conventional radiographs are usually sufficient to diagnose this injury. AP, scapula Y (trans scapular), and axillary views are recommended. The axillary view is essential to rule out a glenohumeral dislocation or concomitant glenoid fracture. If it is impossible in the acute setting to obtain an axillary view with the arm in abduction, the Velpeau view with the arm in a sling is a valuable substitute[32]. Radiographs of the opposite shoulder can be taken for comparison if necessary. The indication for a CT scan in proximal humerus fractures is limited and should be used only in select cases, considering the ionizing radiation on the developing body.

Around 85% of all proximal humerus fractures in the pediatric population are non- or minimally displaced[28]. The amount of displacement can be graded with the Neer-Horwitz classification (Table 1). Type I and II are nondisplaced or minimally displaced fractures, less than 5 mm and less than one-third of the diameter of the shaft. Type III and IV are more severely displaced fractures with displacement of more than one-third of the shaft[33].

The fracture type is influenced by the development of the physis, thus, the patient's age. Pre-puberty children tend to sustain more metaphyseal fractures (around 70%), and epiphyseal fractures occur more frequently in adolescents (around 30%) and are almost always Salter-Harris (SH) type I physeal separations, or SH type II with a wedge extending medially [34].

The direction of displacement is caused by the deforming forces of the muscles around the shoulder. The main direction of dislocation is varus. The supraspinatus, infraspinatus, and teres minor all pull the major tubercle, usually attached to the humeral head, posteriorly and medially, which causes the head to become dislocated in varus and external rotation. The pectoralis major pulls the shaft anteriorly and medially, a so-called "apex anterior fracture", potentially leading to a pro-curvatum deformity (Figure 3).

Treatment

All non- or minimally displaced proximal humerus fractures (Neer types I and II) can be successfully treated conservatively without long-term shoulder complaints[35]. Treatment of displaced proximal humerus fractures remains controversial. The remaining potential for remodeling is an important factor to take into consideration. It is still difficult to judge what amount of deformity will lead to a less-than-desirable clinical outcome, and age does not correspond accurately with skeletal maturity. There are no generally accepted guidelines with clear cut-off values, and there are no randomized trials comparing conservative *vs* operative treatment for displaced proximal humerus fractures. However, modestly increasing trends of surgical treatment for these fractures were found in large database studies in the United States and Finland[28,36]. Most articles on this topic state that until age ten, conservative treatment is a safe option, even

Table 1 Neer and Horwitz classification of pediatric proximal humerus fractures[33]

Grade	Displacement
I	< 5 mm
II	< 1/3 shaft width
III	1/3 – 2/3 shaft width
IV	> 2/3 shaft width

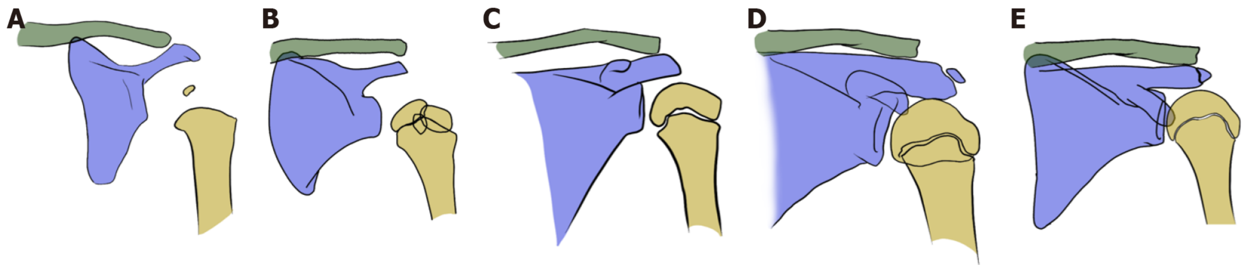

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Figure 2 Schematic drawing of the physis of the proximal humerus during growth. A: 1 mo; B: 5 years; C: 9 years; D: 11 years; E: 15 years of age.

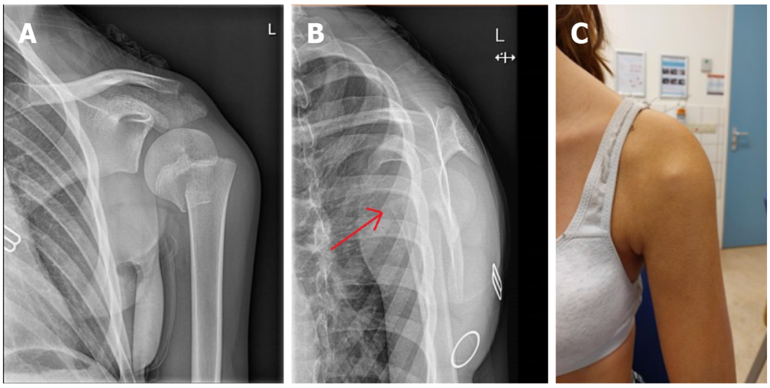

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Figure 3 Case example of a 14-year-old girl. A: Anteroposterior; B: Transscapular radiograph showing an 'apex anterior' displacement of a proximal humerus fracture (arrow); C: Clinical photograph showing the apex anterior displacement visibly beneath the skin.

for severely displaced fractures[37,38]. In a comparative matched case-cohort study from Chaus *et al*[39], surgical treatment was compared to non-operative treatment for Neer type III and IV fractures. There were no patients younger than thirteen with a less-than-desirable outcome in the non-operative group. The risk of a poor (or less than desirable) outcome after conservative treatment of severely displaced fracture did increase substantially from the age of 13. Some authors advocate surgical treatment under the age of ten in case of 100% displacement or over 70 degrees of angulation [28,34]. But this is still debatable because of the remarkable potential of remodeling of the proximal humerus under age 10 (Figure 4).

Surgical treatment should be considered for displaced (Neer type III or IV) fractures in patients older than ten years. Kim *et al*[32] have shown varying cut-off values in the current relevant literature on this topic. In children aged 13 and older, cut-off values from 20 – 40 degrees angulation and over one-third of shaft displacement are found. The least consensus exists in the age group of 10 to 13 years, with 40 to 60 degrees of angulation as cut-off values as an indication for surgical treatment[32]. From the age of 13, surgery seems to have a higher success rate compared to conservative treatment in severely displaced fractures (Neer III/IV or more than 20 degrees of angulation)[37].

If surgical treatment is opted for, one should strive to avoid open reduction because deltopectoral incisions at a young age can lead to unsightly hypertrophic scar formation. Closed reduction should be attempted first. The arm should be brought into abduction (to correct the varus), and the proximal shaft should be pushed posteriorly (to counteract the anterior pull of the pectoralis major)[34]. In a minority of cases, closed reduction cannot be achieved because of interposition of soft tissue, such as the long head of the biceps, periosteum, or deltoid muscle. In these cases, open reduction through the deltopectoral approach should be considered, which is most commonly used[40]. If the reduction is adequate, fixation can be achieved by either percutaneous K-wires or retrograde elastic stable intramedullary nailing

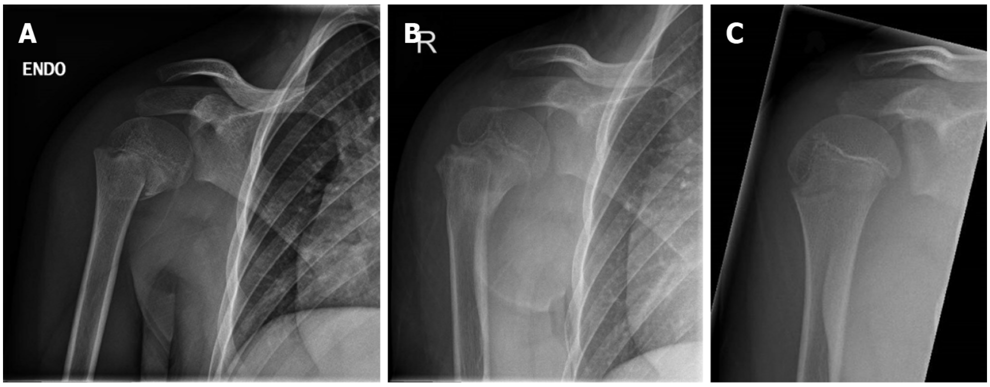

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Figure 4 Remodeling of a proximal humerus fracture in an 8-year-old boy. A: Anteroposterior radiographs taken at the initial trauma; B: After 3 mo; C: After 8 mo.

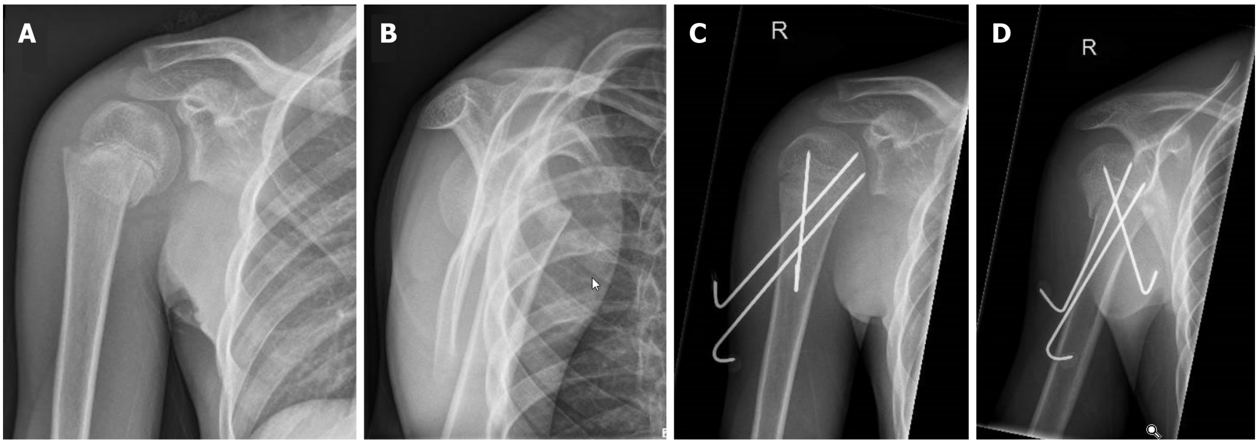

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Figure 5 An example of a Neer type II displaced proximal humerus fracture in a 12-year-old boy. A: Anteroposterior; B: Transscapular radiographs taken after the trauma; C and D: After closed reduction and percutaneous K-wire fixation.

(ESIN). The advantage of percutaneous K-wires is that the surgery is quick, inexpensive, and relatively easy to perform without the need for secondary surgery. Figure 5 Immobilization in a sling or a shoulder immobilizer is required until removal of the K-wires, usually after 3-4 wk. The technique of retrograde ESIN can be somewhat more challenging but is an elegant option to treat these fractures. Two nails, diverging in the proximal fragment, should be used. Both nails should be inserted just proximal to the lateral epicondyle, taking care not to injure the radial nerve. Sharp-tipped nails should be used to perforate into the humeral head, as blunt-tipped nails may push the proximal fragment away. Immobilization can be quite minimal after ESIN, with a sling worn for two weeks. A disadvantage of ESIN is the need for a second surgical procedure to remove the nails. Removing the nails relatively early, starting from the fifth postoperative week, is recommended, given the risk of complete distal penetration into the humeral shaft caused by growth[34,37]. The functional outcome did not differ significantly between surgical treatment options in the most extensive meta-analysis [37].

According to a large meta-analysis, the overall complication rate of ESIN and K-wires was not significantly different, with 7% and 9%, respectively[37]. No cases of radial nerve injury (ESIN group) or axillary nerve injury (K-wires group) were found in this systematic review. However, premature closure of the physis with arm length discrepancy did occur more frequently in the K-wires group, up to 19% in severely displaced fractures. Although it is uncertain to what extent this was clinically relevant. Specific complications for ESIN are penetration of the humeral head, loss of reduction, and temporary elbow stiffness. However, most complications are preventable with an adequate 'two nail' surgical technique.

In summary, proximal humerus fractures can often be treated conservatively because of the large potential for remodeling of the proximal humerus physis, especially under age 10. However, surgery is recommended for displaced fractures (Neer types III and IV) in patients older than 13 years. Closed reduction should be attempted, and fixation with either two retrograde elastic intramedullary nails or K-wires is acceptable. For children between 10 and 13 years of age, the indication for surgical treatment is less clear, with varying cut-off values of angulation (30-60 degrees) or displacement (1/3 – 2/3 shaft width) in the current literature.

CONCLUSION

In conclusion, both clavicle and proximal humerus fractures have a large potential for remodeling in the pediatric population. Expected residual growth, and thus remodeling, is an important factor in decision-making for these fractures. Although rarely mentioned in the relevant literature, especially in young teenagers around 10 to 15 years, there is a considerable difference in residual growth for boys compared to girls at the same age. Future research, such as pediatric trauma registry data with long-term follow-up, should ideally give better insight into cut-off values of the indication for surgery in these fractures, thereby enabling evidence-based, more detailed flowcharts. Because pediatric fractures around the shoulder that need surgical intervention are uncommon, guidelines with clear indications for surgery could take pediatric trauma care to a higher level. Without clear guidelines, there is a potential risk of overtreatment (too much surgery) and the rare case that will benefit from surgery going unrecognized.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Failure rate, return-to-sports and magnetic resonance imaging after meniscal repair: 119 patients with 7 years mean follow up

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Abstract

BACKGROUND

One of the most important factors to consider in relation to meniscal repair is the high failure rate reported in the existing literature.

AIM

To evaluate failure rates, return to sports (RTS) rate, clinical outcomes and magnetic resonance image (MRI) evaluation after meniscus suture repair for longitudinal tears at a minimum 2-year-follow-up.

METHODS

We conducted a retrospective review of meniscal repairs between January 2004 and December 2018. All patients treated for longitudinal tears associated or not with an anterior cruciate ligament reconstruction (ACL-R) were included. Meniscal ramp lesions, radial and root tears, associated with multiligament injuries, tibial fracture and meniscal allograft transplants were excluded. Surgical details and failure rate, defined as symptomatic patients who underwent a revision surgery, were analyzed. As isolated bucket handle tears (BHTs) were usually associated with higher failure rates, we compared BHTs and not BHTs associated or not with an ACL-R. Since 2014, the inside-out technique using cannulas and suture needles with 2-0 Tycron began to predominate. In addition, the number of stitches per repair was increased. In view of differences in surgical technique, we compared two different cohorts: before and after 2014. We recorded the RTS according to the level achieved and the time to RTS. Lysholm and IKDC scores were recorded. Patients were studied with x-rays and MRI as standard postoperative control.

RESULTS

One hundred and nineteen patients were included with a mean follow up of 7 years (SD: 4.08). Overall failure rate was 20.3% at a mean 20.1 mo. No statistically significant differences were found when comparing failure for medial and lateral meniscal repair (22.7% and 15.3%, $P = 0.36$), BHTs and not BHTs (26% and 17.6%, $P = 0.27$), isolated or associated with an ACL-R (22.9% and 18%, $P = 0.47$), or when comparing only BHTs associated with an ACL-R (23% and 27.7%, $P = 0.9$) or not. When comparing cohorts before and after 2014, we found a significant decrease in the overall failure rate from 26% to 11% ($P < 0.03$). Isolated lesions presented a decrease from 28% to 6.6% ($P = 0.02$), BHTs from 34% to 8% ($P = 0.09$) and those associated with an ACL-R from 25% to 10% ($P = 0.09$). Mean RTS time was 6.5 mo in isolated lesions and 8.64 mo when associated with an ACL-R. Overall, 56% of patients returned to the same sport activity level. Mean pre and postoperative Lysholm scores were 64 and 85 ($P = 0.02$), and IKDC 58 and 70 ($P = 0.03$). Out of 84 asymptomatic patients evaluated with MRI, 39% were classified as "not healed" and 61% as "healed".

CONCLUSION

Even though the overall failure rate of our series was 20.3%, we found a statistically significant decrease from 26% to 11%, not only for isolated lesions, but also for BHT's and those associated with an ACL-R when comparing our series in two different cohorts, most probably due to improvements in surgical technique.

Key Words: Meniscus repair; Bucket handle tears; Meniscal suture; Failure rate; Longitudinal meniscus tears

Core Tip: One of the most important factors to consider in relation to meniscal repair is the high failure rate reported in the literature. In this retrospective cohort we observed that new and improved suturing techniques have shown significantly lower failure rates, encouraging the need for meniscal repair whenever possible.

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INTRODUCTION

Due to the high rate of osteoarthritis observed after partial or total meniscectomy[1], meniscal repair techniques have been gaining significance over the last decades[2], total meniscectomy being particularly important in young patients and athletes[3]. Moreover in the case of Anterior cruciate ligament reconstruction (ACL-R), meniscal deficiency is frequently associated with residual rotational laxity affecting long term clinical outcomes[4-6]. Consequently, it is mandatory to preserve the meniscus when performing an ACL-R whenever possible.

The rate of meniscus repair has increased over the past few decades, along with the number of revision surgeries due to failed repair[6-8]. All-inside sutures required mainly for posterior horn lesions had historically been associated with higher failure rates and revision surgery[9]. Recent studies have shown that improvement in surgical strategies coupled with the development of more sophisticated suture devices, has led to an improvement in the success rate of meniscal preservation[10,11].

In our institution, the number of meniscal repairs has been growing exponentially since 2010. In addition, techniques have been changing over time. Therefore, the main purpose of our study was to evaluate failure rates after meniscus suture repair. As secondary objectives we analyzed return to sports (RTS) rate, clinical outcomes and magnetic resonance image (MRI) evaluation.

MATERIALS AND METHODS

After institutional review board approval, we performed a retrospective review of prospectively collected registry data including all patients treated with meniscal repair at our institution between January 2004 and December 2018. We included patients operated on vertical meniscal tears. Ramp lesions, radial lesions and root tears were excluded, as well as patients with meniscal allograft transplant, associated with multiligament knee injuries and patients with less than a two-year follow-up.

All surgical procedures were performed by the same surgical team, followed by a standard rehabilitation protocol. Variables analyzed included the patient's gender and age, tear type and surgical technique. Repair was registered as follows: all-inside, inside-out, outside-in. Failure was defined as symptomatic patients who underwent a revision surgery due to re-rupture at the previously treated portion of the meniscus. Historically, higher healing rates have been associated with meniscal repair in the setting of an ACL-R[12], as well as small vertical lesions have been compared to Bucket Handle Tears (BHTs)[9,13]. Hence, we analyze our cohort in different subgroups: Meniscal repairs associated with

ACL-R compared to isolated meniscal repairs, and BHTs compared to non BHTs.

In addition, rate and time to RTS, subsequent surgeries, preoperative and postoperative subjective assessment (Lysholm and IKDC scores) were reported, and postoperative complications were recorded and analyzed.

X-rays and MRI were routinely obtained during follow-up in order to evaluate meniscal healing. Results were classified and categorized as: "Not healed", when a gap greater than 2 mm was present in the repaired meniscus with a hyperintense continuous homogeneous line (Figure 1) and "healed", when continuity was observed (Figure 2). MRI categorization did not define failure, only a description of the images even in asymptomatic patients.

Indication and Surgical technique

All inside sutures were indicated for posterior horn lesions. Inside-out technique was usually indicated for lesions of the middle third of the meniscus. In selected cases, anterior horn and posterior horn lesions (using a postero-medial or postero-lateral approach to retrieve the sutures) were also treated with this technique. In the case of inside-out technique, specific cannulas were introduced through the contralateral portal, and long needles with 2-0 Tycron sutures were passed through. Outside-in technique was indicated for the anterior third of the meniscus, using 2-0 Tycron sutures or 0 PDS sutures.

In the case of BHTs, usually, two or three of these techniques were combined. In most cases, all-inside devices were used for the posterior horn in combination with inside-out or outside-in techniques for the rest of the meniscus. When all-inside devices were not available, the inside-out technique was used, retrieving the stitches through a postero-medial or postero-lateral approach.

One of the greatest changes in our surgical approach was to begin to perform multiple vertical stitches spaced every 4 mm using cannulas for the inside-out technique with 2-0 Tycron sutures as compared to most sutures performed prior to 2014 using few horizontal inside-out 0 PDS stitches (Figure 3).

Regarding ACL-R, either using hamstrings graft or bone-patellar tendon-bone, we performed transportal anatomic technique, maintaining the anatomic insertion footprint in both the femur and the tibia.

Postoperative Rehabilitation Protocol

Two different protocols were used after surgery for three different scenarios: isolated lesions, lesions associated with ACL-R and BHTs.

Isolated lesions, as well as those associated with an ACL-R were allowed for immediate partial weight bearing using a knee brace for three weeks. Flexion was limited to 90° for the first three weeks with progressive mobilization until complete flexion. Non-impact activities were allowed after three weeks. RTS was allowed by the fourth month. When associated with an ACL-R, RTS was determined according to the ACL-R protocol.

BHTs were indicated for non-weight bearing and flexion 0-70° for three weeks, followed by partial weight bearing for three more weeks and progressive flexion to 90°. After that period, progressive flexion and non-impact activities were indicated until complete range of motion. Impact sports activities were allowed from the fifth month onwards or according to the ACL-R protocol.

Statistical analysis

Descriptive statistics including means, standard deviations, median and quartile ranges were deemed appropriate to assess the available demographic, surgical, physical examination and patient-reported outcome data. Statistical hypothesis testing was performed using the Fisher exact test and Wilcoxon rank-sum test. Chi-square test was performed for categorical data. Analysis was performed with 95%CIs, and P values < 0.05 were considered statistically significant. All statistical analyses were performed using STATA version 15.

RESULTS

A total of 140 patients underwent a meniscal repair during the study period. Ten patients did not meet the inclusion criteria and eleven were lost in follow-up. There were no patients whose meniscus was re-ruptured and declined receiving revision surgery. Therefore, 119 patients were included in the study, 83% (n = 99) males, with a mean age of 27.1 years (SD: 8.02). Mean follow-up was 7 years (SD: 4.08). Table 1 shows the number of meniscal sutures, the distribution for isolated or BHT's, associated or not with an ACL-R, failure rates and time to failure.

Total

Overall failure rate was 20.3% (24/119) at a mean of 20.1 mo (range 11-60 mo). We found no statistically significant differences when comparing BHT's with not BHT's (26% and 17.6%, P = 0.27), associated with an ACL-R with isolated repairs (18% and 22.9%, P = 0.47), or BHT's associated or not with an ACL-R (23% and 27.7%, P = 0.9) (Table 1).

No significant difference was found when comparing overall failure rate for medial *vs* lateral meniscal repair (22.7% and 15.3%, P = 0.36), though medial meniscus lesions were more frequently associated with an ACL-R than lateral meniscus lesions (70% and 41%) (Table 2).

There was an increase in the number of stitches, from a mean of 1.4 (SD: 1.01) to 3.5 (SD: 2.31) for BHTs and 1.2 (SD: 0.5) to 2.1 (SD: 1.1) for isolated repairs. We found a statistically significant decrease (Table 3) in overall failure rate after meniscal repair from 26% for 67 meniscal repairs in the period between 2004 and 2014 to 11% for 52 repairs after that period (P = 0.03) as for isolated lesions (not associated with an ACL-R) with a decrease from 28% (9/32) to 6.6% (1/15) after 2014 (P = 0.02). Although there was no statistically significant difference, overall BHT's failure rate decreased from

Table 1 Demographic data and overall failure rate, *n* (%)

Overall meniscal sutures			
	Total	Failure	Time to failure, months
Total sutures	119 (100)	24 (20.3)	20.1
BHT	34 (28)	9 (26.4)	20.8
Not BHT	85 (72)	15 (17.6)	19.7
Posterior horn	37 (43)	7 (18.9)	19.1
Body	43 (50)	8 (18.6)	20.2
Anterior horn	5 (7)	0 (0)	0
Associated w/ACL-R	71 (60)	13 (18.5)	17
ACL-R + BHT	17 (23)	4 (23)	12.5
ACL-R + Not BHT	54 (77)	9 (16.6)	19.1
Isolated	48 (40)	11 (22.9)	23.8
BHT	18 (37)	5 (27.7)	27.6
Other	30 (63)	6 (20)	20.6

BHT: Bucket handle tear; ACL-R: Anterior cruciate ligament reconstruction.

Table 2 Descriptive data for medial and lateral meniscus, *n* (%)

Location	Total	Failure	Time (months)
Medial meniscus	80	18 (22.7)	18
ACL-R[1]	56 (70)	11 (19.6)	16.6
Isolated	24 (30)	7 (29)	18.5
Lateral meniscus	39	6 (15.3)	28.5
ACL-R[1]	16 (41)	2 (12.5)	19.5
Isolated	24 (59)	4 (16)	33

[1]Results represent patients treated with sutures associated with ACL-R.
ACL-R: Anterior cruciate ligament reconstruction.

34% (8/23) to 8% (1/12) (P = 0.09), and meniscal sutures associated with an ACL-R decreased from 25% (9/35) to 10% (4/37) (P = 0.09).

RTS and Subjective Scores (Patient-Reported Outcome Measures)

Overall mean time to RTS was 7.8 mo (SD: 2.77), 6.55 mo (SD: 2.36) for isolated lesions and 8.64 mo (SD: 2.72) when associated with an ACL-R. At the final follow-up, 67 patients (56%) returned to the same activity level, 28 (24%) reported a lower activity level and 3 patients (2%) decided not to return to sport activities. Twenty-one patients (18%) did not practice any sports at all.

The mean pre and postoperative Lysholm score was 64 (SD: 10.2) and 85 (SD: 14.08) respectively (P = 0.02) and the mean pre and postoperative IKDC score was 58 (SD: 7.51) and 70 (SD: 10.22), respectively (P = 0.03).

Radiological assessment

Eighty-four asymptomatic patients (71%) were evaluated with X-rays and MRI at a mean 3 years postoperative. X-rays did not reveal arthritic changes during that period. A total of 33 MRI's (39%) were classified as "not healed" and 51 (61%) as "healed". It is important to emphasize that these were asymptomatic, active patients.

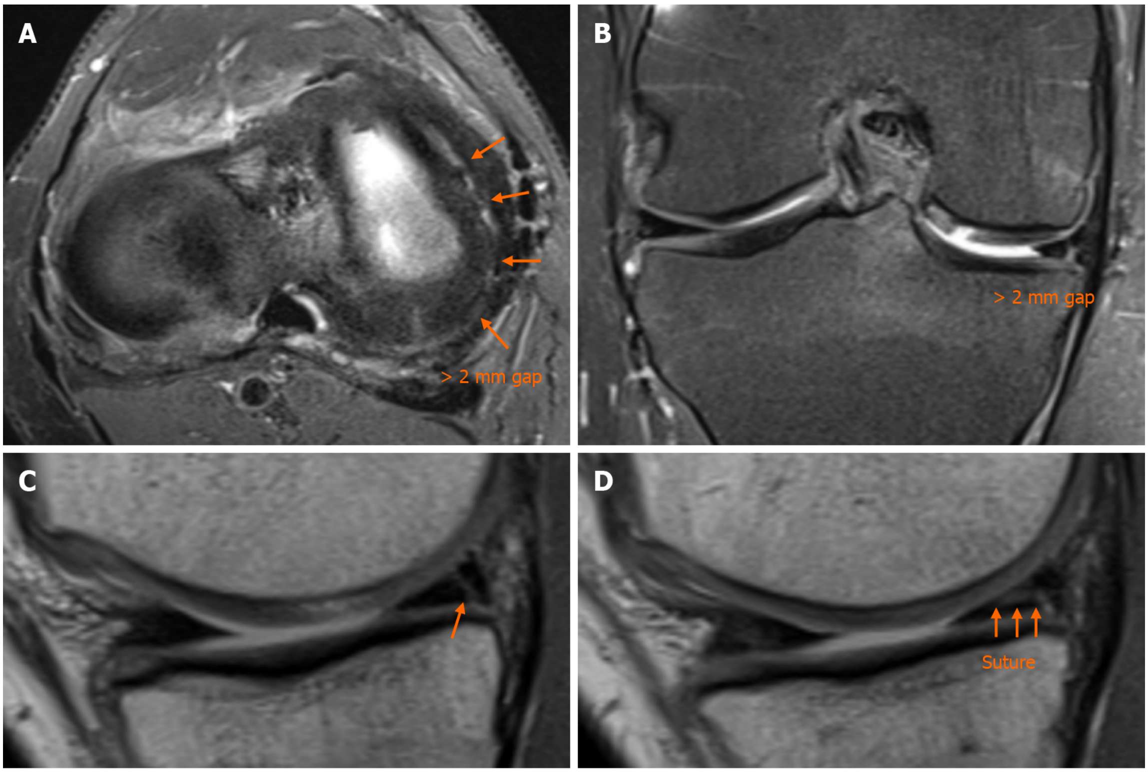
Complications

No intraoperative complications were reported. As to postoperative complications, two cases (1.6%) presented septic arthritis in the setting of an ACL-R and were treated with arthroscopic irrigation and debridement followed by intravenous antibiotics for four weeks, and one (0.8%) patient was operated on for isolated meniscal repair presented a

Table 3 Demographic data and failure rates for patients operated before and after 2014, *n* (%)

Period	2004-2013		2014-2018		*P* value
Age yr (range)	25.94 (16-48)		28.21 (18-59)		0.72
Gender, female	13 (19)		7 (13)		0.12
Total	*n*	Failure	*n*	Failure	0.03
	67	18 (26)	52	6 (11)	
Associated w/ACL-R	35 (52)	9 (25)	37 (71)	4 (10)	0.09
BHT	11 (31)	3 (27)	5 (14)	1 (20)	0.63
Not BHT	24 (69)	6 (25)	32 (86)	3 (9)	0.11
Isolated	32 (48)	9 (28)	15(29)	1 (6.6)	0.02
BHT	11 (34)	5 (45)	7 (47)	0 (0)	0.05
Not BHT	21 (66)	4 (19)	8 (53)	1 (12)	0.57
BHT[1]	23 (34)	8 (34)	12 (23)	1 (8)	0.09

[1]The results represent the overall bucket handle tear before and after 2014.
BHT: Bucket handle tear; ACL-R: Anterior cruciate ligament reconstruction.



DOI: 10.5312/wjo.v14.i8.612

Figure 1 Two-years postoperative magnetic resonance imaging classified as "not healed". This asymptomatic patient was treated with a bucket handle tears suture associated with Anterior cruciate ligament reconstruction. A: Axial plane showing a more than 2 mm gap; B: Same gap in the coronal plane; C: The posterior horn in the sagittal plane shows a gap less than 1mm wide in the meniscus; D: The transversal line in the posterior horn of the meniscus pointed by the arrows is the suture crossing from anterior to posterior.

superficial wound infection which was treated with oral antibiotics for 10 d.

DISCUSSION

The most important finding of our study was that even though the overall failure rate was 20.3% (26% for BHTs, 18%

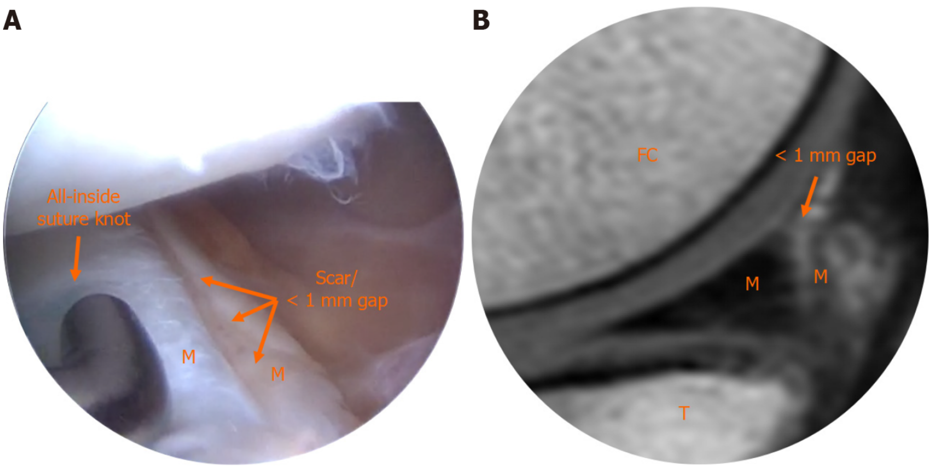


Figure 2 Second look arthroscopy and postoperative magnetic resonance imaging. A: Shows a second look arthroscopy 1 year after posterior horn meniscus repair; B: The < 1 mm gap classified as "healed" in the magnetic resonance is confirmed in the arthroscopy with a fibrous stable scar. FC: femoral condyle, M: Meniscus, T: Tibia.

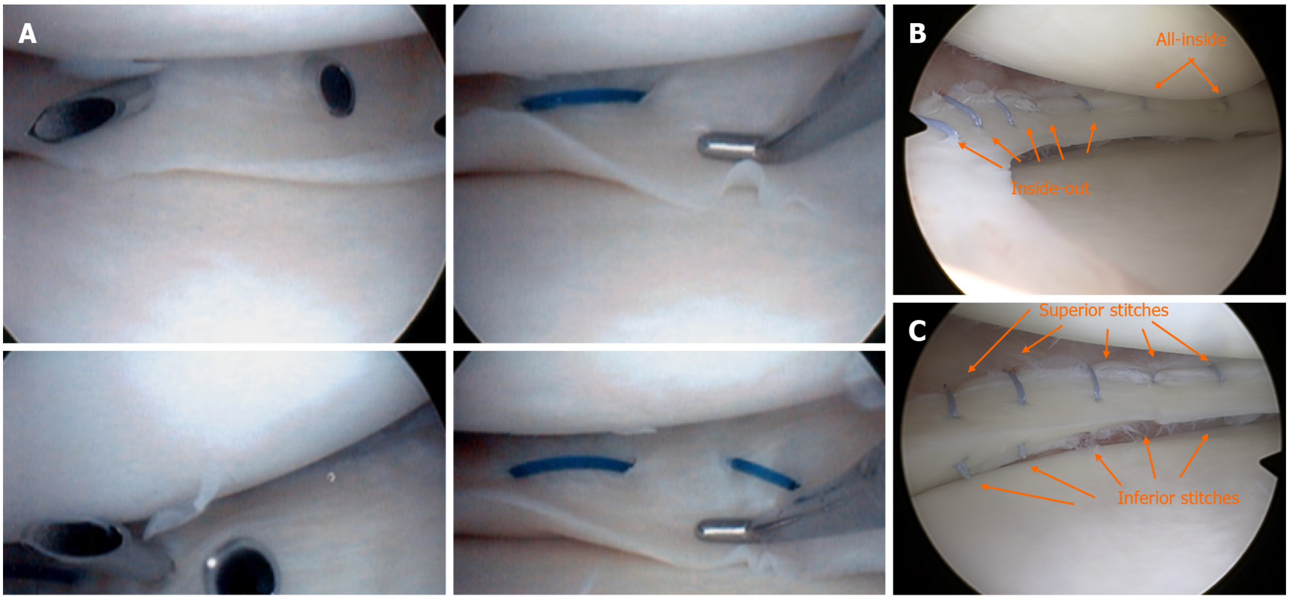


Figure 3 Arthroscopic view of repaired bucket handle tear. A: Shows a bucket handle tear repaired in 2012 using 3 PDS stitches with an outside-in technique; B and C: Show a bucket handle tear repaired in 2016 using 10 inside-out and 2 all-inside 2-0 nonabsorbable high resistant sutures.

when associated with an ACL-R and 22% for isolated lesions), we found a significant decrease of failure rate when comparing two different cohorts in view of differences in surgical technique from 26% to 11% (P = 0.03). Not only for isolated lesions (from 28% to 6.6% for isolated lesions, P = 0.02), but also BHTs (from 34% to 8%, P = 0.09) and those associated with an ACL-R (from 25% to 10%, P = 0.09). These findings add to a growing body of literature on the importance of surgical technique when analyzing failure rate after meniscal repair[7,9,14,15]

For the last two decades meniscal preservation has become the main goal for treatment of meniscal lesions. In 2013, Abrams *et al*[16] reported that between 2005 and 2011 the incidence of meniscal repair has doubled in the United States. This tendency has continued to increase up to date, thus becoming the gold standard procedure when deciding the fate of a meniscus repairable lesion nowadays[1-17].

Systematic reviews prior to 2012, reported failure rates of 18% to 23%[7,15,16] after meniscal repair. Fillingham *et al*[9] in 2017 compared inside-out *vs* modern all-inside devices techniques and reported similar functional outcomes, with equivalent anatomical and clinical failure rates: 11% and 10% respectively. These results were interestingly lower when compared to 17% and 19% previously reported by Grant *et al*[14] in 2012. Fillingham *et al*[9] also found that all-inside repairs had an average of 2 stitches, while inside-out had an average of 3. Therefore, they associated the inside-out technique with more complex lesions.

When we analyzed the overall failure rate for meniscal sutures in our series, we found 20.3% with a mean time to failure of 20.1 mo, which is very similar to prior reports in the literature[7,16,18]. Moreover, an overall failure rate for isolated lesions of 22.9%, (27.7% for BHTs) and 18.5% when associated with an ACL-R (23% for BHTs) was found.

The analysis of the evolution of failure rate during our research yields a significant decrease when comparing our series in two different periods. Even though patients treated after 2014 have a shorter follow up, we consider that it is enough to establish a comparison considering that the overall mean time to failure was 20 mo. There might be multiple factors to explain this decrease in failure rates. Most horizontal mattress sutures (usually no more than 2 stitches) were replaced for vertical sutures (one stitch every 5 to 10 mm), which provides more stability and prevents meniscal cutout [19]. This resulted in an increase in the number of stitches, from a mean of 1.4 (SD: 1.01) to 3.5 (SD: 2.31) for BHTs (Figure 3) and 1.2 (SD: 0.5) to 2.1 (SD: 1.1) for isolated repairs, and it continues to increase up to date. Another important factor might be an improvement in the all-inside devices for meniscal sutures as reported in clinical[9] and biomechanical [20] studies.

Blanchard *et al*[21] reported an overall RTS rate of 83% after 8.7 mo in 21 studies evaluated after isolated meniscal repair. Other authors reported variable time to RTS from 4.2[22,23], 5.6[24] and 5.5[25] mo. When associated with an ACL-R time to RTS is reported from 8.2 (64 Vanderhave) to 11.8 mo (48 Logan). We found a mean RTS of 6.55 mo (SD: 2.36) for isolated lesions and 8.64 mo (SD: 2.72) when associated with an ACL-R. After a mean of 7 years follow-up, only 56% returned to the same activity level and 24% reported a lower activity level. Though this seems to be a low RTS rate, many authors have reported better outcomes after meniscal repair compared with meniscectomy (2018 KSSTA Phillips, 2014 AJSM Westermann, 2021 OJSM Blanchard).

Regarding the role of MRI as a postoperative control measure, we found that it was not useful in evaluating meniscal repairs. We found that 39% out of the 85 asymptomatic patients that performed a routine MRI presented an image compatible with a "not healed" repair. The report even suggested a "failure" or "rupture" of the repair. All of these patients were asymptomatic and performing regular sport activities. Faunø *et al*[26] in 2020 reported 72% sensitivity for finding meniscal re-ruptures in 80 symptomatic patients who underwent a revision surgery. Yamasaki *et al*[27] suggested a T2 mapping to improve the sensitivity for unhealed meniscus after comparing standard and T2 mapping MRI for 26 asymptomatic patients who underwent a second look arthroscopy.

The role of biologics in the setting of meniscal repair in order to increase the chance of healing and reduce failure rate is still controversial and very few clinical studies have been reported. In a recent systematic review, Haunschild *et al*[28] reported that there was considerable heterogeneity in the reporting and preparation of platelet rich plasma (PRP) used for augmentation, and concluded that there was insufficient evidence to support the use of PRP to improve meniscal healing and reduce failure rate. Controversially, Zaffagnini *et al*[29] and Sochacki *et al*[30] reported an improvement in survival rate after isolated meniscal repair augmented with PRP.

Strengths and limitations

The limitations of our study need to be acknowledged. First, the main limitation was the retrospective design, yielding an analysis limited to the data available in the medical record database, with potential for selection bias. Second, the fact that we considered asymptomatic patients and analyzed the results as "healed" or "not healed" for MRI subsequent analysis without a second-look arthroscopy confirmation. And finally, the lack of radiographic evaluations which did not allow us to evaluate any degenerative progression.

Despite these limitations, the large sample size and subgroup analysis, as well as the long term follow-up of 7 years constitute a major strength of our study.

CONCLUSION

The overall meniscal repair failure rate after a mean follow-up of 7 years was 20.3%, with 26% for BHTs, 18% when associated with an ACL-R and 22% for isolated lesions. Interestingly, when comparing our series in two different cohorts in view of differences in surgical technique, we found a decrease from 26% to 11% (P = 0.03), 28% to 6.6% (P = 0.02) for isolated lesions, 34% to 8% (P = 0.09) for BHT's, and 25% to 10% (P = 0.09) for meniscal sutures associated with an ACL-R. The mean time for return-to-sports was 6.5 mo for isolated meniscal repairs and 8.6 when associated with an ACL-R. Finally, MRI was not efficient for evaluating the condition of the meniscal repair in asymptomatic patients. It is recommended that care should be taken when considering MRI as a routine control practice after meniscal repair.

ARTICLE HIGHLIGHTS

Research background

We perform a large number of meniscal repairs every year. Our surgical techniques have been improving along the years, and with it, the outcomes achieved.

Research motivation

We observed a great improvement over the years in our patient outcomes. That is why we decided to analyze and report the long-term results of our series.

Research objectives

To analyze the failure rate and compare outcomes in our series of patients operated on for longitudinal meniscal lesions. It is important to understand that improvement in the number of stitches and surgical technique is associated with better outcomes than what is reported in the literature.

Research methods

We retrospectively analyzed and compared demographic data, surgical details, return to sport and failure rate using specific statistical tools.

Research results

In our series we found an important decrease in failure rates by improving our surgical technique and increasing the number of stitches. Even so, there is still a high percentage of patients in whom this type of repair fails. It is very important to continue investigating complementary methods that can help to further reduce this failure rate.

Research conclusions

The new theory provided by the paper is that the failure rate may continue to fall even further.

Research perspectives

Future work could compare the same type of sutures with biological augmentation such as platelet-rich plasma or stem cells.

FOOTNOTES

Author contributions: Zicaro JP and Garrido N analyzed the data and wrote the manuscript; Garcia-Mansilla I contributed with research and data analysis; Yacuzzi C and Costa-Paz M contributed to the number of patients operated on; Costa-Paz M is the head of the sector; All authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the "Ethics Committee of the Hospital Italiano" (CEPI) Institutional Review Board, No. 5458.

Informed consent statement: Due to the retrospective nature of our study no informed consent was required.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data were required (retrospective study).

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ORIGINAL ARTICLE

Retrospective Study

Survival analysis in nonagenarian patients with non-hip lower limb fractures

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Abstract

BACKGROUND

The United Kingdom has an aging population with nearly 1 in 5 being over the age of 65, and over 0.5 million over the age of 90. The treatment of acute fractures of the lower limb in the nonagenarian cohort of patients poses a technical challenge to orthopaedic surgeons.

AIM

To report the fracture incidence, survival outcomes of treating acute non-hip lower limb fractures in nonagenarians in Major Trauma Centre.

METHODS

Thirty Lower limb long bone fractures in patients of age from 90 to 99 years were identified during 12-mo at a Level 1 trauma centre from a computerized database. A retrospective evaluation performed for fracture incidence, treatment, length of hospital duration and mortality at 30-d, 1-year and 2-year.

RESULTS

Thirty fractures (28 patients) were identified, twenty-four fractures were treated with surgery (mean age 93 years SD ± 2.59) and 6 managed conservatively (mean age 94 years SD ± 2.07). The mean length of the hospital stay was 18.2 d for both groups. The 30-d, 1-year and 2-year mortality risks were 1/23, 6/23 and 9/23 (4%, 26% and 39%) in the surgery group and 0/5, 1/5 and 2/5 (0%, 20% and 40%) in the conservative group, with no evidence for a difference between the two groups at any time point.

CONCLUSION

Nonagenarians in the surgical group had similar length of hospital stay and mortality risks as those treated conservatively. Patients with fewer comorbidities and admitted from their own home were offered surgery.

Key Words: Nonagenarian; Survival; Conservative; Non-hip; Fragility; Orthogeriatrics

Core Tip: The treatment of acute lower limb fractures in nonagenarian population poses a technical challenge to orthopaedic surgeons, given the multiple co-morbidities, complex fracture pattern and poor bone quality. Nonagenarians account for 8% of all patients requiring acute fracture surgery. The main findings of this study are that surgery is more likely to be offered to those patients with fewer co-morbidities and those admitted from their own home, which indicates a higher functional status.

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INTRODUCTION

The treatment of fractures within the nonagenarian population (> 90 years)[1-2] poses a technical challenge to orthopaedic surgeons. This is because patients within this demographic often have multiple co-morbidities, poor bone quality and exhibit complex fracture patterns. 'Super-elderly' patients account for 8% of all patients requiring acute fracture surgery[2]. The World Health Organization has estimated that by 2050 the global population who are 65 years or more will be 1.5 billion and represent 16% of the world's population[2]. This will place an immense burden on the medical resources of the National Health Service for both the acute and rehabilitative care[3].

Much of the work pertaining to fractures in the elderly has centered on hip fractures[3]. There is sparse evidence in literature looking beyond the scope of hip fractures to other lower limb trauma within this patient population. It is unknown whether this group of patients share similar outcomes to those affected by hip fractures.

The purpose of this study is to share our experience at a level 1 major trauma centre in treating long bone fractures of the lower limb in nonagenarians. We aim to report the fracture incidence, short-term outcome and the 30-d, 1-year and 2-year mortality.

MATERIALS AND METHODS

This study was conducted at a level 1 major trauma centre. Interrogation of a prospectively maintained electronic admissions database was performed retrospectively. We included all patients between the ages of 90 and 99 years who were admitted with a long bone fracture of the lower limb during 2015 and 2016, including periprosthetic fractures. We excluded all soft-tissue trauma, foot and ankle fractures and all primary hip fractures.

Within our institution all patients who are fit to undergo anaesthesia are considered for surgery, depending on the fracture configuration, the aim of which is to restore the patient to their pre-injury function. Conservative (non-operative) management is reserved for patients who have undisplaced fractures and those that are unfit for surgery.

Information including patient demographics, place of residence, discharge destination, number of co-morbidities, gender, high or low mechanism of injury, fracture type and treatment, length of hospital stay and time to theatre from admission was collected from electronic patient records and picture archiving communication systems. The 30-d, 1-year and 2-year mortality was calculated for long bone fractures of the lower limb treated with or without surgery and compared using a Fisher's exact test. Statistical analysis was performed using R (R Foundation for Statistical Computing, Vienna, Austria) and a 2-sided P value below 0.05 was assumed to denote statistical significance.

RESULTS

A total of 537 adult lower limb fractures were admitted over a 12-mo period within our institution, with 30 Long bone fractures of the lower limb in 28 patients between 90 and 99 years of age. Twenty-seven patients (96%) were female and 1 (4%) was male (Table 1). The mean age in the surgical group was 93 years (range 90-98 years) (SD ± 2.59) and 94 years (range 91-96 years) (SD ± 2.07) in the conservative group (Figure 1).

Table 1 Patient demographics, fracture type, treatment type, number of comorbidities, length of hospital stay, admission residence, discharge destination and time from admission to death in both surgical and conservative groups

Patient No.	Sex	Age, yr	Fracture type	Treatment	Number of co-morbidities	Length of hospital stay, d	Admission residence	Discharge destination	Time from admission to death, d
1	F	98	Periprosthetic – THR	Surgery	3	22	Home	Institution	Alive
2	F	98	Distal femur	Surgery	3	25	Home	Home	Alive
3	F	96	Periprosthetic - Thompsons	Surgery	4	29	Institutional	Dead	29
4	F	96	Distal femur	Surgery	0	21	Home	Institution	Alive
5	F	96	Distal femur	Surgery	0	30	Home	Home	Alive
6	F	95	Periprosthetic – Thompsons	Conservative	5	20	Home	Institution	Alive
7	F	95	Distal femur	Surgery	3	8	Home	Institution	Alive
8	F	95	Periprosthetic – Thompsons	Surgery	3	12	Home	Institution	Alive
9	F	95	Distal tibia/fibula	Conservative	4	17	Institutional	Institution	237
10	F	95	Distal femur	Surgery	0	11	Home	Institution	300
11	F	94	Distal tibia/fibula	Surgery	0	18	Home	Institution	Alive
12	F	94	Periprosthetic – THR	Conservative	7	17	Home	Institution	376
13	F	94	Distal femur	Surgery	0	12	Home	Institution	429
14	F	94	Distal femur	Surgery	3	14	Home	Institution	264
15	F	93	Distal tibia/fibula	Surgery	3	24	Home	Institution	Alive
16	F	92	Periprosthetic – Thompsons	Conservative	2	24	Institutional	Institution	Alive
17	F	92	Periprosthetic – THR	Surgery	2	11	Home	Institution	Alive
18	F	92	Distal femur	Surgery	0	11	Home	Institution	Alive
19	F	92	Distal femur	Surgery	1	15	Home	Institution	39
20	F	92	Distal tibia/ fibula	Surgery	2	39	Home	Institution	50
21	F	91	Distal femur- bilateral	Conservative	2	13	Home	Institution	Alive
22	F	91	Femoral shaft	Surgery	3	16	Home	Institution	50
23	F	91	Distal femur – Bilateral	Surgery	3	28	Home	Institution	Alive
24	F	90	Periprosthetic – THR	Surgery	1	28	Home	Institution	Alive
25	F	90	Periprosthetic – Thompsons	Surgery	8	28	Home	Institution	505
26	M	90	Distal femur	Surgery	4	11	Home	Institution	451
27	F	90	Femoral shaft	Surgery	2	17	Home	Institution	Alive
28	F	90	Proximal tibia/fibula	Surgery	1	5	Home	Institution	Alive

F: Female; M: Male; THR: Total hip replacement.

Twenty-seven patients (96%) sustained a fracture after low energy trauma with a fall from standing height. One patient sustained bilateral distal femoral insufficiency fractures without any history of trauma. Fracture type consisted of 12 (40%) distal femoral (two patients had bilateral distal femoral fractures), 11 (37%) periprosthetic, 4 (13%) distal tibia/

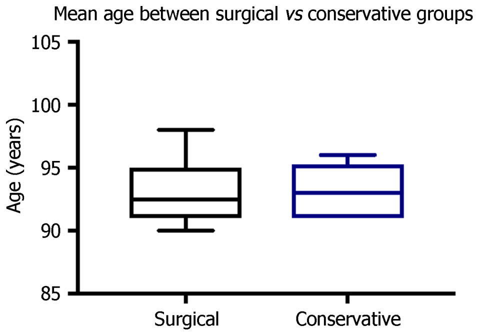

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Figure 1 Mean of the patients age between surgical cohort (nonagenarians undergoing surgery) and conservative cohort (nonagenarians not undergoing surgery).

fibula, 2 (7%) femoral shaft and 1 (3%) proximal tibia (Figure 2).

Twenty-four fractures (80%) in 23 patients were operated on. Surgical intervention consisted of 8 (27%) undergoing open reduction and internal fixation, 5 (17%) a revision arthroplasty, 10 (33%) an intramedullary nail and 1 patient (3%) underwent a distal femoral replacement (Figures 3-5)

The mean time from admission to first surgery was 2.5 d (range 0-9 d). Definitive fracture treatment for all closed injuries was performed within 2.9 d (range 0-9 d). Four patients had open fractures, which were managed in accordance with the British Orthopedic Association Standards for Trauma and Orthopaedics[4] and treated with an initial debridement and external fixation before definitive treatment performed on a designated orthoplastic list. The mean time from admission to definitive fracture treatment in these patients was 2.5 d (range 2-3 d).

In 13 patients' operative records the type of anesthetic used was documented; 5 patients received a general anesthetic, 5 combined with regional blocks and 3 patients had a spinal anesthetic with sedation. In all patients, a tourniquet was not used primarily due to fracture location.

Within the surgical group (n = 23): 22 patients (96%) were admitted from their own home and 1 (4%) from an institution. Physiotherapy and continuous passive motion were started on the postoperative day. On discharge only 2 patients were discharged back home; the rest were transferred to further rehabilitation institutions. It is unknown how many of these patients were subsequently able to return to their prehospital admission residence.

The mean number of co-morbidities was 2.1, time to definitive surgery 2.6 d (SD ± 2.09) and mean length of hospital stay was 18.2 d. The 30-d, 1-year and 2-year mortality in this group was 4.3%, 26% and 39% respectively.

Six fractures in 5 patients (20%) were treated conservatively. Within the conservative group (n = 5): 3 patients (60%) were admitted from their own home and 2 (40%) from an institution (Table 2). On discharge all patients were transferred to an institution. Mean number of co-morbidities was 4; mean length of hospital stay was 18.2 d. There were no deaths within 30 d; the 1-year and 2-year mortality was 20% and 40% respectively.

A comparison of mortality risk between the surgical and conservative groups found no evidence for a difference at any time point (P = 1 for each time point).

DISCUSSION

Long bone fractures of the lower limb in nonagenarians represents 5% of the total adult lower limb trauma admission during 1 year within our major trauma centre. Fractures within this age group nearly all result from low energy trauma and were found to be more prevalent in females. This study has found the most common lower limb fracture to occur is that of distal femoral fractures.

The most interesting finding of this study is surgically treated fractures of the lower limb is associated with an initial higher 30-d and 1-year mortality than those managed conservatively (P = 0.97, Wilcoxon-Rank), despite an increased number of comorbidities (see Figures 6 and 7). Reasons for this are likely to be multifactorial and we are unable to draw any direct conclusions due to a small cohort sample.

We are not aware of any literature which has specifically reported the mortality of fractures of the lower limb in nonagenarians. Streubel *et al*[5] reported a 25% 1-year mortality of patients with distal femoral fractures undergoing surgery with a mean age of 77.9 years[6]. The mortality of hip fractures has been well documented within literature. For similar age-matched groups the literature has reported 30-d and 1-year mortality between 10%-24%[5,7-9], rising to 15%-56%[10-13] in centenarians. Recently, Bolton *et al*[14] reported the 30-d and 1-year mortality rate in the non-agenarian hip fractures to be 12.4% and 38.1%[14].

We found surgery is more likely to be offered to patients with less comorbidity and those admitted from their own home. Postoperatively, however, all patients from both groups required admission into an institution for further rehabilitation. It is unclear how many patients were subsequently able to return to their preadmission residence. Interestingly we found there was no difference in the mean length of hospital stay between the two groups. This is similar to findings by Holton *et al*[15] where the mean hospital admission was longer in patients were their ankle fracture was treated with surgery (P = 0.006), compared to those offered conservative management.

Table 2 Summary showing discharge outcomes of both surgical (group 1) and conservative (group 2)

	No. of patients (%)
Gender	
Male	1 (3.6)
Female	27 (96.4)
Fracture type	
Distal femur	12 (40)
Periprosthetic	11 (37)
Distal tibia/fibular	4 (13)
Femoral shaft	2 (7)
Proximal tibia/fibula	1 (3)
Type of operation	
Open reduction internal fixation	8 (27)
Revision arthroplasty	5 (17)
Intramedullary nail	10 (33)
Distal femoral replacement	1 (3)
No operation	6 (20)
Surgical (Group 1)	
Admitted from home	22 (96)
Admitted from an institution	1 (4)
Discharged home	2 (9)
Discharged to an institution	21 (91)
Conservative (Group 2)	
Admitted from home	3 (60)
Admitted from an institution	2 (40)
Discharged home	0 (0)
Discharged to an institution	5 (100)

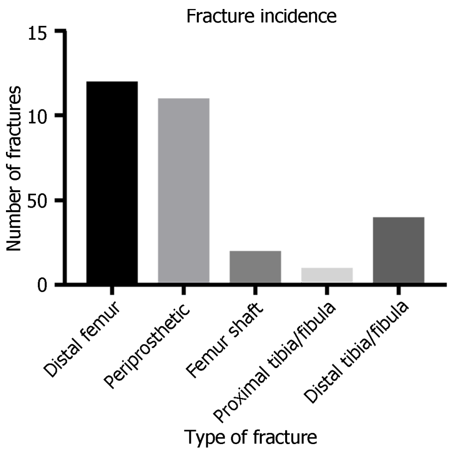

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Figure 2 Anatomical fracture locations in both the surgical and conservative groups.

Surgery in nonagenarian patients is associated with greater anaesthetic risks and technically challenging surgery because of poor bone quality and higher rates of primary fixation failure[16-17]. Despite these factors surgery is often recommended especially for those with femoral neck fractures. Surgery aims to reduce pain, assist with nursing care, and

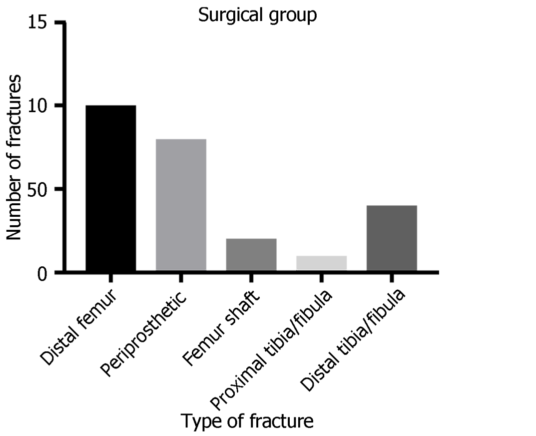

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Figure 3 Anatomical location of fractures with their incidence in surgical group.

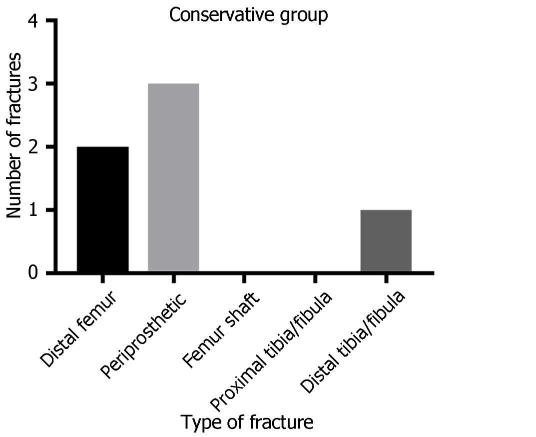

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Figure 4 Anatomical location of fractures with their incidence in conservative group.

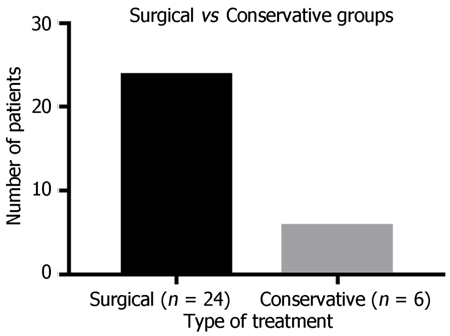

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Figure 5 Number of patients respective to the management offered–surgical and conservative.

reduce the risks and sequela of complications, which can manifest from prolonged bed rest[18]. Contrary to what we have found, recent studies suggest good results may be achieved with surgery. Ng and Kwek[10] reported the operative outcomes of centenarians with hip fractures. They found centenarians had a low Charlson Comorbidity Index, postulating these patients tended to be healthier and found no deaths at 30-d with 1-year mortality of 33.3%.

The timing of surgery is also a crucial factor that must be considered in these patients. Lin *et al*[8] analyzed 101 patients over the age of 90 years undergoing hip fracture surgery. They found the mortality nearly doubled if surgery was not performed within 24 h of admission. Moja *et al*[19] performed a meta-analysis involving 191873 patients, and again demonstrated an increase in the mortality of patients if there was a delay to surgery. Within our institution we recognize this, and the authors advocate early surgery for elderly patients; however, this is not always possible due to the volume of admissions requiring treatment, the surgeon skill set and the requirement for specialized implants.

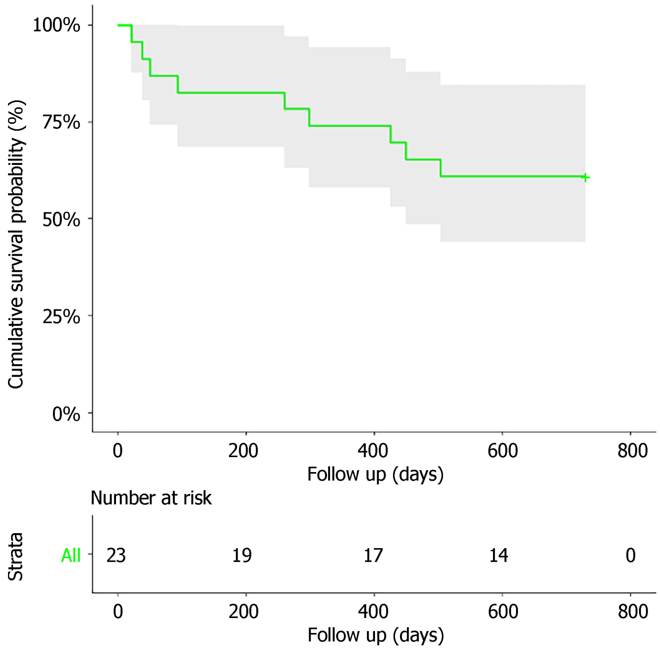

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Figure 6 Cumulative survival probability (Y-axis) and follow-up in days (X-axis) showing survival analysis curve in Surgical group.

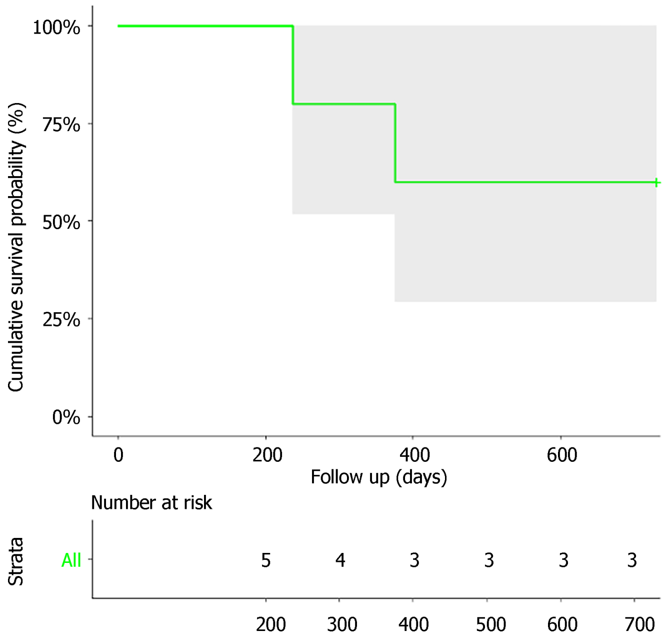

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Figure 7 Cumulative survival probability (Y-axis) and follow-up in days (X-axis) showing survival analysis curve for conservative group.

We recognize the limitations of this study, the most important of which is a small sample size for both groups. This makes it difficult to make a direct comparison between the two groups and as a result we are unable to draw any direct conclusions. Secondly, we are unable to comment on how many patients were able to return to their preadmission residence and functional status. Nevertheless, this study highlights super-elderly patients require further rehabilitation than their younger counterparts[9] and reflects an additional socioeconomic burden on limited health resources which must be addressed.

Nonagenarians have multiple co-existing medical pathologies including frailty, poor visual acuity, and polypharmacy, all of which contribute to increase the risk of falls[16]. We found 23 patients (82%) suffered a fall from standing height at home. This suggests certain patients may benefit from primary prevention strategies by identifying at risk individuals with the focus of creating a safe environment and falls prevention advice through a multidisciplinary team approach and to improve their living environment with assisted living devices.

CONCLUSION

We report the incidence and the short-term outcome of fractures of the lower limb in nonagenarians at our level 1 trauma centre. The main findings of this study are that surgery is more likely to be offered to those patients with fewer co-morbidities and those admitted from their own home, which indicates a higher functional status. Nonagenarians in the surgical group had similar length of hospital stay and mortality risks as those treated conservatively.

Nonagenarians require further rehabilitative support to gain independence and pre-injury functional level, in an institutive setting irrespective of the treatment that is instituted and arrangements for this should be sought as soon as possible. More investment, awareness and socioeconomic support will be required to keep up with current demands.

ARTICLE HIGHLIGHTS

Research background

There is paucity of literature pertaining to the management and survival of non-hip fractures in the nonagenarian population. This is significant, given the rising nonagenarian population in the United Kingdom.

Research motivation

This study aims to analyze the prognosis/survival in a level 1 major trauma centre, in managing non-hip fractures in nonagenarian population in the United Kingdom.

Research objectives

To summarize the survival prognosis on nonagenarian population with non-hip fractures in a level 1 major trauma centre.

Research methods

We referred to the hospital electronic database between 2015 and 2016 to include all patients with age ranging from 90 to 99 years, who had lower limb long bone fractures, including periprosthetic fractures. We excluded all hip fractures, soft tissue trauma, foot and ankle fractures. Both conservative and operative management were considered depending on the anaesthetic fitness and medical background. 30-d, 1-year and 2-year mortality were calculated for both surgical and conservative groups and compared using Fisher's exact test.

Research results

Out of 28 patients, 23 patients (24 fractures) had surgical intervention and 5 patients (6 fractures) were for conservative treatment. The mean time from admission to definitive fracture treatment was 2.5 d (range 2-3 d). In surgical cohort, only 2 patients went home post-discharge, the rest all were transferred to rehabilitation institutions. In the conservative cohort, all patients were transferred to an institution. The 30-d, 1-year and 2- year mortality risks were 1/23, 6/23 and 9/23 (4%, 26% and 39%) in the surgery group and 0/5, 1/5 and 2/5 (0%, 20% and 40%) in the conservative group, with no evidence for a difference between the two groups at any time point.

Research conclusions

Surgery was more likely to be offered to patients with fewer comorbidities and both conservative and surgical groups had similar length of hospital stay and mortality risks. Early planning for institutional rehabilitation and socio-economic support is utmost needed in the management of these patients.

Research perspectives

Standard national guidelines for lower limb fractures in the nonagenarian population would streamline the diagnosis, management, and rehabilitation.

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FOOTNOTES

Author contributions: Narayana Murthy S, Siddiqui RS and Cheruvu MS conceptualized, designed, reviewed the existing literature, did the statistical analysis, wrote the manuscript and prepared the first draft; Dass D and Sharma N critically reviewed the first draft and gave their expert suggestions; Ali A reviewed the final draft before submission and suggested further changes.

Institutional review board statement: This is an observational study which does not include any of the patient identifiable data. Additionally, as there are no interventions, there was no need to obtain an institutional board review statement.

Informed consent statement: Consent for an original study involving humans is not necessary as we have not included any patient identifiable details in our manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: As no patient identifiable data is shared in the manuscript, this is not required. No additional data is available.

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META-ANALYSIS

Cemented *versus* uncemented stems for revision total hip replacement: A systematic review and meta-analysis

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Abstract

BACKGROUND

The popularity of uncemented stems in revision total hip arthroplasty (THA) has increased in the last decade.

AIM

To assess the outcomes of both cemented and uncemented stems after mid-term follow up.

METHODS

This study was performed following both the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement and the Cochrane Handbook for systematic reviews and meta-analysis guidelines. Articles were chosen irrespective of country of origin or language utilized for the article full texts. This paper included studies that reviewed revision THA for both cemented or uncemented long stems.

RESULTS

Three eligible studies were included in the meta-analysis. Analysis was conducted by using Review Manager version 5.3. We computed the risk ratio as a measure of the treatment effect, taking into account heterogeneity. We used random-effect models. There were no significant differences found for intraoperative periprosthetic fractures [risk ratio (RR) = 1.25; 95% confidence interval (CI): 0.29-5.32; *P* =

0.76], aseptic loosening (RR = 2.15, 95%CI: 0.81-5.70; P = 0.13), dislocation rate (RR = 0.50; 95%CI: 0.10-2.47; P = 0.39), or infection rate (RR = 0.99, 95%CI: 0.82-1.19; P = 0.89), between the uncemented and the cemented long stems for revision THA after mid-term follow-up.

CONCLUSION

This study has evaluated the mid-term outcomes of both cemented and uncemented stems at first-time revision THA. In summary, there were no significant differences in the dislocation rate, aseptic loosening, intraoperative periprosthetic fracture and infection rate between the two cohorts.

Key Words: Long stem; Cemented; Uncemented; Revision total hip arthroplasty; Meta-analysis

Core Tip: This paper included a meta-analysis of three studies involving 7600 revision total hip replacements, of which 3050 were performed using cemented stems, while 2539 were performed utilising uncemented stems. Based on the evidence from this study, there are no statistically significant differences in the rates for intraoperative periprosthetic fractures, aseptic loosening, dislocation and periprosthetic joint infection, for the cemented and uncemented long stems in revision total hip arthroplasty. Nevertheless, there was significant heterogeneity in the included studies for periprosthetic fractures, aseptic loosening and dislocation.

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INTRODUCTION

The numbers of revision total hip replacement (rTHR) have been increasing due to increasing numbers of primary hip replacements worldwide[1]. The uncemented femoral stem has shown increasing popularity among revision hip surgeons[2,3]. However, some authors claim that the cemented long stem prothesis has a longer life span than the uncemented stem, especially in the elderly patient cohort[4,5]. Older studies did not find any difference in the survival rate between the two stem types[6]. 71% of Danish orthopaedic surgeons prefer the uncemented stem. However, only 24% in Sweden use this type of femoral stem[7]. For the first decade of this century, there has been a dramatic increase in the number of uncemented primary hip replacements[8]. Evolutions in the design of the uncemented long femoral stem has added more stability to the distal femur, with a marginal effect on the bone loosening process, which is less predictable, especially in revision surgeries[9]. Consequently, the uncemented stem is a good choice in scenarios where there is bone loss[10]. This study aims to use meta-analysis and systematic review techniques to assess the outcomes of both the uncemented and cemented femoral stems in rTHR. The primary outcome measures were periprosthetic fractures and aseptic loosening. The secondary outcome measures were the dislocation and infection rates.

MATERIALS AND METHODS

Literature search

This study was conducted following both the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement as shown in Figure 1, and the Cochrane Handbook for systematic reviews and meta-analysis[11]. An initial search was conducted using PubMed, Google scholar and the Cochrane Library. Grey and unpublished literature were also explored by searching: Grey Matters BIOSIS Previews, International Clinical Trial Registry, ClinicalTrials.gov, UK Clinical Trials Gateway, Networked Digital Library of Theses and Dissertations, UK Clinical Research Network Study Portfolio, Open Grey and Grey Literature Report. The following keywords were used alone or in combinations: Cemented, uncemented, long stem, revision, and total hip arthroplasty (THA). Articles published up to December 2022 were included in the literature search, and were limited to studies in human subjects published in any language. Additionally, we cross-referenced the bibliographies of retrieved articles and review papers to ensure that we captured all relevant studies.

Eligibility criteria

All full-text observational studies that evaluated the outcomes of both cemented and uncemented stems in rTHR were included. All biomechanical, radiological, and cadaveric studies were excluded. Furthermore, any study that did not meet one or more of the eligibility criteria were excluded.

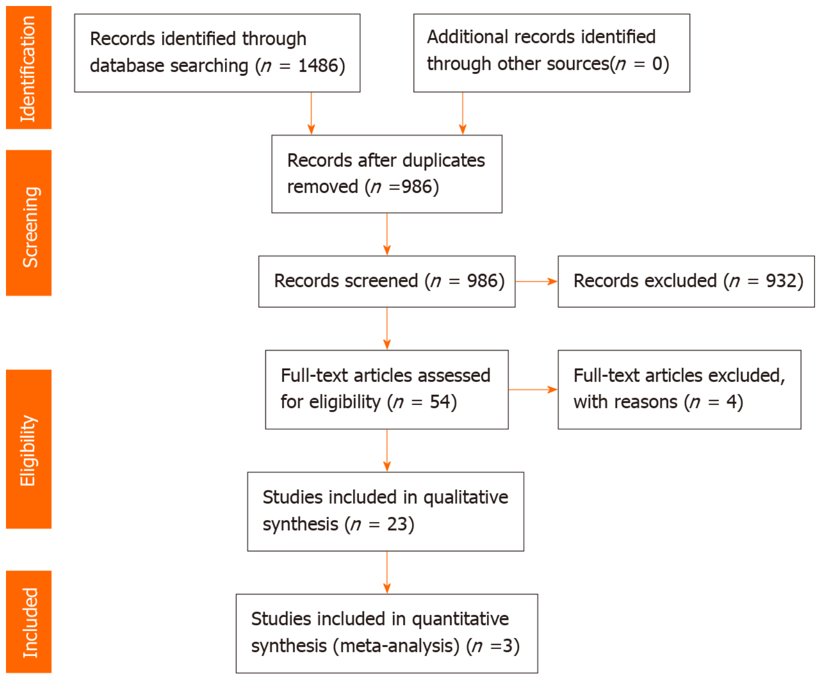

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Figure 1 Preferred reporting items for systematic reviews and meta-analyses flow chart.

Study selection and data extraction

Three authors (Elbardesy H, Anazor F, and Maatough A) independently screened all titles and abstracts identified from the initial search to assess their eligibility for inclusion. Identified titles and abstracts from the initial search were then screened and the full text articles of the eligible manuscripts were obtained. After all eligible full text manuscripts had been evaluated for inclusion criteria eligibility, data extraction was conducted by the same reviewers. Any discrepancies with collected data were resolved by consensus between the reviewers. Outcome measures (periprosthetic fracture, aseptic loosening, dislocation rate, and infection) were recorded. Additionally, the study titles, year of publication, the publishing journal, type of study, level of evidence, number and the brand of the stems, period of follow up, gender and age of the patients included in each study were analysed.

Risk of bias

The risk of bias for retrospective non-randomized studies was assessed using the Newcastle-Ottawa Scale[12], as shown in Table 1. Four reviewers (Elbardesy H, Anazor F, Mirza M, and Maatough A) independently crossed-checked the quality of the included studies. Disagreements were resolved through consensus discussions.

Statistical analysis

Statistical analysis was performed using Review Manager, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2009, Copenhagen, Denmark)[13]. Heterogeneity between studies was evaluated using the I^2 statistic and a χ^2 of < 0.05 was used to determine the significance of the heterogeneity between studies[11]. Risk ratios (RRs) were reported for dichotomous variables such as wound complications, whereas mean differences and standard deviations (SDs) were used for continuous variables. All analyses were conducted using the Mantel-Haenszel random-effects model. The results of our meta-analysis were then illustrated using forest plots, which used a 95% confidence interval (CI) for each study. A P value of < 0.05 was taken to be of statistical significance. Variables that were inconsistently reported were investigated in the systematic review portion of this study[11].

RESULTS

Study characteristics

Our literature search revealed 1486 unique references. After reviewing the titles and abstracts of all studies, three studies were eligible for both quantitative and qualitative analysis. The three selected studies included 7600 revision THRs, of which 3050 were performed using cemented stems, while 2539 were performed utilising uncemented stems. 23 studies were included in the qualitive analysis: Six of them investigated the cemented stems, while 17 focused on uncemented stems (Figure 1). A summary of study characteristics and patients' demographics is presented in Tables 2-6.

Table 1 Newcastle-Ottawa Scale for assessing the quality of observational studies

Ref.	Selection				Comparability	Exposure			Total
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total number of stars
Tyson *et al* [39], 2021	*	*	*	*	**	*	*	*	9
Weiss *et al* [38], 2011	*	*	*	*	*	*	*	*	8
Iorio *et al* [6], 2008	*	*	-	*	*	*	*	*	7

Table 2 Study characteristics

Ref.	Country	Journal	Study type	Centres	Level of evidence	Number of stems	Stem brand for cemented	Stem brand for uncemented
Tyson *et al* [39], 2021	Sweden	*Acta Orthopaedica*	Observational study	Multi	III	266 cemented, 601 uncemented	Lubinus SPII 123 (46%), exeter 94 (35%), spectron 49 (18%)	MP 291 (48%), restoration 162 (27%), wagner 78 (13%), revitan 70 (12%)
Weiss *et al*[38], 2011	Sweden	*Acta Orthopaedica*	Observational study	Multi	III	1073 cemented, 812 uncemented	Lubinus SPII 610 (57%), exeter long stem 248 (23%), spectron revision hip system 215 (20%)	MP stem 812 (100%)
Iorio *et al*[6], 2008	United States	*Journal of arthroplasty*	Prospective cohort study	Single	II	43 cemented, 43 uncemented	13 premise, 6 precision, 5 reliance (stryker), 3 re cemented, 2 charnley elite plus, 2 ultima, 1 PFC (depuy), 4 calcar replacing, 7 extra long	S-ROM modular metaphyseal femoral stem 31 (72%), calcar replacing 9 (23%), extra long 3 (7.7%)

Study characteristic for the studies included in the MA.

Table 3 Patient's demographics

Ref.	Gender M	Age (SD)	Follow up in years (SD)
Tyson *et al*[39], 2021	Uncemented 318 (53%), cemented 138 (52%)	Uncemented 72 (10), cemented 74 (9)	Uncemented 4 (3), cemented 5 (3)
Weiss *et al*[38], 2011	Uncemented 443 (55%), cemented 544 (51%)	Uncemented 72 (11), cemented 76 (9)	Uncemented 3.4 (2.9), cemented 4.2 (2.5)
Iorio *et al*[6], 2008	22 cemented (51%), 22 uncemented (51%)	Uncemented 71.2 (9), cemented 67.5 (10)	Uncemented 7 (1), cemented 9 (1.5)

SD: Standard deviation.

Patient baseline characteristics

For the meta-analysis, the subjects in the uncemented group had an average age of 71 years and 1159 (45.6%) males, with an average follow-up period of 4.8 (± 2.3) years. The cemented cohort had a similar distribution, with an average age of 71.6 years and 1391 (45.6%) males, with an average follow-up period of 6 (± 2.33) years.

Table 4 Study characteristics for the studies about the uncemented stem

Ref.	Total number	Country	Journal	Study type	Centres	Level of evidence
Mahoney *et al*[20], 2010	40	United States	*JOA*	ORS	Single	3
Hasegawa *et al*[22], 2021	45	Japan	*International Orthopaedics*	ORS	Single	3
Zheng *et al*[23], 2021	34	China	*OSJ*	ORS	Single	3
Wallace *et al*[24], 2020	55	United Kingdom	*J Arthroplasty*	ORS	Single	3
Zang *et al*[25], 2019	40	China/Japan	*JOS (Hong Kong)*	ORS	Single	3
Herry *et al*[26], 2019	116	Multi	*International Orthopaedics*	ORS	Multi	3
Shen *et al*[27], 2014	34	China	*COAJ*	ORS	Single	3
Wang *et al*[28], 2020	73	China	*Hip International*	ORS	Single	3
Singh *et al*[34], 2013	53	India	*IJO*	ORS	Single	3
Tsukeoka *et al*[41], 2011	14	Japan	*Modern Rheumatology*	ORS	Single	3
Oetgen *et al*[29], 2008	28	United States	*JOT*	ORS	Single	3
Sotereanos *et al*[36], 2006	16	United States	*JBJS*	ORS	Single	3
Philippot *et al*[35], 2009	43	France	*OTSR*	ORS	Single	3
Thorey *et al*[30], 2008	79	Germany	*AOTS*	ORS	Single	3
Malkani *et al*[31], 1996	74	United States	*JOA*	ORS	Single	3
Mulliken *et al*[32], 1996	66	Canada	*CORR*	ORS	Single	3
Meding *et al*[33], 1994	24	United States	*JOA*	ORS	Single	3

ORS: Observational retrospective study; *JOA*: The Journal of Arthroplasty; *OSJ*: *Orthopaedic Surgery Journal*; *CORR*: *Clinical Orthopaedics and Related Research*; *AOTS*: *Archives of Orthopaedic and Trauma Surgery*; *OTSR*: *Orthopaedics & Traumatology, Surgery & Research*; *JBJS*: *Journal of Bone & Joint Surgery*; *JOT*: *Journal of Orthopaedics & Traumatology*; *IJO*: *Indian Journal of Orthopaedics*; *OSJ*: *Orthopaedic Surgery Journal*; *CJRRS*: *Chinese Journal of Reparative & Reconstructive Surgery*; *JOS*: *Journal of Orthopaedic Surgery (Hong Kong)*; *COAJ*: *Chinese Orthopaedic Association Journal*.

Systematic review

Intraoperative periprosthetic fracture: Six studies reported periprosthetic fractures with the use of cemented stems. Intraoperative periprosthetic fractures were reported in 59 cases (10.64 %) out of a total of 554 hips[14-19]. In the uncemented stem group, 16 studies reported intraoperative periprosthetic fractures in 112 cases out of 824 (13.59 %)[20-35]. The percentage of the periprosthetic fractures was lower in the cemented stem cohort (Tables 7 and 8).

Aseptic loosening: Five studies (with a total number of 375 revision THRs) reported 22 cases of aseptic loosening with cemented stems (5.87%)[14-18]. However, 13 studies with a total of 706 revision THRs, reported 34 cases of aseptic loosening (4.82%)[20,22,26-33].

Dislocation rate: 15 studies which included 689 uncemented stems[20,21-29,31,33-36] reported 29 (4.21 %) cases of dislocation. Conversely, for cemented stems, five studies (with a total of 375 hips) reported a dislocation rate of 4.53 %.

Infection: 14 studies with 626 hips using uncemented long stems reported a total of 28 cases (4.47 %) of post operative infection[20,22-27,30,31,33,35-37]. On the other hand, five studies with a total of 484 cemented hip stems, reported a postoperative infection rate of 4.33%[14,15,17-19].

Meta-analysis

The meta-analysis comparatively assessed the outcomes of both cemented and uncemented stems in rTHR, and the outcomes of both stem types as it correlates to four postoperative outcomes: Intraoperative periprosthetic fracture, aseptic loosening, dislocation rate and infection (after a mid-term follow up period 4.8-6 years). As mentioned earlier, only three studies were eligible for inclusion in the meta-analysis.

Periprosthetic fractures: The three included eligible studies reported on periprosthetic fractures, encompassing a total of

Table 5 Patients demographic for the study involved uncemented stem

Ref.	Gender male/female	Age in years (SD)	Follow up in years (SD)
Mahoney *et al*[20], 2010	18/22	64 (30.5)	10.2 (2.8)
Zhao *et al*[21], 2009	12/8	65 (9.5)	3 (1.1)
Hasegawa *et al*[22], 2021	12/33	62.6 (26)	13.8 (2.2)
Zheng *et al*[23], 2021	16/18	63.9 (11.7)	9.1 (2.5)
Wallace *et al*[24], 2020	19/36	66.4 (9.3)	13.2 (2.17)
Zang *et al*[25], 2019	15/25	62 (19.5)	15.7 (7.1)
Herry *et al*[26], 2019	55/61	68 (12)	10 (3)
Shen *et al*[27], 2014	21/13	65 (13.5)	6 (1.5)
Wang *et al*[28], 2020	33/42	62.6 (16.5)	12.6 (2)
Singh *et al*[34], 2013	42/6	54.7 (15.3)	14 (4.5)
Oetgen *et al*[29], 2008	18/10	59 (12)	5.5 (1.5)
Sotereanos *et al*[36], 2006	9/7	66 (17.5)	7.4 (6.5)
Philippot *et al*[35], 2009	10/33	54 (17.5)	5.3 (1.5)
Thorey *et al*[30], 2008	33/46	72.4 (28.5)	4 (2)
Malkani *et al*[31], 1996	40/ 34	67.1 (10.1)	6.8 (3.9)
Mulliken *et al*[32], 1996	31/32	62 (12)	3 (1)
Meding *et al*[33], 1994	17/7	63.8 (29)	3.6 (2)

SD: Standard deviation.

Table 6 Study characteristics of the cemented stem

Ref.	Country	Journal	Study type	Canters	Level of evidence	Total number	Gender male/female	Age	Follow up in years (SD)
Te Stroet *et al*[14], 2014	Netherlands	*BJJ*	ROS	Single centre	3	37	17/20	76 (39-93)	9 (4)
Randhawa *et al* [15], 2009	United Kingdom	*JOT*	ROS	Single centre	3	57	27/30	73 (37-94)	3.25 (3)
Stigbrand and Ullmark, 2017	Sweden	*JOA*	ROS	Single centre	3	69	40/29	69	7 (3.2)
Pallaver *et al*[19], 2018	Switzerland	*AOTS*	ROS	Single	3	178	126/52	68.4 (36-90)	9.3 (5.2)
Davis *et al*[17], 2003	United States	*JBJS*	ROS	Single	3	48	27/21	67 (47-82)	6.5 (2)
Turner *et al*[18], 1987	United States	*JOA*	ROS	Single	3	165	81/84	62.1 (22-92)	6.7 (1.5)

ROS: Retrospective observational study; *BJJ*: *The Bone & Joint Journal*; *MSM*: *Medical Science Monitor*; *JOT*: *Journal of Orthopaedics & Traumatology*; *JOA*: *Journal of Arthroplasty*; *AOTS*: *Archives of Orthopaedic and Trauma Surgery*; *JBJS*: *The Journal of Bone and Joint Surgery*.

2838 hips. 252 periprosthetic fractures were reported out of the 1382 hips in the cemented long stem cohort, and 84 events were reported in the 1456 hips receiving uncemented stems. Heterogeneity analysis demonstrated high statistical evidence for variation within the studies (I^2 = 94%). Data pooled by random-effects model suggested insignificant difference in periprosthetic fractures among the two cohorts (RR = 1.25, 95%CI: 0.29-5.32; P = 0.76; Figure 2A).

Aseptic loosening: All three studies reported on aseptic loosening after rTHR from a total of 2838 revision hips. Heterogeneity analysis demonstrated high statistical evidence for variation within the studies (I^2 = 96%). Although aseptic loosening rates were less among patients with uncemented stems (RR = 2.15, 95%CI: 0.81-5.70), statistical analysis showed no significant differences (P = 0.13; Figure 2B).

Table 7 Outcomes of the uncemented stem

Ref.	Intraoperative periprosthetic fracture (%)	Aseptic loosening (%)	Dislocation (%)	Infection (%)
Mahoney *et al*[20], 2010	1 (2.5)	1 (2.5)	13 (32.5)	1 (2.5)
Hasegawa *et al*[22], 2021	1 (2.2)	1 (2.2)	1 (2.2)	0 (0)
Zheng *et al*[23], 2021	7 (20.5)	3 (8.8)	1 (2.9)	3 (8.8)
Wallace *et al*[24], 2020	2 (3.6)	0 (0)	3 (5.4)	2 (3.6)
Zang *et al*[25], 2019	11 (27.5)	1 (2.5)	2 (5.0)	2 (5.0)
Herry *et al*[26], 2019	12 (10.3)	4 (3.4)	2 (1.7)	3 (2.5)
Shen *et al*[27], 2014	0 (0)	0 (0)	0 (0)	0 (0)
Tsukeoka *et al*[41], 2011	9 (64.2)	NA	1 (7.1)	NA
Wang *et al*[28], 2020	0 (0)	5 (6.8)	0 (0)	2 (2.7)
Singh *et al*[34], 2013	0 (0)	NA	3 (5.6)	7 (13.2)
Oetgen *et al*[29], 2008	3 (10.7)	0 (0)	0 (0)	NA
Sotereanos *et al*[36], 2006	NA	NA	0 (0)	0 (0)
Philippot *et al*[35], 2009	2 (4.6)	NA	1 (2.3)	3 (6.9)
Thorey *et al*[30], 2008	16 (20.2)	2 (2.5)	NA	2 (2.5)
Malkani *et al*[31], 1996	34 (45.9)	5 (6.75)	2 (2.7)	1 (1.3)
Mulliken *et al*[32], 1996	20 (30.3)	12(18.1)	NA	NA
Meding *et al*[33], 1994	4 (16.6)	0 (0)	3 (12.5)	1 (4.1)

NA: Not applicable.

Table 8 Outcomes of the cemented stem

Ref.	Periprosthetic fracture	Aseptic loosening	Dislocation	Infection
Te Stroet *et al*[14], 2014	9 (24.3)	0 (0)	3 (8.1)	4 (10.8)
Randhawa *et al*[15], 2009	4 (7.0)	1 (1.7)	1 (1.7)	7 (12.2)
Stigbrand and Ullmark, 2017	3 (4.3)	4 (5.7)	2 (2.8)	NA
Pallaver *et al*[19], 2018	2 (1.1)	3 (1.7)	NA	6 (3.3)
Davis *et al*[17], 2003	7 (14.5)	10 (20.8)	7 (14.5)	1 (2.0)
Turner *et al*[18], 1987	34 (20.6)	7 (4.2)	4 (2.4)	3 (1.8)

NA: Not applicable.

Dislocation rate: Of the 1382 cemented stems within the three studies, 146 (10.56 %) dislocations were reported, whereas 568 (39.01%) events were noted in the 1456 rTHAs performed with uncemented stems. Heterogeneity analysis demonstrated high statistical evidence for heterogeneity (I^2 = 98%). Although dislocation rates among patients with cemented stems was more than that seen in the uncemented group, the results were statistically insignificant (RR = 0.50; 95%CI: 0.10-2.47; P = 0.39; Figure 2C).

Infection rate: The three studies reported on infection rate with all of them reporting almost similar infection rates. Heterogeneity analysis demonstrated low statistical evidence for variation within the study (I^2 = 0%). There was no statistically significant difference between the groups (RR = 0.99, 95%CI: 0.82-1.19; P = 0.89; Figure 2D).

DISCUSSION

The most important finding in this review was the lack of statistically significant differences in the assessed outcomes after mid-term follow-up periods (4.8-6 years), between cemented and uncemented stems after first time revision THA.

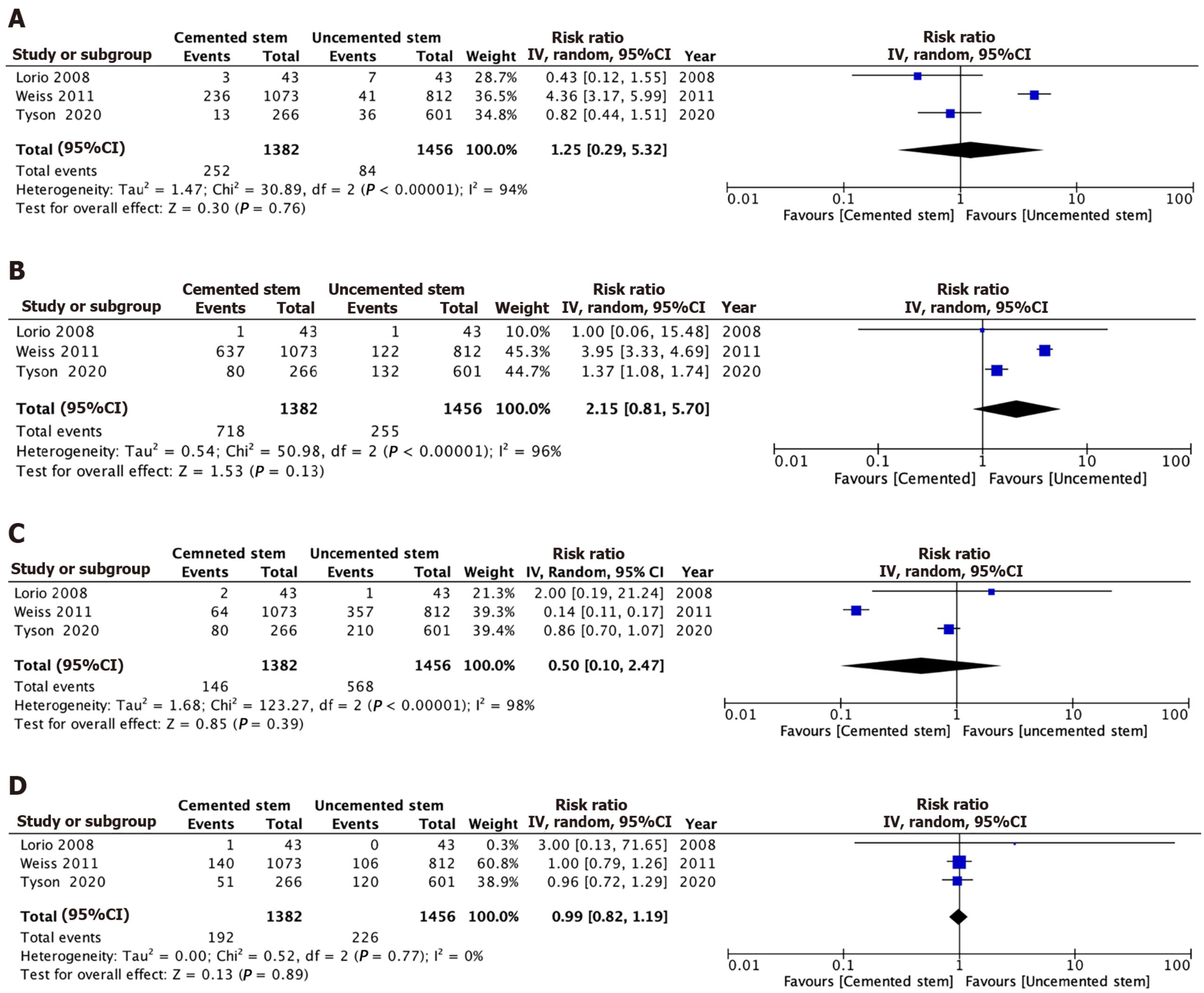

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Figure 2 Forest plot of comparison. A: 1ry outcome, outcome: Periprosthetic fracture; B: 1ry outcome, outcome: Aseptic loosening; C: 2ry outcome, outcome: Dislocation rate; D: 2ry outcome, outcome: 1.4 infection rate. CI: Confidence interval.

To our knowledge, no other meta-analysis or systematic review has compared outcomes between cemented and uncemented stems for first-time revision THRs.

The preference of the femoral stem in revision THA is mainly dependent on the surgeon's choice. However, the uncemented stem is becoming more popular due to the anchoring effect of the distal part of the femoral stem within intact bone. Moreover, the uncemented stem offers different options in the proximal body of the prosthesis to achieve proper soft tissue tension, femoral anteversion, and femoral offset[9]. Some authors claim that the use of the uncemented stem may increase the risk of early postoperative failure but confers less risk of aseptic loosening in the long-term[4,38]. Another study reported better short-term (three years) outcomes for the cemented stem than the uncemented stem[39]. Tyson *et al*[39] reported the findings from a study of 867 uncemented and cemented revision THAs. Their study provided a hazard ratio (HR) of 5 for uncemented *versus* cemented stems for dislocations needing re-revision within the first three years. The HR gradually decreases to 3 between years 4-8. They postulated that the increased risk of subsidence in the uncemented revisions might lead to an increased risk of dislocation[39]. Similarly, Weiss *et al*[9] reported data collected from the Swedish THA register from 1999 to 2007. With a retrospective case-control study design, they showed an increased risk of re-revision in the uncemented hip prostheses in the first three years postoperatively. They included only one design (MP-Waldmar Link) of uncemented, titanium alloy, extensively-coated femoral stem owing to its popularity in Sweden. The control group had a variety of cemented stems implanted. There were 812 and 1073 cases of uncemented and cemented stems, respectively. Over a period of three years, the modular uncemented (MP) stem showed greater risk of re-revision than the cemented group. Crude risk of reoperation in the MP stem group was 5%. The commonest reason for re-revision was dislocation. The difference in re-revision rate was only found in the first 3 years postoperatively. Subsequently, after the three-year period, there was no significant difference in revision rates[38].

Davis *et al*[17] reported 14 (29%) cases of aseptic loosening in a series of 48 hips over a mean follow up period of 6.8 years. 10 (20.8%) of these were revised. The authors suggest that reduced stock of cancellous bone (arising from bone loss which occurs during loosening of the primary stem and during femoral preparation for prosthesis insertion) allows for less interdigitation of cement, which leads to an earlier onset of aseptic loosening. Whilst plausible, when comparing outcomes of primary against revision cemented stems, this does not explain why their figures are lower compared to other series reporting on cemented stems. Earlier generation cementing techniques may explain this[17]. Other authors report aseptic loosening rates as high as 18.1%[32]. There appears to be no inferable pattern that may explain this from data provided. Systematic data aggregating levels of bone defects with rates of aseptic loosening may help shed light on the relationship between bone loss and aseptic loosening.

Te Stroet *et al*[14] reported nine (24%) intraoperative periprosthetic fractures but reported that none occurred during graft impaction[14]. They suggested that consistently worse preoperative bony defects than that seen in comparative studies was the causative factor. Most fractures occurred during stem extraction. They proposed that the use of a Wagner osteotomy may help reduce the risk of such complications[14]. Sierra *et al*[40] do not report on intraoperative fractures but discuss one case of femoral perforation which subsequently led to the development of a post-operative fracture. Impaction bone grafting allows for initial stability[16], but risks inducing fractures[40]. Sierra *et al*[40] suggested that the generous release of a circumferential rim of proximal soft tissues led to reduced bending and torsional forces during stem preparation, thereby reducing the risk of fractures. Relatively higher numbers of periprosthetic fractures were reported with uncemented stems. Tsukeoka *et al*[41] in their series of 20 hips, reported nine fractures (45%) and one perforation. Malkani *et al*[31] reported a similar 45.1% intraoperative fracture rate. Both studies reported on the findings from the use of proximally coated stems that are reliant on the "fit-and-fill" philosophy. Malkani *et al*[31] suggested that the impaired quality of bony, along with the size and stiffness of the implant, might explain the observed numbers of periprosthetic fractures. In conclusion, both types of femoral stems are safe options for revision THA.

Study limitations

One of the limitations of this study, was the fact that there were only three studies included in the meta-analysis. Significant heterogeneity occurred between the studies for the four assessed outcomes except for infection rate. Furthermore, all included studies were retrospective. These types of observational studies are more prone to bias in data collection, and are affected by the inability to control for all the variables assessed between the different cohorts included in each study. Another limitation was the fact that the postoperative follow up period was not long enough. Randomized control studies with long-term follow up periods comparing outcomes between these types of femoral stem are required, in order to provide data of a higher quality in this area.

CONCLUSION

In summary, this study has evaluated the mid-term outcomes of both cemented and uncemented stems for first time revision THA. No statistically significant differences in dislocation rate, aseptic loosening, intraoperative periprosthetic fracture and infection rate between the two cohorts were found. Nevertheless, the evidence from this study should be interpreted with caution, due to the unavailability of any randomized controlled studies for the meta-analysis. Finally, significant heterogeneity occurred between the studies for the four assessed outcomes, except for infection rate.

ARTICLE HIGHLIGHTS

Research background

There is no published systematic review and meta-analysis looking at the research question in this study, despite the large number of revision total hip arthroplasties (THA) performed worldwide.

Research motivation

We have had this nagging question: "Is there any scientific evidence from published studies that shows a difference in outcomes between the cemented and uncemented stems, for revision total hip arthroplasty?"

Research objectives

To assess the outcomes (intraoperative periprosthetic fractures, aseptic loosening, dislocation and infection rates) of both cemented and uncemented stems after mid-term follow up.

Research methods

A meta-analysis of non-randomized interventional studies.

Research results

This paper included a meta-analysis of three studies involving 7600 revision total hip replacements, of which 3050 were performed using cemented stems, while 2539 were performed utilising uncemented stems. There were no statistically significant differences found for intraoperative periprosthetic fractures [risk ratios (RRs) = 1.25; 95% confidence interval (CI): 0.29-5.32; P = 0.76], aseptic loosening (RR = 2.15, 95%CI: 0.81-5.70; P = 0.13), dislocation rate (RR = 0.50; 95%CI: 0.10-2.47; P = 0.39), or infection rate (RR = 0.99, 95%CI: 0.82-1.19; P = 0.89), between the uncemented and the cemented long stems for revision THA after mid-term follow-up.

Research conclusions

Low-moderate quality evidence showing no statistically significant differences between the cemented and uncemented stems for revision THA.

Research perspectives

We believe the evidence from this study should be interpreted with caution, due to the lack of any randomized controlled study being eligible for inclusion in the meta-analysis. Furthermore, significant heterogeneity was found between the included studies.

FOOTNOTES

Author contributions: Elbardesy H and Anazor F involved in the conceptualization of the study and data interpretation; Elbardesy H, Anazor F, and Mirza M contributed to the data analysis; Elbardesy H, Anazor F, and Aly M contributed to the study design; Elbardesy H, Anazor F, and Maatough A involved in the selection and screening of studies; Elbardesy H, Anazor F, Mirza M, Aly M, and Maatough A contributed to the manuscript preparation-writing and editing; and all authors read and approved the final draft of the manuscript.

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SCIENTOMETRICS

Scientific publications on orthopedic surgery from three major East Asian countries (2012-2021)

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Abstract

BACKGROUND

East Asia is the most dynamic region in the world and includes three major countries: Japan, South Korea and China. Due to rapid economic growth, orthopedics research in East Asia has achieved great advances during the past 10 years. However, the current status of orthopedic research in Japan, South Korea and China is still unclear.

AIM

To understand the current status of orthopedic research in Japan, South Korea, and China.

METHODS

Journals listed in the "Orthopedics" category of Science Citation Index Expanded subject categories were included. The PubMed and Web of Knowledge electronic databases were searched to identify scientific publications from the selected journals written by researchers from Japan, South Korea and China. A systematic analysis was conducted to analyze orthopedic research articles published in the three countries based on the number of articles, study design, impact factors (IFs) and citations. Furthermore, we also ranked the top 10 countries worldwide with the highest publications in the past 10 years. Additionally, we ranked the top 10 countries with the highest number of publications in the world in the past 10 years. Statistical analyses were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, United States), and statistical results are given in Tables and Figures. The Kruskal-Wallis test and the Mann-Whitney test were used to detect differences between countries. The tendency regarding the number of articles was analyzed by curvilinear regression. A two-tailed $P < 0.05$ was considered significant.

RESULTS
From 2012-2021, a total of 144518 articles were published in the 86 selected orthopedic journals. During this period, the number of worldwide published orthopedic articles has shown an annual increasing trend. A total of 27164 orthopedic research articles were published by Japan, South Korea and China during the past 10 years; 44.32% were from China, 32.98% were from Japan, and 22.70% were from South Korea. From 2012 to 2021, the annual number of articles markedly increased in each of the three countries. Over time, the worldwide share of articles increased substantially in South Korea (3.37% to 6.53%, $P < 0.001$) and China (5.29% to 9.61%, $P < 0.001$). However, the worldwide share of articles significantly decreased in Japan (5.22% to 3.80%, $P < 0.001$). The annual total IFs of articles from China were well above those of articles from Japan and South Korea (36597.69 *vs* 27244.48 *vs* 20657.83, $P < 0.05$). There was no significant difference among the articles in the top 10 high-IF orthopedics journals published from those three countries [South Korea (800) > China (787) > Japan (646), $P > 0.05$].

CONCLUSION
Over the past 10 years, China's scientific publications in orthopedic journals have shown an increasing trend. Considering the relative scale of the populations, Japan and South Korea have outpaced China with respect to quality.

Key Words: Japan; South Korea; China; Medical publication; Orthopedics; Research

Core Tip: Our study was the first to systematically analyze and compare the scientific publication trends of orthopedic surgery studies over the past 10 years in three major East Asian countries–*i.e.*, Japan, South Korea, and China–and to summarize the current status of orthopedic science research in these three countries, thus providing useful information for orthopedic science research.

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INTRODUCTION

Orthopedic disorders are a general health problem that affects people of all ages and demographic backgrounds. These disorders are a major burden for individuals, health systems, and social care systems, with indirect costs being the most dominant burden. In particular, the majority of the global burden of orthopedic disease occurs in low- and middle-income countries and is susceptible to neglect. China is the largest developing country in the world; it has more than 1.37 billion people, and it is facing the big challenge of reducing the burden of disease. For instance, more than 50000 hip or knee joint replacements are annually performed in China[1-3]. Researchers have progressively focused more attention on this situation and are now trying to advance the understanding, treatment and prevention of musculoskeletal disorders[4,5].

East Asia is an important subregion of Asia and is also the most dynamic region in the world. The countries in East Asia include Japan, North Korea, South Korea, Mongolia, and China. Japan is a world leader in fundamental scientific research[6]. South Korea is one of the new industrial economic countries as well as a leader in scientific research[7,8]. Due to the rapid socioeconomic development that has occurred in China, scientific and medical fields have undergone tremendous changes in the past decade[9,10]. Japan, South Korea and China are non-English-speaking countries that adhere to traditional East Asian cultural practices, and they are well-developed, developed and developing countries, respectively. Scientific publication provides a connection between the production and use of scientific knowledge and is a widely accepted method for evaluating public health and academic achievement. Nonetheless, little is known about the relative contributions of the three major East Asian countries to the field of orthopedics. The quantity and quality of scientific literature can be used to analyze the history and current status of science and technology and to forecast trends. Hence, it is crucial to accurately estimate global and regional productivity in ongoing orthopedic research. The present study was designed to investigate the characteristics and trends in orthopedic research studies from Japan, South Korea and China over the past 10 years.

MATERIALS AND METHODS

This retrospective study investigated 86 journals from the ''Orthopedics'' category of the Science Citation Index

Expanded for 2021[11]. Resources in this category include general orthopedics publications and specialized research on musculoskeletal disorders, spine diseases, injury, arthroplasty, arthroscopy, hand surgery, sport medicine, traumatology, foot and ankle surgery, connective tissue diseases, osteoarthritis and physical therapy. Based on the selection criteria, a total of 86 orthopedics journals were selected, and the journals included in the search are shown in Supplementary Table 1. The selection criteria, which were described in previous studies[12-14], were as follows: (1) The journal was indexed in the PubMed database; and (2) the journal had impact factors (IFs) in accordance with the Journal Citation Reports (JCR) for 2021[15]. On September 1, 2022, the PubMed and Web of Knowledge databases were searched for articles published in the 86 selected journals between January 1, 2012, and December 31, 2021, and written by researchers from Japan, South Korea, and China[16]. The databases were searched using the full journal titles or the ISSN numbers of the journals. The search terms used were "0001-5415 OR 1745-3674 OR 0001-6462 OR 1017-995X OR 1413-7852 OR 0363-5465 OR 0936-8051 OR 1862-3522 OR 0749-8063 OR 2049-4394 OR 2046-3758 OR 1413-3555 OR 1947-6035 OR 0268-0033 OR 1050-642X OR 0009-921X OR 2380-0186 OR 2005-291X OR 0891-8422 OR 0300-8207 OR 1935-973X OR 2396-7544 OR 1473-2262 OR 0940-6719 OR 1071-1007 OR 1083-7515 OR 1268-7731 OR 0966-6362 OR 2151-4585 OR 2192-5682 OR 0749-0712 OR 2468-1229 OR 1120-7000 OR 1556-3316 OR 0019-5413 OR 0020-1383 OR 0341-2695 OR 0959-3020 OR 2687-4784 OR 2572-1143 OR 0883-5403 OR 1053-8127 OR 0021-9355 OR 1863-2521 OR 1067-2516 OR 0363-5023 OR 1753-1934 OR 0894-1130 OR 2054-8397 OR 1538-8506 OR 0190-6011 OR 0736-0266 OR 0949-2658 OR 1022-5536 OR 1749-799X OR 2214-031X OR 0890-5339 OR 1590-9921 OR 0271-6798 OR 1060-152X OR 1836-9553 OR 2000-656X OR 1058-2746 OR 1067-151X OR 8750-7315 OR 0968-0160 OR 0942-2056 OR 0934-6694 OR 0085-4530 OR 0744-6020 OR 1757-7853 OR 1877-0568 OR 0030-5898 OR 0147-7447 OR 1063-4584 OR 0031-9023 OR 0091-3847 OR 0309-3646 OR 0364-2348 OR 0362-2436 OR 1529-9430 OR 0932-0555 OR 1864-6697 OR 2325-9671 OR 1757-1146 OR 1471-2474" AND "Japan [ad]," "South Korea [ad]," and "China [ad]".

The author's institutional affiliation was used to identify the country of the scientific publication. The publication type categories in the PubMed database were used to compile clinical trials, randomized controlled trials (RCTs), and case reports. In accordance with previous studies[12-14], four methods were used to evaluate publication quality. First, the annual total and average IFs were determined according to JCR 2021[15]. Second, the distribution and citation patterns of articles written by researchers from these three countries were analyzed using *Reference Citation Analysis* (https://www.referencecitationanalysis.com/)[17]. Third, we calculated the number of clinical trials, RCTs, systematic reviews/meta-analyses and case reports. Fourth, we quantified the articles published in the top 10 high-IF orthopedic journals and identified the top 10 popular orthopedic journals in the three countries based on the number of articles published in each journal. Moreover, we assessed global trends in orthopedic publications and ranked the top 10 countries with the highest number of publications worldwide over 10 years. Two reviewers (WC and XX) independently extracted the articles. Disagreements between the two reviewers were resolved by consulting a third reviewer (HJ).

RESULTS

Global trends in orthopedic publications

A total of 144518 articles were published in 86 orthopedics journals from 2012 to 2021. The global number of annually published orthopedic research articles showed an increasing trend during the study period. The United States was the highest ranked country in terms of the number of published orthopedic research articles (39017 articles), followed by China (14939), Japan (11525), the United Kingdom (11203), Germany (10080), Canada (7887), South Korea (7664), France (7138), Australia (6849), and the Netherlands (5941). The top 10 countries in the world with the highest number of annual publications are shown in Table 1.

Number of articles in the orthopedic field in Japan, South Korea and China

A total of 27164 articles from Japan, South Korea and China were published in the 86 selected journals between 2012 and 2021 (Figure 1). 44.32% (12040/27164) were from China, 32.98% (8959/27164) were from Japan, and 22.70% (6165/27164) were from South Korea ($P < 0.05$). From 2012 to 2021, the annual number of articles published in the orthopedic field increased noticeably in South Korea (459 to 899, annual rate of increase = 6.95%, $R^2 = 0.798$, $P < 0.001$), China (552 to 2661, annual rate of increase= 17.03%, $R^2 = 0.823$, $P < 0.001$) and Japan (622 to 1620, annual rate of increase = 10.05%, $R^2 = 0.728$, $P < 0.05$) (Figure 2A).

The worldwide share of articles increased remarkably over time in South Korea (3.37% to 6.53%, annual rate of increase = 6.85%, $R^2 = 0.988$, $P < 0.001$) and China (5.29% to 9.61%, annual rate of increase = 6.16%, $R^2 = 0.995$, $P < 0.001$). However, the worldwide share of articles decreased dramatically in Japan (5.22% to 3.80%, annual rate of increase =-3.14%, $R^2 = 0.878$, $P < 0.001$) (Figure 2B). In 2021, China accounted for 11.20% of all articles in the orthopedics field, followed by Japan (6.82%) and South Korea (3.78%) ($P < 0.05$).

Clinical trials, RCTs and case reports

Researchers from China published more clinical trials than researchers from Japan and South Korea [China (634) > South Korea (426) > Japan (330), all P values were less than 0.05] (Figure 3). Between 2012 and 2021, Chinese researchers published 512 RCTs, South Korean researchers published 353 RCTs ($P < 0.05$). Compared to China and South Korea, Japan had a distinctly higher number of case reports ($P < 0.05$) (Figure 3).

Table 1 Top 10 countries according to the annual number of articles from 2012-2021

Year	1	2	3	4	5	6	7	8	9	10
2012	United States	United Kingdom	Japan	China	Germany	South Korea	Canada	France	Netherlands	Australia
2013	United States	United Kingdom	Japan	China	Germany	South Korea	Canada	Netherlands	France	Australia
2014	United States	United Kingdom	China	Japan	Germany	Canada	South Korea	France	Australia	Netherlands
2015	United States	China	United Kingdom	Germany	Japan	Canada	South Korea	Australia	France	Turkey
2016	United States	China	United Kingdom	Japan	Germany	France	Canada	Australia	South Korea	Netherlands
2017	United States	China	Japan	United Kingdom	Germany	Canada	South Korea	France	Australia	Netherlands
2018	United States	China	Japan	United Kingdom	Germany	Canada	South Korea	France	Australia	Netherlands
2019	United States	China	Japan	United Kingdom	Germany	Canada	South Korea	France	Australia	Netherlands
2020	United States	China	Japan	United Kingdom	Germany	Canada	South Korea	France	Australia	Switzerland
2021	United States	China	Japan	United Kingdom	Germany	Canada	France	South Korea	Australia	Switzerland

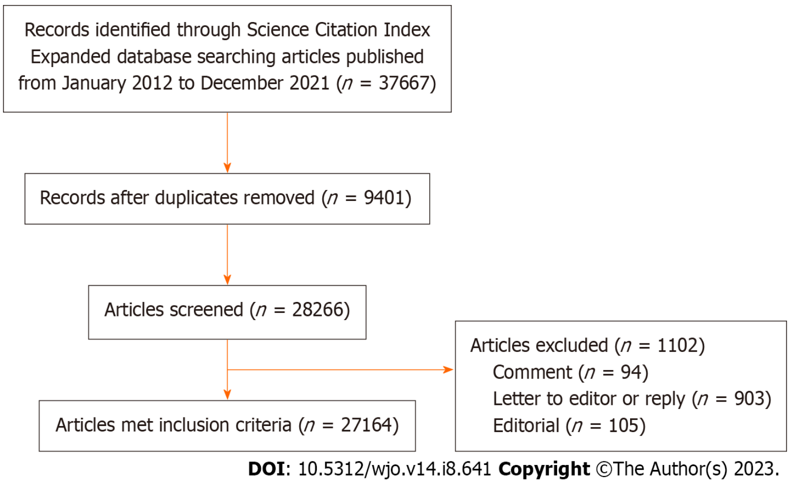

Figure 1 Flow chart for study selection.

IFs

During the past 10 years, the annual total IFs were ranked in the following order: China, Japan and South Korea (36597.69 *vs* 27244.48 *vs* 20657.83, $P < 0.05$) (36597.69 *vs* 27244.48 *vs* 20657.83, $P < 0.05$). The annual total IFs of articles from China were markedly higher than those from South Korea. For the past 10 years, there were no discernible variations in the annual total IFs between Japan and the other two countries ($P > 0.05$). The average IFs of articles from Japan or China were significantly lower than those of articles from South Korea. (2.81 *vs* 2.94 *vs* 3.21; all P values were less than 0.05) (Figure 4). However, there was no significant difference in the average IF between Japan and China ($P > 0.05$).

Citations of articles published in orthopedics journals

Articles from China had the highest number of citations (164175 citations), followed by those from Japan (117323 citations) and South Korea (83118 citations). There was a significant difference in the number of citations between China and the two other countries ($P < 0.001$), but there was no statistically significant difference in the number of citations between Japan and South Korea ($P > 0.05$) (Figure 2C).

Articles in the top 10 high-IF orthopedics journals

The top 10 high-IF orthopedic journals with 2642 articles from the three countries. Among them, 41.75% (1103/2642) were

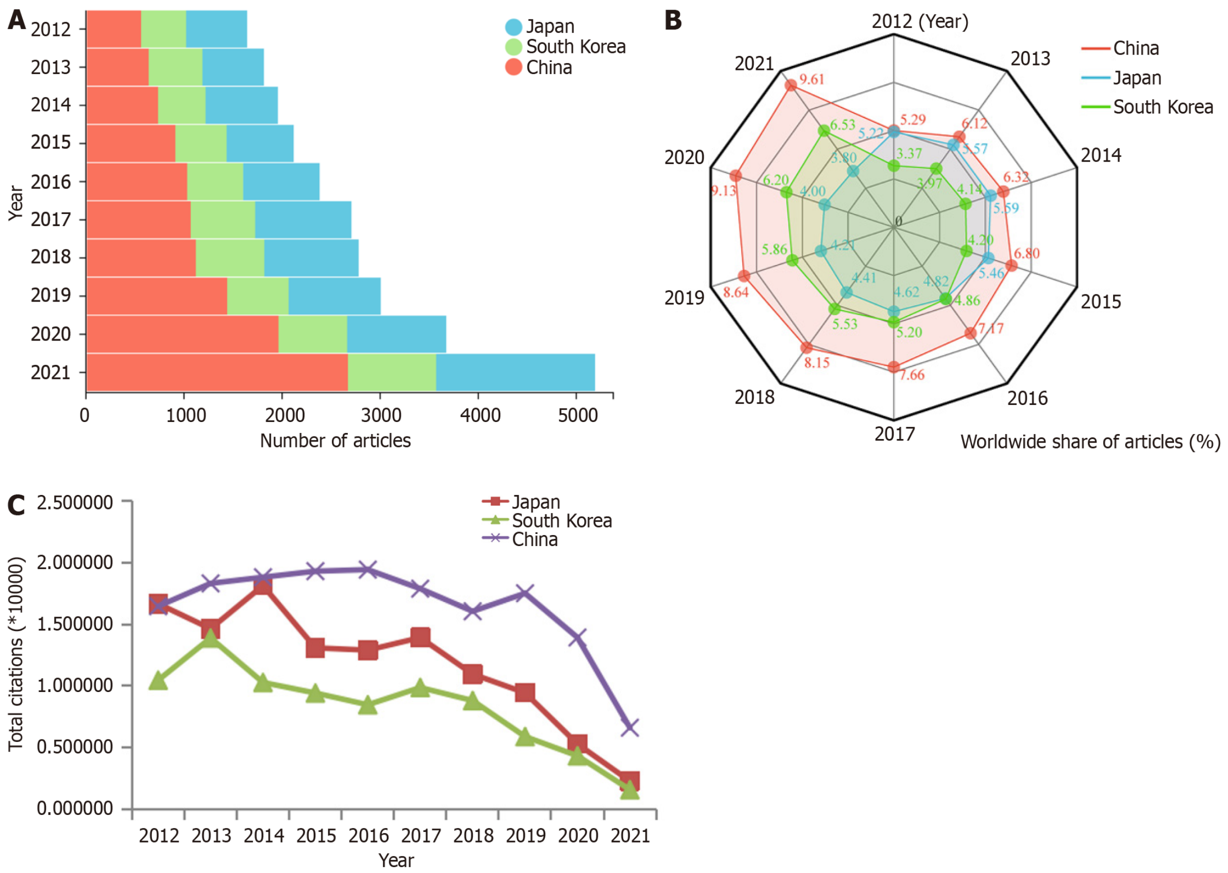

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Figure 2 The articles published in the 86 orthopedics journals by researchers from Japan, South Korea and China (2012-2021). A: Annual numbers; B: Annual proportion; C: Annual citations.

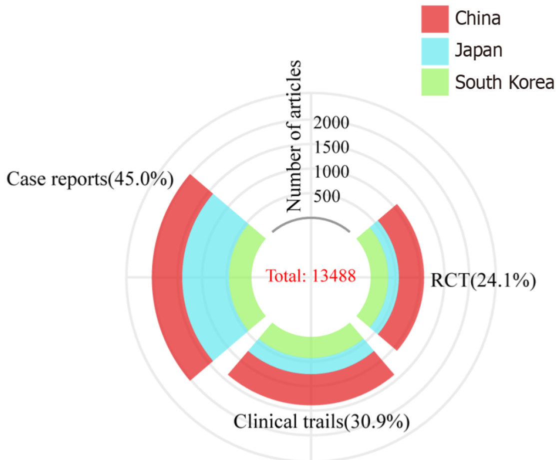

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Figure 3 Number of clinical trials, randomized controlled trials and case reports published by researchers from Japan, South Korea and China from 2012 to 2021. RCT: Randomized controlled trials.

in the top three journals: Journal of Physiotherapy, Osteoarthritis and Cartilage, and American Journal of Sports Medicine. Researchers from Japan published 770 (29.14%) articles in the top 10 high-IF orthopedics journals, those from South Korea published 847 (32.06%) articles, and those from China published 1025 (38.80%) articles (Table 2).

Popular orthopedics journals

The journals with the highest number of articles published by researchers from these three countries are shown in Table 3. Over the past 10 years, most of the orthopedic research studies from China were published in the Journal of Orthopaedic Surgery and Research (1680), most of the articles from Japan were published in the Journal of Orthopedic

Table 2 Articles published in the top 10 high IF orthopedics journals by researchers from Japan, South Korea and China from 2012 to 2021

Rank	Journal	2021 JIF	Japan (%)	South Korea (%)	China (%)	Total
1	*J PHYSIOTHER*	10.714	1 (33.33)	0 (10.00)	2 (66.67)	3
2	*OSTEOARTHR CARTILAGE*	7.507	124 (30.31)	47 (11.49)	238 (58.20)	409
3	*AM J SPORT MED*	7.01	234 (33.86)	290 (41.97)	167 (24.17)	691
4	*J BONE JOINT SURG AM*	6.558	99 (32.57)	112 (36.84)	93 (30.59)	304
5	*J ORTHOP SPORT PHYS*	6.276	5 (38.46)	4 (30.77)	4 (30.77)	13
6	*ARTHROSCOPY*	5.973	166 (28.28)	286 (48.72)	135 (22.99)	587
7	*BONE JOINT J*	5.385	122 (38.00)	94 (29.28)	105 (32.71)	321
8	*J ORTHOP TRANSL*	4.889	13 (4.36)	10 (3.36)	275 (92.28)	298
9	*EFORT OPEN REV*	4.775	2 (25.00)	1 (12.50)	5 (62.50)	8
10	*BRAZ J PHYS THER*	7.507	4 (50.00)	3 (37.50)	1 (12.50)	8
Total			770 (29.14)	847 (32.06)	1025 (38.80)	2642

Table 3 The top 10 popular orthopedics journals publishing the articles written by researchers from Japan, South Korea and China

Rank	Japan	IF	*n*	South Korea	IF	*n*	China	IF	*n*
1	*JOS*	1.805	1427	*COS*	2.503	492	*JOSR*	2.677	1680
2	*Spine*	3.269	622	*KSSTA*	4.114	394	*BMCMD*	2.562	1296
3	*KSSTA*	4.114	506	*AJSM*	5.973	290	*OS*	2.279	920
4	*BMCMD*	2.562	444	*ARTH*	7.01	286	*ESJ*	2.721	759
5	*ESJ*	2.721	421	*Spine*	3.269	261	*Spine*	3.269	691
6	*JA*	4.435	288	*JA*	4.435	241	*IO*	3.479	587
7	*JOR*	3.102	276	*BMCMD*	2.562	241	*Injury*	2.687	378
8	*JOSHK*	2.423	276	*JSES*	3.507	221	*TSJ*	4.297	326
9	*Knee*	1.482	242	*AOTS*	2.928	221	*JOT*	4.239	275
10	*AJSM*	7.01	234	*TSJ*	4.297	199	*AOTS*	2.928	272

AJSM: *Am J Sports Med*; *AOTS*: *Arch Orthop Traum Surg*; *ARTH*: *Arthroscopy*; *BMCMD*: *BMC Musculoskelet Disord*; *COS*: *Clin Orthop Surg*; *ESJ*: *Eur Spine J*; *IO*: *Int Orthop*; *JA*: *J Arthroplasty*; *JOR*: *J Orthop Res*; *JOSHK*: *J Orthop Surg (Hong Kong)*; *JOS*: *J Orthop Sci*; *JOSR*: *J Orthop Surg Res*; *JSES*: *J Shoulder Elbow Surg*; *JOT*: *J Orthop Translat*; *KSSTA*: *Knee Surg Sport Tr A*; *OS*: *Orthopaedic Surgery*; *TSJ*: *The Spine J*.

Science (1427), and most of the articles from South Korea were published in Clinics in Orthopedic Surgery (492). Spine, BMC Musculoskeletal Disorders appeared among the top 10 popular journals for all three countries.

DISCUSSION

To the best of our knowledge, this is the first study to investigate the characteristics of and trends in orthopedic studies from Japan, South Korea and China. The number of worldwide orthopedic publications showed an upward trend from 2012 to 2021. Unquestionably, the United States ranks first in the world in terms of total and annual number of orthopedic publications. Over the past 10 years, there has been a steady increase in the number of articles published each year in highly developed countries, including the United Kingdom, Japan, Germany and France[18,19]. Notably, there has been drastic growth in the annual number of articles published in China and Japan. Their articles disseminate a wealth of scientific knowledge and make significant contributions to the countries' profound emphasis on academic research, as well as active global engagement. Therefore, these countries have contributed to the development of orthopedics over the past 10 years.

During the past 10 years, a considerable increase in the total number and percentage of articles in orthopedic journals from Japan has been observed. Despite substantial growth in the annual number of orthopedic research articles published in Japan (622 in 2012 to 1620 in 2021), the country's worldwide share of articles decreased from 5.22% in 2012 to 3.80% in

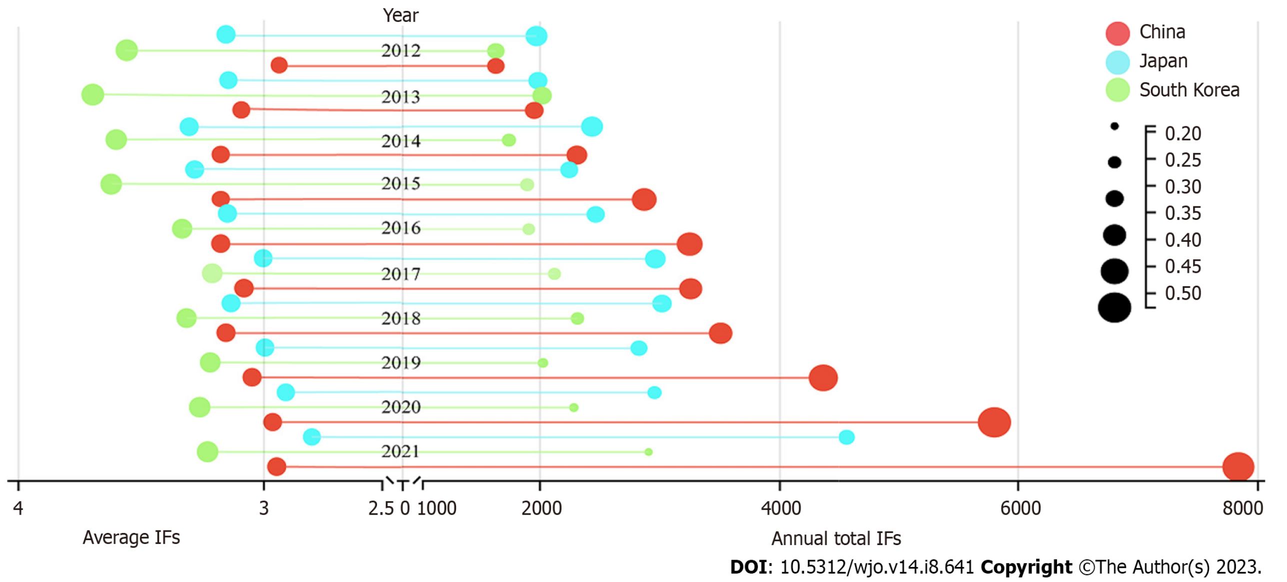

Figure 4 The average impact factors and annual total impact factors of articles published in the 86 orthopedics journals by researchers from Japan, South Korea and China from 2012 to 2021. IF: Impact factors.

2021. This decrease may be attributed to a decrease in government funding allocated for research endeavors[20]. Nevertheless, Japan still has a considerable international impact on scientific research and is a leader in the field of orthopedics. The large amount of research funding and the vast number of well-trained researchers might account for the objective reality that Japan has attained a continuously dominant position. Furthermore, Japan enjoys an efficient and competitive system of scientific research, which may be considered a reference model for some developing countries in Asia.

In the past 10 years, the annual number and worldwide share of orthopedic publications from South Korea have also increased (annual number: 459 in 2012 to 899 in 2021; worldwide share: 3.37% in 2012 to 6.53% in 2021). The rise of scientific research may be ascribed to the aging population. As the population progressively ages, there is a pronounced increase in the prevalence of orthopedic disorders[21]. In response, researchers have redirected their focus toward gaining a better understanding of this situation and advancing the treatment of orthopedic disorders. Consequently, South Korea has emerged as a noteworthy contributor to the development of orthopedic science, gradually gaining recognition for its prowess and innovative approaches.

There has been a strong positive trend in orthopedic publications from China. Our study suggests a 5-fold increase in the absolute number of articles from China in orthopedic journals (from 552 papers in 2012 to 2661 paper in 2021, P < 0.001), and the market share of articles in China has increased markedly (from 5.29% in 2012 to 9.61% in 2021, P < 0.001). In the orthopedics field, China's scientific research has been growing rapidly in the past decade[14,18,19]. In 2013, articles originating in China (629) surpassed those originating in Japan (627) and South Korea (548). Between 2012 and 2021, researchers from China published 634 orthopedic clinical trials, outpacing those from South Korea (n = 426, P < 0.05) and Japan (n = 330, P < 0.05). Only 1083 RCTs were found among all 27164 articles originating in these three countries (Japan 218 *vs* South Korea 353 *vs* China 512; P < 0.05). RCTs are considered to be a higher grade of scientific evidence that influences health care policy. Thus, researchers in East Asia should prioritize more RCTs and consider these findings.

The average number of citations to articles in the publications is indicated by the IF. Although the IF has many limitations[22,23], it remains one of the optimal tools for assessing the relative significance of scientific studies. Researchers from South Korea made the most qualitative contributions to orthopedic research, as evidenced by the number of papers they published in high-IF journals and the highest annual average IFs. Researchers from South Korea published more articles in high-IF journals and had the highest annual average IFs, indicating that they contributed the majority to orthopedic research in terms of quality. Throughout the past 10 years, there has been steady growth in the total annual IF of articles originating from China. However, the annual average IFs still lagged behind South Korea. Undoubtedly, the quality of the articles and the international presence from China requires improvement. Citations are another valuable indication of article quality, revealing the extent to which the article has been accepted by other authors in the same field. In this study, we revealed that articles from China had a fairly high number of citations, followed by those from Japan and Korea. The average number of citations for Chinese studies ranked behind Japan and South Korea. In fact, newly published articles have less time to be cited, and thus, old articles of high quality are usually more often cited. In the past 3 years, China published 6042 articles, accounting for 50.18% (6042/12040) of the total number of articles published from 2012 to 2021, which could explain this phenomenon.

Regarding the orthopedic journals with a top-ten IF, researchers from China (1025) and South Korea (847) published more articles in these journals than researchers from Japan (770), but there was no significant difference among the three countries (P > 0.05). It should be noted that IF is not always the optimum parameter for identifying the quality of journals. Sometimes, a high IF represents a journal with high visibility, prestige, and influence. Researchers with well-designed studies tend to submit their articles to journals with these characteristics. In this study, spine and *BMC Musculoskeletal*

Disorders were considered the most popular journals, ranking among the top 10 popular journals in the three countries. The most popular journals in this study were *Spine* and *BMC Musculoskeletal Disorders*, which were ranked among the top 10 most popular publications in each of the three nations. These two journals mainly publish high-quality clinical and basic research articles, which results in their widespread international influence. However, there were differences in the most popular journals for authors among the three countries. Researchers from Japan publish most in *Journal of Orthopedic Science*. This journal is the official journal of the Japanese Orthopedic Association and has a lengthy and illustrious history of publishing outstanding scientific papers in the field[24]. The top three popular journals for South Korea were *Clinics in Orthopedic Surgery, Knee Surgery Sports Traumatology Arthroscopy and Arthroscopy-The Journal of Arthroscopic and Related Surgery,* suggesting that arthroplasty surgery in South Korea is developing rapidly and has achieved great advances in recent years. On the other hand, the top three popular journals for China were *Journal of Orthopaedic Surgery and Research*, *BMC Musculoskeletal Disorders and Orthopaedic Surgery,* demonstrating that China has markedly improved its research in the field of orthopedic surgery during the past 10 years.

Orthopedic research in China is experiencing a period of immense growth, which is due to several factors. First, numerous newly established institutions and hospitals in China already conduct scientific research and surgical treatment in orthopedics, with recent advances in China’s economy[9,25,26]. Second, the continual development of international cooperation might benefit Chinese orthopedic researchers to strengthen their clinical orthopedic practice and research abilities[27-29]. Third, the number and IF of articles indexed in the SCIE database were recently regarded as important indicators to evaluate the performance and achievements of a researcher or an institution in China. Importantly, SCIE papers are tightly linked to authors' academic status, income, funding and other key benefits[30,31]. However, these policies seem to have resulted in an increase in the number of articles and not in their quality, as indicated by the current citation rates for Chinese-authored articles.

There are some limitations to this study. First, only 86 orthopedic journals included in the SCIE database were analyzed. There were some orthopedic research articles published in general medical journals that were not included in our study. Second, the JCR database was restricted to include studies published in English, which may lead to publication bias. For that reason, we may have neglected the contribution of non-English publications.

CONCLUSION

In summary, some useful information about scientific research in orthopedics is provided in this study. China has maintained an increasing trend of scientific publication in orthopedics journals over the past 10 years and has exceeded Japan and South Korea in some aspects of orthopedics publications. Given the relative size of the populations, China still lags behind Japan and South Korea in terms of quality. Chinese orthopedic researchers must improve their research activities and produce high-quality research.

ARTICLE HIGHLIGHTS

Research background

Orthopedic research in East Asia has made significant strides over the past 10 years. However, the current status of orthopedic research in the three major East Asian countries of Japan, South Korea, and China remains uncertain.

Research motivation

To explore the current state of orthopedic research in Japan, South Korea, and China and provide informative findings in the field of orthopedic science.

Research objectives

To visualize the publication quantity, global share, publication types, impact factor (IF), and citation trends of orthopedic studies from Japan, South Korea, and China during the period of 2012-2021 and to analyze the developmental trends in orthopedic research in East Asia over the past decade.

Research methods

According to the selection criteria, which include: (1) The journal was indexed in the PubMed database; and (2) the journal had IFs in accordance with the Journal Citation Reports for 2021, a total of 86 orthopedic journals were included. The PubMed and Web of Knowledge databases were searched from January 1, 2012, to December 31, 2021, to retrieve articles published in the selected 86 journals by researchers from Japan, South Korea, and China. The publication quantity, global share, publication types, IF, and citation patterns of these papers were then analyzed and visualized. Statistical analyses were performed using SPSS 20.0 software.

Research results

Between 2012 and 2021, a total of 27164 orthopedic studies were published by Japan, South Korea, and China, showing a steady increase over the years. Among them, 44.32% were from China, 32.98% were from Japan, and 22.70% were from South Korea. Over time, the global share of articles significantly increased in South Korea (from 3.37% to 6.53%, $P < 0.001$)

and China (from 5.29% to 9.61%, P < 0.001), while it decreased significantly in Japan (from 5.22% to 3.80%, P < 0.001). The annual total IFs of articles from China were well above those of articles from Japan and South Korea (36597.69 *vs* 27244.48 *vs* 20657.83, P < 0.05). There was no significant difference in the number of top 10 high-IF orthopedics journals published among these three countries [South Korea (800) > China (787) > Japan (646), P > 0.05].

Research conclusions

China's orthopedic publications have seen consistent growth in the past decade, but when considering their population scales, Japan and South Korea still outpace China with respect to quality.

Research perspectives

The authors aim for this article to contribute toward the assessment and enhancement of academic productivity in orthopedic research in East Asia. In the future, it is imperative to foster stronger international cooperation and increase financial support for orthopedic research to produce a high level of evidence research and foster the sustained development of orthopedic research.

FOOTNOTES

Author contributions: Jiang H conceived and designed the study; Chen WY was involved in data retrieval and data selection, analyzed the data, and wrote the manuscript; Xiao X was involved in statistical analysis and manuscript revision; Pan C, Xu HY, and Huang FH were involved in data search; Jiang H and Wei QJ were involved in the selection of data and contributed analysis tools; All authors read and approved the final manuscript.

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CASE REPORT

Metallosis with spinal implant loosening after spinal instrumentation: A case report

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Abstract

BACKGROUND

Spinal metallosis is a rare complication following spinal instrumentation whereby an inflammatory response to the metal implants results in the development of granulomatous tissue.

CASE SUMMARY

We describe the case of a 78-year-old woman who had recurrence of back pain 5 years after lumbar spine posterior decompression and instrumented fusion. Lumbar spine radiographs showed hardware loosening and magnetic resonance imaging showed adjacent segment disease. Revision surgery revealed evidence of metallosis intraoperatively.

CONCLUSION

Spinal metallosis can present several years after instrumentation. Radiography and computed tomography may demonstrate hardware loosening secondary to metallosis. Blood metal concentrations associated with spinal metallosis have yet to be established. Hence, metallosis is still an intraoperative and histopathological diagnosis. The presence of metallosis after spinal instrumentation likely indicates a more complex underlying problem: Pseudarthrosis, failure to address sagittal balance, infection, and cross-threading of set screws. Hence, identifying metallosis is important, but initiating treatment promptly for symptomatic implant loosening is of greater paramount.

Key Words: Metallosis; Spine; Instrumentation; Implant loosening; Corrosion; Case report

Core Tip: This paper describes a rare case of metallosis after spinal instrumentation and discusses the methods of diagnosing and risk factors contributing to spinal metallosis. A review of the current literature as presented in this paper demonstrates the scarcity of studies on spinal metallosis after spinal instrumentation, despite the fact that a diagnosis of spinal metallosis should be promptly identified and treated by revision surgery. It is also important to understand that the presence of metallosis after spinal instrumentation likely indicates a more complex underlying problem, such as instability of the spinal implants.

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INTRODUCTION

Metallosis is postulated to occur due to the corrosion of metal implants leading to metal debris build-up in periprosthetic soft tissue and bone. This precipitates a granulation-type reaction involving phagocytosis of metal particles resulting in osteolysis and local reactions, namely, aseptic fibrosis, local tissue necrosis, and implant loosening, as well as systemic toxicity such as cardiomyopathy and abnormal thyroid function[1]. Posterior spinal fusion involves the placement of metallic rods and screws and these fixtures are not routinely removed except for reasons such as localised pain over implant site, prominent hardware, implant failure, or infection[2]. Metallosis is not uncommon following joint arthroplasties but only a few cases of spinal metallosis have been described in the literature. Hence, we report a case of spinal metallosis with implant loosening after posterior spinal instrumentation.

CASE PRESENTATION

Chief complaints

A 78-year-old woman was admitted in 2019 to the Department of Orthopaedic Surgery in Changi General Hospital, a tertiary hospital in Singapore, for a 4-mo duration of worsening lower back pain with claudication and right lower limb radiculopathy, with onset 5 years after a spinal surgery.

History of present illness

The patient's past medical history was significant for well-controlled hypertension and type 2 diabetes mellitus, gout, gastroesophageal reflux disease, and obesity [body mass index (BMI) of 31.2].

She also had a significant past surgical history of L3 to S1 posterior decompressive laminectomy, stabilisation with pedicle screws, and posterolateral fusion with local bone grafting performed at the same hospital 5 years ago. The surgery was performed for a diagnosis of lumbar spondylosis with central canal stenosis, for which she presented with chronic lower back pain radiating down her bilateral lower limbs. Titanium polyaxial screws (DePuy Synthes) were used in that surgery. The patient's symptoms were relieved after the surgery and she recovered. Postoperative lumbar spine radiographs showed the proper positioning of the spinal implants (Figure 1).

History of past illness

The patient was followed up in the orthopaedic surgery specialist outpatient clinic regularly after her spine surgery. Five years after the surgery, she started to develop progressively worsening lower back pain which radiated to her right lateral thigh and calves. Four months later, her symptoms had slowly deteriorated to the point where she required a motorized wheelchair as she was unable to ambulate long distances due to pain.

Personal and family history

The patient had no relevant personal and family history.

Physical examination

The most significant finding on examination was reduced power in the right L2 and L3 myotomes [grade 4 out of 5 on the Medical Research Council (MRC) scale for muscle strength]. The rest of the myotomes from L2 to S1 were normal, with a grade 5 out of 5 power on the MRC scale. She also had a large body habitus. Her gait was slow but steady over a short distance. The rest of the physical examination was unremarkable: There was no spinal tenderness or significant muscle wasting of her back or lower limbs. The range of movement of her cervical and thoracolumbar spine was normal. Sensation was intact over all dermatomes. Bilateral knee and ankle reflexes were normal. The straight leg raise test was negative as well.

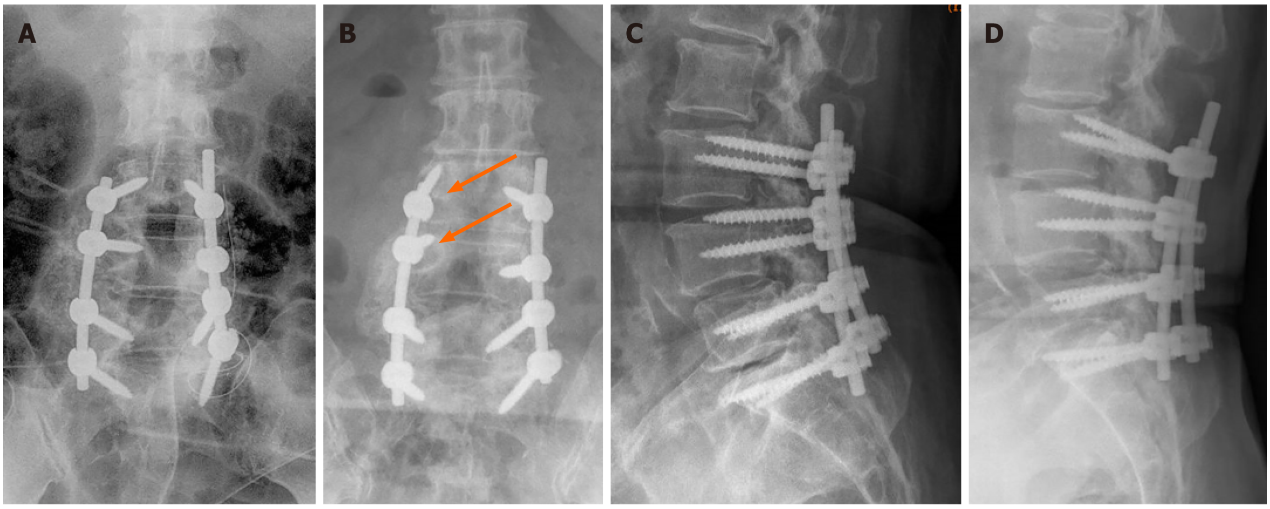

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Figure 1 Postoperative lumbar spine radiographs showing the proper positioning of the spinal implants. A: Lumbar spine antero-posterior radiograph after initial surgery for posterior decompression and instrumented fusion; B: Lumbar spine antero-posterior radiograph at 5 years after initial surgery, showing stable periprosthetic radiolucencies (indicated by arrows) surrounding the right L3 and L4 screws suggestive of instrumentation loosening; C: Lumbar spine lateral radiograph after initial surgery; D: Lumbar spine lateral radiograph at 5 years after initial surgery.

Laboratory examinations

Laboratory blood tests showed normal values, including a white blood cell count of 8.2 × 10^9/L and C-reactive protein level of 4.1 mg/L. Other biochemical parameters were within the normal range. Serum metal concentrations were not performed for the patient due to cost issues.

Imaging examinations

Lumbar spine radiographs and magnetic resonance imaging (MRI) were performed prior to the revision surgery. Lumbar spine anteroposterior and lateral radiographs revealed stable periprosthetic radiolucency surrounding the right upper two screws (L3 and L4 pedicle screws) that suggested loosening of the instrumentation (Figure 1). There was no evidence of fracture of the pedicle screws and rod instrumentation. Narrowing of the L4-L5 and L5-S1 intervertebral disc spaces was noted but vertebral body heights were largely maintained. Spondylotic changes and facet arthropathy were seen. There was no instability noted in the flexion and extension views.

Lumbar spine MRI revealed severe spinal canal stenosis at the L2-L3 level with compression of the cauda equina nerve roots, severe bilateral lateral recess, and neural foraminal stenosis (Figure 2). There was moderate spinal canal stenosis with crowding of the cauda equina nerve roots at L1-L2. Mild peri-screw bony edema was observed around the left L4 screw (Figure 3), otherwise there was no significant evidence of peri-screw edema and screw loosening around the rest of the L3 to S1 screws.

FINAL DIAGNOSIS

Histopathology of the stained tissues that were excised revealed fibroadipose tissue and occasional striated muscle bundles exhibiting degenerative changes. There were aggregates of non-refractile, non-polarisable black granular foreign material mostly in a perivascular location, that were consistent with metallosis. There was no evidence of malignancy. Intra-operative tissue cultures were negative for bacterial growth.

TREATMENT

L2 to S1 posterior decompression and instrumented fusion with O-Arm computer-guided navigation (Medtronic, StealthStation® S7®) were performed. Posterior elements were exposed from L2 to S1, revealing loosened L3 to L5 screws bilaterally, at both the set screw-rod interface and the bone-implant interface. The tissues surrounding the bilateral L3 to L5 polyaxial screw heads and tulips were observed to be stained dark grey (Figure 4). All previous DePuy Synthes screws were removed uneventfully. The loosened screws showed evidence of fretting at the contact surfaces. Newtitanium pedicle screws (Medtronic, CD Horizon® Solera®) were inserted with new trajectories under O-Arm computer-guided navigation. L2 and L3 Laminectomy was carried out. The thecal sac was well decompressed at L2-L3 where there was severe stenosis. A drain was inserted, and the surgical site was closed in layers.

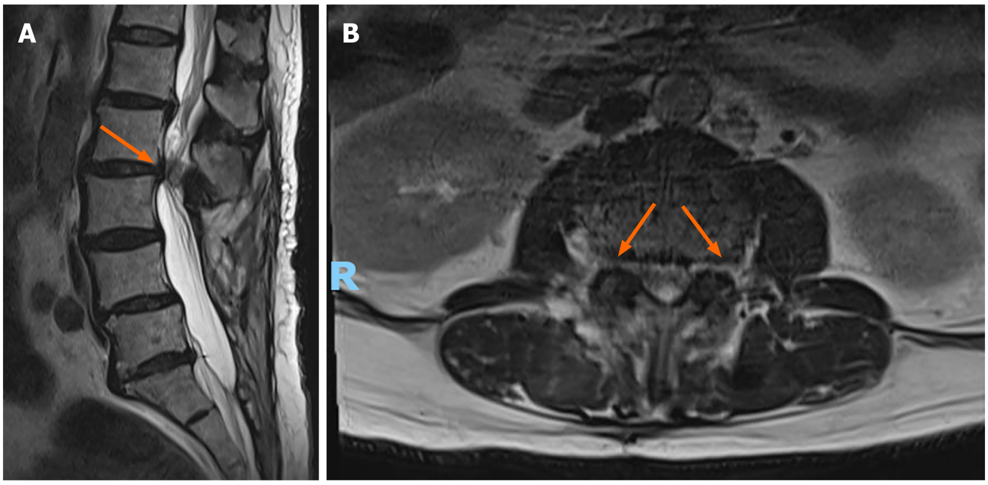

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Figure 2 Lumbar spine magnetic resonance imaging (T2 weighted) 5 years after initial surgery. A: Sagittal view. The arrow indicates herniated disc at L2-L3 level with severe spinal canal stenosis and compression of the cauda equina nerve roots; B: Coronal view demonstrating severe spinal cord compression at L2-L3 level. Arrows indicate protruded disc with bilateral lateral recess and neural foramina stenosis.

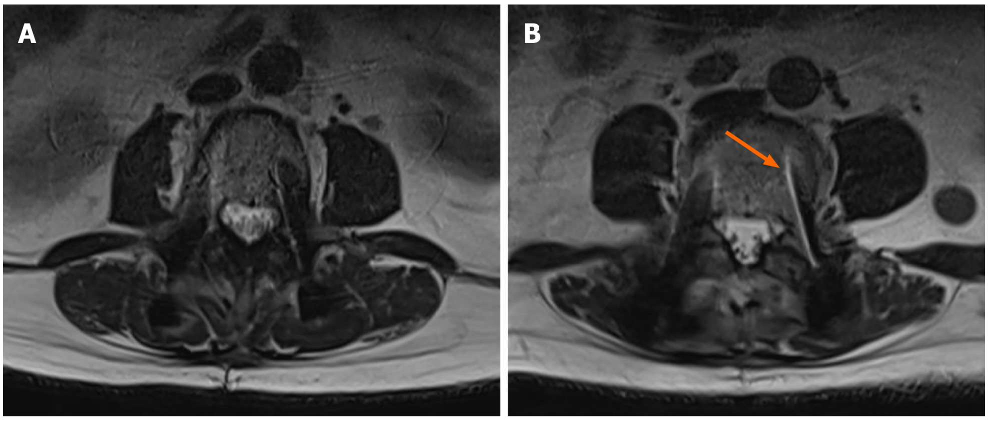

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Figure 3 Lumbar spine magnetic resonance imaging (T2 weighted) 5 years after initial surgery. A: Coronal view showing L3 level with no significant peri-screw bony edema; B: Coronal view showing L4 level with the arrow indicating mild left L4 peri-screw bony edema.

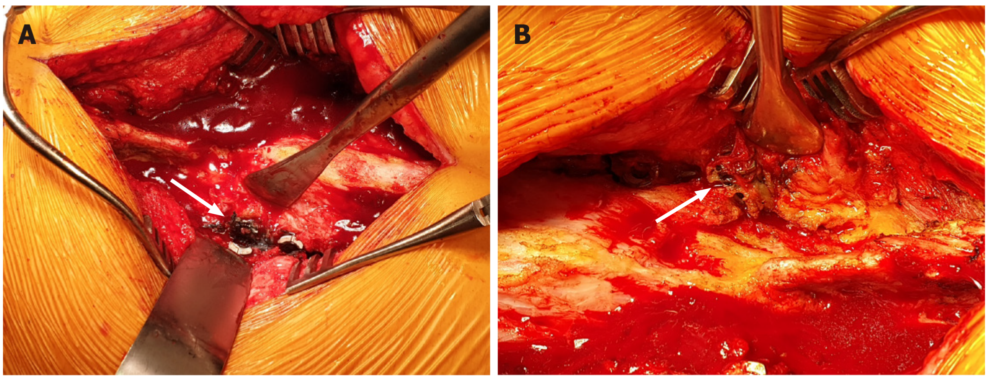

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Figure 4 Intraoperative photographs during revision surgery showing metallic grey-stained tissue surrounding bilateral L3 to L5 polyaxial screw heads. The most prominent staining occurred at A: Left L4 screw (indicated by the arrow); B: Right L4 screw (indicated by the arrow).

OUTCOME AND FOLLOW-UP

The patient's postoperative recovery was uneventful. At the 2-mo follow up, her back pain and lower limb weakness had almost completely resolved. Her postoperative lumbar spine radiographs showed that the new implants were intact (Figure 5).

DISCUSSION

Literature review

Metallosis was first identified as a complication of metal-on-metal total hip arthroplasty[1]. The incidence of metallosis following total hip arthroplasty has been described to be 5.3% and 0.3% after lumbar arthroplasty[3], but the incidence following spinal instrumentation such as posterior spinal fusion is not well estimated currently due to the scarce literature. A literature search detailing other cases of metallosis after spinal instrumentation revealed that it is a rare occurrence. A detailed look of the reported cases of metallosis after spinal instrumentation is summarised in Table 1.

The earliest cases of metallosis following spinal instrumentation were reported by Takahashi *et al*[4]. The authors described two cases of delayed neurological deficits secondary to intraspinal metalloma adjacent to loosened infralaminar hooks. One of the patients had undergone posterior correction and stabilisation and the other had undergone posterior correction and arthrodesis for degenerative scoliosis. Radicular symptoms resolved entirely after revision surgery. The authors speculated that metallosis was caused by abnormal implant movements and chemical reactions from the metal particles. Tezer *et al*[5] then described a case whereby paraparesis secondary to intraspinal metallosis adjacent to the pedicular hook occurred 3 years after posterior spinal instrumentation and fusion for a vertebral compression fracture. The patient's neurological symptoms resolved completely following the excision of the metalloma and removal of the affected instrumentation. The authors concurred with the pathophysiology of metallosis described by Takahashi *et al*[4], and recommended using transpedicular screws sufficiently while carrying out further research to improve the corrosive resistance of spinal instrumentation. Goldenberg *et al*[6] also reported a case of spinal metalloma 18 mo after lumbar laminectomy, posterior spinal instrumentation, and fusion using titanium instead of stainless-steel alloy components. The authors concluded that the metallosis in their case occurred due to the interaction between titanium and the surrounding tissue structures rather than as a result of implant failure, corrosion, or infection as described in previous cases. Li *et al*[7] described another case of metalloma attributed to the wear and loosening of implant. A 2-cm large metalloma could be visualised on MRI. Prior to this study, MRI had not demonstrated much utility in the investigation of metallosis. Subsequently, Ayers *et al*[8] described three more cases of spinal metallosis, two of which had undergone multiple previous spine surgeries complicated by pseudarthrosis and infection and the last had undergone single-level lumbar stabilisation. Neurological symptoms improved in all three cases following revision surgery. The authors hypothesised that biologic mechanisms such as bacterial growth could influence fretting and corrosion of spinal instrumentation leading to metallosis. Richman *et al*[9] then described a young patient with acute onset pain and neurological deficits that progressed quickly. Previous instrument made of stainless steel was removed. They also noted high serum chromium levels. Most recently, Mazur-Hart *et al*[10] reported a case of unilateral metalloma from mixed-metal (titanium and cobalt chrome) instrumentation that resulted in progressive neurological deficit, but not hardware failure. Another unusual finding was the absence of metallosis on the side where the patient had also undergone a hip arthroplasty comprising of the same materials.

Clinical presentation and diagnosis of spinal metallosis

Metallosis is often diagnosed incidentally through intraoperative findings of grey-stained local tissue[8], and definitively through histopathological evidence of macrophages containing metal debris[11]. This is because of the non-specificity of clinical presentations, such as pain, symptoms of infection, and neurological deficits[9]. Based on case studies in the literature (summarised in Table 1), patients with spinal metallosis most commonly presented with lower back or radicular pain. Other symptoms included neurogenic claudication and progressive paraparesis of the lower limbs. It is also challenging to visualise metallosis through standard radiographic evaluation[8]. MRI and computed tomography (CT) are not able to definitively diagnose spinal metallosis due to the presence of artifacts around the metal implants[4,5]. Ayer *et al*'s study showed that all three cases did not have evidence of metallosis on CT prior to surgery[8]. This differs from the usefulness of CT in the diagnosis of metallosis in total hip arthroplasties, in which metallic debris or a high-density material outlining the joint capsule or bursa can be visualised[12]. On the other hand, CT myelography has been the diagnostic imaging modality of choice in a number of studies on spinal metallosis, showing stenotic lesions adjacent to previous instrumentation[4,5,6,9]. In our case, lumbar spine radiographs showed evidence of loosening of pedicle screws. Screw loosening can be secondary to a variety of factors including metal wear debris, microfracture, infection, tumour, and metabolic diseases, with a greater incidence in patients with osteoporosis[13]. Our patient had type 2 diabetes mellitus but was not known to have osteoporosis. She did not have constitutional symptoms and her preoperative routine blood tests were unremarkable. Therefore, osteolysis secondary to fretting of instrumentation was a more probable mechanism for the loosening of screws in this case. MRI was not useful in identifying hardware loosening or spinal metallosis in our case. In a recent clinical trial by Spirig *et al*[14], CT was more sensitive and specific in detecting screw loosening despite applying metal artifact reduction techniques with MRI. However, MRI may be of utility in cases where the metalloma is large enough with compression or extension into surrounding structures, such as in the cases reported by Li *et al*[7] and Mazur-Hart *et al*[10]. Comparing plain radiographs and CT findings of previous studies (Table 1), we suggest adopting a high index of suspicion of metallosis when screw loosening is evident on radiographical imaging in a patient with persistent postoperative back pain or radiculopathy but otherwise medically well. If plain radiographs do not show hardware abnormalities, it may be prudent to proceed with a CT scan or myelogram instead.

Table 1 Summary of the literature

Ref.	Patient biodata	Type of surgery undergone	Instrumentation	Symptoms leading to revision surgery	Radiological findings	Revision surgery	Intraoperative findings	Histopathological findings	Patient outcome
Takahashi *et al*[4], 2001 (case series)	1 Female, aged 58	Posterior correction and stabilisation T10-L3 (no decompression) for degenerative thoracolumbar scoliosis	Stainless steel Cotrel-Dubousset	Left L4-L5 radicular pain several months post-op	Plain radiographs: No implant dislodgement or spinal instability; myelography: Shadow defect adjacent to the tip of the L3 infralaminar hook and dura mater was compressed from the posterior	11 mo post-op; removal of L3 pedicular screws and left L3 infralaminar hook, L3 laminectomy, excision of metallotic mass, instru-mentation elongated to L4 with connecting pieces, posterolateral fusion	L3 hook loose from rod, macroscopic metallosis (8 mm mass of dark grey granulation tissue) at hook-rod junction extending to surrounding fibrous tissues, L2-L3 pseudarthrosis	Not described	Immediate resolution of radicular pain, but continued to have slight low back pain during active trunk motion
	2 Female, aged 54	Posterior correction and arthrodesis T12-L4 for symptomatic degenerative lumbar scoliosis	Stainless steel Cotrel-Dubousset	Right L5 sciatic pain 4 yr post-op	Plain radiographs: No implant dislodgement or spinal instability; myelography: Stenotic lesion at lowest level of instrumented lumbar spine but undisplaced implants; myelotomo-graphy: No migration of the hooks in the spinal canal, stenotic lesion adjacent to tip of L4 supralaminar hook	5 yr post-op; L4 and L5 laminectomy, excision of metallotic mass, instru-mentation elongated down to sacrum	1 cm × 1 cm × 2 cm dark grey granulation tissue under L4 lamina continuous with fibrous membrane of the same colour surrounding right L4 supralaminar hook and compressing right L5 root, loosening implant connection and wear of rod at hook-rod junction, no pseudarthrosis	Granulation tissue consisting of metallic debris – iron staining showed widespread intracellular iron, spectrometry analysis of metal concentrations showed presence of iron, nickel and chromium	Radicular symptoms resolved
Tezer *et al* [5], 2005 (Case report)	Male, aged 57	Posterior spinal instrumentation for T8-9 compression fracture	Stainless steel pedicle screw-hook combination system	Progressive paraparesis 3 yr post-op	Myelography and myelo-CT: Focal image of a mass at T6-7 antero- laterally displacing the dural sac and spinal cord; CT and MRI could not be done due to diffuse metal artefacts	Posterior surgical procedure, complete removal of implants, excision of mass, all metallic debris cleaned	Corroded, black-coloured pedicle hook, no loosening or colour change of other implanted parts, construct stable and strong, fusion complete, granuloma formation in centre of metallic construct, metallic debris had pushed dural sac and spinal cord to anterior and contralateral side resulting in defect of 1.5 cm in diameter in lamina and pedicle	Hematoxylineosin stained sections of paraffin-embedded material showed dense fibrotic tissue heavily stained with black metal debris, foreign body giant cells seen around metallic debris, iron staining by Perls method showed widespread iron within macrophages	Symptom-free 3 mo post-op
Goldenberg *et al*[6], 2016 (Systematic review)	Male, aged 75	Single-level lumbar laminectomy, posterior instru-mentation and fusion	Bilateral L4 and L5 titanium alloy pedicle screws, dual intercon-necting vertical rods, single interconnecting horizontal rod using the	Persistent and progressive severe lower back pain since the surgery, associated with severe left-sided sciatica	CT myelography: Posterior epidural mass causing canal stenosis, no features suggestive of corrosion or loosening of metalwork; SPECT:	Explorative lumbar canal decompression and nerve root neurolysis, dissected down to area of previous surgery, removal of scar tissue and rostral part of L5	Scar tissue in area of previous surgery, intermixed dark brown and pale pink roughened firm tissue compressing thecal sac,	Dense fibrohistiocytic reaction and cystic change associated with granulomas and calcification, multinuc-leated giant cells both encasing and adjacent to	Satisfactory clinical improvement in back pain and sciatica

			DENALI K2M system, interbody device containing bone graft admixed with bone morphogenetic protein, high speed burr used but no contact between metalwork and drill		Increased uptake in keeping with discovertebral disease; MRI not done as incompatible cardiac pacemaker	lamina and spinous process, debulking of mass	no implant loosening or corrosion	foreign black pigmented particles, presence of degenerate bone, cartilaginous material and skeletal muscle, no micro-organisms identified	
Li *et al*[7], 2016 (Case report)	Male, aged 58	Posterior decompression and instrumented fusion	Titanium implant (surgery was done at another institution)	Recurrent lower back pain radiating to left lower limb, dysesthesia, neurogenic claudication	MRI: Severe adjacent stenosis at L3-4, intraspinal extradural tumor-like mass with compression of the neurological elements	Spinal decompression, excision of mass, and extension of instrumented fusion	Metallic soft tissue and a well-capsulated tumor-like mass	Hematoxylin and eosin staining of mass showed many spindle-shaped; fibroblasts. Many macrophages containing dark metallic wear particulates with phagocytosis	Follow-up not reported
Ayers *et al* [8], 2017 (Case series)	Male, aged 74	Multiple previous spinal surgeries including limited lumbar fusion complicated by pseudarthrosis, revision with extension of fusions and infection at subsequent operations	Mix of alloy rods (CoCrMoC, ASTM F-1537 specification) and titanium alloy (Ti6Al4V ASTM F-136 specification) screws	Continued mechanical back and radicular pain	CT: Hardware failure with bilateral fractured L5 screws and sagittal plane deformity	Staged revision surgery; (1) Initial surgery - removal and cleaning of T10-S1 hardware, evacuation of fluid collection, wound debridement, intra-op cultures, and exploration of the fusion, subfascial drains inserted; (2) then 2 further irrigation and debridement procedures until cultures negative and tissues appeared viable; and (3) after 6 wk, final stage – evacuation of smaller fluid collection, revision posterior instrumentation with L3 pedicle subtraction osteotomy	(1) Initial surgery: Large fluid pocket containing approximately 500 mL of grey-black fluid, black discolouration of posterior soft tissues, all rods showed significant evidence of fretting, galling, pitting and crevice corrosion; and (2) final stage: Smaller fluid collection of 300 mL in posterior soft tissues, gram stain negative	Excised tissue consisted of necrotic fibrous tissue with areas of viable fibrous tissue and particle laden histiocytes. Soft tissue, pseudomembrane from L3-S1 consisted of fibrous tissue with refractile material and calcification. Cell culture of infected tissue/fluid showed presence of propionibacterium acnes and staphylococcus aureus	Significant reduction in pain and symptoms 1 yr post-op
	Male, aged 47	Multiple previous lumbar spine procedures complicated by pseudarthrosis and infection	Titanium alloy (Ti6Al4V) components	Recurrent pulmonary infections and continued back and radicular leg symptoms	CT: Likely pseudarthrosis at multiple lumbar spine levels	2 yr post-op; Staged surgery; (1) Initial surgery – wound exploration, removal of hardware, formal irrigation-and-debridement, deep drains placed; (2) another irrigation-and-debridement with post-op antibiotics × 6 wk; (3) after 6 wk, instrumented fusion from T10-Ilium with revision TLIF at L2-3 and Smith-Petersen Osteotomy; (4) irrigation-and-debridement; and (5) removal of right S1 screw as	(1) Initial surgery: Significant fluid collection, soft tissues stained black, all rods showed significant evidence of fretting, galling, pitting and crevice corrosion	(1) Initial surgery: Excised tissue comprised of necrotic adipose and fibrotic connective tissue; and (2) instrumented fusion stage: Cultures grew Mycobacterium phlei	No back or leg pain at follow up (recent to when paper was written)

						it was causing right nerve root irritation			
	Female, aged 61	Single level lumbar stabilisation procedure including instru-mentation with pedicle screws and PEEK rod	Titanium alloy (Ti6Al4V) components	Significant sagittal plane deformity and significant back/radicular leg symptoms	CT: Significant sagittal plane deformity	Instrumentation from T4-pelvis with hardware removal and pedicle subtraction osteotomy, including removal of L2-3 disc to allow greater correction	Significant black staining of the posterior soft tissues, all rods showed significant evidence of fretting, galling, pitting and crevice corrosion	Tissues not submitted to pathology	Complete symptomatic relief at 6 mo post-op
Richman *et al*[9], 2017 (Case report)	Male, aged 19	Posterior spinal fusion	Stainless steel implants	Low back pain, urinary hesitancy, and parasthesias on bilateral anterior thighs, that quickly progressed to flaccid paraparesis, hypoes-thesis, and urinary retention	CT: Cavitation around right L1 pedicle screw CT myelogram: Irregular and inadequate opacification of the thecal sac at L1	(1) Initial surgery: Removal of screw; and (2) posterior laminectomy and decompression from T12 to L2 with removal of all instrumentation	(1) Initial surgery: Black and yellowish corrosive film and tissue around right L1 screw; and (2) subsequent surgery: Gritty yellow-black material tracking through the L1 foramen around left L1 pedicle screw, causing thecal saccompression at T12-L2	Pathologic diagnosis was consistent with metallosis	Pain and urinary retention resolved, complete motor and sensory recovery, but presence of bilateral clonus 3 yr post-discharge
Mazur-Hart *et al*[10], 2022 (Case report)	Male, aged 79	2 previous lumbar decompression, posterior instru-mentation and fusion 2 yr apart. Right hip arthro-plasty 1 yr later	First surgery: Cobalt chrome rods and titanium screws. Second surgery: PEEK spacer and titanium screws and plates	Worsening falls, ataxia and pseudo-claudication	CT and MRI: T1 and T2 hypointense non–enhancing mass around right-sided paraspinal rod extending into spinal canal and surrounding bones and muscle on the same side	L4-S1 biopsy and subtotal resection of paraspinal mass with removal of hardware at L2-S1	Dense fibrotic tissue, black granular material on screws and rods, black staining of adjacent soft tissues and lumbar bone	Extensive necrosis with surrounding inflammation and fibrosis with focal deposition of black pigment of exogenous origin (metallic *vs* carbonaceous), lymphohistiocytic reaction with giant cell formation in rare areas. Gram stain and culture negative	Weaned off walker, reduced dysesthesia but leg weakness still present 3 mo post-op. Leg strength and ambulation continued to improve 7 mo post-op

CT: Computed tomography; MRI: Magnetic resonance imaging; PEEK: Polyetheretherketone.

In regards to the relationship between serum metal concentrations and the development of metallosis, Richman *et al*[9] noted that in asymptomatic patients, serum chromium levels of more than 0.6 ng/mL and more than 3.75 μg/L were indications of implant malfunction and corrosion, respectively. Fernández Bances *et al*[15] found a significant rise (P = 0.00049) in serum titanium concentrations from the levels prior to posterior spinal fusion using titanium instrumentation, similarly to previous studies; however, the correlation of serum titanium concentrations and metallosis was not explored in their study. Cundy *et al*[16] found that serum titanium and niobium levels in children 2 years after instrumented spinal fusion were significantly increased but their clinical significance was not explored. Ayers *et al*[8] reported that muscle concentrations of various metals, namely, aluminium, cobalt, vanadium, and molybdenum, were higher than normal levels in their cases with spinal metallosis due to observed wear and corrosion of the metal instrumentation. However, none of the patients had elevated concentrations of metal in blood. So far, serum metal levels indicating metallosis have yet to be well-defined. We did not check serum metal concentrations in our patient as she did not have symptoms of metal poisoning, there was no baseline data prior to her previous spinal surgery, and investigating metal concentrations

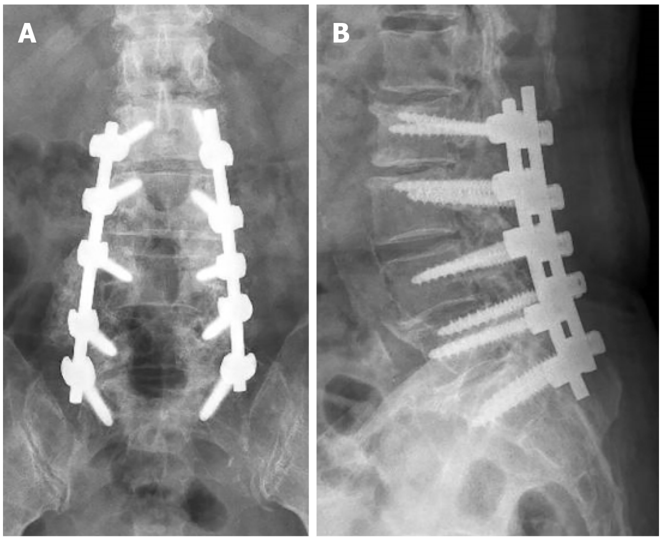

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Figure 5 Lumbar spine antero-posterior and lateral radiographs showing proper positioning of the implants after revision L2-S1 surgery.

this time would be costly and purely academic. However, in patients exhibiting symptoms of metal poisoning, serum metal concentrations will be helpful in confirming a diagnosis of metallosis, potentially leading to timely intervention.

Effect of implant material and factors contributing to metallosis

The mechanism for the development of metallosis following spinal instrumentation is yet to be well-ascertained. It has been postulated that the rigidity that results from instrumentation leads to accelerated degeneration at adjacent spinal levels[7]. The metallic debris from the degeneration of the spinal implants in turn results in a chronic inflammatory process involving a foreign-body granulation-type reaction[1,7]. Spinal metallosis has been described in studies that involved titanium or stainless steel implants[3]. Spinal instrumentation of different metals is commonly used in combination as each metal has a particular mechanical and physical property; for example, cobalt chromium rods have been described to provide stronger correctional forces for scoliotic curves as compared to rods made of other materials [17]. Titanium may be more resistant to crevice corrosion than stainless steel but it has less mechanical resistance and may even stimulate osteolysis[4]. Singh *et al*[18] demonstrated that posterior spinal fusion constructs made of stainless steel were more prone to fretting corrosion as compared to those made with a combination of cobalt chrome with titanium alloy or pure titanium with titanium alloy in a simulated *in vitro* experiment using normal saline. However, the study was unable to account for the actual inflammatory environments present in the human body. Panagiotopoulou *et al*'s study on retrieved spinal implants demonstrated that the risk of corrosion was not increased when two dissimilar metals, namely, cobalt chromium alloy rods and titanium screws, were used in combination[17]. The authors suggested that metallosis may be more dependent on patient factors rather than the corrosiveness of the metals. However, the main limitation of that study was its small sample size, whereby a combination of metals was employed only in two out of seven patients [17].

Vieweg *et al*[19] in an early study on the corrosion of the internal spinal fixator system described that corrosion occurred due to not only the metallurgical composition but the specific construction of the instrument as well. Cundy *et al* [16] described that crevice corrosion was more likely to occur at rod junctions with increased metal-on-metal sites, contributed by micromovements prior to spinal fusion. Takahashi *et al*[4] noted that the lower end of an instrumented fusion was subjected to greater stress hence predisposing the release of metal debris from the hook-rod junction during flexion-extension movement of the lumbar spine. Comparatively, Tezer *et al*[5] felt that metallosis occurred at the middle levels of the spinal construct in their case because of the unequal distribution of chemical properties and degeneration of micromovements in the long term. Interestingly, metallosis occurred at the upper levels of the spinal construct in our patient, where the burden of flexion-extension is not particularly high in day-to-day activities.

Patient factors such as a high BMI as evident in our patient could have accelerated the wear of the titanium screws. As described in the literature review, previous studies have postulated that metallosis results from abnormal micromovements of hardware and a continuous inflammatory reaction[4-6]. Obesity has been associated with the development of spinal disease through both a chronic low-grade inflammatory response as well as biomechanical alterations in the lumbar spine that lead to increased shear forces and torque on the discs and joints[20], hence potentially predisposing to metallosis. However, it is currently difficult to demonstrate an association between patient demographics and spinal metallosis due to the limited number of case reports and case series in the literature so far.

Metallosis is also likely to be a by-product of unstable spinal instrumentation. The increased cyclical loading as a result of implant loosening causes increased fretting at the contact surfaces. This not only produces the characteristic metal debris in metallosis, but ultimately can lead to implant failure. Pseudarthrosis after lumbar spine fusion is a common cause of spinal implant loosening requiring revision surgery[21]. Chronic low-grade spinal surgical site infection is another potential cause for instrumentation loosening, hence stressing the importance of sterile instrumentation[22,23].

Several procedure-related risk factors for implant loosening have also been described. First, inadequate correction of sagittal imbalance has been associated with a negative prognosis for implant anchorage in bone[24], increasing the risks of screw loosening in posterior spine fusion[25]. Inadequate set screw tightening or cross-threading of screw tulips due to improper insertion of set screws into the screw tulip can also predispose to coupling failure, which can occur at any level of a spinal construct[26]. Hence, spinal surgery should be performed only by well-trained spinal surgeons with vast experience and undertaking these operations regularly to minimise these mechanical risk factors. Other possible risk factors for instrumentation loosening are osteoporosis and cobalt chromium rods[23]. Our patient was not known to have osteoporosis, but it may be prudent to commence osteoporosis treatment prior to surgery in patients who have been diagnosed with osteoporosis so as to improve bone density and potentially increase the strength of screw fixation. Utilising a material that is less rigid than cobalt chromium rods may reduce the risk of implant loosening; however, current options are limited, and cases of metallosis including our patient have mainly involved titanium or stainless steel instrumentation. Our patient's symptoms of progressive lower back and radicular pain were due to severe spinal stenosis and compression of the cauda equina nerve roots. Although implant loosening may present similarly even in the absence of metallosis, there was both intraoperative (corrosion of screws and grey-stained surrounding tissues) as well as histopathological (metallic debris in macrophages) evidence of metallosis at the same spinal levels. Ultimately, it is important to recognise symptoms of spinal implant instability and initiate treatment for patients timely.

CONCLUSION

Identifying metallosis prior to surgical exploration is challenging. Clinical presentation tends to be non-specific, most commonly being lower back or radicular pain. CT appears to be the modality of choice to observe for aseptic hardware loosening and pseudarthrosis, while myelography and MRI are able to suggest the presence of a metalloma. A definitive diagnosis of metallosis can only be made from histopathological results, where metallic debris is seen in macrophages.

To date, the relationship between serum metal levels and the presence of metallosis has yet to be established. Currently, implants of various metallic compositions are used, but the individual metallic properties confer theoretical benefits and disadvantages and no particular material has been identified to be least likely to cause metallosis thus far. Furthermore, patient factors may contribute to metallosis but further studies are required to establish an association.

Finally, we would like to highlight that the presence of metallosis after spinal instrumentation likely indicates a more complex underlying problem. Metallosis can occur due to instability of the spinal implants, which may be secondary to pseudarthrosis, failure to address sagittal balance, infection, and cross-threading of set screws. Spinal implant instability manifests commonly as pain and weakness, which were present in most cases involving instrumentation loosening described within this report to varying degrees. However, regardless of the cause for metallosis, the only definitive treatment to date for symptomatic implant loosening is the removal and replacement of the implants. The rate at which metallosis progress and the onset of symptoms is not known. However, it undoubtedly can lead to significant pain and mobility issues. Hence, it is prudent to identify the underlying cause of implant loosening early and commence treatment promptly.

FOOTNOTES

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