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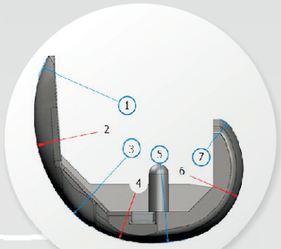

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Sodium hyaluronate is a physiological substance that is widely distributed in the extracellular matrix of connective tissues in both animals and man. For example, it is present in the vitreous and aqueous humor of the eye, the synovial fluid, the skin, and the umbilical cord. Sodium hyaluronate derived from various human or animal tissues does not differ chemically.

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· The safety and effectiveness of the use of HA-KEM concomitantly with other intra-articular injectables have not been established.
· Strict aseptic administration technique must be followed.
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ISKSAA (**I**nternational **S**ociety for **K**nowledge for **S**urgeons on **A**rthroscopy and **A**rthroplasty) is a society of orthopaedic surgeons from around the world to share and disseminate knowledge, support research and improve patient care in Arthroscopy and Arthroplasty. We are proud to announce that ISKSAA membership has crossed the **1000** mark (India & Overseas) making it the fastest growing Orthopaedic Association in the country in just the 3rd year of its inception. With over **140000 hits from over 118 countries** on the website **www.isksaa.com** & more and more interested people joining as members of ISKSAA, we do hope that ISKSAA will stand out as a major body to provide opportunities to our younger colleagues in training, education and fellowships.

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Journal of Arthroscopy and Joint Surgery (JAJS) is committed to bring forth scientific manuscripts in the form of original research articles, current concept reviews, meta-analyses, case reports and letters to the editor. The focus of the Journal is to present wide-ranging, multi-disciplinary perspectives on the problems of the joints that are amenable with Arthroscopy and Arthroplasty. Though Arthroscopy and Arthroplasty entail surgical procedures, the Journal shall not restrict itself to these purely surgical procedures and will also encompass pharmacological, rehabilitative and physical measures that can prevent or postpone the execution of a surgical procedure. The Journal will also publish scientific research related to tissues other than joints that would ultimately have an effect on the joint function.

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Editorial

Role of platelet rich plasma in early osteoarthritis of knee

Osteoarthritis of the knee is one of the commonest degenerative diseases encountered in clinical practice and a solution to provide relief from pain is a challenge faced by pain specialists and orthopaedicians worldwide. Attempts to slow disease progression have used modalities ranging from intra-articular steroids, oral chondroprotectives to viscosupplementations, each with variable outcomes. The 21st century has seen a significant usage of Intra-articular Platelet rich plasma (PRP) injections and the data so far has been promising.

Platelet rich plasma is a process of natural (biological) healing which relies upon the pool of growth factors contained within the alpha granules. Growth factors within alpha granules of platelets are capable of improving the physiology of Osteoarthritic joints by their chondro-protective properties. PDGF and TGF-1 act by upregulating the production of endogenous hyaluronic acid. PDGF also regulates levels of TIMPs which are a critical part of catabolic pathway. There are recent reports that show that PRP use in patients of early osteoarthritis may improve the cartilage structure and helps in slowing down the progression of disease.[1,2]

PRP use in orthopaedics was first explored in tendinopathies; soon investigators started using this in OA knee after preliminary studies by Sanchez and Anitua established the safety of Autologous PRP for intra articular use.[3] They conducted some animal studies and in vitro studies and postulated chondral remodelling as one of a cause for the beneficial effects. Subsequent studies compared PRP with hyaluronic acid,[3–6] and demonstrated the safety profile and beneficial effects of PRP in OA Knee. Spaková et al[4] concluded the effectiveness and safety of autologous PRP in early osteoarthritis knee (Kellgren and Lawrence Grades 1, 2, or 3 osteoarthritis) by comparing PRP injection with hyaluronic acid in their RCT which had 120 patients. Similar observations were noted by Cerza et al[5] in their RCT on 120 patients wherein autologous PRP group had better WOMAC scores than HA group. Kon et al[6] compared autologous PRP with HA injections and observed better symptom control and sustained effects in autologous PRP group. Kon et al[7] in their initial study in 2010 had established the good outcomes (IKDC scores) of intraarticular PRP in early degenerative cartilage lesions. Patients with degenerative chondropathy had better results than patients of early OA, who in turn had better results than advanced OA. In both studies Kon et al[6,7] stressed on better results in younger patients, Low BMI patients and those with less degree of cartilage degeneration.

Indian RCTs[1] have compared physiological control (normal saline) with single and double injections, and showed significant improvement in clinical scores (WOMAC scores) persisting till the 6th months; mechanisms other than chondral remodelling happening within the joint have been postulated to be responsible for the clinical benefit. It is also presumed that the improvement in some patients could be explained by the anti-inflammatory property of injected platelets by acting at different levels rather than stimulating Chondral remodelling[8] as was postulated before. The above hypothesis was based on the findings wherein they noted that patients were experiencing benefits as early as 18 days and also noted a slight worsening of benefits by 6 months. Sundman et al demonstrated the anti-inflammatory and anti-nociceptive activities of PRP and supported its use in OA joints to relieve pain.[2]

With the availability of commercial centrifuge table top devices, PRP therapy can be more easily given by clinicians to their patients in their OPD. Most of the commercial machines now provide Leucocyte free PRP in adequate concentration. Nevertheless the clinician must ensure a closed chain and complete infection protection.

Anitua et al[9] has recently postulated that PRP in combination with HA enhances the migratory potential of fibroblasts based on her in vitro studies. The idea of positive interactions between HA and PRP was further supported by Marmotti et al[10] in his vitro study. Since HA and PRP are not mechanical but biological approaches, the ability of PRP + HA to change the biological status of the joint and promote tissue healing will be particularly critical during the initial stages of OA, before the onset of structural changes. Based on this concept Andia[11] has postulated that a combination of HA and PRP may prove to be better than PRP alone; however this requires controlled studies to verify critical aspects of character and performance of the composite. Several key aspects such as the molecular weight of HA and the concentration to be mixed with PRP should be analysed before conducting clinical trials.

With our evolving understanding, PRP holds a lot of promise for those suffering from pain due to early OA knee; although the evidence available today is not completely confirmatory, many reports point to the fact that WBC filtered PRP injections definitely hold a high position in the pain ladder treatment of early OA compared to other modalities. Nevertheless there is great scope for further research on the role of PRP in OA, both clinically and in vitro, to better understand the mechanism of action and hence evolve further in our understanding.

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Review Article

The shoulder in cricket: What's causing all the painful shoulders?

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ABSTRACT

Background/objectives: Shoulder injuries account for roughly 5% of all injuries sustained by cricketers, most likely an underestimation of a larger problem facing the sport. The cause for shoulder injuries has been sparsely investigated among cricketers. The aim of this review is to summarize the available literature on possible mechanism for shoulder injuries among cricketers.

Method/materials: MEDLINE and EMBASE (Search terms: ''cricket'' AND ''shoulder injuries''; ''cricket'' AND ''rotator cuff tears''; ''cricket'' AND ''impingement''; and associated synonyms) were performed in March 2014. The authors further canvassed the reference list of selected articles and online search engines such as Google Scholar. Inclusion criteria were studies that assessed shoulder injuries among cricketers. A total of 9 studies was identified on primary search, and later expanded to 15 studies.

Results/discussion: Bowlers and fielders are most frequently affected by shoulder injuries, likely a result of their overhead throwing actions. Spin bowlers tend to be worse for wear that fast bowlers. A number of possible theories have been proposed as to the cause for shoulder pain among cricketers including: scapular dyskinesia, glenohumeral internal rotation deficit and weak musculature surrounding the cuff. Most cricketers with shoulder pain appear to have an increase in external rotation and loss of internal rotation range of motion in the affected shoulder.

Conclusion: We propose a combined mechanism of injury that results in shoulder pain among cricketers. Further work is needed to identify the cause of the problem and implement targeted interventions aimed at each step of the proposed pathway.

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1. Introduction

Shoulder injuries account for roughly 5% of all injuries sustained by cricketers,[1] although this is most likely an underestimation of a much larger problem. The cause for shoulder injuries among cricketers has been sparsely investigated, largely because of their small share of global injuries compared to other more common injuries such as hamstring strains. The aim of this review is to summarize the available literature on possible mechanism for shoulder injuries among cricketers and provide recommendations for future research in this field.

2. The problem

Injuries in cricket are common. A review of long-term injury surveillance studies by stretch (2007) across Australia, South Africa and England, found that most injuries occur early in the season when the least cricket is being played.[2] Upper limb injuries constituted 29% of all injuries in this review.

The England and Wales Cricket Board reported that 5.5% of all injuries among first-class County Cricketers, during the 2001 and 2002 season affected the shoulder, with similar findings reported in South Africa (5.2%) and among the first-class Australian teams (7%).[1,3,4] A recent Australian injury study over 11 seasons, found that shoulder tendon injuries account for 0–1.4% of all injuries per season, with other shoulder injuries having an incidence rate of 0–1.5%.[5] Prevalence rates of shoulder tendon injuries range from 0.1 to 1.4% and prevalence for other shoulder injuries range from 0 to 1.0%.[5] In another 10 year study, the mean shoulder injury incidence was 1.1 per season with a mean prevalence of 0.9%.[4] Australian injury surveillance data encompassing the years 1995–2001, demonstrates that shoulder injury prevalence among batters was 0.3%, fast bowlers 0.9% and spin bowlers 1.1%.[1]

In contrast, a recent study of English county cricket players suggested that up to 23% may experience some form of shoulder injury, with the majority affected in the throwing arm.[6] This suggests that there may be an underestimation of shoulder injuries in cricket.[7] A limitation of the above data set is that three countries (Australia, South Africa and England) have produced data with none available from other cricket-playing nations. There is a need for all cricket playing nations to monitor injury rates among cricketers so that inter-country differences may be explored and appropriate targeted interventions developed.

3. Which cricketers are most affected?

Traditionally, overhead athletic activity has been associated with shoulder injuries. Cricket is no different, with fielders and bowlers engaged in overhead throwing activities the most prone to shoulder injury.

Australian data shows that bowlers have roughly three to four times the shoulder injury prevalence rate of batters.[1] Injuries for bowlers are well above the average for all other cricketers at each age group and show an increase as players' age. Interestingly, among bowlers spin bowlers tend to be worse for wear with respect to shoulder injuries than fast-bowlers.[1] In a study of 112 first-class English bowlers ($n = 42$ spin; $n = 70$ fast), Gregory et al (2002) found that spin bowlers have a higher incidence of shoulder injuries (0.055 injuries/1000 balls) versus fast-bowlers (0.007 injuries/1000 balls).[8]

During bowling in cricket, the internal shoulder rotators are involved in the acceleration phase of the arm through concentric contractions, while the external rotators are involved in the deceleration phase.[9] Shoulder injuries were more common in fast bowlers with a front-on action than bowlers with a side-on or mixed-action and shoulder injuries were more common in wrist spinners than finger spinners.[10] In wrist spin the bowlers appear to rotate the bowling shoulder internally, while the arm circumducts.[10] Gregory et al speculated that this action of internal rotation during spin bowling may predispose one to impingement and injury.[8] It has been suggested that the presence of possible dysfunction in the shoulder rotators, combined with front-on bowling action and external rotation hypermobility are possible predisposing factors for chronic shoulder injuries in cricket fast bowlers.[10]

However, the majority of shoulder injuries in cricket are related to tendon injury and though to be more likely related to fielding, particularly throwing, than to bowling.[3,4] Throwing a cricket ball from the outfield is likely to be a provocative activity for shoulder injury. It is common for cricketers with shoulder problems to field in positions that reduce the distance to be thrown.[6]

Clearly, fielders and bowlers engaged in overhead throwing activities and abnormal torques across the shoulder joint are most at risk for shoulder injuries.

4. What causes shoulder injuries among cricketers?

During the overhead throwing motion the shoulder complex functions as a regulator of forces generated by the legs and the trunk.[11] It is this regulating function as well as the high velocities that accompany the throwing motion that places large forces across the glenohumeral joint.[12] These forces as well as the frequent repetition of the overhead throwing action produce severe stresses on the muscles, bones and joints of the upper extremity.[13]

Previous studies of overhead athletes in other sports have found that those with shoulder injuries have higher training loads,[14,15] have altered scapula kinetmatic,[16] altered muscular strength patterns[17] and greater internal rotation (IR) to external rotation (ER) range of motion in the dominant shoulder.[17] Cricketers, similarly, also have been shown to have a glenohumeral internal rotation range of motion deficit[7] and weak scapula stabilizer musculature.[18]

Repetitive overhead activities likely lead to adaptation to the pillars that constitute the shoulder joint – the bones (including the scapula), the cuff and the muscle stabilizers. Whether the subsequent change in shoulder kinematics is adaptive[17,19,20] or the result of pathology[21–23] remains an area of debate.

5. Range of motion

Repetitive overhead activities stretch the anterior joint capsule over time and tighten the posterior capsuloligamentous/muscular complex,[24] leading to decreases in IR and increases in ER.[19,25] The stretching may lead to antero-superior migration of the humeral head, accounting for the development of subacromial impingement and shoulder pain.[26–28] This mechanism of soft tissue adaptation is supported by Hsu et al who stretched the posterior shoulder joint capsule of cadaveric shoulders to demonstrate an increased IR[29] and by Burkhart and colleagues who reported that internal rotation can be increased when the posterior capsule is stretched.[11]

When the decrease in IR is beyond the gain in ER, the condition is known as glenohumeral internal rotation defect (GIRD).[11] Burkhart et al (2003) proposed that GIRD may be associated with injury to the throwing shoulder.[11]

In contrast to the soft tissue adaptation mechanism, GIRD has been attributed to bone remodeling of humeral neck to a retroverted position which may act as a protective adaptation to reduce shoulder injury.[30,31] Our proposed combined mechanism is presented in Fig. 1.

Giles and Musa (2008) in their study of 133 male and female elite junior English cricketers found that cricketers who regularly engage in overhead actions had less internal and greater external rotation in dominant shoulder versus non-dominant shoulder, and that cricketers who experienced shoulder pain had greater internal rotation difference between dominant and non-dominant shoulder than those who did not.[7] Increased ER and decreased IR have been documented in a variety of other unilateral overhead sports including tennis and baseball[32–34].

Stuelcken et al (2008) found significant differences in external rotation range of motion and internal rotation range of motion for bowlers with shoulder pain ($n = 12$) versus total cohort ($n = 26$) of elite female Australian fast-bowlers. However, there was no difference in range of motion or torque between bowlers with and without a history of shoulder pain.[35] Further, in their study of 66 elite bowlers, Sundaram et al (2012) found that fast-bowlers and spin bowlers who bowl regularly have decreased IR and increased ER for dominant shoulder versus non-dominant shoulders.[12]

The role of age is also important. Rotational motion differences between dominant and non-dominant shoulders of baseball players increase as age increases.[25] Kibler and colleagues found a significant correlation between increasing IRD with both increasing age and years of tennis exposure, supporting adaptive change response to repetitive overhead activity among 39 high level tennis players.[34]

There is a need to better determine the range of motion of cricketers with shoulder pain and to actively target physiotherapy interventions to compensating for any losses in IR and gains in ER.

6. The scapula

Scapula dysfunction has been implicated as a contributor to throwing-related to pathologic internal impingement of the

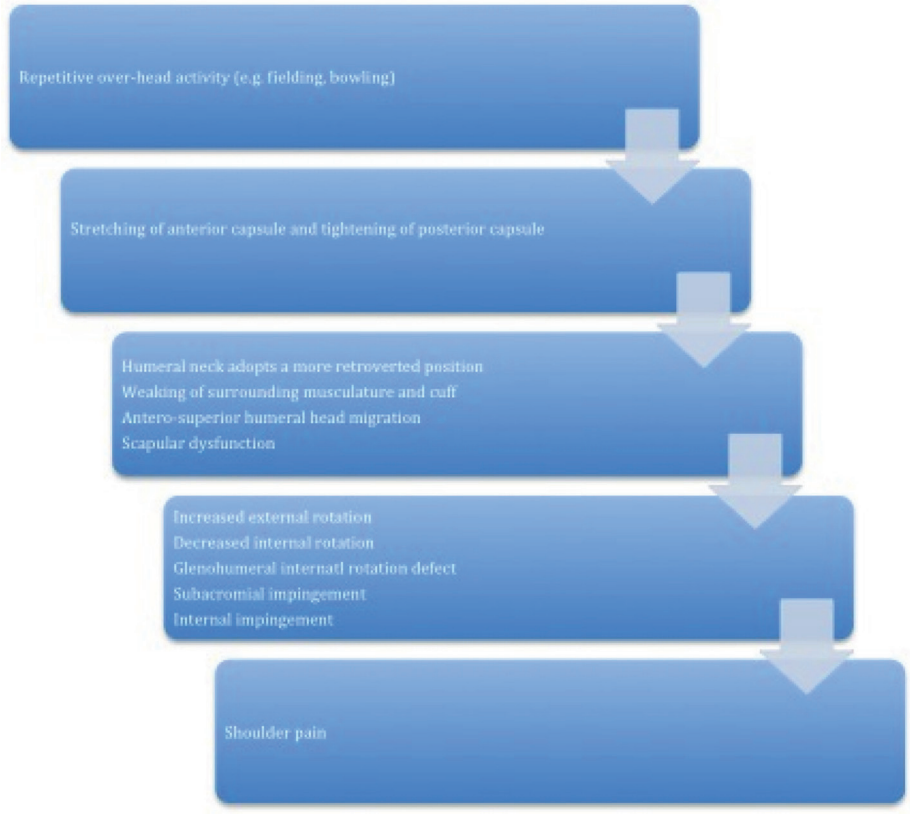

Fig. 1 – Our proposed combined mechanism for shoulder pain in cricketers.

shoulder due to its role in increasing the contact between the greater tuberosity and the posterior-superior glenoid, thereby impinging the posterior rotator cuff tendon/s and labrum (Fig. 1).

In a review of the role of scapula positioning and movement in pathological and non-pathological shoulder, Struyf et al (2011) found that the literature was inconsistent. At rest the scapular is positioned approximately horizontal, 35° of internal rotation and 10° of anterior tilt. During shoulder elevation, most researchers included in the review suggested that the scapula tilts posteriorly and rotates both upwards and externally. It is suggested that during shoulder elevation, patients with shoulder impingement syndrome demonstrate a decreased upward scapular motion, decreased posterior tilt and decrease in external rotation. Similarly, in patients with glenohumeral instability, a decreased scapular upward rotation and increased internal rotation is seen.[36] This suggests that the scapula plays an important role in pathologic states of the shoulder.

Laudner et al (2006) in a case–control study compared scapular position in baseball players with ($n = 11$) and without ($n = 11$) internal impingement (using MRI and EMG motion tracker) found that players with clinical evidence of internal impingement have increased sternoclavicular elevation and scapular posterior tilt position during humeral elevation in the scapular plane.[16]

Green et al (2013) studied scapula position in 60 elite junior male Australian cricketers. Participants were subjectively divided into two groups – those with a shoulder problem in the last 12 months and those without. They found that patients with a shoulder problem had a consistently downward rotated scapula during almost all shoulder positions, suggesting that this scapula position predisposes cricketers to ongoing injury through shoulder impingement syndrome and through increased load placed on the rotator cuff muscles acting along the glenohumeral joint during throwing.[37] A limitation here is that a single subjective tool was used to subdivide cricketers into the two groups.

Further work is needed to study the scapula in the shoulders of cricketers and to determine whether scapular dyskinesia is primary or secondary[22] to overuse.

7. Muscles surrounding the cuff

It has been postulated that weakening of the support musculature around the cuff (Fig. 1) is likely the result of underlying pathology and perpetuates a vicious cycle of altered shoulder kinematics which aggravates shoulder pain.

A video-motion analysis study of 18 Australian female fast-bowlers, found that there was a large peak shoulder distraction force during the early stages of the follow-through of the bowling action.[38] The amount of the force was similar to values reported for baseball and soft-ball pitchers, both high risk groups for shoulder injuries. This peak distraction force, although likely to stretch the capsule primarily, also produces moment stress on the musculature which may allow more force transmission to capsule and also disturb scapula kinematics.

In a video-motion analysis study complemented by EMG testing of seven muscles, two bowlers, with and without current shoulder pathology, were compared.[39] The bowler without a shoulder pathology, had no significant difference for duration of movement and ball velocity, however did have variations for muscle activity particularly for biceps brachii and infraspinatus. Conclusions from this study are limited by the small sample size, however do question whether abnormal muscle firing predisposes to shoulder pathology or vice versa.

There is a need to better understand the status of muscles surrounding the cuff in the shoulders of affected and non-affected cricketers.

8. Conclusion

Shoulder injuries account for roughly 5% of all cricket injuries, most likely an underestimation of the disease burden. Bowlers and fielders are the most affected specialties. The authors propose a combined mechanism for shoulder pain in cricketers which addresses range of motion defects, scapula dyskinesia and abnormalities in musculature surrounding the cuff. Further work is needed to understand and address the problem as cricket becomes increasingly popular in the new century.

Conflicts of interest

All authors have none to declare.

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Original Article

TKR without tourniquet: A laboratory study investigating the quality of the tibial cement mantle when using metaphyseal suction and cement gun☆

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ABSTRACT

Purpose: The majority of cemented knee replacements worldwide are performed with a tourniquet. The benefits of surgery in TKR without a tourniquet have been well described but questions have been raised about the ability to prepare the bone for cementation, and take up of a tourniquet-less technique has been slow. A laboratory based model was constructed to directly compare the quality of cementing between tourniquet and tourniquet-less knee replacement supplemented by metaphyseal suction and a cement gun.

Methods: A Sawbone model to represent the metaphyseal proximal tibia was constructed. The model allowed the inflow of simulated blood and the use of metaphyseal suction. The study compared four different techniques; the use of a tourniquet, no tourniquet, no tourniquet with cancellous suction and no tourniquet with cancellous suction and a cement gun. Each subtype of experiment was repeated 5 times. Quality of cementation was assessed using a calibrated engineering planimeter.

Results: This model has shown that combining the use of metaphyseal suction and a cement gun but without the use of a tourniquet offers significantly better cement penetration ($p < 0.0001$) than cementing using a tourniquet alone.

Conclusions: This study offers further in vitro evidence to the argument that tourniquet-less surgery when supplemented by appropriate techniques can achieve a good cement–bone interface, whilst avoiding the additional risk of using a tourniquet to perform the procedure.

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1. Introduction

Joint Registries consistently demonstrate that cemented total knee replacements are implanted with greater frequency than cementless designs.[1–4]

In total hip replacement it has been shown that better preparation of the femur by blocking the distal canal of the femur, cleaning the cancellous bone with pressure lavage to remove blood and tissue debris and pressurising cement at low viscosity into the bony spaces improves both penetration of cement into bone and the mechanical properties of the cement bone interface.[5–7] The tensile strength of the cement–bone interface also correlates with the amount of bone interdigitated with cement.[8] These techniques are accepted practice in modern cemented hip surgery however such consistency of technique is not demonstrated in total knee replacement.[9,10]

The use of negative pressure techniques combined with pulsed lavage is a contemporary strategy to try to counter the effect of bleeding, remove excess fat and improve cement penetration in total knee replacement.[11,12] A cement gun or syringe may further improve the depth of the cement mantle.[9,13] Although others have demonstrated no advantage of a cement gun over finger packing.[14]

One of the key variables in knee replacement surgery is the use of a tourniquet. Tourniquet use allows a bloodless approach to total knee replacement, which may make the approach and subsequent surgery easier. The previously reported benefit of reduced blood loss has now been called into question by a recent meta-analysis which showed no difference in total blood loss and transfusion requirement when comparing tourniquet and tourniquet less surgery.[15] There is also a perception that it will benefit bony preparation prior to and during cementing as there less back bleeding from the tibia and femur. However, the production of a bloodless field to enable a theoretical improvement in cement mantle does come at a potential cost. The recognised complications of tourniquet use include nerve damage, compartment syndrome, pressure sores, burns and thrombosis.[15–17] Despite these facts, the adoption of a no tourniquet technique has been slow with one study estimating that only 5% of surgeons routinely operate without a tourniquet.[10] This can be attributed to concerns about achieving a bloodless surface for cementing.

It is standard practice at our institution to operate without a tourniquet but use the suction technique combined with a cement gun.

An experimental model has been constructed to investigate whether using negative pressure techniques (cancellous bone suction) and cement injection using the cement gun but without use of the tourniquet could equal or improve on the quality of cement penetration seen in bloodless surgery using the tourniquet.

2. Methods

The study compared four different techniques; the use of a tourniquet, no tourniquet, no tourniquet with cancellous suction and no tourniquet with cancellous suction and cement gun. These groups are described in Table 1. Each subtype of experiment was repeated 5 times.

The experimental model consisted of a metal box simulating the proximal tibia which measured 70 mm × 70 mm × 60 mm. 30 mm from the inferior surface of the box, on the lateral aspect there was a single hole that could be connected to standard suction tubing to allow inflow of liquid. Havoline Motor Oil 10w30 (Chevron Global Lubricants, San Ramon, California, USA) was used to simulate blood and the oil was held in a reservoir stabilised by a retort stand maintained at a vertical height of 25 cm above the level of the surface of the metal box that has been shown previously by Heyse-Moore and Ling to approximate the back-bleeding pressure of the proximal femur.[18] The use of motor oil to simulate blood in this type of model has been previously validated.[19]

On the anterior aspect of the box, 15 mm below the surface and on the left side there was a single outflow hole, through which a simulated Wolff Needle (Inner diameter 2 mm) manufactured within the Engineering Department could be inserted 20 mm ensuring that all vents were within bone. The cancellous bone of the proximal tibia was simulated by open cell foam block (Sawbones, Sweden) that was cut into the correct size to be inserted into the box and the top of which was level with the superior surface of the box (Fig. 1). In order to ensure the box was watertight between experiments the sides were sealed with silicone for each experiment.

The implants used to simulate the tibial component were injection-moulded model of a Size 5 Scorpio tibial tray (Stryker®, Kalamazoo, Michigan, USA). The cement used in all experiments was Palacos R®.

For each type of experiment (see Table 1) the metal box was prepared in an identical way with the Sawbone in place. Standard Scorpio tibial preparation kit was used to prepare the Sawbone in a uniform way in accordance with the manufacturer's guide for tibial preparation. A single mix of cement was prepared according to the manufacturer's instruction and was mixed for 30 s; oil flow if indicated was started at this time. At 90 s, if indicated the suction at −60 KPa via the Woolf needle was turned on and the cement was halved and, according to the experiment type, was placed on top of the simulated tibia using the spatula without pressurizing by hand, (Groups A, B and C) or using the cement gun (Group D).

For group D the cement gun nozzle was carefully applied to the flat tibial surface and cement was injected and then the nozzle was moved across the surface injecting cement until the whole surface had been covered.

The tibial component was then inserted manually and carefully placed under a lever arm device. The pressuriser on top of the tibial plate and the lever arm weight were positioned so that a reproducible force of 196.2N (mass of 20 kg) was applied to the tibial component. The force was maintained on the tibial tray for 15 min for all experiments, ensuring that the cement cured under identical, constant force. All specimens were then labelled according to the group they were in, washed under a tap to remove any excess oil or debris and allowed to dry.

Each specimen was then cut in 4 identical positions: on each side at the point of maximal width (in the A-P plane perpendicular to the transverse axis) and parallel to that at 15 mm laterally (Fig. 2) using a diamond edged band saw. This

Table 1 – Experimental groups.

Group	Technique	Oil inflow	Suction on	Cement gun application
Group A	Tourniquet	No	No	No
Group B	No tourniquet	Yes	No	No
Group C	No tourniquet/suction used	Yes	Yes	No
Group D	No tourniquet/suction used/cement gun used	Yes	Yes	Yes

yielded four slices for measurement. An example of a prepared slice is shown in Fig. 3. Each specimen slice was then cleaned and polished using a standard metallurgical irrigated polishing tray in the laboratory. The amount of cement under the tibial component was measured as an area (in cm^2 to one decimal place) using an engineering planimeter with a Vernier scale which had been previously calibrated. Any part of the simulated component present from the central fin of the tibial baseplate was also included in the surface area measured for every sample to minimize error. Each specimen was measured three times and the mathematical mean was taken as the surface area. There were therefore two central and two peripheral measurements for each specimen, each experiment was repeated five times which gives a total of 20 data points for each technique.

Our regional statistical unit analysed the measurements. The Shapiro–Wilks W test was applied to each sub set of data and it was found that there was no evidence of non-normality ($p < 0.0001$) and therefore it was permissible for the data to be analysed using parametric methods.

3. Results

One way analysis of variance (ANOVA) applied to the central and peripheral measurement groups demonstrated that the populations were different and this was found to be significant at $p < 0.0001$ for the central measurements and $p < 0.0001$ for the peripheral measurements groups comparing techniques. Table 2 and Table 3 below demonstrate the population means and their standard deviations:

The means of the central measurements were all greater than the peripheral measurements for all specimens, which correlates with the fact that at the central level of cut there is more of the tibial component included – the height of the fin on the baseplate being greater medially than laterally. Group B, which corresponds to the no tourniquet and no suction group (i.e. simulating unchecked blood flow), demonstrates the least amount of cement under the tray compared to all other techniques and this was statistically significant both centrally compared to Group A ($p = 0.008$), Group C ($p = 0.002$) and Group D ($p < 0.0001$) and peripherally compared to Group A ($p = 0.087$), Group C ($p < 0.0001$) and Group D ($p < 0.0001$) using the Bonferroni Comparison at the 95% confidence level.

Cement penetration in Group D (no tourniquet, cancellous bone suction and use of cement gun) was found to be better than all other methods of cementing for both the central and peripheral measurements at $p < 0.0001$ using the Bonferroni Comparison at the 95% level. Most importantly the data clearly demonstrate that Group D gives a significantly better quality of cement penetration when it is compared to Group A (Tourniquet).

4. Discussion

Total Knee Replacement is the most commonly performed joint replacement in England and Wales and cemented total knee replacement remains the gold standard. The depth of tibial cement in TKR has been the subject of considerable debate and research. Peters et al[20] looked at the stability of the initial fixation of the tibial component in a cadaveric model placed under eccentric cyclical loading. They found that the initial fixation stability correlated with the depth of cement fixation into the proximal tibial surface, when comparing surface cementation (only under the tray) with full cementation (under tray and stem cemented). Their specimens had cement thicknesses ranging from 3.6 to 4.9 mm. Bert et al[21] performed laboratory testing using an artificial model for the tibia and looked at micromotion of the component, comparing

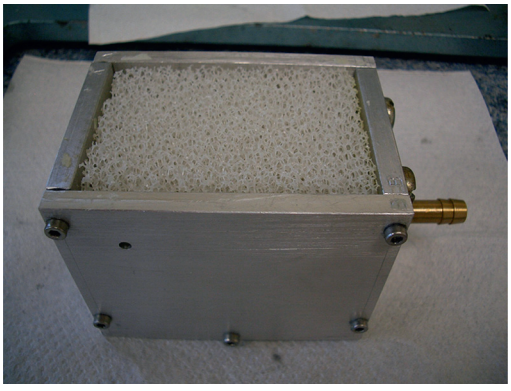

Fig. 1 – Experimental model with Sawbone in place.

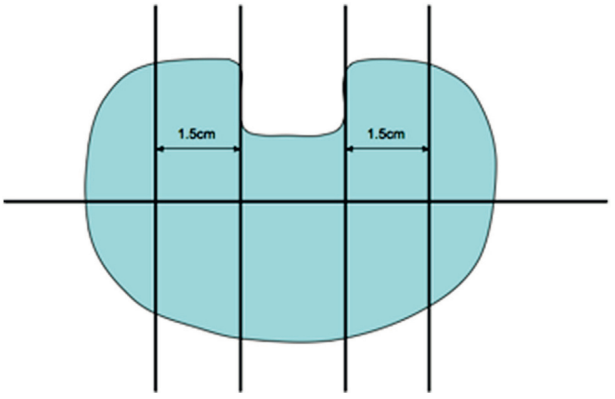

Fig. 2 – Implant schematic from above demonstrating vertical cut lines.

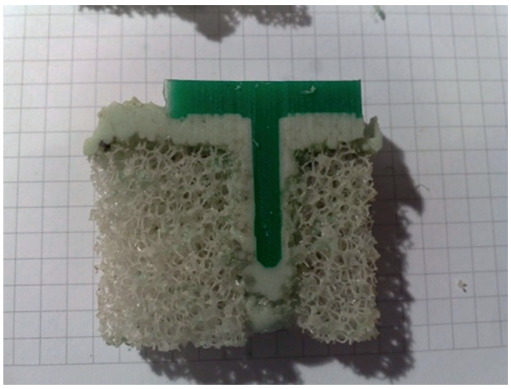

Fig. 3 – A prepared tibial slice.

cement mantles beneath the tibial implant. They concluded that greater than 3 mm of cement mantle gave excellent stability. This was in contrast to their results with only 1 mm of cement mantle, when significant micromotion was demonstrated.

Lutz et al[9] studied cement penetration in-vivo and found that, in terms of corrected depths measured on X-ray, that the use of a cement gun or syringe reliably produced a deeper cement mantle and concluded that a depth of 4–10 mm of penetration is desirable. Overall the literature would seem to support that 3–5 mm is ideal.[11]

We have specifically looked at the area of cement penetration as a better measure of cementation, however other studies quoted depth and so for completeness we have noted the range of depths using our technique and found that the minimum depth achieved with suction and gun (group D) was 5 mm of cement with peaks of up to 11 mm which compared with minimum depth of 3 mm with peaks of 7 mm for the tourniquet group (group A). Although measuring depth gives a more readily understandable value for quality of cementing, it can be argued that using the calibrated planimeter has merit as it directly examines more of the implant and its cement mantle. The planimeter offered an accurate, reliable and reproducible way of commenting on the global quality of cement penetration between different groups. Other authors have used X-rays in the past to give an overview of the maximal penetration at one point, whereas this study physically measured the amount of cement within an entire cross-section.

We have tried to eliminate experimental error by using the same conditions for each individual part of the experiment, with the same surgeon performing all of the experiments in the same conditions and using identical equipment and materials. In the experimental model, pulse lavage irrigation was not used; this is a commonly practiced technique for bone preparation that we also employ clinically. However we felt that there was no reason to assume if pulse lavage was employed in all cases that it would have a more marked effect in one scenario than in another – in fact it could be expected to have a more beneficial effect in the absence of a tourniquet. The authors are also aware that it would be unusual to cement a tibia using no tourniquet and no preparation techniques, as in Group B, and this group was included for comparison only.

Table 2 – Central measurements (Total area of cement penetration in cm^2).

	Group A	Group B	Group C	Group D
Mean	3.195	2.706	3.439	4.254
Standard deviation	0.423	0.356	0.326	0.442

Table 3 – Peripheral measurements (Total area of cement penetration in cm^2).

	Group A	Group B	Group C	Group D
Mean	2.061	1.876	2.419	3.205
Standard deviation	0.192	0.156	0.316	0.246

The open cell foam Sawbone used is porous and compares with the more osteoporotic of bone types and therefore there could be criticism that cement would over-penetrate, however the comparative nature of the study means that this would be the same for all techniques. The same open cell foam from the same batch was used for every experiment and it is the authors' experience that it is not uncommon to find bone of this quality, particularly in older female patients.

There are theoretical concerns if a cement mantle is too deep, including potential for thermal necrosis and weakening of the bone-cement interface.[11] We accept the often reported practical concern of a thick cement mantle causing problems in the revision situation.[9] However, It is clear from examining the samples that the cement does not over penetrate when using the combination of suction and cement gun.

It was interesting to note that the Group C(No tourniquet & Suction) experiments demonstrated slightly better penetration than the Group A (Tourniquet) experiments but this was only significant for the peripheral measurements ($p = 0.0017$), this suggests that bone suction alone in the absence of a tourniquet gives similar, if not slightly better results, than using the tourniquet.

Banwart et al found a trend towards asymmetric cement penetration as a result of a unilateral position of the suction catheter.[11]

However in our study in Groups C and D, where cancellous bone suction was used, unilateral positioning of the simulated Wolff Needle did not give asymetric cement penetration. This justifies the single suction technique and negates the concern that unilateral suction may bias the cement penetration to that side.

Tourniquet use in total knee replacement is common, the argument given for its use is to improve the surgical field for cementing and whilst it does give the benefit of bloodless surgery, it also carries potential serious risks including nerve damage, compartment syndrome, pressure sores, burns and thrombosis.[15–17]

In our institution total knee replacement is carried out without the use of a tourniquet, this has one main theoretical concern over the quality of the cement mantle achieved in the absence of a bloodless field.

This experiment was set up to challenge this hypothesis and compare it to both the current most commonly employed cementing technique (group A) with a number of possible

variations. This experimental model has shown that combining the use of metaphyseal suction and a cement gun but without a tourniquet offers significantly better cement penetration ($p < 0.0001$) than cementing using a tourniquet alone and indeed is than all other methods tested. This study offers further in vitro evidence to the argument that tourniquet-less surgery when supplemented by appropriate techniques can achieve a good cement–bone interface, whilst avoiding the additional risk of using a tourniquet to perform the procedure.

Conflicts of interest

All authors have none to declare.

Author's contributions

TAB: Data analysis, Manuscript writing
MB: Study design, Data collection, Data analysis
CL: Study design, Data collection
KSE: Study design, Manuscript writing
VM: Manuscript writing
ADT: Study design, Manuscript writing

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Original Article

Comparative analysis of chondrogenesis from cartilage tissue and alginate encapsulated human adipose stem cells

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ABSTRACT

Aim: Alternate strategies to regenerate the damaged tissue require exogenous supply of several chondrocyte implants. There are inherent challenges to optimize an appropriate tissue culture methodology that can aid in enrichment of chondrocytes. The aim of the study was to explore the differentiation potential, expansion and growth kinetics of the human adipose derived stem cells (hADSCs) in alginate microspheres in comparison to chondrogenesis from the cartilage tissue.

Methods: Isolated hADSCs and cartilage derived chondrocytes were cultured and characterized. The distribution of stem cells within alginate bead was imaged by scanning electron microscopy (SEM). Encapsulated hADSCs were monitored for their cell viability, cell proliferation and apoptosis via JC-1 staining, MTT assay and Annexin V assays respectively. The alginate cell constructs were analyzed for chondrogenic gene expression by RT-PCR.

Results: The chondrocyte pellet culture from cartilage demonstrated lower growth potential as compared to alginate encapsulation. hADSCs were successfully encapsulated within alginate matrix with >80% cell viability. Apoptotic assays provided safety profile for the alginate during cell growth. The up-regulation of cartilage specific genes like TGF-β, collagen type-X, COMP was observed during the entire period of culture.

Conclusion: The chondrogenesis in pellet culture from cartilage tissue conserved the chondrocyte phenotype better with rich GAG polysaccharides. However, owing to an enriched chondrocyte requirement, alginate as a scaffold design would aid in the treatment of large focal defects.

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1. Introduction

The limited ability of articular cartilage to self-repair has led to a wide variety of treatment approaches for focal chondral defects with varying levels of success. Limited proliferative and regenerative capacity of adult chondrocytes and their potential dedifferentiation upon expansion is an impeding factor and hence it is imperative to explore alternate strategies.[1] An alternative therapy for the repair of damaged articular cartilage resides in the tissue engineering approach.[2] Tissue engineering can potentially use cells taken either from the patient (autologous) or from a donor (allogenic). These cells may be mature cells (e.g., chondrocytes) or immature cells (e.g., mesenchymal stem cells). The adult stem cells could be the solution to differentiate into different types of cells, allowing us to regenerate damaged tissues.[3]

Adipose tissue represents a good candidate tissue for obtaining adult stem cells for regenerative therapy because of least ethical implications and increased voluntary donation.[4] Furthermore, the stromal vascular portion of adipose tissue has been reported to contain up to 2% of cells that are able to differentiate into various cell types compared with only 0.002% of cells with this capability in bone marrow.[5]

A wide variety of scaffolds have been used to mimic the extra-cellular matrix of the cartilage tissue *in vitro*.[6] The most common matrix material used is collagen or alginate. Sodium alginate has been widely recognized as a conventional stem cell delivery system for repair of cartilage defects and as a model for 3D culture system.[7]

This innate feature of alginate hydrogel allows a good transfer of gases and nutrients to maintain cell viability, proliferation and differentiation. Three-dimensional systems could potentially provide the improved ratio of surface to volume necessary to cope with the scale of cell expansion required for allogenic tissue engineering applications. Several studies have shown the induction potential of stromal cells to chondrogenic lineage as evidenced by the expression of aggrecan, type II collagen and collagen IX.[8] However, on prolonged culture and therapy these differentiated stromal cells have resulted in the development of fibrocartilage tissue and scar formation. Failure rate of autologous chondrocyte implantation is about 60% due to de-differentiation phenomenon. It is of utmost importance that chondrocyte cell phenotype should be conserved in the development of *in vitro* chondrocyte culture technologies. The present study was designed to compare the biological performance of articular chondrocytes and the alginate matrix incorporating the hADSCs towards chondrogenic lineage. Calcium chloride was chosen for its' better chelating properties as compared to others, based on the previous reports. The study parameters in 3D alginate matrices as temporary physical support for hADSCs included, the cell proliferation, viability, compatibility, chondrocyte gene expression profile during chondrogenic differentiation. Thus, the current study would provide a preliminary insight to design a strategy for encapsulation and differentiation of hADSCs within the alginates paving for further studies in regenerating the injured tissues.

2. Materials and methods

Low Glucose–Dulbecco's Modified Eagle Medium, FBS (fetal bovine serum), antibiotics (Penicillin, Streptomycin, Gentamicin, Amphotericin B), enzymes (Trypsin–EDTA, Collagenase) were purchased from Gibco (Life technologies, Switzerland). Chemical and growth factor were of the highest grade and purchased from Sigma–Aldrich (St. Louis, USA). SA (250 kDa; medium viscosity, Sigma–Aldrich (St. Louis, USA)), alcian blue, dexamethasone, ascorbate, and insulin–transferrin–selenium (ITS) were purchased from Sigma–Aldrich (St. Louis, USA). Primers were procured from Bioserve (Beltsville, USA).

Prior written informed consent from the patients was obtained after taking clearance from the Global Hospitals, Institutional Ethical (IEC) Ref no. GMERF/BS/SAC/IEC/IC_SCR2014/01. The samples for the study were collected in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki). Human adipose tissue was collected from morbid obese patients undergoing bariatric surgery. The samples were collected in L-DMEM and pooled for further experimentation to circumvent the age variable. The cartilage scrapes were collected in sterile DMEM/F12 medium supplemented with antibiotics during arthroscopy procedure.

2.1. Isolation of chondrocytes from cartilage tissue

The cartilage scrapes of 2×2 mm bits during arthroscopy procedure were obtained in sterile media supplemented with antibiotics. They were subjected to low speed magnetic stirring at 37 °C for 45 m in 0.2% trypsin. The cells dispensed in the media are re-suspended in 0.2% collagenase solution in a CO_2 incubator at 37 °C for 90 m. The digested tissue was filtered using 70 μm cell strainer to separate the chondrocytes from undigested ECM. The cells were cultured as pellet in complete chondrocyte xeno-free media at a density of 5×10^4 cells/ml in a humid, 5% CO_2 incubator at 37 °C. The pellet culture was maintained in a centrifuge tube for 21 days, with the medium replaced at 3 day intervals. The sedimented cells formed spherical aggregates at the bottom of the tube.

2.2. Morphological and histological analysis of pellet

Pellets were harvested after 21 days of culturing, fixed in 10% buffered formalin for 2 h, and kept in 70% ethanol overnight. Samples were embedded in paraffin and 5-μm sections were cut. Hematoxylin and Eosin (H&E) staining of paraffin sections was done for evaluation of cell morphology in pellets. Sulfated glycosaminoglycans (GAG) were visualized by staining with 0.5% alcian blue for 10 m.

2.3. Cell growth kinetics of chondrocytes

The growth rate of human chondrocytes was measured by seeding initial cell density at 4×10^4cells/mL. The cells were harvested periodically to check the growth profile of the cells.

2.4. Isolation and characterization of human adipose derived stem cells

Tissue fragments were washed intensely with phosphate buffer saline (PBS) minced properly and digested with collagenase type I (1 mg/mL) for 30–60 m in a humidified atmosphere of 95% air and 5% CO_2 at 37 °C with gentle agitation. The digested tissue was filtered through a 40 μm cell strainer and cells were centrifuged at 1800 rpm for 5 m. The cell pellet was re-suspended in L-DMEM supplemented with 10% FBS, penicillin (100 IU/mL), streptomycin (100 IU/mL), gentamicin (50 IU/mL), amphotericin B (2.5 μg/mL) and FGF (10 ng/mL) and plated at a density of $5 \times 10^4/cm^2$ in polystyrene T25 culture flasks and were incubated in a humid 5% CO_2 incubator at 37 °C for 48 h. Non adherent cells were discarded and adherent cells were cultured in complete medium for 10 days, with the medium replaced at 3 day intervals. Human adipose tissue derived stem cells (hADSCs) were harvested at 80% confluence. Cell surface antigen phenotype by flow cytometry was performed at each passage to characterize the hADSCs. CD90 (FITC), CD34 (PE), CD73-APC, CD45-FITC and HLA-DR (PE) were used to establish the positive and negative expression of the multipotent stem cells using Cell Quest Software (Becton Dickinson).

2.5. Preparation and encapsulation of hADSCs in sodium alginate beads

Alginate bead culture with cell suspension was adjusted to 2×10^6 cells/mL and added to an equal volume of 4% (w/v) alginate to give a final concentration of 1×10^6 cell/mL in 2% (w/v) alginate. The cell/alginate suspension was slowly expressed through a 23-gauge needle into a solution containing 100 mM $CaCl_2$ in PBS. The resultant beads were incubated in the $CaCl_2$ supplemented media for 10 m at room temperature to induce cross linking of the alginate gel. The beads were subsequently washed in 4 changes of DMEM + 20% FBS and cultured in the defined cell culture media.

2.6. Characterization of hADSCs incorporated in alginate systems

2.6.1. Scanning electron microscopy (SEM) analysis

The encapsulated hADSCs within sodium alginate, maintained in culture for 7 days, were washed twice with PBS and fixed for 6 h at 4 °C with 2.5% glutaraldehyde (Sigma–Aldrich, Co) in PBS, containing 0.1% $CaCl_2$. After 2 h, the samples were dehydrated in a series of graded alcohols and were dried to a critical point using an electron microscopy science critical point drying (CPD) unit. Samples were then scanned at various magnifications using a scanning electron microscope (Model: JOEL-JSM 5600, JAPAN) of the Department of Veterinary Pathology, Ruska Laboratories (Hyderabad, India).

2.6.2. Assessment of cell viability and metabolic activity

The mitochondrial trans-membrane integrity of the alginate encapsulated hADSCs was assessed by a lipophilic cationic probe 5,5′,6,6′-tetrachloro-1,1′,3,3′ tetraethylbenzimidazolcarbocyanineiodide (JC-1). The staining discriminated the healthy cells with intact mitochondria against the dead cells the cell metabolism within the alginate bead was assessed by MTT ((3,4,5-dimethylthiazol-2-yl)-2-5-diphenyltetrazolium bromide) assay by the standard protocol of Mossman et al.[9] The samples were run in triplicates wherein alginate beads without cells were taken as control.

2.6.3. Apoptosis assay

Cell death was determined using an annexin-V-FITC/propidium iodide apoptotic assay. Cells that stain positive for annexin-V-FITC and negative for propidium iodide would undergo apoptosis. Cells that stain positive for both annexin-V-FITC and PI are either in the end stage of apoptosis, undergoing necrosis, or are already dead. Cells that stain negative for both annexin-V-FITC and PI are alive and not undergoing measurable apoptosis. Cells were revived from the beads using dissolution buffer, 55 mM EDTA, 10 mM HEPES, pH 7.4 and stained with annexin-V-FITC as per manufacturer's recommendations (eBiosciences, USA). All studies were performed at least three times for reproducibility.

2.7. Chondrogenic differentiation of encapsulated hADSCs in alginate beads

To induce chondrogenic differentiation, encapsulated hADSCs were cultured in high-glucose DMEM supplemented with 10% FBS, 50 mM ascorbic acid-2-phosphate, 0.1 μM dexamethasone, 1 mM sodium pyruvate and 10 ng/mL transforming growth factor-β (TGF-β) for 21 days. The culture media was changed every 3 days. After defined period of time the beads were washed with PBS and dissolved with dissolution buffer for 15 m. The cells were centrifuged and the resultant pellet was stored for further use.

2.7.1. q PCR analysis of chondrocytes

Relative real-time PCR was performed to assess exact expression ratio of a set of chondrocyte like related genes and the rate of their regulatory mechanisms in chondrocytes during different time points cultured in alginate. Total RNA was prepared from RNeasy mini kits. Standard RT reactions were performed with 2 mg total RNA using Random hexamer as a primer and a cDNA was synthesized. Real-time PCR was carried out on the StepOne™ Real Time PCR system, using the SyGr master mix (Applied Biosystems, Carlsbad, CA, United States of America) in a final volume of 20 μL using standard PCR conditions (40 cycles with an annealing/elongation step at 60 °C). The relative expression of each gene was normalized against the house-keeping gene, β2-microglobulin (β2M). For each sample, a target gene and also a reference gene serving as internal control was carried out. ΔΔCt for each gene was calculated by subtracting the ΔCt of target sample from that of un-induced control sample.

2.7.2. Statistical analysis

Mean values ± SD (Standard Deviation) were calculated for data obtained from the assays for proliferation as well as that obtained from real-time PCR.

3. Results

3.1. *Chondrocytes culture and characterization*

The sedimentation of the isolated chondrocyte pellet into single aggregate was observed after 24 h. During cultivation, the size of the pellet continuously increased, with high cellular density and the pellets became opaque. The rounded morphology was evident by analyzing sections of pellet cultures stained for H&E and alcian blue. Hematoxylin and eosin (H&E) sections showed a homogenous cell distribution in the pellet. The center region contained rounded cells with darkly stained nuclei and surrounded by extracellular matrix, resembling chondrocytes with lacunae and isogenous cell groups. Alcian blue staining showed deposits of acid mucopolysaccharides in the proximity of the cells which is the deterministic feature of the sulfated glycosaminoglycans by cells cultured in the pellet culture (Fig. 1a).

The growth kinetics of the human chondrocytes was evaluated by plotting the growth curve. It was observed that the culture underwent an initial lag phase without increase in cell number for 7 days. The cell multiplication started exhibiting the log phase with rapid increase in cell number upto 28 days. Later the cells attained a stationary phase and then entered into the death phase (Fig. 1b).

3.1.1. *Isolation and characterization of mesenchymal stem cells from adipose tissue*

An average yield of 1×10^6 cells/g was obtained from 2 g of adipose tissue. As the cells were propagated in monolayer culture, they showed a more uniform fibroblast-like morphology. Morphologically hADSCs demonstrated spindle shape and fibroblast-like appearance on 14th day of culture (Fig. 1c).

The third passage hADSCs exhibited a distinct phenotype of MSC origin. Based on these results, we established that the most suitable hADSCs for incorporation into the alginate matrix were the cells corresponding to the third cell passage. The flow cytometric data revealed that the third passage hADSCs are negative for the markers like CD34/45 (1%), HLA-DR (3%) and positive for the stromal cell markers CD73 (90%) and CD90 (98.5%) which are common to stem cells (Fig. 1d).

3.2. In vitro *behavior of hADSCs embedded into alginate hydrogels*

3.2.1. *Evaluation of the cell-laden alginate beads*

The morphology of the cells encapsulated in alginate hydrogels was round in shape, identical in size. The hADSCs were discretely scattered all through the bead, and there were no differences in shape and density from the peripheral to the center of the bead (Fig. 2a).

The investigation of the construct surface using SEM after 7 days of cultivation revealed the presence of numerous cells within the alginate matrix. SEM images of relevant cross-sections showed that hADSCs were distributed in the matrix and exhibited around-shaped morphology within the alginate polymer (Fig. 2b).

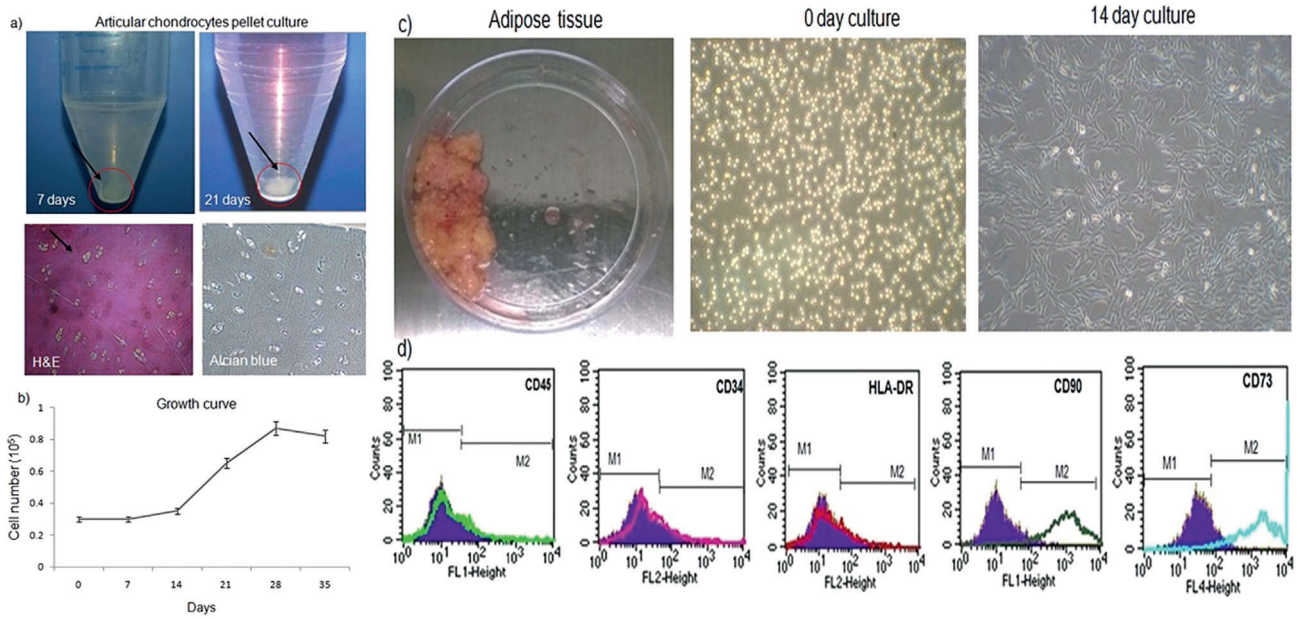

Fig. 1 – Cell morphology and characterization of articular chondrocytes and hADSCs. a) Formation of chondrocyte micro mass aggregates after 7 and 21 days of pellet culture. H&E staining shows polygonal shape of chondrocytes in isogenous group with lacunae and alcian blue positive staining indicating glycosaminoglycans abundantly distributed throughout the cells. b) Growth rate of chondrocytes with increased proliferation after 21 days. c) hADSCs isolated from adipose tissue by enzymatic digestion. Cells attained spindle shaped morphology on 14 day. d) The fluorescence level detected for the stromal stem cells markers was 95% (CD90), 91% (CD73), whereas for CD34/45, HLA-DR only 0.4–0.5% of the gated cells were fluorescently labeled. The positive zones in the histograms were marked as M2 gate based on the control sample.

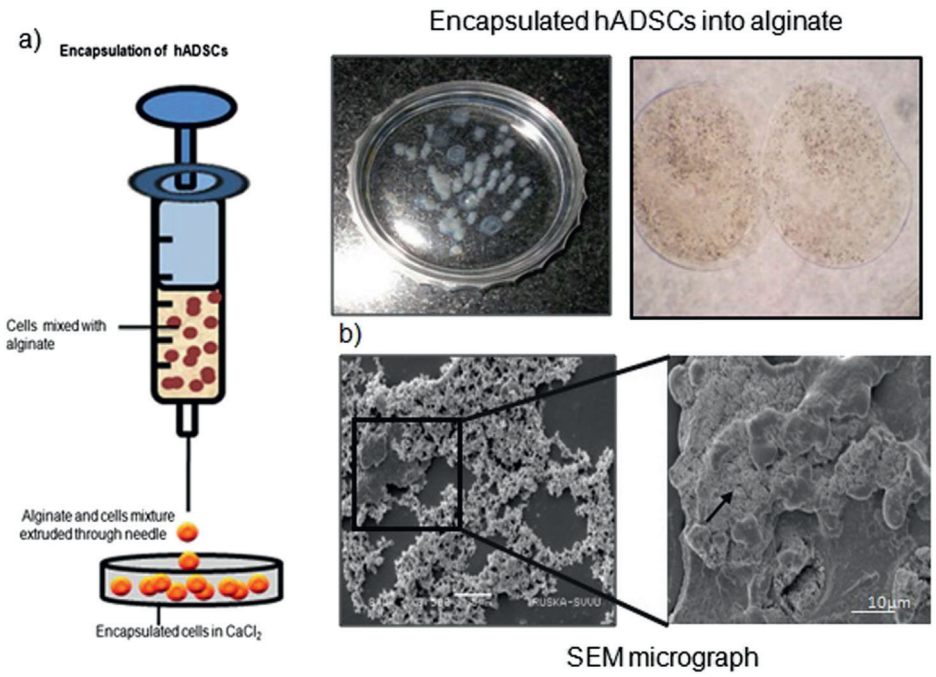

Fig. 2 – Morphological evaluation of alginate encapsulated hADSCs. a) The alginate-hADSCs suspension was added drop wise through a syringe on $CaCl_2$ solution and the plate was incubated for 15 min at 37 °C in a humidified atmosphere of 5% CO_2, The excess of the cross-linking agent was removed resulting in gelled alginate beads with cells. The Phase contrast micrograph of encapsulated hADSCs showing uniform distribution of living cells within alginate bead. Magnification 10×. b) Scanning Electron Microscopy (SEM) micrographs of cross sectioned cells encapsulated in alginate matrix showed that hADSCs were distributed within the matrix and exhibited a round-shaped morphology due to the lack of interactions between cells and alginate as shown by an arrow.

3.2.2. *hADSCs viability and proliferation within the alginate bead*

To examine cell survival during culture, the viability of alginate encapsulated hADSCs was evaluated, using a JC-1 staining. Most of the hADSCs were observed viable as evidenced by the intact mitochondrial membrane potential in fluorescent staining assay (Fig. 3a). The encapsulated hADSCs were retrieved by alginate solubilization to characterize the cell surface markers. Flow cytometric analysis of these recovered cells revealed that more than 80% of the gated cells were positive for CD73, CD90 markers (Fig. 3b). To validate the metabolic/proliferation rate, MTT assay was employed. Alginate beads after MTT staining demonstrated the presence of metabolically active cells upon 7 days of culture. A high number of growing cells converting MTT to formazan crystals were noticed in the cells encapsulated in alginate matrix (Fig. 3c).

3.2.3. *Annexin-V assay*

Cells cultured in alginate beads were analyzed for phosphatidylserine (PS) exposure (annexin-V labeling) and membrane permeabilization (propidium iodide labeling) by flow cytometry, cells were found viable after 21 days of culture. Flow cytometry analysis was performed using gating strategies to obtain a biparametric histograms i.e., FL1 (FITC fluorescence) versus FL2 (PI fluorescence). There was no significant apoptosis in encapsulated cells when compared to the induced cells with 20 μM H_2O_2 indicating it's non-toxic effect (Fig. 4a).

3.3. *Chondrogenic differentiation of hADSCs in the alginate bead system*

In order to demonstrate the differentiation potential of hADSCs to chondrogenic lineage within alginate capsules, cells were cultured in defined chondrogenic medium supplemented with TGF-β. To characterize the kinetics of the changes in gene expression occurring as a consequence of chondrogenic differentiation within alginate matrices, we performed quantitative RT-PCR of a number of well-known chondrogenic marker genes namely, collagen types I and X, COMP, TGF-β, SOX9, CCR1, CCL3 in the cultured cells. qPCR analysis distinctly has shown confirming to the translation signals during the chondrogenesis differentiation pathway. Different chemokines have also been demonstrated to influence bone-cell functions, bone-tissue remodeling and stem-cell engraftment. CCR1, a chemokine receptor showed a significant up-regulation till 21st day. The assays revealed that all four markers had temporally distinct patterns of induction in cells. COMP showed an up-regulation peaking at approximately on day 14. TGF-β mRNA levels increased significantly, followed by a continued gradual increase until 21 days of culture. Collagen type I was down-regulated gradually upon different days of culture. Chemokine motif ligand, CCL3 expression was elevated till 7 day and lowered significantly on 14th day whereas 2 fold increases in expression was observed on 21st day. Collagen type X and SOX9 has shown a progressive increase in their expression heading

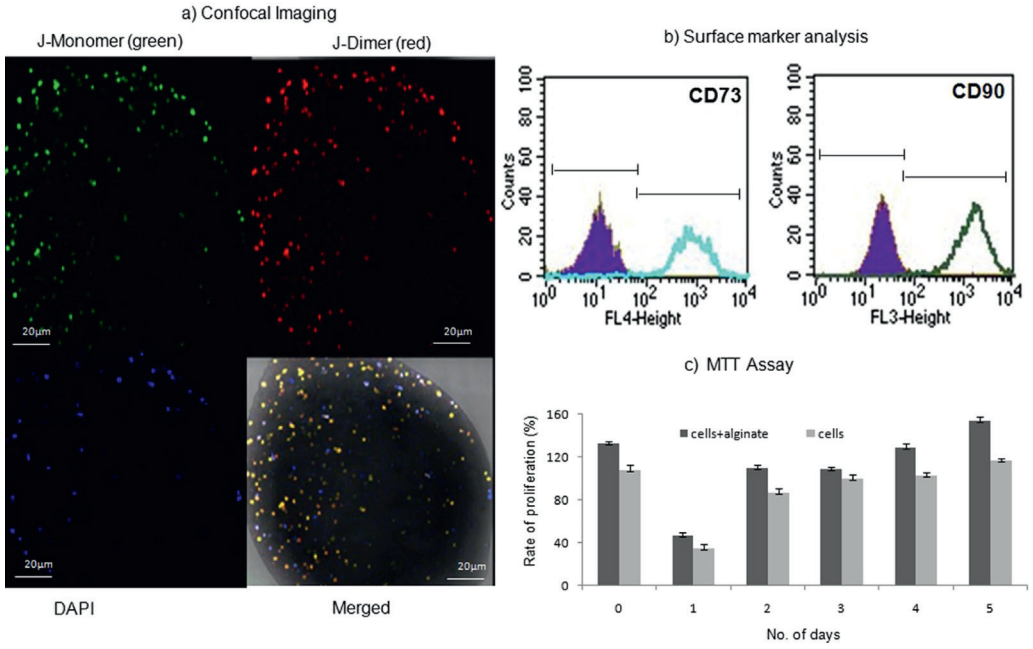

Fig. 3 – Proliferation potential of encapsulated hADSCs within alginate. a) JC-1 dimer formation within the alginate bead, thereby indicating the presence of metabolically active live cells on the hydrogel using CLSM. The monomer emitting at 527 nm (green) after excitation at 490 nm, and J-aggregates emits at 590 nm (orange dots) demonstrating the viability of cells. The DAPI counter staining shows the presence of stem cells within in the alginate matrix. b) Characterization of the cell surface markers for encapsulated hADSCs by flow cytometry: The filled in histograms represent unstained negative control and the retrieved encapsulated cells were positive for expression of CD90 (85%) and CD73 (99%), indicating a stem cell immunophenotype is being maintained within the alginate matrix as well. c) A statistically significant ($p < 0.05$) differences was observed for the cells cultured within the alginate matrix up to 7 days as evident from MTT assay ($n = 3$). High rate of proliferation observed in the encapsulated cells.

towards the chondrogenic lineage of the cells cultured in the alginate bead (Fig. 4b).

4. Discussion

In the present study we cultured articular cartilage derived chondrocytes in the pellet culture system. Chondrocytes require 3-D environment in order to conserve their phenotype. In monolayer culture these cells dedifferentiate and producing matrix components characteristic of fibro-cartilage. This results in variable gene expression pattern.[10] 3D culture systems have frequently been used to mimic *in vivo* conditions.[11,12] As previously reported, the hADSCs could be readily expanded in culture.[13] Based on morphological features and phenotypic analysis by flow-cytometry cell from the third passage was used in the 3-D culture systems. We analyzed the *in vitro* behavior of hADSCs into this matrix. The hADSCs were encapsulated within alginate matrix, and their morphology, proliferation capacity and chondrogenic differentiation were continuously monitored. Additionally, the cell viability remained high throughout the period, a finding consistent with our previous observations with PLL-HA encapsulation.[14] Previous studies have shown that encapsulation of hADSCs leads to an increase in the number of cells in G0–G1 phase and a concomitant decrease in the number of cells in S phase. This suggests that the alginate culture system can synchronize and turn off the proliferation machinery of hADSCs, perhaps by conferring upon them an appropriate 3D state.[15] Consistent with our data, this may enable hADSCs to more readily become committed to a differentiation lineage under the defined conditions rather than continue to propagate. Examination of micrographs confirmed these findings, with spherical cell morphology. MTT assays provided evidence that alginate hydrogels stimulated cell proliferation, as demonstrated by the increased number of hADSCs within alginate, with prolonged incubation period. Cells expanded within alginate typically exhibited a greater viability by Annexin V assay. There was no significant apoptosis after two weeks of culture indicating higher metabolism and non toxicity of alginate on the cultured cells. These results are in keeping with the observation that the alginate matrices provides a structure formed by interconnected pores suitable to accommodate the hADSCs, support their viability, nutrient and protein transport.

Our study demonstrates that the chondrogenic hADSCs assume a rounded shape, simulating chondrocyte morphology. Additionally, the cell viability remained high throughout the experimental period, a finding consistent with previous observations. Real-time PCR analysis revealed significantly lower levels of collagen type I mRNA in chondrocyte culture, which is in agreement with other reports showing that

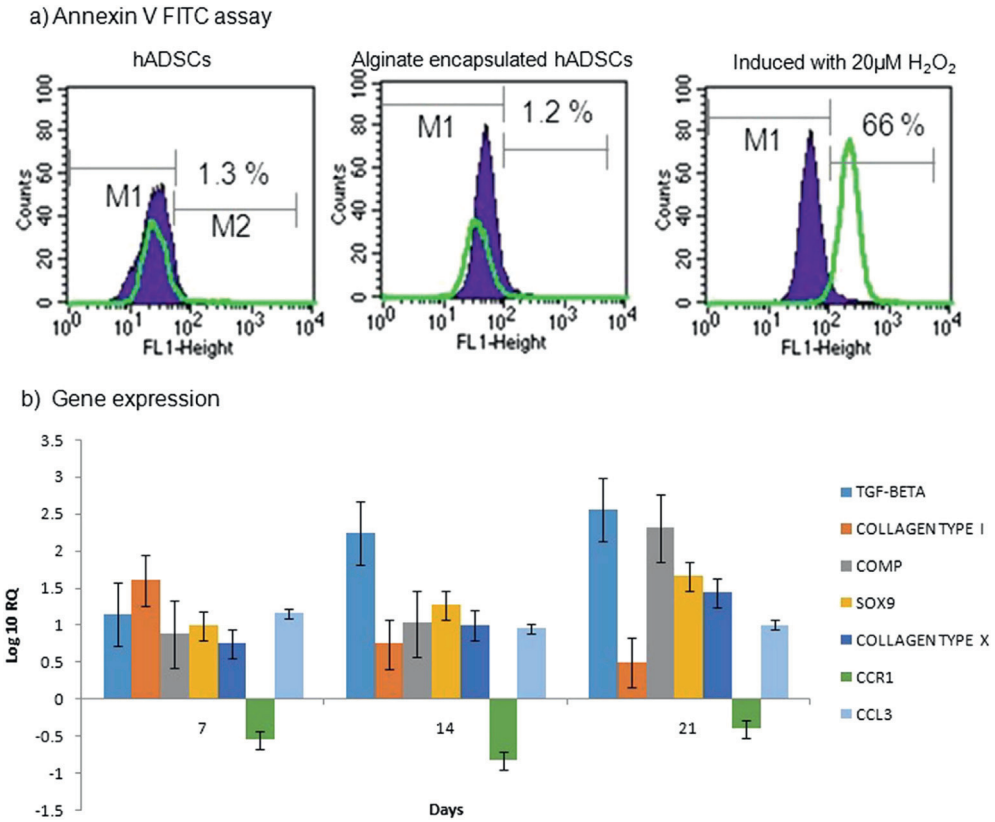

Fig. 4 – Bio-compatibility and differentiation potential of encapsulated cells. a) Annexin-V-FITC of encapsulated cells demonstrated that the cells did not undergo apoptosis when cultured within the alginate matrix. M1: region of fluorescent cells with intact membranes (living cells) and M2: region of nonfluorescent cells with damaged cell membranes (dead cells). In contrast, cells induced with H_2O_2 underwent apoptosis shown as shift in the peak as compared with unstained control (shown as green overlay in the histogram). b) Gene expression study: Chondrogenic differentiation potential of the hADSCs within the alginate matrix was evaluated by gene expression studies using RT-PCR. The graph indicates the expression levels of various chondrogenic genes at different days. The date revealed significantly lower levels of collagen type I mRNA but higher levels of TGF-beta and COMP expressions with $p < 0.05$.

collagen type I is down-regulated during chondrogenic differentiation.[16,17] Further, the observations strengthened the presence of Type X collagen, Sox9 and COMP expression in the cells within beads. Their expression reached peak levels at days 6–12, and these were generally maintained at high expression levels at later stages. Overall, our results are consistent with previous studies in which the temporal expression patterns of collagen types I and X was analyzed during chondrocytic differentiation *in vitro*.[18] As reported in other relevant experimental studies, up-regulation of collagen type X, COMP appeared to be advanced relative to patterns that have been historically reported *in vivo*.[19] The data also presents the differential expression of a number of additional genes like CCR1, CCL3 that may serve as novel stage specific differentiation markers for chondrocytic differentiation.

The chondrocyte culture system represents very low ratios of surface to volume, making them inefficient in terms of scalability. The number of culture units has to be remarkably increased to get significantly increased articular chondrocytes. The process is time consuming and laborious. However, alginate microenvironments provide support to hADSCs to increase in number and remain viable. These matrices do not alter the cell morphology and create conditions that are favorable for chondrogenic differentiation. The alginates do not induce cytotoxicity as evident from mitochondrial staining JC-1 and apoptotic assays. An enhancement of genotypic expression patterns similar to that of chondrogenic lineage was observed in the case of alginate micro-carrier, suggesting its' promising application in soft tissue engineering.

Conflicts of interest

All authors have none to declare.

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Original Article

Lower vitamin D levels in knee arthroplasty candidates as compared with lumbar spondylosis patients

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ABSTRACT

Purpose: Low Vitamin D levels are common in adult Middle-Eastern populations as well as in patients with knee osteoarthritis. The current study was designed in order to assess whether vitamin D levels are different in patients with two types of osteoarthritis.

Methods: A prospective, non-randomized observational study of two groups was performed. Patients with severe knee osteoarthritis requiring knee replacement ($n = 38$) were compared to a control group of osteoarthritic patients suffering from lumbar spondylosis ($n = 24$). KOOS pain subscale scores were used to evaluate knee related pain, and imaging studies were used to define the arthritic process of the knees. Lumbar CT scans were available for most patients.

Results: The study results indicate that vitamin D insufficiency is common in both populations. However vitamin D levels were lower in the knee osteoarthritic patients than in the lumbar spondylosis patients. Low vitamin D levels correlate with worse pain in arthroplasty candidates but not in lumbar spine osteoarthritis patients.

Conclusions: The current study appears to indicate that vitamin D abnormalities are common in both types of osteoarthritis evaluated but are more severe in knee arthroplasty candidates and in this group are related to the pain severity levels.

1. Introduction

Vitamin D insufficiency and deficiency appear to be common in Israel.[1–3] Osteoarthritis has been associated with vitamin D deficiency in middle-eastern populations.[4] While vitamin D deficiency seems to be prevalent in middle-eastern osteoarthritic individuals, the vitamin D levels are not associated with disease severity or knee function.[5] It has been suggested that vitamin D supplementation should be included in the

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treatment algorithm of early knee osteoarthritis, as it might be preferable to long-term anti-inflammatory intake.[6] Vitamin D supplementation appears to be important in improving prognosis of both osteoporosis and osteoarthritis according to some reports.[7] The current cohort evaluation was performed in order to assess whether the evaluation of vitamin D levels is imperative in the evaluation of patients with severe knee osteoarthritis in an Israeli population.

2. Methods

This was a prospective, non-randomized observational study of two groups. Two groups of patients were evaluated: the first group of 38 consecutive patients scheduled for total knee arthroplasty was assessed for levels of knee pain using the KOOS pain subscale. A control group, consisting of 24 patients with lumbar spondylosis and spinal stenosis presenting with thigh and knee pain, was evaluated as well. Vitamin D levels were assessed in both groups as part of the routine clinical assessment.

Inclusion criteria were: 1. Age between 45 and 70 years, 2. Availability of standing knee radiographs, 3. Lack of evidence for sciatica.

Exclusion criteria: 1. Evidence for disc sequestration, 2. Neurological motor deficiency, 3. Known parathyroid hormonal imbalance, 4. Severe renal failure (Creatinine levels $>$ 2 mg/dl).

Vitamin D levels were assessed in a single lab. Blood withdrawal was performed following a12-h overnight fast. Vitamin D levels were classified according to the WHO classification as normal ($>$30 ng/ml), inadequate ($<$29 ng/ml, with levels of 10–29 ng/ml classified as insufficiency) and deficient levels ($<$10 ng/ml).

KOOS questionnaires were routinely administered as part of the clinical assessments of arthroplasty candidate patients. Standing knee radiographs were obtained for all patients. Knee radiography was performed in a single institute according to a routine protocol with a constant (1 m) distance of the knee from the cathode. This allowed assessment in a blinded fashion of the Kelgren Lawrence grade of the radiographs. The radiographic assessment of the control group was performed as part of the routine assessment of thigh and buttock pain.

2.1. *Statistical analysis*

Results are expressed as mean ± standard deviation. Statistical evaluation was performed using the Student's t-test for continuous variables and the Mann–Whitney U-test for non-parametric variables. Correlation was assessed using the Spearman correlation test. Significant difference was defined at the 0.05 level.

3. Results

Demographic data of the groups are presented in Table 1. For all patients in the control group and 19 of 38 patients of the experimental group, computerized tomography of the lumbar spine was performed up to one year prior to evaluation and was available for assessment. Findings are summarized in Table 2. Degenerative discal changes were quite common in both groups.

Table 1 – Demographic data.

	Total knee candidates	Lumbar spondylosis	Statistical significance[a]
Number of subjects	38	24	
Age	67 ± 5 years	61 ± 11	n.s.
Male/female	12/26	11/13	n.s.
Diabetes mellitus	12	11	n.s.
BMI	32 ± 9	33 ± 6	n.s.

[a] Student's t-test for continuous variables. Significant difference is defined at the 5% level.

Radiographic findings are described in Table 2. All patients in the experimental group had K/L grade ≥3 of at least one compartment. K/L grade of the control group averaged 0.5 ± 0.5, however no patient in the control group had K/L grade higher than 2.

Vitamin D levels below the insufficiency cut-off level were common in the osteoarthritis group (18/38 patients) while levels below the deficiency cut-off level were relatively rare (5/38 patients). The mean level of vitamin D in the total knee arthroplasty candidates group was 31 ± 8 ng/ml. In the control group fewer patients had vitamin D insufficiency (8/24 patients) and no patient had vitamin D deficiency. The mean level of vitamin D in the lumbar spondylosis group was 39 ± 5 ng/ml. The intergroup difference between the percentage of individuals with levels at the insufficiency level was statistically significant (Mann–Whitney U-test, $p < 0.05$) as well as at the deficiency level (Mann–Whitney U-test, $p < 0.05$).

Intergroup difference of mean vitamin D levels was found to be significant (Student's t-test, $p < 0.05$). There was no correlation between vitamin D levels and BMI (Pearson correlation coefficient, $r = 0.2$). KOOS pain subscale scores of patients with vitamin D levels lower than the insufficiency cut-off level averaged 33 ± 8 (18/38 patients) compared to the normal vitamin D level group (47 ± 6, 20/38 patients, Student's

Table 2 – Lumbar CT scans and knee radiographs.

	Total knee candidates[a]	Lumbar spondylosis	Statistical significance[b]
Number of subjects with available Scans	19/38	24/24	n.s.
Spinal stenosis	8/19 scans	20/24 scans	$p < 0.05$
No discal disease	2/19	0/24	$p < 0.05$
Bulging disc	19/19	24/24	n.s.
Protruding disc	12/19	14/24	n.s.
Sequestrated disc	0/19	0/24	n.s.
K/L grade 0	0/38	12/24	$p < 0.05$
K/L grade 1	0/38	10/24	$p < 0.05$
K/L grade 2	0/38	2/24	$p < 0.05$
K/L grade 3	29/38	0/24	$p < 0.05$
K/L grade 4	9/38	0/24	$p < 0.05$

[a] Number of positive findings/total available exams.
[b] Mann–Whitney U-test for non-parametric variables. Significant difference is defined at the 5% level.

t-test, $p < 0.01$). KOOS pain subscale score was similar in patients with lumbar spondylosis with normal vitamin D levels (73 ± 9) or below the insufficiency cut-off level (67 ± 11, Student's t-test, n.s.).

4. Discussion

The current study indicates that vitamin D inadequacy is common in adult patients suffering from knee osteoarthritis and was not rare in a control group of patients suffering from lumbar spondylosis without significant gonarthrosis. The prevalence of vitamin D deficiency in the current study is lower than reported in other Middle-Eastern populations.[4,5,8] This difference is possibly due to less common use of long clothes,[3] that limit sun-light related vitamin D synthesis or to genetic differences. The prevalence was higher in patients undergoing knee prosthetic replacement than in a group with an osteoarthritic process limited to the lumbar spine. This might indicate a possible causative role of vitamin D deficiency in the progression of osteoarthritis of the knee, but not of the spine. What might be the mechanism leading to osteoarthritis progression in vitamin D deficient individuals? Vitamin D deficiency is known to increase the risk of cancer, cardiovascular disease and autoimmune disease.[9] Vitamin D ((1,25OH) 2D) regulates cell proliferation, differentiation and apoptosis in many normal and cancer cells, and osteoarthritis is related to abnormal cell differentiation and apoptosis.[10] It is well known that bone structure is abnormal in osteoarthritis, with thickening of the subchondral bone,[11] that exhibits increased turnover, decreased bone mineral content and stiffness, with decreased trabecular numbers. The low vitamin D levels might also lead to subchondral insufficiency fractures and bone edema. It has been shown that increase of bone rigidity can alleviate pain related to bone edema,[12] a procedure called subchondroplasty. The authors hypothesize that the pain experienced by patients that are total knee arthroplasty candidates is partially related to insufficiency fractures of the tibial plateau, due to vitamin D deficiency. Indeed, in the current study an inverse relationship between a validated pain score (KOOS pain subscale) and the vitamin D levels was found. This is similar to a report by Jansen et al who also found a high prevalence of vitamin D deficiency in arthroplasty candidates as well as a worse outcome for patients with low vitamin D levels after arthroplasty.[13] In an Egyptian population it was found that low vitamin D levels are associated with an increased incidence of knee osteoarthritis.[4] The same authors have postulated a protective mechanism of vitamin D against knee osteoarthritis, due to increased nitric oxide synthesis.[8] The possible protective effect of vitamin D on knee osteoarthritis progression has led to a recommendation for vitamin D supplementation in the treatment of early knee osteoarthritis,[6] particularly in patients with low bone mineral density.[14] However, while vitamin D levels are commonly low in knee osteoarthritis patients, there is not a linear correlation between these levels and osteoarthritis grade or functional incapacitation.[5]

In summary, the current study appears to indicate that while vitamin D insufficiency is common in osteoarthritic patients both at the spine and the knee, the levels are lower in the knee osteoarthritic patients (most of whom had degenerative changes of the lumbar spine as well) as compared to patients with spinal degenerative process without significant knee arthritis. This finding might indicate that vitamin D per se is not a cause of the osteoarthritic process, but rather low levels might lead to bone metabolism abnormalities, that worsen the prognosis of the arthritic process in a biomechanically highly loaded skeletal area. This hypothesis is supported by the known lack of correlation between hand osteoarthritis and vitamin D levels.[15] The current study indicates that vitamin D levels are inversely correlated with pain levels in knee osteoarthritis patients. This might be due to the known quadriceps weakness associated with vitamin D deficiency in these patients.[16]

Further research is necessary in order to assess whether vitamin D supplementation will improve post-arthroplasty results in vitamin D deficient individuals.

Conflicts of interest

All authors have none to declare.

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scheduled for total knee replacement associated with poorer preoperative functional state. *Ann R Coll Surg Engl*. 2013;95:569–572.
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Original Article

Comparative study of femoral component sizing in TKA between custom cutting block and intraoperative anterior reference sizing

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ABSTRACT

Background: Correct sizing of prostheses is a considerable factor regarding function and successful rate of total knee arthroplasty (TKA). The purpose of this study is comparing the accuracy of CT-based preoperative sizing in patient-specific guide (PSG) with the conventional femoral component-sizing instrument.

Methods: Fifty-four patients underwent TKA with CT-based PSG. Preoperative sizing was compared to the component size measured intraoperatively by conventional anterior reference femoral-sizing instrument. The actual sizes of implanted components were also recorded to analyze the accuracy of each measurement.

Results: By comparing to CT preoperative planning, the measurement of femoral size with the conventional anterior reference instrument showed 55.6% of equivalent size, 37% of increased size and 7.4% of decreased size with interclass correlation of 0.914 (0.852–0.950). The measurement by two surgeons showed 42.6% and 57.4% equivalent to the actual size (53.7% and 38.9% larger sizes). The accuracy of CT preoperative sizing in femoral component on comparing to the actual size was 96.3%.

Conclusion: Accuracy of femoral component sizing with a conventional instrument remains questionable. It might lead to an oversized component. The accuracy of sizing in PSG is improved due to the advantage of preoperative CT sizing.

1. Introduction

There are several factors affecting the outcome of total knee arthroplasty (TKA) in terms of function and durability. Correct size of the prostheses is one of the important factors that not only causes satisfactory outcome but also reduces the complications of the procedure. Oversized components may cause increments of patellofemoral joint pressure and anterior knee pain.[1,2] On the other hand, undersized components may

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increase postoperative bleeding and permit further osteolysis.[3] In addition, improper size of femoral component can lead to flexion and extension gap imbalance, which is directly associated with the prosthetic instability and range of motion.[4] The oversized femoral component also significantly increases the shear strain up to 126% in peripheral regions of the proximal tibia that may result in early failure of the tibial component.[5]

Femoral component sizing could be performed both preoperatively and intraoperatively by several techniques. Preoperative templating was able to correctly predict the sizes of the femoral and tibial components in 83% and 90% of the cases, respectively.[6] Digital template and measurement from CT or MRI showed more accuracy in sizing.[7–13] According to intraoperative measurement, anterior reference (anterior down) and posterior reference (posterior up) instruments have been served by most manufacturers. The accuracy of femoral sizing with those instruments may be affected by many factors.[14] Sagittal cutting error of the distal femur that resulted in inappropriate component size selection may be caused by saw blade error itself or improper placement of the intramedullary guide rod.[15–17] Sagittal flexion of the distal cut by several degrees associates with the femoral component downsizing.[18] However, the most common error found is the extended resection, which guides the surgeon to select an oversized component and implant it in extended position.[19] The authors also reported that the anteroposterior dimension of the prepared femur was increased by 2 and 3 mm with 3° and 5° extension, respectively. Regarding the prosthetic implantation, the femoral component axis in the sagittal plane was correctly positioned by only 22% of conventional TKA comparing to 80% of computer-assisted navigation TKA.[20]

The computer tomography-based patient-specific guide (CT-based PSG) for TKA has been developed to improve the accuracy and reproducibility of TKA by using the patients' individual CT data to perform the preoperative planning for prosthetic size, alignment and bone resection.[11,12,21] The PSG showed more accuracy and more precision than computer-assisted navigation in predicting femoral component size.[22] In addition, this instrument could help to avoid the risk of improper placement of the intramedullary guide rod, which associates with resection error. Our previous study, comparative study of femoral sizing between intraoperative measurement and CT-based PSG in 2321 Bangkok residents who underwent TKA with the same prosthetic design, showed that CT-based PSG has a tendency to select the smaller size of femoral component comparing to the conventional instrumentation.[23] With preoperative CT sizing, PSG may choose more appropriate size, which is closer to the patient's individual anatomy.

The purpose of this study is comparing the accuracy of CT-based preoperative sizing in PSG with the conventional femoral component-sizing instrument (anterior reference).

2. Methods

This study was approved by our institutional review board. Consent to participate in this research was obtained for all patients. Fifty-four consecutive patients (50 women and 4 men), treated from January 2012 to December 2012, were included in this prospective study. The criteria for inclusion are as follows: patients who underwent primary TKA with CT-based PSG at Phramongkutklao hospital and suited for implantation using custom cutting blocks; no femoral nails or bone plates that extend into the knee, i.e., within 8 cm of joint line; no metal device that could cause CT scatter about the knee and no deformities greater than 15° of fixed varus, valgus or flexion contracture. The patients with previous ipsilateral distal femoral or high tibial osteotomies, ankylosis of the hip joint on the side to be treated, inflammatory arthritis and previous patellectomy were excluded. All fifty-four patients had preoperative three-dimensional (3-D) CT images imported by proprietary software for the planning of component sizes and bone resections. Preoperative femoral sizing by PSG depended on the femoral AP dimension with anterior-reference technique. The planned sizes were chosen to fit the patient's individual anatomy. All participants were operated by our senior surgeon (TC) using custom cutting blocks (TruMatch™ Personalized Solutions; Depuy, Warsaw, Ind.) with the medial parapatellar approach. The posterior stabilized cemented total knee system (PFC sigma; Depuy, Warsaw, Ind.) was implanted and patellar resurfacing was performed in all cases. The default settings for femoral preparation were perpendicular to mechanical axis of the limb and sagittal axis of the femur.[19] The femoral rotation was set parallel to transepicondylar axis. The distal femoral cut was set at 9 mm thickness for the patients who had flexion contracture less than 5° and 10 mm for the patients who had flexion contracture more than 5°. The default settings for tibial preparation were perpendicular to the mechanical axis with 3° posterior slope.

Intraoperatively, after distal femoral bone cut was performed with custom cutting block, the conventional anterior reference-sizing instrument (Sigma HP Fixed reference femoral sizer; Depuy, Warsaw, Ind.) was applied to measure the estimated size of femoral component in order to compare with the preoperative CT sizing using PSG software (Fig. 1). The femoral sizer stylus was placed at the middle and 2 cm above the proximal margin of the anterior femoral condyle, as described by Ng et al.[24] When the measured size was in-between, we recorded the size, which was closer to the marker. The measurements were performed twice by different surgeons (TC and SK) for the analysis of the interclass correlation. Finally, the actual size of femoral component was decided by the gap technique. The chamfer AP cutting block and flexion-spacer were applied to confirm that the flexion gap was equal to the extension gap. Additionally, the thickness of posteromedial femoral cut was measured in order to compare with the CT preoperative planning (Fig. 2). The accuracy of two sizing methods, preoperative CT planning and intraoperative sizing were analyzed by comparing to the actual size of implanted components. The accuracy of tibial component sizing by PSG was also reported. All patients had the same operative setup, wound closure and postoperative care. The statistic analysis was performed using STATA/MP 12 (STATA Corp). The descriptive data were analyzed in mean ± SD and percentage. The measure of agreement was analyzed using Kappa and interclass correlation.

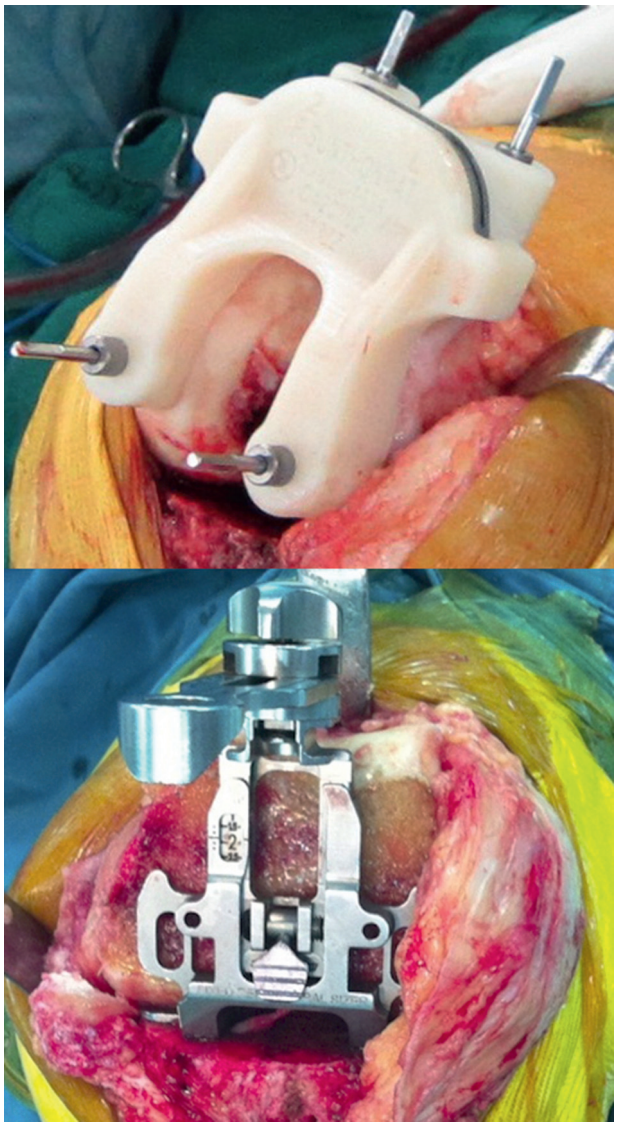

Fig. 1 – The custom cutting block was placed for distal femoral resection (above). Subsequently, the anterior reference femoral-sizing instrument was applied for measurement of component size (below).

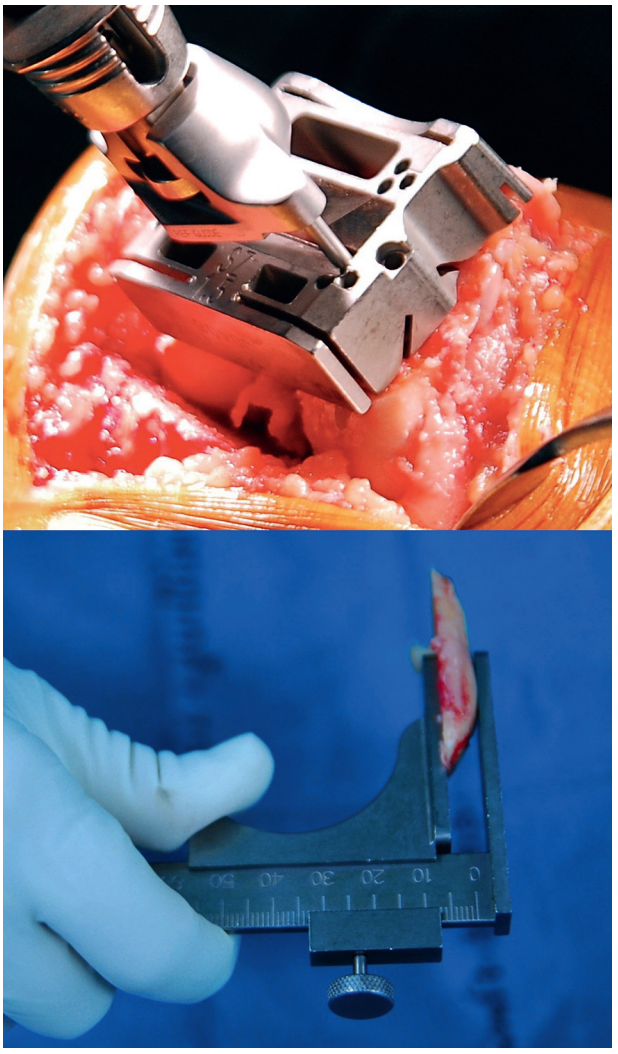

Fig. 2 – The thickness of posteromedial femoral condyle was estimated before the definite AP cut (above). Afterwards, the resected fragment was measured to compare with preoperative planning by CT-based PSI software (below).

3. Results

The mean age of fifty-four patients (50 women and 4 men) was 70.8 years (range: 59–83 years). The mean BMI was $25.0 \pm 2.4\ kg/m^2$ (range: $18.9–30.1\ kg/m^2$). No adverse intraoperative event was observed in all cases. The measure of agreement between intraoperative sizing and CT preoperative sizing was 0.395 ($p < 0.001$). Only 30 patients (55.6%) were recorded the same size using two methods of measurement. There were 20 patients (37%) that the conventional sizing instrument reported larger size. The instrument reported smaller size in 4 patients (7.4%). According to intraoperative measurement using anterior reference instrument, the interclass correlation between two surgeons was 0.914 (0.852–0.950). The sizes measured by surgeon 1 (TC) and surgeon 2 (SK) were the same sizes as implanted components in 42.6% and 57.4%, respectively. The measure of agreement between CT preoperative sizing – actual component size and intraoperative sizing – actual component size was 0.948 and 0.446, respectively ($p < 0.001$). The accuracy of CT preoperative sizing was 96.3% (95%CI: 87–99%). On the other hand, the accuracy of the anterior reference-sizing instrument was only 59.3% (95%CI: 45–72%). The most common actual size of femoral component was size 2 (22 of 54 cases).

The average thickness of posteromedial femoral resection in CT preoperative planning and intraoperative measurement was 10.86 ± 1.51 mm and 10.06 ± 1.88 mm, respectively. The mean difference was 0.8 ± 1.43 mm. All TKA were tested with the spacer block to demonstrate good flexion-extension gap balancing and knee stability. The accuracy of CT preoperative sizing for tibial component was 88.9% (95%CI: 77–95). The most common actual size was size 2 (25 of 54 cases).

4. Discussion

Appropriate prosthetic size in TKA is crucial. The size of tibial component is related to the dimension of cutting surface, which is the consequence of varying thickness of proximal tibial resection. Occasionally, the surgeon intended to reduce the component size in order to shift the tray laterally or medially. On the other hand, the femoral component size is directly associated with the patient's individual anatomy. Proper size selection not only results in flexion-extension gap balancing and knee stability but also decreases the risk of postoperative complications. Several methods have been applied to measure the matched size of femoral component, preoperatively or intraoperatively. The sizing instruments supported by the manufacturers have been widely used and believed to be accurate. Our previous study, CT-based PSG for TKA in Bangkok residents, showed that the surgeon tends to choose a component, which is one size smaller, when operating with PSG rather than conventional TKA in the same population of patients.[23] There is a wide acceptance in terms of the accuracy of preoperative template and sizing by CT or MRI imaging.[9–11,13] According to PSG in TKA, some authors reported that the predicted femoral size was accurate in 89–95% of cases.[12,21,25] Our study showed corresponding results. The accuracy of sizing in femoral and tibial components was 96.3% and 88.9%, respectively.

On the other hand, there has been no study on the accuracy of the conventional sizing instrument. Ng et al. reported excellent intraobserver and interobserver agreements with three anterior referencing tools. Furthermore, the authors informed that placing the femoral sizer stylus at the middle and 2 cm above the proximal margin of the anterior femoral condyle yielded highest precision and accuracy.[24]

Considering high accuracy of component sizing in PSG, which depended on the femoral AP dimension (anterior-reference technique), our study showed that the conventional sizing instrument might lead to the oversized femoral component selection. With high interclass correlation (0.914), 37% of the intraoperative measurements indicated one size larger than the preoperative CT sizing. Although conventional instrument is a simple and commonly used method, its accuracy remains questionable. This study reported only 59.3% accuracy. The surgeon should be aware of misleading size due to the instrument. The oversized component may alter flexion-extension gap balancing and restrict knee flexion. One essential step of prevention is prospective estimation of the thickness of resected posteromedial femoral condyle prior to definite cut. After AP cutting block is placed, inappropriate thickness of expected cut should be recognized. The component size selection must be precise. Our study revealed that the average thickness was 10.06 mm and all patients had stable knee with adequate flexion.

Some authors reported that CT-based PSG might fail to account the thickness of the remaining cartilage (0–5 mm) on posterior femoral condyle, which may lead to undersizing of femoral component.[26] However, a number of studies showed excellent accuracy and almost perfect correlation with intraoperative measurements.[9,11] According to our study, the average difference in thickness between actual posteromedial condyle resection and preoperative planning is 0.8 ± 1.43 mm only. All TKA were tested with the spacer block to demonstrate good flexion-extension gap balancing and knee stability. With the measure of agreement (Kappa = 0.948, $p < 0.001$) and accuracy of 96.3% (95%CI: 87–99%), we conclude that preoperative sizing using CT-based PSG is reliable and useful for component size selection.

5. Conclusion

Comparing to the conventional instrument, PSG selects a more appropriate size of the femoral component due to the advantage of preoperative CT sizing. Further studies may need to prove its cost-effectiveness and correlation with long-term outcomes, such as knee motion, function or patient satisfaction.

Conflicts of interest

All authors have none to declare.

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Case Report

Amiodarone-induced pigmentation of the synovium☆

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ABSTRACT

Intra-articular pigmentation is uncommon. It is seen in pathologic conditions such as Pigmented Villonodular Synovitis and Alkaptonuria. We believe that this is the first report of synovial pigmentation secondary to long-term Amiodarone therapy.

1. Case report

A 72 year old man underwent routine knee arthroscopy for symptoms of mechanical locking. He had a degenerate tear of the medial meniscus that was excised. A diffuse brown-grey pigmentation of the synovium was noted (Fig. 1). Although the entire synovium was discoloured the articular and meniscal cartilages were unaffected. He had no history of knee haemarthroses. He was being treated with a single oral agent for atrial fibrillation daily for seven years and along with the synovial changes he had marked skin pigmentation of his hands, legs (Fig. 2) and face. His symptoms of locking resolved after the arthroscopy.

2. Discussion

It is well recognised that long-term Amiodarone therapy can lead to a dark hyperpigmentation of the skin[1–4] however there are no reports in the literature describing Amiodarone discolouration affecting the synovium. Intra-articular gold therapy and occupational exposure to graphite can also lead to dark pigmentation of intra-articular tissues.[5]

Amiodarone is used in the treatment of cardiac dysrythmias. Abnormal cutaneous and corneal pigmentation secondary to longterm Amiodarone therapy is well recognised.[2–5] However, the underlying mechanism remains unclear. Histopathological examination reveals an accumulation of the

☆ Contribution to this work was shared between the authors.

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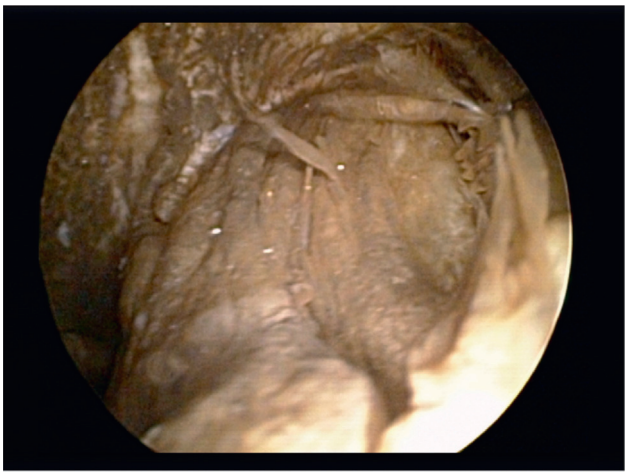

Fig. 1 – Amiodarone-induced pigmentation of knee synovium.

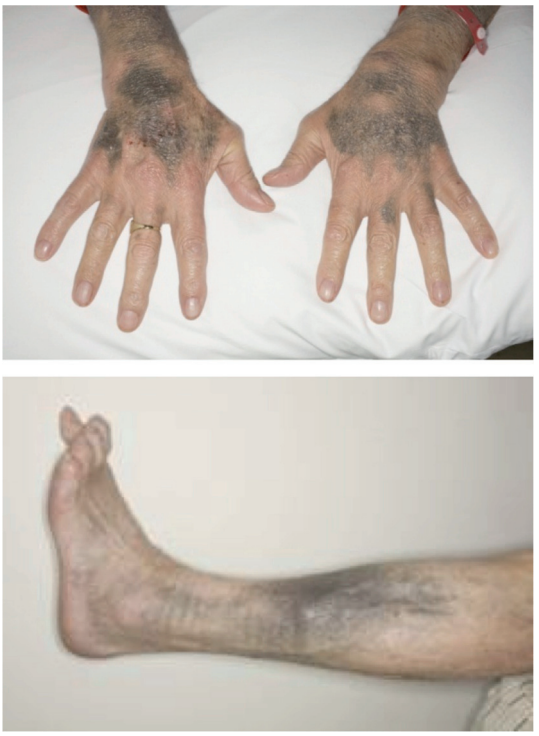

Fig. 2 – Cutaneous pigmentation of the hands and legs.

yellow-brown granules and lipofuscin within dermal macrophages. Sun-exposure can exacerbate the hyperpigmentation with the face, hands and legs commonly affected. To date there have been no reports of Amiodarone-induced hyperpigmentation affecting the synovium. In this case the patient's symptoms completely resolved after arthroscopic partial menisectomy. We therefore believe the observed synovial hyperpigmentation secondary to Amiodarone to be completely benign and the finding to have been purely coincidental.

Conflicts of interest

The authors have none to declare.

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Case Report

Intra-articular pseudorheumatoid nodule with an extension block of knee: A rare case report

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ABSTRACT

Subcutaneous nodules characterized by central fibrinoid necrosis, surrounded by histiocytes and fibroblasts, are suggestive of rheumatoid arthritis or rheumatic fever. These nodules, when observed in otherwise healthy individuals, are termed as pseudorheumatoid nodules. These are seen in the scalp, ulnar aspect of the forearm, palm, orbit and dorsum of the foot, with no manifestations of rheumatic disease. These represent an unusual reaction to trauma. Rheumatoid nodules are the extra-articular manifestations of rheumatoid arthritis and it will mimic pseudorheumatoid nodule clinically and on histopathology. Intra-articular pseudorheumatoid nodules, however, are rare. Our case was a 37-year-old female who presented with difficulty in walking and coming down the stairs. The MR evaluation showed a cyst-like lesion in the intercondylar notch of the knee and arthroscopic evaluation and excision determined it to be a rheumatoid nodule. In the absence of any other significant features of rheumatoid arthritis, it is reckoned to be a case of unusual presentation and location of pseudorheumatoid nodule.

1. Introduction

Pseudorheumatoid nodules are rare occurrence and the characteristic histologic picture shows palisading granuloma with a central focus of necrosis or necrobiosis. These are seen around areas of mechanical irritation like scalp, extensor surface of proximal ulna, heels and the ischial tuberosities.[1–6] When mechanical irritation is suppressed, these nodules may disappear within a few days. It is a well-documented lesion in children and rarely manifests as subcutaneous mass. Nodules are firm, immovable masses when they are small and soft, mobile masses when they are large.[2–4] Rheumatoid nodules, which are similar in appearance, occur in para-articular subcutaneous tissue and are the extra-articular manifestations of rheumatoid arthritis (RA).[2,3,6,7] These occurring in the presence of rheumatoid factor (RF) are features of a severe disease activity.[1–3] In this case, we are reporting a rare case of 37-year-old female who presented with knee pain associated with intra-articular pseudorheumatoid nodule of the knee joint.

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2. Case report

A 37-year-old female presented with gradually progressive right knee pain for 1 year. Pain was continuous, non-radiating and aggravated since 1 month on coming downstairs and walking long distances. No history of trauma, fever, weight loss and any other bone or joint involvement was noted. There was a history suggestive of RA on her paternal side and gouty arthritis on her maternal side. General physical examination was unremarkable and her local examination of right knee showed tenderness over lateral joint line with no local warmth or swelling, with range movements showing 10-degree extension block. McMurray test was positive for the lateral meniscus and stability tests for the ligaments were normal. Routine haematological, biochemical and microbiological tests were unremarkable. MRI of right knee showed a fluid-filled cystic lesion arising from the anterior horn of lateral meniscus extending into the intercondylar notch [Fig. 1a and b]. She was subjected to arthroscopy of the right knee and showed a cyst with a dark reddish brown collection measuring 2 cm × 1 cm over the anterior horn of lateral meniscus [Fig. 2a and b] and the synovial tissue of the knee was normal. The cartilage, both cruciate ligaments and medial meniscus were normal. Arthroscopic excision of cyst [Fig. 2c] and partial lateral meniscectomy were done. The histopathology revealed unremarkable synovial tissue with subepithelial tissue showing palisaded granulomas with central fibrin like material [Fig. 3a and b]. Special stains for mycobacterium and fungus were negative, and hence it was diagnosed as pseudorheumatoid nodule. RF and anti-citrullinated protein (ACP) were negative. The patient was discharged the following day and was begun on rehabilitation and on day 7, sutures were removed. She recovered the extension lag by 3 weeks, was able to return to full activities by 6 weeks and has been on regular follow-up for 1 year with no further signs or symptoms.

3. Discussion

Subcutaneous nodules with central fibrinoid necrosis, surrounded by histiocytes and fibroblasts, are the manifestations of RA or rheumatic fever. However, cases in which nodules with similar morphology seen in healthy individuals are referred to as pseudorheumatoid nodule. These nodules are seen on the scalp, ulnar aspect of the forearm, palm and dorsum of the foot, with no manifestations of rheumatoid disease. It represents an unusual reaction to repeated trauma. This is a rare case of an isolated intra-articular pseudorheumatoid nodule of the knee in a 37-year-old female patient without evidence of RA with very few cases being documented.

Rheumatoid nodules are seen in 20–35% of patients with long standing RA and it is associated with high titres of RF with aggressive articular and extra-articular disease.[1,3,4] The presence of subcutaneous nodules in patients with active inflammatory joint disease in the absence of RF makes the diagnosis of RA improbable, and it is necessary to look for other connective tissue and vasculitic diseases. Another distinct form of rheumatoid nodule, termed as drug-accelerated nodulosis, occurs in patients with long-standing RA and caused or enhanced by various DMARDs and anti-TNF-alpha biological therapies. There is evidence that Rituximab, an anti-CD20 biological agent, can improve it.[2,4] However, in our case, there was no such drug history.

The differential diagnosis for pseudorheumatoid nodule includes rheumatoid nodule, rheumatoid nodulosis and subcutaneous nodules associated with rheumatic fever.[2,3,5] Multiple subcutaneous nodules in the presence of RF and in the absence of any joint complaints suggest a diagnosis of rheumatoid nodulosis. In this case, nodules are mostly numerous, small and concentrated in hands and feet but not limited on the extensor side of fingers and toes. Rheumatoid nodules may be seen without clinical or serological signs of an associated rheumatological or other disease.

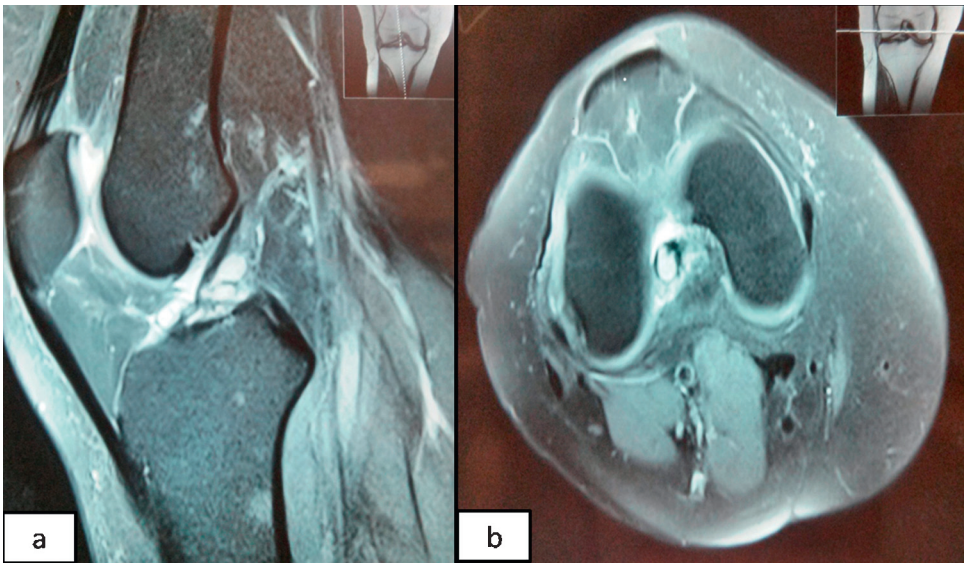

Fig. 1 – (a) MRI showing fluid-filled cyst in anterior horn of the lateral meniscus – right knee [axial view]. (b) MRI with cyst in anterior horn of the lateral meniscus – right knee [sagittal view].

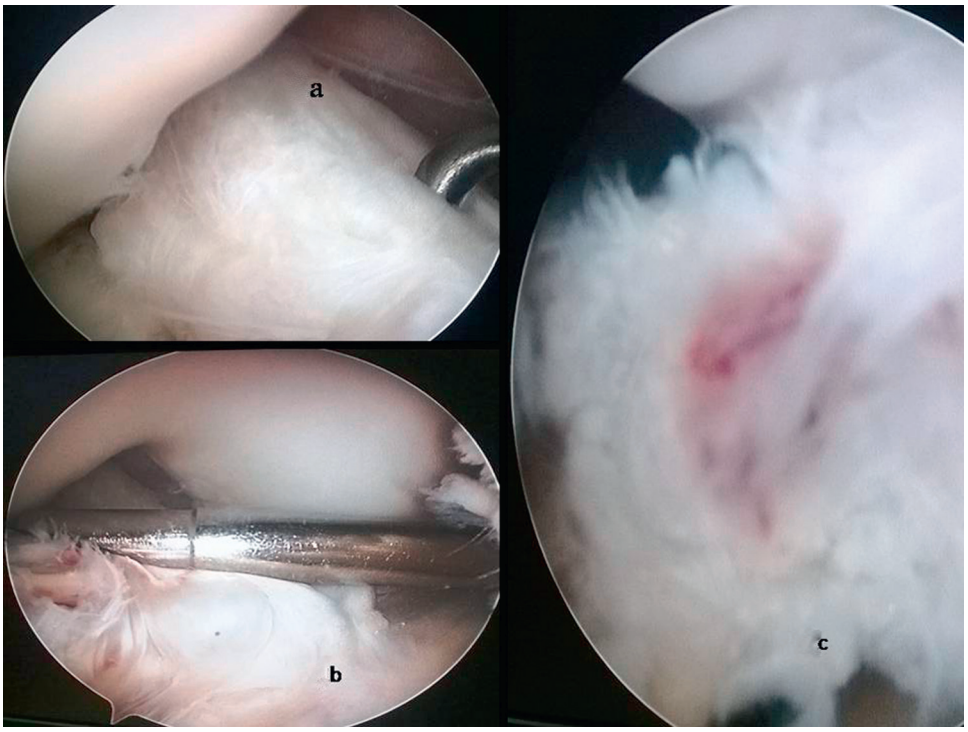

Fig. 2 – (a and b) Arthroscopy showing cyst in the lateral meniscus. (c) Cyst in the lateral meniscus filled with reddish brown material

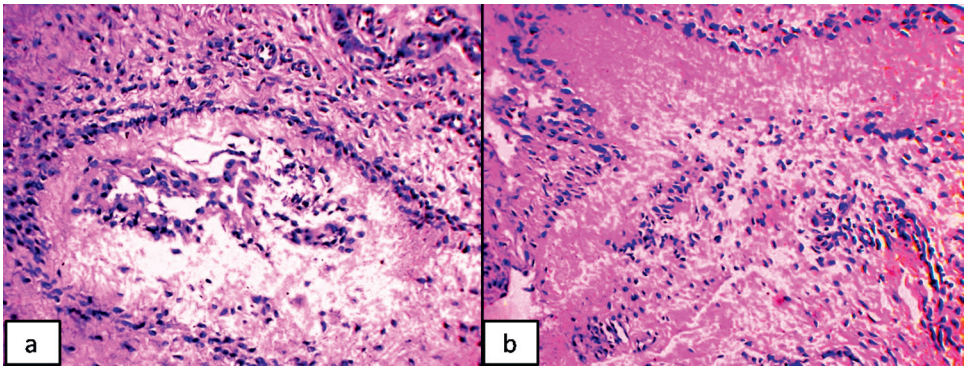

Fig. 3 – Histopathology of the cyst showing (a) palisaded granulomas with central fibrin material [H&E, ×100] and (b) epithelioid cells with central fibrin material [H&E, ×400].

These nodules are non-tender and appear on the pretibial regions, feet and scalp. They increase rapidly in size and resolve spontaneously.[5–7] Other differential diagnoses are granuloma annulare, subcutaneous sarcoidosis, lupus panniculitis, nodular or keloidal scleroderma, histoplasmosis, amyloidosis, ganglion cysts, foreign body granulomas, epidermoid cysts and synovial cysts.[2,5–7] Histology allows the possible causes to be differentiated.[5,6] In our case, histopathology was typical of rheumatoid nodule.

This disease is self-limiting and symptomatically controlled by NSAIDs. Excision is curative in most of the cases. There are few case reports with sequence of (1) the appearance of nodules in an otherwise healthy woman, (2) the subsequent appearance of slightly positive serum RF levels and (3) the final increase in RF titre, the appearance of high-titre ACPA; and the onset of overt RA has been documented.[1,3,5,6] In our case, following excision of the lesion, the patient was symptomatically improved and she is on regular follow-up with serology for 1 year without fresh symptoms.

4. Conclusion

The pseudorheumatoid nodule occurring in the menisci presenting with extension block of the knee without RA manifestations is a rare entity. The case has responded satisfactorily to complete arthroscopic resection of the lesion and has showed no evidence of the recurrence.

Conflicts of interest

All authors have none to declare.

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Resident's corner

Periprosthetic femoral fractures

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Revision hip replacement
Prosthetic loosening

ABSTRACT

This article describes the case of a patient with a periprosthetic femoral fracture. The risk factors and possible reasons for the increasing incidence of this type of fracture in current orthopaedic practice are discussed. A classification is presented and the correct approach to management, with direct application to the case described, is presented.

1. Case summary

An 84-year-old lady tripped and fell onto her left side whilst cleaning at home. She was generally well and had no significant co-morbidities. She had previously had her hips replaced, the right in 1980 with a revision in 2012 and the left in 2001. Before the fall, she was mobilising without walking aids in the house and was using a stick outdoors. She had been having occasional pain in the left thigh aggravated by walking for a year or so prior to the fall. She had no complaints regarding the right hip. She was brought to hospital as she was unable to stand after the fall and had severe pain and an obvious deformity of the left lower limb. This was a closed injury without any neurovascular compromise. Radiographs of the pelvis and left hip were performed (Figs. 1 and 2).

2. Questions (answers overleaf)

1. What is your diagnosis from the radiographs presented?
2. What are the risk factors for periprosthetic femoral fractures?
3. The incidence of periprosthetic hip fractures has been reported to be increasing. What could be the reason(s) for this?
4. What factors influence your decision making with regard to the treatment of periprosthetic femoral fractures?
5. Do you know any of the classification systems that can help in decision making with femoral periprosthetic fractures? How would you classify this fracture?
6. Do you know any clues to help in distinguishing between Vancouver type B1 and type B2/B3 fractures?
7. How would you manage this case?

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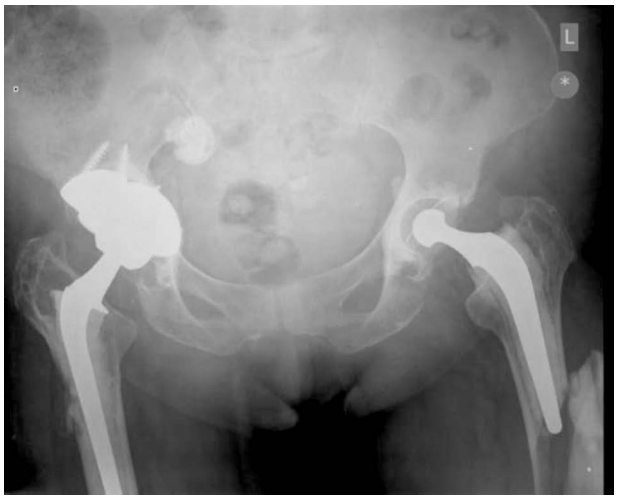

Fig. 1 – Pelvis X-ray (hips) of patient on admission.

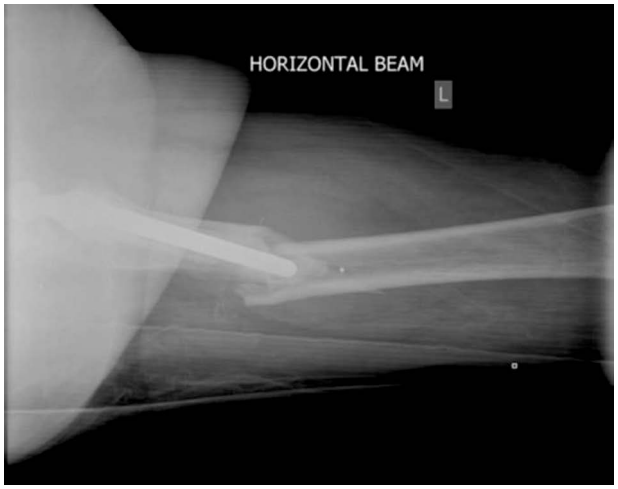

Fig. 2 – Lateral X-ray of left hip (horizontal beam lateral) on admission.

8. What are the reported outcomes and complications related to Vancouver type B2 and B3 fractures?

1. What is your diagnosis from the radiographs presented?

This lady has sustained a displaced left femoral periprosthetic fracture. The fracture is around the tip of the stem, which is a cemented monoblock stem (of Charnley type). There is a cemented polyethylene socket in place.

2. What are the risk factors for periprosthetic femoral fractures?

Risk factors include osteolysis and loosening, trauma, older age, female gender, osteoporosis, previous revision surgery and the type of implant used (uncemented metaphyseal engaging components, particularly flat wedge tapers).[1,2] Osteolysis and loosening are the leading causes, with The Swedish Hip registry showing that 70% of periprosthetic fractures involve loose prostheses. Amongst these, 23% were loose before surgery, and 47% were first identified as being loose at the time of surgery.[3] Biomechanical studies have demonstrated that loose femoral stems have nearly 60% reduction in the torque to failure compared with well-fixed stems.[4]

3. The incidence of periprosthetic hip fractures has been reported to be increasing. What could be the reason(s) for this?

Several reasons for this increase have been proposed. These relate mainly to the ageing population and increased risk of osteoporosis, the increasing number of THAs being done and the increasing prevalence of people with THAs. In addition, the indications for THA are expanding, including younger and more active patients who are exposed to higher energy trauma and therefore are at increased risk of periprosthetic fracture. Increasing numbers of patients are also requiring revision THA, which increases the risk of periprosthetic fractures.[5]

4. What factors influence your decision making with regard to the treatment of periprosthetic femoral fractures?

The treatment of femoral periprosthetic fractures is usually surgical, unless the patient has overwhelming comorbidities which make surgery life-threatening. Deciding which type of surgery (fixation of fracture with a plate or revision surgery) can be challenging. The factors to be taken into consideration are location of the fracture, implant stability (well-fixed/loose) and bone stock available. A common mistake is to plate a fracture around a loose stem, a situation often leading to failure of fixation in the longer-term and the requirement for re-operation. Diagnosis of stem loosening can be challenging in some cases, but there are clinical and imaging clues which can help (see below).

5. Do you know any of the classification systems that can help in decision making with femoral periprosthetic fractures? How would you classify this fracture?

The Vancouver Classification is the most common classification system used for periprosthetic fractures. This classification is based on the use of the 3 factors described above to influence decision making in treating these fractures: fracture location, implant stability (loose or well-fixed) and the integrity of the residual bone stock. There are 3 categories (types) – A, B and C.[6]

Type A fractures occur in peritrochanteric area and are subdivided into Type A(G) which involve the greater trochanter and Type A(L) which involve the lesser trochanter.

Type B fractures occur around the prosthesis stem or at its tip. Type B fractures are further subdivided according to stem stability and bone stock. Type B1 fractures occur around a well-fixed stem with good bone quality. Type B2 fractures occur around a loose femoral component but with supportive bone stock, and type B3 fractures are fractures occurring with a loose femoral component and associated poor bone stock (metaphyseal and diaphyseal bone stocks are deficient and unsupportive, respectively).

In this case, we are dealing with a type B2 periprosthetic fracture, as the implant seems to be loose, but the bone stocks appear supportive.

6. Do you know any clues to help in distinguishing between Vancouver type B1 and type B2/B3 fractures?

It is not uncommon for type B2 fractures to be mistaken for type B1 fractures. Determining whether the stem is well-fixed or loose is critical in appropriate treatment of

periprosthetic fractures. Clinical and radiological clues can help. Preexisting groin or thigh pain (as in this case), pain with non-weight-bearing range of movement, progressive limb shortening and persistent symptoms or signs of infection can point towards septic or aseptic loosening. Comparison with previous serial radiographs, if available, is important, as it can show signs of loosening such as a change in position of the stem, circumferential radiolucent lines (as in this case), evidence of a supportive pedestal in a proximally fixed stem and cement mantle fracture.[7,8] However, ultimately, evidence of loosening may not be revealed until the time of surgery when an intra-operative assessment is conducted.

7. How would you manage this case?

In this case there was evidence of a change of position of the stem on serial radiographs as well as presence of a circumferential lucent line all around the stem at the cement–bone interface. She had also been having thigh pain on mobilisation for some time before the fall. These facts pointed towards the diagnosis of a loose stem. No signs of infection were present. We are therefore dealing with a periprosthetic fracture around a loose stem in the presence of supportive bone stock – a type B2 fracture. The correct treatment involves revision surgery with stabilisation of the fracture (Fig. 3).

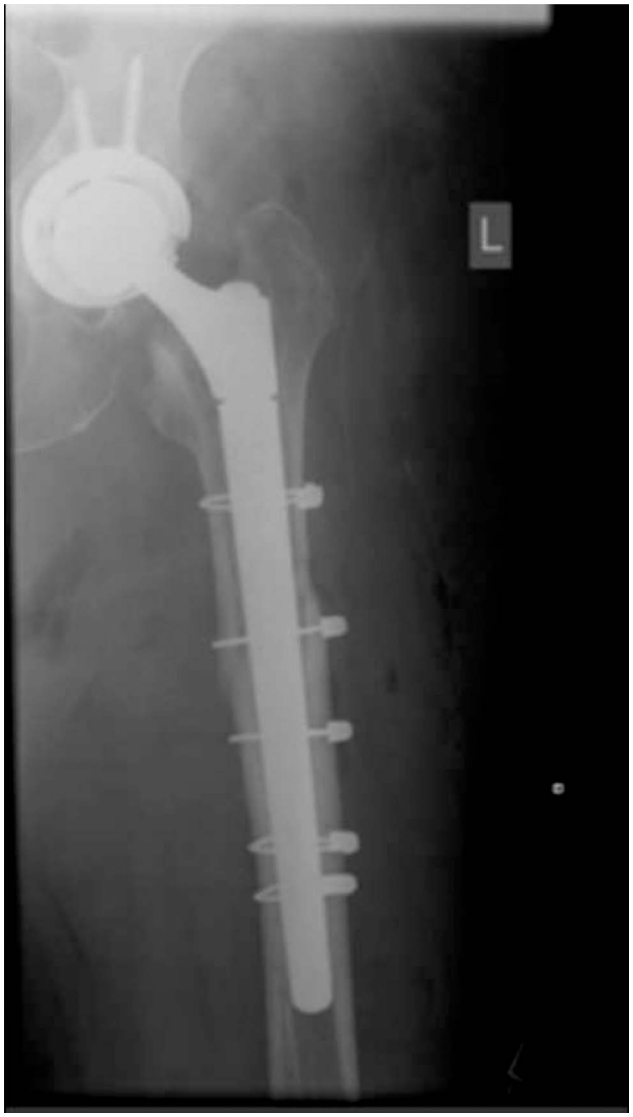

Fig. 3 – Postoperative X-ray of left hip.

A tapered modular fluted uncemented revision stem was used, with prophylactic cabling around the distal part to prevent fracture during revision stem impaction and further proximal cabling to stabilise the fracture. Intra-operative assessment showed a well-fixed cemented cup (22.22 mm internal diameter) but trial with 22.22 mm head revealed that the hip was not stable enough. Therefore, the cup was also revised to optimise component orientation and also allow the use of a larger head to decrease the risk of dislocation after revision surgery.

8. What are the reported outcomes and complications related to Vancouver type B2 and B3 fractures?

Good results with union achieved in more than 95% of cases are reported in the literature.[9–11] However, postoperative complications are not infrequently reported with one study reporting the following complications: bleeding (3.4%), dislocation (3.2%), wound infection (2.7%), deep vein thrombosis (0.8%) and reoperation due to loosening of the revision stem (10.4%).[12]

Mortality is high following periprosthetic hip fractures ranging between 9% and 11% at 1 year after surgery.[3,13]

Conflicts of interest

All authors have none to declare.

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