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Xiu-Xia Song, Director
*World Journal of Orthopedics*
Baishideng Publishing Group Inc
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Telephone: +1-925-2238242
Fax: +1-925-2238243
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REVIEW

# Perioperative blood management strategies for patients undergoing total knee replacement: Where do we stand now?

Tzatzairis Themistoklis, Vogiatzaki Theodosia, Kazakos Konstantinos, Drosos I Georgios

Tzatzairis Themistoklis, Kazakos Konstantinos, Drosos I Georgios, Department of Orthopaedic Surgery, Medical School, Democritus University of Thrace, University General Hospital of Alexandroupolis, 68100 Alexandroupolis, Greece

Vogiatzaki Theodosia, Department of Anaesthesia, Medical School, Democritus University of Thrace, University General Hospital of Alexandroupolis, 68100 Alexandroupolis, Greece

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Correspondence to: Drosos I Georgios, MD, PhD, Associate Professor of Orthopaedics, Department of Orthopaedic Surgery, Medical School, Democritus University of Thrace, University General Hospital of Alexandroupolis, St. Niarhos Street 1, Dragana, 68100 Alexandroupolis, Greece. drosos@otenet.gr
Telephone: +30-255-1352209

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## Abstract

Total knee replacement (TKR) is one of the most common surgeries over the last decade. Patients undergoing TKR are at high risk for postoperative anemia and furthermore for allogeneic blood transfusions (ABT). Complications associated with ABT including chills, rigor, fever, dyspnea, light-headedness should be early recognized in order to lead to a better prognosis. Therefore, perioperative blood management program should be adopted with main aim to reduce the risk of blood transfusion while maximizing hemoglobin simultaneously. Many blood conservation strategies have been attempted including preoperative autologous blood donation, acute normovolemic haemodilution, autologous blood transfusion, intraoperative cell saver, drain clamping, pneumatic tourniquet application, and the use of tranexamic acid. For practical and clinical reasons we will try to classify these strategies in three main stages/pillars: Pre-operative optimization, intra-operative and post-operative protocols. The aim of this work is review the strategies currently in use and reports our experience regarding the perioperative blood management strategies in TKR.

**Key words:** Total knee replacement; Transfusion; Total knee arthroplasty; Blood loss; Autologous blood donation; Blood management; Perioperative; Tranexamic acid; Tourniquet; Haemodilution; Anaemia; Transfusion protocol



**Core tip:** Total knee replacement is one of the most common elective surgeries in orthopaedics. Blood loss during surgery is putting the patient at risk for a blood transfusion. A number of reviews and meta-analyses have tried to analyze the best blood conservation strategy. Our objective is to review any blood saving method/strategy into the preoperative, intraoperative and postoperative period and analyze their possible

combination. A zero allogenic blood transfusion rate with safe and cost-effective methods should be the aim and an achievable goal.

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## INTRODUCTION

Total knee arthroplasty (TKA) is currently the most cost-effective and efficacious way for treating patients with end-stage knee osteoarthritis who suffer from severe pain, activity limitation and for whom conservative treatment is unsuccessful. Based on National registries, TKA is considered to be the most common major orthopaedic surgery performed worldwide[1]. It's really important to mention that the number of TKA surgeries performed each year increases and is projected to have a five to six-fold increase by 2030[2].

Blood loss during TKA is putting the patient at risk for a blood transfusion. It's reported that patients undergoing TKA may result in blood loss between 1000 mL and 1500 mL which necessitates subsequent allogeneic blood transfusion (ABT) in 10%-38% of them[3-7]. Thus, it becomes prudent to minimize the ABTs while trying to maintain hemoglobin (Hb) in a safe and efficient level to help patient's rehabilitation. Many strategies have been used in order to minimize blood loss including preoperative autologous blood donation (PAD), acute normovolemic haemodilution (ANH), autologous blood transfusion (ABT), intraoperative cell saver, drain clamping, pneumatic tourniquet application, and the use of tranexamic acid (TXA)[8-10].

Although many strategies and algorithms have been proposed for ABTs reduction there is not a consensus about the most efficient/successful combination[8,11]. This article will try to review the latest strategies, analyze the results and our experience regarding the use of TXA. Summarizing, these strategies can be divided in three stages: Pre-operative, intra-operative and post-operative (Table 1).

## PRE-OPERATIVE

The main aim of blood management is to eliminate ABTs and prevent anaemia simultaneously. In order to avoid anaemia's clinical symptoms we need to preserve post-operative Hb values as higher as possible. Therefore, we highlight the significant effect of high pre-operative Hb on the requirement of ABT in TKA.

### *Detection of anaemia and iron deficiency treatment*

Anaemia has been defined by the World Health Organization as an Hb concentration < 130 g/L for men, < 120 g/L for non-pregnant women[12]. Regarding patients undergoing TKA it's been reported that 8% to 21% of them were anaemic before the procedure[13,14].

Pre-operative assessment of patients should be performed at least 30 d (some reviews suggest at least 60 d) before the procedure in order to have enough time to investigate the cause and/or plan the required treatment[15-17]. In case of low Hb additional lab tests should be carried out including at least full blood count, serum ferritin, transferrin saturation index (TSAT), vitamin B12, folic acid, a marker of inflammation (*e.g.*, serum CRP) and a marker of renal function (*e.g.*, serum Creatinine) (Figure 1)[18]. Any other low Hb cause apart from iron deficiency anaemia (IDA) should be carefully investigated.

IDA is the main cause of low Hb. It's been reported that IDA counts up to 50% of the patients with Hb lower than 12 g/dL[19,20]. It's been suggested that patients undergoing TKA should meet WHO's criteria regarding the minimum pre-operative Hb. Otherwise, surgery should be postponed[15]. Furthermore, a recent, retrospective study demonstrated that preoperative anaemia (haematocrit < 25%) and ABTs are the two "evils" that increased the post-operative morbidity and mortality[21].

Adult patients with IDA who are candidates for TKA should be treated before the surgery. Either intravenous or oral iron therapy has been found to be effective in the treatment of pre-operative anaemia, meanwhile reducing the rehabilitation's duration[14,22]. Moreover, the superiority of intravenous iron therapy with respect to oral iron therapy has been reported[23]. A 3-wk duration, administration of intravenous iron, just before surgery seems to be the most efficient and safe treatment[24]. Additionally, oral iron may not be efficacious in patients with malabsorption such as coeliac disease[25].

### *Erythropoietin*

Erythropoietin (EPO) is a great tool in correcting anaemia as it is an essential hormone for red blood cell production. Without it, definitive erythropoiesis does not take place. Under hypoxic conditions, the kidney will produce and secrete erythropoietin to increase the production of red blood cells[26,27]. Its role in blood loss management has been thoroughly studied, showing a 60% reduction of ABTs in patients who received EPO compared to control group[28-30]. Three or four weekly subcutaneous injections (600 IU/kg) seems to be the most frequently used protocol with the best results[31-35]. Weber *et al*[36] reports a mean rise in pre-operative Hb of 1.9 g/dL in patients that received EPO. A big disadvantage of EPO is the really big cost which is being estimated to 1500 dollars per patient (4 weekly injections)[37]. For this reason, EPO use is being suggested when the patient has anemia and meets the criteria for blood transfusion, but declines a blood transfusion because of religious beliefs (*e.g.*, Jehovah's Witness), or the appropriate blood type is not available because of the patient's red cell antibodies[38]. Adverse events have been reported in 5% of patients that have been treated with EPO. These complications include deep venous thrombosis (DVT),

**Table 1 Three pillars of patient's blood management and saving**

| Pre-operative | Intra-operative | Post-operative |
|---|---|---|
| Detection of anaemia and iron deficiency treatment | MIS and navigated MIS TKA | Compression and cryotherapy |
| Erythropoietin | Tourniquet | Limb position |
| Perioperative management of antiplatelet agents | Hypotensive epidural anesthesia | Post-operative cell saving |
| Transfusion protocol agreement | Acute normovolemic haemodilution | Drainage clamping |
| Pre-operative autologous blood donation | Antifibrinolytic agents | |
| | Topical fibrin sealants | |
| | Intra-operative cell salvage | |
| | Peri/intra-articular (bupivacaine and epinephrine) injections | |
| | Bipolar *vs* monopolar sealant | |
| | Platelet-rich plasma | |
| | Bone wax | |
| | Sealing femoral tunnel | |

MIS: Minimally invasive; TKA: Total knee arthroplasty.

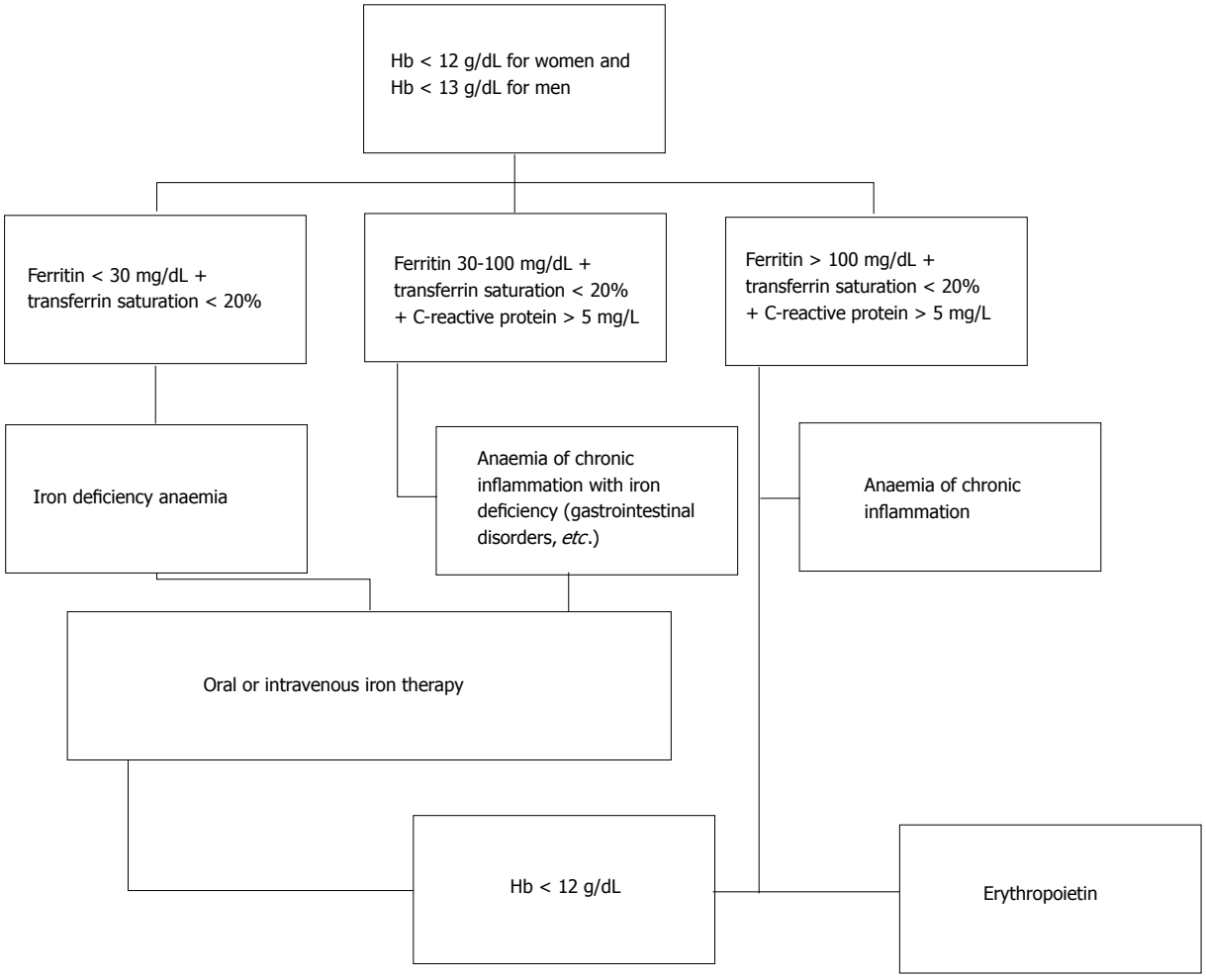


**Figure 1 Algorithm proposed for low hemoglobin investigation.** Hb: Hemoglobin.

pulmonary embolism (PE), fever, hypokalemia, urinary tract infection, nausea, hypoxia, and vomiting[39-41]. Briefly, EPO can reduce the need for ABTs in high-risk patients undergoing TKA; however, it was not found to be cost-effective compared to other blood conservation methods[42].

### *Perioperative management of antiplatelet agents*

Cardiovascular disease is common in patients planning to undergo to TKA. Antiplatelet agents, used as monotherapy or in combination, have a key role in preventing cardiac and vascular events[43]. Many of these patients have already undergone previous percutaneous coronary intervention (PCI) with stent implantation. American Heart Association's/American College of Cardiology Foundation's guidelines suggest dual antiplatelet therapy with

aspirin and an adenosine diphosphate (ADP) inhibitor (*e.g.*, clopidogrel) for at least 1 mo after bare-metal stent implantation and for 1 year after drug-eluting stent implantation in order to avoid late thrombosis[44]. There is a distinct proof that elective surgeries like TKA should be avoided (if it's possible) within the first year of stent implantation, as it's been reported a 5- to 10-fold increase in acute stent thrombosis[45]. Of course, after the first year most of these patients continue with single antiplatelet therapy[46].

Our main concern about antiplatelet agents is the perioperative bleeding that can occur during the procedure. Recent review reports bleeding increase up to 50% in patients with dual antiplatelet therapy. Regarding the monotherapy, the same review found that blood loss increased 2.5%-20%[47]. From an anaesthesiologist's perspective, the incidence of spinal haematomas associated with epidural or spinal anaesthesia is the main reason for antiplatelet's discontinuation. Regarding the literature, 61 cases of spinal haematomas associated with epidural or spinal anaesthesia are reported between 1906 and 1994[48].

The two most prescribed antiplatelet drugs (with different mechanism of action) are aspirin and clopidogrel. Regarding the aspirin, guidelines suggest its discontinuation 7-10 d before surgery without major consequences. Post-operatively, aspirin should be resumed preferably within 24 h (when bleeding risk is low). Conversely, patients who are in high cardiovascular risk should not stop aspirin therapy in the perioperative period[49]. Clopidogrel acts by inhibiting the ADP receptor on platelet cell membranes. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions (ACCF/AHA/SCAI) suggest discontinuation of clopidogrel 5 d prior to surgery and if additional DVT prophylaxis is needed a low molecular weight heparin (LMWH) should be used.

The key point is that both the continuation and the discontinuation of antiplatelet therapy can be associated with major risks. Therefore, (especially in dual antiplatelet therapy) the management of these medications in the perioperative setting should be discussed between the cardiologist, orthopaedic surgeon, and anaesthesiologist. This "team" should weigh the patient's risk of thrombosis with the risk of surgical bleeding to determine the right choice for him and if/when dual antiplatelet therapy can safely be discontinued.

### *Transfusion protocol agreement*

ABTs are responsible for many complications like human immunodeficiency virus (HIV)'s, hepatitis'B and C transmission (despite donor screening), whereas allergic reactions may cause minor reactions (*e.g.*, fever) to fatal ABO blood group incompatibility[50,51]. Therefore, it's really crucial to analyse and update the transfusion protocols that are being used in hospitals and especially in orthopaedic departments. We'd like to notice that although transfusion is a post-operative process, we include it in pre-operative measures as an agreement/protocol about the "transfusion trigger" should be achieved before the surgery.

The main factor that should be investigated is the so called "transfusion trigger". It's the Hb threshold at which the physician decides to transfuse the patient. Many protocols/rules like 10/30 have been used in the past; but it's not the case any longer[52]. Low transfusion trigger point seems to be effective in reducing ABTs[53,54]. Reviews suggest transfusion triggers (Hb levels) between 8 g/dL and 9 g/dL (excluding severe cardiovascular disease, renal failure, and hematologic disorders)[55,56]. Unquestionably, symptomatic anaemia resulting in tachycardia, change in mental status, cardiac ischemia or shortness of breath should always been treated followed by ABT. Based on literature, in our department we use a mini transfusion algorithm/protocol (Figure 2). This protocol has already documented significant reductions in the rates of red cell transfusion and worthwhile blood conservation. Noticeably, this strategy seems to be really cost-effective.

Briefly, a blood management protocol with restrictive typing and screening, cross-matching, and transfusion should be adopted by national health systems in order to reduce the wastage of unused blood units and the rate of ABTs without increasing patients' morbidity or mortality.

### *Pre-operative autologous donation*

In 1980, the recognition that ABTs were associated with potential risks like viral transmission (*e.g.*, HIV) and bacterial infection prompted the development of PAD programs[57,58]. In 1992, PAD accounted for nearly 8.5% of all blood collected in United States. Nevertheless, pre-donation decreased to 3.5% of the blood units collected by 1997[59].

PAD's main target is providing a resource of safe blood for patients that are candidates for scheduled surgery (like TKA). Meanwhile, this process increases the patient's total red blood cell (RBC) mass due to the PAD-induced stimulation of erythropoiesis before elective surgery.

Many studies and meta-analyses concluded that PAD strategy managed to reduce the use of ABTs by 40%-52%, increase the overall transfusions (allogeneic and autologous) by 30%. On the contrary, it's really important to mention that patients' Hb concentration decreased by more than 1 g/dL from before starting PAD to immediately prior to surgery[60-62]. PAD's poorly cost-effectiveness (about 300$ per unit), combined with new blood saving strategies and new drugs has led to a decline in its use[63,64]. In our days, the use of PAD has therefore lost its acceptance and is no longer being used in TKA patients.

## INTRA-OPERATIVE

Plentiful methods, strategies, technologies and drugs have contributed in blood loss minimization and ABTs' reduction. Some of them have gained ground during the last decades and others didn't manage to prove their effectiveness. Intra-operative blood saving seems to play the most important role between the strategies and techniques indicated in the three pillars of patient

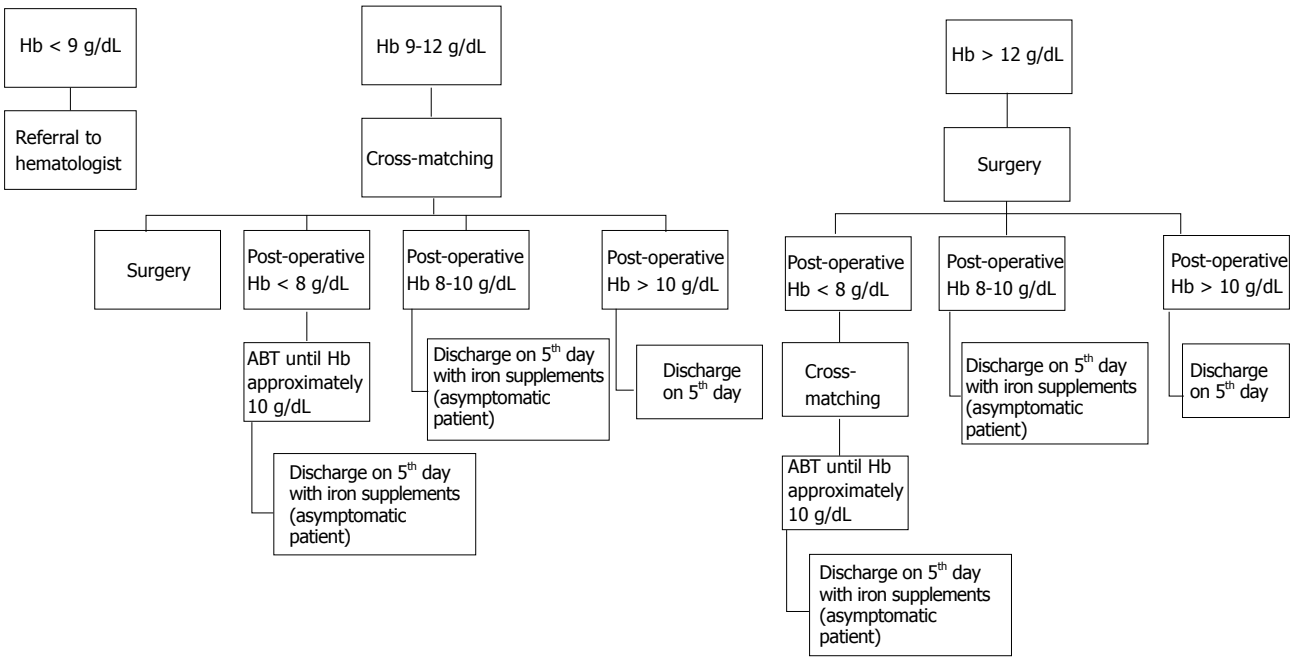


**Figure 2 Algorithm used in our department regarding the allogeneic blood transfusion strategy.** Hb: Hemoglobin.

blood management.

### *Minimal invasive and/or navigated minimal invasive TKA*

Many of the patients that have decided to have a TKA might consider a minimally invasive procedure with or without navigation. This type of surgery uses smaller incisions and less cutting of the tissue surrounding the knee. The advantage of such a surgery except for the smaller incision is the promising recovery, a shorter hospital stay and less blood loss.

A meta-analysis revealed the superiority of minimal invasive (MIS) to the standard parapatellar approach in visual analog score (VAS) and range of motion (ROM) in the short term (postoperative 2 wk)[65]. No differences were noticed in straight leg raise, hospital stay, post-operative complications and blood loss. Comparable results pointed out between MIS TKA and MIS navigated TKA[66]. In conclusion, MIS TKA has proved the ability to couple the benefits of less invasive surgical approach without compromising the long-term established success of conventional TKA, especially in blood loss.

### *Tourniquet*

A tourniquet is a compressing device, used to control venous and arterial circulation to an extremity (lower extremity in TKA) for a period of time. Although the majority of orthopaedic surgeons still use it widely, its role is controversial. Tourniquet's use was believed to be effective in decreasing intraoperative blood loss. However, reactive blood flow after tourniquet's release seems to balance out the total blood loss compared to the non-tourniquet TKA method[67]. A meta-analysis of thirteen randomized controlled trials (RCTs) demonstrated that non tourniquet use in TKA has better clinical outcomes, less complications and better ROM in early postoperative period. The most important finding of this meta-analysis is that the true blood loss in TKA was not reduced using a tourniquet[68]. Therefore, it can be explicitly deduced that TKA with a tourniquet reduces the intra-operative blood loss but postoperatively increases the hidden blood loss[68]. To sum up, tourniquet's effectiveness and safety in TKA should be carefully considered when surgeon decides to use it.

### *Hypotensive epidural anesthesia*

In April of 1989 Sharrock *et al*[69] published the first description of hypotensive epidural anesthesia. To date, HEA is not a popular method in elective orthopaedic surgery like TKA. HEA was developed to combine the advantages of epidural anesthesia (airway problem, reduced rate of DVT) with the benefits of induced hypotension.

Its mechanism of action is well-described. A sympathetic blockade (including cardiac sympathetic fibers), using local anesthetic at an upper lumber interspace (T12-L1/L1-L2), causes a reduction in arterial pressure. Mean arterial pressure (MAP) is maintained at 50-55 mmHg with end result the reduction of blood loss. It's really important to mention that concurrently, a low dose of epinephrine is being infused (till MAP reaches 75-80 mmHg) achieving circulation's stabilisation[70,71].

Although HEA's use seems to be really advantageous, without complications, it's not a "first line" method regarding blood loss in TKA. A few studies have proved its safety and efficacy in total hip arthroplasty (THA), but further studies are needed to assess its use in TKA[70,72,73].

### *Acute normovolemic haemodilution*

Acute normovolemic haemodilution (ANH) is a technique in which whole blood is removed from a patient, while

circulating volume is maintained with crystalloid fluid. It is performed shortly before or shortly after induction of anaesthesia. A close monitoring of the patient is necessary and when Hb level drops down to 8-9 g/dL ANH is being halted[74]. Postoperatively, sufficient blood is administered to maintain patient's Hb over 8-9 g/dL.

Many studies suggest ANH's use in elective orthopaedic surgeries as it contributes in ABT's reduction[75-77]. In contrast, there are studies that noted no significant difference between control and ANH group[78-81]. Undoubtedly, more studies would be needed to prove/rebut its efficacy in blood loss management.

### *Antifibrinolytic agents*

The most famous blood saving management of the last decade is the use of antifibrinolytic agents. TXA, ε-aminocaproic acid (EACA) and aprotinin are the most commonly used antifibrinolytic agents[82-84].

TXA and EACA are lysine analog antifibrinolytics that reversibly bind both plasmin and plasminogen. TXA is a current trend in TKA and THA. Many studies have proved its efficacy without an increased risk of complications (DVT, PE, and wound infection). Latest studies and meta-analyses focused on the best route of administration combined with multiple dose regimens[85-88]. Regarding the route of administration and plasma concentration, maximum plasma concentration of TXA is reached within 5-15 min after intravenous (IV) injection, 30 min after intramuscular (IM) injection and 2 h after oral tablets[89]. IV TXA seems to be more effective compared to topical administration. However, the topical administration seems to outcompete IV in patients with high risk of thromboembolic events[90]. On the contrary, a recent meta-analysis showed no statistically significant difference in total blood loss, drain output, transfusion requirements and thromboembolic complications between topical TXA and IV-TXA in TKA[91].

The most efficacious regimen is still under debate, but multiple IV boluses regimens (pre/intra/post-operatively) prove to have a better result compared to a single IV dose[92]. Nevertheless, two RCTs concluded that intra-articular regimen of TXA is as effective as three doses IV regimen in preventing blood loss without any difference in thromboembolic complications[93,94]. In addition to all these studies some authors have noticed that the combination of IV and intra-articular TXA is more effective than either regimen used alone[95,96]. All these conflicting results suggest that more well-conducted randomised controlled trials are needed to produce strong evidences about it. In our orthopaedic department two RCTs have already been completed, showing the high effectiveness of TXA's both in TKA with tourniquet and TKA without tourniquet and one more is currently running[87,88]. The aim of the current study is to determine whether or not repeated dosing of IV TXA reduces (additionally) the post-operative reduction in hemoglobin, hematocrit, number of transfusions, and post-operative blood loss following primary TKA.

Studies comparing EACA to TXA on the reduction of perioperative bleeding and on the number of transfusions needed showed no significant differences between the two antifibrinolytic agents. The only advantage of TXA compared to EACA is its lower price[97].

Aprotinin, a nonlysine antifibrinolytic agent, was more effective at decreasing blood loss but was associated with increased cardiovascular complications (increased risk for myocardial infarction) and was therefore removed from the market in 2008[98-100].

### *Topical fibrin sealants*

Fibrin sealant is comprised mostly of fibrinogen and human thrombin which form a stable fibrin clot and can mimic the last phase of physiological blood coagulation cascade. Many studies have proved their efficacy without increasing the risk of DVT, PE, hematoma, wound infection or other complications for patients undergoing TKA[101,102]. However, their main disadvantage is the high cost compared to other blood management methods (like TXA)[103,104]. Moreover, newer studies appear to confute the initial hypothesis of fibrin sealants' haemostatic role. All these studies report no effect of fibrin sealant in terms of blood or transfusion savings after TKA[105-107].

### *Intra-operative cell salvage*

Intraoperative blood salvage, also known as cell salvage, is a medical procedure involving recovering blood lost during surgery and re-infusing it into the patient[108]. Many devices and processes have been developed to assist in salvaging the patient's own whole blood since the 1970s, when it was popularized in major thoracic or abdominal procedures[109]. Unwashed blood revealed poor results as it may contain hemolyzed RBC, clotting factors and cytokines[110,111]. Therefore, cell separation and washing showed better results with an autologous red cell concentrate with normal function and no complications[112].

Literature's evidence strength is really limited regarding the safety and effectiveness of this method. Current studies have low level of evidence which means that they are incompetent to compare the post-operative infection rates with and without cell salvage use. A general outcome of these studies is that intra-operative cell salvage reduce ABTs but more studies needed to clarify the importance and the risk of this method[113-115].

### *Peri/intra-articular (bupivacaine and epinephrine) injections*

Epinephrine is the agent of choice for topical haemostatic vasoconstriction[116]. Anderson *et al*[117] injected bupivacaine and epinephrine just before wound closure (one-third pericapsular, two-thirds peri-incisional). They managed to prove a 32% less drain output in study group. However, no statistically significant differences were noticed in the transfusion rate between the two groups. Moreover, a new study by Yang *et al*[118] reports controversial results, as the initial hypothesis regarding the haemostatic role of intra-articular epinephrine after

TKA is not being supported by the various bleeding parameters.

### *Bipolar vs monopolar sealant*

Monopolar electrocautery is a device that delivers electrical current to patient's tissue through a pen-like stylus. Intra-operative temperatures can be higher than 300 ℃, resulting in smoke and eschar formation[119]. Opposed to monopolar electrocautery, bipolar sealing delivers radiofrequency energy combined with continuous-flow saline in order to prevent temperatures higher than 100 ℃. Although bipolar sealant is being used for decades in oncology, thoracic, spine and brain surgery it seems to be a novel approach in TKA[120-123]. However, latest studies (including RCTs) and the results of the comparison between bipolar and monopolar sealers used in TKA report no significant difference in postoperative drain output, postoperative Hb level and transfusion requirement[119,124,125].

### *Platelet-rich plasma*

Platelet-rich plasma (PRP) has been used in surgeries to promote cell regeneration since 1987[126]. Today, PRP injections is being safely used in many fields like cosmetics, sports medicine, orthopaedics, and fasciomaxillary[127,128].

PRP is defined as plasma with a platelet level above peripheral blood concentration. There are two methods to obtain it: (1) ready PRP kits (higher cost); and (2) a wide variation of reported protocols for standardization and preparation of PRP (most of them use two-step centrifugation protocol)[129,130]. The final volume contains platelets and factors (*e.g.*, platelet-derived growth factor and transforming growth factor-β) whose haemostatic and wound-healing effects have been well-described[131-134]. Gardner *et al*[135] in their retrospective study report less blood loss during the post-operative period. Despite that a consensus about the high concentration of growth factors and its efficacy in wound healing has been reached, its haemostatic role is still debatable[136,137].

As a final point, we'd like to note that understanding of basic principles of centrifugation is of vital importance in preparation of PRP. Many protocols have been described with different consistency of PRP yield. Thus, it is advisable to standardize individual, cost-effective preparation protocols, which are easy to adapt in clinical practice[130].

### *Bone wax*

Bone wax is a waxy substance used to help mechanically control bleeding from bone surfaces during surgical procedures. It consists of a mixture of beeswax, paraffin and isopropyl palmitate[138]. Although its use in elective orthopaedic surgery hasn't been well-demonstrated, Moo *et al*[139] suggest bone wax's application in TKA for reducing total blood loss and maintaining higher hemoglobin levels.

It's remarkable to mention that complications like allergic reaction, inflammation and foreign bodies formation need extra attention by the physicians[140]. Undoubtedly, further studies are needed to confirm its safety and efficacy in TKA.

### *Sealing femoral tunnel*

In recent decades most of the orthopaedic surgeons use an intramedullary alignment system regarding the placement of the femoral component in TKA[141]. The intramedullary (IM) femoral rod that is being used damages the cancellous bone and its vascularization resulting in high blood loss. Nowadays, many surgeons seal this tunnel with autologous bone in order to minimize the bleeding. Although autologous bone grafting is a safe and non-time consuming process, its efficacy regarding the reduction in blood loss is still debateable[142,143]. Additionally, studies report that the use of an extramedullary (EM) femoral alignment guide system resulted in reduction of the drained blood and consequently in lower transfusion rates[144,145]. Our only concern is the influence of IM and EM femoral cutting guides on survivorship of the TKA, as IM seems to demonstrate superiority over the EM[146].

## POST-OPERATIVE

Last but not least, post-operatively blood saving methods are integrated in order to reduce blood loss and blood transfusion, and promote the rehabilitation of patients. Post-operative strategies include compression, cryotherapy, use (or not) of drainage systems, cell saving systems and post-operative leg position.

### *Compression and cryotherapy*

Knee swelling after TKA is common and most of the time impairs early rehabilitation. Use of an inelastic compression bandage after TKA seems not to reduce total blood loss. However, it offers a slight but non-significant improvement regarding the postoperative pain and early functional outcomes[147,148]. On the other hand many studies report no difference in compression method[149-151].

Recently Desteli *et al*[152] and Kullenberg *et al*[153] reported that cryotherapy was beneficial in minimizing blood loss after TKA. Many cryotherapy devices have been used in the past (gel packs, circulating ice water) in order to help patients' rehabilitation[154,155]. However, Adie *et al*[156] in their systematic review and meta-analysis does not support the routine use of cryotherapy after TKA.

### *Limb position*

Another option in order to reduce blood loss after TKA is the limb position. Different knee flexion positions (*e.g.*, hip elevation by 60° combined with 60° knee flexion) have been reported to have promising results with respect to reducing perioperative blood loss[157-159]. Based on these studies, we conclude that post-operative knee flexion is an easy, inexpensive and effective method in blood loss reduction.

### *Post-operative cell saving*

It's been calculated that 50% of the total blood loss in a TKA occurs post-operatively[6]. Therefore, post-operative

cell saving and return of unwashed, filtered blood from drains represents an alternative to ABTs method[160]. This system consists of a collection bag and an autologous transfusion bag (filtered blood collected). Re-transfusion can take place in the first 6 h after the end of surgery in order to avoid bacterial infection[161-163]. After this period it can be used as a vacuum drain. Its cost-effectiveness and efficacy seems to be maximized in patients with pre-operative Hb between 12 g/dL and 15 g/dL, whereas in patients with Hb < 12 g/dL post-operative cell saving system should be combined with other blood-saving techniques in order to increase its efficacy[164].

### *Drainage clamping*

Although it is commonly believed that a suction drain, placed intra-articularly reduces the formation of a haemarthrosis and enhances rehabilitation, many studies have yielded controversial results regarding its use[165-169]. Senthil Kumar *et al*[170] in report that most of the post-operative blood loss occurs in the first few hours and especially in the first four hours. As a result, drainage's clamping should help in minimizing blood loss acting like a tamponade. Although drainage's use is still debatable, many different drainage's clamp intervals have been described[168,171-173]. In a prospective study, Yamada *et al*[174] noted that extended drainage's clamping increased complications significantly. There is no consensus about the best protocol but it's noticeable that drainage's clamping combined with TXA can reduce blood loss after TKA[175]. Surprisingly and in contrast with the above literature, 2010 Tai *et al*[176] found no advantage of using the "clamping" method compared with non-drainage at all.

## CONCLUSION

It's more than clear that TKA is a surgery with a blood loss reaching up to 1500 mL. Undoubtedly, the consequent ABTs and/or anaemia occurring post-operatively are causes of increased morbidity, cardiovascular risks, length of stay, decreased vigor and slow rehabilitation. Over recent decades, many blood saving strategies and methods have been described. Nevertheless, there are no concise guidelines, as few/limited studies have compared the relative efficacy of these techniques.

The common target of all blood saving methods is the cost-effective decrease of ABTs. The aim of this review was to evaluate current evidence regarding the efficacy, the safety and the cost-effectiveness on the various pre/intra/post-operative management strategies for patients undergoing TKA. As we described above there is a plethora of methods that can be used in the different periods of the surgery. Many studies have successfully/unsuccessfully described the advantages/disadvantages of each method with/without their limitations. We faced many controversial results in the majority of these strategies. For that reason larger prospective randomized studies comparing not only the individual strategies, but also their combination, are needed.

Scrutinizing the recent literature, we conclude that there is no "consensus success story" about a common efficient/safe blood management strategy in TKA. And if we hazard a guess, we'd say that this consensus cannot be achieved. The current trend is the patient-specific strategy (PSS). This idea is based on the notion that each patient has a different impact on the risk of requiring a transfusion. For example the PSS in a healthy man with Hb > 13 g/dL who undergoes TKA could be a "do nothing" (except Hb reaches transfusion trigger). Conversely, a Jehovah's Witness patient and/or a patient with significant cardiopulmonary compromise should be monitored carefully and more blood management strategies should be considered in order to avoid ABTs. In other words, the above methods that have been analyzed, the advantages and the disadvantages of each method, are just the different parameters that every surgeon should take on board in order to achieve the best result in a specific patient.

The take home message after our in-depth search is that the first important step in blood management is the thorough pre-operative evaluation of each patient. Consideration should be given to the existing physiologic/pathologic variables of the patient and the concomitant actions that should be taken in order to allow prompt optimization of the patient's physiologic status. The 2$^{nd}$ principal arm of effective blood management is the restriction of ABTs' to patients meeting well-established transfusion criteria. Nowadays, this trigger has been decreased to 8 g/dL. The old common belief that all patients with Hb below 10 g/dL should be transfused, has been surpassed. However, when clearly the blood is indicated (clinical signs and symptoms of anemia), administration should not be delayed. Additionally, the use of TXA perioperatively (with different routes of administration) is a widely accepted, effective and safe method in reducing perioperative blood transfusion. These three steps are the "baseline" in our daily practice regarding the perioperative care of the surgical patient.

In our daily practice, it's been proven to be really challenging and unfeasible to apply the same practices in all patients. In simple terms, no single method achieved to provide significantly superior results over another in ABTs' reduction. Primarily, every orthopaedic surgeon should be able to plow through and understand each method separately. Consequently, he must tailor these methods to result in an individualistic blood saving model.

In conclusion, an appropriate combination of the above blood management strategies could further result in ABT's reduction. Additionally, we should highlight the importance of a team approach (*e.g.*, orthopaedic surgeon, anesthesiologist, hematologist) in order to optimize the patients perioperatively and succeeding in the best result.

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MINIREVIEWS

# Sternal metastasis - the forgotten column and its effect on thoracic spine stability

Robert Pearse Piggott, Mark Curtin, Sudarshan Munigangaiah, Mutaz Jadaan, John Patrick McCabe, Aiden Devitt

Robert Pearse Piggott, Mark Curtin, Sudarshan Munigangaiah, Mutaz Jadaan, John Patrick McCabe, Aiden Devitt, Department of Trauma and Orthopaedic Surgery, Galway University Hospitals, the West/North West Hospitals Group, HSE, Galway H91 YR71, Ireland

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Correspondence to: Robert Pearse Piggott, Orthopaedic Specialist Registrar, Department of Trauma and Orthopaedic Surgery, Galway University Hospitals, the West/North West Hospitals Group, HSE, Newcastle Road, Galway H91 YR71, Ireland. robpiggott1@gmail.com
Telephone: +353-091-544000

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## Abstract

Sternal metastases are not studied extensively in the literature. There is a paucity of information on their role in metastatic disease. The concept of the fourth column was described by Berg in 1993, and has been proven in case report, clinically and biomechanical studies. The role of the sternum as a support to the thoracic spine is well documented in the trauma patients, but not much is known about its role in cancer patients. This review examines what is known on the role of the fourth column. Following this we have identified two likely scenarios that sternal metastases may impact management: (1) sternal pathological fracture increases the mobility of the semi-rigid thorax with the loss of the biomechanical support of the sternum-rib-thoracic spine complex; and (2) a sternal metastasis increases the risk of fracture, and while being medical treated the thoracic spine should be monitored for acute kyphosis and neurological injury secondarily to the insufficiency of the fourth column.

**Key words:** Fourth column; Sternal fracture; Sternal metastasis; Sternal-rib-thoracic spine complex; Spine stability



**Core tip:** The sternal-rib complex provides additional support to the thoracic spine. The role of sternal fracture affecting the stability of the thoracic spine is well established in trauma, to date however its role in metastatic disease is unclear. Biomechanical studies highlight its importance and the presence of sternal metastasis should be considered when assessing the stability of the thoracic spine in metastatic disease.

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## INTRODUCTION

Cancer remains the second leading cause of death in the United States, with 589430 cancer related deaths each year[1]. In Europe, collective data from 40 countries has yielded an annual incidence of 3.45 million new cases per year, with 1.75 million cancer related deaths[2]. With early detection and increased treatment options, prolonged survival in patients with metastatic disease will result with increased incidence of skeletal related events (SREs) that will require orthopaedic intervention. The skeleton is the third most common site for metastatic disease to occur in the body, with only the lungs and liver with a higher incidence. Within the skeletal system, the spine is the most common site of metastases. The thoracic spine is most prone to metastatic disease as it contains the greatest volume of bone marrow per vertebrae[3]. Bone metastases are associated with a considerable degree of morbidity both due to pain and SREs. SREs are defined as a pathological fracture, a requirement for surgical intervention and palliative radiotherapy to a bone lesion, hypercalceamia of malignancy, and spinal cord compression. Metastatic spinal cord compression occurs in 3.4% patients with cancer per year in the United States[4] is a source of considerable morbidity. Breast, prostate, renal, lung, and haematopoietic tumours most commonly metastases to the spine and are discussed elsewhere in more detail. But what of sternal metastases which occur in the setting of spinal metastatic disease. Do they have an effect on the spine and its stability?

Sternal metastases are a rare phenomenon[5,6] and there is a paucity of information published regarding their incidence and also their effect on spine stability. Best medical therapy, such as external beam radiotherapy or chemotherapy, is advocated for the vast majority of cases[7] however when a pathological fracture occurs, then there is potential for delayed union and deformity. When present with concomitant thoracic spinal disease then the role of the sternum-rib-thoracic spine complex in thoracic spine stability, as the fourth column, is an important consideration. Berg[8] first proposed the fourth column in 1993, as an adjunct to the three-column theory of spine stability of Denis[9]. To date no study has looked at the role of the sternum in thoracic spine stability in the presence of a sternal metastasis. Hence the focus of this review is to identify what is known on the topic of sternal metastasis in the setting of spinal metastatic disease, and their potential effect on spine stability.

## STERNAL METASTASES - WHAT IS KNOWN?

There has been little focus on the incidence and association of sternal metastatic disease in recent years. A necropsy study by Urovitz *et al*[5] form 1977 remains the largest single study on the topic. In a patient population of 415 patients, the incidence of sternal metastases was found to be 15.1%, of which 30.2% had a sternal fracture[5]. These fractures also demonstrated delayed or nonunion features and were associated with greater deformity than traumatic sternal fractures[5]. Conflicting reports on the commonest location and most prevalent tumours exist. Urovitz *et al*[5] identified the body of the sternum as the commonest site of metastases with breast, lymphoma and myeloma the most prevalent primary oncological processes. This was contrary to what was previously described by Kinsella *et al*[6] who concluded that the manubrium was most at risk, and that thyroid, renal and breast carcinoma were the most common. These findings are summarized in Figure 1.

Once sternal metastases have developed, best medical therapy with either radiotherapy, hormonal therapy or chemotherapy is recommended as per the primary diagnosis[7]. This is regardless of location and size of the metastatic disease as the sternum is a non-weight bearing bone and treatment is not altered by whether the lesion is osteoblastic, osteolytic or mixed on imaging[7]. The treating oncologist should closely evaluate the response of treatment, especially pain relief. If pathological fracture occurs, continued medical therapy is advocated and only those patients who fail best medical therapy are to be referred for consideration for surgical intervention[7]. Sternal metastasis in isolation may be treated by a number of mechanisms. Usually in the setting of isolated metastatic disease, the tumour may be excised and the sternum may be reconstructed with titanium mesh[10], locking titanium plate[11] or even an allogenic transplant[12]. In the palliative setting, kyphoplasty of sternal metastasis has been advocated for pain relief[13]. Unfortunately, all recommendations are for sternal metastases in isolation and do not take into account the sternum-rib-thoracic spine complex in combination. Specifically, there are no recommendations for the prophylactic surgery on the sternum to prevent fracture in a patient with concurrent spinal metastatic disease.

## SPINAL METASTASIS

Spinal metastases can be treated medically, with radiotherapy and or spinal surgery and treatment must be individualized to accommodate for tumour type, performance status of the patient, life expectancy and neurological status. It is a fundamental realization that any intervention with regards spinal metastases is palliative. There are four primary indications to intervening in metastatic disease of the spine: Neurological compromise, spinal instability, unrelenting pain and in the case which histological diagnosis must be established. Historically radiotherapy became the first-line treatment for most patients[14]. Recent advances in imaging, surgical technique and instrumentation systems have improved

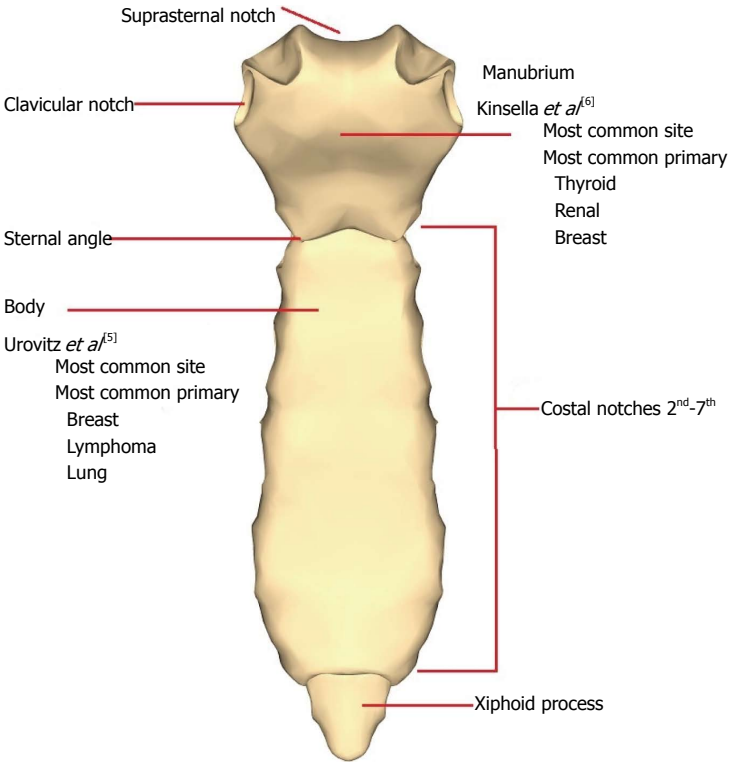


**Figure 1 Sternum.**

outcomes from surgery. Patchell *et al*[15] in a randomized control trial showed that surgery follow by radiotherapy to be superior to radiotherapy alone. These findings were reproduced in a large multicentre observational study[16]. The is a multitude of evidence on surgery in neurological compromise including spinal cord compression, in which cases the spine needs to be decompressed and stabilized[17-19]. The sternum in this setting does not play a role in the management strategy as the evidence supports intervention regardless of sternal disease. Likewise, management of intractable pain and the need for histological diagnosis is not altered by whether disease is present in the sternum. Spinal stability however is directly affected by the sternum in biomechanical studies of the spine[20] and thus it follows that it has the potential to affect stability in the metastatic spine, but remains to be investigated fully.

## STABILITY WITH SPINAL METASTASIS

Assessing the spine stability in metastatic disease however is more difficult, and especially in the setting of impending instability, the sternum could play a role. Form the literature we know that defining instability in the spine using trauma criteria is not directly applicable to the setting of metastatic disease[21]. This is because the injury does not follow typical patterns seen in trauma, and involves different biological healing potential and patient factors[22]. As we have no evidence on the topic then we must be cautious when applying observations from traumatic sternal and spinal injuries to the oncological setting as we assess the thoracic spine as a whole with the sternum-rib-thoracic spine complex.

The Spine Oncology Study Group (SOSG) defines stability as the "loss of spinal integrity as a result of a neoplastic process that is associated with movement-related pain, symptomatic or progressive stability and/or neurological compromise under physiological loads"[22]. It is the major goal of any spinal surgery in oncology to preserve or restore the spines stability. Regardless of indication, surgery is generally reserved for patients with a life expectancy of greater than 3 mo[23]. To determine a patient's life expectancy, multiple scoring systems have been developed. Tokuhashi *et al*[24] developed one example of a scoring system to evaluate prognosis of metastatic spine tumour patients. This was further assessed by Enkaoua *et al*[25] regarding its reliability, and demonstrates a median survival of 5.7 mo with a score $\leqslant$ 7 mo *vs* 23.6 mo for a score of $\geqslant$ 8. Regardless of scoring systems however, establishing survival of patients is subjective and must take into account multiple patient and disease factors before a decision on suitability for surgery is made.

Surgeons rely on their clinical experience as well as internationally accepted scoring systems to determine a spines stability and appropriate treatment. The SOSG have provided a classification n system for spinal instability - The Spinal Instability Neoplastic Score (SINS) - which was developed from existing evidence based medicine and expert consensus opinion[22]. Factors included in the score include location, pain, alignment, vertebral body collapse, posterior element involvement and type of bone lesion (Table 1). The SINS has been shown to have good inter- and intraobserver reliability in determining stability. Stability is derived from overall score out of a max score of 18. Neoplastic disease is

**Table 1 Spinal Instability Neoplastic Score**

| | Score |
|---|---|
| Spine location | |
| Junctional (occiput-C2, C7-T2, T11-L1, L5-S1) | 3 |
| Mobile (C3-C6, L2-L4) | 2 |
| Semi-rigid (T3-T10) | 1 |
| Rigid (S2-S5) | 0 |
| Mechanical or postural pain | |
| Yes | 3 |
| No (occasional pain but not mechanical) | 1 |
| Pain-free lesion | 0 |
| Bone lesion quality | |
| Lytic | 2 |
| Mixed lytic/blastic | 1 |
| Blastic | 1 |
| Radiographic spinal alignment | |
| Subluxation/translation | 4 |
| *De novo* deformity (kyphosis/scoliosis) | 1 |
| Normal | 0 |
| Vertebral body involvement | |
| > 50% collapse | 3 |
| < 50% collapse | 2 |
| No collapse with > 50% involvement | 1 |
| None of the above | 0 |
| Posterior involvement | |
| Bilateral | 3 |
| Unilateral | 1 |
| None | 0 |

deemed unstable with a score of 13-18, stable with a score of 0-6 and indeterminate instability or possibly impending with a score of 7-12. The specificity and sensitivity of the SINS for unstable or potentially unstable spines is 95.7% and 79.5% respectively. The SINS provides a useful tool for assessing spinal disease and aids in the decision making for surgical intervention but is not binding. Unfortunately the sternum is not considered in the SINS in its current format, and thus the fourth column becomes the forgotten column when considering spine stability in metastatic disease.

Further scoring systems exist which can also aid in the decision making process. As survivorship improves with neoplastic conditions so does the incidence of metastatic disease in the axial skeleton. Predicting the survivorship of patients with metastatic disease is important in the planning of surgical intervention. The Oswestry Spinal Risk Index (OSRI) is a simple, reproducible measure of survivorship looking at primary tumor pathology and the patient's general condition[26]. It has been externally validated twice and provides accurate prediction of a patients survivorship which can be used in the decision making process[27,28].

## ROLE OF THE FOURTH COLUMN IN METASTATIC DISEASE

Biomechanically, the inherent stability of the thoracic spine is augmented by the sternum and rib cage, which increases the moment of inertia and stiffens the spine against rotary forces[29]. There is a multitude of evidence from case reports, retrospective reviews and biomechanical studies on the importance of the sternum and ribs in the presence of thoracic spine injury in acute trauma but none on metastatic disease. The association between sternal fractures and spine injuries is well documented in the literature[8,30-32]. In clinical practice a spinal injury must be suspected to exist in the presence of a sternum fracture, even at discordant levels.

A 50-year literature review by Fowler[30] concluded that 43% of sternum fractures had associated spinal fractures. Berg postulated that the sternum and ribs represents a fourth column of structural support for the thoracic spine in addition to the three described by Denis[8]. The three column model divides the osteoligamentous structures of the spinal column into an anterior, middle and posterior column[9]. Involvement of 2 of the 3 columns resulted in potentially unstable spinal injury at risk of progressive deformity and neurological compromise[9]. The additional fourth column theory was based on two cases of displaced sternal fractures with minimally displaced thoracic spine injuries leading to progressive kyphosis[8].

This pattern of injury is often associated with neurological compromise, with increasing degrees of kyphosis being observed. Golpalakrish and Masri reported 83% of patients with sternum and spine fracture combinations had complete neurologic injury and were paraplegic[32]. Vioreanu *et al*[31] in 2005 reported an incidence of 1.4% of sternal fracture with vertebral fracture, which rises to 9.2% when the subset of thoracic fractures is examined in isolation. There is a clear association of neurological compromise in these patients with all six patients suffering neurological injury of which four patients had complete injuries[31].

However, neither Berg nor Vioreanu *et al*[31] described the behavior of a three-column injury with an intact sternum or "fourth column". A case report by Shen describes how the sternum provided sufficient stability for the conservative management of a three-column unstable injury pattern in an ankylosing spondylitis patient without neurological compromise[33]. The authors concluded that the case confirmed the existence and clinical relevance of the fourth column proposed by Berg. An *in vitro* cadaveric study estimated that the sternum-rib complex accounts for up to 78% of thoracic stability[34]. Watkins *et al*[20] examined the biomechanics of the fourth column in 10 human cadaveric thoracic spines using multidirectional flexibility tests. They found that an indirect flexion-compression fracture of the sternum decreased the stability of the thoracic spine by 42% in flexion-extension, 22% in lateral bending and 15% in axial rotation[20]. This is evidence of the importance of the sternum in stability of the thoracic spine, and why the thoracic spine is considered a semi-rigid structure[22]. Following from this we can conclude that sternal and thoracic spine injury is a potentially unstable combination.

Metastasis of the sternum and their role on stability is not addressed in the Spinal Instability Neoplastic

Score (Table 1). There are two areas where they have a potential role, which needs to be further explored. The thorax (T3-T10) is termed semi-rigid in the location score secondary to the biomechanical benefit of the sternum and rib cage, and is only scored 1 out of a possible 3. Concomitant sternal metastasis with pathological fracture would affect the semi rigid nature of the thorax with loss of the stability provided by the fourth column. The flexion-extension stability of the spine is reduced by 42%[20] in this setting regardless of thoracic disease, with rotational and lateral bending also affected. We must ask the question - with the loss of the biomechanical benefit of the sternum, should the thoracic now be considered "mobile" and the location score increased to 2 to reflect this? Secondarily, in the presence of metastases without pathological fracture, a lytic lesion of the sternum would be at risk for impeding fracture and should be observed closely. If the spine is deemed stable, close follow up of both the sternal and thoracic metastatic disease is required as early de novo kyphosis deformity would add an additional 2 points to a patients score and may change management. The association between kyphosis and loss of sternal integrity is well established in case reports and carries a significant risk of neurological injury[8,30,32].

In addition, sternal metastasis may be painful but this would not impact on the SINS pain score. Local pain may be related to the sternal metastases themselves but back pain in the setting of concurrent sternum and spine disease which worsens with movement and loading of the spine and is relieved by recumbence would suggest that it is mechanical in nature and thus increase the patients score, as set out by the SOSG[22].

## CONCLUSION

In conclusion, the thoracic spine should not be examined in isolation. The sternum is a pivotal support in thoracic spine stability and should not be overlooked when assessing a patient's thoracic spine. Assess spinal stability in the metastatic diseased spine is a complex and multifactorial process. The sternum provides essential support to the thorax spine and pathological fracture or impending fracture in the sternum has the potential for acute deformity of the thoracic spine that could lead to neurological injury. No evidence exists on the sternum role in metastatic spinal stability to date and thus hard conclusions cannot be made. We recommend that sternal metastatic disease be assessed in conjunction with spinal metastatic disease, and that treatment be tailored to individual cases. Further study is needed to fully evaluate the role of the sternum in spine stability with metastatic disease. A biomechanical study looking at the location and involvement of the sternum and the subsequent risk of fracture and deformity is needed to quantify the risk to the spine. Following this there may be a role for modification of the SINS once their role has been fully investigated. For now, clinical judgment is recommended until further evidence is provided in the literature.

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MINIREVIEWS

# Role of fetuin A in the diagnosis and treatment of joint arthritis

Eleni Pappa, Despina S Perrea, Spiridon Pneumaticos, Vasileios S Nikolaou

Eleni Pappa, Despina S Perrea, Laboratory of Experimental Surgery "N.S. Christeas", National and Kapodistrian University of Athens, School of Medicine, 11527 Athens, Greece

Spiridon Pneumaticos, 3rd Department of Orthopaedics, KAT Hospital, National and Kapodistrian University of Athens, School of Medicine, 11527 Athens, Greece

Vasileios S Nikolaou, 2nd Department of Orthopaedics, Agia Olga Hospital, National and Kapodistrian University of Athens, School of Medicine, 11527 Athens, Greece

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Correspondence to: Vasileios S Nikolaou, MD, PhD, MSc, Orthopaedic Surgeon, Assistant Professor of Orthopaedics, 3rd Department of Orthopaedics, KAT Hospital, National and Kapodistrian University of Athens, School of Medicine, 21 Dimitriou Ralli Str, 11527 Athens, Greece. bniko@med.uoa.gr
Telephone: +30-693-2543400
Fax: +30-210-8020671

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## Abstract

Osteoarthritis is a slowly progressive disease which includes the intervention of several cytokines, macrophage metalleinoproteinases reaction, leading to the degradation of the local cartilage but also having an impact on the serum acute phase proteins (APPs). Subsequently, biomarkers seem to be essential to estimate its progression and the need for any surgical intervention such as total arthroplasty, but also can be used as therapeutic agents. Recently, among APPs, fetuin A drew attention regarding its possible anti-inflammatory role in animal models but also as a therapeutic agent in the inflammatory joint disease in clinical trials. In contrast with other APPs such as C-reactive protein, fetuin A appears to be lower in the serum of patients with degenerative joint disease in comparison with the healthy ones, and also acts as an antagonist of the anti-proliferative potential of transforming growth factor-β (TGF-β) cytokines. Because of its lower serum levels in arthritis, an unregulated binding of TGF-β and bone morphogenetic proteins takes place leading to further arthritic lesions. The purpose of the present review is to assess the current evidence regarding the multipotent role of the alpha-2-HS-glycoprotein or as also known Fetuin-a in animal models but also as a biomarker of the degenerative joint arthritis in clinical trials.

**Key words:** Fetuin A; Arthritis; Alpha-2-HS-glycoprotein; Bone morphogenetic protein; Inflammation; Glycoprotein; Treatment



**Core tip:** Fetuin A, an acute phase glycoprotein, recently drew scientific attention regarding its anti-inflammatory role. In the case of arthritis, clinical studies have shown

its therapeutic potential as well as its anti-inflammatory role as it has been indicated by animal models. In this manuscript, we intend to review the current evidence concerning its anti-inflammatory and therapeutic role in degenerative joint disease.

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## INTRODUCTION

Osteoarthritis, which is also known as degenerative arthritis, is a deteriorating musculoskeletal condition that includes the decrease in the articular cartilage but also leads to a progressive subchondral erosion of the bone[1]. It is assumed that the joint arthritis consists of an inflammatory response which is introduced by several cytokines which are produced by the local reaction of macrophages, such as interleukin (IL)-1a, IL-8, IL-10 and matrix metalleinoproteinases (MMPs). These agents are measurable in the serum but also in the joint synovial fluid and all lead to cartilage breakdown[2]. Additional to the imbalance of the cytokines driven inflammatory process, the collagen of type 1 is transformed to collagen of type 2, while at the same time a decrease in the joint chondrocytes also takes place. It is widely accepted that the activity of IL-1 has a leading role in the arthritis inflammatory process leading to the production of MMPs which further leads to cartilage degradation. Acute phase proteins (APPs), such as C-reactive protein, are also elevated in patients with severe osteoarthritis[2,3].

Regarding APPs, fetuin A has recently draw attention regarding its possible anti-inflammatory role[4]. The complete structure of the complex oligosaccharides of fetuin A has been established[5]. Thanks to ion exchange chromatography following pronase digestion, identical molar ratios of sialic acid, mannose and N-acetyl-glycosamine of 3:3:3:5 was revealed (Figure 1).

Fetuin A is also known as alpha-2-HS-glycoprotein (AHSG) for the human homologue and was first declared as a fetus major plasma protein. During the fetus growth, it is expressed in the liver, kidney, gastrointestinal tract, skin and brain[6]. Concerning the adults, among APPs, fetuin A is produced by the liver and has recently drawn attention regarding its possible anti- inflammatory role in injury or infection, classifying it as a negative APP due to a regulation of pre-inflammatory cytokines such as tumor necrosis factor (TNF), IL-1, IL-6 and interferon (IFN)-γ, but also as a positive APP thanks to the mediation of HMGB1[7].

The aim of this mini review is to investigate the possible role of fetuin A in the inflammatory response, in processes such as the joint osteoarthritis.

## ETIOPATHOLOGY OF ARTHRITIS

The joint homeostasis seems to take place due to a balance between catabolic factors of the adult joint cartilage (IL-1 and TNF) as well as the anabolic ones [insulin like growth factor (IGF), bone morphogenetic protein (BMP) morphogens such as BMP-7 and cartilage-derived morphogenetic proteins (CDMPs)], transforming growth factor-β (TGF-β) and fibroblast growth factors (FGFs). CDMP-1 is expressed in the deeper damaged areas of the cartilage of osteoarthritic joints where it leads to an increase of the local chondrocytes but also promotes the local production of proteoglycans[8,9].

Among the morphogens above, BMP-7 leads an important role for the maintenance of the joint homeostasis. Normally, BMP-7 emerges in the upper matrix of articular cartilage adhering to the expression of BMP receptors (BMPR-ⅠA, ⅠB, and Ⅱ). BMP-7 has many roles in the inflammatory disease of the joint, including the preservation of surfaces of the articular cartilage by promoting the expression of the chondrocyte phenotype of dedifferentiated cells, increasing synthesis of tissue inhibitor of metalloproteinase (TIMP). Moreover, leads to the expression of IGFI, and cytoskeletal proteins of the chondrocytes[10]. It is also known that multipotent mesenchymal stem cells (MSCs) that express BMPs and BMPRs have been isolated from adult human synovial membrane[11]. So, it is assumed that morphogens from the TGF-β family seem to be involved in the remodeling of the arthritic cartilage. Components of synovial joints, such as the bone marrow, the synovium and the periosteum, contain MSCs that are capable of inducing chondrogenesis. It is suggested that the unregulation and likely the up regulation of the activity of TGF-β and BMP are likely to make MSCs in numerous joint sites to form excessive amounts of tissues of cartilage, bone and fibre, leading to fibrosis and osteophyte formation, characteristics of joint osteoarthritis. So, any imbalance between the factors above is likely to establish the degenerative joint disease (DJD) which with further progression may lead to the need of a total joint replacement[12]. However, the bone itself has a leading role in the pathogenesis of osteoarthritis. The level of bone remodeling plays a critical role under mechanical loading conditions, as demonstrated by consistent experimental studies. Yet, new clinical biomarkers have being developed to assess the bone phenotype of osteoarthritic patients. This stratification strategy is likely to better identify groups of patients who would benefit from bone-acting drugs to decrease disease progression and improve pain and disability[13].

## FETUIN-A (AHSG) IN DJD

As it was stated above, APPs such as C reactive protein is mentioned to be elevated due to arthritis, depending on the severity of the disease[14]. Fetuin A protein is also mentioned to be influenced by the inflammation as an APP[15,16], in addition to other biomarkers which have

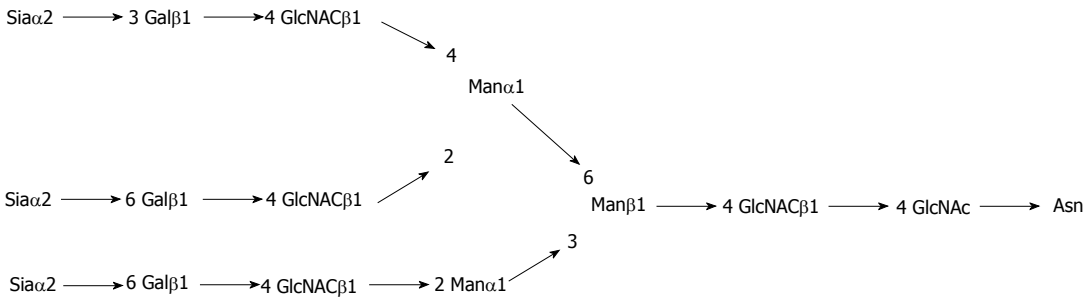


**Figure 1 Structure of fetuin A.**

been recently studied. For example, serum cartilage oligometric matrix protein was also found elevated in cases of knee joint osteoarthritis[17,18]. Interestingly, recent research has shown lower serum levels of AHSG in patients with DJD, accompanied with lower BMP levels than the healthy ones[12].

Studies have shown that AHSG is a negative acute phase reactant and its level is correlated with CRP circulation in the serum inversely[19]. Further research has also shown a close association between fetuin A and metabolic syndrome[20], obesity and dyslipidemia[21], or even blood pressure regulation[22]. Additionally, it has been linked closely with type 2 diabetes mellitus and many authors have suggested that it may be an independent risk factor for the expression of the disease. Specifically, patients with high levels of serum AHSG may have increased risk of incident diabetes[23,24]. Mixed results have been drawn regarding the role of fetuin A in the cardiovascular disease. However, all studies have shown a positive or negative effect of the circulating levels and the presence of the disease[19,25,26]. With no exaggeration, one can admit that AHSG is indeed a multifunctional protein[16]!

AHSG is an antagonist of the TGF-β/BMP, as it is mentioned that it antagonizes the osteogenic as well as the anti-proliferative actions of TGF-β cytokines *in vitro*. More specifically, the 18-19 amino acid region in the AHSG molecule is identical to the TGF-β receptor type Ⅱ (TBRⅡ) and appears to be the BMP antagonist site. This domain is also designated the TGF-β receptor Ⅱ homology 1 domain (TRH1), which is essential for the cytokine binding and as a result leads to the non binding with the TBRⅡ[27]. So, inflammatory diseases characterized by low serum AHSG, such as DJD, leads to an unregulated binding of TGF-β and BMP, having further fibrosis, osteophyte and ectopic bone formation as a result[28].

During the progression of the arthritis, a down regulation of the liver production of AHSG leads to it lower serum levels[12]. Another explanation for that is likely to be the elevated figures of MMPs which are produced by the inflamed tissues, Especially, MMP-1, 3 and 9 are increased in inflamed joints. However, recent studies suggest that AHSG can be eliminated by MMPs, either systematically or locally in the joint[29]. As a result, this could lead to increased activity of the BMPs that would also lead to further progression of the arthritis.

Regarding the prevention of DJD, it is important to state that the therapeutic interventions and goals should take place during the early stages of the arthritis, as chondrocytes are still able to respond to the anabolic factors[9]. The existence of a therapeutic window should be established regarding the concentration and the exposure of BMP-7. Moreover, in order to maintain the joint homeostasis it is important that other proteins such as AHSG that are down-regulators of the BMPs, should be available in order to enhance the protective role of the cytokines above.

As for the therapeutic potential of AHSG in the DJD, Rittenberg *et al*[30] described in 2005 the regulated release of intrarticular injections on experimental level of BMP7 by co-injection of its regulatory molecules such as AHSG in clinical trials. Moreover, besides to the regulation of BMPs, therapeutic potential of AHSG is also based on its ability to eliminate the inflammation and the local tissue destruction. In 1998, Wang *et al*[31] proved through examination of murine cell cultures that AHSG can be used by the local macrophages as an opsonin for macrophage deactivating molecules. Furthermore, Wang *et al*[32] in 2010 established the protective role of AHSG in the ischemic cerebral inflammation in animal models of rats, as well as the the suppression of sepsis mediators in late stages of sepsis in the same animal model. Also, TNF increase from lipopolysaccharide stimulated macrophages was inhibited significantly in an animal model of inflammation which was carried out by Wang *et al*[33] in 1997. Consequently, the co-administration of AHSG and BMPs is able to set a therapeutic intervention for the degenerative bone disease, taking into account the anti-inflammatory role of the agents above.

## CONCLUSION

In conclusion, joint arthritis' diagnosis and treatment as well as its pathophysiology have been studied during the years. However, further research seems to be essential for more effective prevention. The protein Fetuin A has the potential to be used as a biomarker of the disease, as well as a therapeutic agent for the DJD. As a result, physicians should be aware of the fetuin A as a marker of activity and also to be informed in order to have a correct approach to the patients disease and treatment, but also for additional inflammatory diseases. Besides, additional clinical studies are likely to validate the measurement of BMPs as well as AHSG serum levels as a diagnostic means in the

clinical entity of DJD. The identification of AHSG levels in combination with the clinical evaluation of the patients, are not only likely to diagnose the disease in even subclinical stage but also to reduce the need for any further joint salvage procedures, such as total arthroplasty.

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ORIGINAL ARTICLE

Retrospective Study

# Emergent reintubation following elective cervical surgery: A case series

Joshua Schroeder, Stephan N Salzmann, Alexander P Hughes, James D Beckman, Jennifer Shue, Federico P Girardi

Joshua Schroeder, Stephan N Salzmann, Alexander P Hughes, James D Beckman, Jennifer Shue, Federico P Girardi, Spine Service, Hospital for Special Surgery, New York, NY 10021, United States

Author contributions: Schroeder J designed and performed the research, analyzed the data and wrote the paper; Salzmann SN analyzed the data and wrote the paper; Hughes AP designed the research and provided clinical advice; Beckman JD designed the research and provided clinical advice; Shue J analyzed the data and provided research advice; Girardi FP designed the research and provided clinical advice.

Institutional review board statement: This retrospective case series has received approval from the authors' institutional review board.

Informed consent statement: For the patients presented in this case series, a waiver of patient informed consent and U.S. Health Insurance Portability and Accountability Act (HIPAA) authorization were sought. Information contained in this case report contains no personal identifiers to ensure patient confidentiality and protections. Under these provisions, the Institutional Review Board (IRB) at our institution provided approval of this study (IRB#2014-062).

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Correspondence to: Federico P Girardi, MD, Spine Service, Hospital for Special Surgery, 535 East 70th Street, New York, NY 10021, United States. girardif@hss.edu
Telephone: +1-212-6061559
Fax: +1-212-7742870

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## Abstract

***AIM***

To review cases of emergent reintubation after cervical surgery.

***METHODS***

Patients who were emergently intubated in the post-operative period following cervical surgery were identified. The patients' prospectively documented demographic parameters, medical history and clinical symptoms were ascertained. Pre-operative radiographs were examined for the extent of their pathology. The details of the operative procedure were discerned.

***RESULTS***

Eight hundred and eighty patients received anterior- or combined anterior-posterior cervical surgery from 2008-2013. Nine patients (1.02%) required emergent reintubation. The interval between extubation to reintubation was 6.2 h [1-12]. Patients were kept intubated after reintubation for 2.3 d [2-3]. Seven patients displayed moderate postoperative edema. One patient was diagnosed with a compressive hematoma which

was subsequently evacuated in the OR. Another patient was diagnosed with a pulmonary effusion and treated with diuretics. One patient received a late debridement for an infected hematoma. Six patients reported residual symptoms and three patients made a complete recovery.

***CONCLUSION***

Respiratory compromise is a rare but potentially life threatening complication following cervical surgery. Patients at increased risk should be monitored closely for extended periods of time post-operatively. If the airway is restored adequately in a timely manner through emergent re-intubation, the outcome of the patients is generally favorable.

**Key words:** Cervical surgery; Complication; Airway compromise; Reintubation; Hematoma



**Core tip:** The rate of cervical spine surgery has increased over the last years. Airway compromise is a rare but potentially life threatening complication following this type of procedure. This case series represents a single institution's experience of 9 cases requiring emergent reintubation after anterior- or combined anterior-posterior cervical spine surgery. Besides reporting patient characteristics and operative details, our approach to evaluating and treating these cases is presented. In addition the literature addressing reintubation after cervical spine surgery is reviewed.

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## INTRODUCTION

Degenerative conditions of the cervical spine result from disk degeneration and the subsequent osteophytic bone formation extending along the affected vertebrae[1-3]. The uncinate processes as well as the ligamentum flavum may hypertrophy[1]. All of these mechanisms constitute the body's natural response to restore stability and alignment of the cervical spine. Less commonly, cervical kyphosis, compensatory subluxation and the ossification of the posterior longitudinal ligament are factors which may contribute to a progression of the disease resulting in a wide spectrum of clinical signs and symptoms[4].

Overall, up to 89%-95% of men and women aged 60 and above will have degenerative changes visible in their cervical spine imaging, C5-6 being the most commonly affected level[5-7]. Dependent on the degree of nerve root- and spinal cord compression, patients may present with neck pain, radiculopathy or paresthesias of the upper extremities, or signs of myelopathy such as gait- and fine motor control impairment and weakness[8,9]. In cases of myelopathy, severe radicular pain, and patients with progressive neurologic deficits, cervical spine surgery is performed as these patients generally have debilitating sequelae[10].

The safety profile of cervical spine surgery is high, however a mortality rate of 0.14% and an incidence of major complications of 3.93% have been associated with cervical surgery. Patient age > 74 years, a primary diagnosis of cervical spondylosis with myelopathy and large cervical procedures such as long posterior fusions or combined anterior and posterior fusion were found to be predictive of an increased risk of complications[11].

A more dangerous complication is breathing insufficiency, resulting in urgent reintubation. It has been reported in 0.14%-1.9% of patients undergoing cervical surgery[12-14]. Postoperative reintubation has been correlated with advanced age, chronic pulmonary disease, preoperative hypoalbuminemia and anemia, recent weight loss, a high serum creatinine, three or more cervical levels operated on and prolonged surgical time[12-15]. As urgent reintubation is a lifesaving procedure, timely management is critical in order to avoid grave morbidities and mortalities.

We present a detailed case series of a single institution's experience with postoperative reintubation in patients receiving anterior- or combined anterior-posterior cervical surgery.

## MATERIALS AND METHODS

### *Study population*

Data was reviewed from a prospectively maintained hospital database of 880 patients who underwent cervical spine surgery over a 5 year period (2008-2013) at a single institution. Nine patients that required emergent postoperative reintubation following previous extubation were identified.

### *Data collection*

Data was retrospectively collected on patient demographics, past surgical- and medical history, evidence of osteopenia or osteoporosis, primary diagnosis, and surgical details. Data was collected using intra-operative and discharge reports through SRS (SRSsoft, Montvale, NJ, United States). The patients prospectively documented clinical findings and the diagnostic details of their pre-operative imaging were recorded.

## RESULTS

The incidence of emergent reintubation following anterior- or combined anterior-posterior cervical surgery was found to be 1.02%.

### *Patient characteristics*

Detailed patient parameters are presented in Table 1. The

**Table 1 Patient demographic parameters**

| No. | Gender | Age (yr) | BMI | Smoking Status | Comorbidities |
|---|---|---|---|---|---|
| Case 1 | Male | 53 | 29.3 | Never | Hyperlipidemia |
| Case 2 | Female | 70 | 26.7 | Never | hypertension, Von willebrand disease, hypoglycemia, visual migraines |
| Case 3 | Male | 44 | 23.7 | Current, 15 P-Y | - |
| Case 4 | Male | 58 | 26.5 | Former, 15 P-Y | Diabetes mellitus type Ⅰ, asthma |
| Case 5 | Female | 58 | 22.9 | Never | Rheumatoid arthritis, hypertension, GERD |
| Case 6 | Male | 56 | 27.7 | Never | Coronary artery disease, hypertension, benign prostate hyperplasia |
| Case 7 | Female | 71 | 29.3 | Current, 8 P-Y | COPD, pulmonary hypertension, obstructive sleep apnea, GERD |
| Case 8 | Female | 51 | 25.6 | Never | - |
| Case 9 | Female | 61 | 21 | Never | GERD |

P-Y: Pack-years; GERD: Gastroesophageal reflux disease; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease.

average age of the patients was 58 [44-71]. The average BMI of the patients was 25.86 [21-29.3]. The male to female ratio was 4:5. Three patients had a history of tobacco consumption, with two patients remaining active smokers with an average number of 11.5 pack years [8-15]. The patients' medical histories were significant for systemic heart disease in five patients, and for pulmonary disease in two patients. One patient suffered from rheumatoid arthritis. Overall, five patients had multiple systemic comorbidities. One patient's surgical history was significant for a prior emergent posterior cervical decompression from C2-5 for a spontaneous epidural hematoma.

### *Initial evaluation and diagnostic studies*

Five patients complained of myelopathic gait changes. Neck pain was the main complaint of four patients, with three patients each reporting additional shoulder pain or paresthesias. Two patients suffered from upper extremity weakness and numbness, whilst one patient each complained a loss of fine motor control and arm- or hand pain. 8 patients exhibited evidence of a cord signal change in their MRIs.

### *Initial surgical management*

Operative details are presented in Table 2. The average length of surgery was 7.67 h [4.5-11.5], with an average of 3.78 cervical levels fused [2-6]. Three cases were combined anterior and posterior cervical surgeries. The average estimated intraoperative blood loss was 639 mL [150-1100]. No intra-operative complications were recorded in any of the patients. Four patients were kept intubated after completion of the case and extubated on average on the postoperative day number 2 [1-4]. Five patients were extubated at the end of the case. All patients were kept in the post-anesthesia care unit after surgery to monitor airway compromise.

### *Respiratory distress diagnosis and intervention*

Details on postoperative airway management are presented in Table 3. The average interval between extubation to reintubation was 373.3 min [60-720]. The symptoms leading to a pulmonary reevaluation and emergent reintubation varied. Four patients presented with progressive onset of dyspnea, in some cases in combination with stridor, dysphagia or dysphonia. Three patients had no physical complaints but developed hypoxemia with an oxygen saturation ranging from 70%-80%. Two patients developed a spontaneous severe cough. One of the patients was still intubated and inadvertently extubated himself whilst convulsively coughing, leading to his emergent reintubation.

In general, patients were reintubated nasally after topical lidocaine using a flexible fiberoptic bronchoscope to allow for assessment of airway swelling and vocal cord function. Reintubations were easily performed, however, all were done by experienced attending anesthesiologists. None of the patients required tracheostomy for initial reintubation.

The patients were kept intubated after their emergent reintubation for a mean of 2.3 d [2-3]. Urgent fibroscopic ENT examination and imaging identified a compressive hematoma in one patient that was evacuated in the OR. One patient was diagnosed with pulmonary edema and subsequently desaturated and was transferred to the intensive care unit. The remaining seven patients showed no clear signs of respiratory obstruction, with only moderate pharyngeal edema being identified in diagnostic imaging. Due to the severity of their symptoms, four of the patients with this diagnosis received decadron - three of them in combination with racemic epinephrine.

### *Follow-up*

The patients were followed for an average 21.7 mo [2-26.9]. Residual complaints are summarized in Table 4. One patient who was not diagnosed with a hematoma upon emergent airway reevaluation leading to reintubation required a late debridement for an infected hematoma. Three patients made a complete recovery. The remaining six patients reported residual primary complaints of neck pain, paresthesias, numbness and radicular pain. One patient reported a new onset of headaches. None of the patients complained of persistent dysphagia or dysphonia. Overall, none of the patients experienced any clinical sequelae of their reintubation.

## DISCUSSION

In this series of 880 patients undergoing cervical surgery, the overall incidence of emergent reintubation following anterior- or combined anterior-posterior cervical surgery was 1.02%.

**Table 2 Primary operative details**

| No. | Cord signal change (MRI) | Symptoms | Operated levels | Approach | Operative time (min) | Estimated blood loss (mL) |
|---|---|---|---|---|---|---|
| Case 1 | Yes | Neck- and hand pain, gait change, paresthesias | C3-7 | Anterior | 360 | 750 |
| Case 2 | Yes | Upper extremity weakness, shoulder pain, paresthesias | C2-6 | Combined | 690 | 750 |
| Case 3 | Yes | Right arm pain | C3-7 | Anterior | 390 | 850 |
| Case 4 | Yes | Shoulder pain, paresthesias | C3-7 | Anterior | 570 | 800 |
| Case 5 | Yes | Gait change, numbness, weakness | C4-T3 | Combined | 600 | 950 |
| Case 6 | Yes | Neck pain, numbness, gait change | C3-7 | Anterior | 330 | 300 |
| Case 7 | Yes | Neck pain, gait change | C2-T6 | Combined | 660 | 1100 |
| Case 8 | No | Neck pain, shoulder pain | C4-6 | Anterior | 270 | 150 |
| Case 9 | Yes | Neck pain, shoulder pain, gait change, decreased fine motor control | C3-7 | Anterior | 270 | 100 |

MRI: Magnetic resonance imaging.

**Table 3 Postoperative airway management**

| No. | Primary post-op extubation (d) | Time to reintubation (min) | Symptoms preceding reintubation | Diagnosis | Length of reintubation (d) | Therapeutic measures |
|---|---|---|---|---|---|---|
| Case 1 | 1 | 360 | Dyspnea, stridor | Pharyngeal edema | 2 | Decadron |
| Case 2 | 1 | 600 | Hypoxemia (70%) | Hematoma | 3 | Surgical evacuation |
| Case 3 | 0 | 60 | Coughing white, thick mucous | Pulmonary edema | 2 | Decadron, epinephrine, diuretics |
| Case 4 | 0 | 60 | Hypoxemia (80%) | Pharyngeal edema | 3 | - |
| Case 5 | 1 | 600 | Dyspnea, stridor | Pharyngeal edema | 3 | Decadron, epinephrine |
| Case 6 | 0 | 60 | Coughing whilst intubated: Inadvertently extubated | Pharyngeal edema | 2 | - |
| Case 7 | 4 | 720 | Hypoxemia (70%-80%) | Pharyngeal edema | 2 | - |
| Case 8 | 0 | 420 | Dyspnea, dysphagia, dysphonia | Pharyngeal edema | 2 | - |
| Case 9 | 0 | 480 | Dyspnea | Pharyngeal edema | 3 | Decadron, epinephrine |

The early signs and symptoms of airway compromise varied. Some patients developed a spontaneous severe cough, progressive dyspnea, stridor, dysphagia or dysphonia. However, some patients had no apparent physical complaints but developed hypoxemia, leading to reintubation. The timely diagnosis of the airway compromise and the subsequent management thereof resulted in a lack of longterm morbidity and mortality related to the complication. Pharyngeal edema was the leading pathology causing postoperative airway compromise.

Postoperative airway compromise is a rare complication of anterior- or combined anterior-posterior cervical surgery. Nandyala *et al*[15] examined 8648 patients from the American College of Surgeons National Surgical Quality Improvement Program database. They found that 0.62% of patients analyzed in their study who had undergone cervical spine surgery required prolonged ventilation. An additional 0.64% was reintubated postoperatively. Emergent reintubation was correlated with advanced age and a greater comorbidity burden, demonstrating similar findings as our case series. Marquez-Lara *et al*[12] examined a patient sample which underwent anterior cervical surgery from the Nationwide Inpatient Sample database. They reported an incidence of reintubation of 0.56% and reaffirmed the correlation of reintubation with old age and an increased comorbidity burden. Additionally, they reported a correlation with fusions of three or more levels. Hart *et al*[16] experienced a high postoperative incidence of airway edema requiring continuous intubation or emergent reintubation in 45% of cervical surgeries crossing the cervicothoracic junction. All but one of the patients presented here demonstrate at least one of the risk factors reported in the literature such as multi-level fusions, pulmonary disease, advanced age or prolonged surgical time[12-15].

A variety of conditions have been implicated as the cause of postoperative airway compromise in cervical surgery. Emery *et al*[17] presented a series of seven patients who required emergent reintubation following upper-airway compromise after multi-level corpectomies

**Table 4 Follow-up**

| No. | Residual complaints |
|---|---|
| Case 1 | Persistent neck pain and numbness |
| Case 2 | Trapezius pain, paresthesias |
| Case 3 | Residual neck pain |
| Case 4 | - |
| Case 5 | - |
| Case 6 | - |
| Case 7 | Intermittent neck pain, radiculopathy of the right arm |
| Case 8 | Not reported |
| Case 9 | Intermittent neck pain, paresthesias, headaches, numbness and paresthesias of the left thumb and index finger |

for myelopathy with a mortality rate of 28.6%. They believed that the cause of the conditions was predominantly hypopharyngeal and supraglottic swelling. Additional studies have discussed their experience with retropharyngeal postoperative hematoma, cerebrospinal fluid collection, angioedema and hardware dislodgement as causes of respiratory distress[18-22]. The point in time at which the airway compromise occurs has been described as a possible indicator of the etiology. Wound hematomas and pharyngeal edema normally occur within the first hours after the procedure, while respiratory compromise after three days indicates pathologies including abscess formation, cerebrospinal fluid leak or hardware failure[23]. An optimization of inter-departmental cooperation and the capability of emergent imaging may expedite the diagnosis, resulting in a timely intervention and re-establishment of airway control. In our case series, the diagnosis was made with the help of ear, nose, and throat specialists evaluating the patients combined with an emergent intubation by trained anesthesiologists. Seventy-seven point seven percent of the patients requiring reintubation were subsequently diagnosed with a radiographically not impressive pharyngeal edema. This finding is concurrent with the reports found during our review of the literature.

Few studies discuss the treatment or prevention of airway compromise. Hart *et al*[16] examined the effect of the implementation of a fluid management protocol in cervical surgery crossing the cervicothoracic junction. They found that none of the patients who received limited intraoperative fluid resuscitation with crystalloids and a maintenance of constant blood pressure after the implementation of the protocol experienced postoperative airway compromise *vs* the 45% of patients who had experienced complaints previously. We found that our strict adherence to hospital protocol of keeping the patient in the step down unit for 24 h, uninterrupted postoperative monitoring of the vital signs of the patient, as well as continuous regular examinations of the patient contributed to prompt airway management resulting in a lack of mortality amongst these patients.

Sabaté *et al*[24] examined the implications of post-operative pulmonary complications and reported an increased incidence of mortality, length of stay, readmissions, and costs. Our case series gives a limited account of the clinical progression of the patients as well as long term follow up examining the clinical sequelae of their complication. It lacks an analysis of risk factors or a prospective examination of the pathophysiology of the complication. Given the overall increases in cervical surgery over the past years due in part to the aging population and novel technological developments, the clinical as well as the economic burden of this potentially life-threatening complication merits more detailed examination[25]. This is also important since an increasing number of cervical spine surgeries are being performed in the outpatient setting[26,27].

In conclusion, careful monitoring, timely intervention, and a standardized protocol of intervention in patients with respiratory failure after cervical surgery can provide patients with a favorable long term outcome. Extended care in a monitored environment is recommended for multi-level anterior and anterior posterior complex cervical cases.

## COMMENTS

### Background

The rate of cervical spine surgery has increased over the last years. Airway compromise is a rare but potentially life threatening complication following this type of procedure.

### Research frontiers

There is a paucity of literature on incidence, risk factors and management of postoperative airway compromise following cervical spine surgery.

### Innovations and breakthroughs

The incidence of emergent reintubation following anterior- or combined anterior-posterior surgery was found to be 1.02%.

### Applications

Patients at increased risk should be monitored closely for extended periods of time post-operatively.

### Peer-review

The authors present a detailed paper on reintubation after cervical surgery. This is an important issue as reintubation frequency is in literature less than 1% of the cases. They give valuable information of the seven cases in several tables, combining that important information with a very concise paper, ending in useful conclusions. Therefore this is a very interesting, well-written and succinct paper.

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ORIGINAL ARTICLE

Retrospective Study

# Two-stage surgical treatment for septic non-union of the forearm

Fabrizio Perna, Federico Pilla, Matteo Nanni, Lisa Berti, Giada Lullini, Francesco Traina, Cesare Faldini

Fabrizio Perna, Federico Pilla, Matteo Nanni, Lisa Berti, Giada Lullini, Francesco Traina, Cesare Faldini, Istituto Ortopedico Rizzoli, 40136 Bologna, Italy

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Correspondence to: Fabrizio Perna, MD, Istituto Ortopedico Rizzoli, Via G. C. Pupilli 1, 40136 Bologna, Italy. fabrizio.perna@ior.it
Telephone: +39-051-6366368
Fax: +39-051-6366212

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## Abstract

### AIM

To investigate the effectiveness of a two-stage surgical procedure for the treatment of septic forearm non-union.

### METHODS

Septic non-unions are rare complications of forearm fractures. When they occur, they modify the relationship between forearm bones leading to a severe functional impairment. Treatment is challenging and surgery and antibiotic therapy are required to achieve infection resolution. It is even harder to obtain non-union healing with good functional results. The aim of this study is to present a two stages surgical treatment for septic forearm non-union with revision and temporary stabilization of the non-union until infection has cleared and subsequently perform a new synthesis with plate, opposite bone graft strut and intercalary graft. We retrospectively reviewed 18 patients with a mean age at the time of primary injury of 34.5 years (19-57 years) and a mean follow-up of 6 years (2-10 years). All patients presented an atrophic non-union with a mean length of the bone defect of 1.8 cm (1.2-4 cm). Complications and clinical results after surgical treatment were recorded.

### RESULTS

Mean time to resolution of the infectious process was 8.2 wk (range 4-20 wk) after the first surgery and specific antibiotic therapy. All the non-union healed with an average time of 5 mo (range 2-10 mo) after the second step surgery. Cultures on intraoperative samples were

positive in all cases. No major intraoperative complications occurred. Two patients developed minor complications and one needed a second surgical debridement for infection resolution. At the last follow-up functional results were excellent in 5 (27.8%) patients, satisfactory in 10 (55.5%) and unsatisfactory in 3 (16.7%) patients. No activities of daily living (ADLs) limitations were reported by 12 (66.6%) patients, slight by 3 (16.6%) and severe limitation by 3 (16.6%) patients. Mean visual analog scale at the last follow-up was 1 (0-3).

***CONCLUSION***

The two-step technique has proven to be effective to achieve resolution of the infectious process and union with good functional results and low rate of complications.

**Key words:** Forearm fractures; Non-union; Delayed union; Infection; Open fracture; External fixation; Bone graft



**Core tip:** Forearm non-union represent a challenging condition for the orthopaedic surgeon. Septic forms are even more difficult to overcome. However, in the present study we found that good clinical results can be achieved using a dual stage surgical technique with the first aim to resolve the infection process and subsequently achieve bone union.

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## INTRODUCTION

Septic non-union are defined as the absence of evidence of fracture healing and persistence of infection at the fracture site for 6 to 8 mo[1,2]. Current fixation techniques in forearm fractures with the application of the AO principles have proven to be quite effective to achieve healing with a reported non-union rate below 5%[3-6], and infection rate following open reduction and internal fixation (ORIF) for diaphyseal forearm fractures ranges between 2% and 6%[7-10].

Forearm non-unions generally occur as a consequence of inadequate initial reduction, unstable fixation or too early limb mobilization. Whereas in case of septic non-union multiple others factors like open injuries, significant soft tissue trauma, highly comminuted fractures, inadequate surgical fixation, patient characteristics and infection may be involved[7,11-13].

Forearm has the function to support and guide the hand movements through the pronation and the supination at the radio-humeral joint, and at the proximal and the distal radio-ulnar joints. A non-union of one or both the forearm bones modifies their relationships evolving towards proximal and/or distal joints impairment and forearm dysfunction. Furthermore, segmental bone defects in radius, ulna, or both may worsen functional impairment of the elbow and wrist with also difficulties in positioning the hand in space. Finally, a forearm non-union may compromise the strength in lifting objects and gripping.

Surgical treatment of septic forearm non-union may present many difficulties in addition to the well-known difficulties related to the treatment of bone infection, because of the poor bone quality resulting from the septic process, the bone necrosis and the scar adhesion of the soft tissue due to multiple previous surgeries[7,9]. Septic non-unions of the forearm are mostly atrophic non-unions, presenting both mechanical failure and severe biological impairment, and in these cases the bone gap and the bad trophic conditions make the surgical restoration of the shape and the function of the forearm even harder. Proper planning of the treatment should consider first to eradicate the infection, then to promote bone healing, restoring as much as possible bone length and shape, with the aim to restore a physiologic function of the upper limb, minimizing possible impairment of elbow and wrist range of motion, forearm pronation and supination and grip strength.

A series of patients affected by septic forearm non-union who underwent surgical treatment was retrospectively reviewed as part of this study with the aim of presenting a protocol for treatment of septic forearm non-union in two surgical steps: (1) revision of the non-union and temporary stabilization with external fixation, followed by antibiotic therapy until healing of the infection; and (2) new synthesis with plate and opposite bone graft strut, with interposition of intercalary bone graft to fill the bone gap. Results and complications at mid to long-term follow-up are reported.

## MATERIALS AND METHODS

From January 2002 to December 2015 a total of 34 patients presenting septic forearm non-union were treated in our institution and retrospectively reviewed. Inclusion criteria of this study were: (1) patients with septic diaphyseal forearm non-union; (2) patients with a complete clinical and radiologic documentation of the whole treatment; and (3) patients with at least 2 years' follow-up. Exclusion criteria were as follow: (1) presence of other fractures in the same limb at the time of the primary forearm injury; and (2) patients with neurological impairment on the same side of the non-union. Sixteen patients did not satisfy the inclusion criteria and were therefore excluded from the study. This left a total of 18 patients eligible for this retrospective review.

There were 15 men and 3 women with a mean age at the time of our observation and treatment of 34.5

years (range 19-57 years). The initial trauma was caused by road accident in 13 cases, injuries by machines in 4 and accidental fall in 1 case. The fracture involved the radius alone in 5 patients, the ulna alone in 11 patients and both the radius and the ulna in 2 patients.

The dominant limb was involved in 12 cases. An open fracture was present in 6 cases. The initial treatment consisted in ORIF with plate and screws in 10 patients, 3 of them presenting a Gustilo Ⅰ open fracture treated within 24 h from the trauma, one of these treated with also intramedullary nailing (ulna) along with plate and screws (radius); fixation with intramedullary rod in 4 patients; external fixation in 3 patients and close reduction in 1 patient. Fourteen of the 18 patients underwent to further surgery after initial treatment, before our observation.

All patients were evaluated clinically in terms of pain and functional impairment, with blood tests including ESR and C-reaction protein (CRP), and with standard X-rays of the forearm in orthogonal projections. Septic non-union was considered on the basis of the absence of bone healing on radiographs after at least 6 mo from the initial treatment in presence of septic signs such as altered blood test with increase of white blood cell and/or ESR and/or CRP, presence of fistula or obvious soft tissue damage over the non-union site, positive specimens available from previous surgery. All patients presented an atrophic non-union with a mean length of the bone defect of 1.8 cm (range 1.2-4 cm) measured on radiographs.

The performed surgical treatment included two stages. The initial treatment consisted in the removal of the fixation devices, debridement and freshening of the non-union site removing fibrous and necrotic tissue in order to obtain healthy bone ends. The scar of the previous surgery was used to perform the skin incision when possible. Otherwise radius exposure was performed through dorsal Thompson approach, while ulna was exposed through direct posterior approach. The medullary canal of the bones was opened to allow good blood supply to the non-union site. Segmental bone defect up to 3 cm after the debridement were left free; conversely, in cases of bone loss greater than 3 cm and large infectious outbreak, a gentamicin-loaded cement spacer was applied. Samples of infected tissue from the wound, the bone and the deep soft tissue adjacent the non-union were cultured and bone specimens were sent to the pathology for analysis. New synthesis with mono-axial external fixator was performed in order to keep the length of the bone segment and the shape and the function of the forearm.

A targeted antibiotic therapy based on the culture performed on intraoperative samples was set, each patients received a specific antibiotic therapy according to the sensibility of the culture to the antibiotic therapy. Dosage, duration and any drug changes were discussed and decided by our infectious diseases consultant considering the patient's comorbidities, liver and kidney function and response to therapy. Monthly, all patients were evaluated clinically, radiographically and with blood tests, these repeated every two weeks. When normal values of ESR and CRP were observed, antibiotic therapy was interrupted and after 4-6 wk without antibiotic therapy, if ESR and CRP were still normal, and there weren't clinical signs of infection, resolution of the infection was considered.

The second surgical stage consisted into removal of the external fixator and new synthesis with plate and opposite homologous bone graft strut with intercalary graft inserted between the bone ends to restore proper bone length. Intraoperative specimens from the surgical site were taken again and cultured to further confirm the resolution of the infection. Segmental bone defects were quantified and length of the bones were measured using the image intensifier according to Szabo and Weber[14]. The mean length of the intercalary graft was 2.3 cm (range 1.5-5 cm). In case of both bone non-union, fixation of the ulna was performed first in order to properly restore length and alignment of the forearm[15]. No antibiotic therapy was performed after the second surgical stage because all the patients were considered cured from infection. Standard prophylaxis at anaesthetic induction was performed according to the guideline of our hospital.

A long-arm cast with elbow 90° flexed and forearm in intermediate rotation was applied after surgery and maintained for 3 wk. Subsequently an articulate elbow brace was applied for another 3 wk allowing flexion-extension of the elbow and physiotherapy was prescribed. Patients were checked monthly until there was radiographic evidence of bone healing, and thereafter, yearly for a mean postoperative follow-up of 6 years (range 2-10 years).

A combined clinical and radiographic evaluation was used to assess the healing of the non-union. Clinical parameters of healing were: (1) absence of pain or tenderness on palpation; (2) painless grip strength recovery; and (3) painless recovery of elbow and wrist range of motion. Whereas radiographic criteria were: (1) bridging of the non-union seen at three cortices; and (2) obliteration of the non-union line or cortical continuity.

The forearm, elbow and wrist flexion, extension, supination, and pronation were assessed using the Anderson system which classifies results as excellent, satisfactory and unsatisfactory. Excellent result was considered in case of united fracture with loss of less than 10° of elbow or wrist flexion-extension or less than 25% of forearm pronation-supination; satisfactory result was considered in case of healed fracture with loss of less than 20° of elbow or wrist flexion-extension or less than 50% of forearm pronation-supination; unsatisfactory was considered in case of healed fracture with a loss greater than 20° of elbow or wrist flexion-extension or greater than 50% of forearm pronation-supination whereas persistent non-union or malunion was considered a failure[3].

The return to activities of daily living (ADLs) and to job was evaluated in terms of time to return and possible limitation (no limitation, slight and severe limitation).

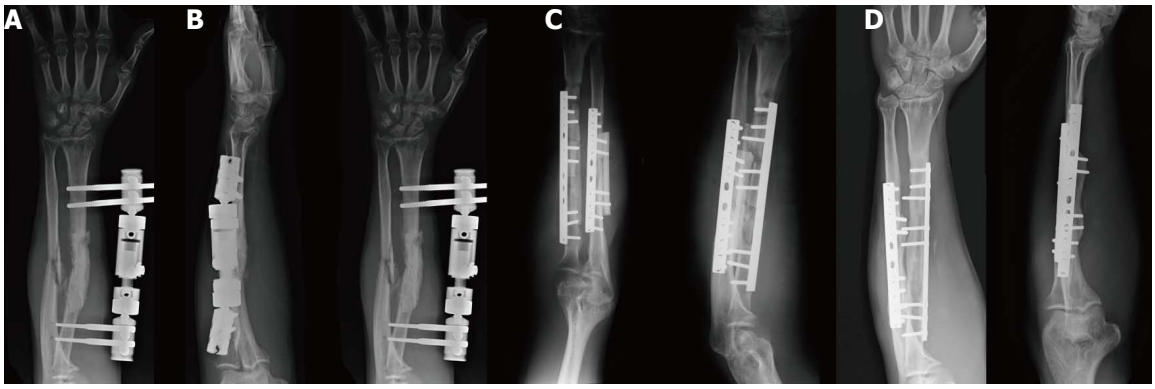


**Figure 1 Radiographic aspect of a both radius and ulna non-union in a 25-year-old man.** A: Occurred after a Gustilo I open fracture undergone open reduction and internal fixation by plate and screws and intramedullary nailing; B: Once a septic non-union was diagnosed, removal of fixation devices and surgical debridement were performed and an external fixator was applied; C: Eight weeks after the surgical toilette the infection has resolved and thus new synthesis with plate, opposite strut and intercalary bone graft was performed; D: At follow-up both non-unions appear healed with noticeable remodelling of the bone graft.

Visual analog scale (VAS) was used to evaluate any residual pain.

## RESULTS

The average follow-up was 6 years (range 2-10 years). At the last follow-up all non-unions healed with evidence of graft integration and bone remodelling (Figure 1).

Cultures on intra-operative samples (harvested during the first surgery) were positive in all patients finding *S. aureus* in 9 patients, *S. epidermidis* in 4 patients, *P. aeruginosa* in 2 patients, both *S. aureus* and *P. aeruginosa* in one patient, both *S. aureus and P. acnes* in one patient and both *S. hominis* and *K. pneumoniae* in one patient. The mean time to resolution of the infectious process was 8.2 wk (range 4-20 wk) after the first surgery and specific antibiotic therapy. Average time of healing of the non-union was 5 mo (range 2-10 mo) after the second surgery (Table 1).

No major intraoperative complications occurred. In three patients skin wound healed by secondary intention and one of them required a skin graft. One patient suffered an incomplete transient palsy of posterior inter-osseous nerve that completely resolved 6 mo after surgery. One patient developed radio-ulnar impingement with prono-supination impairment and underwent further removal of the hardware with functional improvement. After first surgery one patient needed a second surgical debridement and to change the antibiotic therapy due to resumption of infection seen clinically and through blood tests.

At the last follow-up forearm functional results according to the Anderson scale were excellent in 5 (27.8%) patients, satisfactory in 10 (55.5%) and unsatisfactory in 3 patients (16.7%), no failures were recorded. Patients resumed ADLs at a mean of 3 mo after surgery. No limitations were reported by 12 (66.6%) patients, slight limitation by 3 (16.6%) and severe by 3 (16.6%). The original work activity was resumed at a mean of 5 mo after surgery, without limitations in 9 (50%) cases, slight limitation in 6 (33.3%), and with severe limitation that required to change the type of activity in 3 cases (16.6%). At the last available follow-up mean value of pain according to VAS was 1 (range 0-3) (Table 2).

## DISCUSSION

In this study a two-step protocol for surgical treatment of septic forearm non-unions is presented including: (1) extensive surgical debridement of the non-union and temporary external fixation followed by targeted antibiotic therapy; and (2) new synthesis of the non-union with plate and screws, opposite homologous bone graft strut and intercalary allograft after the healing of infection. This technique allowed to achieve good radiographic and clinical outcome, healing of all non-unions with 83.3% of excellent and satisfactory results, and low rate of complications.

The treatment of septic forearm non-unions must consider first the resolution of the infectious process and then the achievement of the fracture union providing a proper reconstruction of the fractured bones and hence adequate function of the forearm. Septic forearm non-unions are mainly atrophic with severe biologic impairment of the bone and the soft tissues. Commonly there may be a various amount of bone gap characterized by scarring, bone sclerosis and absorption, and poor blood supply. All these problems make more challenging to achieve bone healing and good clinical outcomes. Various surgical options are reported in the literature for the treatment of aseptic forearm non-unions[6,7,9,11-13], but there is paucity of studies concerning the treatment of the septic ones. Baldy dos Reis *et al*[16] using autologous bone graft and compression plate reported a high rate of good functional results (29 cases out of 31), but their study included mixed cohorts of patients with both septic and aseptic non-unions and a direct comparison with our study is difficult. In a retrospective review of 35 patients presenting forearm non-unions, 11 septic, Ring *et al*[9] reported a success rate of 100% using plate fixation and autologous cancellous bone-grafting, recovering a mean

**Table 1 Patient and fracture data and treatment**

| Patient | Age (yr) | Bones involved | Open/ closed | Initial treatment | Speciments | Time to infection resolution (wk) | Bone defect and intercalary graft size (cm) | Time to healing (mo) |
|---|---|---|---|---|---|---|---|---|
| 1 | 27 | Radius | Closed | Intramedullary rod | *S. epidermidis* | 6 | 2.2 | 5 |
| 2 | 31 | Ulna | Open | ORIF | *S. aureus* | 4 | 1.8 | 4 |
| 3 | 41 | Radius | Closed | ORIF | *S. aureus* | 6 | 1.5 | 2 |
| 4 | 24 | Ulna | Closed | ORIF | *S. hominis* + *K. pneumoniae* | 8 | 2.0 | 4 |
| 5 | 19 | Ulna | Closed | Intramedullary rod | *S. epidermidis* | 6 | 1.8 | 3 |
| 6 | 42 | Ulna | Closed | ORIF | *P. aeruginosa* | 8 | 2.0 | 6 |
| 7 | 39 | Ulna | Open | ORIF | *S. aureus* | 6 | 1.6 | 3 |
| 8 | 34 | Radius | Closed | ORIF | *S. aureus*[1] + *P. aeruginosa* | 20 | 2.2 | 4 |
| 9 | 45 | Ulna | Closed | Intramedullary rod | *S. aureus* | 8 | 1.7 | 3 |
| 10 | 25 | Radius + Ulna | Open | ORIF + intram. rod | *S. aureus* + *P. acnes* | 8 | 2.2 | 8 |
| 11 | 57 | Ulna | Open | External fixator | *S. aureus* | 10 | 4.0 | 7 |
| 12 | 38 | Ulna | Closed | ORIF | *S. epidermidis* | 6 | 1.8 | 4 |
| 13 | 20 | Radius + Ulna | Open | External fixator | *S. aureus* | 6 | 2.8 | 8 |
| 14 | 31 | Ulna | Closed | Close reduction | *S. aureus* | 10 | 2.0 | 4 |
| 15 | 52 | Radius | Closed | ORIF | *S. aureus* | 12 | 2.5 | 5 |
| 16 | 40 | Ulna | Open | External fixator | *S. epidermidis* | 6 | 5.0 | 10 |
| 17 | 22 | Ulna | Closed | Intramedullary rod | *S. aureus* | 6 | 1.8 | 4 |
| 18 | 34 | Radius | Closed | ORIF | *P. aeruginosa* | 12 | 2.5 | 6 |

[1]Bacterial resistant strain, second debridement performed. ORIF: Open reduction and internal fixation.

**Table 2 Results**

| Patient | Age (yr) | Follow-up (yr) | Anderson | ADLs limitations | Job limitations | VAS |
|---|---|---|---|---|---|---|
| 1 | 27 | 6 | Excellent | No | No | 0 |
| 2 | 31 | 4 | Satisfactory | No | No | 0 |
| 3 | 41 | 8 | Satisfactory | No | No | 0 |
| 4 | 24 | 3 | Satisfactory | Slight | Slight | 1 |
| 5 | 19 | 10 | Satisfactory | No | No | 0 |
| 6 | 42 | 4 | Satisfactory | Slight | Slight | 2 |
| 7 | 39 | 10 | Satisfactory | No | Slight | 1 |
| 8 | 34 | 8 | Excellent | No | No | 0 |
| 9 | 45 | 4 | Excellent | No | No | 0 |
| 10 | 25 | 6 | Satisfactory | No | Slight | 2 |
| 11 | 57 | 4 | Unsatisfactory | Severe | Severe | 2 |
| 12 | 38 | 5 | Excellent | No | No | 0 |
| 13 | 20 | 8 | Satisfactory | Slight | Slight | 2 |
| 14 | 31 | 8 | Satisfactory | No | No | 0 |
| 15 | 52 | 2 | Unsatisfactory | Severe | Severe | 3 |
| 16 | 40 | 4 | Unsatisfactory | Severe | Severe | 3 |
| 17 | 22 | 6 | Excellent | No | No | 0 |
| 18 | 34 | 8 | Satisfactory | No | Slight | 1 |

VAS: Visual analog scale.

bone defect of 2.2 cm. The results reported by Ring *et al*[9] limited to the 11 septic non-unions seem to confirm the results presented in this paper with a 100% of union rate, however Ring *et al*[9] study lacks of an adequate description of the surgical procedure and of the treatment of the infection. Similar results are reported by Prasarn *et al*[7] in a retrospective analysis of 15 infected forearm non-unions. Prasarn *et al*[7] achieved union in all patients using a two-stage surgical procedure with extensive debridement followed by plate and screws fixation with autologous iliac crest bone graft. Differently to the protocol detailed in this paper, Prasarn *et al*[7] repeated surgical debridement every 48-72 h: It's the authors' opinion that this procedure could be considered hard and painful to bear for the patient and expensive in terms of overall cost of the whole treatment. Furthermore, Prasarn *et al*[7] used an autologous iliac crest bone grafting that presents high morbidity on the donor site and it increases the surgical time. It's the authors' belief that the homologous bone graft may present more advantages than the autologous one, mainly consisting in: (1) short surgical time; (2) possibility to customize the graft according to the patient's characteristics; and (3) neglectable differences in terms of osteoinductive and osteoconductive properties compared to autologous bone graft[6,17]. Furthermore, a cortical strut graft may provide additional stability than a metal plate alone, and thus improvement of the non-union healing may be postulated. Moreover, a stable fixation usually

allows earlier recovery of active motion of the limb.

One of the limit of the present study is related to the supposed risk of disease transmission with homologous graft, but bacterial infection due to contaminated bone have been rarely reported in literature with an overall risk similar to other major orthopaedic procedures[17]. It's the authors' opinion that the biomechanic advantages related to the homologous graft are greater than its estimated risk of disease transmission, even if the authors are also aware that a case-control study would be necessary to establish the real advantages from an autologous graft rather than a homologous. Another limit of this study is related to the relatively small average length of the bone defect of 2.2 cm, so the authors are not able to determine if our protocol could bring the same good results also in case of massive bone defect. In these cases the use of vascularized fibular graft has been described with successfully results[18-21], reporting though major disadvantages related to the risk of infection and thrombosis of the graft vessels[22], technical difficulties of the procedure and comorbidity on the donor site[23]. Recently Zhang *et al*[24] retrospectively analysed the results of a series of 16 patients affected by septic forearm non-union treated with external fixation and bone transport. The union in all patients was achieved with average good clinical results, nevertheless this technique requires high patient's compliance due to the demanding and long treatment and moreover some concerns about the effectiveness of this treatment may still be raised when it is applied on likely avascular post-infected tissue[18-20]. Others limitations of this study are mainly related to be retrospective, to the relatively small number of patients, the non-homogeneous series and the absence of a control group.

In the authors' experience some technical precautions must be respected. First, placing the plate and the opposite graft too close to the interosseous membrane must be avoided in order to prevent impingement between radius and ulna and prono-supination impairment. Second, care should be taken to ensure adequate coverage of the bone and the graft by muscles with the aim to enhance blood supply and surgical wound healing. Third, adequate extensive debridement should be performed in order to expose healthy bone ends and to promote biological stimulation. Finally, the new synthesis must be performed only after complete resolution of the infection, documented by clinic and radiographic signs and blood tests.

Septic forearm non-unions are rare and challenging to treat. The infection represents an obstacle to the healing process that frequently requires prolonged treatment, deferred therapeutic interventions and good patient's compliance.

The two steps technique for the treatment of septic forearm non-unions based on revision of the non-union and temporary stabilization with external fixation, targeted antibiotic therapy and finally new synthesis with plate and homologous bone graft has proven to be effective in achieving union. Good clinical results have been obtained in the majority of cases with low rate of significant complications. Despite the unsatisfactory functional results in 16.7% of the patients according to the Anderson scale, the study presented in this paper obtained resolution of the infectious process and healing of the non-unions in all cases. Accurate debridement and postoperative targeted antibiotic therapy are mandatory to eradicate the infection and thus to allow bone healing. The synthesis with plate and opposite bone graft strut, with intercalary graft, can ensure both stability and biological enhancement so as to promote healing of the non-union and restore good function of the forearm. Despite the average good results of the present study, considering its aforementioned limitations, prospective randomized controlled trial would be desirable to better define the best strategy for treatment of septic forearm non-unions.

## COMMENTS

### Background

Septic non-union of the forearm represent a challenging condition because of the poor bone quality due to the septic process and the forearm function impairment. Septic non-unions of the forearm are mostly atrophic non-unions, presenting both mechanical failure and severe biological impairment, and in these cases the bone gap and the bad trophic conditions make the surgical restoration of the shape and the function of the forearm even harder. Only few reports are available in literature on this topic because of its infrequence.

### Research frontiers

Aim of this study was to evaluate the effectiveness of a two-stage surgical procedure for the treatment of septic non-union of the forearm.

### Innovations and breakthroughs

In this study, a two-step protocol for surgical treatment of septic forearm non-unions is presented including: (1) extensive surgical debridement of the non-union and temporary external fixation followed by targeted antibiotic therapy; and (2) new synthesis of the non-union with plate and screws, opposite homologous bone graft strut and intercalary allograft after the healing of infection. Good radiographic and clinical results have been recorded with an average follow-up of six years. Only limited studies are reported in literature on the same topic, moreover with various limitations such as: Groups heterogeneity and lack of information on the technique used. In the present study, we tried to focalize attention on a homogeneous group of patients and to carefully report the technique used exploring its advantages and disadvantages.

### Applications

This study suggests a new surgical technique for septic forearm non-union treatment. Readers may use it as a stimulus to change their clinical practice or to assess new research frontiers.

### Terminology

Septic non-union are defined as the absence of evidence of fracture healing and persistence of infection at the fracture site for 6 to 8 mo.

### Peer-review

This is a well written paper.

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ORIGINAL ARTICLE

Observational Study

# Upper extremity disorders in heavy industry workers in Greece

Thomaella Tsouvaltzidou, Evangelos Alexopoulos, Ioannis Fragkakis, Eleni Jelastopulu

Thomaella Tsouvaltzidou, Eleni Jelastopulu, Department of Public Health, Medical School, University of Patras, 26500 Patras, Greece

Evangelos Alexopoulos, Medical School, University of Athens, 11527 Athens, Greece

Ioannis Fragkakis, Department of Orthopaedic Surgery, General Hospital of Patras "Agios Andreas", 26335 Patras, Greece

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Correspondence to: Eleni Jelastopulu, MD, PhD, Professor of Public Health, Department of Public Health, Medical School, University of Patras, Hippokrates Avenue, 26500 Patras, Greece. jelasto@upatras.gr
Telephone: +30-2610-969878
Fax: +30-2610-991606

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## Abstract

### AIM

To investigate the disability due to musculoskeletal disorders of the upper extremities in heavy industry workers.

### METHODS

The population under study consisted of 802 employees, both white- and blue-collar, working in a shipyard industry in Athens, Greece. Data were collected through the distribution of questionnaires and the recording of individual and job-related characteristics during the period 2006-2009. The questionnaires used were the Quick Disabilities of the Arm, Shoulder and Hand (QD) Outcome Measure, the Work Ability Index (WAI) and the Short-Form-36 (SF-36) Health Survey. The QD was divided into three parameters - movement restrictions in everyday activities, work and sports/music activities - and the SF-36 into two items, physical and emotional. Multiple linear regression analysis was performed by means of the SPSS v.22 for Windows Statistical Package.

***RESULTS***

The answers given by the participants for the QD did not reveal great discomfort regarding the execution of manual tasks, with the majority of the participants scoring under 5%, meaning no disability. After conducting multiple linear regression, age revealed a positive association with the parameter of restrictions in everyday activities (b = 0.64, *P* = 0.000). Basic education showed a statistically significant association regarding restrictions during leisure activities, with b = 2.140 (*P* = 0.029) for compulsory education graduates. WAI's final score displayed negative charging in the regression analysis of all three parameters, with b = -0.142 (*P* = 0.0), b = -0.099 (*P* = 0.055) and b = -0.376 (*P* = 0.001) respectively, while the physical and emotional components of SF-36 associated with movement restrictions only in daily activities and work. The participants' specialty made no statistically significant associations with any of the three parameters of the QD.

***CONCLUSION***

Increased musculoskeletal disorders of the upper extremity are associated with older age, lower basic education and physical and mental/emotional health and reduced working ability.

**Key words:** Upper extremity disorders; Heavy industry; QuickDASH; Movement restrictions; Occupational diseases



**Core tip:** To our knowledge, this is the first study to use the QuickDASH questionnaire for the evaluation of the physical functionality of the upper extremities in the heavy industry sector. Furthermore, it has proved that the presence of musculoskeletal disorders is negatively associated with the reported working ability of the participants, as well as their physical and emotional health. These data will assist in taking measures for the prevention of occupational accidents and injuries in manual labor.

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## INTRODUCTION

Working in the heavy industry sector can cause the manifestation of occupational diseases and injuries, having a direct impact on the employee, the employer and the state's economy. It can lead to permanent disability or even the death of a worker, the loss of working hours and the reduction of production, as well as the indebtedness of pension funds due to compensations and disability pensions[1]. According to the World Health Organization's (WHO) data, one third of all occupational illnesses are musculoskeletal disorders, with 23.3% being located in the upper extremities[2].

The mechanism involved in the manifestation of musculoskeletal disorders of the upper arm include the use of intense muscular strength, vibrations, painful working positions and rapid and repeated movements, which all result in the great manual strain of the upper extremities[3-5]. Several questionnaires have been suggested for the measurement and evaluation of the physical functionality and the restriction of movement of the upper arm, amongst them the Quick Disabilities of the Arm, Shoulder and Hand (QD) Questionnaire.

The purpose of this study was to analyze disability due to musculoskeletal problems of the upper extremity in heavy industry workers and to identify relationships between movement restrictions in work, everyday and leisure activity and specific individual and job-related characteristics as well as the working ability of the population under study.

## MATERIALS AND METHODS

The population under study consisted of 802 employees, both white- and blue-collar, working in a shipyard industry in Athens, Greece. The white-collar category consisted of secretaries, managers-engineers (civil-, mechanical-, chemical-, metallurgy-, electrical-), draughtsmen, accountants, clerks, computer operators, nurses, electricians with license, inspectors, supervisors, store workers, material suppliers, tool repairs, security men and fire watchmen, while the blue-collar population included manual labor workers, *i.e.*, sand (grit) blasters (simon operators), painters, welders, flame cutters, riggers, dry-dock laborers, fitters, platters, plate fitters, crane operators, chippers, riveters,carpenters and technicians.

Data were collected through the distribution of questionnaires as part of the employees' periodic medical examination in the occupational health department during the period 2006-2009. All employees gave their informed consent for their participation. At the beginning of this study the participants were asked to answer questions regarding individual and job-related characteristics such as age, duration of employment, specialty and basic education. The questionnaires used were the QD Outcome Measure and the Work Ability Index (WAI) for the evaluation and recording of their symptoms and their ability to perform specific tasks, as well as the Short-Form-36 (SF-36) Health Survey, for the assessment of the respondents' general health.

The QD questionnaire evaluates the musculoskeletal symptoms of the participants, as well as their ability to perform certain activities. It consists of three sections. The first section includes eleven five-point scale questions regarding the execution of everyday tasks. The other two parts of the questionnaire are optional and involve 8 five-point scale questions in total, which measure performance during the execution of the participants' usual work demands and sport/music activities. The

**Table 1 Individual and job-related characteristics of the population under study (*n* = 802)**

| | *n* (%) |
|---|---|
| Sex | |
| Male | 763 (95.1) |
| Female | 39 (4.9) |
| Age (yr) | |
| < 40 | 407 (50.7) |
| 40-50 | 301 (37.5) |
| > 50 | 94 (11.7) |
| Marital status | |
| Married | 63 (7.9) |
| Single | 739 (92.0) |
| Basic education | |
| University/PhD | 83 (10.3) |
| Technical school | 503 (62.7) |
| Elementary/high school | 216 (27) |
| Specialty | |
| White-collar workers | 91 (11.3) |
| Blue-collar workers | 711 (88.7) |

scores of the three items of the QD range between 0 (no disability) and 100 (most severe disability)[6,7].

The WAI questionnaire evaluates the participants' ability to work. It consists of seven dimensions, which cover the participants' current work ability compared with their lifetime best, their work ability in relation to the demands of the job, the number of current diseases diagnosed by a physician, their estimated work impairment due to diseases, the amount of sick leaves during the past year, their own prognosis of their work ability in two years time and their mental resources. The total WAI score results from the sum of the subscores of the seven parameters (7-49 points) and is divided into four categories: Poor (7-27 points), medium (28-36), good (37-43) and excellent (44-47) work ability[8].

The SF-36 health survey includes 36 descriptive questions that involve the evaluation of eight parameters of the physical and mental/emotional health of the correspondent. In particular, it includes questions regarding the physical functionality, the bodily pain, role restrictions due to physical or emotional problems, mental state, social functionality and general perception of the patient's health, as well as questions regarding the participant's subjective opinion of the change in the state of his/her health. By summing up the scores of the eight parameters, two further categories are formed the physical and the mental/emotional component of the SF-36. In particular, the physical component consists of the four parameters of physical functionality, bodily pain, general perception of health and role restrictions due to physical health, while the remaining four parameters form the emotional component. The final score for each component ranges from 0 to 100, with a high score predicting a more favorable situation[9,10].

Descriptive analysis took place for the available measurements per occupational category. Linear regression analysis was performed to evaluate the influence of possible determinants on the physical dysfunction of the upper extremity. Coefficients (b) with 95% confidence intervals (95%CI) were calculated as measure of association. For the initial selection of potential factors that influence the ability to perform certain activities, univariate regression analysis was used with a significance level of $P < 0.05$. Subsequently, all independent variables that showed significant associations were considered for inclusion into the multiple linear regression model. Data entry and analysis were conducted by means of the SPSS v.22 for Windows Statistical Package.

## RESULTS

The population under study consisted of 802 heavy industry employees, mostly male (95.1%) and under 50 years of age (88.2%). The majority (88.7%) were blue-collar workers, while only 27% were compulsory education graduates (Table 1).

The answers given by the participants for the QD did not reveal great discomfort regarding the execution of manual tasks. The final scores and the mean values for each of the three categories, everyday, work and sports/music activities, are shown in Table 2, with the majority of the participants scoring under 5%, meaning no disability. Full disability wasn't recorded in any of the categories, with the highest scores reaching 77.27%, 87.5% and 75% respectively. Comparing the mean values, the work category scores were slightly lower than the other two, with a 1.704 mean value (Table 2).

The univariate analysis linear regressions that were conducted for the parameters of the QD - daily activities, work and leisure - revealed statistically important associations with WAI's final score and SF-36 two components, physical and emotional. Furthermore, age was linked with everyday and work restrictions of movement of the upper arm, while basic education showed statistically important correlation with the sports/music parameter. The participants' specialty made no statistically significant associations with any of the three parameters of the QD.

After conducting multiple linear regression, age revealed a positive association with the first parameter of everyday restrictions (b = 0.64, $P = 0.000$), but was rejected in the regression model of the work parameter. Basic education remained statistically significant regarding restrictions during leisure activities, with b = 2.140 ($P = 0.029$) for lower educated workers. WAI's final score displays negative charging in all three analyses, while the physical and emotional components of SF-36 associated with movement restrictions in daily activities and work (Tables 3-5).

## DISCUSSION

The general health of every person depends largely on the nature of their work, on the working environment and on the physical and psychological burden involved in their job. Reasonably, the heavy industry sector is associated with increased morbidity, affecting the level

**Table 2 Final scores and mean values of the three categories of the QuickDASH Questionnaire**

| | Mean value | Score (0-100) | *n* (%) |
|---|---|---|---|
| Everyday restrictions (*n* = 802) | 2786 | < 5 | 681 (85.1) |
| | | 5-50 | 118 (14.5) |
| | | > 50 | 3 (0.4) |
| Work restriction (*n* = 802) | 1704 | < 5 | 731 (91.2) |
| | | 5-50 | 66 (8.2) |
| | | > 50 | 5 (0.6) |
| Sports/music restrictions (*n* = 364) | 2490 | < 5 | 324 (89) |
| | | 5-50 | 33 (9.1) |
| | | > 50 | 7 (1.9) |

< 5 = no disability, 5-50 = slight disability, > 50 = medium to full disability.

**Table 3 Multiple linear regression of upper arm disability during everyday activities**

| | *P*-value | b | 95%CI | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Age | 0 | 0.64 | 0.28 | 0.1 |
| Physical SF-36 | 0 | -0.157 | -0.194 | -0.12 |
| Mental SF-36 | 0 | -0.061 | -0.093 | -0.028 |
| WAI | 0.08 | -0.142 | -0.246 | -0.037 |

Covariates of the final model ($P < 0.05$), b = unstandardized coefficient. CI: Confidence interval; SF-36: Short-form-36; WAI: Work Ability Index.

**Table 4 Multiple linear regression of upper arm disability during work**

| | *P*-value | b | 95%CI | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Physical SF-36 | 0 | -0.066 | -0.102 | -0.03 |
| Mental SF-36 | 0.008 | -0.042 | -0.073 | -0.011 |
| WAI | 0.055 | -0.099 | -0.2 | -0.002 |

Covariates of the final model ($P < 0.05$), b = unstandardized coefficient. CI: Confidence interval; SF-36: Short-form-36; WAI: Work Ability Index.

**Table 5 Multiple linear regression of upper arm disability during sport/music activities**

| | *P*-value | b | 95%CI | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Elementary/high school education | 0.029 | 2.14 | 0.223 | 4.056 |
| WAI | 0.001 | -0.376 | -0.593 | -0.16 |

Covariates of the final model ($P < 0.05$), b = unstandardized coefficient. CI: Confidence interval; WAI: Work Ability Index.

of workers' health, increasing the number of absences from work and thus reducing productivity. The upper extremities are a part of the body that receives intense strain during manual labor, resulting into frequent injuries and causing transient or even permanent disabilities. Therefore, it is important to investigate the links between musculoskeletal disorders of the upper arm and the individual and job-related characteristics of heavy industry workers.

The QD questionnaire was used in the present study as a measuring tool of the physical functionality and the musculoskeletal disorders of the upper extremities, which constitute a main stress point of the body in heavy industry workers. In all three parameters which involve movement restrictions in daily activities, work and leisure, the results showed a positive outcome, since the majority of the participants denied any restrictions in the functionality of their upper extremities. This could be attributed to efficient prevention strategies being applied in the specific shipyard industry, which prevent the impairment of an upcoming disability.

The statistically important association of the everyday restriction parameter with age was expected and comes to match previous studies[11]. Workers over 40 years of age are linked with greater difficulty in executing daily activities, because of their reduced strength and their increased musculoskeletal disorders. The fact though that the same association wasn't noticed for the work parameter of the QD is a paradox. Especially given certain specialties in the heavy industry sector involve great strain of the joints of the upper extremities, and in combination with the reduced stamina and osteoarthritis lesions that accompany older age, there should be a statistically significant association with the final score of the work QD. A possible explanation for this outcome could be the tactic of the industry to place younger workers in positions that require great manual strain. However, this result could also be justified by a possible reluctance of the participants to express their true opinion regarding their physical functionality under the fear of dismissal.

Both parameters of the SF-36, physical and mental/emotional, are negatively associated with everyday and work restrictions of the upper limp[12]. Lower values of the physical component of the SF-36 are interpreted as restriction of movement and bodily pain, similar to the higher scoring of the QD. In the same way and in agreement with other studies, depression, fatigue and emotional restrictions that are expressed through the emotional component of the SF-36 are associated with greater upper extremity disability and a higher QD score[13].

The strongly negative association of WAI's final score with all three parameters of the QD can be explained accordingly, although no previous studies have been conducted to support our findings. Work ability is highly affected by any dysfunction of the upper limbs due to repetitive and stereotyped movements and maintenance of awkward positions for prolonged periods of time, both in white- and blue-collar workers. Additionally, blue-collar workers are often exposed to vibration or heavy loads, while white-collar workers perform more computer-based tasks and have more constrained posture, which can also lead to cumulative musculoskeletal disorders. According to previous studies, chronicity, fatigue and pain

severity are the primary factors that determine care-seeking and sickness absenteeism and subsequently lead to financial consequences and productivity loss due to medical expenses and workers' compensations[14-17].

The basic education of the participants proved to be statistically significant only regarding the sports/music parameter, with compulsory education graduates being associated with greater disability of the upper arms. Lower educated workers are usually occupied in positions with more intense manual strain, which could justify the high scores in movement restrictions, in contrast with university graduates, who are usually white-collar employees[18]. Moreover, lower educated workers are usually related to lower incomes, which comes to agree with previous studies declaring that socioeconomic deprivation is associated with poorer health status[19].

It is very interesting though, that the same association wasn't noticed for the other two parameters of the QD, everyday activities and work. This could be attributed to similar levels of strain of the upper extremities in both educational categories and by extension in both working categories, since the majority of blue-collar workers have a lower educational level, while white-collar workers are usually university graduates. The difference lies in the mechanisms that lead to movement restrictions in these two categories and not in the level of discomfort or the severity of pain that is caused. Musculoskeletal disorders in the heavy industry sector, both acute and cumulative, can be caused by various mechanisms such as repetitive movements, maintenance of awkward postures, vibration exposure and handling of heavy loads. Office work, which is usually computer-based, can also lead to cumulative musculoskeletal disorders, since it involves stereotyped movements of the upper arm and a more restricted posture for prolonged periods of time[20].

The positive outcomes of this study are very encouraging and could be attributed to the proper appliance of prevention strategies by the shipyard industry and the occupational doctors. Prevention and early interventions are in the benefit of both the employer and the employee, in order to reduce disabilities, as well as sickness absences[21].

## COMMENTS

### Background

The heavy industry sector has been linked with occupational accidents and injuries, a great percentage of which involving musculoskeletal disorders of the upper extremities. This can lead to permanent disability of a worker, the loss of working hours and the reduction of production, influencing both, employer and employee. The Quick Disabilities of the Arm, Shoulder and Hand (QD) Questionnaire provides an effective tool for the assessment of the physical functionality of the upper arm and the recording of musculoskeletal problems in manual labor.

### Research frontiers

Various studies have aimed to investigate the prevalence of musculoskeletal disorders of the upper extremities and possible aggravating factors in the industry sector. To the author's knowledge, this is the first study to use the QD questionnaire and correlate it with the working ability and the general physical and emotional health status of a heavy industry worker.

### Innovations and breakthroughs

The present study is the first to use the QD questionnaire for the evaluation of physical dysfunction in heavy industry and to demonstrate its effectiveness in recognizing musculoskeletal disorders of the upper arm. Age and lower basic education have been highlighted as aggravating factors. Furthermore, important negative associations have been made with working ability and the physical and emotional health status of the workers.

### Applications

The provided data may assist industries in planning prevention strategies to reduce occupational injuries of the upper extremities and motivate occupational physicians into using the QD questionnaire as a screening tool for physical dysfunctions of the upper arm. This study forms a base for future research investigating larger groups of heavy industry workers to provide the most reliable data on upper extremity disabilities.

### Peer-review

This manuscript is well-written. The introduction and purpose statement were appropriate. The methods were clearly described. Overall, presentation of the results was appropriate and conclusions appear to be appropriate given the data collected and analysis conducted.

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ORIGINAL ARTICLE

Observational Study

# Medial tibial plateau morphology and stress fracture location: A magnetic resonance imaging study

Kiminori Yukata, Issei Yamanaka, Yuzuru Ueda, Sho Nakai, Hiroyoshi Ogasa, Yosuke Oishi, Jun-ichi Hamawaki

Kiminori Yukata, Issei Yamanaka, Yuzuru Ueda, Sho Nakai, Hiroyoshi Ogasa, Yosuke Oishi, Jun-ichi Hamawaki, Department of Orthopedic Surgery, Yamaguchi University Graduate School of Medicine, Yamaguchi 755-8505, Japan

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**Correspondence to:** Kiminori Yukata, MD, PhD, Department of Orthopedic Surgery, Yamaguchi University Graduate School of Medicine, 1-1-1 Minami-Kogushi, Ube, Yamaguchi 755-8505, Japan. yukata@ogoridaiichi.jp
**Telephone:** +81-83-6222268
**Fax:** +81-83-6222267

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## Abstract

***AIM***

To determine the location of medial tibial plateau stress fractures and its relationship with tibial plateau morphology using magnetic resonance imaging (MRI).

***METHODS***

A retrospective review of patients with a diagnosis of stress fracture of the medial tibial plateau was performed for a 5-year period. Fourteen patients [three female and 11 male, with an average age of 36.4 years (range, 15-50 years)], who underwent knee MRI, were included. The appearance of the tibial plateau stress fracture and the geometry of the tibial plateau were reviewed and measured on MRI.

***RESULTS***

Thirteen of 14 stress fractures were linear, and one of them stellated on MRI images. The location of fractures was classified into three types. Three fractures were located anteromedially (AM type), six posteromedially (PM type), and five posteriorly (P type) at the medial tibial plateau. In addition, tibial posterior slope at the medial tibial plateau tended to be larger when the fracture was located more posteriorly on MRI.

***CONCLUSION***

We found that MRI showed three different localizations of medial tibial plateau stress fractures, which were associated with tibial posterior slope at the medial tibial plateau.

**Key words:** Magnetic resonance imaging; Runner; Stress fracture; Tibial plateau; Tibial posterior slope

**Core tip:** Stress fracture of the medial tibial plateau is a rare injury. No studies have investigated detailed magnetic resonance imaging features of this fracture type. We found three distinct location types of isolated stress fractures of the medial tibial plateau. Posterior tibial slope serves as an indicator to determine the fracture site at the medial tibial plateau.

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## INTRODUCTION

Stress fractures of the lower extremity commonly occur in athletes and military personnel. The tibial shaft is the most common location for stress fractures during running and marching activities, whereas the medial tibial plateau is a relatively uncommon site. Engber *et al*[1] reported a series of 36 patients (57 fractures) including 21 bilateral in 1977. Harolds[2] also reported 105 fractures in 71 soldiers in 1981. They documented that this fracture type is difficult to detect on initial roentgenograms at the onset of symptoms. This injury is easily misdiagnosed because the location of pain and tenderness is very similar to the meniscal injury and pes anserinus bursitis, which are common problems in running activities.

Bone scintigraphy, computed tomography (CT), and magnetic resonance imaging (MRI) are widely used for early detection of stress fractures. Among them, MRI has been found to be more sensitive than CT and more specific than scintigraphy[3]. Clinical case reports have described that MRI is a more sensitive method for evaluating stress fractures of the medial tibial plateau compared with X-rays[4-6]. T2- and STIR-MR images are useful for detecting edema of the cancellous bone that usually presents as a linear fracture line at the medial tibial plateau[7]. However, no studies have investigated more detailed MRI features of medial tibial plateau stress fractures.

The purpose of this study was to determine the detailed MRI appearance of medial tibial plateau stress fractures including localization and morphology. We found three different types of location in stress fracture of the medial tibial plateau. Thus, the geometry of the tibial plateau in patients with stress fractures of medial tibial plateau and the relationship with the fracture location were also evaluated.

## MATERIALS AND METHODS

### Patients

The study protocol was approved by the institutional review board, and the requirement for informed consent was waived. For the present study, we searched the key words "tibial plateau" and "stress fracture" using a database of our institutes' medical records between April 2010 and March 2015, and identified 22 patients. The authors reviewed all medical records. No fractures were observed on MRI in 3 patients, and MRI was not taken in 4 other patients. We excluded these 7 patients in the present study. In addition, one patient was excluded because of a fracture of the medial tibial plateau for which a traumatic event of the affected knee could be identified. Finally, we selected a total of 14 patients [eleven men and three women; mean age, 36.4 years (range, 15-50 years)] with eight right and six left medial tibial plateau stress fractures (Table 1). All patients did not have any relevant medical co-morbidities, such as rheumatoid arthritis, metabolic disease, or osteoporosis in the medical record review, although we did not evaluate bone mineral density (BMD) in the present patients.

The main complaint of all patients was pain in the medial aspect of the proximal part of the tibia, without any traumatic events. On physical examination, tenderness was consistent with the pain site. All cases had no limitation of knee range of motion for reasons other than pain. We did not identify an apparent joint effusion in any patients. All cases did not report sudden onset of discomfort. Thirteen cases were associated with long-distance running (jog or marathon), and one case was associated with rope jump. The delay between symptom onset and seeking medical service ranged from 0 to 120 d (average, 21.9 d).

### X-rays and MRI examinations

Initial anterior-posterior and lateral plain radiographs of the affected knee were taken within 2 wk of onset of symptoms (average, 7.9 d) in 12 of 14 patients. No fracture lines on X-rays were observed in these patients.

MRI scans were completed in all 14 patients. MRI of the knee was performed with a 1.5-T MRI scanner (EXCELART Vantage, TOSHIBA, Japan) using a knee coil. Proton density (PD) weighted MRI (TR/TE, 3750/18) and T2-weighted MRI scans (4100/90) sequences were performed in coronal, sagittal, and axial planes according to our routine knee MRI protocol. MRI parameters for all sequences were as follows: FOV, 16-16 cm; 1 excitation; matrix size, 256 × 368; section thickness, 3 mm for coronal, sagittal, and axial planes; and intersection gap, 1 mm. MRI revealed a linear or stellate PD and T2-low weighted image at the medial tibial plateau in all 14 cases (Figure 1). We did not identify any other associated findings on the MRI scans like osteoarthritis, ligament or meniscal pathology, or articular cartilage lesions.

### Classification and measurements on MRI

Stress fractures of the medial tibial plateau were characterized on the basis of its regional location and morphology (linear or stellate). We classified fracture locations using both sagittal and coronal T2-weighted images. Images between the image slice that had the

**Table 1 Clinical and radiological information in patients with stress fractures of the medial tibial condyle**

| MRI classification | Case No. | Age (yr) | Gender | Affected side | Activity | MRI after onset (d) | Fracture pattern | Medial slope (degrees) | Posterior slope (degrees) |
|---|---|---|---|---|---|---|---|---|---|
| AM type | 1 | 48 | Male | Right | Jog | 16 | Linear | 4.7 | 4.5 |
| | 2 | 29 | Male | Right | Jog | 12 | Linear | 1.7 | 4.9 |
| | 3 | 15 | Male | Left | Jog | 13 | Linear | 6.1 | 5.5 |
| PM type | 4 | 46 | Male | Right | Jog | 14 | Linear | 3.3 | 9.9 |
| | 5 | 48 | Male | Left | Marathon | 0 | Linear | 2.4 | 6.7 |
| | 6 | 29 | Male | Right | Jog | 12 | Linear | 0.9 | 7 |
| | 7 | 44 | Female | Left | Jog | 9 | Linear | 4.5 | 7.7 |
| | 8 | 30 | Female | Right | Rope jump | 13 | Linear | 3.3 | 7.8 |
| | 9 | 40 | Male | Left | Jog | 14 | Linear | 0.9 | 8.2 |
| P type | 10 | 33 | Male | Right | Jog | 18 | Linear | 5.4 | 10.1 |
| | 11 | 50 | Male | Right | Jog | 99 | Linear | 4.8 | 12.2 |
| | 12 | 20 | Male | Left | Jog | 25 | Linear | -0.2 | 12.4 |
| | 13 | 39 | Male | Left | Jog | 127 | Stellate | 2.2 | 11 |
| | 14 | 38 | Female | Right | Jog | 17 | Linear | 0.9 | 11.4 |

MRI: Magnetic resonance imaging.

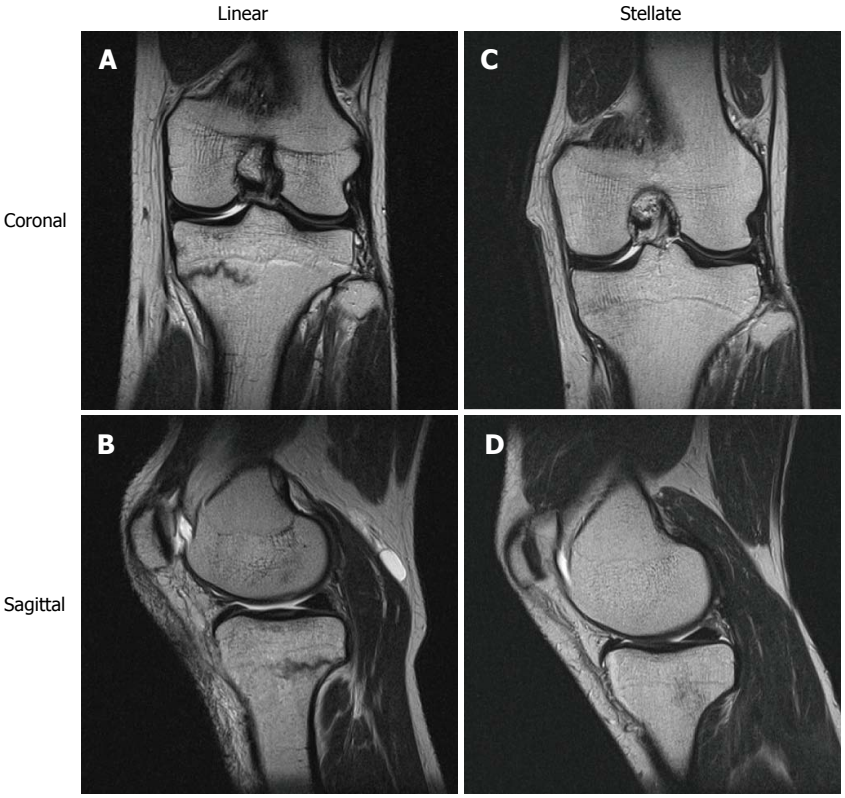


**Figure 1 Representative magnetic resonance imaging images of T2-weighted coronal and sagittal views of linear type (A and B) and stellate type (C and D) in stress fractures of the medial tibial plateau.**

tibial insertion of both the anterior and posterior cruciate ligaments, to the most medial slice that included the tibial condyle at the fracture level, were 7 or 8 slices in the present cases. At first, we divided the fracture locations into the following two types: Anterior (more images that included a fracture line at the anterior tibial cortex) and posterior (more images that included a fracture line at the posterior tibial cortex). Next, they were divided into two subtypes (medial or not) based on whether the most medial slice included a fracture line or not.

In addition, to investigate the relationship between the fracture location and the geometry of the medial tibial plateau, we measured the posterior tibial slope and medial tibial slope at the medial tibial plateau on the sagittal and coronal planes of T2-weighted images using ImageJ software according to the measurement reported by Hashemi *et al*[8]. Briefly, the transverse image passing through the tibiofemoral joint was used to identify the coronal plane that passed closest to the centroid of the tibial plateau and the sagittal plane that included both anterior and posterior cruciate ligaments. The longitudinal axis of the tibia in the coronal and sagittal planes was defined by determining the midpoint of the medial-to-lateral and anterior-to-posterior widths of the tibia at two points located approximately 3 cm apart and as distally in the image as possible (Figure 2). The medial slope in

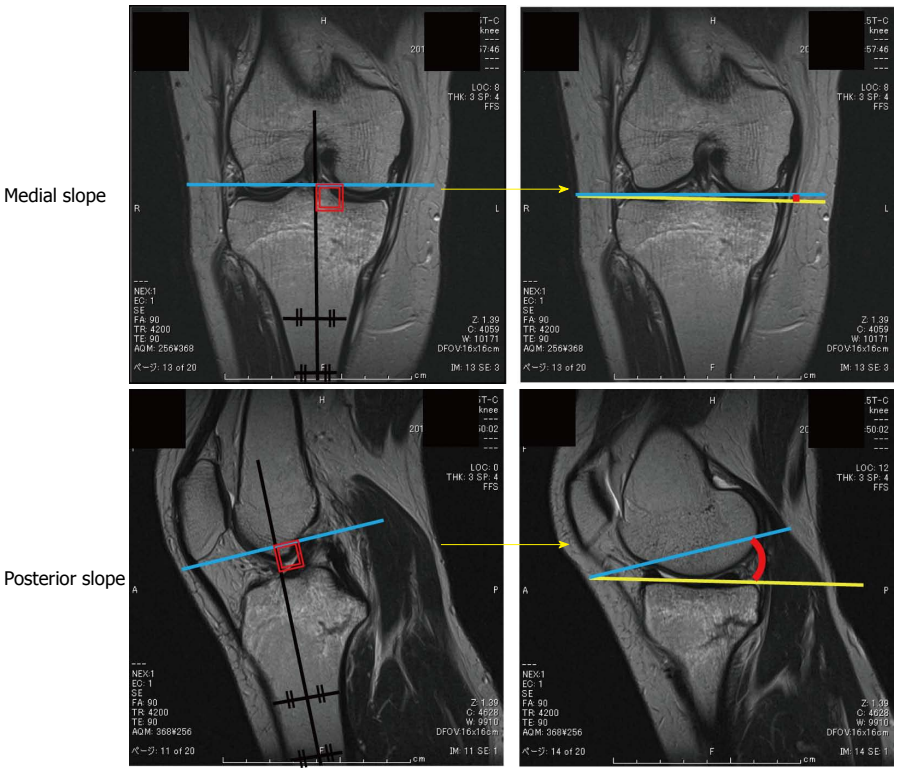


**Figure 2 Magnetic resonance imaging illustrating the method used to determine the medial and posterior slopes.** The angles of tibial medial and posterior slopes were represented by a segment of red circle between blue and yellow lines.

the coronal plane and the sagittal slope of the medial tibial plateau in the sagittal plane were then measured as the angle between a line joining the peak points on the medial-to-lateral, and the anterior-to-posterior aspects of the plateau and the longitudinal axis. The measured value was rounded off to the first decimal place. Two orthopaedic surgeons (KY and YU) separately measured both tibial posterior and medial slope of fourteen MRIs in a blind manner. Two investigators evaluated the parameters twice with a 1-wk interval. To test intra- and inter-observer reliability, the intraclass correlation coefficient (ICC) was calculated for two assessors.

### *Statistical analysis*

All statistical analyses were performed with R2.8.1. Intra-interobserver agreement was assessed by ICC. The data was analyzed by Kruskal-Wallis and *post-hoc* Mann Whitney with Holm's correction for determination of differences between three groups, and presented as the mean ± SE. $P$ value < 0.05 was considered statistically significant.

## RESULTS

MRI of the affected knee demonstrated a PD-low and T2-low linear fracture line at the medial tibial plateau in 13 of 14 patients (Figure 1A and B). One patient had a stellate pattern at the posteromedial part of the tibial plateau (Figure 1C and D). In this case, a linear fracture line might have disappeared because initial MRI was taken at 127 d after the onset. Location of the medial tibial plateau stress fractures was divided into three groups; 3 fractures at the anteromedially (AM) type (Figure 3A-C), 6 posteromedially (PM) type (Figure 3D-F) and 5 posteriorly (P) type (Figure 3G-I). There were no fractures with anterior (A) type. We further investigated the correlation between the fracture type and tibial plateau geometry. Intra-interobsever agreement for the detection of the medial slope and posterior slope at the medial tibial plateau on MRI was very good (tibial posterior slope; intra ($r$ = 0.972; 95%CI, 0.917-0.990), inter ($r$ = 0.933; 95%CI, 0.811-0.978), tibial medial slope; intra ($r$ = 0.935; 95%CI, 0.814-0.978), inter ($r$ = 0.895; 95%CI, 0.715-0.965). The posterior slope in P type was average 11.4 degrees (range: 10.1-12.4 degrees), which was significantly larger than that in AM (average 5.0 degrees (range: 4.5-5.5 degrees) ($P$ = 0.048) and PM (average 7.9 (range: 6.7-9.9 degrees) types ($P$ = 0.013) (Figure 3J). The posterior slope in PM type was also significantly larger than that in AM type ($P$ = 0.048). While, there were no differences between three fracture types about the medial slope.

## DISCUSSION

Harolds[2] posited that the location of medial tibial plateau fatigue fractures are medial and posterior because it is here that weight-bearing stress is greatest. In agreement, the more frequent site of these stress fractures was medial and posterior in our study. But, we found that it occurred antero-medially in some cases. As a result, localization of the medial tibial plateau stress fracture was classified into the following three patterns based on MRI findings: AM, PM, and P types. Furthermore, fracture classification was correlated with

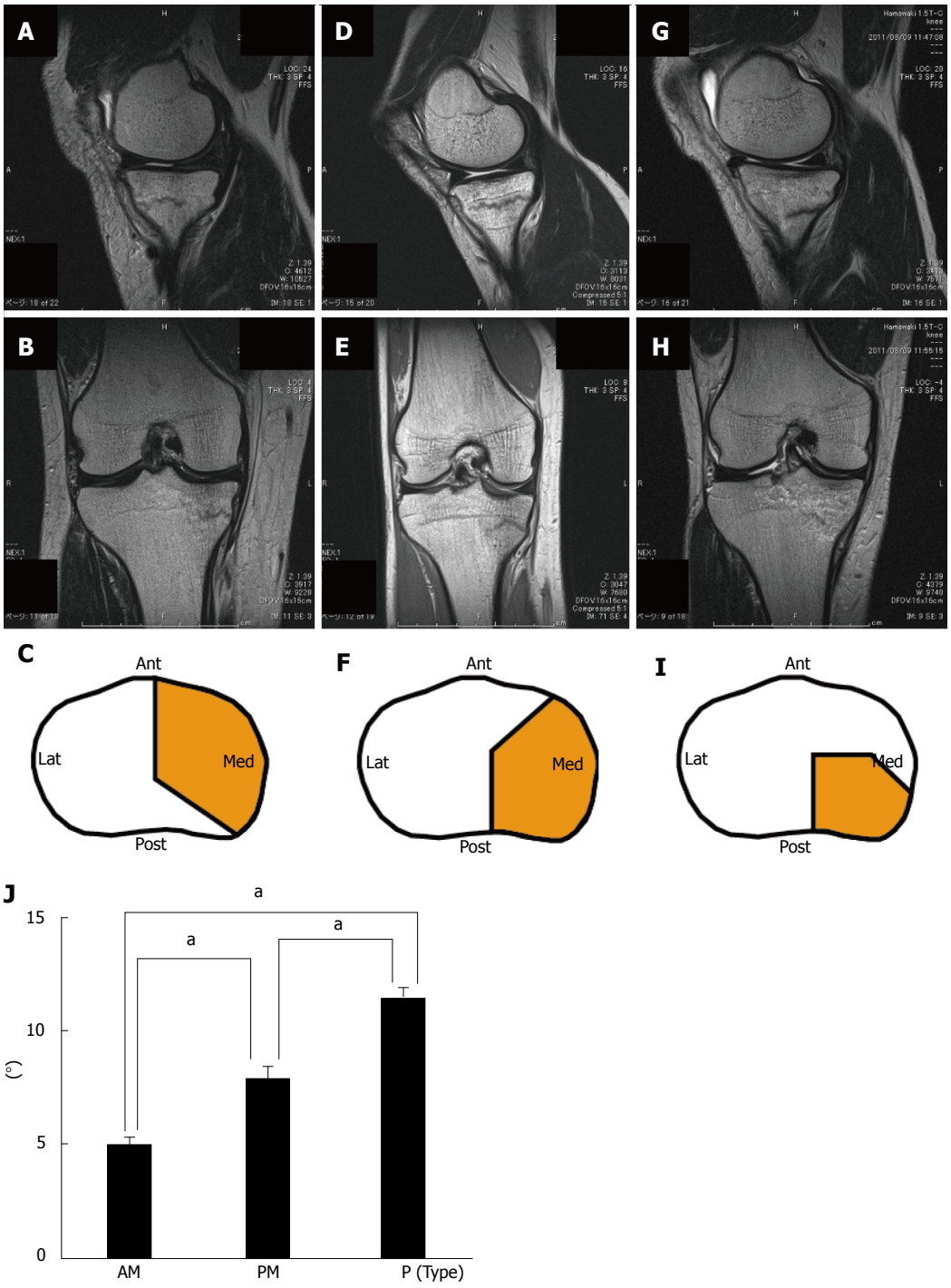


**Figure 3 Representative magnetic resonance imaging of T2-weighted sagittal (A, D, and G) and coronal (B, E, and H) views in the anteromedial (AM), posteromedial (PM), posterior (P) types of medial tibial plateau stress fractures.** Illustrative diagrams of the fracture area (orange) of AM (C), PM (F), and P (I) types at the tibial plateau. Ant: Anterior; Lat: Lateral; Med: Medial; Post: Posterior. J: Relationship between fracture location and posterior tibial slope of the medial tibial plateau. Error bar indicates standard error, $^{a}P < 0.05$.

the posterior slope of the medial tibial plateau.

Dynamic contact mechanics of the tibial plateau during running have not been elucidated, but cadaver studies have described the pressure distribution pattern of the knee during a simulated gait[9,10]. Bedi *et al*[9] demonstrated that the posterior portion of the plateau had higher peak contact pressures than the anterior portion in the stance phase of gait at 14% of the gait cycle, which correspond to 15° knee flexion with axial loads of 2280N. Wang *et al*[10] also reported that one of the most prominent contact stress patterns was observed at the posterior aspect of the medial tibial plateau in nine of 12 cadaveric knees with a single peak stress that occurred at 14%-18% of the gait cycle during the early stance phase. These results are consistent with the fact that more frequent location of medial tibial plateau stress fractures is posterior, although tibial posterior slope was not taken into consideration in their studies.

The tibial posterior slope is originally defined by the angle perpendicular to the longitudinal axis of the bone and tangent to the plateaus on the lateral radiographs. But, it is difficult to discriminate between the medial and lateral plateaus[11,12]. Recent studies have recommended separate assessment of tibial posterior slopes of the medial and lateral plateaus[8,13,14]. Matsuda *et al*[14] reported that the mean tibial posterior slope in the medial plateau on MRI examination was 10.7° (range, 5°-15.5°) in the normal knees of Japanese populations. This average value was similar to that of the present Japanese patients group. The present study indicated that increased the posterior slope caused the plateau to fracture more posteriorly. Giffin *et al*[15] reported that an increase in tibial posterior slope shifted the resting position of the tibia anteriorly relative to the femur. These data suggest that loading of the medial tibial plateau from the femoral condyle may shift from anterior to posterior due to the increased posterior tilt of the tibial plateau. However, the relationship between dynamic contact stress pattern on the tibial plateau and tibial posterior slope during gait and running still remains unclear.

In general, medial tibial plateau stress fractures are more common than stress fractures of the lateral tibial plateau[16,17]. Mizuta *et al*[16] reported a case of the lateral tibial plateau stress fracture, which was associated with knee valgus angulation with 92 degrees of medial tibial slope on radiographs. Hashemi *et al*[8] described that the lateral-to-medial slope of the tibial plateau, which they used the term "coronal tibial slope", ranged between -1° and 6°, whereas the only one subject had a coronal tibial slope of 91° in normal subjects. In our cases of medial tibial plateau stress fractures, medial tibial slope ranged between -0.2° and 6.1°. These data suggest that the patient, who has medial tibial slope within normal limits, is subjected to medial tibial plateau stress fracture, but not lateral.

This fracture type most frequently occurs in soldiers and marathon runners[1,2]. In our series, thirteen of 14 cases were recreational runners. Running has positive effects on physical fitness including reduction in the incidence of obesity, cardiovascular disease, and the other chronic health problems. On the other hand, more people may sustain a running-related injury of the lower extremity. Physicians should be aware of a stress fracture at the medial tibial plateau when patients, particularly runners, present with medial knee pain. Tibial plateau stress fractures in athletes or soldiers are usually self-limiting disease without any persistent deformities because they are comparatively young and they do not have osteoporosis. In fact, all of the present cases did not have any changes of tibial plateau morphology in the follow-up X-rays. On the other hand, insufficiency fractures of the tibial plateau caused by osteoporosis, steroid-use, and rheumatoid arthritis occur in elderly patients[17,18]. We believe that BMD should be evaluated for older runners because delayed diagnosis and treatment can lead to deformity of the knee if osteoporosis is more severe.

One of the limitations of the present study is a small number of the patients because of its rarity. The second limitation is an insufficient length of the tibia on MRI because we used the knee MRI to measure the tibial and medial slopes, which includes only proximal one-third of the whole tibia. MR images of whole tibia might result in more precise slope measurements.

In conclusion, we found three distinct location types of isolated stress fractures of the medial tibial plateau based on MRI. MRI is the preferred technique to correctly diagnose these fracture types because X-rays might not detect the fracture for two week after the onset. Other modalities, such as ultrasound or CT, may be considered as alternatives to diagnose to tibial plateau stress fractures[4]. At that time, tibial posterior slope could serve as an indicator to find out the fracture location at the medial tibial plateau.

## ACKNOWLEDGMENTS

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## COMMENTS

### *Background*

Stress fractures of the lower extremity commonly occur in athletes and military personnel. The tibial shaft is the most common location for stress fractures during running and marching activities, whereas the medial tibial plateau is a relatively uncommon site. This fracture type is difficult to detect on initial roentgenograms at the onset of symptoms. This injury is easily misdiagnosed because the location of pain and tenderness is very similar to the meniscal injury and pes anserinus bursitis, which are common problems in running activities.

### *Research frontiers*

Bone scintigraphy, computed tomography (CT), and magnetic resonance imaging (MRI) are widely used for early detection of stress fractures. Among them, MRI has been found to be more sensitive than CT and more specific than scintigraphy. T2- and STIR-MR images are useful for detecting edema of the cancellous bone that usually presents as a linear fracture line at the medial tibial plateau. No studies have investigated more detailed MRI features of medial tibial plateau stress fractures.

### *Innovations and breakthroughs*

The authors found three different types of location in stress fracture of the medial tibial plateau. The geometry of the tibial plateau in patients with stress fractures of medial tibial plateau and the relationship with the fracture location were also evaluated.

### *Applications*

The authors found three distinct location types of isolated stress fractures of the medial tibial plateau based on MRI. Other modalities may be considered as alternatives to diagnose to tibial plateau stress fractures. Tibial posterior slope could serve as an indicator to find out the fracture location at the medial tibial plateau.

### *Peer-review*

It is a very interesting study. The authors present a series of patients with imaging regarding stress fractures of the tibial plateau.

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SYSTEMATIC REVIEWS

# Clinical application of concentrated bone marrow aspirate in orthopaedics: A systematic review

Arianna L Gianakos, Li Sun, Jay N Patel, Donald M Adams, Frank A Liporace

Arianna L Gianakos, Li Sun, Jay N Patel, Donald M Adams, Frank A Liporace, Division of Orthopedic Surgery, Department of Orthopedic Surgery, Jersey City Medical Center - RWJ Barnabas Health, Jersey City, NJ 07302, United States

Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: Disclosures for Frank A Liporace include AO: Unpaid consultant, Biomet: IP royalties; Paid consultant; Medtronic: Paid consultant, Stryker: Paid consultant, Synthes: Paid consultant.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at algianakos@gmail.com, who will provide a permanent, citable and open-access home for the dataset.



Manuscript source: Invited manuscript

Correspondence to: Frank A Liporace, MD, Chairman, Division of Orthopedic Surgery, Department of Orthopedic Surgery, Jersey City Medical Center - RWJ Barnabas Health, 355 Grand Street, Jersey City, NJ 07302, United States. liporace33@gmail.com
Telephone: +1-201-3092427
Fax: +1-201-9152025

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## Abstract

### *AIM*

To examine the evidence behind the use of concentrated bone marrow aspirate (cBMA) in cartilage, bone, and tendon repair; establish proof of concept for the use of cBMA in these biologic environments; and provide the level and quality of evidence substantiating the use of cBMA in the clinical setting.

### *METHODS*

We conducted a systematic review according to PRISMA guidelines. EMBASE, MEDLINE, and Web of Knowledge databases were screened for the use of cBMA in the repair of cartilage, bone, and tendon repair. We extracted data on tissue type, cBMA preparation, cBMA concentration, study methods, outcomes, and level of evidence and reported the results in tables and text.

### *RESULTS*

A total of 36 studies met inclusion/exclusion criteria and were included in this review. Thirty-one of 36 (86%) studies reported the method of centrifugation and preparation of cBMA with 15 (42%) studies reporting either a cell concentration or an increase from baseline. Variation of cBMA application was seen amongst the studies evaluated. Twenty-one of 36 (58%) were level of evidence Ⅳ, 12/36 (33%) were level of evidence Ⅲ, and 3/36 (8%) were level of evidence Ⅱ. Studies evaluated full thickness chondral lesions (7 studies), osteochondral lesions (10 studies), osteoarthritis (5 studies), nonunion or fracture (9 studies), or tendon injuries (5 studies). Significant clinical improvement with the presence of hyaline-like values and lower incidence of fibrocartilage on T2 mapping was found in patients receiving cBMA in the treatment of cartilaginous lesions. Bone consolidation and time to bone union was improved in patients receiving cBMA. Enhanced healing

rates, improved quality of the repair surface on ultrasound and magnetic resonance imaging, and a decreased risk of re-rupture was demonstrated in patients receiving cBMA as an adjunctive treatment in tendon repair.

***CONCLUSION***

The current literature demonstrates the potential benefits of utilizing cBMA for the repair of cartilaginous lesions, bony defects, and tendon injuries in the clinical setting. This study also demonstrates discrepancies between the literature with regards to various methods of centrifugation, variable cell count concentrations, and lack of standardized outcome measures. Future studies should attempt to examine the integral factors necessary for tissue regeneration and renewal including stem cells, growth factors and a biologic scaffold.

**Key words:** Concentrated bone marrow aspirate; Bone; Cartilage; Osteochondral lesion; Osteoarthritis; Tendon



**Core tip:** With the widespread use of orthobiologics in everyday practice, attention must be directed to substantiate the evidence for their current use and to direct future practice guidelines. The use of concentrated bone marrow aspirate (cBMA) has become an increasingly popular alternative and adjunct in the treatment of cartilaginous lesions, bony defects, and tendinous injuries. This systematic review demonstrates the potential benefits of utilizing cBMA for the repair of different tissue types in the clinical setting. This systematic review also highlights discrepancies between the literature with regards to various methods of centrifugation, variable cell count concentrations, variable methods of application of cBMA, and the lack of standardized outcome measures.

Gianakos AL, Sun L, Patel JN, Adams DM, Liporace FA. Clinical application of concentrated bone marrow aspirate in orthopaedics: A systematic review. *World J Orthop* 2017; 8(6): 491-506 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i6/491.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i6.491

## INTRODUCTION

With the widespread use of orthobiologics in everyday practice, attention must be directed to substantiate the evidence for their current use and to direct future practice guidelines. In any bioengineered environment, three components are required to provide the necessary biologic milieu for cell regeneration and renewal. The presence of stem cells, growth factors, and a biologic scaffold are integral to this process. Bone marrow aspirate (BMA) has been utilized as a source of bone marrow-derived mesenchymal stem cells (BM-MSC) with its relative ease of harvest, low morbidity, and feasible cost. BMA alone has a relatively low percentage of MSCs with only 0.001% to 0.01% of all nucleated cells in BMA being MSCs[1]. Therefore, the aspirate is typically concentrated by centrifugation in order to increase the ratio of MSCs. Concentrated bone marrow aspirate (cBMA) provides both stem cells and growth factors and relies on the host tissue to provide scaffold. The use of cBMA has become an increasingly popular alternative and adjunct in the treatment of cartilaginous lesions, bony defects, and tendinous injuries. Despite both basic science and clinical evidence of its efficacy, recent literature suggests that cBMA has different functions and roles in each biologic environment. Evidence suggests that stem cells act to direct local cells to stimulate regeneration and repair that is specific to each tissue. This process is mediated by secretomes from the stem cells, which allow their adaptation in each environment and therefore provides the appropriate growth factors and cytokines necessary to stimulate each tissue in a different fashion[2]. Growth factors derived from cBMA may be required for cell lineage differentiation although the exact growth factors have not to date been fully elucidated. The available literature regarding the use of cBMA in different tissue repair is highly heterogeneous with regards to indications, concentrations and overall functional outcomes.

This review attempts to examine the evidence behind the use of cBMA in cartilage, bone, and tendon regeneration and repair and to establish proof of concept for the use of cBMA in these biologic environments. In addition our systematic review will provide the reader with a reference of the level and quality of evidence of the current available literature evaluating the uses of cBMA in the treatment of lesions in cartilage, tendon, and bone.

## MATERIALS AND METHODS

A systematic review was conducted according to PRISMA guidelines[3]. The following search terms were used in MEDLINE, EMBASE, and Web of Science databases on November 22, 2016: "cBMA OR concentrated bone marrow aspirate OR BMC OR bone marrow concentrate OR bone marrow derived mesenchymal stem cells". This was paired with one of the following search strategies: (1) "cartilage OR chondrocytes OR chondrogenesis OR arthritis OR osteoarthritis OR osteochondral OR chondral"; (2) "tenocytes OR tendon OR tendinitis OR tendinosis OR tendinopathy"; or (3) "bone OR bone healing OR malunion OR delayed union OR osteocyte OR osteogenesis". Inclusion criteria were: (1) clinical studies demonstrating the effect of cBMA in cartilage, bone; or tendon (2) published in peer-reviewed journal; and (3) written in English. Exclusion criteria included review articles, case reports, basic science studies, and studies evaluating additional pathologic processes. Two independent reviewers performed the literature search screening both title and abstract for all results. Potentially

eligible studies received a full text review. The reference list of the identified articles in the results were manually screened for additional articles. A senior author was consulted if a consensus could not be reached. The following information was extracted and recorded from the included studies: Number of patients, preparation method of cBMA, cell count, treatment groups, adjunctive therapies/scaffolds, follow-up, objective and subjective outcomes, and level of evidence.

## RESULTS

The initial literature search resulted in 1202 total studies. Once duplicates were removed and articles were screened for inclusion/exclusion criteria, 135 were included and full texts were assessed for eligibility. A total of 36 studies met inclusion/exclusion criteria and were included in this review.

### *Study characteristics*

Thirty-one of 36 (86%) studies reported the method of centrifugation and preparation of cBMA. Fifteen of 36 (42%) studies reported either a cell concentration or an increase from baseline. There were no studies that reported on the minimal number of colony forming units in which below that number, cBMA did not provide significant benefit. Twenty-one of 36 (58%) were level of evidence Ⅳ, 12/36 (33%) were level of evidence Ⅲ, and 3/36 (8%) were level of evidence Ⅱ. Two studies were industry funded while 37 declared no conflict of interest.

### *cBMA in full thickness cartilage lesions*

Seven studies evaluated the effect of cBMA in the treatment of full thickness cartilage defects in the knee and all reported significant clinical improvement post-operatively summarized in Table 1[4-10]. Three studies evaluated the effect of cBMA combined with microfracture and demonstrated improved clinical outcomes with reconstitution of original cartilage on magnetic resonance imaging (MRI). All three studies reported bone marrow edema and/or subchondral irregularities[4-6]. One study evaluated the effects of cBMA when compared with matrix-induced autologous chondrocyte implantation (MACI) and found that patients receiving cBMA had a significantly improved IKDC subjective score ($P$ = 0.015) with 81% complete cartilage filling on MRI[7]. One study compared the effects of cBMA to PRP and reported that patients who received cBMA had T2 values closer to that of superficial hyaline cartilage ($P$ = 0.01)[10]. Variation of cBMA application was seen amongst the studies evaluated. Several studies used cBMA in isolation, while other studies combined cBMA with either a collagen or hyaluronic acid scaffold. Many of these studies prepared the defect site and implanted cBMA through arthroscopic techniques.

### *cBMA in osteochondral lesions*

Ten studies evaluated the effect of cBMA in the treatment of osteochondral defects in the talus (7/10) and the knee (3/10) summarized in Table 2[2,11-19]. All ten studies reported both clinical and radiologic improvements post-operatively after receiving cBMA. Six studies evaluated the effects of cBMA with no concomitant procedure and reported good clinical outcome scores including AOFAS, IDKS, and KOOS. For studies that utilized either a collagen or a hyaluronic acid scaffold, no significant difference was reported between the two groups. Buda[11] evaluated cBMA compared to autologous chondrocyte implantation (ACI) and reported no clinical difference between the two treatment strategies but found a higher presence of hyaline like values and lower incidence of fibrocartilage on T2 mapping in the cBMA group. One study favored treatment with cBMA when comparing cBMA to microfracture reporting 100% and 28% normal IDKC values at 5-year follow up, respectively[18]. Lastly, one study reported higher MOCART scores and T2 relaxation values with measurements resembling those of native cartilage in groups that received both microfracture with cBMA compared to groups that received microfracture alone[19]. cBMA had also been used as an adjunctive treatment to autologous osteochondral transplantation and resulted in overall improved FAOS scores post-operatively[2]. Variation of cBMA application was seen amongst the studies evaluated. These included the use of either a collagen powder or hyaluronic acid scaffold, with the majority of studies using arthroscopic techniques for cBMA implantation.

### *cBMA in osteoarthritis*

Five studies evaluated cBMA in the treatment of knee osteoarthritis (OA) summarized in Table 3[20-24]. Only two studies evaluated the efficacy of cBMA without an adjunctive procedure. One reported better clinical outcomes at one week and three months in patients who received cBMA but found no difference in these scores after six months[24]. One study reported significant clinical improvements but found that 76% of patients had abnormal International Cartilage Repair Society repair scores[23]. Three studies evaluated cBMA combined with either PRP or PRF and found functional and clinical improvements in the cBMA groups with improvement in cartilage repair, although not significant[20-22]. Variation of cBMA application was seen amongst the studies evaluated, which utilized ultrasound or fluoroscopy for needle placement or was performed under arthroscopic guidance.

### *cBMA in bone healing*

Nine studies evaluated the use of cBMA in bone healing summarized in Table 4[25-33]. Eight of nine studies reported on the use of cBMA in either non-union or delayed union. One study demonstrated initial radiographic and functional improvements in the cBMA group, but reported similar outcomes after one year post-operatively[31]. All studies reported either lower or similar complication rates post-operatively in groups that received cBMA compared to groups receiving no additional treatment. Bone

**Table 1 Studies evaluating concentrated bone marrow aspirate in the treatment of full thickness chondral lesions**

| Ref. | Tissue | BMAC preparation | Concentration | Study design/ methods/follow up | Outcomes measured | Results | LOE |
|---|---|---|---|---|---|---|---|
| Enea *et al*[4] | Knee | 60 mL BMA from iliac crest processed with MarrowStim Concentration Kit (Biomet) resulting in 3-4 mL of BMAC. Chondral lesion debrided and microfracture performed. Biocollagen MeRE collagen membrane (Bioteck) cut to match shape and immersed in BMAC until implantation. 10:1 mixture of 1-2 mL fibrin glue and BMAC laid on lesion. Membrane inserted and placed. 2-3 mL of fibrin glue-BMAC injected over and left to solidify | NS | $n$ = 9. Arthroscopic microfracture covered with collagen membrane immersed in autologous BMAC from iliac crest. Follow up: 29 mo | Biopsy cartilage evaluated by surgeon using criteria of international cartilage repair society. The following items were utilized: Cartilage repair assessment, MRI, IKDC, Lysholm, VAS (pre and post op), Tegner (pre and post op). Four patients had second look arthroscopy and biopsy | Significant clinical improvement ($P$ < 0.005). Cartilage macroscopic assessment at 12 mo revealed all repairs appeared almost normal. Histo-analysis showed hyaline-like cartilage repair in 1 lesion, fibrocartilaginous repair in 2 lesions and a mixture of both in 1 lesion. Post op MRIs (6-9 mo out) all showed reconstitution of original cartilage. Bone marrow edema and/or subchondral irregularities observed in all cases. Non-homogeneous cartilage signal and fissuring observed in 2 of 3 cases | Ⅳ |
| Enea *et al*[5] | Knee | 60 mL of BMA from the iliac crest was obtained and processed with MarrowStim Concentration Kit (Biomet) to obtain 3-4 mL of BMAC. Cartilage was treated with arthroscopic microfracture and the defect was covered with PGA-HA scaffold matrix (Chondrotissue) seeded with autologous BMAC. 10:1 mixture of 1-2 mL of fibrin glue and BMAC was then applied to lesion bed. PGA-HA soaked in BMAC was then applied with 2-3 mL additional fibrin glue-BMAC mixture dispersed over the matrix until solidification at 2-3 min | NS | $n$ = 9 (Outerbridge type III/IV) Consecutively treated with arthroscopic Polyglycolic acid/ hyaluronan - covered microfracture and BMAC. Follow up: 22 mo | Clinical scoring, IKDC, Lyshold, VAS, Tegner, cartilage microscopic examination at 12 mo, MRI at 8-12 mo post op. 5 patients underwent second look and 2 had biopsy | All patients but one showed improvement in clinical scoring from pre-op sto last follow-up (22 mo). All other variables increased from baseline to latest follow-up. Nineteen cartilage exams appeared normal, three almost normal, and one abnormal at 12 mo. Histo showed hyaline-like cartilage repair tissue formation in one case. MRI showed complete defect filling | Ⅳ |
| Gigante *et al*[6] | Knee | NA | NA | $n$ = 5. MACI augmented with BMAC | Second look arthroscopy biopsy, CRA, ICRS Ⅱ Visual Histological Assessment Scale | Normal ICRS/CRA at arthroscopic evaluation and had mean overall histological ICRS Ⅱ of 59.8 ± 14.5. Hyaline-like matrix only found in one case. Mixture of hyaline/ fibrocartilage was found in one case and fibrocartilage was found three cases | Ⅳ |
| Gobbi *et al*[7] | Patello-femoral | 60 mL of BMA from ipsilateral iliac crest concentrated by BMAC Harvest Smart PreP2 system to obtain concentration of BMC 4-6 times baseline value | 4-6 × baseline | (1) MACI $n$ = 19; (2) BMAC $n$ = 18. Both with HYAFF1 scaffold. Follow up: 3 yr | XR, MRI, IKDC score, KIOOS score, VAS, Tegner | Both groups showed significant improvements in all scores from preop to final follow up ($P$ = 0.002). There was no difference between the two groups except in the IKDC subjective scores which favored BMAC group ($P$ = 0.015). MRI showed complete filling of defect in 76% of MACI and in 81% of BMAC | Ⅲ |
| Gobbi *et al*[8] | Knee | 60 mL of BMA from ipsilateral iliac crest concentrated by BMAC Harvest Smart PreP2 system to obtain concentration of BMC 4-6 times baseline value. Activated using batroxobin enzyme to form sticky clot. Implanted and covered with collagen-based membrane scaffold (ChondroGide) and sealed with fibrin glue (Tissucol) | 4-6 × baseline | $n$ = 25. Cartilage transplantation with mulipotent stem cells and collagen type Ⅰ/Ⅲ matrix | XR, MRI, VAS, IKDC, KOOS, Lysholm, Marx, Tegner | Significant improvement at follow up across all measures. < 45-year-old and smaller lesions = better results. MRI = good stability of implant, hyaline-like cartilage found is histo analysis of biopsied tissue | Ⅳ |

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|---|---|---|---|---|---|---|---|
| Gobbi *et al*[9] | Knee | 60mL BMA from ipsilateral iliac crest (PreP2) and concentrated to 4-6 times baseline value, after activation with batroxobin enzyme (Plateltex Act) and pasted into lesion Covered with collagen type Ⅰ/Ⅲ matrix (Chondro-Gide) and sealed with fibrin glue (Tissucol) | 4-6 × baseline | $n$ = 15. One step surgery with BMAC and Collagen Ⅰ/Ⅲ matrix (chondro-gide) | XR, MRI at 1 and 2 yr. VAS, IKDC, KOOS, Lysholm, Marx, SF-36, Tegner at 6, 12, 24 mo. 3 had second look biopsy | Significant improvement at follow up across all measures ($P$ < 0.0005). Single lesion and smaller lesions had better improvement. MRI showed greater hyaline-like tissue in all patients. Hyaline-like cartilage on histology in 3 biopsies | Ⅳ |
| Krych *et al*[10] | Distal femur | NS | NS | (1) $n$ = 11 control scaffold; (2) $n$ = 23 scaffold + PRP; (3) $n$ = 12 scaffold + BMAC. Follow up: 12 mo | MRI, T2 mapping | BMAC and PRP groups had superior cartilage infill ($P$ = 0.002, $P$ = 0.03). BMAC demonstrated mean T2 value closer to that of superficial hyaline cartilage ($P$ = 0.01) | Ⅲ |

BMA: Bone marrow aspirate; NS: Not significant; CRA: Cartilage repair assessment; MRI: Magnetic resonance imaging; MACI: Matrix-induced autologous chondrocyte implantation; PRP: Platelet-rich plasma.

**Table 2 Studies evaluating concentrated bone marrow aspirate in the treatment of osteochondral defects**

| Ref. | Tissue | BMAC preparation | Concentration | Study design/ methods/follow up | Outcomes measured | Results | LOE |
|---|---|---|---|---|---|---|---|
| Buda *et al*[11] | OCL of talus | Scaffold was a hyaluronic acid membrane loaded with previously cultured chondrocytes (ACI) or with BMAC. Platelet rich fibrin gel was produced the day before surgery using Vivostat System 1 (vivolution A/S). Harvested and processed 120 mL of the patient's venous blood to obtain 6 mL of platelet rich fibrin gel. 60 mL BMA was harvested from posterior iliac crest using Smart PRepI to obtain 6 mL of BMAC. 1 g powder mixed with 2 mL BMAC and 1 mL platelet rich fibrin gel. The hyaluronic acid membrane was cut and loaded with 2 mL BMAC and 1 mL platelet rich fibrin gel. A layer of platelet rich fibrin gel was placed over the implant once in place to provide additional stability | NS | $n$ (total) = 80: (1) $n$ = 40 - autologous chondrocytes implantation; (2) $n$ = 40 with BMAC. Follow up: 48 mo | Clinical scores, XR, MRI Mocart score, T2 mapping | Groups had similar results at 48 mo. No statistically significant difference in clinical outcomes. Return to sport was slightly better with BMAC. MRI MOCART score was similar in both groups. T2 mapping highlighted a higher presence of hyaline like values and lower incidence of fibrocartilage in BMAC group | Ⅳ |
| Buda *et al*[12] | OCL of knee | Combined with either MAST or HA matrix | NS | $n$ = 30. One step arthroscopic BMAC transplant with scaffold. Follow up: 29 mo | Clinical inspection, MRI, IKDC, KOOS | Good clinical outcome and osteochondral regeneration on MRI and biopsies in both groups | Ⅳ |
| Buda *et al*[13] | OCL of talus | Scaffolds either: (1) porcine collagen powder SpongostanI Powder (J and J) mixed with autologous cell concentrate and platelet gel; or (2) hyaluronic acid membrane (fidia advanced biopolymers) with addition of platelet gel. Platelet rich fibrin gel was produced the day before surgery using Vivostat System 1 (vivolution A/S). Harvested and processed 120 mL of the patient's venous blood to obtain 6 mL of platelet rich fibrin gel. 60 mL BMA was harvested from posterior iliac crest using Smart PRepI to obtain 6mL of BMAC. 1 g powder mixed with 2 mL BMAC and 1ml platelet rich fibrin gel. The hyaluronic acid membrane was cut and loaded with 2 mL BMAC and 1 mL platelet rich fibrin gel. A layer of platelet rich fibrin gel was placed over implant once in place to provide additional stability | NS | $n$ = 64. One step arthroscopic BMAC transplant with scaffold (collagen powder of hyaluronic acid membrane) and platelet gel. Follow up: 53 mo | AOFAS scale score, radiographic, scaffold type, lesion area, previous surgery, lesion depth | Mean preop AOFAS was 65.2. Regardless of scaffolding type all patients showed similar pattern of clinical improvement at each follow-up. No correlation between area of lesion and pre-op AOFAS score but did observe relationship between area and AOFAS at each follow up post-operatively. No relationship between AOFAS score and depth of lesion | Ⅳ |

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|---|---|---|---|---|---|---|---|
| Buda *et al*[14] | OCL of knee | Scaffold either MAST or HA matrix + PRF | NS | $n$ = 20. Follow up: 24 mo | Clinical, MRI | Significant improvement at 12 and 24 mo, satisfactory MRI | Ⅳ |
| Giannini *et al*[15] | OCL of talus | Porcine collagen powder (J and J) or hyaluronic membrane scaffold. 60 mL of bone marrow harvested from posterior iliac crest and concentrated by SmartPrep to 6 mL of BMC. One step delivery system | NS | $n$ = 49 received either BMA with collagen scaffold or BMA with HA membrane scaffold. Follow up: 48 ± 6 mo | AOFAS, radiograph, MRI | AOFAS improved $P$ < 0.0005. T2 mapping analysis showed regenerated tissue with T2 values similar to hyaline cartilage in a mean of 78% of the repaired lesion area | Ⅳ |
| Giannini *et al*[16] | OCL of talus | One step arthroscopic transplantation. Platelet gel using Vivostat system. 60 mL BMA harvested from posterior iliac crest. Concentrated using SmartPReP in order to obtain 6 mL of concentrate. Scaffold: Either collagen powder (Spongostan1 Powder) or hyalyronic acid membrane. Scaffold was loaded with 2 mL BMAC and 1 mL PRF | NS | $n$ = 25 in BMAC group. Study also compared to ACI | AOFAS, histology | Statistically significant improvement in mean AOFAS scores post-operatively ($P$ < 0.0005). Only 1 superficial infection noted. Nearly homogeneous regenerated tissue on MOCART MRI in 82% of cases. Hypertrophy found in 2 cases on histology | Ⅳ |
| Giannini *et al*[17] | OCL of talus | Porcine collagen powder (J and J) or hyaluronic membrane scaffold. 60 mL of bone marrow harvested from posterior iliac crest and concentrated by SmartPrep to 6 mL of BMC. One step delivery system | NS | (1) $n$ = 23 - Collagen scaffold + BMA; (2) $n$ = 25 HA membrane scaffold + BMA. Follow up: 29 mo (24-35) | AOFAS, histology | AOFAS improved, Histology showed regenerated tissue in various degrees of remodeling | Ⅳ |
| Gobbi *et al*[18] | OCL of knee | Hyaluronic acid-based scaffold was used with BMAC | 6 × baseline | $n$ = 25 HA-BMAC, $n$ = 25 microfracture. Observed prospectively for 5 yr | Patient-reported scoring tools: IKDC Subjective Knee Evaluation, KOOS, Lysholm Knee Questionnaire, and Tegner activity scale | Microfracture - 64% normal/nearly normal according to IKDC objective score at 2 yr and declined to 28% at 5 yr | Ⅱ |
| | | 60 cc of BMA from Iliac Crest spun to 6 × normal concentration. Batroxobin enzyme used to activate BMAC | | | | HA-BMAC - 100% normal/nearly normal objective IKDC at 2 yr, 100% at 5 yr for ALL outcomes measured | |
| Hannon *et al*[19] | OCL of talus | 60 mL of BMA from ipsilateral iliac crest, concentrated by Arteriocyte Magellan Autologous Platelet Separator System to obtain 3 mL of BMAC | NS | (1) $n$ = 12 BMS; (2) $n$ = 22 BMAC+BMS. Follow up: 48.3 mo for BMAC + BMS, 78.3 mo for BMS | AOFAS, FAOS, SF-12, MOCART | Mean FAOS and SF-12 PCS scores improved pre to post operatively ($P$ < 0.01) for both groups. MOCART score significantly higher in cBMA + BMS ($P$ = 0.023). T2 relaxation values in cBMA + BMS group significantly higher with measurements of adjacent cartilage | Ⅲ |
| Kennedy *et al*[2] | OCL of talus | 60 mL of BMA from ipsilateral iliac crest, concentrated by commercially available BMAC centrifuge system to obtain 4 mL of pluripotent cells | NS | $n$ = 72. AOT with BMAC. Follow up: 28 mo | FAOS, SF-12 | FAOS, SF-12 significantly improved from pre to post-op | Ⅲ |

KOOS: Knee injury and Osteoarthritis Outcome Score; NS: Not significant; OCL: Osteochondral lesions; BMA: Bone marrow aspirate; MRI: Magnetic resonance imaging.

consolidation and time to bone union was improved in patients receiving cBMA, with faster healing rates when

**Table 3 Studies evaluating concentrated bone marrow aspirate in the treatment of osteoarthritis**

| Ref. | Tissue | BMAC preparation | Concentration | Study design/ methods/follow up | Outcomes measured | Results | LOE |
|---|---|---|---|---|---|---|---|
| Centeno *et al*[20] | Knee | 60 mL of BMA from iliac crest was obtained toproduce 1-3 mL of BMAC. 60 cc of heparinized Ⅳ venous blood drawn to be used for isolating PRP and platelet lysate. Lipoaspirate - miniliposuction of the posterior superior buttocks or lateral thigh was performed under ultrasound and minimally processed (centrifuged) adipose tissue was injected into the articular space. Preparations were injected into the articular space of the knee together (5-10 cc) between the meniscus on the most painful side and over lying collateral ligament | NS | Data from registry. (1) $n$ = 616 - BMAC+ PRP *vs* (2) BMAC + PRP + adipose graft. Outcomes and complication questionnaires at 1, 3, 6, 12 mo completed. 2 groups (A-BMAC and PRP protocol, B BMAC and PRP plus adipose fate graft (lipoaspirate) | LEFS, NPS, subjective percentage improvement rating, frequency and type of adverse events | Mean LEFS score increased in both groups and mean NPS decreased in both groups. AE rates were 6% without graft and 8.9% with graft. No difference between groups. Addition of adipose graft did not provide a detectible benefit over BMAC alone | Ⅳ |
| Centeno *et al*[21] | Knee | 10-15 cc whole bone marrow aspirate harvested from 6-8 sites on posterior iliac crest (3-4 each side). Centrifuged and cells isolated. Patient heparinized blood for PRP and PL. Aspirates mixed together and injected into joint. Cell counts were counted four times and average was taken under microscope for total nucleated cell count | Lower and higher cell count groups defined using threshold of $4 \times 10^4$ cells | Data from registry. $n$ = 373 patients that received BMAC combined with PRP and PL injections for 424 OA knees | Clinical scales assessed at baseline, 1, 3, 6, 12 and annually thereafter. NPS, LEFS, pain and functional outcome measures | Significant positive results with treatment for all pain and functional metrics. Higher cell group reported lower post treatment numeric pain scale values ($P$ < 0.001). No significant difference detected for other metrics | Ⅳ |
| Haleem *et al*[22] | Femoral condyle | 20 mL BMA from iliac crest isolated with density gradient (Ficoll-Paque), supplemented with 10% fetal bovine serum and penicillin streptomycin. Microfracture performed and sclerotic bone curetted. Autologous periosteal flap harvested from anteromedial ispilateral proximal tibia to fit defect size and stuffed into place. 1 mL platelet concentrate and 1 mL fibrinogen and 1 mL thrombin placed with BMAC PR fibrin glue | NS | $n$ = 5, treated with BMAC + PRF | At 6 and 12 mo: Lysholm and Revised HHS Knee Score, XR and MRI. 2 patients had follow up arthroscopy at 12 mo rated by ICRS | All patients had statistically significant improvement at 6 and 12 mo ($P$ < 0.005). No statistically significant difference between 6 and 12 mo post op in clinical scores. ICRS were near normal for 2 patients who consented to arthroscopy. MRI of 3 patients at 12 mo showed complete defect filling and complete surface congruity with native cartilage. Two patients showed incomplete congruity. BMAC on platelet rich fibrin gel as a scaffold may be effective to promote repair of articular cartilage defects | Ⅳ |
| Koh *et al*[23] | Knee | 60 mL BMA from Iliac crest processed with MarrowStim Concentration Kit (Biomet) to obtain 3-4 mL of BMAC. Adipose tissue harvested from buttocks through liposuction. All fluid removed from knee arthroscopically. Lesion filled with cell suspension and held stationary for 10 minutes with defect facing upwards. Adherence of MSC confirmed. No marrow stimulation procedures were performed | Average of $3.8 \times 10^6$ ($2.5\text{-}6.1 \times 10^6$) | $n$ = 37 knees using second-look arthroscopy after mesenchymal stem cell implantation for cartilage lesions done 12 mo post op | IKDC, Tegner, cartilage repair assessed using ICRS grading | IKDC and Tegner sores significantly improved ($P$ < 0.001). ICRS overall repair grades 2/37 were normal, 7/37 were near normal, 20/37 abnormal, 8/37 severely abnormal.). Patient satisfaction: 33/34 reported good to excellent satisfaction. High BMI (> 27.5) and large lesion (> 5.4 $cm^2$) had significant prediction of poor clinical and arthroscopic outcomes ($P$ < 0.05) | Ⅳ |

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|---|---|---|---|---|---|---|---|
| Shapiro *et al*[24] | Knee | 52 mL BMA from iliac crest concentrated in Arteriocyte Magellan Autologous Platelet Separator System centrifuge to yield 6 mL of cellular product | NS | $n$ = 25 BMAC, $n$ = 25 saline (patients had bilateral knee pain) | OARSI measure, VAS score, safety outcomes, pain relief, function | OARSI and VAS decreased significantly from baseline at 1wk, 3 mo, 6 mo ($P$ < 0.019), no difference in pain relief | Ⅱ |

BMA: Bone marrow aspirate; MRI: Magnetic resonance imaging; NS: Not significant; OA: Osteoarthritis; BMI: Body mass index; VAS: Visual analogue scale; OARSI: Osteoarthritis Research Society International.

**Table 4 Studies evaluating concentrated bone marrow aspirate in bone healing**

| Ref. | Tissue | BMAC preparation | Concentration | Study design/methods/follow up | Outcomes measured | Results | LOE |
|---|---|---|---|---|---|---|---|
| Bastos Filho *et al*[25] | Tibia/femur nonunion | 11G × 10 cm bone marrow aspiration needle into posterior iliac crest to obtain a total of 100 to 110 mL for each patient - concentrated to 20 mL with Sepax system | NS | $n$ = 6 patients with nonunion of tibia or femur. Four received percutaneous infusion of autologous bone marrow aspirated without Sepax processing. Two received with processing. Follow up to 6 mo | Clinical examination and radiographic evaluation at 2, 4, 6 mo. Clinical criteria included full weight bearing tolerance and absence of pain upon palpation at the fracture site. Radiographic healing checked with AP, lateral and oblique films to look for bone callus. Patient satisfaction questionnaire scale from 0-10 | Bone consolidation obtained in all the patients. Bone callus observed in the radiographic between 3 and 24 wk, average 13.8 wk in group without processing. Mean satisfaction increased in all patients | Ⅱ |
| Desai *et al*[26] | Nonunion/delayed union of tibia | Total of 60 cc bone marrow aspirated from iliac crest with 16 gauge Jamshidi needle (Harvest system). Concentrated to 10 cc for injection | 101.48 ± 64.13/cc | $n$ = 49 patients with tibial nonunion had BMAC injection with DBM and/or rhBMP-2. Follow up until radiographic union or another procedure was performed | Radiographic healing (bridging of 3 out of 4 cortices on AP and lateral films) | No difference in healing rate between patients with fracture gaps less than and greater than 5 mm | Ⅲ |
| Garnavos *et al*[27] | Humeral shaft delayed union | With the use of a 10 cm long and 3 mm wide biopsy needle, 60 mL of bone marrow was aspirated from each patient's iliac wing and was centrifuged to provide 10 mL of concentrated mesenchymal stem cells. The concentrated bone marrow mixed with 10 cc of DBM putty | NS | $n$ = 5. Intramedullary nailing with antegrade/unreamed technique was performed for 4 patients. One patient was treated previously with retrograde/unreamed nailing left in situ. The concentrated mixture was infused percutaneously in the area of nonunion with a biopsy needle under fluoroscopy. Patients were followed up every 4-6 wk for 12 mo | Patients were assessed for union process, discomfort, level of activities and functional improvement | There were no peri- or postoperative complications. Sound union was obtained in all cases from 12 to 20 wk after the operation. At final followup, all patients had regained a satisfactory range of shoulder and elbow motion. They had also returned to pre-injury level of activities and were happy with their treatment and outcome | Ⅳ |
| Guimaraes *et al*[28] | Femoral shaft nonunion | 11G × 10 cm needle used for aspiration from iliac crest. The marrow samples were harvested in small amount (2 mL) and the contents of each syringe were pooled in the container of the bone-marrow-collection kit containing anticoagulant solution. The final volume of bone marrow aspirate (200 mL) was then filtered through a sequence of successively | 9.8 ± 4.3 × $10^6$ *vs* 20.2 ± 8.6 × $10^6$ | $n$ = 16 patients with aseptic nonunion of femur were treated with injection of BM-MSCs who had locked IMN. Follow up: 3-8 mo | Radiographic RUST scores | Bone union occurred in 8 of 16 patients according to RUST. The grafts used in patients whom treatment failed contained significantly lower number of total nucleated cells (9.8 ± 4.3 × $10^6$ *vs* 20.2 ± 8.6 × $10^6$) | Ⅳ |

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| | | smaller-diameter mesh filters. The cells were finally collected in a blood transfer pack unit. The aspirated material was reduced to a final volume of 40 mL by removing most of the RBC the plasma by centrifugation | | | | | |
| Hernigou *et al*[29] | Ankle nonunion | 150 mL of bone marrow aspirate obtained from anterior portion of the ipsilateral iliac crest then treated with a cell separator | 27.3 ± 14.6 × $10^6$ | *n* = 86 ankle nonunion in diabetic patients treated with BM-MSCs *vs* *n* = 86 diabetic matched nonunion treated with a standard bone iliac crest autograft | Time of union, callus volume, complication, morbidity of graft harvesting *vs* bone marrow aspiration in diabetic patients | 70 out of 86 patients (82.1%) treated with BMC achieved healing with a low number of complications; 53 (62.3%) of patients treated with iliac bone graft had healing and major complications were observed: Amputations, osteonecrosis of fracture wound edge, infections | Ⅲ |
| Hernigou *et al*[30] | Tibial shaft nonunion | Bone marrow aspirated from anterior iliac crest total of 300 mL then concentrated to 50 mL | 18 ± 7 million | BMAC injected into 60 noninfected atrophic nonunion of tibia. Follow up until union | Radiographic union; healing time; volume of callus | Patients who did not achieve union had significantly lower number of progenitor cells comparing to the 53 patients who achieved union. There was positive correlation between the volume of mineralized callus at 4 mo and the number and concentration of fibroblast colony-forming units in the graft; there was a negative correlation between the time needed to obtain union and the concentration of CFU in the graft | Ⅳ |
| Ismail *et al*[31] | Long bone nonunion | 40 mL of bone marrow was aspirated from posterior iliac crest and transferred into a container prefilled with 5000 U/mL of heparin. Aspirate was diluted with phosphate-buffered saline at a ratio of 1:1 and centrifuged at room temperature at 3000 rpm for 30 min. The collected buffy coat was washed and transferred into a culture flask containing Dulbecco's Modified Eagle Medium supplemented with 10% fetal bovine serum. Cells were incubated at 37 ℃ at 5% $CO_2$ with a routine culture medium change every two to three days. Subculture was performed between | 14-18 million BMSCs | *n* (total) = 10. *n* = 5, treated with combination of 15 million BM-MSCs, 5 g/$cm^3$ (HA) granules and internal fixation. *n* = 5, control subjects were treated with iliac crest autograft, 5 g/$cm^3$ HA granules with internal fixation. Follow up = 12 mo | VAS, LEFS, DASH score. Radiological assessments for union were conducted by a blinded radiologist using two radiological scoring systems: The Lane-Sandhu and Tiedeman radiological scores | No significant differences in post-op pain between the two groups. The treatment group demonstrated initial radiographic and functional improvements. Statistically significant differences in functional scores were present during the first ($P$ = 0.002), second ($P$ = 0.005) and third ($P$ = 0.01) month. Both groups achieved similar outcomes by the end of one year follow up | Ⅲ |

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| | | days 7 and 10. Mixed with 5 g/cm$^3$ defect of HA granules | | | | |
| Le Nail *et al*[32] | Open tibia fracture | Hernigou's technique. Bone marrow from posterior iliac crest by needle aspiration. Around 500 mL concentrated by centrifugation to obtain 50 mL | 171 ± 107 × 10$^6$ *vs* 118 ± 28 × 10$^6$ | *n* = 43 cases of open tibial fractures with initial surgical treatment that developed nonunion or delayed union, subsequently treated with injection of BMAC | Clinical success (consolidation without any subsequent procedure): Non painful callus palpation and a full weight bearing without any contention system. Radiographic bone healing 3 out of 4 cortices | 23 successes (53.5%) within 17 wk after BMAC | Ⅳ |
| Thua *et al*[33] | Long bone nonunion | BMA (300-350 mL) were obtained by Jamshidi vacuum. Both posterior iliac crests of patients were harvested under loco-regional anaesthesia. BMAC was produced *via* density gradient centrifugation using the Sorvall centrifuge at 3670 rpm for 7 min. Afterwards, a total volume of 8 mL BMAC was mixed with freeze-dried allograft cancellous bone chips. BMAC was incubated for 15 min with bone chips as a composite of BMAC-ACB prior to transplantation | 2.43 ± 1.03 (× 10$^6$) CD34 cells/mL (staining) | *n* (total) = 27. *n* = 9 control treated with autologous cancellous bone graft from iliac crest. *n* = 18 clinical trial group treated with BMSCs and allograft cancellous bone chips. Correction and optimization of fixation device were done for previously failed procedures. Patients were followed up in outpatient clinic for 1, 3, 6, 9 12, 18, 24 mo | Functional outcomes, radiographic outcomes based on modified Lane and Sandhu radiological scoring system | Bone consolidation was obtained in 88.9% and mean interval between cell transplantation and union was 4.6 ± 1.5 months in autograft group. Bone union rate was 94.4% in group of composite BMAC-ACB implantation. The time to union in BMAC-ACB grafting group was 3.3 ± 0.9 mo, and led to faster healing when compared to the autograft | Ⅲ |

NS: Not significant; BM-MSC: Bone marrow-derived mesenchymal stem cell; BMA: Bone marrow aspirate; RBC: Red blood cell; CFU: Colony-forming units; BMSC: Bone marrow derived stroma cell.

compared to patients in the autograft group[33]. One study found a significantly lower number of progenitor cells in patients who did not achieve union as well as a negative correlation between the time needed to obtain union and the concentration of colony forming units in the graft[30]. Lastly, one study evaluated the efficacy of cBMA in the treatment of open tibia fractures and found adequate bone consolidation and bone callus formation in all patients[25]. Variation of cBMA application was seen amongst the studies evaluated. These methods utilized cBMA in isolation or in combination with DBM/rhBMP-2, freeze-dried allograft, or cancellous bone chips. Application of cBMA to the site of nonunion was accomplished by either fluoroscopic visualization or percutaneous injection.

### *cBMA in tendon repair*

Five studies evaluating cBMA in tendon repair were included and summarized in Table 5[34-38]. One study evaluated open Achilles tendon repair augmented with cBMA and reported excellent functional outcomes, early mobilization, normal range of motion, and no re-ruptures at a mean follow up of 29.7 mo[38]. One study evaluated the use of cBMA during rotator cuff repair and reported enhanced healing rates, improved quality of the repair surface on ultrasound and MRI, and a decreased risk of re-rupture when compared to the control group[34]. The MSC content in rotator cuff tears was evaluated in one study, which demonstrated a moderate-to-severe reduction in content at the tendon-bone interface tuberosity relative to the control[35]. Lastly, one study showed that MSCs treated with insulin had an increase in tendon-specific markers, content of tendon specific proteins, and receptors on the cell surface compared with control cells[36]. None of the studies specifically described the method of cBMA injection.

## DISCUSSION

### *cBMA in cartilage repair*

Articular cartilage injury presents orthopedic surgeons with a difficult challenge as its inherent avascularity and poor healing potential can hinder its self-regenerative capacity. This poor repair capacity has been implicated in the development of post-traumatic osteoarthritis (PTOA) and osteochondral lesions (OCL). Traditional techniques for surgical stimulation of cartilage repair include microfracture and micropicking. These techniques penetrate the subchondral bone in order to stimulate blood flow and allow MSCs access to the cartilage defect. In addition,

**Table 5 Studies evaluating concentrated bone marrow aspirate in tendon repair**

| Ref. | Tissue | BMAC preparation | Concentration | Study design/ methods/follow up | Outcomes measured | Results | Level of evidence |
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| Hernigou *et al*[34] | Rotator cuff | 150 mL BMA from iliac crest mixed with an anticoagulant solution (citric acid, sodium citrate, dextrose). MSCs were injected in the tendon at the junction between the bone and tendon (4 mL), and in the bone at the site of the footprint (8 mL). Each patient in the MSC-treated group received a total of 12 mL of bone marrow concentrate | 51000 ± 25000 cells in 12 mL of injected BMC | $n$ = 45 received MSCs during repair. $n$ = 45 matched control group of 45 patients who did not receive MSCs. Follow up: 3, 6, 12, 24 mo and 10 yr | RTC healing and re-tear rate confirmed by ultrasound and MRI | 45/45 repairs with MSC augmentation had healed by six months *vs* 30/45 repairs without MSC treatment by 6 mo. Intact rotator cuffs were found in 39/45 patients in the MSC-treated group, but just 20/45 patients in the control group. Patients with a loss of tendon integrity at any time up to the ten-year follow-up milestone received fewer MSCs as compared with those who had maintained a successful repair during the same interval | Ⅲ |
| Hernigou *et al*[35] | Tendon-bone interface rotator cuff | NS | NS | $n$ = 125 symptomatic patients. $n$ = 75 control patients. Assessed the level of MSCs in the tuberosity of the shoulder of patients undergoing a rotator cuff repair | Mesenchymal stem cell content at the tendon–bone interface tuberosity was evaluated by bone marrow aspiration collected in the humeral tuberosities of patients at the beginning of surgery | A significant reduction in MSC content (from moderate, 30%-50%, to severe > 70%) at the tendon–bone interface tuberosity relative to the MSC content of the control was seen in all rotator cuff repair study patients. Severity of the decrease was statistically correlated to the delay between onset of symptoms and surgery, number of involved tendons, fatty infiltration stage and increasing patient age | Ⅲ |
| Mazzocca *et al*[36] | Rotator cuff | MSCs were exposed to either insulin or tendon-inducing growth factors or were left untreated to serve as a control. The BMA was overlaid onto a 17.5% sucrose gradient and centrifuged for 5 min at 1500 rpm (205 g), and the resulting pink middle layer was obtained. After the isolation of bone marrow, MSCs were exposed to a 1-time dose of 10-9-mol/L, 10-10-mol/L, 10-12-mol/L, or 10-13-mol/L insulin from bovine pancreas or were left untreated to serve as a control | NS | $n$ = 11 patients undergoing arthroscopic RCR. After the determination of the optimal dose of insulin, MSCs were (1) exposed to the hormone insulin; (2) exposed to the growth factors IGF-1, bFGF, and GDF-5, which served as a positive control for MSCs' differentiation into a tendon; or (3) left untreated to serve as a negative control. In the growth factor group, MSCs were treated with a 1-time dose, 10 ng/L, of IGF-1, bFGF, and GDF-5 or 10–10-mol/L insulin | Cell count, gene expression, protein analysis, and immunocytochemical analysis. Confirmation of protein levels was verified on immunocytochemistry analysis by 4 independent evaluators blinded to group assignment | MSCs treated with insulin showed increased gene expression of tendon-specific markers ($P$ > 0.05), increased content of tendon-specific proteins ($P$ > 0.05), and increased receptors on the cell surface ($P$ > 0.05) compared with control cells. Histologic analysis showed a tendon-like appearance compared with the control cells | Ⅲ |
| Mazzocca *et al*[37] | Rotator cuff | Isolation 1: one 5 min centrifugation at 1500 rpm in which BMA was overlaid onto a 17.5% sucrose gradient in a 50-mL conical tube followed by extraction of CTPs in the fractional layer. Isolation 2:30 min | Nucleated cells harvested from fractionated layer were counted and plated | $n$ = 23 BMAC harvested through the anchor tunnel of the humeral head during arthroscopy. $n$ = 23 matched controls. Mean time to follow-up was | Reverse transcription polymerase chain reaction analysis, Single Assessment Numeric Evaluation score | Reverse transcription polymerase chain reaction analysis and cellular staining confirmed the osteogenic potential of the connective tissue progenitor cells. There was no statistically | Ⅲ |

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| | | centrifugation at 1500 rpm followed by fractionated layer extraction of CTPs using a Histopaque gradient | on 100 mm Primaria dishes at a concentration of $0.5 \times 10^6$ cells/9.6 $cm^2$ then incubated | 10.6 ± 6.7 mo in the aspirate group and 10.0 ± 6.2 mo in the control group | | significant difference in the Single Assessment Numeric Evaluation score, range of motion measures or post-operative strength measures between groups | |
| Stein *et al*[38] | Achilles | 30 to 60 mL of BMA, combined with a standardized mixture of anticoagulant citrate dextrose solution A and separated by centrifugation at 3200 rpm for 15 min. The aspirate was concentrated to yield a volume of 6-9 mL of BMAC | NS | *n* = 28 open repairs with BMAC. Mean follow up: 29.7 mo. Patients were followed postoperatively at two weeks, six weeks, three months, six months, one year and annually thereafter | Calf atrophy, maximum dorsi- and plantarflexion, and fatigue limit during single-limb heel raise. Functional and activity status was measured in terms of time to walking, light activity (such as cycling or jogging) and return to sport, as with the validated Achilles Total Rupture Score. Self-reported functional status, activity level and ATRS | All patients achieved good or excellent outcomes postoperatively by attaining functional use or return to sport. At final follow-up of 29.7 ± 6.1 mo, mean calf circumference for paired operative and nonoperative extremities was 37.7 ± 2.0 and 38.2 ± 2.0 (difference -0.5 ± 1.3) cm, respectively, for the 26 patients with single Achilles tendon repair. Walking without a boot was at 1.8 ± 0.7 mo, and participation in light activity was at 3.4 ± 1.8 mo. Overall, 92% (25 of 27) patients returned to their preferred sport successfully at 5.9 ± 1.8 mo. Mean ATRS at final follow-up was 91 (range 72-100) points, with no single mean item score below 8 points. All patients were able to achieve a ROM of neutral dorsiflexion or greater and were able to successfully perform a single-limb heel raise at final follow-up | Ⅳ |

NS: Not significant; MSC: Mesenchymal stem cell; BMA: Bone marrow aspirate.

mosaicplasty and autologous chondrocyte implantation (ACI) have been utilized to repair chondral damage. First and second-generation ACI procedures, as well as mosaicplasty, have several concerns including donor site morbidity, cost, and lack of availability to all surgeons due to FDA restrictions. The inability of chondrocytes to self-regenerate and self-renew has directed surgeons to investigate alternative biologic augments in the traditional surgical treatment for cartilage defects. cBMA is a rich source of mesenchymal stem cells and has emerged as a treatment strategy to regenerate cartilage defects in OCL and PTOA.

Several *in vivo* models have demonstrated production of type II collagen and hyaline-like repair tissue when introducing MSCs to a cartilage defect, therefore the use of cBMA may provide further stimulation of chondrogenesis when addressing cartilaginous lesions[19]. There have been a number of studies evaluating the use of cBMA in cartilage regeneration and repair in the animal model. Saw *et al*[39] investigated the use of cBMA combined with hyaluronic acid in the treatment of full-thickness chondral defects in a goat model and reported hyaline regeneration after 24 wk. Fortier *et al*[40] evaluated the treatment of full-thickness cartilage defects with cBMA combined with microfracture in the equine model. Improvements in both macroscopic and histologic scores in tissue treated with cBMA were reported with MRI demonstrating an increase in defect filling and improved repair tissue integration with normal surrounding cartilage[40].

The current literature demonstrates the potential benefits of utilizing cBMA for the repair of cartilage injury in the clinical setting. Significant clinical improvement in functional scores was demonstrated with the use of cBMA in the treatment of full thickness cartilage injury, post-traumatic osteoarthritis, and osteochondral lesions. Improved clinical and histologic results were reported when cBMA was used as an adjunctive procedure with either microfracture or MACI in the treatment of full thickness chondral lesions[4,6,7]. On MRI, groups treated with cBMA demonstrated superior cartilage ingrowth with T2 values closer to that of superficial hyaline cartilage when compared to either a control scaffold or MACI alone[7,10]. These positive results were also demonstrated when utilizing cBMA in the treatment of OCLs. Gobbi *et al*[18] compared with microfracture with cBMA in the treatment of OCLs and found that microfracture resulted

in 65% normal IKDC at 2 years with decline to 27% at 5 years *vs* 100% normal at 2 years and no decline at 5 years for patients treated with cBMA. Buda *et al*[11] reported a higher presence of hyaline like values and lower incidence of fibrocartilage on T2 mapping in patients who received cBMA when compared to those who received ACI. Hannon *et al*[19] also demonstrated better T2 relaxation values with higher measurements of adjacent cartilage in patients treated with bone marrow stimulation (BMS) with cBMA than those treated with BMS alone. Surprisingly, these positive results were not translated as effectively when evaluating cBMA in the treatment of knee OA. Overall, studies demonstrated positive results with improved pain and clinical scores initially but after one-year follow-up, there was no significant difference between groups receiving cBMA and those that did not.

### *cBMA in bone regeneration*

Nonunion is a catastrophic failure of bone healing, which has gained increased attention over the last two decades. It is estimated that 5% to 10% of fractures will result in delayed union or nonunion resulting in prolonged treatment and repeated hospitalizations, longer rehabilitation protocols, and increased overall morbidity[41]. The financial burden posed by nonunion remains a challenge for orthopedic surgeons with a total estimated cost of these complications ranging between $23000 and $60000 per patient[42]. Numerous techniques of treating nonunion have been described in the literature including invasive interventions such as open reduction internal fixation with the use of bone graft or bone graft substitutes. Autologous cancellous bone graft derived from the iliac crest is still considered the gold standard graft option due to its high potentials of osteoconduction, osteoinduction, and osteogenesis. However, there is a limit to the amount of bone graft from iliac crest donor site that can be harvested in the reconstruction of large osseous defects. In addition, there are disadvantages of chronic donor site pain, cosmetic concern, and nerve injury, which have been documented in the literature[33].

The use of cBMA as an adjunctive procedure has gained attention in the treatment of nonunions[30]. The current literature demonstrates faster healing with greater than 94% union rate when using cBMA combined with allograft compared with conventional autologous cancellous bone graft[33]. Ismail *et al*[31] reported similar union rates and outcomes when comparing cBMA and iliac crest autograft. The benefits of cBMA as an adjunctive therapy has also been demonstrated in the treatment of upper extremity long bone nonunion. Garnavos *et al*[27] described successfully using a minimal invasive approach by injecting cBMA to address humeral diaphyseal fractures, thereby avoiding potential complications associated with the conventional compression plating technique for treating humeral nonunions. Hernigou *et al*[29] utilized the same minimally invasive technique to treat diabetic ankle fractures nonunion. The diabetic population poses a challenge for orthopedic surgeons with well-documented increased complications and increased time to bony union. Hernigou *et al*[29] also reported a union rate of 82.1% with minimal complications in patients who received cBMA compared to a union rate of 62.3% with major complications in patients who received iliac bone graft alone.

Several studies evaluated the effect of BMA concentration on functional outcomes when treating long bone nonunions. Hernigou *et al*[30] demonstrated that improved time to union with the use of cBMA was potentially related to the number of progenitors in the graft. The amount of bone healing may be directly related to the concentration of cells and the time to union may be indirectly related to the number of cells[30]. This finding was also supported by Guimaraes *et al*[28] demonstrating that grafts used in patients whom treatment failed contained significantly lower number of total nucleated cells. Bastos Filho *et al*[25] compared using cBMA *vs* whole volume BMA reporting no significant difference in time to union and patient satisfaction score. Although no significant difference was reported, this may be attributed to the small sample size in the cBMA group ($n$ = 2) and minimal follow up. In addition, this study highlighted that unprocessed cBMA contains larger volume and fatty content in the graft increasing the risk of pulmonary embolism, therefore the smaller volume of cBMA may in fact be a safer alternative.

### *cBMA in tendon repair*

Tendon injuries typically result from repetitive motions or overuse and can be difficult to treat as many patients either present late or after a prolonged period of non-operative management making treatment challenging due to the chronicity of the injury. It has been well documented that delayed presentation of rotator cuff tears decreases the MSC content and healing potential in patients[35]. A study by Hernigou *et al*[35] reported a significant reduction in the number of MSCs at the tendon-bone interface of the greater tuberosity in patients with a rotator cuff injury. In addition, they found that the severity of the decrease in MSC content correlated to increasing patient age, delay between onset of symptoms and surgery, fatty infiltration stage of muscle, and the number of involved tendons[35]. It has been demonstrated that MSCs have the potential to develop into tenocytes and can be a source of growth factors to establish an environment conducive to tendon tissue regeneration. MSCs in the form of cBMA have been shown to improve the strength and quality of tissue formed when used in tendon repair[34,35,38].

The current literature has demonstrated that the addition of cBMA can help to heal tendon injuries and at times may decrease the healing time and rate of re-rupture. Hernigou *et al*[35] reported enhanced healing and improved quality of the repair surface on ultrasound and MRI in patients receiving cBMA during rotator cuff repair. They reported that 100% of the rotator cuff repairs healed by six months compared to 67% in the control group. Furthermore, 87% of the study group had an intact rotator cuff repair compared to 44% of the control at ten year follow up indicating superior outcomes in the longer term[34]. The benefits of cBMA in tendon repair

have also been demonstrated in the Achilles tendon model. Stein *et al*[38] reported excellent results with no re-ruptures, decreased calf atrophy, early mobilization, a 92% return to sport, and better ankle range of motion in patients receiving adjunctive cBMA during Achilles tendon repair compared to those who received no additional treatment.

One of the difficulties in analyzing BMA literature is the variable methods of harvesting, preparing, and concentrating cBMA. Mazzocca *et al*[37] devised a novel technique for harvesting BMA in patients undergoing rotator cuff repair with no donor site morbidity. BMA was harvested through the anchor tunnel of the humeral head during routine arthroscopic rotator cuff repair. No additional complications during the procedure, no significant delay in the procedure, and no difference in functional patient outcomes were reported when using this harvest technique[37]. Lee *et al*[43] studied the use of two different concentrations of allogenic cBMA in patients with lateral epicondylitis. They found no significant differences in the changes of elbow pain and performance between the two groups on follow up visits but they did note faster pain improvement and an earlier plateau of performance scores in the group that received a higher concentration of MSCs[43]. Lastly, Mazzocca *et al*[36] showed that MSCs treated with insulin showed statistically significant increase in gene expression of tendon-specific markers, increase in content of tendon-specific proteins, and increase in receptors on the cell surface. Therefore, these studies demonstrate that there are many factors that can increase the potential for tenocyte differentiation and enhanced tendon repair and regeneration.

### *Level of evidence*

Although the literature highlights the potential benefit of cBMA as either a primary or adjunctive treatment strategy in the treatment of cartilaginous lesions, bony defects, and tendon injury, the majority of these studies were of clinical level of evidence Ⅲ or Ⅳ. This review demonstrates the need for future randomized clinical trials with larger numbers of subjects and standardization of harvesting and application. Although several studies evaluated the effect of cell concentration on healing potential, an effective therapeutic range has yet to be established for each tissue environment.

### *Summary of MSC mechanism*

Adult BMSCs have two primary functions: (1) to differentiate into distinctive end-stage cell types such as bone, cartilage, and tendon; and (2) to secrete bioactive macromolecules that are both immunoregulatory and regenerative[44]. Every cell has a half-life with a turnover sequence mechanism that gives rise to the phenotypes in complex tissues. This allows for both replacement of cells, as well as, the capacity for differentiation into bone, cartilage, and tendon. BMSCs also have characteristic markers of pericytes, which are smooth muscle vascular support cells that may play an important role in stem cell differentiation[44,45]. MSCs also demonstrate trophic activity through secretion of both cytokines and growth factors[46]. The intrinsic secretory activity of MSCs affords a regenerative environment for the repair of injured or damaged tissues[44]. Tissue-specific scaffolds have also been utilized in tissue engineering to reform tissues when MSCs are implanted into different tissue sites. The capacity for cell regeneration and repair relies on several additional factors including patient age, extent of injury/damage, and the functional ability of MSCs to grow and repair. Tissue engineering allows for the manipulation of both the delivery of MSCs to targeted tissue sites and the microenviroment for which cells grow in order to enhance differentiation[44]. Future investigations will continue to focus on harnessing the therapeutic potential of MSCs in tissue specific environments to enhance regeneration and repair of cartilage, bone, and tendon.

### *Conclusion*

The current literature demonstrates the potential benefits of utilizing cBMA for the repair of cartilaginous lesions, bony defects, and tendon injuries in the clinical setting. The studies have demonstrated using cBMA as an adjunctive procedure can result in cartilage healing similar to that of native hyaline tissue, faster time to bony union, and a lower rate of tendon re-rupture. This systematic review also demonstrates discrepancies between the literature with regards to various methods of centrifugation, variable cell count concentrations, and lack of standardized outcome measures. Although several studies evaluated the effect of cell concentration on healing potential, an effective therapeutic range has yet to be established for each tissue environment. Future studies should attempt to examine the integral factors necessary for tissue regeneration and renewal including stem cells, growth factors and a biologic scaffold.

## COMMENTS

### *Background*

Bone marrow aspirate (BMA) has been utilized as a source of bone marrow-derived mesenchymal stem cells (BM-MSC) with its relative ease of harvest, low morbidity, and feasible cost. BMA alone has a relatively low percentage of MSCs and therefore concentrated bone marrow aspirate (cBMA) has gained increased attention. cBMA stimulates tissue regeneration and repair and has become an increasingly popular alternative and adjunct in the treatment of cartilaginous lesions, bony defects, and tendinous injuries.

### *Research frontiers*

Current research has focused on the use of cBMA in cartilage, bone, and tendon regeneration and repair. The available literature regarding the use of cBMA in different tissue environments is highly heterogeneous with regards to indications, concentrations and overall functional outcomes. This systematic review attempts to establish proof of concept for the use of cBMA in these biologic environments.

### *Innovations and breakthroughs*

This systematic review demonstrates the potential benefits of utilizing cBMA for the repair of different tissue types in the clinical setting based on the most up-to-date published clinical studies. This systematic review also highlights

discrepancies between the literature with regards to various methods of centrifugation, variable cell count concentrations, variable methods of application of cBMA, and the lack of standardized outcome measures.

### Applications

The current literature demonstrates the potential benefits of utilizing cBMA for the repair of cartilaginous lesions, bony defects, and tendon injuries in the clinical setting. The studies have demonstrated using cBMA as an adjunctive procedure can result in cartilage healing similar to that of native hyaline tissue, faster time to bony union, and a lower rate of tendon re-rupture.

### Terminology

cBMA: Concentrated bone marrow aspirate; BMA: Bone marrow aspirate concentrated by centrifugation in order to increase the ratio of MSCs.

### Peer-review

The authors present a well written systematic review examining the use of BMA in the management of cartilage, bone, and tendon injuries. Overall, the paper is very well organized and reads well.

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SYSTEMATIC REVIEWS

# Distal triceps injuries (including snapping triceps): A systematic review of the literature

Kimberley Shuttlewood, James Beazley, Christopher D Smith

Kimberley Shuttlewood, James Beazley, Christopher D Smith, Royal Devon and Exeter Hospital, Exeter, Devon EX2 5DW, United Kingdom

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Correspondence to: Christopher D Smith, Shoulder and Elbow Consultant, PEOC, Royal Devon and Exeter Hospital, Barrack Road, Exeter, Devon EX2 5DW, United Kingdom. christophersmith3@nhs.net
Telephone: +44-1392-406354

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## Abstract

### *AIM*

To review current literature on types of distal triceps injury and determine diagnosis and appropriate management.

### *METHODS*

We performed a systematic review in PubMed, Cochrane and EMBASE using the terms distal triceps tears and snapping triceps on the 10th January 2017. We excluded all animal, review, foreign language and repeat papers. We reviewed all papers for relevance and of the papers left we were able to establish the types of distal triceps injury, how these injuries are diagnosed and investigated and the types of management of these injuries including surgical. The results are then presented in a review paper format.

### *RESULTS*

Three hundred and seventy-nine papers were identified of which 65 were relevant to distal triceps injuries. After exclusion we had 47 appropriate papers. The papers highlighted 2 main distal triceps injuries: Distal triceps tears and snapping triceps. Triceps tear are more common in males than females occurring in the 4th-5th decade of life and often due to a direct trauma but are also strongly associated with weightlifting and American football. The tears are diagnosed by history and clinically with a palpable gap. Diagnosis can be confirmed with the use of ultrasound (US) and magnetic resonance imaging. Treatment depends on type of tear. Partial tears can be treated conservatively with bracing and physio whereas acute tears need repair either open or arthroscopic using suture anchor or bone tunnel techniques with similar success. Chronic tears often need augmenting with tendon allograft or autograft. Snapping triceps are also seen more in men than women but at a mean age of 32 years. They are characterized by a snapping sensation mostly medially and can be associated with ulna nerve subluxation and ulna nerve symptoms. US is the diagnostic modality of choice due to its dynamic nature and to differentiate between snapping triceps tendon or ulna nerve. Treatment is conservative initially with activity avoidance and if that fails surgical management includes resection of triceps edge or transposition of the tendon plus or minus

ulna nerve transposition.

***CONCLUSION***
Distal triceps injuries are uncommon. This systematic review examines the evidence base behind diagnosis, imaging and treatment options of distal triceps injuries including tears and snapping triceps.

**Key words:** Triceps; Distal; Tear; Rupture; Snapping; Partial thickness; Biomechanical; Anatomy



**Core tip:** The anatomy, demographics, associations and mechanisms of triceps injuries are presented from the evidence base in the literature. Partial thickness tears and snapping triceps can be difficult to diagnose and appropriate assessment and imaging is essential. The surgical management available in the literature is presented for these uncommon injuries.

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## INTRODUCTION

Triceps injuries are relatively rare in comparison to other tendons around the elbow and found to be present on 3.8% of elbow magnetic resonance imaging (MRI) studies following elbow injury[1]. Lateral and medial epicondylitis being the most commonly encountered pathology and distal biceps ruptures presenting more frequently[2]. However, triceps pathology can cause significant symptoms and due to its less common nature can cause problems with diagnosis and treatment. The aim of this study was to review all current literature and present the best evidence for the management of distal triceps injuries.

## MATERIALS AND METHODS

A systematic review was conducted using three search strategies (distal [All Fields] AND triceps [All Fields] AND ("1996/12/31" [PDAT]: "2017/01/10" [PDAT]), (triceps [All Fields] AND tear [All Fields] AND ("1996/12/31" [PDAT]: "2017/01/10" [PDAT]) and (snapping [All Fields] AND triceps [All Fields] AND ("1996/12/31" [PDAT]: "2017/01/10" [PDAT]) in PubMed on January 10th 2017. EMBASE and Cochrane databases were also searched with the same strategy. Additional references were looked for in the citations of the selected studies.

### *Inclusion criteria*

Clinical studies investigating distal triceps injuries in English.

### *Exclusion criteria*

Review articles; studies in foreign languages; animal studies; double publication of data; letters to authors.

Forty-seven studies were eligible for review and a further three studies were found from citations within the selected studies (Figure 1).

## RESULTS

### *Appraisal of literature*

All studies identified by the above search were case series and case reports. Inclusion criteria in the series was generally poorly described. Study number were small with the largest series being only 37 patients[3]. The tears were assessed by a number of modalities with no standard assessment utilised. Patient reported outcome measures were inconsistently used. As a consequence of this heterogeneity of patient groups, imaging and outcomes reported, reliable synthesis of data is not possible. As such the data is reported in a descriptive manner. Four distinct entities were identified. Acute tears, chronic tears, partial tears (either acute of chronic) and snapping triceps.

### *Anatomy*

The triceps brachii is composed of three muscle bellies. The long head arises off the infraglenoid tubercle of the scapula, the medial head off the posterior aspect of the distal to the spiral groove and the lateral head off the lateral intermuscular septum and the posterolateral aspect of the humerus above the spiral groove. The triceps inserts as a bilaminate tendon over a wide area onto the tip of the olecranon. The average triceps width at its distal insertion, including the tendon and lateral expansion, has been reported as 40.6 mm[4]. With the tendon being a mean width of 30.6 mm and the distance from its medial edge to the ulna nerve at 10.2 mm[4]. Its footprint has a mean length of 22.5 mm and a width of 22.7 mm, giving the footprint an area of 466.2 $mm^2$[4]. In around half of specimens a discrete tendinous portion of the medial triceps deep to the long and lateral head has been reported in cadaveric dissection, with the long and lateral portion forming a tendon superficial to it[5]. The mean dimensions of this medial head insertion were 16 mm × 4 mm, with a mean area of insertion of 44 $mm^2$[5]. This study also demonstrated a second variant in the other half of specimens. This had a common combined tendon insertion, but still with the medial fibres deep to the long and lateral head.

Partial tears can be located on the superficial tendon only (combined lateral or long head)[6-8] but have also been described for the deep portion of the tendon in isolation (medial head)[5,9,10] the central one third of the tendon in isolation[10], the lateral portion in isolation[10], the lateral and central portion combined[10] or involving the medial and long head insertions with the lateral portion intact[10,11].

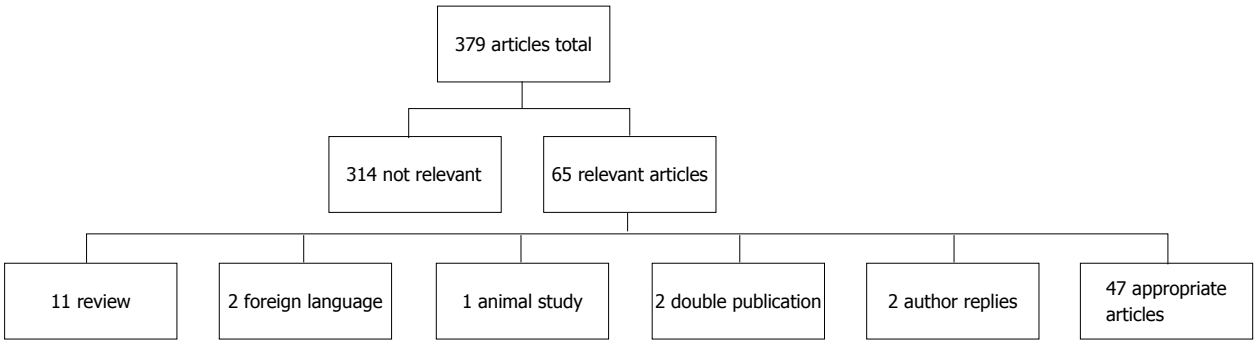


**Figure 1 Flow diagram of systematic review process.**

### Demographics

Triceps tendon ruptures most commonly affect men in the 4th and 5th decades of life. From our pooled results we observed the mean age at rupture to be 47.5 years with a range from 12 to 75 years[1,3,5,8-28]. There was an 11:1 ratio of males to females ($n$ = 170)[1,3,5,8-29]. Three paediatric cases have been reported in the literature in 12 and 16 year olds[11,22,26].

### Associations

Triceps tendon ruptures are reported to be more common in systemic disease or entities such as chronic renal failure with secondary hypo-parathyroidism, rheumatoid arthritis and diabetes[8]. Localised infection has also been reported as a cause of rupture[1]. Interestingly chronic pre-existing posterior elbow pain may be present in up to a third of the patients[25] and with histology demonstrating chronic tendinopathy features in patients with pre-existing pain[17]. In traumatic ruptures, one study observed intra-articular fractures or collateral ligament ruptures in 3 of 6 patients (50%) and advised arthroscopic assessment of the joint at the same time as repair[12]. Concurrent olecranon fractures[16] and ulna neuropathy secondary to haematoma[23] have also been observed with traumatic ruptures. Bilateral tears have been reported in patients with a history of anabolic steroid use[26-28].

### Mechanism of injury

The two described mechanisms for acute tears of the triceps are direct contact trauma, such as a fall or hitting fixed resistance with the posterior elbow[5,14,19,21,25]. Weightlifting[1,5,17,19,23-25,27,30] was the most common sport associated with acute tears and was often associated with a history of steroid use[1,23,30]. American football[3,29] and general sports injuries[8], as well as direct lacerations[10] have all also been reported as mechanisms.

### Investigation

History and examination form the mainstay of diagnosis. Patients typically present with ecchymosis, pain, swelling, extension lag and a decreased active range of motion[10,19,21,22,31]. Palpable defects are commonly found and present in up to 80% of patients[10,21,22,31]. Partial tears may be easily missed as patients may have a good range of active motion, but do typically present with reduced power on extension of the elbow[5,6,9,15,18,20,31].

A bony fleck proximal to the olecranon is commonly identified on lateral radiographs[10,12,17,23,25,27] and is strongly suggestive of a triceps avulsion injury The bony fleck may also be demonstrated on ultrasound (US)[7,8]. This radiological sign reflects the intra-operative observation that 33%-73% of patients have avulsion fractures off the olecranon. The remainder of patients have a rupture at the bone tendon junction[19,25]. Triceps ruptures can be missed on X-ray[22,25] and both US and magnetic resonance imaging (MRI) have been used to diagnosis complete tears and partial tears[7,17,19,25,27]. US has been reported to be as accurate as MRI for both complete and partial ruptures, including identifying the location of partial rupture[8,22].

### Treatment

**Partial tears:** Good results of non-operative treatment even in patients with high functional demands have been reported for the treatment of partial tears. Treatment involves physiotherapy, bracing and avoidance of heavy lifting, pushing or resisted extension for a period of up to 12 wk[27,31]. Harris *et al*[27] reported good results in a single high demand patient with bilateral tears treated with a conservative regime. Platelet rich plasma (PRP) injection has also been advocated for the treatment of partial tears[18,29]. Cheatham *et al*[18] reported the results of a single patient treated with PRP with resolution of pain and return to gym 4 mo after a PRP and physiotherapy regime.

### Complete tears

**Acute tears:** Early primary repair is indicated for complete acute ruptures. Surgery is preferably preformed within the first three weeks of injury. Numerous surgical techniques have been reported. These include suture anchors in the triceps footprint[5,6,21,25,32], bone tunnels[10,14,20,22,31,33] or a combination of both tunnels and anchors[15,19,33]. Suture anchors repairs have also been performed arthroscopically[5,6,32].

Bava *et al*[21] reported the results of 5 male patients treated with an open suture anchor technique. They reported a mean American Shoulder and Elbow Surgeons elbow score of 99.2 at an average of 32 mo follow-up[21]. Lempainen *et al*[25] also reported excellent

results in three athletes treated with an open suture anchor technique for acute tendon rupture. van Reit and Neuerman[10] report on the largest series of open bone tunnel repairs. van Reit *et al*[10] reported the results of 14 patients treated for acute tendon rupture with a bone tunnel technique. Triceps strength was noted to be 4/5 or 5/5 on manual testing in all examined subjects post operatively. Isokinetic testing of ten patients showed that peak strength was, on the average, 82% of that of the untreated extremity. Three re-ruptures were reported in their series[10]. van Riet *et al*[10] reported the results of six patients treated with a bone tunnel technique and reported good to excellent results at 12 mo post op with no cases of re-rupture. Kokkalis *et al*[19], Paniago *et al*[15] and Paci *et al*[33], all report good results utilising a combined bone tunnel and suture anchor technique in three separate case reports with no adverse advents reported.

Techniques utilising arthroscopic repairs for acute injuries have been reported by Athwal *et al*[5] and Ng *et al*[32]. Athwal *et al*[5] reported good results for the arthroscopic repair of two acute tears treated with an arthroscopic technique at 2 years' follow-up with respect DASH and Mayo elbow scores. Ng *et al*[32] did not report outcomes for their technique.

Because of the heterogeneity of types of tear, repair techniques, and outcome measures it is impossible to determine superiority of one technique over another. Generally surgery has been reported to give good improvement in the Morrey score, Mayo, ASES, Oxford elbow scores and DASH[6,9,14,21,29]. It is reported to significantly reduce pain and improve muscle strength[6,10,19]. Our pooled results have demonstrated that in three studies, all patients achieved full extension in some studies with flexion to at least 110 degrees[10,14,15], whereas others achieve an average loss of 7-10 degrees of extension[10,19]. Three of 14 (21%) re-ruptures were reported in van Reit[10]'s study, one suture anchor pullout was been reported and needed revision[14], and one asymptomatic partial re-rupture was detected on post-operative MRI[6]. Otherwise no re-ruptures were reported or commented on.

**Chronic tears:** The management of chronic tendon ruptures is a challenge. Occasionally it is possible to repair the tendon using one of the techniques described above. For chronic ruptures with significant tendon retraction, reconstruction with a graft may be required. Grafts include achilles allograft[11,13] or ipsilateral semitendinous tendon[10,15], aconeus[10,11], Latisimus Dorsi[10], plantaris[10] and palmaris longus[10]. Aconeus[26] and palmaris longus have also been used in augmentation of primary repairs[20]. Sanchez-Sotelo *et al*[11] reports the largest case series of chronic rupture reconstruction from the Mayo clinic. They utilised an achilles tendon allograft in three cases or an anconeus muscle flap in four cases. One rotation flap failed six months after operation. At an average of 33 mo follow-up the remaining six patients had no or slight pain, restoration of a functional arc of movement and normal or slightly decreased power of extension[11].

### *Biomechanical studies*

Petre *et al*[34] reported the intact triceps tendon has a peak load to failure of 1741N, in comparision to peak load to failure of 317N, and 593N for a direct repair, and augmented repair tendons respectively. Comparison made between peak load to failure for a trans-osseous cruciate suture technique[10] and a two bone tunnel and knotless sutures technique[33], showed a significant difference of 510N for the knotless technique and 283N for the cruciate technique[35]. A similar peak load to failure of 317N was found for the same trans-osseous cruciate suture technique[10], but found to be less than the peak load of 593N when the repair was augmented with interwoven flexor carpi radialis[34]. Interestingly Yeh *et al*[4] observed no significant difference in the peak load to failure for an "anatomic" double row trans-osseous repair[4], the trans-osseous cruciate suture technique[10] and a 2 suture anchor with Krakow-type whip-stitch technique[4].

### *Snapping triceps*

The snapping triceps occurs in a younger population than triceps tendon rupture with a mean age of 32 years ($n$ = 30), ranging from 14-65 years[36-42] and slightly reduced male to female ratio of 6.5:1[36-42].

Snapping triceps is a dynamic condition occurring during flexion or extension[43] of the elbow and is characterised by a snap on both active and passive movement[43]. The triceps can dislocate on either the medial or lateral side, but is much more common medially[41]. It can be asymptomatic, cause snapping, elbow pain or ulna neuropathy if dislocating medially[42-44]. Snapping triceps has been demonstrated to be bilateral in some patients, but is not necessarily symptomatic on both sides[42]. On the medial side, the snapping can be attributed to the ulna nerve, but snapping may still occur despite ulna nerve transposition[36]. Snapping triceps may be associated with dislocation of the ulna nerve[43]. Spinner *et al*[42] reported all 17 patients in his series (100%) having concurrent dislocation of the ulna nerve with the snapping triceps. Spinner postulated that a snapping ulna nerve and snapping triceps could be differentiated by the angle at which the snapping occurred. The ulna nerve is thought to snap at 70-90 degrees of flexion, whereas the triceps is thought to snap at around 115 degrees of flexion[43].

### *Aetiology*

Snapping triceps is thought to be due to the medial vector placed on triceps that can occur in cubitus varus and is not thought to be associated with rotational deformities[44] or muscle activation patterns[40]. This medial vector is a function of the T angle where the T angle is the angle between the subtended line of pull of triceps (humeral shaft with extended elbow) and the longitudinal line of proximal ulna[44].

On the medial side snapping triceps can be a com-

plication of displaced supracondylar fractures[36,45], inherited as an accessory medial triceps or abnormal insertion[43,46], due to hypertrophy of the medial triceps in athletes[43,47], associated with hypermobility of the ulna nerve[42], associated with osseous abnormalities[42] and as a complication of ulna nerve transposition[48,49]. On the lateral side it has been associated with a widened triceps tendon inserting more laterally and is treated with resection of the lateral edge[41].

### Diagnosis

US, MRI, CT and sonoelastography have been used for diagnosis[37-39,43,50]. Ultrasound is the imaging modality of choice of some as can be used as a dynamically to differentiate between a snapping medial triceps and a subluxing medial nerve[37].

### Treatment

Initially conservative treatment can be attempted with NSAIDS and avoidance of provoking activities for 3-6 mo[43]. If this is unsuccessful surgery can be considered[36]. Surgery can include resection of the triceps edge, transposition of the tendon, transposing an associated ulnar nerve and correction of cubitus varus[43,45]. Transposition involves transferring the medial third of the tendon to the lateral position[36,47].

## DISCUSSION

The distal insertion of the triceps anatomy is presented and relates to the different types of tears seen in clinical practice. Distal triceps tears can present in a wide age group, but are much more common in males. They can be associated with a history of steroid use and sports injuries, especially weightlifting. Full thickness tears are usually easily diagnosed on clinical examination, but partial thickness tears can be missed and require imaging with either MRI or US. They can be associated with intra-articular fractures and collateral ligament injuries around the elbow. Some partial thickness tears can be managed with nonsurgical treatment, and full thickness tears can be treated with reattachment *via* anchors or transosseous sutures. Chronic tears may require augmentation with tendinous allograft or autograft. Snapping triceps presents in a younger age group, but still with predominance in males. It is much more common on the medial side and can present with an array of symptoms apart from snapping. It can be misdiagnosed as an ulnar nerve subluxation and can be a cause of persistent symptoms after surgery for this. Treatment initially is non-surgical, but can involve resection of the thickened edge of the tendon, transposition of the tendon and management of the ulnar nerve.

## COMMENTS

### Background

Distal triceps injuries are rare and therefore can be misdiagnosed and poorly managed. The purpose of the systematic review of distal triceps injuries was to identify the main injuries that occur and how to diagnose these as well as to identify if there was a consensus or how to manage these.

### Research frontiers

The main hotspot identified in this review is the best type of fixation for distal triceps ruptures and if these injuries are being better diagnosed then hopefully there will be larger numbers of cases to investigate clinically with regards to superiority of fixation.

### Innovations and breakthroughs

The systematic review has shown that magnetic resonance imaging is superior at confirming the diagnosis of distal triceps tears when there is clinical doubt whereas snapping triceps are better diagnosed using ultrasound due to its dynamic nature. Partial tears of the distal triceps can be initially treated conservatively but full tears need to be treated surgically. Snapping triceps can also be treated conservatively initially but failure to resolve symptoms can be treated surgically with resection of the snapping edge of triceps and/or transposition.

### Applications

The systematic review will hopefully make readers more aware of distal triceps injuries and the differential diagnosis of snapping triceps when faced with a subluxing ulna nerve. The authors hope that as there is no gold standard for distal triceps tear fixation that future research can investigate these in the clinical setting as opposed to the cadaveric setting to identify which fixation is superior.

### Peer-review

This is a review article on the topic of distal triceps lesions. The authors perform a systematic review of the literature and present their conclusions based only in original data form the search. This is a well written paper that is interesting to read and will be of help to the readers of the journal.

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SYSTEMATIC REVIEWS

# Worldwide orthopaedic research activity 2010-2014: Publication rates in the top 15 orthopaedic journals related to population size and gross domestic product

Erik Hohmann, Vaida Glatt, Kevin Tetsworth

Erik Hohmann, Medical School, University of Queensland, Herston 4006, Australia

Erik Hohmann, Medical School, Faculty of Health, University of Pretoria, Pretoria 0002, South Africa

Erik Hohmann, Department of Orthopedic Surgery and Sports Medicine,Valiant Clinic/Houston Methodist Group, Dubai 414296, United Arab Emirates

Vaida Glatt, University of Texas Health Science Center, San Antonio, TX 78229, United States

Kevin Tetsworth, Department of Orthopaedic Surgery, Royal Brisbane Hospital, Herston 4006, Australia

Kevin Tetsworth, Department of Surgery, School of Medicine, University of Queensland, Herston 4006, Australia

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Correspondence to: Erik Hohmann, FRCS, FRCS (Tr&Orth), MD, PhD, Department of Orthopedic Surgery and Sports Medicine, Valiant Clinic/Houston Methodist Group, Dubai 414296, United Arab Emirates. ehohmann@hotmail.com
Telephone: +971-4-3788818
Fax: +971-4-3788718

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## Abstract

### AIM

To perform a bibliometric analysis of publications rates in orthopedics in the top 15 orthopaedic journals.

### METHODS

Based on their 2015 impact factor, the fifteen highest ranked orthopaedic journals between January 2010 and December 2014 were used to establish the total number of publications; cumulative impact factor points (IF) per country were determined, and normalized to population size, GDP, and GDP/capita, comparison to the median country output and the global leader.

### RESULTS

Twenty-three thousand and twenty-one orthopaedic articles were published, with 66 countries publishing. The United States had 8149 publications, followed by the United Kingdom (1644) and Japan (1467). The highest IF was achieved by the United States (24744), United Kingdom (4776), and Japan (4053). Normalized by population size Switzerland lead. Normalized by GDP, Croatia was the top achiever. Adjusting GDP/capita, for publications and IF, China, India, and the United States

were the leaders. Adjusting for population size and GDP, 28 countries achieved numbers of publications to be considered at least equivalent with the median academic output. Adjusting GDP/capita only China and India reached the number of publications to be considered equivalent to the current global leader, the United States.

***CONCLUSION***

Five countries were responsible for 60% of the orthopaedic research output over this 5-year period. After correcting for GDP/capita, only 28 of 66 countries achieved a publication rate equivalent to the median country. The United States, United Kingdom, South Korea, Japan, and Germany were the top five countries for both publication totals and cumulative impact factor points.

**Key words:** Bibliometrics; Orthopedic surgery; Impact factor; Publication productivity



**Core tip:** The total number of publications by a country is one of the best indicators of research output and productivity, and is an important aspect of clinical excellence. Our results demonstrate that the United States collectively published more articles and accumulated the highest number of impact factors during the study period, and confirms its overwhelming dominance of publications in the fifteen highest ranked journals in orthopaedics. However, after adjusting for population size, Switzerland was the most academically productive nation. Similarly, after adjusting the number of publications with respect to GDP, Croatia was the most productive, and "cost effective" country.

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## INTRODUCTION

The total number of publications by a country is one of the best indicators of research output and productivity[1], and is an important aspect of clinical excellence[2,3]. Prior bibliographic analyses of orthopaedic academic output have concentrated on the total number of publications per country over various periods ranging from five to ten years[4-6]. The United States, United Kingdom, Germany, Japan, and South Korea have all consistently ranked among the five most productive countries.

The availability of funding has been shown to result in higher publication output, favoring those countries with a larger population size and more powerful economies[6,7]. However, no prior bibliographic analysis of orthopaedic research and publications has accounted for population size or economic discrepancies. To adjust for these inconsistencies, the use of the gross domestic product (GDP) and gross domestic product per capita (GDP/capita) may provide a more meaningful result, and allow for a better comparison between countries[8]. Although the number of publications per capita is one simple way to minimize this inherent bias, it is not the only approach that can be used to determine how academically productive various nations have been. The reciprocal, population size per publication for example, is an equally valid metric that perhaps better expresses this relationship. This reciprocal approach has been employed instead in various iterations throughout this study, to more directly investigate how academically active each nation has been in the field of orthopaedics over the past five years.

Using the fifteen highest rated orthopaedic journals over a five year period, based on the 2015 impact factor, the purpose of this study was threefold: First, to investigate the number of publications and total impact factor from each country, and to then relate these variables to population size, GDP, and GDP per capita. Second, to determine the minimum number of publications required to be comparable to the country producing the median number of publications, when normalized for GDP per capita. Finally, to establish the number of publications that would be required from each country to be equivalent to the country having the highest research output, when normalized for GDP per capita.

## MATERIALS AND METHODS

The 2015 Journal Citation report was accessed on the Web of Science (Thomson Reuters, New York, United States)[9], and the fifteen highest ranked journals based on their 2015 impact factor were selected from the category "orthopedics". Journals were excluded from this list if they were not directly related to the field of orthopedics, or if their main purpose was to provide narrative review articles (Table 1). The abstracts of all articles published in these 15 journals between January 2010 and December 2014 were screened *via* the journals' websites. Letters to the editor, editorials, editorial comments, historical articles, errata, proceeding papers, meeting abstracts, and notes were excluded. Only research articles (levels 1-4), systematic reviews, meta-analyses, non-solicited review articles, and case reports were included. The level of evidence was recorded for each published article; if the journal did not assign the level of evidence, the levels of evidence chart published by the Journal of Bone and Joint Surgery was used[10]. Each publication was assigned a country of origin defined by the location of the the authors' principal institution, or defined by the country of origin of the corresponding author if the manuscript did not provide details about study location. Any discrepancies were resolved by agreement between the two senior authors.

**Table 1 Impact factors (2015 Journal Citation Reports - Thomson Reuters) and number of included publications from 2010-2014**

| | Journal | Impact points | Publications 2010-2014 |
|---|---|---|---|
| 1 | Journal of Bone and Joint - American Volume | 5.280 | 1833 |
| 2 | American Journal of Sports Medicine | 4.362 | 1561 |
| 3 | The Bone and Joint Journal | 3.309 | 1379 |
| 4 | Arthroscopy – The Journal of Arthroscopic and Related Surgery | 3.206 | 1072 |
| 5 | Knee Surgery Sports Traumatology Arthroscopy | 3.053 | 1747 |
| 6 | Journal of Orthopaedic Research | 2.986 | 1301 |
| 7 | Acta Orthopaedica | 2.771 | 565 |
| 8 | Clinical Orthopaedics and Related Research | 2.765 | 2027 |
| 9 | Journal of Arthroplasty | 2.666 | 1873 |
| 10 | Spine Journal | 2.426 | 1029 |
| 11 | Spine | 2.297 | 2848 |
| 12 | Journal of Shoulder and Elbow Surgery | 2.289 | 1324 |
| 13 | Injury – International Journal of the Care of the Injured | 2.137 | 1133 |
| 14 | International Orthopaedics | 2.110 | 1477 |
| 15 | European Spine Journal | 2.066 | 1852 |
| | Total number of publications | | 23021 |

Excluded journals: Osteoarthritis Cartilage ( No. 3 - IF: 4.165); Journal of Physiotherapy (No.4 - IF: 3.708); Journal of Orthopaedic Sports Physiotherapy (No. 8 - IF: 3.011); Gait Posture (No. 12 - IF: 2.752); Journal of the American Academy of Orthopaedic Surgeons (No. 14 - IF: 2.527); Physical Therapy (No 15 - IF: 2.526); Clinical Journal Sports Medicine (No 19 - IF: 2.268)

The total number of publications and the total number of impact factor points per country were collated.

GDP and GDP per capita were sourced from the World Bank website[11], and population size was extracted from the CIA World Factbook[12]. To describe the relationship between population size and the number of publications from a given nation, the population size of that country was divided by their total number of publications. The resulting value describes the population size per publication (PSPP) for that nation; in other words, the calculated value defines the population size per published article, allowing for a better and more direct comparison accounting for population size. Likewise, to define the population size per impact factor point (PSIP) from a given nation the population of that country was divided by their total impact factor points.

Extending this analysis, the gross domestic product was also divided by the total number of publications and impact factor points. These values provide an overview of the gross cost associated with producing a manuscript (GDPP), as well as the gross cost associated with producing one impact factor point (GDPI) for each country. Finally, to simultaneously adjust for population size and economic strength, the GDP per capita was divided by either the total number of publications or by cumulative impact factor points. These values then provide information regarding the gross cost per capita associated with producing a manuscript (GDPCP), or the gross cost per capita associated with producing one impact factor point (GDPCI) for each country.

The list for GDPCP was next ranked lowest to highest to identify the median country. This median country then served as the benchmark, and a correction coefficient was calculated that was normalized to this median country. In this way the number of publications of the median country could then be used to calculate the number of publications every country would need to produce to be considered equivalent to that median country. Dividing the GDPCP of each country by this normalizing coefficient, ($NC_{med}$) determined the number of publications that would be necessary for each country to produce to be considered equivalent to the median country. This provides an excellent measure, corrected for economic power (GDP/capita) and population size, of the expected academic output of different countries, normalized to the output of the median nation.

Finally, a very similar process was followed where a correction coefficient was determined that was instead normalized to the publication output of the current global leader in orthopaedic research. The most active country then served as the benchmark, and a coefficient was calculated that was normalized to the academic activity of that country ($NC_{top}$). This value was then used to calculate the number of publications every country would need to produce to be considered equivalent to the global leader. Dividing the GDPCP of each country by this $NC_{top}$ thus determines the number of publications that would be necessary for each country to produce to be considered equivalent to the global leader. This provides an excellent measure, corrected for economic power (GDP/capita) and population size, of the expected academic output of different countries, normalized to the output of the leading nation.

## RESULTS

A total of 23021 orthopaedic articles were published in the 15 highest ranked orthopaedic surgery journals during the study period, between January 2010 and December 2014 (Table 1). Table 2 demonstrates the top ten countries for each of the fifteen journals, in terms of number of publications. The United States was consistently the leading country in ten of the fifteen journals, and was also the most productive country with a total of

**Table 2 Top 10 Number of publications per country for each of the 15 selected journals**

| Journal | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| JBJS-Am | USA–1124 | CAN-107 | KOR-84 | UK-75 | JAP-52 | HOL-46 | GER-45 | FRA-39 | SWIS-37 | AUS-27 |
| Am J Sports Med | USA-819 | KOR-117 | JAP-84 | GER-82 | UK-49 | AUS-40 | ITA-25 | CAN-34 | SWE-32 | SWIS-31 |
| BJJ | UK-545 | USA-115 | KOR-76 | JAP-75 | HOL-50 | CAN-46 | AUS-43 | GER-41 | CHINA-35 | SWIS-31 |
| Arthroscopy | USA-513 | KOR-105 | JAP-63 | GER-55 | CHINA-40 | CAN-34 | ITA-27 | UK-22 | FRA-18 | SPAIN-18 |
| KSSTA | USA-242 | GER-195 | KOR-157 | ITA-149 | JAP-144 | UK-85 | HOL-76 | TURK-70 | SWE-64 | CHINA-62 |
| J Orthopaedic Research | USA-535 | JAP-107 | GER-96 | CAN-69 | CHINA-67 | UK-48 | TAIW-45 | AUS-37 | KOR-31 | HOL-31 |
| Acta Orthopaedica | SWE-125 | DEN-76 | NOR-69 | HOL-59 | FIN-40 | GER-34 | UK-34 | USA-21 | JAP-17 | AUS-13 |
| CORR | USA-1155 | CAN-110 | KOR-98 | JAP-71 | UK-60 | SWIS-60 | GER-59 | FRA-49 | ITA-45 | HOL-33 |
| J Arthroplasty | USA-934 | JAP-136 | CAN-124 | UK-117 | KOR-114 | AUS-72 | CHINA-64 | GER-37 | SPAIN-29 | HOL-26 |
| Spine Journal | USA-491 | KOR-78 | CHINA-62 | JAP-56 | CAN-48 | HOL-29 | UK-24 | SWIS-23 | INDIA-21 | ITA-21 |
| Spine | USA-1168 | JAP-307 | CHINA-255 | CAN-166 | KOR-163 | UK-73 | GER-65 | AUS-59 | HOL-57 | TAIW-49 |
| J Shoulder Elbow Surg | USA-659 | JAP-79 | UK-72 | KOR-65 | CAN-60 | SWIS-49 | FRA-42 | GER-36 | ITA-35 | BELG-34 |
| Injury | UK-215 | USA-126 | GER-114 | ITA-89 | CHINA-78 | HOL-57 | GREEC-48 | SPAIN-37 | SWIS-34 | AUS-34 |
| International Orthopaedics | GER-232 | CHINA-198 | UK-101 | USA-97 | FRA-97 | JAP-81 | ITA-76 | A-76 | CRO-54 | SWIS-49 |
| European Spine Journal | CHINA-251 | JAP-182 | GER-161 | USA-150 | ITA-133 | UK-124 | FRA-104 | KOR-90 | SWIS-84 | HOL-81 |

Excluded journals: Osteoarthritis Cartilage ( No. 3 - IF: 4.165); Journal of Physiotherapy (No.4 - IF: 3.708); Journal of Orthopaedic Sports Physiotherapy (No. 8 - IF: 3.011); Gait Posture (No. 12 - IF: 2.752); Journal of the American Academy of Orthopaedic Surgeons (No. 14 - IF: 2.527); Physical Therapy (No 15 - IF: 2.526); Clinical Journal Sports Medicine (No 19 - IF: 2.268). USA: United States; UK: United Kingdom; SWE: Sweden; GER: Germany; Can: Canada; Kor: Korea; JAP: Japan.

8149 publications; they were followed by the United Kingdom and Japan, having 1644 and 1467 publications, respectively. A total of 66 countries had published at least one article (Table 3) during the study period. Similar to the number of publications, the United States also accumulated the largest number of impact factor points (24744) followed by the United Kingdom (4776) and Japan (4053) (Table 3). Overall, the top five countries were the United States, United Kingdom, Japan, South Korea, and Germany, and these countries were together responsible for 60.4% of all publications, and 61.4% of all impact factor points.

However, when adjusted for population size (PSPP), Switzerland was the leading country with one publication per 15300 people, followed by Norway with one publication per 21100, and Denmark with one publication per 22300. Switzerland was also the leader in the category of impact factor (PSPI), accumulating one impact factor point per 5400 people, followed by Norway with one impact factor point per 6700, and Holland with one impact factor point per 7800 (Table 4).

The number of publications, when normalized with respect to economic activity (GDPP), was highest for Croatia, with one publication per $772000, followed by Korea with $1042000, and Greece with $1294000. For impact factor (GDPI) Croatia was again the leader, and produced one impact factor point per $359000, followed by South Korea with $375000, and Holland with $408000 (Table 5). When adjusting for both GDP and population simultaneously (GDPCP) China was the leader, producing one publication per $6200, followed by India with $6400, and the USA with $6700. The United States was the leader in the impact factor category (GDPCI), producing one impact factor point per $2200, followed by India with $2400 and China $2500 (Table 6). However, these results need to be interpreted carefully, and it is probable that the extremely large population size of both China and India resulted in data distortion.

When ranked with respect to GDPCP Poland was the median country, publishing 61 articles, and served as the median academic output benchmark. The results showed that 28 countries were able to achieve this academic output (Table 7). As an example, for the United States to achieve this benchmark a minimum of 235 publications were required; however, a total of 8149 publications were recorded, which was 3,468% greater than the requisite number. For Norway, to achieve this benchmark a minimum of 414 publications were required, but only 240 publications were recorded; this was only 58% of the number of publications necessary to have achieved an academic output equivalent to the median activity (Table 7).

The United States was the leader when ranked with respect to GDPCP, publishing 8,149 articles, and served as the leading academic output nation. Using the $NC_{top}$ to calculate the required number of publications to be equivalent with the global research leader (United States), only two other countries, China and India, were considered equivalent or superior (Table 8). For example, for Korea 4174 publications would have been needed to have an academic output equivalent to that of the United States, but only 1354 articles (32%) were published. Again, these results need to be interpreted carefully, and it is highly probable that the large population size of both China and India resulted in data distorsion.

## DISCUSSION

These results demonstrate that the United States collectively published more articles and accumulated the highest number of impact factor points during the study period from 2010 through 2014, and confirms its overwhelming dominance of publications in the fifteen highest ranked journals in the field of orthopaedics.

**Table 3 Highest number of publications and impact points for each country**

| Rank | Country | Publications | Rank | Country | Impact points |
|---|---|---|---|---|---|
| 1 | United States | 8149 | 1 | United States | 24744 |
| 2 | United Kingdom | 1644 | 2 | United Kingdom | 4776 |
| 3 | Japan | 1467 | 3 | Japan | 4053 |
| 4 | South Korea | 1354 | 4 | South Korea | 3765 |
| 5 | Germany | 1272 | 5 | Germany | 3491 |
| 6 | China | 1222 | 6 | China | 3034 |
| 7 | Canada | 930 | 7 | Canada | 2774 |
| 8 | Italy | 737 | 8 | Holland | 2155 |
| 9 | Holland | 663 | 9 | Italy | 1982 |
| 10 | France | 548 | 10 | Switzerland | 1507 |
| 11 | Switzerland | 527 | 11 | Australia | 1412 |
| 12 | Australia | 485 | 12 | France | 1382 |
| 13 | Sweden | 403 | 13 | Sweden | 1187 |
| 14 | Spain | 311 | 14 | Spain | 833 |
| 15 | Austria | 295 | 15 | Austria | 801 |
| 16 | Taiwan | 264 | 16 | Norway | 755 |
| 17 | Denmark | 254 | 17 | Taiwan | 729 |
| 18 | India | 246 | 18 | Denmark | 710 |
| 19 | Norway | 240 | 19 | India | 646 |
| 20 | Turkey | 235 | 20 | Turkey | 630 |
| 21 | Belgium | 219 | 21 | Belgium | 614 |
| 22 | Greece | 182 | 22 | Greece | 508 |
| 23 | Finland | 167 | 23 | Brazil | 408 |
| 24 | Brazil | 147 | 24 | Finland | 402 |
| 25 | Hong Kong | 130 | 25 | Hong Kong | 371 |
| 26 | Israel | 119 | 26 | Israel | 315 |
| 27 | Ireland | 98 | 27 | Singapore | 295 |
| 28 | Singapore | 84 | 28 | Ireland | 262 |
| 29 | New Zealand | 78 | 29 | New Zealand | 227 |
| 30 | Croatia | 74 | 30 | Iran | 174 |
| 31 | Egypt | 68 | 31 | Egypt | 168 |
| 32 | Iran | 65 | 32 | Croatia | 159 |
| 33 | Poland | 61 | 33 | Poland | 141 |
| 34 | Thailand | 52 | 34 | Thailand | 128 |
| 35 | Czech Republic | 39 | | Slovenia | 128 |
| 36 | Slovenia | 32 | 35 | Czech Republic | 84 |
| 37 | Hungary | 29 | 36 | Hungary | 71 |
| 38 | Portugal | 25 | 37 | Portugal | 71 |
| 39 | Chile | 24 | 38 | Chile | 66 |
| 40 | Malaysia | 23 | 39 | Malaysia | 63 |
| 41 | South Africa | 21 | 40 | South Africa | 59 |
| 42 | Argentina | 20 | 41 | Argentina | 55 |
| 43 | Serbia | 19 | 42 | Serbia | 43 |
| 44 | Luxemburg | 14 | 43 | Luxemburg | 43 |
| 45 | Saudi Arabia | 12 | 44 | Saudi Arabia | 29 |
| 46 | Mexico | 10 | 45 | Mexico | 26 |
| 47 | Lebanon | 9 | 46 | Lebanon | 23 |
| | Lithuania | 9 | | Lithuania | 23 |
| | Russia | 9 | 47 | Russia | 21 |
| 48 | Estonia | 7 | 48 | Estonia | 17 |
| 48 | Nigeria | 7 | 49 | Nigeria | 15 |
| 49 | Pakistan | 6 | 50 | Romania | 13 |
| | Romania | 6 | | Philippines | 13 |
| 50 | Columbia | 5 | 51 | Pakistan | 12 |
| | Kuwait | 5 | 52 | Columbia | 11 |
| | Philippines | 5 | | Tunisia | 11 |
| | Tunisia | 5 | 53 | Kuwait | 9 |
| 51 | Bulgaria | 3 | 54 | Iceland | 7 |
| | Iceland | 3 | 55 | Bulgaria | 6 |
| | Iraq | 3 | | Iraq | 6 |
| 52 | Malawi | 2 | 56 | Malawi | 5 |
| | Morocco | 2 | | Nepal | 5 |
| | Nepal | 2 | | Uganda | 5 |
| 53 | Ethiopia | 1 | 57 | Morocco | 4 |
| | Sudan | 1 | 58 | Ethiopia | 3 |
| | Uganda | 1 | | Sudan | 3 |

**Table 4 Number of publications (PSPP) and impact (PSPI) normalized for population size (publication/impact point per in thousand populations)**

| Rank | Country | PSPP | Rank | Country | PSIP |
|---|---|---|---|---|---|
| 1 | Switzerland | 15.3 | 1 | Switzerland | 5.4 |
| 2 | Norway | 21.1 | 2 | Norway | 6.7 |
| 3 | Denmark | 22.3 | 3 | Holland | 7.8 |
| 4 | Sweden | 24.1 | 4 | Denmark | 7.9 |
| 5 | Holland | 25.4 | 5 | Sweden | 8.2 |
| 6 | Austria | 28.7 | 6 | Austria | 10.6 |
| 7 | Finland | 32.3 | 7 | Canada | 12.1 |
| 8 | Canada | 35.9 | 8 | Luxemburg | 12.6 |
| 9 | Luxemburg | 38.9 | 9 | United States | 12.9 |
| 10 | South Korea | 38.9 | 10 | United Kingdom | 13.4 |
| 11 | United Kingdom | 38.9 | 11 | Finland | 13.4 |
| 12 | United States | 39.3 | 12 | South Korea | 13.6 |
| 13 | Australia | 44.3 | 13 | Australia | 15.2 |
| 14 | Belgium | 51.1 | 14 | Belgium | 18.2 |
| 15 | Hong Kong | 55.3 | 15 | Singapore | 18.3 |
| 16 | New Zealand | 57.3 | 16 | Hong Kong | 19.4 |
| 17 | Croatia | 57.8 | 17 | New Zealand | 19.7 |
| 18 | Greece | 60.4 | 18 | Greece | 21.6 |
| 19 | Germany | 63.1 | 19 | Germany | 23 |
| 20 | Singapore | 64.3 | 20 | Slovenia | 24 |
| 21 | Slovenia | 64.3 | 21 | Ireland | 24.3 |
| 22 | Ireland | 65.1 | 22 | Israel | 25.6 |
| 23 | Israel | 67.7 | 23 | Croatia | 27 |
| 24 | Italy | 82.4 | 24 | Italy | 30.7 |
| 25 | Japan | 86.8 | 25 | Japan | 31.4 |
| 26 | Taiwan | 88.4 | 26 | Taiwan | 32 |
| 27 | Iceland | 107.7 | 27 | Iceland | 46.1 |
| 28 | France | 121.5 | 28 | France | 48.1 |
| 29 | Spain | 151.9 | 29 | Spain | 56.7 |
| 30 | Estonia | 185.7 | 30 | Estonia | 76.5 |
| 31 | Czech Republic | 269.2 | 31 | Turkey | 121.7 |
| 32 | Turkey | 326.2 | 32 | Czech Republic | 125 |
| 33 | Lithuania | 333.3 | 33 | Lithuania | 130.4 |
| 34 | Hungary | 341.4 | 34 | Hungary | 139.4 |
| 35 | Serbia | 379.5 | 35 | Portugal | 147.3 |
| 36 | Portugal | 418.4 | 36 | Serbia | 167.7 |
| 37 | Lebanon | 551.8 | 37 | Lebanon | 215.9 |
| 38 | Poland | 631.6 | 38 | Chile | 247.6 |
| 39 | Kuwait | 673.8 | 39 | Poland | 272 |
| 40 | Chile | 680.8 | 40 | Kuwait | 374.3 |
| 41 | China | 1110.5 | 41 | Iran | 443.5 |
| 42 | Egypt | 1176.5 | 42 | China | 447.3 |
| 43 | Iran | 1187.3 | 43 | Malaysia | 471.7 |
| 44 | Thailand | 1283.1 | 44 | Egypt | 476.2 |
| 45 | Malaysia | 1292.1 | 45 | Brazil | 491.2 |
| 46 | Brazil | 1363.2 | 46 | Thailand | 521.2 |
| 47 | Argentina | 2072.5 | 47 | Argentina | 753.6 |
| 48 | Tunisia | 2178.0 | 48 | South Africa | 915.2 |
| 49 | Saudi Arabia | 2402.5 | 49 | Tunisia | 990 |
| 50 | Bulgaria | 2421.7 | 50 | Saudi Arabia | 12108.3 |
| 51 | South Africa | 2571.4 | 51 | Bulgaria | 15353.8 |
| 52 | Romania | 3326.7 | 52 | Romania | 15353.9 |
| 53 | India | 5089.4 | 53 | India | 19380.8 |
| 54 | Malawi | 8180.0 | 54 | Malawi | 32720 |
| 55 | Ethiopia | 9410.0 | 55 | Columbia | 43649 |
| 56 | Columbia | 9602.8 | 56 | Mexico | 45536.5 |
| 57 | Iraq | 11140 | 57 | Nepal | 55600 |
| 58 | Mexico | 11839.5 | 58 | Iraq | 55700 |
| 59 | Nepal | 13900 | 59 | Russia | 68333.3 |
| 60 | Russia | 15944.4 | 60 | Uganda | 75160.0 |
| 61 | Morocco | 16505 | 61 | Philippines | 75684.6 |
| 62 | Philippines | 19678 | 62 | Morocco | 82525.0 |
| 63 | Nigeria | 24800 | 63 | Nigeria | 115733.3 |
| 64 | Pakistan | 32695.7 | 64 | Sudan | 126533.3 |
| 65 | Uganda | 37580 | 65 | Pakistan | 163478.3 |
| 66 | Sudan | 37976 | 66 | Ethiopia | 313666.7 |

**Table 5 Number of publications (GDPP) and impact points (GDPI) related to GDP ( in thousand dollars)**

| Rank | Country | GDPP | Rank | Country | GDPI |
|---|---|---|---|---|---|
| 1 | Croatia | 772 | 1 | Croatia | 359 |
| 2 | South Korea | 1042 | 2 | South Korea | 375 |
| 3 | Greece | 1294 | 3 | Holland | 408 |
| 4 | Holland | 1326 | 4 | Greece | 464 |
| 5 | Switzerland | 1330 | 5 | Switzerland | 465 |
| 6 | Denmark | 1348 | 6 | Sweden | 481 |
| 7 | Sweden | 1417 | 7 | Denmark | 482 |
| 8 | Slovenia | 1417 | 8 | Slovenia | 576 |
| 9 | Austria | 1547 | 9 | Austria | 579 |
| 10 | Finland | 1630 | 10 | United Kingdom | 626 |
| 11 | United Kingdom | 1818 | 11 | Canada | 644 |
| 12 | Taiwan | 1852 | 12 | Norway | 662 |
| 13 | Canada | 1920 | 13 | Taiwan | 671 |
| 14 | Norway | 2083 | 14 | Finland | 677 |
| 15 | Malawi | 2129 | 15 | United States | 704 |
| 16 | United States | 2138 | 16 | Hong Kong | 784 |
| 17 | Hong Kong | 2237 | 17 | New Zealand | 829 |
| 18 | Serbia | 2309 | 18 | Malawi | 852 |
| 19 | New Zealand | 2412 | 19 | Belgium | 866 |
| 20 | Belgium | 2427 | 20 | Israel | 970 |
| 21 | Ireland | 2559 | 21 | Ireland | 975 |
| 22 | Israel | 2569 | 22 | Serbia | 1020 |
| 23 | Italy | 2905 | 23 | Australia | 1032 |
| 24 | Australia | 3003 | 24 | Singapore | 1044 |
| 25 | Germany | 3041 | 25 | Italy | 1080 |
| 26 | Japan | 3137 | 26 | Germany | 1108 |
| 27 | Turkey | 3398 | 27 | Japan | 1135 |
| 28 | Singapore | 3665 | 28 | Turkey | 1267 |
| 29 | Estonia | 3784 | 29 | Luxemburg | 1509 |
| 30 | Egypt | 4213 | 30 | Estonia | 1558 |
| 31 | Spain | 4442 | 31 | Spain | 1658 |
| 32 | Hungary | 4471 | 32 | Egypt | 1706 |
| 33 | Luxemburg | 4634 | 33 | Hungary | 1949 |
| 34 | Lebanon | 5081 | 34 | Lebanon | 1988 |
| 35 | France | 5163 | 35 | France | 2047 |
| 36 | Czech Republic | 5263 | 36 | Lithuania | 2102 |
| 37 | Lithuania | 5372 | 37 | Iceland | 2434 |
| 38 | Iceland | 5679 | 38 | Czech Republic | 2444 |
| 39 | Iran | 6543 | | Iran | 2444 |
| 40 | Thailand | 7785 | 39 | Thailand | 3163 |
| 41 | India | 8327 | 40 | India | 3171 |
| 42 | China | 8474 | 41 | Portugal | 3241 |
| 43 | Poland | 8933 | 42 | China | 3413 |
| 44 | Portugal | 9204 | 43 | Poland | 3865 |
| 45 | Tunisia | 9722 | 44 | Chile | 3910 |
| 46 | Nepal | 9884 | 45 | Nepal | 3954 |
| 47 | Chile | 10752 | 46 | Tunisia | 4419 |
| 48 | Malaysia | 14700 | 47 | Malaysia | 5367 |
| 49 | Brazil | 15960 | 48 | Uganda | 5400 |
| 50 | South Africa | 16671 | 49 | Brazil | 5750 |
| 51 | Bulgaria | 18906 | 50 | South Africa | 5934 |
| 52 | Argentina | 26833 | 51 | Bulgaria | 9452 |
| 53 | Uganda | 26998 | 52 | Argentina | 9757 |
| 54 | Kuwait | 32722 | 53 | Romania | 15311 |
| 55 | Romania | 33174 | 54 | Kuwait | 18179 |
| 56 | Pakistan | 40605 | 55 | Ethiopia | 18540 |
| 57 | Morocco | 55004 | 56 | Pakistan | 20303 |
| 58 | Ethiopia | 55621 | 57 | Philippines | 21906 |
| 59 | Philippines | 56955 | 58 | Sudan | 24734 |
| 60 | Saudi Arabia | 62187 | 59 | Saudi Arabia | 25733 |
| 61 | Sudan | 74202 | 60 | Morocco | 27502 |
| 62 | Iraq | 74503 | 61 | Columbia | 34340 |
| 63 | Columbia | 75448 | 62 | Iraq | 37251 |
| 64 | Nigeria | 81215 | 63 | Nigeria | 37901 |
| 65 | Mexico | 129469 | 64 | Mexico | 49796 |
| 66 | Russia | 206733 | 65 | Russia | 88600 |

**Table 6 Number of publications (GDPCP) and impact points (GDPCI) related to GDP per capita (in thousand dollars)**

| Rank | Country | GDPP | Rank | Country | GDPI |
|---|---|---|---|---|---|
| 1 | China | 6.2 | 1 | United States | 2.2 |
| 2 | India | 6.4 | 2 | India | 2.4 |
| 3 | United States | 6.7 | 3 | China | 2.5 |
| 4 | South Korea | 20.7 | 4 | South Korea | 7.4 |
| 5 | Japan | 24.7 | 5 | Japan | 8.9 |
| 6 | United Kingdom | 28.2 | 6 | United Kingdom | 9.7 |
| 7 | Germany | 37.6 | 7 | Germany | 13.7 |
| 8 | Turkey | 44.7 | 8 | Turkey | 16.7 |
| 9 | Egypt | 47 | 9 | Italy | 17.6 |
| 10 | Italy | 47.4 | 10 | Canada | 18.1 |
| 11 | Canada | 54 | 11 | Egypt | 19 |
| 12 | Brazil | 77.4 | 12 | Holland | 24.2 |
| 13 | France | 78 | 13 | Brazil | 27.9 |
| 14 | Holland | 78.7 | 14 | France | 30.9 |
| 15 | Iran | 83.7 | 15 | Iran | 31.3 |
| 16 | Spain | 95.4 | 16 | Spain | 35.6 |
| 17 | Thailand | 114.9 | 17 | Greece | 42.3 |
| 18 | Greece | 118.1 | 18 | Taiwan | 43.8 |
| 19 | Taiwan | 120.8 | 19 | Australia | 43.9 |
| 20 | Malawi | 127.5 | 20 | Thailand | 46.7 |
| 21 | Australia | 127.7 | 21 | Sweden | 49.6 |
| 22 | Sweden | 146.2 | 22 | Malawi | 51 |
| 23 | Switzerland | 162.4 | 23 | Switzerland | 56.8 |
| 24 | Austria | 173.5 | 24 | Austria | 63.9 |
| 25 | Croatia | 182.1 | 25 | Belgium | 77.1 |
| 26 | Belgium | 216.2 | 26 | Croatia | 84.7 |
| 27 | Pakistan | 219.5 | 27 | Denmark | 85.5 |
| 28 | Poland | 235.1 | 28 | Poland | 101.7 |
| 29 | Denmark | 239 | 29 | Hong Kong | 108.3 |
| 30 | Finland | 298.3 | 30 | Pakistan | 109.7 |
| 31 | South Africa | 308.7 | 31 | South Africa | 109.9 |
| 32 | Hong Kong | 309 | 32 | Israel | 118.1 |
| 33 | Israel | 312.7 | 33 | Finland | 123.9 |
| 34 | Serbia | 323.8 | 34 | Norway | 128.9 |
| 35 | Nepal | 351 | 35 | Nepal | 140.4 |
| 36 | Norway | 405.4 | 36 | Uganda | |
| 37 | Nigeria | 457.6 | 37 | Serbia | 143.1 |
| 38 | Hungary | 483.7 | 38 | New Zealand | 166.9 |
| 39 | New Zealand | 485.8 | 39 | Malaysia | 179.5 |
| 40 | Malaysia | 491.6 | 40 | Singapore | 190.8 |
| 41 | Czech Republic | 500.8 | 41 | Ethiopia | 191.3 |
| 42 | Ireland | 554.8 | 42 | Hungary | 197.6 |
| 43 | Ethiopia | 574 | 43 | Ireland | 207.5 |
| 44 | Philippines | 574.4 | 44 | Nigeria | 213.5 |
| 45 | Chile | 605.3 | 45 | Chile | 220.1 |
| 46 | Argentina | 625.4 | 46 | Philippines | 220.9 |
| 47 | Singapore | 670 | 47 | Argentina | 227.4 |
| 48 | Uganda | 715 | 48 | Czech Republic | 232.5 |
| 49 | Slovenia | 750 | 49 | Slovenia | 279.1 |
| 50 | Tunisia | 884.2 | 50 | Portugal | 311.7 |
| 51 | Portugal | 885.3 | 51 | Sudan | 371.7 |
| 52 | Mexico | 1032.6 | 52 | Mexico | 397.1 |
| 53 | Sudan | 1115 | 53 | Tunisia | 401.9 |
| 54 | Lebanon | 1117.6 | 54 | Lebanon | 437.3 |
| 55 | Russia | 1415.1 | 55 | Russia | 606.5 |
| 56 | Columbia | 1580.8 | 56 | Lithuania | 717.8 |
| 57 | Morocco | 1595 | 57 | Columbia | 718.5 |
| 58 | Romania | 1666.2 | 58 | Romania | 769 |
| 59 | Lithuania | 1834.1 | 59 | Morocco | 797.5 |
| 60 | Saudi Arabia | 2013.4 | 60 | Saudi Arabia | 833.1 |
| 61 | Iraq | 2140 | 61 | Iraq | 1070 |
| 62 | Bulgaria | 2617 | 62 | Estonia | 1186 |
| 63 | Estonia | 2880.3 | 63 | Bulgaria | 1308.5 |
| 64 | Luxemburg | 8333.1 | 64 | Luxemburg | 2713.3 |
| 65 | Kuwait | 8718.8 | 65 | Kuwait | 4843.8 |
| 66 | Iceland | 17334.5 | 66 | Iceland | 7429.1 |

**Table 7 Number of publications required to equivalent with the median (Poland $n$ = 61) using the benchmark measure**

| Rank | Country | Published publications 2010-2014 | Papers to be published | % of published papers |
|---|---|---|---|---|
| 1 | China | 1222 | 32 | 3783 |
| 2 | India | 246 | 7 | 3656 |
| 3 | United States | 8149 | 235 | 3505 |
| 4 | South Korea | 1354 | 119 | 1137 |
| 5 | Japan | 1467 | 235 | 952 |
| 6 | United Kingdom | 1644 | 197 | 833 |
| 7 | Germany | 1272 | 203 | 625 |
| 8 | Turkey | 235 | 45 | 525 |
| 9 | Egypt | 68 | 14 | 499 |
| 10 | Italy | 737 | 148 | 496 |
| 11 | Canada | 930 | 214 | 435 |
| 12 | Brazil | 147 | 48 | 303 |
| 13 | France | 548 | 182 | 301 |
| 14 | Holland | 663 | 222 | 298 |
| 15 | Iran | 65 | 23 | 280 |
| 16 | Spain | 311 | 126 | 246 |
| 17 | Thailand | 52 | 25 | 204 |
| 18 | Greece | 182 | 91 | 198 |
| 19 | Taiwan | 264 | 136 | 194 |
| 20 | Malawi | 2 | 1 | 184 |
| 21 | Australia | 485 | 263 | 183 |
| 22 | Sweden | 403 | 251 | 160 |
| 23 | Switzerland | 527 | 364 | 145 |
| 24 | Austria | 295 | 218 | 135 |
| 25 | Croatia | 74 | 57 | 129 |
| 26 | Belgium | 219 | 201 | 109 |
| 27 | Pakistan | 6 | 6 | 100 |
| 28 | Poland | 61 | 61 | 100 |
| 29 | Denmark | 254 | 258 | 98 |
| 30 | Finland | 167 | 212 | 79 |
| 31 | South Africa | 21 | 28 | 76 |
| 32 | Hong Kong | 130 | 171 | 76 |
| 33 | Israel | 119 | 158 | 75 |
| 34 | Serbia | 19 | 26 | 72 |
| 35 | Nepal | 2 | 3 | 67 |
| 36 | Norway | 240 | 414 | 58 |
| 37 | Nigeria | 7 | 14 | 50 |
| 38 | Hungary | 29 | 60 | 49 |
| 39 | New Zealand | 78 | 161 | 48 |
| 40 | Malaysia | 23 | 48 | 47 |
| 41 | Czech Republic | 39 | 83 | 47 |
| 42 | Ireland | 98 | 231 | 42 |
| 43 | Ethiopia | 1 | 2 | 50 |
| 44 | Philippines | 5 | 12 | 41 |
| 45 | Chile | 24 | 62 | 39 |
| 46 | Argentina | 20 | 53 | 38 |
| 47 | Singapore | 84 | 239 | 35 |
| 48 | Uganda | 1 | 3 | 33 |
| 49 | Slovenia | 32 | 102 | 31 |
| 50 | Tunisia | 5 | 19 | 26 |
| 51 | Portugal | 25 | 94 | 26 |
| 52 | Mexico | 10 | 44 | 23 |
| 53 | Sudan | 1 | 5 | 20 |
| 54 | Lebanon | 9 | 43 | 21 |
| 55 | Russia | 9 | 54 | 17 |
| 56 | Columbia | 5 | 34 | 15 |
| 57 | Morocco | 2 | 14 | 15 |
| 58 | Romania | 6 | 42 | 14 |
| 59 | Lithuania | 9 | 70 | 13 |
| 60 | Saudi Arabia | 12 | 103 | 12 |
| 61 | Iraq | 3 | 27 | 11 |
| 62 | Bulgaria | 3 | 33 | 9 |
| 63 | Estonia | 7 | 86 | 8.1 |
| 64 | Luxemburg | 14 | 496 | 2.8 |
| 65 | Kuwait | 5 | 185 | 2.7 |
| 66 | Iceland | 3 | 221 | 1.4 |

**Table 8 Number of publications required to equivalent with the leader (United States) the benchmark measure**

| Rank | Country | Published publications 2010-2014 | Papers to be published | % of published papers |
|---|---|---|---|---|
| 1 | China | 1222 | 1132 | 108 |
| 2 | India | 246 | 236 | 104 |
| 3 | United States | 8149 | 8149 | 100 |
| 4 | South Korea | 1354 | 4174 | 32 |
| 5 | Japan | 1467 | 5402 | 27 |
| 6 | United Kingdom | 1644 | 6915 | 24 |
| 7 | Germany | 1272 | 7138 | 18 |
| 8 | Turkey | 235 | 1569 | 15 |
| 9 | Egypt | 68 | 477 | 14 |
| 10 | Italy | 737 | 5210 | 14 |
| 11 | Canada | 930 | 7498 | 12 |
| 12 | Brazil | 147 | 1699 | 8.6 |
| 13 | France | 548 | 6378 | 8.6 |
| 14 | Holland | 663 | 7787 | 8.5 |
| 15 | Iran | 65 | 812 | 8 |
| 16 | Spain | 311 | 4429 | 7 |
| 17 | Thailand | 52 | 892 | 5.8 |
| 18 | Greece | 182 | 3208 | 5.6 |
| 19 | Taiwan | 264 | 892 | 5.5 |
| 20 | Malawi | 2 | 38 | 5.2 |
| 21 | Australia | 485 | 9243 | 5.1 |
| 22 | Sweden | 403 | 8797 | 4.6 |
| 23 | Switzerland | 527 | 12775 | 4.1 |
| 24 | Austria | 295 | 7640 | 3.9 |
| 25 | Croatia | 74 | 2011 | 3.7 |
| 26 | Belgium | 219 | 7068 | 3.1 |
| 27 | Pakistan | 6 | 197 | 3 |
| 28 | Poland | 61 | 2141 | 2.8 |
| 29 | Denmark | 254 | 9091 | 2.7 |
| 30 | Finland | 167 | 7436 | 2.2 |
| 31 | South Africa | 21 | 968 | 2.1 |
| | Hong Kong | 130 | 5995 | 2.1 |
| | Israel | 119 | 5553 | 2.1 |
| | Serbia | 19 | 918 | 2.1 |
| 32 | Nepal | 2 | 105 | 1.9 |
| 33 | Norway | 240 | 14523 | 1.6 |
| 34 | Nigeria | 7 | 487 | 1.5 |
| 35 | Hungary | 29 | 2094 | 1.4 |
| | New Zealand | 78 | 5656 | 1.4 |
| | Malaysia | 23 | 1688 | 1.4 |
| 36 | Czech Republic | 39 | 2915 | 1.3 |
| | Ireland | 98 | 8115 | 1.2 |
| | Ethiopia | 1 | 86 | 1.2 |
| | Philippines | 5 | 429 | 1.2 |
| 37 | Chile | 24 | 2168 | 1.1 |
| | Argentina | 20 | 1867 | 1.1 |
| 38 | Singapore | 84 | 8401 | 1 |
| 39 | Uganda | 1 | 107 | 0.94 |
| 40 | Slovenia | 32 | 3582 | 0.89 |
| 41 | Tunisia | 5 | 660 | 0.76 |
| 42 | Portugal | 25 | 3303 | 0.75 |
| 43 | Mexico | 10 | 1541 | 0.65 |
| 44 | Sudan | 1 | 166 | 0.6 |
| | Lebanon | 9 | 1502 | 0.6 |
| 45 | Russia | 9 | 1901 | 0.47 |
| 46 | Columbia | 5 | 1180 | 0.42 |
| 47 | Morocco | 2 | 476 | 0.42 |
| 48 | Romania | 6 | 1492 | 0.4 |
| 49 | Lithuania | 9 | 2464 | 0.36 |
| 50 | Saudi Arabia | 12 | 3606 | 0.33 |
| 51 | Iraq | 3 | 958 | 0.31 |
| 52 | Bulgaria | 3 | 1172 | 0.26 |
| 53 | Estonia | 7 | 3009 | 0.23 |
| 54 | Luxemburg | 14 | 17412 | 0.08 |
| | Kuwait | 5 | 6507 | 0.08 |
| 55 | Iceland | 3 | 7762 | 0.04 |

However, after adjusting for population size, Switzerland was the most academically productive nation. Similarly, after adjusting the number of publications with respect to GDP, Croatia was the most productive, and "cost effective" country.

Over the last 30 years, English has become the international language of medical science[13]. Of the current top 50 highest impact journals in orthopaedics, 45 are based in English speaking countries; all 50 of these journals publish their manuscripts in English only[9]. The majority of those countries where English is the primary language also enjoy a high standard of living, and would appear to have advantages in terms of research funding and academic opportunity. Although this suggests an inherent bias towards authors from those countries where English is the principal language, over this 5-year period articles were published by a total of 66 different countries; in many of those countries English is not the main language. Strategies were employed here to attempt to eliminate or minimize any of these potential socio-economic advantages, and therefore obtain a better measure of the relative academic activity and orthopedic research output from various nations around the world. This study has revealed superior academic activity outcomes has been achieved by several of these countries, when adjusted for population size and GDP.

Both GDP and GDP per capita are indicators of economic strength, representing the value of all goods and services produced over a specified time period[7]. The cost of producing a research paper per GDP/capita is theoretically a better indicator of a country's research productivity, one that takes into consideration some of the socio-economic conditions that might favor more populous or prosperous nations. After adjusting for GPD per capita both India and China were the leading countries, but due to their inordinately large population size the calculated figures are most likely biased. After eliminating these two countries, the United States, South Korea, Japan, Germany, and the United Kingdom ranked among the top five countries with the highest number of both publications and impact factor points. One possible explanation could be that the research output of these countries is directly related to economic vitality, although none of these five leading countries had the highest GDP per capita. For example, the United States, ranked 8$^{th}$, Germany 15$^{th}$, the United Kingdom 17$^{th}$, Japan 23$^{rd}$ and South Korea 27$^{th}$. Earlier research by Meo *et al*[7] and Halpenny *et al*[8] also failed to demonstrate a correlation between GDP per capita, total number of publications, and h-index in different science fields and social science disciplines. However, they were able to confirm a strong and positive correlation between the number of publications and the percentage of GDP spent on research.

This study introduced a new metric to bibliographic analysis, normalizing the collective publications and impact factor points of individual nations to that of the output of the median nation, after first correcting for both population size and economic activity. Although

this measure has not been validated yet and may lack the robustness of standard citation and content analysis, it is nevertheless similar to other accepted bibliometric measures. In our opinion it facilitates a better comparison between countries, by defining the number of publications that would be necessary for a particular country to produce to have an output equivalent to that of the median nation.

After normalizing research output, 28 countries exceeded this benchmark, whereas 38 were below the level of the median nation. These findings unequivocally demonstrated the dominance of the United States compared to all other countries. To have an output equivalent to the median nation, Poland, it was necessary for the United States to publish 235 articles: However, they collectively published 8149 and were the global leader by an overwhelming margin. China and India were ranked even higher by this metric, but this might demonstrate an inherent limitation of this methodology related to population size. Those countries with a very low GDP per capita, a large population size, and a relatively large number of publications will most likely result in a ceiling effect, and normalizing research output to that of the median nation would thus be unreliable. Therefore, further research is required to better define the extent of this problem and to validate this approach.

Research output is an important determinant of economic growth, and an increase in service delivery, education, and innovation is often an indicator of a society's shift from a producing economy to a knowledge-based economy[14]. In fact, publications of scientific literature can indicate a nation's growth and progress in science and technology[5]. Moir *et al*[15] observed a 21% increase in orthopaedic publications from 1980 to 1994 in six selected journals. More recently, Bosker and Verheyen[4] also reported an increased number of orthopaedic publications in the 15 major clinical orthopaedic journals from 2000-2004, with a total of 13311 articles. The present bibliometric analysis counted over 23000 articles, representing a 73% increase over a 10 years interval. Several authors have previously performed subspecialty analyses[1,16]. Luo *et al*[1] showed that high income countries published 90% of all articles in foot and ankle research, with the United States publishing the highest number; however, Switzerland took the lead when it was normalized to population size and GDP. Liang *et al*[16] reported that the United States published the largest number of publications in the subspecialty of arthroscopy, but when adjusted for population size Switzerland was again the country with the highest number of publications. Similar findings were reflected in our results, although in their study Korea ranked first when academic output was adjusted for GDP.

Bibliometric analysis has also been performed by other disciplines. In emergency medicine, the United States was the most productive country followed by the United Kingdom and Australia. When normalized to population size, Australia had the highest number of articles per million persons, but Germany had the highest mean impact factor and citations[17,18]. In the specialty of critical care medicine, the United States has published the most articles, followed by the United Kingdom, Germany, France, and Australia. The United States also had the highest number of randomized controlled trial publications, the highest total impact factor points, and the highest total citations[17,18]. Halpenny *et al*[8] performed a bibliographic analysis in radiology. In their study, the United States published 42% of the 10,925 papers, followed by Germany and Japan. When corrected for GDP, Switzerland (0.925), Austria (0.694), and Belgium (0.648) produced the most publications per billion of GDP. Robert *et al*[19] evaluated the pain medicine literature over a period of 30 years and reported that the United States, the United Kingdom and Germany were the highest ranking countries. The pattern of publication rates are comparable to orthopaedics and these findings can possibly be generalized to other disciplines of medicine.

This study has recognized limitations. While the total number of articles and cumulative impact factor points was determined for each nation, the value of individual articles was not assessed; it is possible that there was a significant discrepancy in the manuscript quality between countries, potentially introducing selection bias. Even the selection of impact factor as an outcome measure to evaluate publication quality has been criticized, as it is determined by technicalities that are not related to the scientific value of the research studies themselves[20,21]. Citation analysis was also not performed, and it is acknowledged that the number of citations are a proxy measure of influence reflecting the recognition and quality of the published research by its peers[22]. However, using the impact factor reflects citation counts indirectly, as article citation rates ultimately determine the journal's impact factor[20]. Nevertheless, overcitation, biased citing, audience size, biased data, and ignorance of the literature are additional common criticisms of bibliometric studies[23]. Another potential limitation of this method is that the research output of the median nation was based on data collected over a specific five-year period from the fifteen currently highest ranked orthopaedic journals. These results will almost certainly change if more journals are included, or the time interval is either extended or shortened.

In conclusion, the results of this study demonstrate that five countries were responsible for 60% of the research output in orthopaedic surgery over a 5-year period, when restricted to the 15 highest ranked journals specific to the field. Only 28 of 66 countries were able to achieve a publication rate equivalent to that of the median nation, after first correcting for GDP per capita. The United States was unequivocally the global leader when judged by this measure, and exceeded the median production by more than 34 times. Although China and India ranked the highest after correcting for both GDP and population size, this probably reflects the inordinately large populations of both countries. The United States, United Kingdom, South Korea, Japan, and Germany placed in the top five countries with respect to both publication totals and cumulative impact factor points.

## COMMENTS

### Background

Bibliographic analysis of academic output has been performed for many indications and can be an indicator for academic excellence. However most studies have focussed on the total number of publications without accounting for gross domestic product or economic discrepancies between countries. The primary aim of this study was therefore to investigate the number of publications and total impact factor from each country, and to then relate these variables to population size, gross domestic product (GDP), and GDP per capita. Secondly they determined the minimum number of publications required to be comparable to the country producing the median number of publications, when normalized for GDP per capita. The final aim was to establish the number of publications that would be required from each country to be equivalent to the country having the highest research output, when normalized for GDP per capita.

### Research frontiers

Over the last 30 years English has become the international language of medical science. In Orthopedics 45 of the 50 highest impact orthopaedic journals are based in English countries. Based on these facts the majority of publications in these journals should come from primary English speaking countries.

### Innovations and breakthroughs

Based on the total number of publications and impact points the United States was the undebated leader for both the total number of publications and impact points. However when adjusting for publication size and GDP per capita, it was Switzerland respectively Croatia which were the most productive nations. When using a newly introduced benchmark to adjust for both population size and GDP, 28 countries exceeded and 38 nations were below the median nation.

### Applications

This review suggests that the total number of publications and impact points are not representative of true research output and other factors should be included into bibliometric analysis.

### Terminology

Bibliometric analysis is based on quantitative variables such as number of publications, impact points and citation rates. Analysis can be performed at the macro-level comparing countries performances, at the middle level analyzing Universities or other institutional output or at the microlevel investigating research output of departments or individuals.

### Peer-review

The authors present a very interesting paper on the worldwide orthopaedic research activity. They relate the scientific production with the GDP, and per capita GDP. This sort of information, although known for general science, was unknown in the orthopaedic field. The relevance of this paper is not only related to science but also to politics.

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