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AIMS AND SCOPE

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EDITORIAL

Exercise as medicine to be prescribed in osteoarthritis

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Abstract

Inactivity contributes to chronic diseases, including diabetes, hypertension, cardiovascular disorders, and obesity. Sedentary habits can shorten life expectancy. Exercise has been widely proposed as a valuable approach to prevention. Regular physical activity, as part of one's daily routine, may help to manage pathological conditions. This editorial especially addresses osteoarthritis (OA), a degenerative disease of the articular cartilage, which is one of the most common causes of disability worldwide. Standard treatments for this illness include surgical procedures and pharmacological management; behavioural approaches are also strongly recommended. Physical exercise represents a practical strategy to preserve function, decrease pain and fatigue, and increase muscle strength and flexibility. We suggest that physical activity be considered as an established form of treatment, which means including exercise in standard therapeutic guidelines. A growing number of patients suffer from preventable chronic conditions that impose a heavy social and economic burden on the healthcare system. Preventive exercise training should be prescribed in the same way as pharmaceuticals.

Key words: Physical activity; Exercise; Training; Chronic disease; Osteoarthritis

Core tip: A sedentary lifestyle is one of the leading causes of morbidity and mortality, whereas physical activity is preventive and effective in the management of chronic diseases. Osteoarthritis is one of the conditions that considerably benefits from exercise. General practitioners need to learn to prescribe physical training in the same way as they prescribe medication, using specific protocols for specific patients.

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INTRODUCTION

The culture of physical activity is not new; a healthy body was vital in prehistoric times, when facility in climbing, running or swimming was essential to escape predators and capture prey. It meant the difference between life and death. Escaping from dangers, hunting and gathering food, as well as building shelters and tools for everyday survival were all activities in which physical effort was essential. As civilisation progressed, hunter-gatherer tribes stopped being nomadic and settled in villages, where the primary resources of sustainment became agriculture and farming. These occupations required fewer physical efforts than those needed to chase animals or climb trees for fruit, but entailed more repetitive movements during the day. Great ancient societies, like the Greeks and Romans, endorsed the pursuit of physical fitness in order to be prepared for war. Epochs of conquests and territorial dominations gave birth to troops of soldiers who were able to conduct long and exhausting battles, where muscle strength, physical resistance and psychological endurance would have decided personal and collective survival. The institution of the γυμνάσιον (gymnasium) and the Olympic Games were symbols of the Greeks' paramount principle that physical and mental wellness were part of a complete education. In his Memorabilia (371 BC ca.), Xenophon shared a dialogue about exercise that took place between Socrates and his disciples. He concluded with a fascinating thought: "It is a disgrace to grow old through sheer carelessness before seeing what manner of man you may become by developing your bodily strength and beauty to their highest limit"[1].

The XVIII century was the framework in which the Industrial Revolution took place, and marked the passage from manual work to machine-based production. This is when the demand for physical efforts began to decrease, and men became less prone to maintaining fitness in order to be able to perform their work. It is worth mentioning that gymnastics was also a mandated obligation during some historical periods; for instance, during World War II, totalitarian regimes used it to promote Nazi philosophy and, in the Soviet Union, mandatory physical training was required to maintain a productive workforce. As daily life resources became more accessible, a fit body became progressively less important and, nowadays, physical training has become the domain of mainly military and athletic worlds. Leading an active lifestyle implies avoiding sedentary habits and including active mobility as part of a daily routine. This lifestyle does not only refer to sports practice, but also to positive everyday activities ranging from walking to housekeeping. Exercising is part of this concept, and represents a planned activity focused on benefitting both mental and physical health. The type of exercise itself varies depending on the group of muscles or parts of the body involved, the frequency, intensity and duration of movement, the equipment used, and the personal abilities required. Physical training has several purposes: to maintain fitness, reduce weight, boost strength and flexibility, improve mood, treat pathological conditions, and prevent disease. The effects can be evaluated by analysing short-term responses, monitoring a single or acute bout of training, or measuring long-term improvements in a variety of functions after repeated and chronic periods of exercise[2]. Intensity and duration of acute training are involved in the dose-dependent and transient stimulation of the hypothalamic–pituitary–adrenal axis and sympathetic nervous system. These are responsible for the mobilisation of energy reserves for increasing heart rate and blood pressure, as well as for the improvement of mental vigilance and activation of the immune system. Repeated exercise followed by recovery appears to be associated, in the long term, with adaptive and optimised control of neuroendocrine factors, anti-inflammatory states, increased production of growth factors and enhanced neural plasticity[3]. Acute and chronic exercise effects have been investigated, for example, for their effect on inflammatory states[4], the cardiovascular system[5], the skeletal muscle morphology[6] and cognitive performance[7,8].

PHYSICAL ACTIVITY AND DISEASES

It is known that a sedentary lifestyle is a significant cause of morbidity and mortality[9]. Although many evidence-based data link physical inactivity to numerous disorders (cardiovascular diseases, diabetes, forms of cancer, obesity), many people do not take it seriously[10]. A high incidence of sedentary habits can shorten life expectancy and raise medical costs of sedentary-related diseases. The World Health Organisation reported in The Lancet Global Health that more than one in four adults globally (28% or 1.4 billion people) is physically inactive[11]. To draw more attention to this alarming problem, the term "Sedentary Death Syndrome" was coined in order to make people aware of the potential consequences of such behaviour. The cause is an imbalance between calories consumed and calories expended, which eventually results in a state of hyperinsulinemia and, thus, adiposity. Overweight or obesity leads to insulin resistance, which could result in diabetes and cardiovascular disorders, as well as several other diseases such as osteoporosis, muscle wasting and general debility[12]. If lack of mobility is responsible for all these concerning health complications, then physical activity could represent a life-saving solution (Figure 1). A study revealed that 150 min of regular exercise a week leads to a decrease in the risk of diabetes, cancer, depression, stroke as well as a 30% reduction in mortality risk[13]. Data in the literature highlight that exercise has a therapeutic role for diseases such as diabetes, obesity, pain, neurological disorders and heart failure[14-17].

Furthermore, physical activity has been reported as an effective intervention in neuropsychiatric conditions; for example, it can improve mood symptoms in depressed pregnant women[18], and may benefit patients with attention-deficit/hyperactivity disorder[19]. In a very compelling and detailed review, Pedersen *et al*[20] analysed a sizeable set of data concerning the role of exercise as a first-line treatment for several chronic diseases. The authors included twenty-six diseases in their analysis, ranging from psychiatric, neurological, metabolic and cardiovascular diseases, to musculoskeletal disorders including osteoarthritis (OA), osteoporosis, back pain and rheumatoid arthritis[20].

OA EXPERIENCE

In our research experience, we paid particular attention to the musculoskeletal disorder OA. OA is a prevalent chronic disease of the joints in older people. Pharmacological treatment of OA involves the use of non-steroidal anti-inflammatory drugs, opioid and non-opioid analgesics, and intra-articular injections of steroids and hyaluronic acid, which may have significant negative gastrointestinal side effects[21]. This has led physicians to consider non-pharmacological, regenerative and behavioural treatments[22,23]. Among these, exercise is a good and useful tool to alleviate symptoms of OA and slow its progression[24-26]. The literature has demonstrated that physical exercise has short-term benefits in reducing pain, improving physical function, balance, muscle strength and flexibility[27,28]. Training tailored to improve OA includes anaerobic, aerobic, flexibility workouts and aquatic exercise[29,30]. It is essential to plan a protocol of movement whose type, duration and intensity represents the best approach to induce positive changes within the joint and for the chondrogenesis[31], but does not worsen the pathological condition by excessive load bearing or exhausting exercise[32]. It seems that a combination of aerobic fitness training and strengthening exercises should be optimal to address the spectrum of impairments associated with OA, taking into account the preferences and tolerance of patients in order to maintain a high level of adherence to the exercise program[33,34].

Medicine is more inclined to attempt to cure instead of prevent. As a consequence, human beings are subjected to many chronic illnesses that could have been avoided by observing a few simple health rules. Being physically active should be part of a daily health routine, much like hand washing or wearing a bicycle helmet. It should be prescribed in the same way as pharmacological treatment[35], deciding on the "dosage" and "formulation" for each patient. The "dosage" is calculated to reach a specific level of efficacy that prevents or improves symptoms, but does not result in toxic effects.

It is known that exercise can involve a risk of injury (fractures, muscle strain, torn ligaments), mainly when movements are performed improperly, or the equipment is inappropriate. Strenuous training could impair the immune system, and may be responsible for structural changes of the heart and large arteries, loss of electrolyte balance, and cardiac or respiratory distress[36]. Exercise can influence the blood levels of neurotransmitters, including glutamine, serotonin and dopamine, and misregulation of these could lead to depression, fatigue and confusion. Insomnia can also be caused by exercise-induced cortisol levels. Because of psychological stress about performance and body image, symptoms of anxiety and aggression, eating

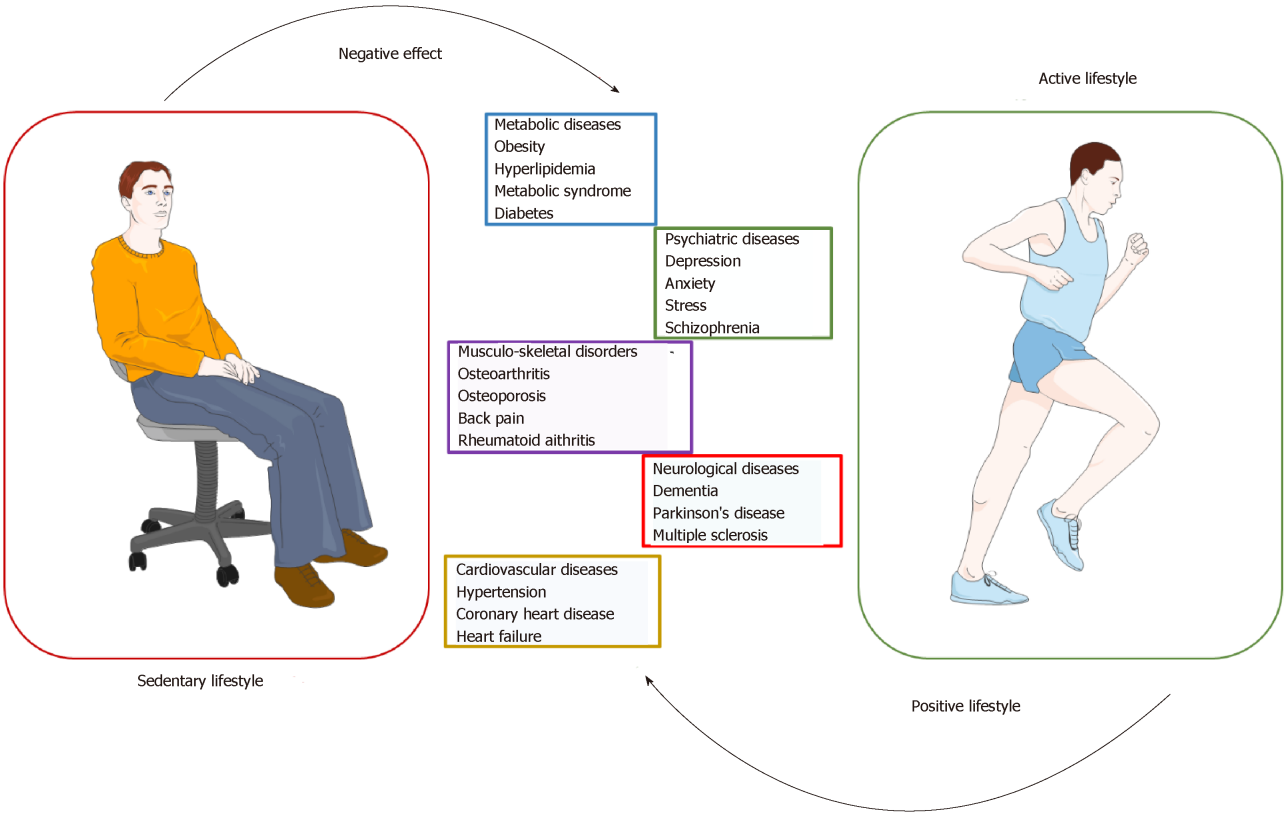

Figure 1 Clinical conditions negatively affected by sedentary lifestyle and positively affected by active lifestyle.

disorders, as well as drugs and alcohol addictions are common in athletes and team players[37]. Specific instructions or "formulations" for specific individuals, undergoing or at risk for such difficulties, are vital (Figure 2). Special categories of patients require special attention: Pregnant women, for example, cannot perform strenuous activities that could put their pregnancy at risk. Children and the elderly are not always able to perform exhausting movements and can, more easily, incur injuries. Importantly, prior to prescribing exercise, chronic or pre-existing pathological conditions, like cardiovascular, metabolic, musculoskeletal and neurological disorders, must first be evaluated.

PROSPECTS

Maintaining awareness of the severe implications of inactivity, as well as the benefits derived from exercise, is crucial. Even more important is to translate into practice what we know from the literature. We suggest that general practitioners consider physical activity seriously, and be prepared to prescribe it knowledgeably. Certified personal trainers could assist in this endeavour, and the government might want to consider incentives like free gym membership. Physicians should not only be knowledgeable in this area of therapy, but should themselves become role models of healthy living.

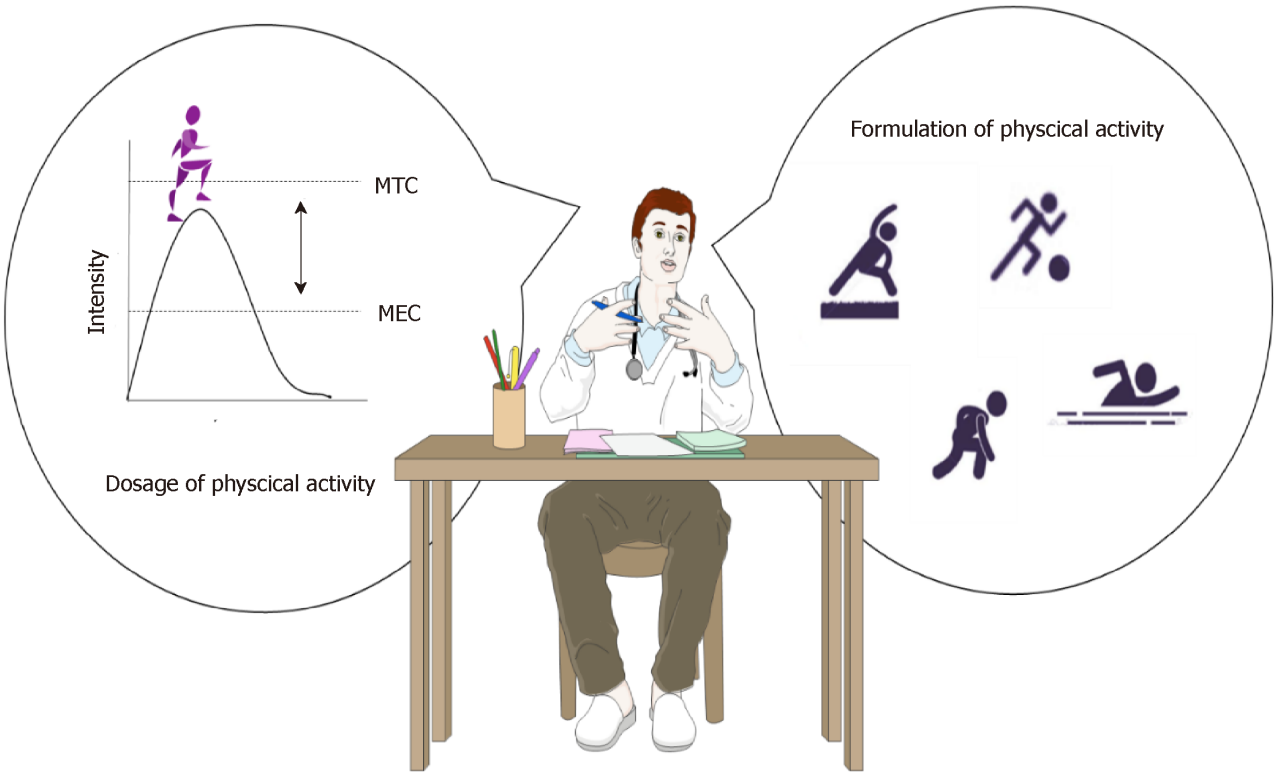

Figure 2 Prescription of exercise might take dosage and formulation into account. Dosage of physical activity could be ruled by a modified plasma concentration time curve. Formulation refers to the different kinds of training that can be performed. MEC: Minimum effective concentration; MTC: Minimum toxic concentration.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Randomised controlled trial of triclosan coated *vs* uncoated sutures in primary hip and knee arthroplasty

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Author contributions: Sukeik M, George D, Gabr A, Kallala R, Wilson P and Haddad FS contributed equally to this paper with conception and design of the study, literature review and analysis, drafting, critical revision and editing, and approval of the final version.

Institutional review board statement: The study has local R&D approval to proceed and recruit participants and the approval is granted on the basis of the key documents provided which are ethically approved by the Research Ethics Committee.

Clinical trial registration statement: A favourable ethical opinion has been granted for the research study on the basis described in the application form, protocol and supporting documentation as revised.

Informed consent statement: Patients agreed to take part in the study after reading the detailed consent form.

Conflict-of-interest statement: No potential conflicts of interest to declare. No external financial support.

Data sharing statement: Following the study, there will be access to

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Abstract

BACKGROUND

Triclosan-coated vicryl plus suture (Ethicon, Inc.) was developed to reduce microbial colonisation during surgical procedures. However, its effect on wound healing and surgical site infections remain unclear after hip and knee arthroplasty surgery.

AIM

To determine the effect of triclosan-coated sutures (TCS) *vs* non-coated sutures on wound healing, following primary hip and knee arthroplasties.

METHODS

A single-centred, double-blind randomised controlled trial (RCT) was undertaken. We randomly allocated patients to receive either the triclosan-coated sutures (TCS vicryl plus) or non-coated sutures (NCS vicryl) during the closure of unilateral primary hip and knee arthroplasties. We utilised the ASEPSIS wound scoring system to evaluate wound healing for the first 6 weeks post-operatively.

RESULTS

One hundred and fifty patients undergoing primary total hip or knee arthroplasty over a one-year period were included. Eighty-one were randomised to the TCS group and 69 to the NCS group. Despite no statistically significant difference in the ASEPSIS scores among the study groups (P = 0.75), sensitivity analysis using the Mann Whitney test (P = 0.036) as well as assessment of the wound complications at 6 weeks follow up, demonstrated significantly higher wound complication rates in the TCS group (8 *vs* 1, P = 0.03).

raw data and right to publication freely by all investigators in the study. The study results will also be presented at various national and international meetings.

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CONCLUSION
No clear advantage was demonstrated for using the TCS. However, larger multi-centred RCTs are required to validate their use in hip and knee arthroplasty surgery.

Key words: Triclosan; Hip; Knee; Replacement; Arthroplasty; Wound healing; Complications

Core tip: This randomised controlled trial does not support the hypothesis that triclosan-coated sutures are superior to non-coated sutures in wound healing and wound complications, following primary hip and knee arthroplasty surgery.

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INTRODUCTION

Periprosthetic infections after hip and knee arthroplasties remain a challenging problem with rates ranging between one to two percent for primary and up to five percent for revision procedures[1,2]. Management of such infections often requires a prolonged course of treatment; is associated with a cost to the healthcare system estimated at four times the cost of a primary procedure without infection and leads to dissatisfied patients with poor function[2,3].

Methods to prevent, diagnose and treat infection must be optimised in order to reduce both direct and indirect costs to patients and healthcare systems. Preventative measurements have so far been the single most effective method in managing such infections[4].

Intra-operative wound contamination is the main route for contracting a post-operative infection[5], with various bacteria contaminating the surgical wound and the suture material[6,7]. To prevent microbial colonisation of the suture material, the triclosan-coated vicryl plus suture (Ethicon, Inc.) was developed. Triclosan is a broad-spectrum antiseptic which has been widely used in humans for more than 30 years and is effective against *Staphylococcus aureus* and *Staphylococcus epidermidis* including methicillin-resistant and vancomycin-resistant strains[8,9].

Triclosan-coated sutures (TCS) have demonstrated favourable outcomes, in terms of wound healing[10,11] and reducing surgical site infections (SSIs) in general surgery[12-14], neurosurgery[15] and cardiac surgery[16]. In orthopaedic surgery, there have only been two recent RCTs which investigated the rates of SSIs in hip and knee arthroplasty surgery and showed conflicting results of TCS effect on rates of SSIs[17,18].

We therefore hypothesised that TCS may be associated with better wound healing characteristics and fewer infections than non-coated sutures (NCS), and as a result may potentially be more appropriate for total hip and total knee arthroplasty wound closures.

MATERIALS AND METHODS

Ethical approval

The local Research and Development department within our institute and the Regional Ethics Committee (REC) approved the trial (REC reference number: 11/LO/0196) which was also registered with an International Standard Randomised Controlled Trials Number (ISRCTN) 21430045. Written informed consent was obtained from all patients.

Patient cohort

This single-centred, double-blind RCT included adult patients (≥ 18 years old)

undergoing primary total hip (THA) or knee arthroplasty (TKA) under the care of one surgical team at our institute.

Patients were excluded if they met one of the following criteria: (1) Unilateral primary total hip or knee arthroplasty performed for trauma; (2) Revision procedure or a previous incision in the operative field; (3) History of tendency for keloid formation; (4) Allergy to triclosan/vicryl; (5) Bleeding tendency (*e.g*., haemophilia and platelet disorders) or being on regular anticoagulation treatment (*e.g*., warfarin, treatment dose of low molecular weight heparin (LMWH) or conventional heparin); (6) Underlying malignancy and immunocompromised status; and (7) Dementia and mental illnesses preventing informed consent, and children (age < 18 years).

Surgical technique

The operations were performed according to the senior surgeon's default procedure, which include using a medial parapatellar approach and cement for knee arthroplasty, and a posterior approach and uncemented prostheses for hip arthroplasty.

Closure of the TKA wounds included using interrupted 1 vicryl or vicryl plus for the medial parapatellar incisions and 2-0 vicryl or vicryl plus for the subcutaneous tissues followed by skin clips. Closure for the THA wounds included using interrupted 1 vicryl or vicryl plus for the fascia lata and 2-0 vicryl or vicryl plus for the subcutaneous tissues followed by skin clips. For TKAs, a tourniquet was only inflated at the time of cementation and was released after dressing the wound. No drains were used.

Antibiotic prophylaxis included 3 doses of cefuroxime 750mg or alternatively 2 doses of teicoplanin 400mg if the patient was allergic to cefuroxime, with the first dose given at induction of anaesthesia and the rest within the first 24 hours from the operation. All patients received anti-embolism stockings as well as low molecular weight heparin (LMWH) for thromboprophylaxis. Perioperative care plans were similar for each type of operation.

Randomisation

Participants were randomly assigned to two groups. "Cases" received coated polyglactin 910 sutures with triclosan (Vicryl Plus; Ethicon, Inc.), whilst "controls" received the coated polyglactin 910 sutures (Vicryl; Ethicon, Inc.).

Randomisation and blinding were performed by SealedEnvelope Ltd. with assignment of letter codes to cases and controls. The suture type corresponding to a particular letter code was known only to the member of team who received the codes and was not part of the operating surgeons or the operating room nurses. An equal number of cases and control letter code cards were prepared and placed individually in sealed envelopes.

The nurses used consecutive allocation, which was concealed from all professionals delivering patient care including the surgeons and the team involved in assessment of the wounds. Patients, surgeons and the team assessing the wounds were all blinded to treatment assignment (double-blinded study), because both sets of sutures are indistinguishable after removal of the package labelling by the nurses.

Block randomisation was used, with unequal block sizes in order to keep the sizes of treatment groups similar. Randomisation codes were only broken in a case of a serious adverse event.

Outcome measures

The primary outcome was the ASEPSIS wound scoring system[19]. This quantitative wound scoring method is calculated using objective criteria based both on visual characteristics of the wound and the consequences of infection[20-23]. A score of > 10 indicates an increasing probability and severity of infection (Table 1). Surgical wounds were inspected two or three days after the operation, and again on days four or five if the patient was still in hospital. The proportion of each wound exhibiting erythema, serous discharge, purulent discharge or dehiscence was recorded. At each post-operative visit, the notes and drug charts of each patient were inspected. The diagnosis of a wound infection by a medical practitioner, the prescription of prophylactic or therapeutic antibiotics, and the opening of a wound or drainage of an abscess was recorded.

Infection was considered superficial if resolved with oral antibiotics only and deep if not controlled with oral antibiotics or required a washout/debridement or revision surgery.

At the time of discharge patients were given a simple "yes/no" questionnaire regarding their wound, which they have been asked to complete and return in a pre-paid envelope two months later. Patients were contacted by telephone if no postal questionnaire was returned. The questionnaire was used to ascertain whether a

Table 1 Criteria and points allocation used in calculating the ASEPSIS score

ASEPSIS Score calculation	
Points	**Criterion**
	Additional treatment
10	Antibiotics
5	Drainage of pus under local anaesthetic
10	Debridement of wound under general anaesthetic
0-5	Serous discharge
0-5	Erythema
0-10	Purulent exudate
0-10	Separation of deep tissues
10	Isolation of bacteria
5	Stay in hospital over 14 d
Breakdown of ASEPSIS score	
0-10	No infection, normal healing
11-20	Disturbance of healing
21-30	Minor infection
31-40	Moderate infection
> 40	Severe infection

wound infection had been diagnosed since discharge, whether antibiotics had been prescribed for the wound, whether any further surgery had been necessary and whether the hospital stay had been longer than 14 d. Additionally, each patient attended our arthroplasty clinic at 2 and 6 wk postoperatively for assessment of the wound, and received any additional treatment if necessary.

The secondary outcomes included: (1) Time for wound closure, defined as the time period in minutes after insertion of the prosthesis and commencing closure of the fascia in case of THAs or retinaculum for TKAs until completion of skin clips insertion; (2) Length of operation in minutes; (3) Length of hospital stay in days; (4) Pain assessment using the visual analogue scale scores (1-10) measured at 1, 3 and 5 d postoperatively; and (5) Post-operative complications.

Patient demographics and co-morbidities were collected for baseline comparison of the study groups through attendance of pre-assessment clinics, operative lists and follow-up clinic appointments. This included patient age, gender, body mass index, diabetes, smoking and performance level classified according to the American Society of Anaesthesiologists grade[24].

Statistical analysis

A clinically important difference would be the TCS reducing the ASEPSIS score by 10. A preliminary audit suggested that if the TCS reduced all patients with a score of 11 to 20 to 10 and below and everyone else to a score 10 lower, then we would expect 97.5% of patients to score 10 and below. Sample size calculation was undertaken using Stata 11 based upon the following assumptions: a two group RCT with equal group sizes, 90% of patients with the NCS to have a score of ten and below and 97.5% of patients with the TCS to have a score of 10 and below. Therefore, we required 210 patients in each group to demonstrate a two-sided 5% significance, with 80% power, and 10% dropout rate.

The two study groups' baseline characteristics were compared using means and standard deviations (SDs) for continuous data and frequency counts and percentages for categorical data. The data was analysed using a chi-squared test, Mann-Whitney *U* test, or Fisher exact test where appropriate. Furthermore, we undertook a logistic regression to determine what patient and operative factors, if any, were independently risks of developing a post-operative complication. All statistical analyses were performed with SPSS version 21.0 software (SPSS, Inc.). A P-value < 0.05 was deemed statistically significant.

The proportion of dropouts from the study was reported. Data analysis was done on an intention to treat basis.

RESULTS

Patient cohort

Patients were recruited between November 2013 and December 2014. During this period, there were 210 patients scheduled for primary hip and knee arthroplasty. Thirty-four patients were excluded for various reasons such as history of previous trauma accounting for the osteoarthritis, revision surgery or being on warfarin. Twenty-six patients refused to take part in the study. Therefore, the study consisted of 150 participants, 81 were randomised to the TCS group (cases) and 69 were randomised to the NCS group (controls) (Figure 1).

After December 2014, our institute terminated the contract with Ethicon to move to another supplier and hence the sutures were no longer available and the trial had to be ended prematurely with inclusion of 150 out of the 420 intended patients and the results analysed.

The patient cohort included 49 males and 101 females, with a mean age of 68 years (SD 10). The primary indication for surgery was osteoarthritis in 145 (96%) patients. Ninety-six THAs and 54 TKAs were performed; with a mean length of hospital stay of 6 days (SD 4). One hundred and forty-four patients (96%) completed the full follow-up needed for the study. The demographics were comparable for the two groups (Table 2).

Operative data

There were 96 THAs and 54 TKAs performed during the study. Table 3 demonstrates the difference between the operative data between cases and controls.

Wound outcomes

No statistically significant difference was seen between the two study groups when comparing an ASEPSIS score of ≤ 10 compared to > 11 (P = 0.75). However, a score of greater than 10 was seen in only 6 cases and 4 controls. On the other hand, a statistically significant difference was demonstrated when comparing the overall mean ASEPSIS scores among the study groups (cases = 2.5, controls = 1.4, P = 0.036) (Table 4).

DISCUSSION

This RCT was undertaken to compare the wound healing characteristics and wound complications, following wound closure with triclosan-coated and non-coated sutures in primary THA and TKA surgery. Despite the premature termination of this study, there was evidence that the TCS were associated with more wound complications than NCS, rejecting our hypothesis (P = 0.03).

Triclosan-coated sutures have recently gained popularity in Orthopaedics, due to its perceived advantages seen in other surgical specialities. Whilst the majority of evidence in the literature supports the use of TCS in surgical wound closures including recent meta-analyses[25-29], there have been several recent studies questioning its efficacy and complication rates.

Mattavelli *et al*[30] demonstrated no advantage in reducing SSI rates after colorectal surgery in a multi-centred RCT, which included 281 patients (P = 0.564). The overall incision complication rate was noted to be more in the TCS group (45.7%), compared to the control group (38.3%; P = 0.208). Other RCTs concluded similar findings following abdominal wall closure[31], colorectal surgery[32], and leg wound closure following graft harvest in coronary artery bypass patients[11].

The two RCTs published on TCS and rates of SSIs in hip and knee arthroplasty surgery show conflicting results[17,18]. Lin *et al*[18] randomised 102 patients to TCS or a control group in TKA surgery and concluded that none of the patients in the TCSs group developed a superficial infection whereas 2 patients in the control group (3.9%) developed superficial infections. They also reported lower serum interleukin-6 levels and lower local skin temperature recorded at 3 mo using infrared thermography in the TCS group[18]. On the other hand, Sprowson *et al*[17] conducted the largest multi-centred double-blinded quasi-RCT to date including 2546 patients who underwent either hip or knee arthroplasty surgery and concluded that TCSs did not lead to a reduction in the rate of SSIs (0.7% TCS *vs* 0.8% control groups). Despite the difference in the primary outcome measured between our study and this RCT, our study findings support higher wound complication rates related to the TCS. Additionally, it is worth noting that this was a quasi-randomised trial conducted at 3 sites with a large number of contributing surgeons and different. Furthermore, the surgeons were not blinded to the type of suture utilised, but both the patients and assessors of outcomes were.

Considering the lack of significant improvement in wound complications, we

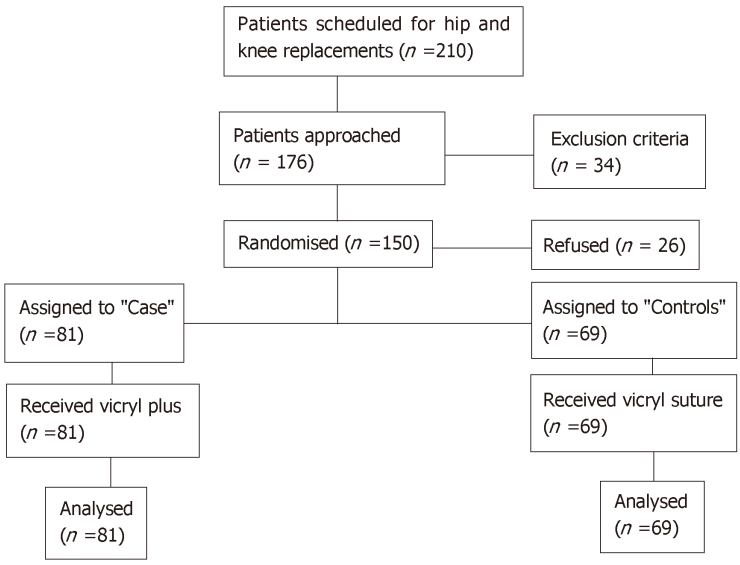

Figure 1 Consort diagram of patients' recruitment and allocation to treatment group.

cannot advocate the continued use of TCS in these procedures. Whilst not the objective of this study, one has to also consider the financial implications of the two suture types. The price per suture will vary amongst institutions, but based upon National Health System (NHS) Supply Chain data[33], the TCS is typically 20% more expensive than the standard NCS [£3.82 compared to £2.99 respectively]. Whilst suture costs are minimal when reviewing the overall costs of arthroplasty procedures, if no benefit has been shown between the two in reducing rates of infection, there may be significant savings should the standard NCS be the suture of choice.

Strengths of this RCT include the robust inclusion and exclusion criteria and randomisation process, the double blinding of the study including the surgeons performing the operations and inclusion of a single surgeon's cohort of patients to reduce bias in the surgical technique in wound closure among various surgeons.

The incidence of wound infection and poor wound healing, is multifactorial due to a combination of both patient and provider risk factors. In this study, the baseline demographics were similar for both groups, having all undergone pre-operative optimisation prior to surgery. However, after the surgery we were unable to control patient factors following their discharge from hospital, which no doubt may have had an impact on wound healing. Other limitations of this study included the premature termination of the trial due to the unavailability of the sutures after December 2014. This may have resulted in a type II error due to the study being underpowered; hence the binary variable ASEPSIS score ≤ 10 versus > 10 was insignificant. However, sensitivity analysis using the Mann Whitney test (P = 0.036) as well as assessment of the wound complications at the last follow up (P = 0.03), demonstrated significantly higher wound complication rates in the TCS group. Additionally, we utilised the ASEPSIS scoring system which addresses acute postoperative wound healing only, and therefore the protocol for wound surveillance continued for only 6 weeks post-operatively. We acknowledge that the results of this study cannot be applied to delayed onset periprosthetic joint infections.

This double-blinded RCT was undertaken according to a strict inclusion and exclusion criteria to address the intervention of interest. It is the first of its kind reporting the outcomes investigating the effect of TCS on wound healing after primary THA and TKA surgery.

In conclusion, our study has demonstrated that TCS are not associated with improved wound healing or reduction of infections, when compared to NCS. However, larger multi-centred RCTs are required, with adequate power, to fully validate the use TCS in hip and knee arthroplasty surgery.

Table 2 Patient demographics between the two groups

		Trial group		*P* value
		Controls (*n* = 69)	Cases (*n* = 81)	
Age	mean (SD)	67.85 (9.85)	68.65 (10.90)	*0.44*
Diagnosis	OA	68	77	0.33
	SUFE	0	2	
	AVN	1	0	
	Hip dysplasia	0	1	
	Perthes	0	1	
Gender	Male	24	25	0.73
	Female	45	56	
BMI	mean (SD)	28.70 (5.13)	29.14 (4.97)	0.54
Smoker	Yes	6	6	0.64
	Never	42	57	
	Ex-smoker	13	12	
Diabetic	Yes	4	10	0.26
	No	57	64	
ASA Grade	1	9	9	0.68
	2	47	52	
	3	13	20	

OA: Osteoarthritis; SUFE: Slipped upper femoral epiphysis; AVN: Avascular necrosis; BMI: Body mass index; ASA: American Society of Anesthesiologist.

Table 3 Comparison of operative data between the two groups

		Trial group		*P* value
		Controls (*n* = 69)	Cases (*n* = 81)	
Site	Hip	42	54	0.5
	Knee	27	27	
Surgeon	Consultant	25	29	0.63
	Registrar	38	41	
	Fellow	6	11	
Anaesthetic	General	45	50	0.56
	Regional	17	26	
	Both	3	2	
Local anaesthetic	Yes	67	77	0.38
	No	1	4	
Length of operation	mean (SD)	88.44 (23.84)	91.24 (26.5)	0.67
	mean (SD)	3.75 (0.87)	3.53 (0.81)	0.12
Number of sutures used	2	1	7	0.26
	3	23	29	
	4	30	30	
	5	6	8	
	> 5	1	0	
Prosthesis hip	Synergy – R3	37	48	0.30
	Trifit – Trinity	3	3	
	Exeter	0	3	
Knee	Triathalon	21	23	0.70
	Saiph knee	5	3	
Wound closure (min)	mean (SD)	14.64 (5.51)	13.89 (5.13)	0.47
VAS score (mean, SD)	Day 1	6.47 (2.62)	6.20 (2.35)	0.34
	Day 3	4.75 (2.33)	4.18 (2.33)	0.15

	Day 5	4.67 (1.75)	2.92 (2.87)	0.18
Length of stay (d)	mean (SD)	6.13 (4.23)	6.23 (4.11)	0.95

VAS: Visual analogue scale.

Table 4 Outcomes at follow-up

		Trial group		*P* value
		Controls (*n* = 69)	Cases (*n* = 81)	
ASEPSIS scores				
0-10		65	75	0.75
> 10		4	6	
mean (SD range)		1.41	2.54	0.036
		(0.38-2.43)	(1.41-3.68)	
Follow-up outcomes (2-wk)				
Site of follow-up	Hospital	35	37	0.21
	Community	27	28	
	Inpatient	2	10	
	Did not attend	5	6	
Wound complications	Yes	1	6	0.22
	No	63	69	
	Superficial SSI	1	2	
	Erythema	0	3	
	Serous discharge	0	1	
Follow-up outcomes (6-wk)				
Attended hospital	Yes	61	65	0.189
	No	8	16	
Wound complications	Yes	1	8	0.03
	No	60	57	
	Superficial SSI	1	3	
	Wound dehiscence	0	1	
	Irritation from suture	0	2	
	Serous discharge	0	1	
	Deep SSI	0	1	
Systemic complications	Nausea and vomiting	0	2	0.12
	Dizziness	0	0	1.00
	Bleeding(not from wound)	1	2	0.26
	Stiffness	4	5	0.30
	Neurovascular injury	0	0	1.00
	DVT	1	0	0.18
	PE	0	1	0.19
	Chest infection	1	2	0.26
	MI	0	0	1.00
	CVA	0	0	1.00
	Fracture	0	2	0.12
	Dislocation	0	0	1.00
	Loosening	0	0	1.00
	Mortality	0	0	1.00
	Missing data	8	16	

SSI: Surgical site infection.

ARTICLE HIGHLIGHTS

Research background
Despite the lack of evidence that using triclosan-coated sutures has any benefits in hip and knee arthroplasty surgery, they have been used widely due to the potential benefit of improving wound healing and reducing surgical site infections.

Research motivation
We sought to compare the wound healing characteristics and wound complications associated with the use of triclosan-coated sutures and compared them to non-coated sutures in primary hip and knee arthroplasty surgery.

Research objectives
Our main objective was to investigate the potential benefits of using triclosan-coated sutures in hip and knee arthroplasty surgery using a well designed randomised controlled trial to guide future practice.

Research methods
A single-centred double blinded randomised controlled trial was conducted according to strict inclusion and exclusion criteria and following the Research and Development and Regional Ethics Committee guidelines for conducting high-quality well-designed trials with the above objectives. Primary and secondary outcomes were defined, computer randomisation was performed through Sealed Envelope and statistical analysis including power calculation was planned and approved prior to conducting the trial.

Research results
Utilising the ASEPSIS scoring system, there were no significant differences between the triclosan-coated and non-coated sutures. However, wound complications were noted more frequently at the 2 and 6 wk follow up in the triclosan-coated sutures group. As the study has been terminated earlier than planned due to the unavailability of the sutures, further randomised controlled trials are still warranted to fully answer the question of whether triclosan-coated sutures provide any protection against wound complications and infections after hip and knee arthroplasty surgeries.

Research conclusions and perspectives
The current literature supports the use of triclosan-coated sutures in some disciplines of general surgery but the evidence in orthopaedic surgery especially in arthroplasty procedures remains inconclusive. This trial supports the findings from other studies that triclosan-coated sutures do not provide any benefits over non-coated sutures in protecting against wound complications and infections after hip and knee arthroplasty surgery. Therefore, we recommend against the routine use of those sutures and advise that efforts should continue to emphasise the benefits of preventative measures against infections and explore new modalities of reducing surgical site infections. The utilisation of a well-designed randomised controlled trial will help in answering whether any of those new modalities will stand the challenge of time and optimal outcomes.

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SYSTEMATIC REVIEWS

Platelet-rich plasma for muscle injuries: A systematic review of the basic science literature

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Abstract

BACKGROUND

Platelet-rich plasma (PRP) is an increasingly used biologic adjunct for muscle injuries, as it is thought to expedite healing. Despite its widespread use, little is known regarding the mechanisms by which PRP produces its efficacious effects in some patients.

AIM

To clarify the effects of PRP on muscular pathologies at the cellular and tissue levels by evaluating the basic science literature.

METHODS

A systematic review of PubMed/MEDLINE and EMBASE databases was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and checklist. Level III *in vivo* and *in vitro* studies examining PRP effects on muscles, myocytes and/or myoblasts were eligible for inclusion. Extracted data included PRP preparation methods and study results.

RESULTS

Twenty-three studies were included (15 *in vivo*, 6 *in vitro*, 2 *in vitro*/*in vivo*). Only one reported a complete PRP cytology (platelets, and red and white blood cell counts). Five *in vitro* studies reported increased cellular proliferation, four reported increased gene expression, and three reported increased cellular differentiation. Five *in vivo* studies reported increased gene expression, three reported superior muscle regeneration, and seven reported improved histological quality of muscular tissue.

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CONCLUSION
The basic science literature on the use of PRP in muscle pathology demonstrates that PRP treatment confers several potentially beneficial effects on healing in comparison to controls. Future research is needed to determine optimal cytology, dosing, timing, and delivery methods of PRP for muscle pathologies.

Key words: Platelet rich plasma; Basic science; Muscle; Musculoskeletal; Injury

Core tip: Platelet-rich plasma (PRP) has gained much attention in the treatment of muscle injuries for its potential beneficial effects in both operative and non-operative settings without knowledge of its mechanism of action. The current systematic review synthesizes the effects of PRP at the basic science level. PRP was found to induce cellular proliferation and differentiation, the production of various growth factors, muscle regeneration, and changes in gene expression. Only one study reported a complete PRP cytology. This study highlights the underlying mechanisms of PRP in muscle pathology at the basic science level, and emphasizes the need for standardization in PRP preparation and reporting.

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INTRODUCTION

Over the past several years, there has been increasing interest in biologic agents as both nonoperative treatment modalities and augments to surgical procedures, to potentially accelerate the healing process and expedite return to sport after muscle injury. Platelet-rich plasma (PRP) is a blood product that is rich in platelets and many different cytokines and growth factors, such as transforming growth factor beta (TGF-β1), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF), whose influence on the healing of ligaments, muscles, tendons, joints, and soft tissue has been extensively studied[1-5]. In muscle pathology in particular, PRP's abundance of growth factors and cytokines is purported to expedite healing through the induction of cellular proliferation and migration, increased angiogenesis, and muscle tissue regeneration[6-8]. These notions have led to the clinical use of PRP for both acute and chronic muscle injuries, despite the lack of both basic science and clinical evidence that justifies its use and efficacy[7,9,10]. At best, several clinical studies and trials on the use of PRP for muscle injuries have been published with varying results[3,7-9]. Therefore, it is imperative to clarify which mediators in particular facilitate these potential effects, both to better understand PRP as a biological augment, and to aid in the optimization of PRP preparations for clinical use.

The use of PRP in clinical settings requires controlled clinical trials, with consistent methodology in terms of dosing and preparation. However, what must precede is a rigorous examination of the effects of PRP *in vitro* and *in vivo* to fully understand its mechanisms of action and appropriate clinical targets. The purpose of this systematic review is to clarify the effects of PRP on muscular pathologies at the cellular and tissue levels by evaluating the basic science literature. Furthermore, the authors hypothesized that the use of PRP would confer multiple beneficial effects in the healing of muscle injuries in comparison to controls.

MATERIALS AND METHODS

A systematic review of the PubMed/MEDLINE and EMBASE databases was performed in December 2017 using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines with a PRISMA checklist. The search was performed using the following keywords: (platelet rich plasma OR PRP OR

autologous conditioned plasma OR ACP) AND (muscle OR myocyte OR skeletal muscle OR muscle injury).

The inclusion criteria for full-text reviews were level III *in vivo* and *in vitro* studies examining the effects of PRP on muscles, myocytes and/or myoblasts, that also included a well-defined control group (saline solution, no treatment, or control cell medium). Animal studies that observed the effects of PRP on traumatic and surgically-induced muscle injuries were included. In studies that reported results with additional treatments, only results that compared PRP directly with the control were analyzed. Exclusion criteria included non-English language articles, clinical studies, randomized controlled trials, review articles, articles not published in peer-reviewed journals, and studies without a control group. All references within included studies were cross-referenced for potential inclusion. One author independently performed the search and identified studies for inclusion.

Two authors extracted data using a predefined data collection sheet. Collected data included the characteristics and cytology of PRP, growth factor concentration, adhesive protein concentration, clotting factor concentration, fibrinolytic factors, proteases and antiproteases, basic proteins, membrane glycoproteins, dense granule bioactive molecules, pro-inflammatory cytokine concentration, anti-inflammatory cytokine concentration, and other proteins. In addition, study design and methods, study subjects, outcomes measured, and results were recorded. These variables included cell viability, cell proliferation, cell migration, gene expression, mechanical properties, gross appearance, and mechanical or histological examinations. If results were significantly different between the experimental and control cohorts, it was considered to be a positive or negative result based on the relative change observed. If no difference was observed between the experimental and control cohort groups, it was recorded as no change observed. Once data analysis was complete, data were analyzed for trends in outcomes by comparing the PRP treatment with controls.

RESULTS

Search and literature selection

The search for studies on the use of PRP in muscle pathology yielded 1013 results on PubMed/Medline and 1117 results from EMBASE. Duplicates were excluded, and 1570 studies fit the inclusion criteria for systematic review according to the search parameters described above (Figure 1). The full-text review yielded 23 articles that met the inclusion criteria for muscle pathology. Of the included studies, 15 were *in vivo*, 6 were *in vitro*, and 2 had both *in vitro* and *in vivo* study arms.

In vitro muscle studies

Of the 6 *in vitro* muscle studies (Table 1), 4 (66.6%) studied myoblasts[1,11-13], one studied a range of human-derived cells (myocytes, tenocytes, osteocytes and osteoblasts)[7], and one solely studied myocytes[14]. Of the first group, two studied human-derived myoblasts[11,12], while the other two studied murine-derived myoblasts[1,13].

Two studies (33.3%) reported that the platelet concentration of the final PRP preparation was increased compared to control (Table 2)[7,12]. Only one *in vitro* muscle study reported white blood cell concentration[7]. In this study, 3 different PRP preparations at varying platelet and leukocyte concentrations were created, and cytology was reported. Only one study reported a complete cytology of PRP, which included platelet count, red blood cell count, and white blood cell count.

All six studies analyzed cell proliferation in response to PRP treatment, and all reported significant increases[1,7,11-14] (Table 3). In 4 studies (66.6%), the effect of PRP on cell differentiation was examined, and 3 (50%) observed increases[1,7,11,12] (Table 3). One study (16.7%) analyzed cell signaling in response to PRP treatment, reporting no effect[1] (Table 3). All 6 studies examined the effect of PRP on the regulation of gene expression, and reported significant increases in stem cell markers[7], particularly those indicative of early differentiation[1], cell-cycle mediators[13], myosin heavy chain expression[12], and mediators of cellular migration[14] (Table 3). One study reported a dose-dependent increase in cell migration and spreading with PRP treatment[14]. None of the *in vitro* studies assessed inflammatory mediation, proteoglycan or collagen content (Table 3).

In vivo muscle studies

Of the 15 *in vivo* studies, 11 (73.3%) reported platelet concentrations in their final PRP preparations[2,3,8,15-22] (Table 2). All 11 studies reported platelet concentrations greater than that of whole blood. Five studies (33.3%) reported PRP WBC concentration. Two

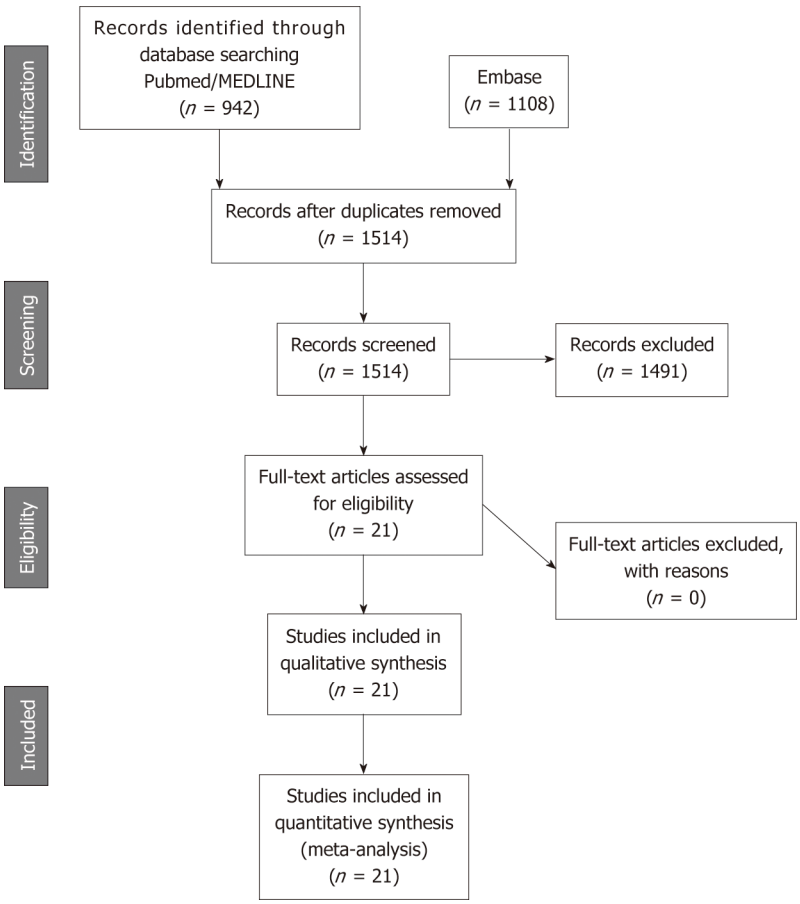

Figure 1 PRISMA diagram representing the process of individual study inclusion after application of the study algorithm, and each of the exclusion criteria.

of these studies reported an increase in WBC concentration relative to whole blood[15,17]. One study reported an increased RBC count relative to whole blood in their PRP preparation[15]. None of the studies reported a complete cytology of PRP.

A variety of animal models and muscles were used (Table 4). Studies also performed histologic[3,6,8,9,15,17,18,20-25] and gross anatomical[6,15,17,20,21,23] assessments of the muscles (Table 5). Eight studies reported improved functional and structural variables, reduced fibrosis, and increased muscular regeneration in PRP-treated muscle compared to control muscle[6,15,17,20-23,25]. Several studies reported increased angiogenesis after PRP treatment[17,20,21,23]. Four studies reported increased leukocyte infiltration at the injection site[8,9,18,25]. With regards to changes in collagen deposition, one study reported increased type III collagen, one reported increased type I collagen[25], and two reported no change in collagen content[2,8]. One study reported significant increases in growth factor concentrations (EGF, PDGF-BB, PDGF-AA, HGF, IGF, TGF-β1) compared to control groups, as well as a greater number of VEGF receptors[15] (Table 5). In this study, it was found that the growth factors with the most robust increase relative to baseline were PDGF and HGF, and that leukocytes were the main source of VEGF[15].

Combined in vivo and in vitro muscle studies

Of the 2 studies that examined both the *in vivo* and *in vitro* uses of PRP, one used human muscle-derived progenitor cells (hMDPCs) from unspecified skeletal muscle from living and post-mortem biopsies for the *in vitro* component[26], while the other used an established murine myogenic cell line (C2C12)[27] (Table 6). Only one study reported platelet count and WBC concentration[24], while neither reported RBC count. For the *in vivo* component, the gastrocnemius muscle of a mouse[26] and the rotator cuff muscles (supraspinatus and infraspinatus) of a rat[27] were used. The *in vitro* studies reported the following with regards to PRP treatment relative to controls: Increased cell proliferation[27], increased expression of stem cell markers[26], increased myotube formation and area[27], increased myogenic proliferation and decreased lipid droplets[27], and increased Pax7 and myogenin gene expression[27] (Table 7). Furthermore, the *in vivo* component of one study assessed hMDPC expansion[26] (Table 6).

Table 1 *In vitro* PRP and muscle studies – summaries

Ref.	PRP preparation	Cytology findings	Study design	Outcomes measured	Results
Kelc *et al*[11], 2015	Whole blood in citrate dextrose anticoagulant spun 10 min at 1500 rpm. Three PRP solutions prepared at differing "growth factor concentrations" by diluting with DMEM (5%, 10% and 20%)	Not reported	Human CD56+ Myoblast cells cultured and treated with PRP (5,10,20%) and/or decorin for 4 d of treatment	Cell viability, proliferation. Myogenic differentiation, TGF-β and other fibrotic cytokine expression, MRF	PRP increased myoblast proliferation, viability, and differentiation. PRP supported myogenic shift in differentiation. Decreased TGF-β and other fibrotic cytokine expression and increased expression of MRFs
Mazzocca *et al*[7], 2012	PRP-LP (low platelet) – single 1500 rpm spin for 5 min. Plasma layer isolated. PRP-DS (High Platelet, high WBC) – double spin first at 1500 rpm for 5 min then again at 6300 rpm for 20 min. PRP-HP (High platelet, low WBC) – single 3200 rpm spin for 15 min	PRP-LP – Platelet (Plt) count equal to 382.0 ± 111.6 10^3/μL; RBC 0; WBC 0.6 ± 0.3 10^3/μL. PRP-HP – Plt count equal to 940.1 ± 425.8 × 10^3/μL; RBC 1.5± 2.5 × 10^3/μL; WBC 17.0 ± 5.2 × 10^3/μL. PRP-DS - Plt count equal to 472.6 ± 224.2 × 10^3/μL; RBC 0.0 ± 0.1 × 10^3/μL, WBC 1.5 ± 0.6 × 10^3/μL	Human muscles isolated from lattisimus dorsi transfer procedures cultured for 2 wk to allow for myocyte outgrowth. Myocytes treated with three PRP treatments for 96 h	Cell proliferation, growth factor concentrations (EGF, FGF2, HGF, IGF-1, PDGF, TGF-β, VEGF)	PRP-DS and PRP-LP increased cell proliferation. PRP-LP increased concentration of all growth factors except HGF, FGF, & EGF. PRP-DS increased concentration of all growth factors except FGF & HGF. PRP-HP increased concentration of all growth factors except FGF
McClure *et al*[1], 2016	Prepared with commercial SmartPReP® 2 system. Frozen thaw protocol to lyse platelets. Product then frozen and lyophilized to create dry PRGF	Not reported	C2C12 murine myoblasts cultured and expanded and treated with PRGF at various concentrations for 7 d	Proliferation (MTS proliferation assay), myogenic regulatory factor (MRFs) concentration, cell differentiation, skeletal muscle cell signaling, scaffold fiber alignment	PRP dose dependently increased myoblast cell proliferation, differentiation, skeletal muscle cell signaling, and concentration of MRFs (MyoD, MyoG)
Miroshnychenko *et al*[12], 2017	50 mL whole blood from seven volunteers processed with Pure PRP kit (EmCyte Corp) into: (1) Single spin leukocyte poor PRP; (2) Single spin mod-PRP with TGF-β1 and MSTN depletion; (3) Dual spin PRP; (4) Dual spin Mod-PRP; and (5) PPP. Second spin was 550 × *g* for 5 min and removed all platelets	PRP - Plt count equal to 879 ± 350.6 10^3/μL; WBC 1.8 ± 2.3 10^3/μL. PPP -Plt count equal to 9.9 ± 4.9 10^3/μL	Human skeletal muscle myoblast (HSMM) cell culture (CC-2580, Lanza) used to produce positive control (treated with 2% horse serum in myogenic DMEM/F-12 medium) and negative control (treated with 10% FBS in SkBM-2 basal medium). HSMM treated at varying concentrations with plasma formulations	Cell proliferation, protein production, myoblast differentiation, gene expression (MYH, MYH2, MSTN, MEF2C)	Single spin PRP & single spin Mod-PRP greatest influence on myoblast proliferation, but did not promote myogenic differentiation or formulation of myotubules. PPP and double spin PRP had little effect on proliferation, but greatest effects on promotion of myogenic differentiation and myotubule formation. PPP had a dose-dependent effect (peaking at 4%) on increasing MYH expression
Tsai *et al*[13], 2017	Whole blood from Sprague-Dawley rats in acid citrate-dextrose, spun at 800 × *g* for 30mins. Plasma isolated and spun at 3000 × *g* for 20 min. 10% thrombin solution added and again centrifuged at 5500 × *g* for 15 min. Final release filtered by 0.22 μm ultra-filtration and frozen at -20 °C	Not reported	Skeletal muscle cells isolated from Sprague-Dawley rats cultured and treated with PRP releasate. MTT assay and Immunohistochemistry with ki-67 stain also used to determine cell proliferation. Western blot used to determine changes in protein expression. Flow cytometry used to evaluate cell-cycle progression	Cell proliferation, cell viability, protein expression (cyclin A2, cyclin B1, cdk1, cdk2, PCNA)	PRP increased skeletal muscle cell viability & cell proliferation by shifting cells from the G1 phase to the S1 phase and G2/M phases. PRP increased protein expression of cyclin A2, cyclin B1, cdk1, cdk2, PCNA

Tsai *et al*[14], 2017	Whole blood from Sprague-Dawley rats in acid citrate-dextrose, spun at 800 × *g* for 30 min. Plasma isolated and spun at 3000 × *g* for 20 min. 10% thrombin solution added and again centrifuged at 5500 × *g* for 15 min. Final release filtered by 0.22 μm ultra-filtration and frozen at -20 °C	Not reported	Myocyte migration evaluated by trans-well filter migration assay and electric cell-substrate impedance sensing. Myocyte spreading evaluated microscopically. Formation of filamentous actin (F-actin) cytoskeleton assessed by immunofluorescence staining. Protein expressions of paxillin and focal adhesion kinase (FAK) assessed by Western blot analysis	Myocyte migration, spreading, FAK and Paxillin expression, F-actin formation	PRP dose-dependently promoted (1) Myocyte migration, (2) Spreading, (3) Paxillin and FAK expression, (4) F-actin formation, and (5) Wound healing

PRP: Platelet-rich plasma.

DISCUSSION

The principle findings of this systematic review are as follows: (1) In the majority of studies, PRP treatment increased myocyte proliferation, growth factor expression (*e.g.*, PDGF-A/B and VEGF), leukocyte recruitment, and angiogenesis in muscle models when compared to control groups; (2) PRP preparation techniques remain inconsistent across studies in the basic science literature; and (3) Evidence from *in vitro* and *in vivo* basic science studies suggest that PRP has the potential to serve as an efficacious treatment modality that may expedite the healing process for muscular pathologies, based off of the observed effects at the cellular and tissue levels in treatment groups relative to control groups.

The results from the current study suggest that PRP may have differential effects on myoblast proliferation and differentiation, depending on the formulation of PRP at the basic science level. The traditional formulation of leukocyte-poor PRP that is not modulated to remove specific growth factors or platelets was shown to promote myoblast proliferation. Significant increases in myocyte proliferation were observed in all of the *in vitro* studies included in this review[1,7,11-13,26]. Li *et al*[26] reported that PRP upregulated the expression of stem cell markers in hMDPCs. Miroshnychenko *et al*[12] also found that traditional unmodified leukocyte-poor PRP increased proliferation of human skeletal muscle myoblasts. However, the unmodified leukocyte-poor PRP had very little effect on myoblast differentiation. On the other hand, platelet-poor plasma and double spin PRP (aimed to remove platelets) significantly promoted the induction of human myoblasts into the differentiation state. Early cell differentiation was also observed in an additional three *in vitro* studies[1,11,12]. It is plausible that the increases in both differentiation and proliferation underlie some of the histological findings in the *in vivo* muscle publications, which demonstrated that PRP treatment accelerated muscular regeneration and reduced fibrosis when compared to controls[6,15,17,20,21,23].

The differential effects of different PRP formulations on myoblast proliferation and differentiation suggest that the growth factors that promote the proliferation of myoblasts may be very different than those that promote myoblast differentiation. Several studies demonstrated PRP-induced quantifiable increases in growth factor expression[15,16], as well as observable histological increases in leukocyte recruitment to the area of injury[8,9,18]. Denapoli *et al*[15] reported significant increases in VEGF receptors, as well as growth factors including but not limited to PDGF, Flt-1, and EGF in PRP-treated groups when compared to the control group. PRP treatment was also found to increase angiogenesis when compared to the control[17,20,23].

Several studies also demonstrated that PRP formulations that limit the presence of growth factors that are detrimental to muscle regeneration, such as TGF-ß1 and myostatin, had greater influence on myoblast differentiation and healing. Both Denapoli *et al*[15] and Miroshnychenko *et al*[12] found that leukocyte-poor formulations of PRP that significantly limited the presence of TGF-B1 had more beneficial effects on muscle healing. These results support the hypothesis that leukocyte-poor PRP may be most effective at mediating skeletal muscle repair through limiting detrimental growth factors and increasing the concentrations of beneficial growth factors that promote angiogenesis, proliferation and differentiation at the site of injury. A significant amount of further research is warranted to determine the optimal growth factor milieu that promotes muscular regeneration and healing. The differential responses of myocytes and myoblasts to different PRP formulations demonstrates the

Table 2 Cytology reporting in all platelet-rich plasma muscle studies

Component	Reported studies, *n* (%)	Studies not reporting, *n* (%)
Platelet count	15 (65.2)	8 (34.8)
White blood cell count	6 (26.1)	17 (73.9)
Red blood cell count	1 (4.3)	22 (95.7)

need for a better basic science understanding of muscular regeneration and healing, and how PRP influences each phase from inflammation to regeneration and fibrosis.

Limitations

This study has limitations for its interpretation. First, several studies reported the cytology of PRP. For comparative purposes, standardization in protocol and PRP composition is required to document the efficacy of PRP across research studies[28]. The clinical literature on PRP for orthopedic pathologies has been greatly limited by the lack of impressive reporting of the PRP preparation protocol. Only 10% of clinical studies reported a clear description of the preparation of the PRP utilized, allowing it to be reproduced, which is consistent with the most recent systematic review of PRP protocol standardization that reports a 16% rate of reporting quantitative metrics[28]. The results from this study demonstrate that the same shortcomings exist in the basic science literature on the use of PRP for muscle pathology. Given that both Mazzocca *et al*[7] and Miroshnychenko *et al*[12] reported differences in findings depending on what PRP preparations they use, it is essential that this important information is documented and standardized. In both clinical and basic science studies on PRP, the authors agree with Chahla *et al*[28] that the protocol of PRP preparation must be clearly articulated and reproducible in both basic science and clinical studies, so that the results across studies can be compared to ultimately allow us to determine the optimal preparation to treat both chronic and acute muscle injuries. The minimum reporting guidelines established by consensus and published by Murray IR *et al*[28]. should be utilized by all journals as the minimum requirements a study on PRP must meet before publication.

Another limitation of the basic science literature is that the majority of the injuries to animal models are surgically-induced instead of occurring from trauma or wear. It is not uncommon for muscle injuries to present chronically in the clinic, and even acute lesions to muscles may present after a delay. Chronic degeneration and acute injury lead to distinctively different cellular and molecular responses that may respond differently to PRP. In addition, the biologic milieu created by the cellular and molecular responses in both chronic and acute muscle pathology changes over time. Thus, a better understanding of these time-dependent changes in the biologic milieu (*e.g.*, host pH, cytokine and growth factor concentration), and the influence of timing, delivery, and dosing of PRP, needs to be better understood and further studied.

In conclusion, the basic science literature on the use of PRP in muscle pathology demonstrates that PRP confers several potentially beneficial effects on healing in comparison to controls at the basic science level. Future research is needed to determine the optimal cytology, dosing, timing, and delivery method of PRP for both chronic and acute muscle pathology.

Table 3 *In vitro* platelet-rich plasma and muscle studies – variables reported

Outcome	Studies reporting, *n* (%)	Significant increase, *n*	No significant change, *n*	Significant decrease, *n*
Cell viability	2 (33.3)	2	0	0
Cell proliferation	5 (83.3)	5	0	0
Proteoglycan and collagen content	0 (0)	0	0	0
Gene expression	5 (83.3)	4	0	1
Cell migration	1 (16.7)	1	0	0
Cell differentiation	3 (50)	3	0	0
Inflammatory mediation	0 (0)	0	0	0

Table 4 *In vivo* platelet-rich plasma and muscle studies - summaries

Ref.	PRP preparation	Cytology findings	Study design	Outcomes measured	Results
Borrione *et al*[9], 2014	Whole blood collected in sodium citrate spun twice first at 220 × *g* for 15 min and again at 1270 × *g* for 5 min. Pellet re-suspended and activated with 10% $CaCl_2$ (20 mL)	Not reported	102 Wistar male adult rats had flexor sublimis muscle surgically cut and PRP immediately applied	Macroscopic evaluation, H&E changes, Leukocyte infiltration & WBC numbers, MyoD protein expression, gene expression of CD3, CD8, CD19, and CD 68, Myo D. Outcomes measured up to 7 d	PRP led to greater & earlier leukocyte infiltration (lymphocytes & monocytes) than control. PRP increased gene & MyoD protein expression
Cunha *et al*[2], 2014	Whole blood spun at 220 × *g* for 20 min at 20 °C. PRP combined with thrombin and activated with 10% $CaCl_2$ to yield PRP gel	Not reported	20 Wistar adult male rats had vastus lateralis surgically injured. Rats randomized to treatment with and without PRP +/- exercise training	Serum lactate levels, histological analysis measuring type 1 and type 3 collagen at 3 wk after treatment	Exercise training + PRP led to greatest increase in type 3 collagen and decrease in type 1 collagen
Delos *et al*[3], 2014	Whole blood collected in citrate phosphate dextrose. Spun at 1000 × *g* for 15 min at 4 °C. Second spin under same conditions. 100 μL of PRP used for treatment	PRP – Plt count equal to $2.19 \times 10^6 \pm 2.69 \times 10^5$ μL, WBC 22.54×10^3/μL	46 male Lewis rats underwent single blunt injury to gastrocnemius muscle. Four treatment groups: Immediate PRP, Immediate saline, PRP day 1, PRP day 3	Histology, biomechanical testing (maximal isometric torque), amount of fibrosis (Masson's trichome staining), IHC. Outcomes measured at day 15	PRP did not demonstrate any effects on outcomes including isometric torque strength, amount of fibrosis, or inflammation
Denapoli *et al*[15], 2016	Pure leukocyte poor PRP: Blood in 70% EDTA HEPES buffer spun at 300 × *g*/15 min and again 1000 × *g*/10 min. Platelets separated and 70% EDTA HEPES buffer added	Pure PRP- Plt count equal to $1090.0 \pm 70.7 \times 10^3$/μL	30 male 10– to 12-week-old C57BL/6 wild-type mice had surgically induced blunt contusion to tibialis anterior muscle. 10 μL, pure PRP was injected at day 1, 4 and 7 d after injury. Outcomes measured at day 30	Histologic assessment of repair. Treadmill exercise for functional performance. Other PRP preparations were created and cytology & growth factor concentrations were compared between PRP groups. However, only pure leukocyte poor PRP was used in muscle contusion model	The day 7 PRP treated group had best functional performance and the most peripheral nucleated fibers on histology suggesting fastest recovery and decreased fibrosis
Dimauro *et al*[16], 2014	Whole blood collected in citrate phosphate dextrose. Spun at 220 × *g*/15 min, and again at 1270 × *g*/5 min. Pellet re-suspended and activated with 10% $CaCl_2$	Averages not reported. However, PRP reported to have platelet concentration > 1250000 and WBC, neutrophils < baseline	40 Wistar male adult rats had surgical lesion made in flexor sublimus muscle. 20 rats immediately treated with PRP, other 20 untreated. Additional 10 rats anesthetized with lesion made. Outcomes measured at days 2 and 5	Gene expression of many intrinsic factors in regenerating skeletal muscle (*e.g.* cytokines, MRFs, growth factors), protein expression of MyoD1, Pax7, myogenin, stress response proteins, and apoptotic markers	PRP increased early expression of pro-inflammatory cytokines (*e.g.*, TGF-β1, IL-1β. Increased expression of MRFs. No effect on VEGF. Increased ERK activation & IGF-1Eb expression
Gigante *et al*[23], 2012	Whole blood collected in citrate phosphate dextrose (1:5). Spun at 1000 × *g*/6 min. Supernatant activated with $CaCl_2$ and then spun at 1450 × *g*/15 min	Not reported	Surgically induced bilateral lesions of longissimus dorsi muscle and subsequently treated with PRP matrix evaluated over 60 d	Histologic evaluation of neovascularization, muscle regeneration, fibrosis and inflammation. IMHC of myoD and Myogenin	Improved fibrosis, muscular regeneration and neovascularization. Increased expression of Myogenin

Hammond *et al*[6], 2009	Femoral/renal veins or intracardiac punctures on five adult male Sprague-Dawley rats (20 mL blood/each). PRP separated from whole blood (Symphony II Platelet Concentration System, DePuy). PPP used for control. Remaining PRP subjected to high frequency ultrasound (10 s). 100 μL used for injections	Not reported	72 adult male Sprague-Dawley rats had strain of tibialis anterior induced with superimposed lengthening contraction onto maximal isometric contraction using either a single repetition or multiple repetitions. Outcomes measured at days 3, 5, 7, 14, 21	Maximal isometric contraction and torque, Isometric torque, histology, and gene and protein expression of MyoD and myogenin, PDGF and IGF-1 concentrations in PRP and PPP	PRP had higher concentrations of PDGF and IGF-1. In single repetition group, PRP resulted in increased force only at day 3. No difference in return to function. For multiple repetitions, PRP improved force at multiple time points and faster return to function
Li *et al*[17], 2016	PRP isolated from three rats and mixed in citrate-phosphate-dextrose isolated as above. Centrifuged at 160 × *g*/20 min. Supernatant transferred, centrifuged 400 × *g*/15 min. Pellet re-suspended with remaining plasma to yield PRP	PRP - Plt count equal to 6.44 ± 0.64 × 10^6/μL, WBC 22.37 ± 2.25 × 10^3/μL	16 male Fisher rats injured with cardiotoxin injection into tibialis anterior. Four treatments: (1) Control, (2) 50 μL PRP, (3) 50 μL PRP neutralized with 280 ng/μL TGF-β1 antibody, (4) 50 μL PRP neutralized with 1400 ng/μL TGF-β1 antibody. Outcomes at 7, 14 d	Assessed muscle regeneration and collagen deposition with histology. IMHC for CD31, Alpha-SMA, Pax-7, CD68, transglutaminase-2, dystrophin to determine differentiation and mechanism for repair	PRP accelerated muscle regeneration (increased regenerating myofibers), increased angiogenesis (increased MVD-CD31, MVD-α-SMA) TGF-β1 neutralization of PRP reduced collagen deposition, PRP reduced macrophages and inflammatory response
Martins *et al*[19], 2016	Whole blood centrifuged 180 × *g*/10 min. Supernatant transferred and centrifuged at 1000 × *g*/10 min. Pellet re-suspended and activated with 10% calcium gluconate	PRP - Plt count equal to 4904/μL	Gastrocnemius Muscle contusion model studying the effect of PRP and reactive oxygen species over a 7-d treatment course	Reactive species byproducts (TBARS, DCFHRS), mitochondria function (MTT assay), antioxidant enzyme activities (GSH, CAT, SOD) and myeloperoxidase	PRP reduces oxidative damage and MPO enzyme, increases antioxidants
Ozaki *et al*[21], 2016	4mL blood from cardiac puncture combined with 0.2 mL 10% sodium citrate. Centrifuged 200 × *g*/15 min. Top two fractions isolated and centrifuged, at 500 × *g*/10 min	PRP- Plt count equal to 4999 × 10^3/μL	Thirty-five male Wistar rats in 5 groups (*n*=7): control (C), control lesion (CL), lesion treated with low-level laser therapy (LLt), lesion treated with PRP (LP), and lesion treated with both techniques (LLtP). Muscle injury by stretching gastrocnemius muscle. PRP (100 μL) injected into distal third of tibia to be applied to gastrocnemius muscle belly	Histology for morphology, inflammatory infiltrate, oxidative stress using Raman scattering spectroscopy, collagen content	CL group had increased macrophages and oxidative stress. LP group had decreased inflammation, increased tissue organization, and increased presence of regeneration cells
Pinheiro *et al*[24], 2016	Intracardiac puncture -3 mL blood/each rat centrifuged 1200 × *g*/15 min to yield three layers. Isolated PRP/RBC layer, centrifuged 1min. PRP (0.2 mL) separated and activated with calcium gluconate (0.01 mL) to yield PRP gel	Cytology not provided	Ultrasound study following PRP therapy in a gastrocnemius muscle injury model	Pennation angle, Muscle thickness, Mean pixel intensity, claudication scores	No significant difference found
Quarteiro *et al*[8], 2015	Four blood samples (8 mL/rat) from five rats mixed with anticoagulant Samples centrifuged and plasma separated. Plasma centrifuged and supernatant removed leaving PRP (1mL)	PRP - Plt count equal to 1019 ± 182.25 × 10^3/μL	Gastrocnemius muscle injury model	Histologic assessment	No difference in collagen content at 21 days. Inflammatory process observed in groups treated with PRP

Terada *et al*[20], 2013	Blood obtained from intracardiac puncture. Centrifuged 800 rpm/ 15 min at 25 °C. Three PRP preparations created (rPRP, gPRP and hPRP). All three activated with 10% $CaCl_2$ and bovine thrombin (300 IU, Fibriquik Thrombin, BioMerieux Inc., Durham, NC, United States)	PRP - Plt count equal to 208.0 ± 25.8 × 10^3/mL	PRP +/- Losartan in a tibialis anterior contusion model	IMHC (VEGF, CD31, Follistatin), Isometric Torque, Histological assessment (fibrosis and number of regenerating myofibers)	PRP in conjunction with losartan improved muscle recovery, reduced fibrosis. increased angiogenesis. PRP alone had similar but lesser effects
Contreras-Muñoz *et al*[22], 2017	3.5-4 mL whole blood obtained from intracardiac puncture, added to citrate phosphate dextrose, spun at 400 × *g* for 10 min. Plasma fraction extracted and spun at 800 g for 10 min	PRP - Plt count equal to 3.73 ± 0.25 × 10^6 platelets/ μL; WBC - 0.004 ± 0.0054 × 10^3 /μL	40 rats assigned to five groups: Injured rats (medial gastrocnemius injury) + single PRP injection (PRP group), daily exercise training (Exer group), or combination of single PRP injection and daily exercise training (PRP-Exer group). Untreated and intramuscular saline–injected animals were used as controls	Histologic and immunofluorescence analysis, force assessment, cross-sectional area of newly formed muscle fibers, dMHC and presence of collagen 1 in scar formation	18%, 20%, and 30% strength increase in PRP, PRP-Exer, and Exer groups. 1.5-, 2-, 2.5-fold increase in myofiber cross sectional area in PRP, PRP-Exer, and Exer groups. 20%, 34%, 41% of reduction scar formation in PRP, PRP-Exer, and Exer groups. 35% and 47% decrease in percentage of dMHC-positive regenerating fibers in PRP-Exer and Exer groups
Garcia *et al*[25], 2017	Cardiac puncture (4 mL) combined with 10% sodium citrate, spun at 200 × *g* for 15 min. Top layer + buffy coat extracted, spun at 500 × *g* for 10 minf	PRP – Plt count equal to 4998.676 × 10^3 platelets/μL	35 rats assigned to five groups: Control (C), Injury (soleus) Control (IC), injury PRP (IP), injury LLLT (ILT) and injury LLLT and PRP (ILTP)	Histologic assessment of muscle fiber morphology, collagen, inflammatory infiltrate	Intense polymorphic fibers (> 75%) in ILTP and IP groups. Lowest inflammatory infiltrate (< 20%) in ILTP compared to other injured groups. Significantly more focused collagen in ILT compared to IP and C groups

Table 5 Variables reported - *in vivo* muscle studies

Outcome	Studies reporting, *n* (%)	Significant increase, *n*	No significant change, *n*	Significant decrease, *n*
Cell viability	0 (0)	0	0	0
Gene expression	5 (33.3)	5	0	0
Gross appearance of muscle repair	1 (6.67)	0	1	0
Histologic assessment of muscle repair	8 (53.3)	7	1	0
Proteoglycan content	0 (0)	0	0	0
Collagen deposition	7 (46.7)	2	3	2
Muscle strength	4 (26.7)	3	1	0
Inflammatory mediation	8 (53.3)	4	1	3
Growth factors	1 (6.67)	1	0	0

Table 6 *In vivo* and *in vitro* muscle studies

Ref.	PRP preparation	Cytology findings	Study design	Outcomes measured	Results
Takase *et al*[27], 2017 (*In vitro* arm)	Whole blood extracted from male volunteers, combined with 12 mL 3.13% sodium citrate. Centrifuged 2400 rpm/10 min, again at 3600 rpm/15 min for 10 mL PRP and PPP. PRP activated by freezing at -80 °C; centrifuged again at 10000 rpm/10 min	PRP – Plt count equal to 7.2×10^5 - 9.4×10^5 platelets/mL	Murine myogenic cell line (C2C12 cells) subjected to PRP treatment. Cell morphology assessed by phase microscopy. Myotube quantification assessed by immunocytostaining. Cell proliferation assessed using water-soluble tetrazolium salt (WST) assay using a cell counting Kit-8. Oil Red-O staining used to identify lipid droplets and accumulation determined by phase contrast microscopy. rt-PCR used to quantify myogenic and adipogenic markers	Cell proliferation, myogenic differentiation (Pax7, myogenin), adipogenic differentiation [PPARγ, CCAAT/enhancer binding protein (C/EBPα)]	PRP inhibited myotube formation, decreased average area of myotubes, induced myogenic proliferation compared to myogenic group. Number of lipid droplets in PRP-adipogenic group was lower than adipogenic group. PRP suppressed expression of Pax7, myogenin, PPARγ and C/ERPα
(*In vivo* arm)	8 mL blood retrieved from one, 3-mo old, Sprague-Dawley rat, combined with 2 mL 3.13% sodium citrate Centrifuged at 1500 rpm for 10 min. Second spin at 3000 rpm for 10 min yielded PRP (1mL) and PPP. PRP frozen at -80 °C until needed	PRP - Plt count equal to 1.6×10^9 platelets/mL	PRP injection into subacromial space of five rat rotator cuff tear models Infraspinatus used for histology. Muscles cryosectioned, fixed with 4% PFA, stained with Oil Red-O and hematoxylin. Supraspinatus used for biochemical assays. rt-PCR to quantify genes	Oil Red-O positive lipid droplet formation, adipogenic differentiation [PPARγ, CCAAT/enhancer binding protein (C/EBPα)], and muscular atrophy [(Muscle RING Finger Protein-1 (MuRF-1) and atrogin-1]	Rotator tear groups had increased MuRF-1, atrogin-1, PPARγ and C/EBPα PRP decreased lipid droplet presence. PRP decreased expression of PPARγ and C/EBPα
Li *et al*[26], 2013 (*In vivo* arm)	Human whole blood from Central Blood Bank, Pittsburgh, PA, United States centrifuged 3000 g/ 10 min. Fraction of PRP poor supernatant transferred, PRP pellet re-suspended. PRP concentration measured by hemocytometer, activated with human thrombin (1U/mL). PRP releasate separated from cellular debris by centrifugation 3000 × *g*/30 min. PRP releasate stored at -80 °C	Cytology not provided	Gastrocnemius of mdx-SCID mice damaged with cardiotoxin and treated with hMDPCs treated with PRP	Histological assessment of as the number of hMHC-I-positive myofibers/1×10^5 injected cells	PRP maintained hMDPCs growth and regeneration of myofibers
(*In vitro* arm)	Centrifuged at 3000 × *g* for 10 min at RT. PRP activated with one unit per mL human thrombin. After activation, the PRP releasate obtained by centrifugation at 3000 × *g* for 30 min	PRP – Plt count equal to 2000/μL	hMDPCs isolated from donors cultured in PRP *versus* 20% FBS as a control. Assessed Proliferation, role of exogenous growth factors, gene expression, and cell differentiation	Proliferation, growth factor PDGF, VEGF, TGF-B1 RT-PCR for expression profile of stem cell markers and differentiation	PRP increased cell proliferation. PRP with anti TGF-B1 and anti VEGF did not. PRP increased the expression of BMPR1-A, BMPR1-B, BMPR2, ALDH, SOX2, Aggrecan, and Desmin. No difference in differentiation capacity

PRP: Platelet-rich plasma.

Table 7 Variables reported – combined *in vivo* and *in vitro* muscle studies

Outcome	Studies reporting, *n* (%)	Significant increase, *n*	No significant change, *n*	Significant decrease, *n*
Cell viability	0 (0)	0	0	0

Cell proliferation	1(25)	1	1	
Cell differentiation	1 (25)	1	0	0
Gene expression	3 (75)	3	0	2
Gross appearance of muscle repair	0 (0)	0	0	0
Histologic assessment of muscle repair	2 (50)	2	1	1
Proteoglycan content	0 (0)	0	0	0
Collagen deposition	0 (0)	0	0	0
Muscle strength	0 (0)	0	0	0
Inflammatory mediation	0 (0)	0	0	0

ARTICLE HIGHLIGHTS

Research background

Platelet-rich plasma (PRP) is a biological adjunct derived from autologous blood, which is thought to aid the healing of various bone, ligament, cartilage, and muscle injuries. PRP is composed of various cytokines, growth factors, and concentrations of leukocytes and platelets. PRP is often used clinically to expedite healing as a non-operative treatment or operative adjunct. However, studies have reported mixed effects of PRP, and clinicians continue to employ this adjunct despite little understanding of its mechanism of action.

Research motivation

The main topics of the current study are (1) The various mechanisms of PRP action at the molecular and tissue levels for muscle injuries; and (2) Reporting patterns of PRP preparations in these studies. The current study seeks to clarify the underlying mechanisms of action of PRP, in terms of its ability to induce cellular changes and changes at the histologic and tissue levels, which are not well-described.

Research objectives

The main objective of the current study is to clarify the effects of PRP at the cellular and tissue levels through synthesizing its mechanisms of action from available basic science studies on muscle injuries. A secondary objective that was realized was that it is important to understand PRP preparations across multiple studies to allow for the standardization of study protocols and better comparisons.

Research methods

A systematic review of basic science studies from the PubMed/MEDLINE and EMBASE databases was conducted, as these studies would allow for the best understanding of the mechanism of action of PRP at the cellular and tissue levels. Using a custom pre-determined spreadsheet of a wide variety of growth factors, cytokines, and other molecular markers, each study was analyzed, and these variables were subsequently extracted. The PRP preparation methods were also extracted.

Research results

A total of 23 articles were identified. PRP conferred multiple beneficial effects on muscles both *in vitro* and *in vivo* through the upregulation of genes beneficial to healing and muscle regeneration, increasing cellular proliferation and differentiation, and producing superior tissue quality and biomechanical properties in comparison to placebo. However, this study also identified the lack of PRP cytology reporting among these studies, of which only one study reported a full cytology.

Research conclusions

PRP confers multiple beneficial effects at the basic science level in models of muscle injury compared to placebo through changes at the cellular level, which include gene expression, growth factor and cytokine concentrations, increased angiogenesis, and cellular differentiation and proliferation. PRP also mediates increased muscle regeneration at the gross level, and superior histologic quality when compared to placebo in a few studies. There was significant variability in both PRP preparation and reporting among the included studies.

Research perspectives

This study highlights the importance of understanding processes at the basic science level in order to provide better insight into clinical practice. Future research is needed to determine the optimal cytology, dosing, timing, and delivery method of PRP for muscle injuries. Higher level randomized studies will need to be performed in order to determine these factors. Furthermore, it will be essential for future studies to use standardized protocols, such that outcomes and practices with PRP become reproducible.

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CASE REPORT

Os calcis lipoma: To graft or not to graft? - A case report and literature review

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Abstract

BACKGROUND

Intraosseous lipoma is a rare benign lesion, commonly affecting the os calcis. Its pathogenesis and natural history are not fully understood, and its management remains controversial.

CASE SUMMARY

A 56-year-old male complaining of heel pain was diagnosed with an os calcis lipoma. The lesion was treated with curettage and it was filled with impacted allograft and demineralized bone matrix. Histological examination confirmed the above diagnosis. Six months postoperatively, the patient returned to recreational long-distance running. Repeated computed tomography scanning, up to five years postoperatively, showed almost complete resorption of the graft over time.

CONCLUSION

The treatment of an os calcis lipoma should be individualized, depending on the symptoms, the location and size of the lesion. Surgeons, electing to proceed with bone grafting, should consider the probability of bone graft resorption.

Key words: Benign bone tumor; Os calcis lipoma; Calcaneus; Intraosseous lipoma; Bone graft; Case report

Core tip: This is the first report of a patient with a surgically treated os calcis lipoma, showing spectacular graft resorption at a long-term follow up. Previous studies, which report satisfactory graft performance, rely on plain radiographs for follow-up imaging and they have not used computed tomography to assess the incorporation of bone graft. The complex interplay of biomechanical and biological factors in Ward's neutral triangle

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of the os calcis may account for the failure of graft integration. The possibility of bone graft resorption must be taken into account when surgical treatment is considered.

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INTRODUCTION

Intraosseous lipoma is a rare benign tumor, with an estimated prevalence of around 0.1% of primary bone tumors[1,2]. The os calcis is affected in up to 63% of lesions, with the rest presenting in long bones[3,4]. Because many cases remain undetected, it can be assumed that its actual prevalence may be significantly higher than estimated. Most authors accept that this lesion represents a true benign bone tumor or even a unicameral bone cyst, whose fluid content has been replaced with adipose tissue[1,5-7]. Others suggest an ischemic etiology, with subsequent necrosis of bone, leading to adipose metaplasia, or point towards a posttraumatic bone reaction[2,5,8]. It has also been proposed that a lipoma in the os calcis represents a well-defined "normal" radiolucency in Ward's neutral triangle, where it is invariably located. This is an unloaded area at the base of the neck of the os calcis, bounded by the compressive and tensile lines of biomechanical stress[5,9]. As predicted by Wolff's law, stress-shielding in this area leads to a paucity of trabeculae, which are replaced with adipose tissue[10,11]. It is postulated that in some individuals this process may be more pronounced, leading to the development of a radiographically detectable pseudocyst[5,9,12]. Symptomatic cases present with dull pain at rest and soft tissue swelling. At least one third of the cases are asymptomatic and are discovered incidentally in radiological investigations, conducted for an injury or for unrelated disorders[13].

There is no consensus, regarding the optimal treatment of an os calcis lipoma. The proponents of conservative treatment claim that spontaneous resolution of symptoms may occur[14]. Those favoring operative treatment recommend curettage of the cyst and application of bone graft or substitutes, particularly when the lesion is large or painful[15-17]. Most reports of operative treatment show resolution of symptoms and consolidation of the bone grafts[8,18-21]. We present the case of a patient treated with curettage and application of bone graft, who demonstrated almost complete resorption of the impacted material.

CASE PRESENTATION

Chief complaints

A 56-year-old, otherwise healthy, Caucasian male attended the outpatient clinic of another institution in November 2011. He presented with a three-month history of increasing pain in his right heel, as a result of which he had to give up running.

Imaging and diagnosis

Radiographic investigation and computed tomography (CT) at that time, revealed a hypodense cystic area with a central calcification in Ward's triangle of the os calcis (Figure 1A). The lesion had a diameter of 18.7 mm and extended between the superior and the inferior calcaneal cortex. The borders were well demarcated and the periphery of the area was filled with a meshwork of fine bone trabeculae. A linear hyperdense area appeared at the center of this lytic lesion. The lesion did not show any evidence of fracture or expansion in the soft tissues. Magnetic resonance imaging (MRI) showed a homogeneous high intensity signal on T1 weighting and fat suppression on T2 short tau inversion recovery sequence (STIR). In the center of the lesion, a linear area was apparent, with low-intensity signal on T1 sequence and high intensity on STIR sequences (Figure 1B-D).

FINAL DIAGNOSIS

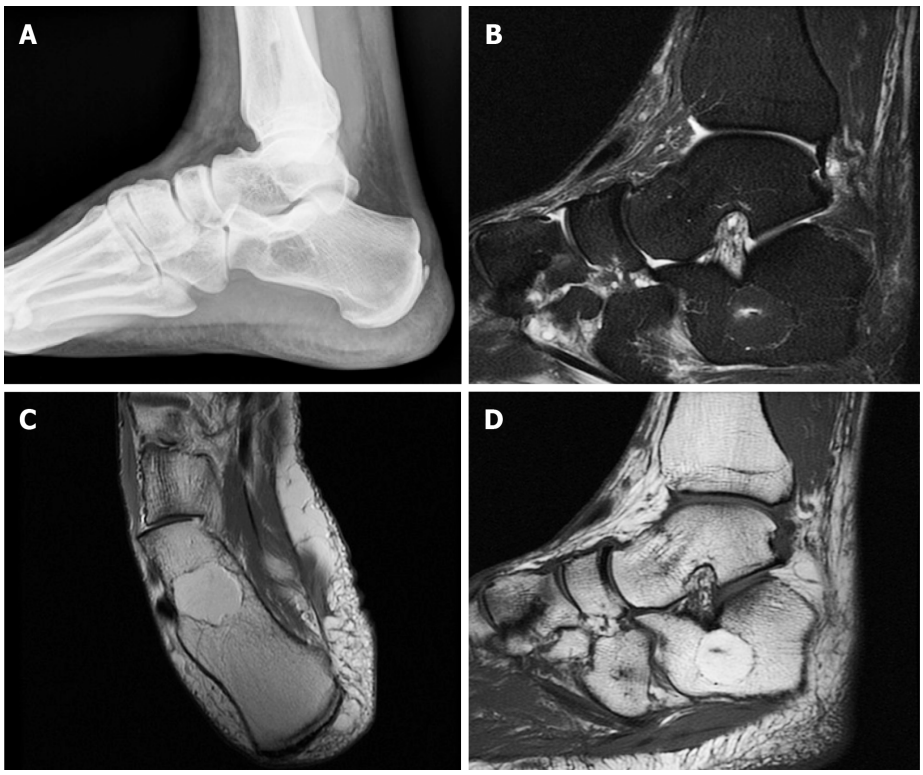

Figure 1 Preoperative imaging of the os calcis lipoma. A: Initial radiographic presentation. B: T2 STIR sequence magnetic resonance imaging (MRI) image, sagittal view. Fat suppression is presented at the area of the lesion, with high intensity linear signal at the center. No fracture or expansion into the soft tissues was identified. C: T1 sequence MRI, transverse view. D: Sagittal view. Sharply demarcated lesion with homogeneous high intensity signal at Ward's neutral triangle, with linear low intensity signal at the center. The high signal denotes lipid content of the lesion, whereas the central low intensity signal is compatible with local infarction and necrosis.

Based on the characteristic radiological findings, a diagnosis of intraosseous lipoma was made.

TREATMENT

Operative treatment of the lesion was decided. With the guidance of an image intensifier, the os calcis was exposed with a lateral approach and a window was opened in the lateral cortex of the calcaneus with an osteotome. A significant amount of yellow, fatty tissue was encountered and was sent for microbiological and histopathological examination. No fracture was identified. The cavity was curetted to bleeding bone and subsequently filled with impacted crushed allograft and demineralized bone matrix (Orthoblend, Osteotech, Eatontown, NJ, United States) (Figure 2A and B). The wound was treated in the usual manner and a postoperative shoe was used for weight protection.

Laboratory examinations – Cultures and histology

The cultures were sterile. Histological examination of the extracted material revealed abundant mature adipose tissue, interspersed with sparse, thin, osseous trabeculae. Vascularity was poor. Areas of amorphous calcific deposits were seen, with scattered ghost outlines of necrotic lipocytes and with prominent histiocyte infiltration. Cellular atypia was not identified. This picture was compatible with the initial diagnosis of an intraosseous lipoma.

OUTCOME AND FOLLOW-UP

Six months postoperatively, the patient was free of pain and returned to recreational long distance running. However, a new CT revealed resorption of the margins of the bone graft (Figure 2C and D). Fifteen months postoperatively, the patient was examined, for the first time by our team, for slight pain of about two-month duration

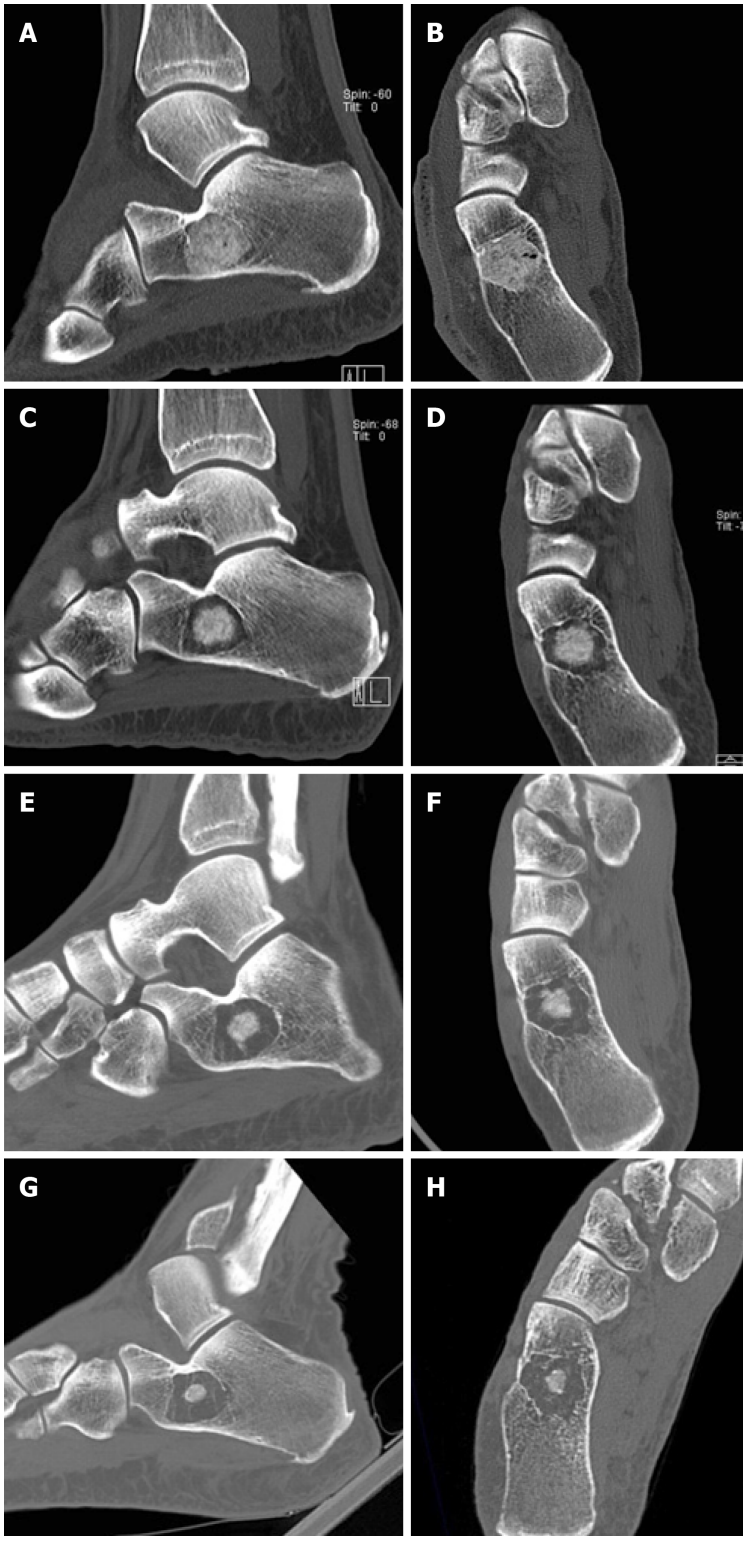

Figure 2 Serial computed tomography evaluation of os calcis lesion. A and B: Computed tomography images immediately postoperatively. Complete filling of the cavity has been obtained with bone graft. C and D: Six months postoperatively, circumferential graft absorption is present. E and F: Fifteen months postoperatively, further graft absorption is noted. G and H: At five years, the greatest part of the bone graft has been resorbed. A mesh of thin osseous septa is seen around the remaining bone graft. The lesion has not expanded since the first postoperative image.

in his right heel. The pain was felt mostly with the first steps in the morning and after prolonged standing, and responded to oral non-steroidal analgesics. Apart from the operation at his heel, his medical history was unremarkable. Physical examination revealed a well-healed surgical scar at the lateral surface of the heel. No swelling, inflammation or palpable masses were evident. There was tenderness on palpation of

the plantar surface of the heel. The patient was able to walk with no limp. The range of active and passive motion of all the joints of the lower limb was normal. Passive extension of the first toe while standing (windlass test) elicited slight pain. Neurological examination was unremarkable. Blood tests, including routine metabolic and rheumatologic assays and markers of infection, were normal. A diagnosis of plantar fasciitis was established. However, due to his previous operation, a new foot CT was obtained. When compared to the images taken six months postoperatively, it was evident that the hypodense area at the periphery of the lesion had expanded considerably (Figure 2E and F).

The patient was reassured that his heel pain was probably unrelated to the previous pathology. Conservative treatment was chosen, with heel pads and followup as necessary. On his latest follow-up, five years postoperatively, the patient was free of symptoms. However, a new CT showed further resorption of the implanted graft (Figure 2G and H).

DISCUSSION

In plain radiographs, an intraosseous lipoma presents as an osteolytic lesion with marginal sclerosis. There is often central calcification, corresponding histologically to localized infarction and necrosis[5,8,20]. Typically, a CT shows a well circumscribed, non-expansile, osteolytic lesion with negative Hounsfield units, corresponding to the values for subcutaneous fat[22]. Marginal sclerosis is always present[22]. MRI can be helpful for the confirmation of presence of adipose tissue in the tumor by presenting homogeneous high intensity signal on T1 sequences and low intensity on fat-suppression, similar to those of the subcutaneous tissue[23]. The characteristic presentation, using these imaging modalities, usually obviates biopsy and histological evaluation.

The treatment of an os calcis lipoma should be decided on an individual basis. Most authors agree that an intraosseous lipoma of the os calcis can be managed with watchful waiting[3,9,14,24,25]. It is understood that pain may not be caused by the lesion itself but rather by unrelated pathology from the surrounding soft tissues or a nearby joint[5]. Surgical treatment is reserved for patients with persistent pain, related to the lesion, or indeed large lesions[15-19,25]. However, Tscherne *et al*[14] observed in their patients that heel pain can persist after curettage and grafting. Based on this observation, they reserved operative treatment for heel pain not responding to conservative treatment or for biopsy, in cases with atypical radiological presentation.

The possible association of the size of a cystic lesion with a subsequent pathological fracture has been an issue of concern. In a series of 50 os calcis cysts, Pogoda *et al*[16] reported four patients with fractures on presentation. These fractures were all associated with large lesions. The authors proposed a "critical size", occupying the entire distance from the medial to the lateral cortex and at least 30% of the anteroposterior dimension. They concluded that cystic lesions exceeding this critical size should be managed surgically[16]. Nevertheless, in a meta-analysis of 54 cases with os calcis lipoma, Bertram *et al*[24] did not find any reported fractures. Also, in a literature review in 2014, Pappas *et al*[19] identified only two reported cases with calcaneal fracture associated with an intraosseous lipoma. It can be postulated that the presence of a cavity at this normally hypodense area is less significant for bone strength and only rarely leads to fractures under physiological loading.

To our knowledge, this is the first report of a surgically treated os calcis lipoma, showing spectacular graft resorption in long-term radiological follow-up, despite the resolution of clinical symptoms. Most patient series on the surgical treatment of intraosseous lipoma have reported satisfactory pain relief and graft incorporation[7,8,18,21,25,26]. However, authors relied on plain radiographs for postoperative imaging. Unavailability of data from CT for follow-up represents a significant limitation of these studies.

The incorporation of graft, implanted in bone defects, represents a complex process, which depends upon various biological and biomechanical factors. Ischemia in the margins of the grafted cavity can adversely affect the integration of the implanted graft[27]. Also, the importance of mechanical stimuli in osteoinduction and osteoconduction has been stressed in numerous *in vitro* and *in vivo* experiments[28-30]. It can be assumed that lack of loading in Ward's neutral triangle, which may have led to the development of a cystic lesion in the first place, also contributed to the resorption of the implanted bone graft.

In any case, grafting of benign tumors following curettage has been questioned altogether by Hirn *et al*[31]. They reported on the treatment of 146 cases of large, metaphyseal femoral and tibial benign bone tumors with curettage alone. Successful

consolidation occurred in 89%. The rest of the cases developed local recurrence and were subsequently treated with further curettage and bone grafting. The authors concluded that augmentation is not necessary for most benign bone defects. It should be noted that, in this study of long bone metaphyseal defects, fractures occurred predominantly in defects greater than 5 cm, whereas calcaneal cysts are considerably smaller.

CONCLUSION

The treatment of an os calcis lipoma should be individualized, depending on the symptoms, the location and the size of the lesion. When surgical treatment of an os calcis lipoma is considered, orthopaedic surgeons should be aware of the possibility of bone graft resorption.

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