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REVIEW

# Platelet rich plasma intra-articular injections: a new therapeutic strategy for the treatment of knee osteoarthritis in sport rehabilitation. A systematic review

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**Abstract** Osteoarthritis (OA) is the most common joint disease and the prevalence of knee OA among athletes is higher than in the general population, especially after injury or in association with high-impact sport. We evaluated the clinical evidence and the persistence of the beneficial effects of intraarticular injections of platelet-rich plasma (PRP) in patients affected by knee OA. A systematic computerized literature search of following databases was conducted: PubMed, Medline, Cochrane, CINAHL, Embase, SportDiscus, Pedro and Google scholar. PRP has been shown to be an effective and well-tolerated treatment option in OA, with greater and longer effects in young men with a low degree of cartilage degeneration. The role of growth factors and inflammatory mediators in the pathophysiology of OA suggest that PRP may be useful in the early stages to modulate inflammatory processes. Although current studies are encouraging, more data and long-term follow-up are required before PRP can be recommended in the treatment of OA. Future PRP research should involve questions regarding the mechanism of actions, formulation, and number and timing of injections to better identify patient selection criteria.

**Key words** Platelet-rich plasma · Knee osteoarthritis · Growth factors · Intraarticular injection · Cartilage degeneration

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## Introduction

### Osteoarthritis

Osteoarthritis (OA) is a progressive, chronic condition leading to pain and loss of function that reduces patients' quality of life. It has a multifactorial aetiology and occurs as a result of various biochemical, biomechanical, inflammatory and immunological factors. Excessive musculoskeletal loading, high body mass index, previous knee injury, female gender and muscle weakness are well-known risk factors [1]. Animal and human studies have shown no evidence of increased risk of knee OA with moderate exercise and in the absence of traumatic injury, sporting activity has a protective effect [2]. The prevalence of knee OA among athletes is higher than in the nonathletic population, in particular [1] early OA development and intense participation in high-impact, high-stress élite sports at an early age may be associated [3]. It is well known that vigorous sports activities increase the risk of acute joint injuries [4], and notably follow-up studies in young athletes, former athletes and adults confirm a high risk of OA after meniscus or anterior cruciate ligament

**Table 1** Therapeutic approaches to knee osteoarthritis (EULAR 2003)

| Nonpharmacological | Pharmacological | Intraarticular | Surgical |
|---|---|---|---|
| Patient education | Acetaminophen | Glucocorticoid | Arthroscopic |
| Exercise | Nonsteroidal antiinflammatory drugs | Hyaluronic acid | Osteotomy |
| Orthotic instruments | Opioid analgesics | | |
| Weight loss | Sex hormones | | |
| Laser | Symptomatic slow-acting drugs in osteoarthritis (SYSADOA) | | |
| Ultrasound | Psychotropic drugs | | |
| Thermal treatment | Topical NSAIDs | | |
| Acupuncture | Topical capsaicin | | |
| Nutritional supplementation, vitamins | | | |
| Phytotherapy | | | |

APAP,; NSAIDs,.

(ACL) injury [5, 6]. The clinical symptoms of OA are joint pain, limitation of range of motion and joint stiffness.

The diagnosis of OA is primarily a clinical one based on history of joint pain worsened by movement and physical examination findings. Plain radiography may help in the diagnosis, even if the degree of pain does not correlate with severity of radiographic disease, especially in the early stages. Laboratory testing usually is not necessary [7, 8].

The goal of OA treatment is to control symptoms and to prevent disease progression [9]. Both the European League against Rheumatism and the Osteoarthritis Research Society International convened an expert review committee and developed guidelines for the management of knee OA. Each recommends a combination of nonpharmacological and pharmacological modalities [10–12] (Table 1). Pharmacological treatment options include analgesics, nonsteroidal antiinflammatory drugs (NSAIDs), selective cyclooxygenase-2 inhibitors, glucosamine sulphate plus chondroitin sulphate and the intraarticular injection of steroids or hyaluronan (HA). Finally, surgical interventions should be reserved as a last-line management strategy for OA symptoms and may be warranted in patients who are refractory to less-invasive methods.

Over the last two decades, OA research has increasingly focused on drugs that not only improve the patients' symptoms, but additionally are capable of interfering with the progression of cartilage damage [13]. In particular, thanks to new information regarding OA pathophysiology, in which imbalance between anabolic and catabolic mechanisms, growth factors (GFs) and inflammatory mediators has been shown to play an important role, the current research trend is towards preventive interventions, including platelet-rich plasma (PRP) and autologous conditioned serum, that through the release of GFs, regulation of antiinflammatory signals and modulation of angiogenesis, may contribute to the prevention of joint degenerative progression and enhance the repair process [14].

## PRP technique

PRP is defined as autologous blood with a concentration of platelets above baseline values [15]. More specific elements of PRP have not been uniformly defined in the literature. A commonly accepted PRP concentration is approximately 400% of the peripheral blood platelets count, and it should contain 1 million platelets or more per microlitre [16]. There are many preparative methods that produce PRP with different characteristics, based on the presence of other cells, in particular leucocytes, activation and storage modalities, and many other variables that are not of secondary importance for determining PRP properties and clinical effects. In particular some data show better results with PRP formulations with leucocyte depletion, because of the negative effects of proteases and reactive oxygen released from white cells. They are also considered as a source of cytokines and enzymes that may also play a role in the prevention of infections [17].

Dohan et al. described three methods of producing PRP: (1) the double-spinning method, that yields a four- to eightfold change in platelet concentration over baseline levels and also concentrates leucocytes, (2) the single-spinning method, that yields a one- to threefold change in platelet concentration over baseline levels, and (3) selective blood filtration. Thus, according to the preparation method, platelet concentrates have been described as pure platelet-rich plasma (P-PRP), and leucocyte and platelet-rich plasma (L-PRP), which also contains a high concentration of leucocytes [18].

Autologous PRP was first used in 1987 by Ferrari et al. [19] following open heart surgery. Since that time, PRP has been used in sports medicine, orthopaedics, dentistry, dermatology, ophthalmology, and plastic, cardiothoracic and maxillofacial surgery [20]. The use of PRP in cartilage repair is relatively new. In the first studies, chondrocytes and mesenchymal stem cells exposed to PRP both showed increased cell proliferation and cartilage extracellular matrix synthesis of proteoglycans and collagen type II compared

with unexposed cells [21], and synoviocytes from patients with OA cultured with PRP demonstrated increased hyaluronic acid production and secretion, suggesting that PRP could act as an endogenous source of chondroprotection and joint lubrication after intraarticular administration [22]. Data presented at the 2007 International Cartilage Repair Society Meeting in Warsaw indicate that PRP enhances chondrocyte cell proliferation and has positive clinical effects on degenerative knee cartilage [23, 24].

The benefits of this new procedure seem to be associated with the pools of GFs stored in the a-granules of platelets, including platelet-derived GF (PDGF), transforming GF beta (TGF-β) , insulin-like GF-I (IGF-I), basic fibroblast GF (bFGF) and vascular endothelial GF (VEGF), which have been found to take part in the regulation of articular cartilage [25]. Among these, TGF-β activates cartilage regeneration and matrix synthesis [26, 27], PDGF promotes the proliferation of chondrocytes and the synthesis of proteoglycans [28], IGF-I stimulates proteoglycans and collagen synthesis, and bFGF and VEGF play a role in chondrocyte induction [29, 30].

On the other hand recent studies on platelets have undermined the primacy of GFs by demonstrating new classes of cytokines which are crucial to several biological processes involved in tissue healing [31]. Given the redundancy and pleiotropy of the PRP cytokine network, the specific actions of every cytokine and the molecular mechanisms behind their functions have not yet been identified. Although the biology of PRP is not completely understood, in a recent review Andia et al. [32] analysed the role of PRP in the regulation of inflammation and in the modulation of angiogenesis, and its potential anabolic and chondroprotective actions. They concluded that although the effectors mediating the beneficial effects of PRPs have not been identified and research is complex because platelets contain more than 300 proteins, this innovative therapy can delay joint deterioration by interfering with the early catabolic and inflammatory events and by subsequently promoting anabolic responses [32].

### Aim of the study

We review the current knowledge on the beneficial effects and durable results of PRP intraarticular injections in knee OA.

## Literature search and data extraction

We performed a comprehensive search of PubMed, Medline, Cochrane, CINAHL, Embase, SportDiscus, Pedro and Google scholar databases using various combinations of the commercial names of each scaffold and the keywords ‘platelet rich plasma’, ‘knee osteoarthritis’, ‘growth factors’, ‘intra-articular injection’, ‘cartilage degeneration’. We excluded case reports and letters to editors. Eligible studies had to show clinical effectiveness and safety of PRP in animal OA models and in human clinical studies for the treatments of knee OA. Given the linguistic abilities of the research team, we considered publications in English, Italian, French and Spanish. Articles reporting the use of PRP in other diseases, including musculoskeletal injuries and orthopaedic surgery were excluded from the study.

## Results

### PRP in animal model of OA

Studies have been conducted in a rabbit model of the OA knee. Saito et al. administered PRP contained in gelatin hydrogel microspheres into the rabbit knee joint twice at an interval of 3 weeks, beginning 4 weeks after ACL transection (ACLT) [33]. Adult rabbit chondrocytes were cultured in alginate beads in the presence of 3% PRP or platelet-poor plasma. Outcome measures were quantification of glycosaminoglycan synthesis and examination of cartilage matrix gene expression. Gross morphological and histological examinations were performed 10 weeks after ACLT. The synthesis of chondrocyte glycosaminoglycans was significantly stimulated and the expression of proteoglycan core protein mRNA increased after administration of PRP. The progression of OA in the ACLT rabbit model was significantly suppressed morphologically and histologically after intraarticular injections of PRP. These preventive effects against OA progression were considered possibly to have been secondary to stimulation of cartilage matrix metabolism, caused by release of GFs [33].

In another study [34], of 48 osteochondral defects created in the femoropatellar groove in rabbits, 16 were untreated (control group), 16 were treated with autogenous PRP in polylactic-glycolic acid (PLGA, PRP/PLGA group) and 16 were treated with PLGA alone (PLGA group). PRP was obtained by two centrifugation steps from whole blood, and platelets were enriched 5.12-fold compared to normal blood with over 1 million platelets per millilitre. After 4 and 12 weeks, explanted tissue specimens were assessed by macroscopic examination, microcomputed tomography and histological evaluation. At 4 weeks, the PRP/PLGA group showed a much greater extent of neochondrogenesis in the cartilage defect areas and there were more infiltrated cells than the PLGA group. A high content of glycosaminoglycans of the extracellular matrix and a cell morphology similar to that

of chondrocytes were seen in the PRP/PLGA group. At 12 weeks after implantation, the repair tissue only in the PRP/PLGA group was fully filled with regenerated tissue similar to hyaline cartilage. There was a larger amount of subchondral bone formed in the PRP/PLGA group than in the PLGA group. PRP resulted in better osteochondral formation than the empty PLGA scaffold after 12 weeks and incorporated in PLGA, successfully resurfaced the defect with cartilage and restored the subchondral bone in this rabbit model.

Although these preliminary results are encouraging, the short-term follow-up in both studies and the lack of a group treated only with autogenous PRP in the second study are limitations. Further controlled clinical trials should be performed to confirm these results and to investigate the role of PRP in OA progression.

## PRP in human clinical studies

Sampson et al. [35] evaluated the clinical effects of intraarticular PRP injections in 13 patients with primary and secondary OA in a prospective, nonrandomized, open-enrolment pilot study. Patients received one injection of PRP every 4 weeks over 12 weeks. These patients were followed up for 52 weeks. Inclusion criteria and exclusion criteria are shown in Table 2. PRP was obtained using a GPS III platelet concentration system (Biomet Biologics, Warsaw, IN) following the manufacturer's instructions. The RRP was injected into the suprapatellar bursa of the affected knee under musculoskeletal ultrasound guidance. Patients were given acetaminophen and hydrocodone for pain and instructed to limit the use of the affected knee for 24 h after injection, after which normal activities could resume. The outcome measures, Brittberg-Peterson VAS score and the knee injury and osteoarthritis outcome score (KOOS), were determined at a preinjection visit and at 2, 5, 11, 18 and 52 weeks. At the 1-year follow-up patients also completed a questionnaire regarding satisfaction with the treatment. The same ultrasound device that was used to guide the PRP injections was used to measure the thickness of the femoral articular cartilage at the preinjection and 6-month follow-up visits. Although ultrasound measurements of the cartilage were not significantly different during the first 6 months, 6 of the 13 patients showed increased femoral articular cartilage at the lateral condyle, medial condyle and intercondylar notch. There were significant and linear improvements in the KOOS and in VAS scores at 1-year follow-up compared with preinjection values. Eight patients were satisfied at the end of treatment. The clinical relevance of these results is uncertain. Of particular concern are the lack of a control group, the small sample size, the nonrandomized nature of the study design, the nonstandardized physical therapy protocol and the short follow-up.

Several studies have been conducted in the Rizzoli Orthopaedic Institute, in which PRP preparation followed the same procedure. The enrichment procedure results in a mean increase in platelets of 600% compared with whole-blood values, and an average of 6.8 billion platelets administered to the lesion site in each injection. Infiltration is performed through a classical lateral approach with a 22-gauge needle, and 5 ml of PRP is injected. The knee is then bent and extended to allow the PRP to distribute itself all over the joint. No major adverse events have been observed [36–38].

In a pilot study [36], 115 knees in 91 patients were treated with three PRP injections every 21 days for 2 months, and were prospectively evaluated before treatment, at the end of treatment, and at 6 and 12 months after treatment. Inclusion criteria and exclusion criteria are shown in Table 2. Of the 115 knees, 58 showed a degenerative chondral lesion (Kellgren-Lawrence score 0), 33 showed early OA (Kellgren-Lawrence score I-III), and 24 showed advanced OA (Kellgren-Lawrence score IV). Of the 91 patients, 27 had previously undergone knee surgery. IKDC (Subjective International Knee Documentation Committee) scores (both objective and subjective) and the EQ VAS were used for clinical evaluation. Patient satisfaction was also recorded. A statistically significant improvement in all clinical scores was obtained from the basal evaluation to the end of treatment. These improvements were maintained at 6 months but the scores tended to be worse at 1 year, but 80% of patients were satisfied. The objective IKCD scores showed a statistically significant decrease between 6 and 12 months ($P<0.0005$) and the IKDC scores were significantly worse at 12 months ($P<0.02$). Older patients had a lower improvement at 6 months ($P<0.049$) than younger patients, and showed more severe changes in the joint ($P<0.0005$). Worse results were seen in women ($P<0.0005$) and in patients with higher BMI ($P<0.045$). The lack of a control group and a rehabilitation programme and a short follow-up were limiting factors.

Of the 115 knees evaluated, 114 were available for the 2-year follow-up. One woman with early OA was lost to follow-up. The same inclusion and exclusion criteria and clinical evaluation were used [37]. The evaluation performed at 2 years confirmed the same trend with an overall worsening of the results obtained, even though they remained better than the basal level ($P<0.0005$). The level of satisfaction was confirmed at the 24-month evaluation. The median duration of the beneficial effect was 9 months. A greater and longer effect was found in young men with a low BMI and degree of cartilage degeneration. PRP probably influences

**Table 2** PRP in clinical human studies for the treatment of knee osteoarthritis

| Reference | No. of patients | Inclusion criteria | Exclusion criteria | Injections | Characteristics of PRP | Follow-up | Outcome measures |
|---|---|---|---|---|---|---|---|
| 35 | 13 | Knee OA >3 months; age >18 years; damage to articular cartilage seen on arthroscopy or radiography; VAS 60/100 mm; discontinued use of NSAIDs for at least 1 month after treatment; unresponsive pain to at least two conventional therapies | Pregnancy or breast-feeding; drug abuse; steroid injection within 6 weeks; use of NSAIDs <1 week before; anaemia; bleeding disorders; rheumatoid arthritis; knee surgery within 3 months of treatment; infections of the knee joint within 6 months; infection; malignancy | Three at 4-week intervals | Obtained using GPS III platelet concentration system (Biomet Biologics) | 52 weeks | VAS; KOOS; ultrasound measurement of cartilage thickness |
| 36 | 91 | Chronic (at least 4 months) pain or swelling of the knee; imaging findings (plain radiography or MRI) of degenerative changes in the joint | Diabetes; rheumatoid arthritis; varus >5°, valgus >5°; haematological disease; cardiovascular disease; infection; immunosuppression; anticoagulant therapy; antiaggregant therapy; NSAIDs in the 5 days before taking blood; haemoglobin <11 g/dl; platelets <150,000/mm$^3$ | Three at 21-day intervals | Platelets per millilitre PRP >600% vs. whole blood; average 6.8 billion platelets at the lesion site for each injection | 12 months | IKCD; VAS |
| 37 | 90 | Chronic (at least 4 months) pain or swelling of the knee; imaging findings (plain radiography or MRI) of degenerative changes in the joint | Diabetes; rheumatoid arthritis; varus >5°, valgus >5°; haematological disease; cardiovascular disease; infection; immunosuppression; anticoagulant therapy; antiaggregant therapy; NSAIDs in the 5 days before taking blood; haemoglobin <11 g/dl; platelets <150,000/mm$^3$ | Three at 21-day intervals | Platelets per millilitre PRP > 600% vs. whole blood; average of 6.8 billion platelets at the lesion site for each injection | 24 months | IKCD; VAS |
| 38 | 150 | Unilateral lesion with chronic (at least 4 months) pain or swelling of the knee; imaging findings (plain radiography or MRI) of degenerative changes in the joint; knee surgery at least 1 year before injection treatment | Diabetes; rheumatoid arthritis; haematological disease; cardiovascular disease; infection; immunosuppression; anticoagulant therapy; antiaggregant therapy; NSAIDs in the 5 days before taking blood; haemoglobin <11 g/dl; platelets <150,000/mm$^3$ | Three PRP, or 30 mg/ 2 ml high molecular weight HA or 20 mg/ 2 ml high molecular weight HA every 14 days | Platelets per millilitre PRP >600% vs. whole blood; >6 billion platelets at the lesion site for each injection | 6 months | IKDC; EQ VAS |
| 39 | 144 | Chronic (at least 4 months) pain or swelling of the knee and imaging findings (plain radiography or MRI) of degenerative changes of the joint; knee surgery at least 1 year before injection treatment | Diabetes; rheumatic disease; haematological disease; severe cardio-vascular disease; infection; immunosuppression; anticoagulant therapy; antiaggregant therapy; NSAIDs in the 5 days before taking blood; haemoglobin <11 g/dl; platelets <150,000/mm$^3$ | Three at 21-day intervals | PRGF: platelets 315,000/μl; concentration factor 1.59; PRP: platelets 949,000/μl; concentration factor 4.79 and leucocytes 8,300/μl | 12 months | IKDC; EQ VAS; Tegner |
| 41 | 27 | Diagnosis of degenerative disease of knee for more than 1 year; NSAIDs during the period of treatment | Diabetes mellitus; cardiovascular disease or immunosuppression; anticoagulant treatment; haemoglobin <11 g/dl; white blood cells >10 × 10$^9$/l; platelets <120 × 10$^9$/l | Three at weekly intervals | Platelet recovery (evaluated in PRP) approximately 30% (mean 230 × 10$^9$/l platelets in peripheral blood); platelet concentration factor 2.3 | 6 months | NRS, WOMAC |

*IKDC*, Subjective International Knee Documentation Committee; *NRS*, numerical rating scale; *WOMAC*, Western Ontario and McMaster Universities osteoarthritis index

the overall joint homeostasis and this may have led to the improvement in clinical outcome, but this was possibly temporary and without effect on the cartilage tissue structure or progression of joint degeneration.

Kon et al. in a prospective study comparing the efficacy of PRP and HA intraarticular injections for the treatment of OA knees, divided 150 patients (inclusion criteria and exclusion criteria are shown in Table 2) into three groups of 50 patients [38]. In different centres each group was treated with three injections of PRP, HA of high molecular weight (HW), or HA of low molecular weight (LW) administered every 14 days. All the patients were evaluated at 2 and 6 months. IKDC and EQ VAS scores were used for clinical evaluation. Statistically significant improvements in all clinical scores relative to the basal evaluation at 2 and 6 months were observed in all treatment groups, with the worst results obtained in older patients and in those with higher degrees of cartilage degeneration.

The IKDC and EQ VAS scores at 6 months showed better results in the PRP group than in the LW HA and HW HA groups. In patients aged 50 years or younger, PRP was more effective than LW HA or HW HA at 6 months. In patients older than 50 years the results were equivalent at both 2 and 6 months. PRP was superior at 6 months in those with cartilage degeneration and early OA. None of these procedures resulted in important improvements in OA progression. Better results in young patients with a low degree of cartilage degeneration could be explained by the mechanism of action hypothesized for PRP treatment. Older and more degenerated joints have a low percentage of living and vital cells and therefore a low response potential to GFs. PRP injections showed more and longer efficacy than HA injections in reducing pain and symptoms and for the recovery of articular function. The lack of a structured rehabilitation protocol, randomization and a placebo control group, the primary outcome scale (probably less sensitive for OA and in older patients) and evaluations in different centres, and the short follow-up were limitations of this study.

A recent prospective study compared the effects of two different approaches to the production of PRP: single- and double-spinning procedures [39]. Enrolled in this study were 144 patients who were divided into three groups: degenerative chondral lesion (Kellgren-Lawrence score 0), early OA (Kellgren-Lawrence score I-III), and advanced OA (Kellgren-Lawrence score IV). Inclusion criteria and exclusion criteria are shown in Table 2. Of the 144 patients, 72 received three injections at intervals of 21 days of platelet concentrate prepared with a single-spinning procedure (PRGF) and 72 received three injections at intervals of 21 days of PRP prepared with a double-spinning approach. PRGF was produced from 36 ml of venous blood for every knee treated. Four tubes of 9 ml of blood were centrifuged at 580 *g* for 8 min to obtain a concentration suspended in plasma that was extracted by pipetting carefully to avoid leucocyte aspiration. Every injection contained 5 ml of PRGF [40]. In the PRP procedure 150 ml venous blood was centrifuged twice (the first at 1,800 rpm for 15 min to separate the erythrocytes, and the second at 3,500 rpm for 10 min to concentrate the platelets) to obtain and produced 20 ml of PRP that was divided into four 5-ml aliquots. PRGF contained 315,000 platelets per microlitre with a concentration factor of 1.59, and the PRP contained 949,000 platelets per microlitre with a concentration factor of 4.79 and 8,300 leucocytes per microlitre. The procedure and the recommendations after every injection were the same as in previous studies [36–38]. The outcome measures, IKDC, EQ-VAS and Tegner scores, were administered at enrolment and at 2, 6 and 12 months. Patient satisfaction was also recorded. No major adverse events were observed.

Both treatment groups showed a statistically significant improvement in all the scores evaluated. In fact the subjective IKDC score showed a statistically significant improvement ($P<0.0005$) at 2 months, which was maintained at 6 and 12 months ($P<0.0005$). Similarly, the EQ-VAS score showed statistically significant improvements ($P<0.0005$) at 2, 6 and 12 months with respect to the basal levels. Finally the Tegner score showed a statistically significant improvement at 2 months ($P<0.0005$). Further improvement was seen at 6 months and then the results remained stable at 12 months. The satisfaction levels were similar: 76.4% in the PRGF group and 80.6% in the PRP group. In accordance with previous data, better results were achieved in younger patients with a low degree of cartilage degeneration. However, the two methods showed a statistically significant difference in the number of minor adverse events observed after the injections: both pain ($P = 0.0005$) and swelling ($P = 0.03$) were more frequent in the PRP group. To explain this difference, the authors hypothesized, in the absence of a biological analysis, that the presence of leucocytes might have caused local inflammation, but this phenomenon did not influence the final clinical outcome. The limitations of this study are the lack of randomization and a placebo control group, the lack of imaging and biological results and the short follow-up.

This first study of PRP and PRGF treatments showed the same results at 12 months in the treatment of knee OA. Although the patients analysed were homogeneous and the injection protocols were similar, many aspects are still controversial, such as the number of platelets, activation and function due to the different centrifugation protocols, and the effect of leucocytes.

Napolitano et al. in a pilot study [41] divided 27 patients into two groups: those with arthritis of the knee (13 patients with Kellgren-Lawrence score I-III) and those

with cartilage disease (first or second degree lesions according to the classification of Outherbridge). Inclusion and exclusion criteria are reported in Table 2. Patients received three PRP injections (for a total of about 15 ml) at weekly intervals and were prospectively evaluated before treatment, and 7 and 180 days after the end of treatment (6 months follow-up), using specific questionnaires: the Numerical Rating Scale (NRS) for subjective measurement of pain and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score. PRP was produced from venous whole blood, collected into a specific fibrin polymer two test-tube kit from RegenLab, and subsequently centrifuged at 3,100 rpm for 8 min. Approximately 5 ml of PRP were obtained and was prepared under a laminar flow hood and immediately administered by infiltration. Gellification was complete within 2–7 min on contact with the body heat. Intraarticular infiltration is conducted with the knee flexed at 90°. For at least 2 weeks after the procedure patients are advised not to engage in heavy physical activity involving the lower limb. None of the patients had any adverse effects or allergic reactions.

Both groups studied had improvement in the long-term and pain decreased substantially from the time of the first infiltration and in line with the findings of other published studies [36, 37], this treatment gave better results in younger patients with less severe joint degeneration. The limitations of this study are the short follow-up and the small number of patients analysed, who were not homogeneous between the two groups (seven men and six women in the arthritis group, and 14 men with cartilage disease).

## Discussion

The knee is the joint most commonly associated with sports injuries, and therefore is most at risk of developing degenerative changes. OA in an injured joint is caused by intraarticular pathogenic processes initiated at the time of injury, combined with long-term changes in dynamic joint loading [6]. The high-level athlete with a major knee injury has a high incidence of knee OA. Cartilage injuries are frequently observed in young and middle-aged active athletes [1]. Pharmacological treatment options for OA are very limited.

PRP therapy is an alternative, simple and minimally invasive method that provides a concentrate of autologous blood GFs that can be used to favour the healing process and tissue regeneration. PRP intraarticular injections are clinically safe because of their autologous origin. No serious side effects were observed in the PRP groups in the analysed studies. Moreover, these preliminary results indicate that this procedure has potential to relieve pain, improve knee function and quality of life with greater and longer effects in young men with a low degree of cartilage degeneration [37]. The median duration of the beneficial effects of PRP was 9 months and, as for the other injective treatments, some authors consider that the procedure may be repeated cyclically in order to improve knee function, making evaluations over longer follow-up periods difficult [37].

Despite these beneficial effects, PRP is based on human serum and the quality of the product may be variable between patients, especially in the amount of platelets, GFs and cytokines. Moreover, longer follow-up periods are necessary to investigate possible long-term adverse events, and further research should be directed towards evaluating the quality of the product, the injection technique, the timing of the injection in relation to the injury, single injection versus a series of injections, and the most effective rehabilitation protocol to use after PRP injection.

The various methods for preparing PRP, as well as activation modalities and volume of injection/administration are confounding factors when comparing the results obtained in different studies, and limit the ability to understand and investigate the effects of PRP. Standardization of the methods of plasma preparation and procedures for administration is necessary for further advances.

Another important aspect is that it is unknown whether PRP is capable of inducing cartilage synthesis, and prospective controlled randomized trials with analysis of imaging or biological changes would allow a better understanding of the effect and mechanism of action of PRP. A current hypothesis is that PRP GFs further stimulate mesenchymal stem cells, which eventually directly mature to form cartilage This hypothesis has been confirmed by a study by Drengk et al. demonstrating chondrogenic and proliferative effects of PRP on these cells [42]. Finally, randomized controlled studies are needed to confirm the real potential and to evaluate the durability of this procedure, and to better identify the indication criteria and to improve administration modalities. These aims could best be achieved by a multidisciplinary team seeking to optimize the methods of selecting, diagnosing and treating patients.

**Conflict of interest statement** None.

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