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REVIEW



# Platelet-rich plasma for the treatment of knee osteoarthritis: an expert opinion and proposal for a novel classification and coding system

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**ABSTRACT**

**Introduction:** Platelet-rich plasma (PRP) is able to modulate the joint environment by reducing the inflammatory distress and promoting tissue anabolism. Therefore, it has gained increasing popularity among clinicians in the treatment of osteoarthritis (OA), and it is currently proposed beside consolidated options such as viscosupplementation.

**Areas covered:** A systematic review of all available meta-analyses evaluating intra-articular PRP injections in patients affected by knee OA was performed, to understand how this biologic treatment approach compares to the traditional injective therapies available in clinical practice. Moreover, a novel coding system and 'minimum reporting requirements' are proposed to improve future research in this field and promote a better understanding of the mechanisms of action and indications.

**Expert opinion:** The main limitation in the current literature is the extreme variability of PRP products used, with often paucity or even lack of data on the biologic features of PRP, which should not be considered as a simple substance, but rather a 'procedure' requiring accurate reporting of the characteristics of the product but also all preparation and application modalities. This approach will aid in matching the optimal PRP product to specific patient factors, leading to improved outcomes and the elucidation of the cost-effectiveness of this treatment.

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Prp; growth factors; osteoarthritis; hip; knee; injection; classification

## 1. Introduction

Osteoarthritis (OA) is a common cause of disability: 9.6% of men and 18.0% of women aged ≥60 years have symptomatic OA characterized by joint pain, swelling, and loss of function with consequently a negative impact on patients' quality of life [1]. Different treatments have been developed to manage OA and delay joint replacement surgery, especially in younger patients with earlier stages of OA. Available conservative treatments include non-pharmacological therapies such as dietary supplements, muscle strengthening exercises, non-steroid and steroid anti-inflammatory drugs, intra-articular corticosteroid (CS) injection, hyaluronic acid (HA) injections and, more recently, newer biological therapies including platelet-rich plasma (PRP) injections. The rationale for using PRP is the restoration of joint homeostasis, which is one of the driving factors of OA disease [2–4]. PRP consists of a volume of autologous plasma with a concentration of platelets above the baseline [5], containing a high level of several growth factors, such as IGF-1, TGF- β, EGF, PDGF, VEGF, FGF, which have shown anabolic properties [6–8]. PRP also contains cytokines and bioactive molecules with immunomodulatory properties able to counteract inflammatory and catabolic molecules characterizing the OA joint environment [9,10]. Various studies, mainly focused on the knee joint, supported PRP efficacy in mild to moderate OA [11,12]. Furthermore, several studies demonstrated that intra-articular PRP injections are safe with a rate of adverse events not higher compared to the other intra-articular injectable products [13,14]. Therefore, PRP has gained increasing popularity among clinicians in the last 10–15 years and, given its current wide availability even in the outpatient setting [15,16], it has become a common injective option proposed to patients similar to more traditional 'on

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**Article highlights**

- The use of PRP as an injective treatment for osteoarthritis is safe and provides symptomatic relief and functional recovery.
- PRP injections do not provide direct cartilage regeneration but rather a modulation of the articular environment, with a reduction of the inflammatory distress.
- The evaluation of literature revealed that the majority of meta-analyses found better results of PRP compared to viscosupplementation at short to middle term evaluation.
- PRP should be considered a 'procedure' rather than a simple injective substance; therefore, preparation methods, storage, activation modalities, therapeutic protocols need to be clearly reported in trials.
- A great inter-product variability exist among different PRP products, so there is a stringent need for a classification system and 'minimum reporting requirements' to be universally adopted by basic researchers and clinicians.

the shelf' approaches such as HA and CS. So nowadays the injective 'armamentarium' of the physician can rely on very different therapeutic options, with different mechanisms of action and, inevitably, variable costs. Nevertheless, despite almost 15 years of research in the field of PRP, no consensus or guidelines exist among scientific societies of rheumatologists, orthopedic surgeons, and physiatrists, on the most suitable indications for the use of PRP in the treatment of OA.

Given this current environment, the purpose of this systematic review was to analyze the outcomes of all the available meta-analyses evaluating intra-articular PRP injections in patients affected by knee OA, to understand how this biologic treatment approach compares to the traditional injective therapies available in the clinical practice. Moreover, a novel classification and coding system is proposed to improve future research in this field, to promote a better understanding of the mechanisms of action and indications for this biological approach and, in the end, foster a better use of PRP products for the treatment of OA.

## 2. Materials and methods

A literature search was carried out on the PubMed, EMBASE, Scopus, and PEDro databases on 15 March 2020, using the following keywords that were combined together to achieve maximum search strategy sensitivity: 'PRP,' 'platelet rich plasma,' 'platelet gel,' 'platelet derived growth factors,' 'platelet concentrate,' 'PRGF,' 'ACP,' 'autologous conditioned plasma,' 'platelet lysate,' 'platelet rich fibrin,' 'platelet rich membrane,' 'platelet derived,' 'autologous protein solution' in association with: 'meta-analysis' and in association with: 'osteoarthritis,' 'OA,' 'chondropathy,' 'articular degeneration,' 'cartilage.'

First, all the retrieved articles were screened by title and abstract, using the following inclusion criteria for article selection: 1) meta-analysis, 2) dealing with knee OA, 3) comparing the use of intra-articular PRP injections to other injectables such as HA, CS, or placebo, 4) written in the English language, and 5) published from 2005 to 2020. Exclusion criteria were: 1) studies not containing any meta-analysis, 2) dealing with other applications of PRP than knee OA, 3) written in other languages than English, 4) published before 2005. We further excluded all duplicate articles and articles from non-peer-reviewed journals. Conference presentations, narrative reviews, editorials, and expert opinions were also excluded. A PRISMA flowchart of the selection and screening method is provided in Figure 1. Two investigators extracted relevant data independently. The following data were extracted from each included meta-analysis: first author, year of publication, number of studies included in each meta-analysis, number of patients evaluated, age, OA grade, outcome measures, methods, overall clinical findings, which are summarized in Table I. Discrepancies were resolved by discussion and consensus, and the final results were reviewed by the senior investigators.

## 3. Results

### 3.1. Identification of studies

A total of 48 articles were identified through databases searching. After title and abstract screening, 47 studies were included. As shown in Figure 1, 34 articles were excluded and, ultimately, a total of 12 meta-analyses published from 2013 to 2020 were included, dealing with the comparison of intra-articular PRP injection to intra-articular HA, CS, or placebo for the treatment of knee OA [17–28]. A synopsis of all papers included in the present systematic review is shown in Table 1.

### 3.2. Patients and evaluation methods

Twelve meta-analyses on knee OA were included, with a number of patients ranging from 577 to 1,543. Patients with all grades of OA were included, with a majority of patients being affected by mild to moderate OA (Kellgren-Lawrence I–III and Ahlbäck I–III). Of the 12 meta-analyses, 6 were conducted in China [22–26,28], 1 in Canada [17], 1 in Taiwan [18], 1 in the Netherlands [19], 1 in Iran [20], 1 in Thailand [21] and 1 in South Africa [27]. Knee pain and function were evaluated using the scores Western Ontario and McMaster Universities Arthritis Index (WOMAC), International Knee Documentation Committee (IKDC), Lequesne, Visual Analog Scale (VAS), EuroQol-VAS (EQ-VAS), Knee injury and Osteoarthritis Outcome Score (KOOS).

### 3.3. Reported clinical outcomes

Overall, considering the findings of the meta-analyses included, intra-articular PRP injection led to an improvement in all clinical scores (WOMAC, IKDC, VAS, EQ-VAS, Lequesne, KOOS) with greater and lasting efficacy compared to HA or placebo.

Western Ontario and McMaster Universities Arthritis Index (WOMAC)

WOMAC score was considered in 12 meta-analyses, and 11 found superiority of PRP compared to HA or placebo in terms of WOMAC score. In particular: 3 meta-analyses

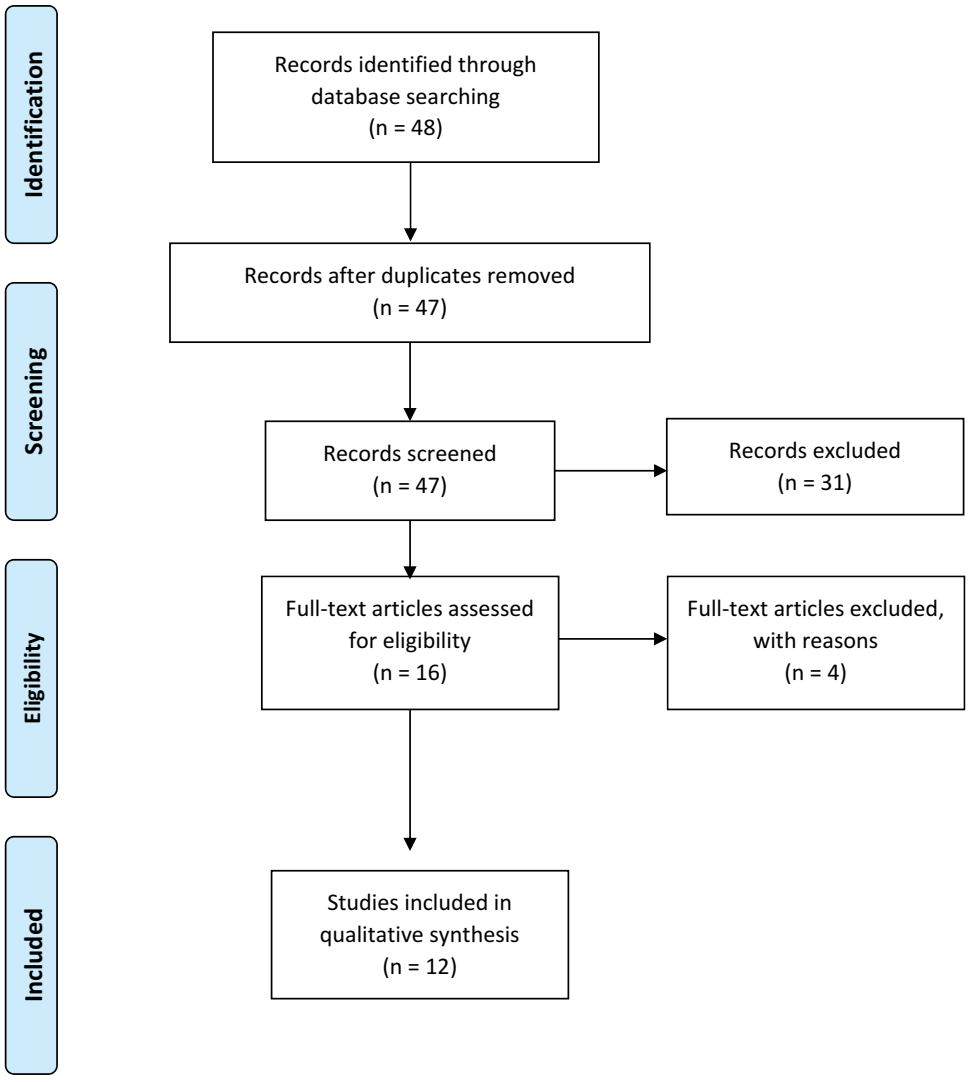


Figure 1. PRISMA Flowchart resuming the papers' selection process.

[17,22,28] documented better results for PRP at the 6 months' evaluation; 7 meta-analyses [18,19,21,23–26] revealed better results up to the 12 months' evaluation; 1 meta-analysis [20] showed superior results of PRP at 24 months.

In one meta-analysis, no statistically significant differences was observed between PRP and HA group up to 12 months [28].

### 3.4. International knee documentation committee (IKDC)

The IKDC subjective score was considered in eight meta-analyses, and seven of them found superiority of PRP: four of them reported better results for PRP at 6 months [17,22,26,28] and three meta-analyses [18,21,23] showed the superior outcome of PRP compared to HA or placebo up to the 12 months' follow-up.

In one meta-analysis no statistically significant differences were observed between PRP and HA groups up to 12 months [27].

#### 3.4.1. VAS for pain

Six meta-analyses considered VAS for pain in knee-treated patients, and three of them documented some superiority of PRP: in two meta-analyses PRP injections were superior to HA or placebo at 6 months [19,28]; in one meta-analysis PRP (and ACP – autologous-conditioned plasma, which was separately analyzed) was demonstrated to be clearly superior over HA up to 12 months [27].

In three meta-analyses there was no statistical difference in VAS scores between the PRP group and HA or placebo at 6 months [17,22,26].

#### 3.4.2. EQ-VAS

Two meta-analyses evaluated the EQ-VAS: in one study [25] no difference emerged between PRP and HA for up to 12 months, whereas in another study [21], the PRP group had statistically significantly better quality of life than the HA group at 12 months.

Table 1. Synopsis of all the meta-analyses included in the present systematic review.

| Authors | No. and design of studies included | No. of patients | Mean age | OA grade | Treatment arms | Outcome measures | Mean follow-up | Comment on results | COMPARISON PRP VS CONTROL * |
|---|---|---|---|---|---|---|---|---|---|
| Khoshbin et al. [17] | 6 studies: 4 RCTs, 2 prospective non-randomized studies | 577 | 56.6 years | 3 KL 0-III<br>1 KL 0-IV<br>1 KL I–III<br>1 Ah 1–3 | 5 PRP vs HA,<br>1 PRP vs placebo | WOMAC, IKDC, VAS | 7 months (min 4 weeks – max 48 weeks) | As compared with HA or placebo, PRP had more beneficial effects in the treatment of mild to moderate knee OA | ++ (WOMAC 6 m, IKDC 6 m) = (VAS 6 m) |
| Chang et al. [18] | 16 studies: 8 single-arm, 3 comparative, 5 RTCs | 1543 | 53.3 years | 1 KL 0-II<br>3 KL 0-III<br>4 KL 0-IV<br>4 KL I–III<br>2 Ah 1–3 | 8 PRP single arm,<br>6 PRP vs HA,<br>1 PRP vs placebo,<br>1 single PRP vs multiple PRP | IKDC, KOOS, WOMAC | 10.2 months (min 24 weeks – max 96 weeks) | Significant functional improvement after PRP compared with their pretreatment baseline. PRP likely superior to HA, with a longer duration of effects. | +++ (WOMAC 12 m, IKDC 12 m, KOOS 12 m) |
| Laudy et al. [19] | 10 studies: 6 RCTs, 4 non-randomized clinical trials) | 1113 | 56.4 years | 1 KL 0-III<br>3 KL 0-IV<br>3 KL I–III<br>1 KL II–IV<br>2 Ah 1–3 | 1 PRP vs placebo,<br>8 PRP vs HA,<br>1 single PRP vs double PRP | VAS, WOMAC | 7.8 months (min 24 weeks – max 48 weeks) | PRP reduced pain more effectively than did placebo or HA. Function improved significantly more with PRP injections compared to controls | ++ (WOMAC 12 m, VAS 6 m) |
| Sadabad et al. [20] | 6 RCTs | 722 | 60.6 years | 2 KL I–III<br>1 KL I–IV<br>1 KL II–IV<br>1 Ah 1–3<br>1 Ah 1–4 | PRP vs HA | WOMAC | 7.2 months (min 5 weeks – max 48 weeks) | PRP more effective than HA at 24 months' evaluation in terms of WOMAC score | + (WOMAC 24 m) |

(*Continued*)

Table 1. (Continued).

| Authors | No. and design of studies included | No. of patients | Mean age | OA grade | Treatment arms | Outcome measures | Mean follow-up | Comment on results | COMPARISON PRP VS CONTROL * |
|---|---|---|---|---|---|---|---|---|---|
| Kanchanatawan et al. [21] | 9 RCTs | 1146 | 58.2 years | 2 KL 0-III<br>1 KL 0-IV<br>1 KL I–III<br>2 KL I–IV<br>1 KL II–IV<br>2 Ah 1–3 | 7 PRP vs HA<br>2 PRP vs placebo | WOMAC, Lequesne score, IKCD, EQ-VAS | 9 months (min 24 weeks – max 48 weeks) | PRP more effective than HA and placebo in reducing symptoms, improving function and improving quality of life in patients with mild-to-moderate OA of the knee | +++ (WOMAC 12 m, IKDC 12 m, EQ-VAS 12 m) = (Lequesne score 12 m) |
| Xu et al. [22] | 10 RCTs | 1184 | 57.1 years | 1 KL 0-III<br>2 KL 0-IV<br>1 KL I–III<br>1 KL I–IV<br>2 KL II–III<br>1 KL II–IV<br>2 Ah 1–3 | 8 PRP vs HA,<br>2 PRP vs placebo | WOMAC, IKCD, VAS, Lequesne score | 9 months (min 1 week – max 48 weeks) | PRP was found effective to relieve pain and improve function, with a satisfactory level observed for at least 6 m | ++ (WOMAC 6 m, IKDC 6 m) = (VAS 6 m, Lequesne score 6 m) |
| Dai et al. [23] | 10 RCTs | 1069 | 57.9 years | 1 KL 0-III<br>1 KL 0-IV<br>1 KL I–III<br>1 KL I–IV<br>3 KL II–III<br>1 KL II–IV<br>2 Ah 1–3 | 8 PRP vs HA,<br>2 PRP vs placebo | WOMAC, IKCD, Lequesne score | 8.7 months (min 12 weeks, max 48 weeks) | Compared with HA and saline, intra-articular PRP injection may have more benefit in pain relief and functional improvement | +++ (WOMAC 12 m, IKDC 12 m, Lequesne score 12 m) = (WOMAC 6 m, IKDC 6 m, Lequesne score 6 m) |
| Shen et al. [24] | 14 RCTs | 1423 | 59.1 years | 3 KL 0-IV<br>3 KL I–III<br>1 KL I–IV<br>4 KL II–III<br>1 KL II–IV<br>2 Ah 1–3 | PRP vs HA/ placebo/ ozone/ CS | WOMAC | 9.9 months (min 8 weeks, max 52 weeks) | PRP probably is more effective in terms of pain relief and self-reported function improvement, compared with placebo, HA, and CS | + (WOMAC 12 m) |

(*Continued*)

Table 1. (Continued).

| Authors | No. and design of studies included | No. of patients | Mean age | OA grade | Treatment arms | Outcome measures | Mean follow-up | Comment on results | COMPARISON PRP VS CONTROL * |
|---|---|---|---|---|---|---|---|---|---|
| Zhang et al. [25] | 13 studies: 10 RCTs, 3 prospective studies | 1390 | 58.2 years | 1 KL 0-III<br>2 KL 0-IV<br>5 KL I–III<br>1 KL I–IV<br>2 KL II–III<br>1 KL II–IV<br>1 Ah 1–3 | PRP vs HA, | WOMAC, EQ-VAS | 8.7 months (min 4 weeks – max 48 weeks) | PRP reduced pain more effectively than HA. WOMAC score at 6 months' f-up was superior in PRP group | + (WOMAC 6 m) = (WOMAC 12 m, EQ-VAS 12 m) |
| Han et al. [26] | 15 RCTs | 1314 | 56.5 years | 5 KL I–III<br>3 KL I–IV<br>4 KL II–III<br>1 KL II–IV<br>1 KL III–IV<br>1 Ah 1–3 | PRP vs HA | WOMAC, VAS, IKDC, Lequesne score | 9 months (min 12 weeks – max 72 weeks) | PRP has a positive effect on pain levels and functional outcomes compared with HA injections. | ++ (WOMAC 12 m, IKDC 6 m) = (IKDC 12 m, VAS 6 m, Lequesne score 6 m) |
| Hohmann et al. [27] | 12 studies | 1248 | 58.8 years | 2 KL 0-III<br>4 KL I–III<br>1 KL I–IV<br>2 KL II–III<br>1 KL II–IV<br>2 Ah 1–3 | 9 PRP vs HA,<br>3 ACP vs HA | WOMAC, IKCD, VAS | 10 months (min 24 weeks – max 48 weeks) | PRP is superior to HA in knee pain reduction; in particular, ACP appears also to be clearly superior over HA; there were no advantages of PRP over HA in other clinical parameters | + (VAS 12 m) = (WOMAC 12 m, IKDC 12 m) |
| Wu et al. [28] | 9 RCTs | 1063 | 56.5 years | 2 KL 0-III<br>1 KL 0-IV<br>2 KL I–II<br>4 KL I–III | PRP vs HA | IKCD, WOMAC, VAS, KOOS | 8.1 months (min 4 weeks – max 52 weeks) | PRP appears to be better for pain relief and self-reported functional improvement than HA. | +++ (WOMAC 6 m, IKDC 6 m, VAS 6 m) = (KOOS 6 m) |

**KL: Kellgren-Lawrence OA classification**
**Ah: Ahlbäck OA classification**
* In this column we report eventual superiority of PRP compared to control. '**+**' means that PRP is better in the specific parameter described in parentheses. When multiple **+** were used (maximum three +) that means that PRP proved to be more effective in multiple clinical parameters. **' = '** means no difference between PRP and controls.

#### 3.4.3. Lequesne score

Four meta-analyses considered the Lequesne score, and three of them [21,22,26] found no difference in favor of PRP, neither at 6 [22,26] nor at 12 months' follow-up [21].

In one meta-analysis instead, PRP provided better results than HA at the 12 months' evaluation [23].

### 3.5. Knee injury and osteoarthritis outcome score (KOOS)

Two meta-analyses analyzed the KOOS score: one did not find any difference between PRP and HA at 6 months [28], whereas the other found that PRP injections led to a better KOOS score at 12 months compared to HA or placebo [18].

### 3.6. A novel coding system of PRP products and minimum reporting requirements for future trials

One of the major limitations in the field of PRP is that most studies include PRP formulations obtained by different methods, with different compositions and characteristics, and therefore the outcomes could be different depending on the product used, even though they are all called PRP. This makes the comparison among results of different studies often confusing and contradictory. Beyond the wide variability among products, literature is often characterized by the paucity of data provided by authors on the composition and biologic activity of the particular PRP adopted [29]. This limitation occurs both in clinical and pre-clinical research [31–33]: a recent paper by Chahla et al. [34] found that only 11/105 studies (10%) provided comprehensive reporting of the PRP preparation protocol, and only 17/105 studies (16%) provided quantitative metrics on the composition of the final PRP product.

In response to this, several classification systems have been proposed to report the most relevant parameters of PRP [35–38] and, in recent years, these classifications have become more sophisticated by including features such as erythrocytes, recovery efficiency, or centrifugation type [39–41]. However, none of them have been able to reach the agreement of experts. Our aim is to present a novel classification and minimal reporting requirements reached by consensus among main opinion leaders in this field. This consensus statement consists of: (1) a code that quickly identifies and gives an idea of the type of PRP used in each study, based on parameters that are easy to measure and affordable for any research team; (2) three tables to be used depending on the study (*in vitro, in vivo*, or clinical) in which the preparation, characterization, and application of PRP are described in a concise and structured way.

#### 3.6.1. Code system

The code is a sequence of six digits grouped in pairs indicating parameters of platelet composition, purity, and activation: $N_1N_2$-$N_3N_4$-$N_5N_6$. We tried to simplify the code as much as possible because the complex never prevails. Besides, it is only composed of numbers, since these are 'the most universal language.' Each digit refers to the following parameters summarized in Table 2.

The digits $N_1$ and $N_2$ indicate the platelet composition of PRP. It takes into account the concentration of PRP with respect to the basal levels in blood. By associating the digits $N_1$ and $N_2$ with platelet concentrations (2 = 200,000–300,000 or 4 = 400,000–500,000), it is very simple to deduce both the platelet concentration and the concentration ratio. If a PRP is '24-$N_3N_4$-$N_5N_6$,' it can be already deduced that this PRP has a platelet concentration around double above the basal values (which are around 200,000 platelets/μL in blood), and that PRP platelet concentration is between 400,000 and 500,000 platelets/μL. In addition to providing information about platelet concentration and concentration ratio, the total number of platelets administered can also be calculated by a simple multiplication taking into account the volume of PRP injected.

Table 2. Explanation of the digits of the novel PRP coding system.

| | | |
|---|---|---|
| **Number 1 ($N_1$)** | Basal platelet concentration in blood | 0 = 0–100,000 platelets/μL<br>1 = 100,000–200,000 platelets/μL<br>2 = 200,000–300,000 platelets/μL<br>3 = 300,000–400,000 platelets/μL<br>4 = 400,000–500,000 platelets/μL<br>5 = 500,000–600,000 platelets/μL<br>6 = 600,000–700,000 platelets/μL<br>7 = 700,000–800,000 platelets/μL<br>8 = 800 …<br>9 = 900 …<br>10 = … . |
| **Number 2 ($N_2$)** | Platelet concentration in PRP | 0 = 0–100,000 platelets/μL<br>1 = 100,000–200,000 platelets/μL<br>2 = 200,000–300,000 platelets/μL<br>3 = 300,000–400,000 platelets/μL<br>4 = 400,000–500,000 platelets/μL<br>5 = 500,000–600,000 platelets/μL<br>6 = 600,000–700,000 platelets/μL<br>7 = 700,000–800,000 platelets/μL<br>8 = 800 …<br>9 = 900 …<br>10 = … . |
| **Number 3 ($N_3$)** | Red Blood Cells in PRP | 0 = No presence/traces ($<1x10^6$/μL)<br>1 = Presence ($>1x10^6$/μL) |
| **Number 4 ($N_4$)** | White Blood Cells in PRP | 0 = Less than baseline<br>1 = 1.01 to 2 x baseline<br>2 = 2.01 to 3 x baseline<br>3 = 3.01 to 4 x baseline<br>4 = 4.01 to 5x baseline<br>5 = > 5x baseline |
| **Number 5 ($N_5$)** | External Activation | 0 = No (endogenous)<br>1 = Yes |
| **Number 6 ($N_6$)** | Calcium Addition | 0 = No<br>1 = Yes |

These data are indicated in the summary tables below (Table 1, 2, and 3).

The digits $N_3$ and $N_4$ indicate the purity of the PRP, referring to the absence (0) or presence (1) of erythrocytes and the concentration of leukocytes (0, 1, 2, 3 …). The effect of the PRP is not only conditioned by the presence of leukocytes, which is a widely studied issue, but also by the presence of erythrocytes (red blood cells – RBCs), which can affect PRP due to possible toxicity produced by hemolysis and eryptosis [42]. The limit of $1x10^6$/µL was defined based on the data coming from studies were RBC count in PRP products was specifically assessed: depletion of RBCs always led to products with RBC<$1x10^6$/µL [43,44].

Finally, the digits $N_5$ and $N_6$ refer to the activation. $N_5$ indicates if activation is endogenous (0) or if PRP is activated before its injection (1). $N_6$ mentions the addition of calcium for activation (0 = no, 1 = yes), as it is important to know if the calcium sequestered to prevent blood clotting during PRP preparation has been added again: previous studies reported that calcium concentration has an influence on the cellular and tissue response produced by the PRP [45].

### 3.6.2. Examples

(1) PRP obtained from blood with a mean concentration of 150,000 platelets/µL and reaching a mean concentration of 430,000 platelets/µL; presence of erythrocytes and no leukocytes; activation with thrombin: PRP code is 14–10-10.

(2) PRP obtained from blood with a mean concentration of 230,000 platelets/µL and reaching a mean concentration of 310,000 platelets/µL; no erythrocytes; double leukocyte concentration compared to blood levels and without exogenous activation: PRP code is 23–02-00.

(3) PRP obtained from blood with a mean concentration of 212,900 platelets/µL and reaching a mean concentration of 420,000 platelets/µL; with no leukocytes and no erythrocytes; and activation with calcium: PRP code is 24–00-11.

### 3.6.3. Summary tables

The following tables are intended to summarize in a quick and simple way the aspects of the studies related to PRP and to complete the information provided by the code previously explained. There are three tables depending on whether they are *in vitro* (Table 3), *in vivo* (Table 4), or clinical studies (Table 5). These tables, in addition to indicating the PRP code, report information about PRP and include four sections.

Section 1 refers to the preparation method and it includes parameters such as blood drawn, centrifugation or other preparation methods, and PRP volume obtained, which also provides information on PRP characteristics and on the effectiveness of the method itself.

Section 2 refers to PRP characterization and includes the PRP type defined by the code previously described and parameters such as platelet size (MPV), which can be easily obtained when concentrations are measured by a hematological analyzer. This value is an important indicator of platelet biomass and it relates to platelet content [46]. This section also summarizes the concentration values of erythrocytes, leukocytes, and leukocyte formula, as well as the activation method and its timing with respect to the *in situ* injection. It also includes the possibility of adding more details on the composition of PRP, such as the amount and concentration of different growth factors and biomolecules (to understand their mutual interactions), as well as any other analyses relevant to the researchers.

Table 3. Summary of characteristics for *in vitro* PRP studies.

| | |
|---|---|
| 1. **PRP Preparation** | |
| Initial blood volume | *mL* |
| Anticoagulant | *type* |
| System | *Open/Close* |
| Centrifugation | *Yes/No (detail in point 4)* |
| *number* | *1, 2, …* |
| *speed* | *g* |
| Other preparation methods … | |
| Final PRP volume | *mL* |
| **2. PRP Characteristics** | |
| PRP Type | $N_1N_2$-$N_3N_4$-$N_5N_6$ |
| MPV | *fL* |
| Red Blood Cells | *Concentration* |
| White Blood Cells | *Concentration* |
| *Neutrophils* | *Concentration* |
| *Lymphocytes* | *Concentration* |
| *Monocytes* | *Concentration* |
| *Eosinophils* | *Concentration* |
| *Basophils* | *Concentration* |
| Activation | *Method and timing (further details in Section 4)* |
| GF/Molecule 1 | *Concentration* |
| GF/Molecule 2 | *Concentration* |
| GF/Molecule 3 … | *Concentration* |
| **3. Application Characteristics** | |
| Dose | |
| Direct/Indirect (transwell.) | *% culture media* |
| Cell line | |
| **4. Other remarkable PRP and study features** | |
| *e.g. further data about PRP preparation, activation, quantification, application … combination with other products (i.e. anesthetics, others.), fresh-frozen* | |

Section 3 refers to the application method and reports application data such as the formulation type, administration route, dosage, volume, number of platelets, tissue, pathology, which are fundamental parameters for determining the clinical response.

Section 4 includes additional information that researchers consider relevant and that are not included in the previous sections.

As explained above, the Classification and Information System described here is based on a consensus reached by the authors of this article with the intention of establishing a reference in the medical and scientific community to improve the research carried out in the field of the PRP. Accordingly, this system is not intended to be fixed but to be updated as knowledge advances.

## 4. Conclusion

Based on the evaluation of the available meta-analyses, we found an overall support for a beneficial effect of PRP in the treatment of OA symptoms. The data suggest that PRP may be superior to viscosupplementation in terms of pain reduction and functional recovery for the treatment knee OA, as several

Table 4. Summary of characteristics for *in vivo* PRP studies.

| | |
|---|---|
| **1. PRP Preparation** | |
| Initial blood volume | *mL* |
| Anticoagulant | *type* |
| System | *Open/Close* |
| Centrifugation | *Yes/No (detail in point 4)* |
| *number* | *1, 2, …* |
| *speed* | *g* |
| Other preparation methods … | |
| Final PRP volume | *mL* |
| **2. PRP Characteristics** | |
| PRP Type | $N_1N_2$-$N_3N_4$-$N_5N_6$ |
| MPV | *fL* |
| Red Blood Cells | *Concentration* |
| White Blood Cells | *Concentration* |
| *Neutrophils* | *Concentration* |
| *Lymphocytes* | *Concentration* |
| *Monocytes* | *Concentration* |
| *Eosinophils* | *Concentration* |
| *Basophils* | *Concentration* |
| Activation | *Method and timing (further details in Section 4)* |
| GF/Molecule 1 | *Concentration* |
| GF/Molecule 2 | *Concentration* |
| GF/Molecule 3 … | *Concentration* |
| **3. Application Characteristics** | |
| Formulation type | *Liquid, gel, scaffold …* |
| Administration route | *including image guidance* |
| Dosage | *number of applications and interval* |
| Volume | *ml PRP* |
| Dose | *number of injected platelets (range)* |
| Tissue | |
| Pathology | |
| Animal | |
| **4. Other remarkable PRP and study features** | |
| *e.g. further data about PRP preparation, activation, quantification, application … combination with other products (i.e. anesthetics, others.), fresh-frozen* | |

Table 5. Summary of characteristics for clinical PRP studies.

| | |
|---|---|
| **1. PRP Preparation** | |
| Initial blood volume | *mL* |
| Anticoagulant | *type* |
| System | *Open/Close* |
| Centrifugation | *Yes/No (detail in point 4)* |
| *number* | *1, 2, …* |
| *speed* | *g* |
| Other preparation methods … | |
| Final PRP volume | *mL* |
| **2. PRP Characteristics** | |
| PRP Type | $N_1N_2$-$N_3N_4$-$N_5N_6$ |
| MPV | *fL* |
| Red Blood Cells | *Concentration* |
| White Blood Cells | *Concentration* |
| *Neutrophils* | *Concentration* |
| *Lymphocytes* | *Concentration* |
| *Monocytes* | *Concentration* |
| *Eosinophils* | *Concentration* |
| *Basophils* | *Concentration* |
| Activation | *Method and timing (further details in Section 4)* |
| GF/Molecule 1 | *Concentration* |
| GF/Molecule 2 | *Concentration* |
| GF/Molecule 3 … | *Concentration* |
| **3. Application Characteristics** | |
| Formulation type | *Liquid, gel, scaffold …* |
| Administration route | *including image guidance* |
| Dosage | *number of applications and interval* |
| Volume | *ml PRP* |
| Dose | *number of injected platelets (range)* |
| Tissue | |
| Pathology | |
| **4. Other remarkable PRP and study features** | |
| *e.g. further data about PRP preparation, activation, quantification, application … combination with other products (i.e. anesthetics, others.), fresh-frozen* | |

meta-analyses were identified and the majority reported superiority of PRP in one or more clinical parameters: in particular, looking at the functional scores most commonly used by clinicians, 11 out of 12 meta-analyses found better WOMAC score, and 7 out of 8 meta-analyses found superior IKDC-subjective in PRP group compared to HA or placebo.

The main limitation in the analysis of the literature comes from the extreme variability of PRP products used, with often paucity or even lack of data provided by authors to understand the biologic features of the PRP used in the specific trial considered. Comparing the results of similar substances, as well as distinguishing those of different products, would be fundamental to understand what works better for a selected clinical indication. Only recently there has been increasing awareness of the necessity of measuring and reporting the complete features of PRP, and the classification and coding system presented in this review should be considered as a proposal for a 'roadmap' to guide future pre-clinical and clinical research. PRP should not be simply considered a product to inject but rather we should think it as a 'procedure,' since the number of injections, the time interval among administrations, the storage, and activation methods could also play a significant role in determining the clinical outcomes. Therefore, more useful data will be obtained when researchers compare similar 'PRP procedures,' dealing not only with comparable substances but also with comparable application methods.

## 5. Expert opinion

At the beginning of the application of PRP in musculoskeletal diseases, there were high expectations supported by encouraging data from *in vitro* and animal trials, both in terms of safety and efficacy [47–49]. Therefore, PRP was soon applied in a wide range of pathologies, from OA to tendinopathies and muscle injuries [50–53]. Despite the initial enthusiasm leading often to an indiscriminate use of this product [54], based on the current knowledge and technologies available, tissue regeneration by simple PRP injection is still a difficult challenge to achieve. As largely expected, the promising laboratory or animal results could not be reproduced in the clinical practice, as the complex networks and the many etiopathogenetic factors that come into play *in-vivo* cannot be easily mimicked in controlled experimental conditions, a general rule that should always be remembered when dealing with biologic products [55].

So, what have we learned in the last 10–15 years of research about PRP and its application? First, it has become clear that the aggressive marketing of novel biologic products should be limited until we gain enough data [54]. The clinical application of PRP increased markedly in a relatively short timespan, much before reliable data and sound randomized trials were available to support its use. Recently, some clinicians even proposed PRP as a first-line treatment for the management of OA and tendinopathies without the backup of solid evidence [56]. This was made possible by a 'loop whole' in regulations concerning blood-derived products. In the USA, for example, biotech companies took advantage of the 510(k) exemption [57], based on which new medical devices 'substantially equivalent' to others already marketed can skip the 'standard' FDA approval process. So, after the first devices for the preparation of PRP were released on the market, quickly similar devices directly came to the market supported by a great deal of media exposure for this 'innovative' biologic product. With the market full of devices, various PRP products were provided to patients with great inter-product variability. Different devices and different preparation methods produce different PRPs in terms of number of platelets, presence of red blood cells, leukocytes, platelet activation status, and so on [39].

Platelet content has been the first field of debate among scientists. Despite the recognition that both platelet concentration and their total amount are key factors, since the majority of growth factors are stored in their alpha-granules, no clinical studies have yet reported a correlation between platelet count and clinical outcome. Even platelets' ratio (compared to whole blood) has not been correlated with the results. This could be due to several causes, such as the different responsivity of platelets in releasing their growth factors, the presence of many other relevant bioactive molecules in the plasma (separate from platelets), and the influence of the individual patients' features, comorbidities, and concurrent medications [58,59]. Some recent insights have suggested that the mean platelet volume (MPV) might be a parameter worth of further investigation, since it could reflect the 'storage capability' of platelets, which are the most heterogeneous blood components in terms of sizes: larger MPV could, therefore, mean higher content of bioactive molecules. Furthermore, the variability in sizes influences platelet density, so that the same centrifugation process could produce PRP with similar platelets' concentration but different MPV and, therefore, different biologic properties [60]. Another relevant issue is the micro-environment where PRP is applied, since this could also influence PRP biologic actions, given the difference existing between joints and soft tissues such as muscles and tendons [61,62].

Beyond platelet count, another debated issue has been the role of leukocytes which, based on *in vitro* experiments, have been considered to potentially be detrimental due to the release of pro-inflammatory and catabolic mediators such as metalloproteinases [10,63]. Despite these premises, there are still limited clinical data on the comparison between leukocyte-rich and leukocyte-poor PRP products [64–66], and actually, a trend reversal has been observed in the last years, with attempts to 'take advantage' of the properties of leukocytes in modulating the joint environment [67]. This may be due to the fact that leukocytes include a variety of cell types including neutrophils, lymphocytes, and monocytes with various biologic activities. Some studies have shown that it is possible to stimulate monocytes to become M2 pro-healing macrophages in the joint [68,69] and that white blood cells may down-regulate NFκβ expression through both an inhibition of cyclooxygenase 2 (COX2) expression and a higher production of NFκβ inhibitor α (Iκβα) by chondrocytes [70]. In addition, aspects such as pathology and tissue where PRP is applied may also be a determining factor in whether the presence of white blood cells is beneficial or harmful. Similarly, the role of red blood cells within PRP products should be carefully considered: although in vitro studies demonstrate a dose-responsive detrimental effect of RBC on the intra-articular environment with decreased proteoglycan synthesis and chondrocyte apoptosis, the effects on RBC in vivo are still not elucidated [71,72].

Additional variables to consider include: 1) the volume of blood to harvest, which is related to the volume of PRP to inject; 2) the preparation method (number of centrifugations, revolutions per minute, timing, etc., …); 3) the use of fresh or freeze-thawed product; 4) activation by different substances (calcium, thrombin, polyacrylamide beads, etc., …); 5) the timing of activation with respect to intra-articular PRP injection, which could influence the physical state of PRP and also the kinetic of growth factors' release; 6) the number and the time interval between injections [73,74]. Unresolved issues related to each of these parameters must be addressed to optimize the therapeutic strategy in the use of PRP.

All of these factors highlight that PRP should not be considered as a simple substance, but rather a 'procedure' requiring the above-noted parameters to be clearly reported. In the last 10 years, at least 6 different classification systems of PRP products have been proposed, but none of them has reached universal acceptance or widespread use [38]. This could be due to various reasons, such as the lack of a comprehensive method that includes all the biologic and 'procedural' aspects related to PRP preparation and administration, and also to the impossibility for many researchers to obtain 'first-hand' data on PRP products, especially in case they were using commercial kits in an outpatient setting.

The coding system and the 'minimum reporting requirements' presented here are suggested as a tool to help basic researchers as well as clinicians in the difficult process of delineating more precise information. This requires that researchers and clinicians use a common reference system: starting from the classification systems already available, we tried to provide a comprehensive instrument that conveys all the essential data that researchers need to compare results of different trials and orient future investigations. The proposed system suffers some limitations: for example, some cutoff values have been arbitrarily established and likely they will need adjustment over time. Furthermore, we still do not know all the molecules with a relevant biologic action within PRP, so

the list shall be updated in the future. Lastly, the data concerning PRP should always be matched to those concerning the population of patients treated, since responsiveness might be influenced by a wide range of receiver's features: therefore a 'definitive classification system' will need to include simultaneously data on PRP procedure, type of disease, and patients' features. Applying this strategy at the onset of research and clinical use would have likely contributed to a better current understanding of the true scientific evidence for PRP in the treatment of OA and other conditions.

Today we have an abundance of clinical trials but just a few of them are high quality, double-blinded RCTs. This is a major limitation considering the huge impact of placebo in the setting of intra-articular injections and the need for a strong study design to properly investigate PRP results [75]. There is also a plethora of systematic reviews (perhaps more than high-quality trials) and an interesting number of meta-analyses, mainly comparing PRPs to viscosupplementation in the knee, the most commonly injected joint. The majority of these studies and meta-analyses are flawed by the lack of consistent reporting of the PRP products used [34]. Still, the analysis of the outcomes from all the available meta-analyses, performed by different authors with different methods, provided us some insights into the therapeutic potential of PRP. The fact that PRP provides better outcomes compared to saline has been confirmed by the available RCTs regardless of the different PRP procedures. Even with the aforementioned limitations, the current literature supports the conclusion that PRP is superior to HA. Our research included meta-analyses published in the timespan of 7 years (2013 to 2020): none of the included meta-analyses revealed inferiority of PRP compared to HA and, instead, the majority of them revealed the superiority of PRP in at least one clinical parameter, as summarized in Table 1. The evaluations were mainly performed in the range of 6–12 months' follow-up, which is a common time-point for injective treatments, since the duration of their beneficial effects is limited and just a few trials evaluated the long-term survival curve of intra-articular injections [76–78]. Interestingly, we found substantial agreement among meta-analysis independently of the publication time: 'early' meta-analyses reported similar findings compared to more recent publications. This is partly due to the fact that the same trials were included in most of the meta-analyses but, in the last years, it should be noted an increasing number of RCTs published: we believe that the higher quality of the 'recent literature' could further endorse the role of PRP. In any case, it should be acknowledged that meta-analyses are not always characterized by flawless methodology: for example, some of them included also comparative nonrandomized trials, thus reducing the overall quality of the evidence found. However, the apparent superiority of PRP should be interpreted carefully in light of the drawbacks of the available evidence, as it is acknowledged that pooling different PRP products is not ideal from a methodological point of view. The literature on HA is also confounded by the many HA preparations available on the market, differing in terms of molecular weight and chemical structure [79,80]. Furthermore, a flaw of the present review should be acknowledged: the lack of an analysis of studies reporting objective assessment (i.e. radiologic and histologic data following PRP application). This could be justified by the intention of the authors to focus more on the clinical efficacy of PRP, which prompted to prioritize subjective patients' reported outcomes.

Based on the available data, PRP appears to be safe and effective in the treatment of knee OA but patients should be fully informed of its potential, avoiding unrealistic expectations. In particular, despite in some trials PRP has been used to treat end-stage knee OA (Kellgren Lawrence grade 4 or Alback grade more than 3), it should be pointed out that PRP injections are not routinely indicated in severe OA with concurrent bone deformity. This is an important consideration, since PRP is not covered by National Health Systems in most countries and requires the patient to pay for this treatment [81].

Over time, the scientific understanding of PRP effects led to a change in perspective, progressing from the expectation of tissue regeneration to rather a modulation of the articular environment, especially at the synovial level, down-regulating the degenerative process promoted by chronic inflammation while improving anabolic pathways [2,82]. In this regard, recent studies have been oriented toward the development of 'autologous anti-inflammatory' blood-derived products, which can modulate inflammation without the well-known side effects associated with traditional synthetic drugs (i.e. CS and NSAIDs) [83,84]. The real game-changers in the field will be, on one hand, the possibility of studying the interactions of single bioactive molecules and their behavior within the joint [85], and, on the other hand, the patient profiling strategy, i.e. identifying specific features of the subject that play a role in determining the success or failure of PRP administration. To this purpose, international electronic-based registries could help in pooling together a significant amount of data to find prognostic factors and elucidating the cost-effectiveness of this treatment. Moreover, an important aspect is a better understanding of the pathology itself, as OA is a multifaceted disease with a variety of features triggered by different etiopathogenetic pathways [86,87].

The advent of biologic strategies has initiated a path to 'personalized medicine' which has tremendous potential for improved treatments, but will also require further significant research effort since tailoring a therapy to target a specific category or even a single patient will require close collaborations between basic scientists and clinicians. In this light, having a common language is paramount, and this new PRP classification and coding system could provide a step forward in this direction, fostering further development of this promising biological approach for the treatment of OA and other musculoskeletal conditions.

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