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# State of the art in the treatment of knee osteoarthritis using platelet-rich plasma alone or in combination: a systematic review

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## Abstract

**Introduction:** Bone diseases comprise a large group of common diseases, including fractures, osteoporosis, and osteoarthritis that affect a large number of individuals. Knee osteoarthritis (KOA) refers to a chronic joint disease characterized by degenerative lesions of the knee cartilage, causing pain, swelling, dyskinesia, and other symptoms of the knee joint. According to the World Health Organization (WHO), KOA has an incidence of approximately 10-15%, with the elderly population accounting for 95%. **Objective:** This was to conduct a systematic review to present state of the art, through randomized clinical trials and meta-analyses, of the treatment of knee osteoarthritis using platelet-rich plasma alone or in combination with bone marrow aspirate concentrate (stem cells and other cells), mesenchymal stem cells, hyaluronic acid, and corticosteroids. **Methods:** The systematic review rules of the PRISMA Platform were followed. The search was conducted from November 2024 to January 2025 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 126 articles were found, of which 39 articles were fully evaluated and 11 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 31 studies with a high risk of bias and 22 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with $X^2$=79.9%>50%. The symmetrical funnel plot suggests no risk of bias among studies with small sample sizes. Based on the results, platelet-rich plasma demonstrated a significant advantage over hyaluronic acid, as well as improved symptom relief, lower reintervention rates, and pain improvement. At a minimum follow-up of 6 months, platelet-rich plasma has been shown to significantly improve pain and function in patients with knee osteoarthritis compared with placebo. Furthermore, platelet-rich plasma exhibited the highest values compared to bone marrow aspirate concentrate, hyaluronic acid, and corticosteroids. Furthermore, arthroscopically guided high-dose subchondral injection of primary synovial mesenchymal stem cells cultured in platelet-rich plasma and hyaluronic acid medium can regenerate cartilage defects, improving clinical outcomes. Meta-analyses have shown that the benefits of platelet-rich plasma injections are primarily apparent in the medium- to long-term management of clinical symptoms, including pain relief, improved quality of life, increased activities of daily living, and improved sports capabilities. Clinical outcomes of platelet-rich plasma injections for knee osteoarthritis may be related to the higher dose of platelets.

**Keywords:** Osteoarthritis. Regeneration. Bone. Cartilage. Platelet-rich plasma. Treatments.

## Introduction

Bone diseases comprise a large group of common diseases, including fractures, osteoporosis, and osteoarthritis, that affect a large number of individuals, especially the elderly. Knee osteoarthritis (KOA) refers

to a chronic joint disease characterized by degenerative lesions of the knee cartilage, causing pain, swelling, dyskinesia, and other symptoms of the knee joint [1,2].

According to the World Health Organization (WHO) [3], KOA has an incidence of approximately 10-15%, with 95% of the elderly population being affected. As treatment modalities, anti-inflammatory and analgesic drug patches, oral medications, and surgical procedures are commonly used in clinical practice to treat patients, reduce inflammatory reactions, and promote their physical recovery.

In addition, platelet-rich plasma (PRP) is an emerging biological intervention for osteoarthritis (OA), especially for knee and hip OA. Recent systematic reviews have found significant clinical improvements in outcomes after PRP administration compared to hyaluronic acid (HA) in patients with knee OA, and studies have shown no statistically significant difference in bone marrow aspirate concentrate compared to PRP outcomes [3,4].

In this context, the use of PRP injections in the treatment of KOA appears to be favorable, resulting in clinically comparable or superior outcomes compared to other injection treatments. As an information gap, there is a lack of evidence to suggest that the presence of leukocytes significantly influences clinical outcomes [4].

Also, together with PRP, adult tissue stem cells (mesenchymal stem cells) mediate homeostasis and regeneration of tissues and organs, making decisions about whether to remain quiescent, proliferate, or differentiate into mature cell types [5]. In this sense, it is suspected that the quiescent state of stem cells is characterized by an inherently glycolytic metabolism, followed by a transition to favor mitochondrial oxidative phosphorylation during differentiation [6-9]. However, increasing evidence suggests that metabolism during quiescence, activation, and differentiation may vary between tissues, integrating signaling cues and metabolic inputs with the release of exosomes and microRNAs as important metabolic messengers in the organism, with regenerative potential for knee bone and cartilage [10-14].

Therefore, the present study aimed to perform a systematic review to present state of the art, through randomized clinical trials and meta-analyses, of the treatment of knee osteoarthritis using platelet-rich plasma alone or in combination with bone marrow aspirate concentrate (stem cells and other cells), mesenchymal stem cells, hyaluronic acid, and corticosteroids.

## Methods

### Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 01/12/2025. The AMSTAR-2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 01/12/2025.

### Data Sources and Search Strategy

The bibliographic search process was carried out from November 2024 to January 2025 and developed based on the Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar databases, covering scientific articles from various periods to the present day. The following descriptors (DeCS/MeSH Terms) were used: *Osteoarthritis. Regeneration. Bone. Cartilage. Platelet-rich plasma. Treatment*s, and using the Boolean "and" between MeSH terms and "or" between historical findings.

### Study Quality and Risk of Bias

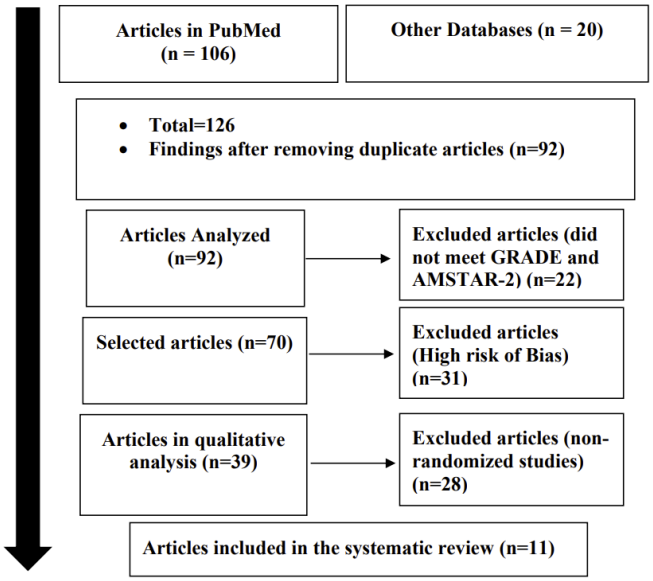
Quality was classified as high, moderate, low, or very low regarding risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized controlled trials, followed by randomized clinical trials. Low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (sample size versus effect size), using Cohen's d test.

## Results and Discussion

### Summary of Findings

A total of 126 articles were found and submitted to eligibility analysis, and 31 final studies were selected to compose the results of this systematic review. The listed studies were of medium to high quality (Figure 1), considering the level of scientific evidence of the studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with $X^2$=79.9%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 31 studies with a high risk of bias and 22 studies that did not meet GRADE and AMSTAR-2.

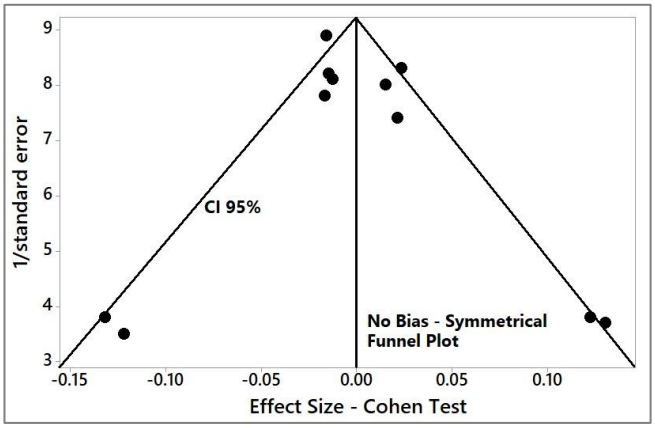
Figure 1. Flowchart showing the article selection process.




Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies through the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). The precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the base of the graph and in studies with large sample sizes that are presented in the upper region.

Figure 2. The symmetric funnel plot suggests no risk of bias among the small sample size studies shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n=11 studies).




Source: Own authorship.

## Major Outcomes of Randomized Clinical Trials and Meta-Analysis

According to the American Academy of Orthopaedic Surgeons, a review of the current best evidence evaluated the efficacy of PRP for patients with knee osteoarthritis, resulting in 54 articles, 36 of high quality and 18 of moderate quality. The results of PRP versus control/placebo, acetaminophen, nonsteroidal anti-inflammatory drugs, corticosteroids, exercise, prolotherapy, autologous conditioned serum, bone marrow aspirate concentrate, hyaluronic acid, and ozone therapy were reviewed [15]. Based in part on the results of randomized controlled trials suggesting a beneficial effect over alternative treatment options, the use of PRP for the treatment of KOA is widespread and growing. A recent meta-analysis study examined the statistical weakness of the conclusions of randomized controlled trials (RCTs) that reported outcomes of patients with KOA who were treated with PRP versus alternative nonoperative treatment strategies. The frailty index (FI) and reverse FI were applied to assess the robustness of conclusions about the efficacy of PRP for KOA. A total of 1993 patients with a mean age of 58.0 ± 3.8 years were analyzed. The mean number of events needed to reverse the significance of individual RCTs (FI) was 4.57 ± 5.85. Based on random-effects meta-analyses, PRP demonstrated a significantly higher rate of successful outcomes when compared with hyaluronic acid (p=0.002; OR=2.19; 95% CI, 1.33–3.62), as well as higher rates of patient-reported symptom relief (p=0.019; OR, 1.55; 95% CI, 1.07–2.24), not requiring reintervention after the initial injection treatment (p=0.002; OR, 2.17; 95% CI, 1.33–3.53), and achieving the minimal clinically important difference in pain improvement (p=0.007; OR, 6.19; 95% CI, 1.63–23.42) when compared with all alternative nonoperative treatments [16].

The authors Jawanda et al. (2024) [17] performed a meta-analysis study to compare the efficacy of common intra-articular injections used in the treatment of KOA, including corticosteroid (CS), hyaluronic acid (HA), platelet-rich plasma (PRP), and bone marrow aspirate concentrate (BMAC). Level I to II randomized controlled trials with a minimum follow-up of 6 months that investigated the treatments of interest were included. A total of 48 studies comprising a total of 9,338 knees were included. The most studied intra-articular injection was HA (40.9%), followed by placebo (26.2%), PRP (21.5%), CS (8.8%), and then BMAC (2.5%). HA and PRP led to a significant improvement in pain compared with placebo. HA, PRP and BMAC led to a significant improvement in function scores when compared with a placebo. The surface under the cumulative rating curves (SUCRAs) of the interventions revealed that PRP, BMAC, and HA were the treatments most likely to improve pain and function, with overall SUCRA scores of 91.54, 76.46, and 53.12, respectively.

A recent meta-analysis study by Wang et al. (2024)

[18] evaluated the clinical efficacy of intra-articular PRP versus CS injections in the treatment of KOA. The efficacy of PRP versus CS injections across multiple studies was compared based on the weighted mean difference and 95% confidence interval for Visual Analog Scale (VAS) scores, Knee Osteoarthritis Outcome Score (KOOS), and Western Ontario and McMaster University Osteoarthritis Index (WOMAC). A total of 12 studies covered a total of 801 joints, of which 404 were in the PRP group and 397 in the CS group. The PRP group significantly reduced the VAS score than the CS group at 3 months ($p=0.003$), 6 months ($p=0.007$) and 9 months ($p<0.00001$); the PRP group significantly reduced the WOMAC total score compared to the CS group at 1 month ($p=0.01$), 6 months ($p=0.003$), 9 months ($p=0.005$) and 12 months ($p<0.00001$); At 3 and 6 months, the PRP group significantly increased the KOOS pain relief score (3 months: $p=0.002$, 6 months: $p < 0.00001$), KOOS activities of daily living scores (3 months: $p < 0.00001$, 6 months: $p<0.00001$), and KOOS quality of life score (3 months: $p = 0.003$, 6 months: $p < 0.00001$) compared with the CS group; the PRP group also significantly increased the KOOS sports score at 3 months compared with the CS group ($p=0.04$). The leukocyte-poor PRP (LP-PRP) group significantly reduced the VAS score compared with the CS group ($p = 0.04$).

Berrigan et al. (2025) [19] studied whether the platelet dose administered during a PRP injection for KOA affects clinical outcomes at 6 months. A total of 29 studies were analyzed. The mean platelet dose with a positive result was $5,500 \pm 474 \times 10^6$, while the 3 that did not show a positive difference had a mean platelet dose of $2,302 \pm 437 \times 10^6$ ($p < 0.01$). The positive studies had a mean platelet dose of $5,464 \pm 511$, while the studies that did not show a statistical difference had a mean platelet dose of $2,253 \pm 753 \times 10^6$ ($p < 0.05$).

In addition to these clinical findings, Tjandra et al. (2024) [20] highlighted that mesenchymal stem cells (MSCs) are promising for the treatment of KOA, potentially enhanced by their combination with PRP and HA. Based on this, these authors performed a meta-analysis and meta-regression study to evaluate the synergy of MSCs, PRP, and varying doses of HA from the perspective of Lysholm score, VAS score, KSS score, and WOMAC score. A total of 9 studies met the final inclusion criteria. The meta-analysis revealed a significant improvement in Lysholm score (17.89), a notable reduction in VAS score (-2.62), elevated KSS (29.59), and a reduced WOMAC score (-12.38). Arthroscopically guided high-dose subchondral application of primary synovial MSCs cultured in PRP medium and with HA effectively regenerates cartilage defects and improves clinical outcomes in early-stage osteoarthritis. A randomized clinical trial compared subjective outcomes and graft maturity in patients aged 16 to 45 years undergoing anterior cruciate ligament (ACL) surgery with and without postoperative intra-articular PRP injection. Participants were randomized 1:1 to the PRP group (n = 60), which received 3 doses of postoperative intra-articular PRP injection at monthly intervals, or to the control group (n=60), which received no postoperative PRP injection. The primary outcome was the mean score for 4 subscales of the Knee Injury and Osteoarthritis Outcome Score (KOOS4) (range, 0-100, with higher scores indicating better knee function and fewer symptoms) at 12 months postoperatively. Among the 120 randomized participants (mean age 29.0 years; 84 men (70%), 114 (95%) were available for analysis of the primary outcome. The mean KOOS4 scores at 12 months were 78.3 in the PRP group and 76.8 in the control group [21].

A randomized clinical trial investigated the variations in clinical efficacy among patients diagnosed with knee osteoarthritis who underwent intra-articular administration of platelet-rich plasma using single, triple, or quintuple injections. Patients with grade I– III knee osteoarthritis were randomly assigned to three groups: the PRP1 group, which received a single injection of platelet-rich plasma; the PRP3 group, which received three PRP injections one week apart; and the PRP5 group, which received five PRP injections one week apart. Of the total 120 participants, 106 (30 men and 76 women) completed the study. The PRP score WOMAC pain scores recorded significant improvements in all groups when compared to pretreatment levels. However, the application of 3 and 5 injections of platelet-rich plasma was substantially more effective than a single injection in reducing knee pain and stiffness, as well as improving physical function in patients with knee osteoarthritis. No statistically noticeable difference was observed between PRP3 and PRP5 at all follow-up intervals, and there was also no noticeable difference between 3 and 5 PRP injections. The use of three PRP injections is recommended in the treatment of patients with grade I–III knee osteoarthritis [22].

The authors Ghorbani et al. (2024) [23] investigated the therapeutic effects of intra-articular injection of PRP and HA in KOA through a randomized clinical trial. A total of 90 patients with KOA were randomly divided into two groups KOA and intra-articular PRP. The patients in both groups were followed for five months and different outcomes were recorded. The McMaster Index (WOMAC) evaluated all patients at rest and during movements. In the fifth month, the mean knee pain, stiffness, physical function, and finally total score in the PRP group were

significantly lower than in the HA group. The mean knee pain, stiffness, physical function and finally total score in the PRP group were significantly lower than in the HA group in all grades of osteoarthritis.

The authors Fossati et al. (2024) [24] evaluated the efficacy of combined intra-articular injections of PRP and HA in the treatment of mild to moderate KOA, compared with PRP and HA alone. A total of 174 patients were prospectively enrolled and randomized to undergo three intra-articular injections of HA or PRP or the combination of PRP and HA with a two-week washout period. All treatments proved to be effective in reducing pain and improving joint function. Analysis of covariance showed no statistically significant differences between the three groups for any of the outcome parameters investigated after 6 and 12 months.

Finally, one study analyzed the clinical efficacy of autologous PRP injection in the treatment of KOA and its influence on related biomarkers, such as interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and high-sensitivity C-reactive protein (hs-CRP). A total of 150 study subjects were randomly selected. The total effective rate of 94.67% (71/75) in the observation group was higher than that of 84.00% (63/75) in the other group ($p<0.05$). Before treatment, the comparison in IL-1β, TNF-α, hs-CRP, Lysholm knee joint score, and FMA scale score is with $p>0.05$. When the treatment period is 1 and 2 months, the levels of IL-1β, TNF-α, and hs-CRP within the group were lower than that before treatment, while the Lysholm knee joint score and FMA scale score were higher than that before treatment ($p<0.05$). When the treatment period is 1 and 2 months, the levels of IL-1β, TNF-α, hs-CRP, and the scores of knee joint Lysholm scale and FMA scale in the observation group were lower and higher than those in the other group, respectively ($p<0.05$). The use of autologous PRP in KOA can significantly improve its related biomarker levels, effectively improve knee joint function, and motor function, and have good clinical efficacy [25].

## Conclusion

It was concluded that platelet-rich plasma demonstrated a significant advantage over hyaluronic acid, as well as improved symptom relief, lower reintervention rates, and pain relief. At a minimum follow-up of 6 months, platelet-rich plasma was shown to significantly improve pain and function in patients with knee osteoarthritis compared with placebo. Furthermore, platelet-rich plasma exhibited the highest values compared to bone marrow aspirate concentrate, hyaluronic acid, and corticosteroids. Furthermore, arthroscopically guided high-dose subchondral injection of primary synovial mesenchymal stem cells cultured in platelet-rich plasma and hyaluronic acid medium can regenerate cartilage defects, improving clinical outcomes. Meta-analyses studies have shown that the benefits of platelet-rich plasma injections become apparent mainly in the medium to long-term management of clinical symptoms, including pain relief, improved quality of life of patients, increased activities of daily living, and improved sports capabilities. Clinical outcomes of platelet-rich plasma injections for knee osteoarthritis may be related to the higher platelet dose.

## CRediT

Author contributions: **Conceptualization -** João Paulo Rodrigues Pacheco, Yuri de Freitas Tobias, João Paulo Ramos de Morais; **Data curation-**João Paulo Rodrigues Pacheco, Yuri de Freitas Tobias, João Paulo Ramos de Morais; **Formal Analysis -** João Paulo Rodrigues Pacheco, Yuri de Freitas Tobias, João Paulo Ramos de Morais; **Investigation -** João Paulo Rodrigues Pacheco, Yuri de Freitas Tobias, João Paulo Ramos de Morais; **Methodology-**João Paulo Rodrigues Pacheco, Yuri de Freitas Tobias, João Paulo Ramos de Morais; **Project administration-**João Paulo Rodrigues Pacheco, Yuri de Freitas Tobias, João Paulo Ramos de Morais; **Supervision-** João Paulo Rodrigues Pacheco, Yuri de Freitas Tobias, João Paulo Ramos de Morais; **Writing - original draft-** João Paulo Rodrigues Pacheco, Yuri de Freitas Tobias, João Paulo Ramos de Morais; **Writing-review & editing-** João Paulo Rodrigues Pacheco, Yuri de Freitas Tobias, João Paulo Ramos de Morais.

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## Ethical Approval

Not applicable.

## Informed Consent

Not applicable.

## Funding

Not applicable.

## Data Sharing Statement

No additional data are available.

## Conflict of Interest

The authors declare no conflict of interest.

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