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The use of platelet-rich plasma injections in the treatment of knee osteoarthritis - review of the literature

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Abstract

Introduction: Knee osteoarthritis (KOA) is one of the most common degenerative joint diseases, affecting millions of people worldwide. It is characterized by progressive cartilage degradation, chronic pain, joint stiffness, and functional impairment. Traditional treatment methods, including pharmacotherapy and intra-articular injections of corticosteroids or hyaluronic acid, provide limited and often short-term relief. Platelet-rich plasma (PRP) has emerged as a promising regenerative therapy due to its high concentration of growth factors that may stimulate tissue healing and reduce inflammation.

Objective: The aim of this study is to review the latest literature on the use of platelet-rich plasma injections in patients with knee osteoarthritis.

Material and methods: A literature review was conducted on databases such as PubMed, Google Scholar, and SciSpace using the terms: "knee osteoarthritis", "platelet-rich plasma", "PRP injections", "intra-articular injections", "knee OA treatment".

Conclusions: Knee osteoarthritis is a highly prevalent condition that significantly impacts quality of life. Platelet-rich plasma has demonstrated positive effects on pain reduction and functional improvement in patients with KOA. PRP injections lead to superior outcomes compared to placebo and hyaluronic acid, with therapeutic effects lasting 12-24 months. However, there is lack of standardization in PRP preparation protocols, and further studies are necessary to establish optimal treatment parameters.

Keywords: platelet-rich plasma; knee osteoarthritis; PRP injections; intra-articular therapy; regenerative medicine

Introduction

Knee osteoarthritis (KOA) is a chronic, progressive degenerative disease affecting around 250 million people worldwide [1]. It is characterized by articular cartilage degradation, subchondral bone remodeling, synovial inflammation, and osteophyte formation [1]. This condition leads to chronic pain, joint stiffness, limited mobility, and significant deterioration in patients' quality of life. KOA affects not only physical function but also psychological well-being, social participation, and economic productivity.

Epidemiological evidence suggests that KOA is placing an increasing strain on healthcare systems worldwide. The prevalence increases with age, affecting approximately 10% of men

and 13% of women over 60 years of age [2]. However, recent epidemiological studies indicate that OA may be more widespread when radiographic findings are considered, with evidence present in up to 30–40% of individuals over 65 years of age [2].Identified risk factors include older age, female sex, obesity, prior joint injury, excessive mechanical stress, genetic susceptibility, joint malalignment, and a history of meniscal or ligament damage [2]. As populations age and obesity rates continue to climb worldwide, KOA incidence is projected to increase substantially, with more than 78 million adults in the United States expected to be affected by symptomatic OA by 2040 [2].

Pathophysiology of knee osteoarthritis

The pathophysiology of KOA involves complex interactions between mechanical stress, inflammatory mediators, and metabolic factors. Traditionally viewed as a "wear and tear" disease, KOA is now recognized as a whole-joint disease involving not only cartilage but also subchondral bone, synovium, menisci, ligaments, and periarticular muscles [1]. Cartilage breaks down due to an imbalance between tissue-building and tissue-breaking processes, driven by enzymes like matrix metalloproteinases (MMPs) and aggrecanases (ADAMTS) [1]. These enzymes degrade key cartilage components, including collagen type II and aggrecan, causing the cartilage to lose strength and function.

Pro-inflammatory cytokines such as interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) play central roles in disease progression by promoting chondrocyte apoptosis and inhibiting extracellular matrix synthesis [1]. These cytokines trigger more inflammatory mediators, driving a self-perpetuating cycle of inflammation and tissue destruction. The synovial membrane becomes inflamed, producing excess synovial fluid that causes joint effusion and pain. Subchondral bone remodels with higher turnover, sclerosis, and bone marrow lesions, linked to pain and disease progression.

Recent work highlights metabolic factors in OA, giving rise to metabolic osteoarthritis. Obesity adds mechanical stress and systemic inflammation via adipokines. Leptin, adiponectin, and other adipokines directly affect cartilage and promote joint inflammation. Metabolic syndrome components—diabetes, dyslipidemia, and hypertension—are linked to higher OA risk and progression, underscoring metabolic dysregulation’s role in disease development.

Clinical presentation and diagnosis

KOA often presents as gradually worsening knee pain with activity that eases with rest. Morning stiffness is typically under 30 minutes, helping distinguish OA from inflammatory arthritis. On exam, you may find joint line tenderness, crepitus, reduced motion, effusion, and, in advanced cases, deformity (varus/valgus). Functional limits include climbing stairs, long walks, and kneeling or squatting.

Diagnosis combines clinical criteria and imaging. Clinically, adults over 50 with morning stiffness under 30 minutes, crepitus, bony tenderness/enlargement, and no warmth support KOA. Weight-bearing X-rays (AP, lateral, and skyline views) assess structural changes, and the Kellgren-Lawrence scale (0–4) gauges radiographic severity- from grade 0 being normal and grade 4 showing large osteophytes, marked narrowing, severe sclerosis and definite deformity. MRI offers detailed cartilage, bone, and soft-tissue insights, mainly for research or complex cases. Biomarkers are under investigation but not yet standard in routine care.

Traditional treatment approaches

Traditional treatment methods for KOA include conservative approaches such as pharmacotherapy, physiotherapy, weight reduction, and surgical interventions in advanced cases [3]. Management is tailored to the patient and disease, using a stepwise approach from non-surgical to surgical interventions.

Non-pharmacological interventions form the foundation of OA management. Patient education, self-management, and structured exercise—including aerobic conditioning, quadriceps strengthening, and range-of-motion training—improve symptoms and function. In overweight and obese patients, weight reduction decreases knee joint load and improves symptoms, with a 10% body weight loss associated with significant pain relief and functional gains. Adjunctive measures such as braces, orthotics, and assistive devices can further support joint stability and mobility.

Pharmacological management includes oral and topical therapies. Acetaminophen (paracetamol) is first line for mild pain, though its effect is modest. NSAIDs provide greater analgesia but carry gastrointestinal, cardiovascular, and renal risks, while topical NSAIDs offer a safer alternative for localized knee OA with reduced systemic exposure. Duloxetine, a

serotonin-norepinephrine reuptake inhibitor, may be considered for centralized pain or comorbid depression.

Intra-articular injections represent an important treatment modality for patients with moderate symptom severity who have not responded adequately to conservative measures [4]. Corticosteroid injections offer rapid, short-term pain relief, usually lasting 4–6 weeks, but repeated use may damage cartilage; guidelines recommend no more than 3–4 injections per year [4]. Hyaluronic acid (HA) injections aim to restore joint viscoelasticity and provide lubrication. Clinical evidence regarding HA efficacy remains controversial, with some studies showing modest benefits while others demonstrate no superiority over placebo [4]. Differences in HA formulations, including molecular weight, concentration, and injection protocols, contribute to inconsistent clinical outcomes.

Surgical interventions are reserved for severe or refractory KOA. Arthroscopic debridement is no longer recommended due to lack of benefit. Osteotomy may be considered in younger patients with unicompartmental OA and malalignment. Partial or total knee arthroplasty provides definitive treatment for end-stage OA providing substantial pain relief and functional improvement but carries surgical risks, potential complications, and requires extensive rehabilitation.

Platelet-rich plasma (PRP)

In recent years, regenerative medicine, particularly platelet-rich plasma (PRP) therapy, has gained increasing interest as a potential treatment method for KOA [5]. Platelet-rich plasma (PRP) therapy shifts focus from symptom relief to potential biological regeneration, aiming for disease modification. PRP is an autologous blood product enriched with platelets and growth factors [6]. PRP is obtained by centrifuging the patient's blood to concentrate platelets, usually 3–5 times above baseline, occasionally up to 10-fold [6].

PRP therapy originated in oral and maxillofacial surgery in the 1990s and has since been applied in orthopedics, sports medicine, dermatology, and wound healing. Its rationale lies in platelets' alpha granules, which release growth factors that initiate and regulate tissue repair.

Growth factors and bioactive molecules in PRP

PRP contains bioactive molecules and growth factors essential for tissue repair. Key factors include platelet-derived growth factor (PDGF), which promotes collagen production, angiogenesis, and mesenchymal stem cell proliferation and migration [6,7]. PDGF exists in

multiple isoforms (PDGF-AA, PDGF-BB, PDGF-AB) with distinct biological activities and receptor binding affinities.

Transforming growth factor-beta (TGF-β) regulates endothelial, fibroblast, and osteoblast proliferation and promotes mesenchymal stem cell growth [6,7]. TGF-β promotes matrix synthesis, limits degradation, and supports immune regulation, stimulating chondrocyte growth and proteoglycan production in cartilage.

Insulin-like growth factor (IGF-1) promotes chondrocyte proliferation and matrix synthesis, enhances protein synthesis, and inhibits protein degradation [6,7]. IGF-1 works with other growth factors to support tissue regeneration. VEGF stimulates angiogenesis and increases vessel permeability, aiding nutrient supply to damaged tissue [6,7]. Although cartilage is avascular, VEGF may support angiogenesis in the synovium and subchondral bone.

Fibroblast growth factor (FGF) promotes cell proliferation, differentiation, and migration, and plays a role in angiogenesis [6,7]. Epidermal growth factor (EGF) promotes proliferation and differentiation of epithelial and mesenchymal cells, while connective tissue growth factor (CTGF) supports matrix production and tissue remodeling. PRP also contains platelet factor 4 (PF4), angiopoietin-1 (Ang-1), thrombospondin-1, and various cytokines and chemokines that regulate inflammation and immune responses.

Mechanism of action in knee osteoarthritis

The mechanism of action of PRP in the context of KOA is multifactorial and involves multiple biological processes working synergistically to promote tissue repair and reduce symptoms [7,8]. Understanding these mechanisms is crucial for optimizing treatment protocols and identifying patients most likely to benefit.

Firstly, PRP modulates inflammatory processes through reduction of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) and increase in anti-inflammatory mediators such as IL-10 and IL-1 receptor antagonist (IL-1Ra) [7,8]. This anti-inflammatory effect interrupts the cycle of cartilage degradation, with PRP growth factors inhibiting NF-κB–mediated cytokine production.

Secondly, PRP stimulates chondrocyte anabolism and extracellular matrix synthesis, promoting cartilage repair [7,8]. TGF-β and IGF-1 promote cartilage matrix gene expression including collagen type II (COL2A1) and aggrecan (ACAN) while suppressing catabolic genes such as matrix metalloproteinases (MMPs), favoring matrix preservation.

Thirdly, PRP both prevents chondrocyte apoptosis, maintaining existing cartilage cells, and enhances the synovial environment by regulating fluid composition and reducing inflammation [7,8]. In OA, PRP protects chondrocytes from apoptosis via PI3K/Akt and ERK1/2 signaling and simultaneously modulates the synovium, reducing inflammation and effusion while improving fluid quality and lubrication.

Additionally, PRP may modulate subchondral bone remodeling by influencing osteoblast and osteoclast activity, potentially reducing bone marrow lesions. Its effects on the whole joint, beyond cartilage, likely contribute to its clinical benefits.

PRP preparation and classification

Preparation methods

PRP preparation is based on centrifugation of whole blood to concentrate platelets, but protocols vary widely. Typically, 20–60 mL of peripheral venous blood is collected into citrate-based anticoagulants such as acid-citrate-dextrose (ACD) or sodium citrate, which can affect platelet activation and growth factor release. Centrifugation may be performed using single-spin or double-spin protocols. Single-spin methods are simpler but yield lower platelet concentrations and less control over leukocyte content, whereas double-spin protocols achieve higher platelet concentrations and more precise composition. Commercial PRP systems aim to standardize preparation but differ in centrifugation parameters and collection methods, significantly influencing platelet concentration, leukocyte content, and growth factor levels.

Classification systems

Several classification systems exist for PRP, including the PAW system, which categorizes preparations by platelet concentration, activation method, and leukocyte content.

PRP preparations can be classified as leukocyte-rich (LR-PRP) or leukocyte-poor (LP-PRP), with debate ongoing regarding which formulation is optimal for intra-articular use [9]. LR-PRP contains leukocytes, including neutrophils, which may offer antimicrobial effects but can also contribute to inflammation through cytokine and protease release.

LP-PRP, obtained by leukocyte reduction via centrifugation or filtration, achieves platelet concentrations of 3–5× baseline (≈200,000 to >1,000,000/μL) and may be preferable for joint use because of reduced inflammatory potential [9]. Comparative studies of LR-PRP and LP-

PRP show inconsistent results, suggesting that both leukocyte content and platelet concentration influence outcomes in a non-linear, application- and patient-dependent manner.
PRP protocols vary in activation method, using exogenous agents such as calcium chloride or thrombin to induce platelet degranulation, and in formulation as liquid PRP or platelet-rich fibrin, each with distinct release kinetics and biological properties [10]. Pre-activated PRP delivers growth factors immediately but risks premature release and degradation, whereas in situ activation by joint tissue contact allows slower, more sustained release. Likewise, liquid PRP spreads quickly within the joint, while platelet-rich fibrin forms a three-dimensional scaffold for prolonged growth factor release over days to weeks, though it is less commonly used in knee osteoarthritis.

Standardization challenges

The lack of standardization in PRP preparation represents a significant challenge in comparing clinical studies and establishing evidence-based treatment protocols. Different preparation methods may yield PRP products with variable platelet, leukocyte, and growth factor concentrations, which may influence clinical outcomes [10]. PRP heterogeneity limits assessment of efficacy and the development of standardized guidelines.
Standardization of PRP involves reporting standards, expert consensus, and proposed nomenclature, with guidelines from the ICMS and other organizations. Broad adoption is limited by varied commercial systems, clinical applications, and institutional practices. Quality control—including platelet counts, activation, growth factor levels, and sterility—is crucial but inconsistently applied. Emerging point-of-care devices may enable real-time assessment, improving consistency and protocol optimization.

Platelet-rich plasma injections in knee osteoarthritis

Many clinical studies have assessed PRP injections for knee osteoarthritis, generally reporting positive outcomes. Over the past decade, the evidence base has expanded to include randomized controlled trials (RCTs), systematic reviews, meta-analyses, and observational studies, collectively involving thousands of patients and strengthening guidance for clinical decision-making [11–29].

Efficacy compared to placebo and saline

Multiple studies show PRP is superior to placebo or saline for knee osteoarthritis, confirming efficacy beyond placebo. A 2021 meta-analysis by Belk et al. reported significant improvements in pain and function, with a mean WOMAC pain score reduction of –8.06 (P=0.004) [11]. This difference exceeds the minimal clinically important difference (MCID) for WOMAC pain, indicating a clinically meaningful, not just statistically significant, improvement.

Improvements were observed at 6–12 months post-injection, with PRP providing clinically meaningful pain relief, functional gains, and quality-of-life benefits across diverse patient ages, disease severities, and baseline functional levels [11].

Placebo-controlled trials are essential, since intra-articular injections can reduce pain by 20–30% through mechanical and psychological effects. PRP's superior outcomes confirm genuine biological efficacy beyond these non-specific responses.

Efficacy compared to hyaluronic acid

Comparing PRP and hyaluronic acid (HA) is important, as both treat knee osteoarthritis. Meta-analyses consistently show PRP provides greater pain relief and functional improvement across patient populations and follow-up durations.

Belk et al. (2023) reported that PRP showed significantly better outcomes than HA across multiple outcome measures, including pain, function, and stiffness subscales of the WOMAC score [12]. The mean difference in WOMAC pain scores favored PRP over HA (MD: -0.74, P<0.00001), indicating superior pain relief with PRP therapy [12]. While this difference may appear small numerically, it represents a clinically meaningful advantage that persists over time.

Furthermore, PRP demonstrated advantages in improving physical function and reducing stiffness compared to HA. Subgroup analyses revealed that these benefits were consistent across different PRP preparation protocols, injection regimens, and patient populations [12,13]. Some studies suggest its superiority over HA becomes more pronounced at longer follow-up, indicating potentially more durable effects.

The therapeutic effect of PRP appears to be more durable than HA, with sustained improvements observed at 12-month and even 24-month follow-up periods [13,14]. This durability is particularly relevant for clinical practice, as it may reduce the need for repeated injections and provide better long-term symptom control. Despite higher initial costs, PRP may be cost-effective compared to HA because its longer-lasting effects reduce the need for repeat treatments.

Studies comparing PRP with various HA formulations consistently show PRP's superiority, indicating its advantage reflects true biological effects rather than differences between HA products.

Dose-response relationship and optimal treatment protocols

Recent data indicate a dose-response relationship in PRP therapy for knee osteoarthritis, with higher platelet concentrations and multiple injections generally linked to better outcomes, though the effect may not be strictly linear [15,16].

Hooper et al. (2025) demonstrated that the total number of deliverable platelets is a critical factor determining treatment success, with higher platelet doses associated with greater pain reduction and functional improvement [22]. Data from several studies suggest that while increasing platelet dose usually improves results, there's a limit beyond which more platelets don't add extra benefit.

Bensa et al. (2025) confirmed that platelet concentration significantly influences clinical outcomes, with higher concentrations generally producing superior results [23]. However, there may be a limit to the advantages of higher platelet concentrations, with excessive levels providing no added benefit and possibly increasing side effects [23]. The concept of an optimal "therapeutic window" for platelet concentration is supported biologically, as excessive growth factor concentrations could potentially disrupt normal cellular regulation or cause unintended effects.

Regarding injection frequency, multiple studies have compared single versus multiple PRP injections, with most finding advantages for repeated administration. Yurtbay et al. (2022) found that multiple PRP injections (typically 2-3 injections administered at 2–4-week intervals) were superior to single injections in providing sustained pain relief and functional improvement at 2-year follow-up [21]. This indicates that repeated PRP injections may boost and extend therapeutic effects, potentially by maintaining growth factor exposure or counteracting OA progression [21].

The ideal PRP injection interval and volume are still unclear. Protocols commonly space injections 1–4 weeks apart, with some exploring maintenance doses every 6–12 months. Volumes typically range from 3–8 mL, where larger volumes may enhance distribution and growth factor delivery but can increase post-injection discomfort. The relationship between volume, platelet concentration, and total dose warrants further study.

Duration of therapeutic effects

The duration of PRP's effects is a key clinical consideration, influencing treatment planning, patient counseling, and cost-effectiveness. Studies report sustained benefits for 6–12 months, with some lasting 24 months or longer [14,17,24].

Shen et al. (2017) conducted a temporal analysis of PRP effects, demonstrating that pain reduction and functional improvements were maintained throughout the 12-month follow-up period [24]. Interestingly, PRP's effects may continue to build for several months after injection before gradually tapering, implying that its benefits emerge over time rather than providing instant symptom relief.

This durability of effect represents a significant advantage over corticosteroid injections, which typically provide only short-term relief lasting 4-8 weeks [24]. PRP appears to match or exceed the 6–12-month benefit of hyaluronic acid, with some evidence suggesting even more durable effects in certain patient groups.

The sustained effects of PRP may result from its potential disease-modifying actions, such as promoting cartilage repair, modulating inflammation, and improving synovial fluid quality[7,8]. These effects target underlying pathology rather than simply relieving symptoms, potentially slowing disease progression. However, PRP does not cure OA, and symptoms may eventually return as the disease advances.

Factors that may influence the duration of PRP effects include disease severity at baseline, with patients having less advanced OA potentially experiencing more durable benefits. Age, BMI, activity level, and concurrent treatments can also influence outcomes. Understanding these factors helps clinicians set realistic expectations and plan appropriate follow-up or retreatment strategies.

Safety and adverse events

PRP therapy for knee osteoarthritis has shown a favorable safety profile in multiple trials. Being autologous, it poses minimal risk of allergy, disease transmission, or immune reaction

[25], an important advantage compared to the potential adverse effects of NSAIDs and corticosteroids.

Most side effects of PRP are mild and short-lived, typically involving temporary pain or swelling at the injection site that resolves within a few days [25,26]. Around 10–30% of patients report post-injection discomfort, likely due to joint distension, inflammation, or platelet activation, which is usually manageable with ice and pain relievers and resolves within 48–72 hours.

Serious complications from PRP injections are rare. Most randomized trials find no difference in adverse events between PRP and control groups [25,26], and systematic reviews report very few serious issues, with no systemic reactions, infections, or thromboembolic events. When sterile technique is followed, the risk of infection is extremely low estimated at less than 1 in 10,000 injections similar to or lower than other intra-articular therapies.

The low incidence of complications, combined with the autologous nature of the treatment, makes PRP an attractive option for patients seeking minimally invasive therapies [25,26]. This safety profile is particularly advantageous for patients who may have contraindications to other treatments, such as those with cardiovascular risk factors precluding NSAID use, diabetes or immunosuppression increasing infection risk with corticosteroids, or concerns about potential cartilage damage with repeated steroid injections.

Emerging long-term data indicate that delayed adverse events are uncommon, and repeated PRP injections over several years have not increased complication rates. Nonetheless, continued monitoring and thorough reporting remain important as PRP use expands and protocols evolve.

Comparison with other regenerative therapies

Beyond comparisons with HA and placebo, recent studies have assessed PRP versus other regenerative therapies, including bone marrow aspirate concentrate (BMAC), mesenchymal stem cells (MSCs), and stromal vascular fraction (SVF). These comparisons help clarify the relative benefits of different biologic approaches and guide clinical decision-making in regenerative orthopedics.

Belk et al. (2023) found that both PRP and BMAC produced superior outcomes compared to HA, with no significant differences between PRP and BMAC in most outcome measures [28]. This suggests that many regenerative therapies may work through similar pathways, with overlapping growth factors and anti-inflammatory effects contributing to comparable

outcomes [28]. Both treatments rely on autologous preparations rich in growth factors and cells that can influence the joint environment and support tissue repair.

Comparisons of PRP with mesenchymal stem cells (MSCs) show mixed results, and MSCs' higher cost, complexity, and regulatory hurdles may limit their use. Combination PRP+MSC approaches are being explored to enhance MSC effects. Adipose-derived stromal vascular fraction (SVF) is another emerging option, with promising early results versus PRP, though direct comparisons are limited. Choice of therapy depends on availability, cost, regulation, patient preference, and individual factors.

Patient selection and prognostic factors

Understanding which patients are most likely to respond to PRP is key to optimizing therapy. While potential predictors have been proposed, further research is needed to develop reliable prediction tools.

Disease severity, as measured by Kellgren-Lawrence (KL) grading, appears to influence outcomes, with patients having mild to moderate OA (KL grades 1-3) generally responding better than those with severe disease (KL grade 4) [13,16]. Biologically, the capacity for tissue repair is greater in patients with milder OA, whereas those with advanced, bone-on-bone changes have limited potential for PRP and may be better treated surgically.

Age may influence PRP response, with some studies suggesting younger patients achieve greater improvements, possibly due to stronger regenerative capacity and cellular responsiveness [16]. However, findings are inconsistent, and older patients can still benefit. Age effects may also be influenced by comorbidities, activity level, and biological versus chronological age.

Body mass index (BMI) has been studied as a predictor of PRP response, with mixed findings. Some evidence suggests obesity may reduce efficacy, possibly due to greater joint stress, systemic inflammation, or altered pharmacokinetics [16], while other studies show no clear association. Regardless, weight management remains important in overall OA care.

Both platelet characteristics and individual genetic or growth factor profiles may contribute to the heterogeneity in PRP treatment responses [22]. PRP efficacy may be influenced by platelet function, affected by medications, smoking, or systemic conditions, and by genetic variations in growth factor receptors, inflammatory mediators, or matrix proteins. While platelet or genetic testing is not routinely performed, these factors highlight potential avenues for personalized PRP therapy in the future.

PRP response may be shaped by a combination of clinical and psychological factors, such as symptom duration, joint effusion, alignment abnormalities, meniscal lesions, and pain-related psychological traits. Multivariate prediction models incorporating multiple patient characteristics may be more useful than single factor analyses in clinical decision-making.

Limitations and controversies

Although evidence supporting PRP for KOA is increasing, several limitations and controversies remain. Recognizing these challenges is crucial for interpreting research, guiding future studies, and making informed clinical decisions.

The lack of standardization in PRP preparation protocols remains a major challenge, making it difficult to compare studies and establish optimal treatment parameters [9,10]. Variability in platelet concentration, leukocyte content, activation methods, and injection protocols contributes to heterogeneity in clinical outcomes [9,10]. Differences in PRP formulations complicate study comparisons and meta-analyses, since results may not be directly comparable. Standardization efforts are ongoing, but consistent adoption across studies remains limited.

The optimal PRP formulation for intra-articular use remains debated. While some advocate for leukocyte-poor PRP to minimize inflammatory responses, others suggest that leukocyte-rich PRP may provide additional benefits through enhanced antimicrobial properties and growth factor release [9]. Evidence on PRP formulation efficacy is mixed, suggesting that the optimal approach may vary based on individual patient characteristics, clinical context, and OA stage.

Clinical guidelines from different medical organizations vary in their recommendations regarding PRP therapy for KOA. Some guidelines support PRP use based on available evidence, while others remain cautious due to concerns about study heterogeneity and lack of long-term data [27]. Differences in guideline recommendations highlight ongoing debate and varying interpretations of the evidence [27]. For example, the American Academy of Orthopaedic Surgeons (AAOS) has been criticized for not recommending PRP despite positive studies, while Osteoarthritis Research Society International (OARSI) provides conditional support for its use.

Cost-effectiveness represents another important consideration. While PRP may provide superior outcomes compared to some alternatives, the higher cost of treatment and lack of insurance coverage in many healthcare systems may limit accessibility [27]. Preparing PRP

requires specialized equipment, trained personnel, and quality controls, which contribute to its cost. Thorough cost-effectiveness studies are needed to understand its economic value, considering factors like the duration of benefit, reduced need for other treatments, and the potential to postpone or avoid surgery [27].

The mechanism of action of PRP in OA, while theoretically sound, is not fully elucidated. Most evidence for biological effects comes from in vitro studies and animal models, which may not fully recapitulate human OA. More research is needed to understand how PRP affects different joint tissues in vivo, how effects vary with disease stage, and which components of PRP are most important for clinical efficacy.

The placebo response in PRP trials is notable, driven by the invasive procedure, patient expectations, and autologous blood use. While PRP shows clear benefits over saline injections, careful trial design and transparent communication with patients remain essential. Publication bias and small, single-center studies may overstate efficacy, making trial registration and full reporting critical.

Future directions

Optimizing PRP for KOA will require further investigation in multiple domains, from understanding underlying mechanisms to conducting clinical trials and evaluating health system impacts.

Standardizing PRP preparation is crucial for comparing clinical studies and developing evidence-based guidelines [9,10]. Expert consensus can help define optimal parameters, including platelet concentration, leukocyte content, activation methods, and injection protocols [9,10]. Achieving meaningful standardization will require international collaboration among clinicians, researchers, industry, and regulators, while point-of-care testing devices could support quality control and protocol optimization.

Predictive biomarkers could enable a more personalized approach to PRP therapy by identifying patients most likely to respond [16,22]. Potential markers include platelet count and function, genetic variants, inflammatory cytokine profiles, and imaging indicators such as cartilage integrity or synovitis. Combining these factors through machine learning could help guide treatment selection.

Studies with follow-up beyond two years are needed to fully assess the durability of PRP's effects and its potential to modify disease progression [14,17]. These should include structural measures, such as MRI assessment of cartilage, alongside long-term safety, need for

retreatment, surgical progression, and patient-reported outcomes. Registries capturing real-world PRP use could provide valuable complementary long-term data.

Comparative effectiveness research is needed to evaluate PRP versus other regenerative approaches, such as mesenchymal stem cells, stromal vascular fraction, and combination therapies, to guide treatment selection across patient groups [28]. Well-designed trials and studies of PRP in combination with supportive interventions may identify strategies that maximize outcomes.

Gaining a deeper understanding of PRP's mechanisms is vital for refining therapy. Investigating growth factor activity, cellular responses, and interactions with the OA joint, supported by advanced analytical techniques, can improve treatment protocols. Modified PRP formulations—through added factors, scaffolds, hydrogels, genetic enhancement, or lyophilization—offer opportunities to address current limitations and broaden clinical applications.

Understanding the economic value of PRP is important, including its cost-effectiveness compared with other treatments and the broader impact on productivity and healthcare use. Research should also explore barriers to access, such as insurance coverage, geographic limitations, and socioeconomic factors. Implementation studies can help translate evidence into practice by guiding clinician education, setting quality standards, integrating PRP into care pathways, and supporting shared decision-making with patients.

Conclusions

Knee osteoarthritis (KOA) is a common degenerative joint disease that lowers quality of life and strains healthcare systems. With aging and rising obesity, there is an urgent need for safe, effective, and accessible treatments that relieve symptoms and may slow progression.

Platelet-rich plasma (PRP) has shown consistent improvements in pain and function in KOA across many trials. Meta-analyses indicate PRP often outperforms placebo and hyaluronic acid, with benefits lasting roughly 12–24 months. Higher platelet concentrations and multiple injections tend to yield better results, though optimal parameters are not yet defined. PRP's mechanisms include anti-inflammatory effects, stimulation of repair, protection of cartilage, and favorable changes in the joint environment.

PRP generally has a favorable safety profile since it is autologous, minimizing allergy and infection risks. Serious adverse events are rare, making PRP a appealing minimally invasive option.

Challenges persist due to wide variability in PRP preparation and treatment protocols, which limits standardization and cross-study comparisons. Research is needed to identify the patients most likely to benefit, establish optimal dosing, and evaluate long-term disease-modifying effects.

Despite limitations, PRP is a promising option for mild-to-moderate KOA, especially after other conservative treatments have failed. It fits a personalized, multimodal care approach that combines biology with lifestyle, physical therapy, and appropriate medications.

Looking ahead, ongoing research aims to refine protocols, pinpoint ideal patients, and clarify potential disease-modifying benefits. As evidence grows, PRP could become a well-established component of OA care, offering a safe, biologically rational option that targets underlying pathology rather than just symptoms.

Disclosure

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Conceptualization: J.B and GŁ.; Methodology: S.C, E.D. and H.B.; Formal analysis: J.D., A.D. and K.B.; Investigation: A.W. and O.B.; Resources: S.C. and A.D.; Data curation: O.B. and K.B.; Writing - original draft preparation: A.W., H.B. and G.Ł.; Writing - review and editing: J.B., E.D. and J.D.; Visualization: S.C.; Supervision: J.B.; Project administration: J.B. All authors have read and agreed with the published version of the manuscript.

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