

General

Platelet-Rich Plasma and Stem Cell Therapies for Musculoskeletal Rehabilitation: Current Evidence on Dosing, Activation, and Functional Performance

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Background

Musculoskeletal disorders are one of the most common causes that lead to disability throughout the world and routinely present with only limited or short-term symptom relief following traditional treatments. Recent developments, such as platelet-rich plasma (PRP) and mesenchymal stem/stromal cell (MSC) interventions, are being used as regenerative biologic adjuncts in musculoskeletal medicine, yet significant variability exists in preparation strategies, activation methods, and dosing protocols. In addition, clinical interpretation remains limited by inconsistent biologic characterization and protocol variability.

Objective

A comprehensive review of current clinical evidence regarding dosing parameters, activation methods, and functional outcomes of PRP and MSC therapies for musculoskeletal recovery, focusing on protocol variability and clinical reproducibility.

Methods

A structured literature search was conducted using predefined search terms in PubMed, BMJ Journals, and SpringerLink to identify human clinical studies evaluating platelet-rich plasma and mesenchymal stem cell therapies for musculoskeletal conditions. Studies published between January 2016 and December 2025 were screened. An updated search extending through December 31, 2025 identified additional records published after February 2025; however, none met the predefined inclusion criteria.

Results

Five controlled trials featuring PRP or MSC techniques met inclusion criteria. Significant heterogeneity was observed across studies in biologic preparation techniques, leukocyte content, activation methods, cell expansion protocols, dosing regimens, and follow-up duration. While improvements in pain and functional scores were reported across both types of interventions, dose-response relationships were inconsistently evaluated and direct protocol comparisons were limited.

Conclusion

Although regenerative biologic therapies such as PRP and MSC are associated with improvements in musculoskeletal rehabilitation, significant variability and inconsistent reporting in dosing, activation, and preparation limit generalizability and reproducibility. Prospective clinical trials featuring standardized biologic characterization and uniform reporting frameworks are necessary to begin defining evidence-informed dosing recommendations and rehabilitation delivery.

INTRODUCTION

- **Contextualize the burden of musculoskeletal injuries and limitations of current rehabilitation strategies.**

Roughly 1.7 billion people worldwide experience musculoskeletal injuries.¹ These injuries are among the most frequently seen problems in clinical settings and can cause a wide variety of pain symptoms, as well as neurological issues like numbness, tingling, or muscle weakness. Individuals with these conditions often struggle to move around and may experience difficulty performing everyday tasks.

Conventional therapies may provide short-term symptom relief, but variability in durability and adverse-effect profiles has increased interest in orthobiologic therapies such as platelet-rich plasma (PRP) and mesenchymal stem/stromal cells (MSCs).²⁻⁵ Despite growing clinical utilization, the translation of these biologic therapies into consistent clinical practice is challenged by substantial heterogeneity in preparation methods, activation strategies, dosing parameters, and outcome reporting, which complicates interpretation across studies and limits reproducibility.⁵⁻⁷

The incorporation of physical therapy (PT) into a patient's treatment regimen is a common practice. While highlighting the positive outcomes of PT is beneficial, patient adherence is essential for optimal results. Given that PT is in high demand and necessitates active patient engagement, it is not unusual for some patients to struggle with adherence to their prescribed therapy.⁸

- **Introduce regenerative medicine approaches — PRP and stem cell therapies — and their growing clinical interest.**

Platelet-rich plasma (PRP) is a concentrated preparation of platelets that release various growth factors, thereby stimulating cellular proliferation and extracellular matrix remodeling. These processes are crucial components of the body's inherent repair mechanisms. Notable growth factors in PRP include platelet-derived growth factor (PDGF), transforming growth factor beta (TGF- β), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF). In addition to its capacity to promote proliferation, PRP is instrumental in mitigating inflammation driven by pro-inflammatory cytokines.⁴ The low immunogenicity risk associated with PRP injections makes them an appealing option for patients, given their demonstrated efficacy in improving recovery outcomes.

Mesenchymal stem/stromal cell (MSC) therapies have demonstrated significant effects on patient rehabilitation outcomes due to their specific mechanisms of action. MSCs secrete soluble factors, including growth factors, and facilitate the formation of new blood vessels, thereby supplying damaged tissue with essential nutrients and oxygen.⁵ Furthermore, through their capacity to reduce pro-inflammatory molecules, MSCs promote a transition of inflamed and damaged tissue toward a state of healing and regeneration.

- **Explain the gap in standardization for dosing, activation, and outcome measurement that this review seeks to address.**

Numerous studies have examined the roles of PRP and MSC; Such studies often emphasize pain and functional scores.^{6,7,9} Despite a significant increase in research on PRP and stem cell therapies over the past 20 years, substantial uncertainty remains regarding optimal dosing, preparation, and integration with rehabilitation, including dosing volume and frequency.¹⁰⁻¹⁴ The objective of this literature review is to investigate the effects of these treatments on patients' functional recovery and overall performance, with a focus on reported dosing approaches and rehabilitation-relevant outcomes

- **Conclude with a clear purpose statement and research question.**

This literature review was conducted to identify trends in the effective use of PRP and SCT. The findings aim to provide medical practitioners with guidance on developing comprehensive plans and methodologies for implementing these regenerative medicine techniques.

BACKGROUND / THEORETICAL FRAMEWORK

BIOLOGICAL BASIS OF TISSUE REGENERATION IN MUSCULOSKELETAL SYSTEMS

Wound healing is divided into four overlapping phases: hemostasis, inflammation, proliferation, and remodeling.¹⁵ These phases represent biological programs that restore tissue continuity and function. Hemostasis is the earliest response to tissue injury, rapidly activating hemostatic agents to prevent blood loss and providing a scaffold for subsequent cellular infiltration. The inflammatory phase begins immediately after injury alongside hemostasis. Macrophages are the key regulators, releasing cytokines and growth factors that initiate repair. During the proliferative phase, fibroblasts synthesize extracellular matrix, forming granulation tissue, while angiogenesis and epithelialization restore tissue structure and vascular supply. Growth factors such as TGF- β , VEGF, and PDGF regulate cell migration, proliferation, and neovascularization through intracellular signaling pathways. Lastly, the remodeling phase involves replacing type 3 collagen with type 1 collagen, thereby increasing tensile strength.¹⁵

PLATELET-RICH PLASMA (PRP): COMPOSITION AND MECHANISMS

Platelet-rich plasma is an autologous blood product that is acquired from plasma fractionation via centrifuging whole blood with a platelet concentration that is above normal physiological levels.¹⁶ There are two principal methods of producing PRP: the PRP method and the buffy-coat method. The PRP method uses fresh venous blood, which is then centrifuged to obtain platelet concentrate. The buffy-coat method uses whole blood stored at room temperature, which is then centrifuged into three layers: RBCs, platelets,

and white blood cells.¹⁶ It is later classified into leukocyte-rich and leukocyte-poor preparations. Leukocyte-rich PRP contains higher levels of white blood cells and is associated with increased levels of inflammatory cytokines. Leukocyte-poor PRP minimizes leukocytes to reduce inflammation.¹⁶

STEM CELL THERAPY: SOURCES, TYPES, AND MECHANISMS

Mesenchymal stem cells (MSCs) are multipotent stromal cells capable of self-renewal and differentiation into adipocytes, osteocytes, and chondrocytes. They are

low-immunogenic and can exert immunosuppression, making them ideal for cell therapy. Bone marrow-derived MSCs exhibit osteogenic and chondrogenic potential, but the yield is limited.¹⁷ Adipose-derived MSCs are the most abundant and exhibit extensive proliferative and immunomodulatory properties, while umbilical-derived MSCs exhibit high proliferative capacity and low immunomodulatory activity, posing minimal ethical concerns.¹⁷ MSCs contribute to tissue repair through paracrine signaling by excreting growth factors and cytokines, promoting angiogenesis, tissue repair, and extracellular matrix remodeling. Key factors include VEGF, IGF-1, and TGF- β , which all enhance cell survival and regeneration.¹⁷

SYNERGISTIC POTENTIAL OF PRP AND STEM CELL INTEGRATION

Preclinical and experimental studies suggest that PRP may support mesenchymal stem/stromal cell (MSC) viability, migration, and paracrine activity through growth factor-mediated mechanisms. However, clinical studies directly comparing combined PRP-MSC therapy with either modality alone in human populations remain limited. Accordingly, any potential additive or synergistic effects should be considered biologically plausible but not yet clinically established and must be interpreted cautiously.¹⁸

METHODS (FOR A NARRATIVE REVIEW)

STUDY DESIGN

This study was conducted as a structured narrative literature review aimed at evaluating dosing strategies, activation protocols, and functional rehabilitation outcomes associated with platelet-rich plasma (PRP) and mesenchymal stem/stromal cell (MSC) therapies in musculoskeletal conditions. This review was not designed as a systematic review or meta-analysis and did not follow PRISMA guidelines.

CONSENT STATEMENT

This literature review was granted exempt status by the NYIT College of Osteopathic Medicine Institutional Review Board. The IRB waived informed consent requirements as no human subjects were directly involved. No funding or financial compensation was received for this study.

SEARCH STRATEGY

A comprehensive literature search was conducted independently by two reviewers (A.O. and A.B.). The final search was performed on February 10, 2025. Electronic databases searched included PubMed/MEDLINE, BMJ Journals, and SpringerLink.

Search terms were developed by consensus and included combinations of the following keywords:

“platelet-rich plasma” OR “PRP”
 “mesenchymal stem cells” OR “MSC”
 “musculoskeletal” OR “osteoarthritis” OR “low back pain” OR “tendinopathy”
 “dose” OR “injection protocol” OR “activation” OR “functional outcome.”

The search was limited to studies published in English between January 2016 and February 2025.

STUDY SELECTION AND SCREENING PROCESS

Titles and abstracts identified through database searches were screened independently by both reviewers. Studies meeting preliminary eligibility criteria underwent full-text review for inclusion. Disagreements regarding study eligibility were resolved through discussion and consensus. Given the structured narrative design, no formal risk-of-bias scoring or quantitative synthesis was performed. Inclusion was restricted to controlled or prospective comparative studies that explicitly reported biologic preparation methods, activation strategies, and dosing parameters to improve interpretability across heterogeneous orthobiologic protocols and to ensure that biologic dosing, preparation, and activation parameters could be meaningfully compared and reproduced.

INCLUSION CRITERIA

Studies were included if they:

- Investigated PRP and/or MSC therapy for musculoskeletal conditions
- Included human participants
- Reported clinical outcomes related to pain and/or functional performance
- Provided details regarding injection technique, dosing parameters, preparation methods, or activation strategies
- Included controlled clinical trials or prospective comparative designs

EXCLUSION CRITERIA

Studies were excluded if they:

- Focused primarily on non-musculoskeletal conditions
- Were animal studies or in vitro mechanistic studies
- Were case reports or expert opinion articles
- Lacked clinical functional outcome data
- Were inaccessible in full-text format

RESULTS / LITERATURE REVIEW

PRP THERAPY: DOSING AND ACTIVATION CONSIDERATIONS

Article 1 Summary: (Department of Rehabilitation Medicine at St. Mary's Hospital/college of medicine- Platelet rich plasma injections for chronic nonspecific low back pain)

Researchers from the Department of Rehabilitation Medicine at St. Mary's Hospital conducted a double-blind, randomized controlled trial involving 34 patients with chronic non-specific low back pain that had persisted for more than three months. Participants were randomly assigned to receive either platelet-rich plasma (PRP) injections or lidocaine injections. Injections were given at the lumbopelvic ligament attachment points once a week for two weeks. This was followed by another two weeks of 15% glucose prolotherapy. Six months later, patients who received PRP reported greater pain relief than those who got lidocaine. These findings suggest that short-term PRP injections followed by glucose prolotherapy may provide clinically meaningful pain relief for patients with chronic non-specific low back pain.¹⁹

Article 2 Summary: (Post graduate Institution of medical education and Research in India- comparing the effects of steroid and PRP injections in ultrasound-guided Sacroiliac Joint injections for chronic low back pain)

Researchers from multiple postgraduate medical institutes in India conducted a randomized controlled trial comparing platelet-rich plasma (PRP) injections with corticosteroid injections for treating chronic low back pain associated with sacroiliac joint (SIJ) dysfunction. A total of forty participants were randomized into two groups: the PRP cohort received 3 mL of leukocyte-poor PRP activated with 0.5 mL of calcium chloride, whereas the control group received 1.5 mL of methylprednisolone, 1.5 mL of 2% lidocaine, and 0.5 mL of saline. At the three-month follow-up, the data indicated that a single administration of leukocyte-poor PRP activated with calcium chloride resulted in significantly greater and more sustained analgesic and functional improvements than corticosteroid injections in patients with SIJ-mediated chronic low back pain.²⁰

Synthesis: Discuss dose-response trends, growth factor release kinetics, and clinical recovery metrics.

Both studies highlight the significant impact of activation methods and growth factor kinetics on the therapeutic efficacy of platelet-rich plasma (PRP) in the management of chronic low back pain. Won et al. (2022) administered non-activated PRP to the lumbopelvic ligaments twice weekly, reporting progressive pain reduction and functional improvement over six months, attributable to the sustained release of growth factors.¹⁹ In contrast, Singla et al. (2017) delivered a single 3 mL leukocyte-poor PRP injection, activated with calcium chloride, into the sacroiliac joint (SIJ), resulting in a more rapid onset of pain relief and functional recovery by the three-month follow-up, which was primarily associated with an immediate, high-concentration re-

lease of growth factors.²⁰ Taken together, these results suggest a possible threshold effect in PRP treatment, though this inference is based on between-study comparisons rather than direct dose-response trials. Even single or lower-volume PRP injections were associated with meaningful clinical improvement. This suggests that higher doses or repeated injections may not always be necessary for patient benefit.

STEM CELL THERAPY: DOSE AND DELIVERY CONSIDERATIONS

Article 3 Summary: University of Navarra's medical centers, with collaboration from Salamanca Hospital and the Spanish national stem cell research network (TerCel) in Spain compared the effects of different doses of autologous bone marrow mesenchymal stem cells (MSC) and HA in the treatment of Knee osteoarthritis (OA).

Researchers in Spain conducted a study to compare the effects of bone marrow mesenchymal stromal cells (BM-MSCs) at two different doses with those of hyaluronic acid (HA) in treating knee osteoarthritis (OA).²¹ MSCs were obtained from each patient's own bone marrow (iliac crest), processed to isolate the cells, and then cultured in a nutrient medium supplemented with 5% platelet lysate and specific growth factors. After about two weeks, MSC colonies developed. Before injection, the cells were washed and suspended in Ringer's solution containing 1% human albumin. Patients were randomly assigned to three groups: one received only HA, one received a low dose of MSCs (10 million cells plus HA), and another received a high dose (100 million cells plus HA). Each participant received a single intra-articular knee injection and was subsequently monitored over a 12-month period through scheduled clinical assessments and imaging studies. Individuals treated with mesenchymal stem cells, particularly at higher doses, reported greater pain relief and improved knee mobility compared to those who received only hyaluronic acid. Radiological evaluations indicated that joint degeneration was less pronounced in the high-dose MSC group.²¹

Article 4 Summary: (Randomized controlled trial comparing mesenchymal stem cells and hyaluronic acid in knee osteoarthritis)

Researchers from multiple medical institutions in China conducted a randomized controlled trial comparing intra-articular autologous bone marrow-derived mesenchymal stem cells (BM-MSCs) with hyaluronic acid (HA) in surgically naïve patients with knee osteoarthritis. Patients receiving BM-MSC injections (6 mL at 1×10^6 cells/mL) demonstrated significant reductions in pain, as measured by the Visual Analog Scale (VAS), along with improvements in functional outcomes assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Improvements in patient-reported quality-of-life measures were also observed during follow-up. These findings suggest that appropriately dosed intra-articular MSC therapy may confer functional benefits in degenerative knee osteoarthritis, though interpretation remains limited by study size and protocol heterogeneity.²²

Article 5 Summary: A study conducted in South Korea focused on determining the efficacy of Adipose Tissue-Derived MSCs for knee osteoarthritis.

A study was conducted by Yonsei University College of Medicine to evaluate the benefits of utilizing adipose tissue-derived mesenchymal stem cells (MSCs) for knee osteoarthritis. At 6 month follow-up, patients who received AD-MSC injections (3 mL at 1×10^8 cells) demonstrated significant improvements in pain, stiffness, and physical function subscores with an average 55% reduction in total WOMAC score.²³ In contrast, the control group which received normal saline injection showed no significant clinical improvement. These findings help suggest the utilization of autologous AD-MSCs in an outpatient setting in the functional improvement and stabilization of cartilage degeneration in patients with knee osteoarthritis.²³

Synthesis: Dose-Dependent Effects of Intra-Articular MSC Therapy on Musculoskeletal Functional Outcomes

All three studies demonstrated improvements in pain and functional outcomes in patients with knee osteoarthritis following intra-articular mesenchymal stem cell (MSC) therapy, with outcomes influenced by cell dose, cellular source, and protocol variability.²¹⁻²³ These findings collectively suggest possible clinical benefit, particularly in optimizing functional performance and symptom control, but remain limited by protocol variability.

Lamo-Espinosa et al. reported dose-dependent effects of autologous bone marrow-derived MSCs (BM-MSCs), with higher MSC concentrations associated with greater reductions in pain and WOMAC scores.²¹ Similarly, a randomized controlled trial from China demonstrated significant improvements in pain (VAS), function, and quality-of-life measures following a single intra-articular BM-MSC injection.²² Although the absolute dosage differed in both studies, functional gains remained significant compared to hyaluronic acid (HA) controls, suggesting the therapeutic potential of MSC therapy even at moderate concentrations. However, despite both studies expanding upon the idea of potential benefits of local MSC delivery for musculoskeletal rehabilitation, heterogeneity in preparation techniques, total cell counts, and follow-up duration limits direct comparison and underscores the need for standardized protocols and larger clinical trials.^{21,22}

Expanding beyond bone marrow-derived sources was the Yonsei University evaluation of adipose tissue-derived MSCs (AD-MSCs) administered at a higher total cell count, resulting in a significant reduction in total WOMAC score and improvements in pain, stiffness, and physical function.²³ These findings suggest that both bone marrow-derived as well as adipose-derived MSCs may offer comparable functional improvements in outpatient settings. The use of adipose tissue as a cellular source as opposed to a painful bone marrow harvest also introduces considerations regarding ease of MSC harvest, cell yield, and scalability in regenerative rehabilitation protocols. Taken collectively, these studies suggest that intra-articular MSC therapy may confer measurable improvements in pain and functional performance in knee osteoarthritis; however, evidence for dose-dependent effects is derived primarily from

individual trials rather than direct head-to-head comparisons across studies. Variability in dosing strategies, cellular source, MSC expansion protocols, and study design limits cross-study inference and precludes definitive conclusions regarding optimal dosing thresholds, underscoring the need for standardized biologic preparation methods and larger, longitudinal trials.²¹⁻²³

DISCUSSION

COMPARATIVE ANALYSIS OF DOSING AND ACTIVATION PROTOCOLS

Across reviewed studies, there has been a lack of standardized protocols, with considerable variability in platelet concentration, stem cell dose, and activation strategies.¹⁹⁻²³ There has also been a variation among PRP preparations regarding platelet concentration and leucocyte content. In addition, the activation methods used in the studies varied, with some protocols relying on endogenous activation via tissue collagen exposure, while others used exogenous agents such as calcium chloride or thrombin. These factors influence inflammatory responses and the kinetics of growth factor release, thereby causing Dose-response relationships to remain inferential rather than experimentally defined.

Similar to MSC studies, there has been variability in cell source, expansion techniques, injected cell counts, and dosage. MSC expansion protocols were also inconsistently reported, limiting potential trends or findings to be extrapolated from available data. This variability complicates direct comparisons across studies and renders dose-response relationships unknown. The lack of uniformity in reporting standards creates challenges for protocol reproducibility and interpretation across different studies. This emphasizes the need for consensus guidelines on biologic characterization and dosing. Ultimately, without standardized biologic characterization, observed clinical improvements cannot be reliably attributed to specific dosing or preparation parameters.

MECHANISTIC INSIGHTS AND BIOLOGICAL RATIONALE

Despite protocol heterogeneity, the biological rationale underlying PRP and MSC therapies remains consistent across studies.¹⁹⁻²³ PRP provides a concentrated domain of growth factors that regulate inflammatory responses, promote angiogenesis, and stimulate local cell proliferation. Activation methods can affect tissue-healing cascades and biomechanical recovery by influencing the temporal release of growth factors.¹⁹⁻²³

It was observed that benefits provided by MSC therapies were mostly correlated with their paracrine signaling rather than direct engraftment. Paracrine signaling mediates the secretion of anti-inflammatory cytokines and trophic factors that modulate tissue repair and the immune response. Preclinical data suggest that platelet-rich plasma may enhance mesenchymal stem/stromal cell viability, proliferation, and differentiation; however, comparative human tri-

als directly evaluating combined PRP–MSC therapy versus either modality alone are lacking, and any clinical synergy therefore remains hypothetical.

CLINICAL TRANSLATION AND REHABILITATION INTEGRATION

From a rehabilitation perspective, most studies have naturally targeted chronic conditions^{19–23}; however, current evidence does not allow clear determination of optimal patient selection, timing of intervention, or integration into rehabilitation protocols. Implementing rehabilitation protocols becomes essential for clinical translation as biological therapies may need mechanical loading and neuromuscular retraining to translate cellular effects into functional gains. For physical medicine and rehabilitation (PM&R) physicians and physical therapists, practical considerations should include procedural timing and categorization of post-injection rehabilitation; ultimately however, in the reviewed studies, post-injection rehabilitation was inconsistently described and frequently left to clinician discretion, limiting clinical reproducibility. Coordination efforts may include strategies such as gradual loading following injections, based on clinical judgment and patient tolerance to enhance tissue remodeling while minimizing the risk of reinjury.

CHALLENGES AND LIMITATIONS

Several limitations hinder the interpretation of current evidence for platelet-rich plasma (PRP) and mesenchymal stem cell (MSC) therapies in musculoskeletal rehabilitation. This is mainly due to substantial biological heterogeneity, significant reporting variability, and methodological weaknesses across studies. These factors are culprits in limiting cross-study comparisons, meta-analytic synthesis, and clinical reproducibility.

Marked heterogeneity in biological preparation protocols is a significant challenge. For PRP, centrifugation techniques vary considerably between studies, including differences in spin speed, duration, single- versus double-spin systems, and commercial versus manual preparation kits.²⁴ These variations directly influence platelet concentration, leukocyte content, and final injectate composition. Similarly, MSC-based therapies demonstrate wide variability in cell source (bone marrow, adipose tissue,

umbilical-derived), isolation techniques, and culture expansion methods.²⁵ Reported MSC cell counts vary by orders of magnitude between studies, ranging from minimally manipulated concentrates to extensively culture-expanded products.²⁶ This degree of biological variability limits confidence in dose-response conclusions and complicates efforts to define optimal therapeutic thresholds.

In addition to biological heterogeneity, inconsistent reporting further hinders interpretation. Many studies lack reporting on platelet concentrations or fold increases above baseline, making it difficult to evaluate dose-dependent effects or replicate preparation protocols.²⁷ Rehabilitation protocols following injection are also poorly documented in many trials, with key factors such as weight-bearing restric-

tions, physical therapy intensity, and return-to-sport timelines often neglected in reporting.²⁸ Isolating the biological contribution of PRP or MSC therapy in rehabilitation becomes increasingly challenging without this key provision of documented post-procedure regimens. Adverse event reporting is similarly inconsistent, with complications often being broadly categorized.²⁹

Methodological limitations further weaken the available evidence from clinical studies.

Many studies feature small sample sizes that limit statistical robustness and increase susceptibility to type II error.³⁰ Follow-up durations are frequently inconsistent, restricting assessment of durability of benefit and long-term safety.²⁹ Direct head-to-head comparisons of different dosing regimens, activation methods, or preparation techniques are also notably absent from most analyses,³¹ inhibiting proper study of how these factors influence outcomes and leading and leading recommendations regarding optimization to be largely inferential rather than evidence-driven.

Finally, as a structured narrative review, the authors acknowledge this study as lacking formal risk-of-bias assessment or meta-analytic synthesis, which limits quantitative interpretation. While this format is intended to enable broad thematic synthesis and discussion of protocol variability, it does not provide pooled effect size estimates or graded certainty of evidence. Therefore, conclusions drawn should be interpreted as qualitative appraisal rather than definitive comparative efficacy or quantitative optimization.

FUTURE DIRECTIONS

PROTOCOL STANDARDIZATION

There are no established guidelines for biologic therapy in musculoskeletal rehabilitation, as seen by variations in PRP preparation and administration techniques among the five trials.²³ PRP processing techniques, injection volume, dosing frequency, and therapy duration were all shown to vary. Instead of using regular multi-dose regimens, most studies used single- or limited-dose regimens. Platelet content, leukocyte composition, and activation methods were inconsistently reported, even though each study provided a basic explanation of PRP delivery.²³ Direct comparisons between other studies are hampered by such inconsistencies. Additionally, post-injection care procedures were delivered inconsistently and often left to the doctors' discretion rather than following recognized rehabilitation routes.^{19–23} The early and developing nature of biologic therapy standardization is further highlighted by the scarcity of suitable MSC clinical studies that meet the inclusion criteria. To increase repeatability and enable the evidence-based clinical application of biologic therapies in musculoskeletal rehabilitation, our findings collectively highlight the need for future research to adopt uniform reporting standards and protocol frameworks.^{19–23}

PERSONALIZED REHABILITATION

Across included studies, post-treatment rehabilitation was individualized, as most PRP studies allowed patients to return to activity based on functional improvement and pain tolerance.¹⁹⁻²³ Various recommendations included brief rest periods and gradual progression of physical activity. Such individualized approaches may lead to heterogeneous reporting outcomes, as each patient responds differently to treatment. In contrast, MSC therapy is underutilized in rehabilitation settings, underscoring the need for future research.¹⁹⁻²³

RESEARCH PRIORITIES

While only three RCTs were able to be utilized in this literature review, shared trends in administration, dosage, and implementation of PRP therapy suggest that future long-term RCTs and head-to-head studies could be conducted to determine a comprehensive set of treatment regulations and patient selection criteria to further promote the standardized implementation of PRP in addressing musculoskeletal rehabilitation.¹⁹⁻²¹ The variations among injection protocols, patient selection criteria, and reported outcome measures underscore the need for future long-term RCTs to better compare and define optimal treatment frameworks.¹⁹⁻²¹ In addition, there is a need for high-quality

randomized clinical trials using MSCs to evaluate MSC therapy within rehabilitation-focused frameworks.²¹⁻²³

CONCLUSION

As featured in all five articles, current evidence suggests possible clinical benefit; however, heterogeneity in preparation, dosing, activation, and outcome reporting precludes definitive protocol recommendations. Activation strategy appears to influence outcomes through effects on growth factor release kinetics, though conclusions remain limited by study heterogeneity. When integrated with rehabilitation, PRP may plausibly augment MSC activity based on mechanistic rationale; however, clinical confirmation of synergistic effects in comparative human trials is currently lacking. Overall, heterogeneity in biologic preparation, dosing strategies, activation methods, rehabilitation integration, outcome measures, and follow-up duration limits cross-study comparability and reproducibility, underscoring the need for standardized biologic characterization, consistent dosing frameworks, and transparent reporting in future clinical trials.

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Table 1. Detailed Characteristics of Included Clinical Studies.

Study	n	Design	Biologic Type & Preparation	Activation	Dose / Volume	# Injections	Follow-up	Primary Functional Outcomes	Key Result
Won et al., 2022 ¹⁹	30 (14 PRP, 16 lidocaine)	Double-blind RCT	Autologous Platelet-Rich Plasma (PRP)	No exogenous activation reported	~5–6 mL PRP per patient per session	2 PRP injections	6 months	VAS, ODI, RMDQ	Significant pain reduction at 6 months
Singla et al., 2017 ²⁰	40 (randomized into two groups; PRP vs steroid)	PROBE randomized controlled trial	Leukocyte-free platelet-rich plasma (PRP)	Calcium chloride activation (0.5 mL added)	3 mL leukocyte-free PRP + 0.5 mL calcium chloride	Single injection	3 months	VAS, MODQ, SF-12	significantly greater pain reduction compared with steroid
Lamo-Espinosa et al., 2016 ²¹	30 patients randomized	Randomized controlled trial (active control)	Autologous BM-MSCs	No biologic activation reported	1×10^7 - 1×10^8 cells in 1.5 mL LRS + 4 mL HA; Control: 60 mg HA in 4 mL	Single intra-articular injection	12 months	VAS, WOMAC, Knee range of motion (goniometer), X-ray, MRI using WORMS protocol	Significant and sustained pain reduction with BM-MSCs vs HA alone
Ho et al., 2022 ²²	20 (10 BM-MSC, 10 HA)	Randomized controlled trial	Autologous BM-MSCs	No biologic activation reported	6 mL intra-articular injection at 1×10^6 cells/mL	Single intra-articular injection	12 months	VAS, WOMAC, SF-36, KSS, KSFS; MRI T2 mapping (secondary)	BM-MSCs significantly reduced pain, improved WOMAC, improved SF-36
Lee et al., 2019 ²³	24 (12 AD-MSC, 12 control)	Randomized controlled trial	Autologous AD-MSCs	None reported	1×10^8 cells in 3 mL saline	Single intra-articular injection	6 months	VAS, WOMAC, KOOS, ROM, MRI cartilage defect size	VAS and KOOS improved, WOMAC improved 55% at 6 months in MSC group

Table 2. Dosing and activation parameters across studies.

Study	Leukocyte Content	Platelet Conc.	Cell Source	Expansion Method	Injection Site	Rehab Protocol Reported?	Adverse Events Reported?
Won et al., 2022 ¹⁹	Not applicable	Not reported	Autologous peripheral blood	Double-spin centrifugation	Tenderness points in lumbosacral spine and lumbopelvic ligaments/region	None reported	No severe adverse events; transient post-injection pain in 2 PRP patients and 3 control patients
Singla et al., 2017 ²⁰	Leukocyte-free PRP	$2.94 \pm 1.43 \times 10^9$ platelets (≈ 2.94 billion platelets in final 3 mL preparation)	Autologous peripheral whole blood	No cell expansion.	Ultrasoundguided sacroiliac joint (SIJ) injection	None reported. NSAIDs discontinued.	No serious adverse events; Higher incidence of transient post-injection pain/stiffness in PRP group (resolved ~ 2 days)
Lamo-Espinosa et al., 2016 ²¹	Not applicable	Not applicable (no PRP used)	Autologous bone marrow aspirate	In vitro expansion under GMP conditions	Intra-articular knee injection via lateral patellar approach	None reported	No serious adverse events; transient post-injection pain reported in some patients
Ho et al., 2022 ²²	Not applicable	Not applicable (no PRP used)	Autologous bone marrow-derived mesenchymal stem cells	in vitro expansion using Ficoll density separation	Intra-articular knee injection via lateral parapatellar approach	No restriction on medication, treatment, or activity before or after intervention	No complications observed; one patient required repeat bone marrow aspiration due to insufficient initial yield
Lee et al., 2019 ²³	Not applicable	Not applicable (no PRP used)	Autologous adipose tissue	Culture expansion in keratinocyte-SFM-based media with growth factors	Ultrasoundguided Intra-articular injection into the knee joint	None reported	Arthralgia (most common), Joint effusion; no serious adverse events

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