

## Effects of Plasma-Rich Protein in Musculoskeletal Injuries; Insights into Inflammatory Markers, Growth Factors and Healing: A Narrative Review

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### Abstract

This narrative review was planned to explore the efficacy of plasma-rich protein in musculoskeletal injuries, emphasising its impact on inflammatory markers, growth factors and the healing process. Musculoskeletal disorders pose a significant global health concern, with the plasma-rich protein therapy emerging as a promising rehabilitative technique due to its potential to enhance healing. The therapy utilises the patients' cells to stimulate growth, repair tissues, and modulate inflammation, offering a shift towards patient-friendly, non-hospitalised treatment. Through the modulation of inflammatory phases, stimulation of proliferative phases, and enhancement of remodelling phases, the plasma-rich protein therapy contributes to the expedited healing of musculoskeletal injuries. Clinical evidence supports its efficacy in reducing recovery time and managing pain, underscoring its therapeutic potential in musculoskeletal rehabilitation.

**Keywords:** Plasma-rich protein, Musculoskeletal injuries, Inflammatory markers, Growth factors, Musculoskeletal healing.

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### Introduction

Musculoskeletal injuries represent a significant global health burden, affecting millions of people worldwide, leading to severe long-term pain and physical disability. These injuries, particularly common among athletes, range from muscle and joint to tendon, ligament, nerve and bone issues, collectively referred to as musculoskeletal disorders (MSDs).<sup>1</sup> MSDs are the primary cause of disability, attributed to over 150 diseases and syndromes that diminish mobility, function and quality of life (QOL). In the United Kingdom, work-related MSDs (WMSDs) were recognised as the most common occupational diseases,<sup>2</sup>

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while in the United States, they constituted a significant portion of workers' compensation claims and were responsible for substantial worktime losses.<sup>3</sup> These disorders not only affect QOL of the affected individuals, but also impose a considerable economic burden on society.<sup>4</sup> As such, there is a need to address these conditions through effective rehabilitation measures.<sup>2,3</sup> Similarly, the prevalence of musculoskeletal injuries, alongside the advancement in imaging methods, like ultrasonography and magnetic resonance imaging (MRI), has illuminated the need for innovative rehabilitation strategies.<sup>5</sup> Among the innovative approaches, rehabilitation based on plasma-rich protein (PRP) has emerged as a promising avenue.

The current narrative review was planned to explore available literature on the role of PRP in musculoskeletal injuries through the modulation of inflammatory markers, facilitating growth factors, and enhancing healing components.

### PRP-based rehabilitation in musculoskeletal injuries

In recent years, the appeal of biological agents, particularly PRP, as innovative therapies for MSD has surged, both as standalone non-operative treatments and as supplements to surgical interventions.<sup>6,7</sup> PRP therapy, a cornerstone of regenerative medicine, leverages the patients' own cells to treat various conditions, with a special emphasis on growth factors and anti-inflammatory mediators. These factors are critical for promoting growth, tissue repair, and wound healing. They also play a significant role in the migration and differentiation of mesenchymal and epithelial cells by enhancing collagen and matrix synthesis, further underlining the therapeutic potential of PRP in managing a broad spectrum of injuries.<sup>8</sup> Extensive research has delved into PRP's potential to promote healing through the involvement of multiple mechanisms, highlighting PRP's pivotal role in clinical settings.<sup>6,7</sup> For musculoskeletal injuries, PRP therapy has gained recognition as an effective treatment, especially for its capability to expedite the healing process. The application of PRP therapy underscores a shift towards more patient-friendly, non-hospitalised treatments that promise a faster return to normalcy for individuals suffering from musculoskeletal injuries.<sup>9,10</sup>

### Classification of PRP

The PRP can be prepared by a variety of preparation techniques<sup>11</sup> that can be divided into four classes based on their cellular content and fibrin network.<sup>12</sup> This classification is also supported by a multidisciplinary consensus conference, and provides a crucial framework for the standardisation and comparison of PRP research.<sup>13</sup>

- i. Pure PRP (P-PRP), or leukocyte-poor PRP, products are characterised by the absence of leukocytes, and possess a low-density fibrin network once activated. These preparations are designed to promote healing without the inflammatory response typically associated with leukocyte presence.
- ii. Leukocyte- and PRP (L-PRP) products contain leukocytes and a low-density fibrin network upon activation. This category includes the most diverse range of commercial and experimental systems. These protocols, often necessitating specific kits, target minimal handling of blood samples and maximal standardisation of the PRP preparations.
- iii. Pure platelet-rich fibrin (P-PRF), or leukocyte-poor PRF, products lack leukocytes, and are characterised by a high-density fibrin network. P-PRF exists only in a highly activated gel form, making it unsuitable for injection or use as conventional fibrin glues.
- iv. Leukocyte and PRF (L-PRF), or second-generation PRP, products incorporate leukocytes and exhibit a high-density fibrin network. These preparations are recognised for their enriched content, potentially offering enhanced healing properties due to the synergistic effects of growth factors and leukocytes.<sup>12</sup>

### Role of inflammatory markers and growth factors in PRP

In musculoskeletal injuries, PRP therapy's mechanism involves an array of components rich in proteins and growth factors found within platelets that significantly contribute to the healing process. It includes platelet-derived growth factors alpha-alpha (PDGF $\alpha\alpha$ ), PDGF beta-beta ( $\beta\beta$ ) and PDGF $\alpha\beta$ , transforming growth factor  $\beta_1$  (TGF $\beta_1$ ) and TGF $\beta_2$  and vascular endothelial growth factor (VEGF), among others.<sup>14</sup> These elements are instrumental in orchestrating the repair and regeneration of tissues. For instance, TGF $\beta_1$ , alongside other growth factors, such as PDGF, plays a role in cell activation and muscle fibrosis regulation.<sup>15</sup> Research has also highlighted the critical role of other growth factors, such as insulin-like growth factor-1 (IGF-1), hepatocyte growth factor (HGF), and fibroblast growth factor-2 (FGF-2), in muscle regeneration and myogenesis. These factors have shown promising results in

enhancing muscle recovery through various mechanisms. In vitro studies have demonstrated IGF-1's capability to stimulate myoblast proliferation and differentiation, thereby aiding muscle regeneration. Similarly, in vivo research has found that FGF-2 can improve the diameter and number of regenerating muscle fibres, while HGF activates quiescent satellite cells.<sup>16-18</sup>

The efficacy of PRP also extends beyond tissue repair to the modulation of inflammation and pain management, possibly through its influence on inflammatory pathways. PRP contains interleukins (IL), such as IL-1, IL-6, IL-7 and IL-10, which possess both pro- and anti-inflammatory properties.<sup>19</sup> A study examining the effects of PRP on gastrocnemius muscle tears observed that PRP not only expedited muscle healing, but also reduced the presence of pro-inflammatory and apoptotic cells, marking a significant advance in our understanding of PRP's therapeutic potential.<sup>20,21</sup>

### Mechanism of PRP in the healing of musculoskeletal injuries

The healing of musculoskeletal injuries involves a well-orchestrated series of biological processes, categorised into three overlapping phases: inflammation, proliferation, and remodelling. PRP therapy influences each of these phases, thereby enhancing the natural healing process.

#### Modulation of the inflammatory phase

The initial response to tissue injury is characterised by inflammation, intended to eliminate debris and prepare the wound bed for healing. However, excessive inflammation can delay healing and lead to fibrotic tissue formation.<sup>22</sup> PRP modulates the inflammatory phase by releasing anti-inflammatory cytokines, such as IL-1 receptor antagonist (IL-1ra), which mitigate the detrimental effects of pro-inflammatory cytokines. Moreover, the growth factors in PRP recruit reparative cells to the injury site, initiating the healing process.<sup>23,24</sup>

#### Stimulation of the proliferative phase

The proliferation phase is characterised by the formation of new blood vessels (angiogenesis), the production of granulation tissue, and the recruitment of progenitor cells necessary for tissue regeneration.<sup>25</sup> PRP therapy significantly enhances this phase through the action of growth factors, such as PDGF, VEGF and FGF. These molecules stimulate endothelial cells, fibroblasts and other resident cells to proliferate and migrate to the site of injury, promoting the formation of new blood vessels and granulation tissue. Additionally, PRP induces the differentiation of stem cells into musculoskeletal cells, such as chondrocytes and osteoblasts, contributing to the

regeneration of cartilage and bone, respectively.<sup>26,27</sup>

### Enhancement of the remodelling phase

The final phase of healing involves the remodelling of granulation tissue into mature tissue, with the restoration of tissue structure and function. TGF- $\beta$  plays a critical role in this phase by stimulating the synthesis of collagen and other components of the extracellular matrix, which provide structural support to the newly-formed tissue.<sup>28</sup> PRP also contributes to the alignment and organisation of collagen fibres, enhancing the mechanical properties of the repaired tissue and reducing the risk of re-injury.<sup>27</sup>

### Clinical evidence of PRP in musculoskeletal healing

There are several studies that support the effectiveness of PRP in speeding up recovery, managing pain, and enabling a faster return to work activities in musculoskeletal injuries (Table). Rossi et al. made a comparison between recreational and competitive athletes treated for acute grade 2 muscle injuries with either conservative measures alone or augmented with PRP.<sup>20</sup> The study, involving 34 patients in the PRP group and 38 in the control group, revealed a significant reduction in the mean time to return to play by approximately four days in favour of the PRP group (21.1 days vs. 25 days,  $p=0.001$ ), though no significant difference in pain reduction or re-injury rate was observed.<sup>20</sup> Similarly, Orlandi et al. reported the high efficacy of ultrasound-guided PRP injections for sports-related muscle injuries.<sup>29</sup> A single-blinded randomised controlled trial (RCT) by Hamid et al. assessed PRP's efficacy in treating acute grade 2 hamstring injuries, finding a significant decrease in return-to-play time for the PRP group compared to controls (26.7 days vs. 42.5 days).<sup>30</sup>

However, Hamilton et al.<sup>31</sup> presented a more nuanced picture of PRP's efficacy and superiority. The study compared PRP, platelet-poor plasma (PPP) and no-injection groups in treating hamstring injuries. It showed no significant difference in recovery time between the PRP and no-injection groups. The findings also indicated no significant advantage of PRP over PPP or no-treatment

groups in terms of re-injury rates or muscle strength at 6 months post-treatment.<sup>31</sup>

### Clinical applications of PRP in specific musculoskeletal injuries

The therapeutic potential of PRP in treating a wide range of musculoskeletal injuries has been extensively documented through numerous reviews and meta-analyses. These investigations highlighted PRP's role in accelerating recovery and promoting healing across various conditions. In a systematic review by Hamid et al., which encompassed 4 studies on the efficacy of PRP in acute musculoskeletal injuries, the findings underscored PRP's critical role in the healing process. The review revealed that PRP facilitated anti-inflammatory markers, mitigated inflammation, and initiated tissue regeneration through the early release of growth factors and cytokines, thereby aiding in muscle recovery and regeneration of the affected area.<sup>32</sup> Another systematic review and meta-analysis conducted by Miller et al., which included 16 RCTs, focussed on PRP injections in symptomatic tendinopathy. The outcomes demonstrated significant improvement in tendon healing post-PRP treatment, attributed to reduced inflammation and enhanced expressions of cyclooxygenase-1 (COX-1), COX-2 and microsomal prostaglandin E synthase-1 (mPGES-1) alongside significant prostaglandin E2 (PGE2) generation. HGF, which is identified as a key growth factor in PRP, also plays a pivotal role in exerting anti-inflammatory effects akin to PRP itself.<sup>33</sup>

Aidan O'Dowd et al. conducted a systematic review examining the effectiveness of PRP injections in managing musculoskeletal soft tissue injuries across 32 studies. The analysis concluded that PRP injections served as a beneficial nonsurgical treatment for meniscal injuries, plantar fasciitis, and rotator cuff problems. However, the review noted that the application of PRP as a primary or adjunct treatment for all musculoskeletal injuries was not universally justified, particularly highlighting the lack of significant benefits in trials involving surgical interventions,

**Table:** Summary of studies on the efficacy of plasma-rich platelets (PRP) treatment in musculoskeletal injuries.

Study Reference	Study Design	Participants	Intervention	Comparison	Findings
Rossi et al. (2017) <sup>20</sup>	RCT	72 athletes with acute grade 2 muscle injuries	PRP treatment	Conservative measures alone	PRP group returned approx. 4 days earlier than control (21.1 vs. 25 days, $p=0.001$ ) while no significant difference in pain reduction/reinjury rate.
Orlandi et al. (2016) <sup>29</sup>	Review	Athletes with muscle injuries	Ultrasound-guided PRP injections	NA	PRP has high efficacy the placebo for the treatment of sport-related muscle injuries.
Hamid et al. (2014) <sup>30</sup>	RCT	Athletes with acute grade 2 hamstring injuries	PRP treatment	Controls	Return to play was significantly reduced for PRP group (26.7 vs. 42.5 days).
Hamilton et al. (2015) <sup>31</sup>	RCT	Participants with hamstring injuries	PRP and PPP injections	No injections	No significant difference between PRP and no-injection groups or between PRP and PPP for recovery time/reinjury rate/muscle strength.

such as arthroscopic rotator cuff repair and anterior cruciate ligament restoration.<sup>34</sup>

Jie Fang et al. reviewed the application of PRP in treating diseases associated with orthopaedic injuries, underscoring PRP's capacity to reduce inflammation and promote tissue anabolism for regeneration. Given the rich concentration of growth factors and cytokines in PRP, which are crucial for initiating and managing regenerative microenvironments for soft and hard tissues alike, the findings aligned with the broader literature, indicating PRP's effectiveness in enhancing muscle recovery, and reducing pain and swelling.<sup>35</sup>

Collectively, the studies cited above affirmed the significant role of PRP in the treatment and management of musculoskeletal injuries, highlighting its potential to expedite the healing process, reduce inflammation, and facilitate tissue regeneration.

### Limitations and future directions

Despite the promising therapeutic potential of PRP, its use is mired in controversy. These controversies arise from a multitude of factors, including divergent PRP preparation techniques, which influence the concentration of platelets, growth factors, and leukocytes in the final product.<sup>12</sup> This variability has led to a lack of standardised protocols for PRP therapy, making it challenging to compare outcomes across different trials and to establish best practices for its clinical application. The absence of a universally accepted method for preparing PRP means that treatments can vary significantly in their composition, potentially affecting their efficacy.<sup>11</sup> Additionally, studies often differ in their selection criteria, sample size and outcome measures, further complicating the ability to draw generalised conclusions about the effectiveness of PRP in musculoskeletal injury rehabilitation. The varied responses observed across different types of injuries and patient demographics suggest that the effectiveness of PRP may be contingent on specific conditions, underscoring the need for more targeted research.

Future research should, therefore, focus on addressing the current gaps in knowledge through the development of standardised protocols for PRP preparation and administration. Moreover, there is a critical need for larger, more rigorous RCTs that are adequately powered to detect meaningful differences in outcomes between PRP and control groups. Such studies should strive for methodological rigour, including appropriate blinding and randomisation procedures, to mitigate bias and enhance the reliability of findings. In addition to empirical research, there is a growing recognition of the role of personalised medicine in optimising PRP therapy. Individual patient

characteristics, such as age, gender, injury severity and overall health status, could influence the response to PRP, suggesting that tailored treatment approaches may be more effective than one-size-fits-all protocols.

### Conclusion

Literature has highlighted the promising role of PRP in the rehabilitation of musculoskeletal injuries, showcasing its potential to expedite the healing process, mitigate inflammation and promote tissue regeneration. Despite the optimism surrounding PRP therapy, controversies regarding preparation techniques and variability in clinical outcomes persist, underscoring the need for standardised protocols and further rigorous research.

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**Author Contribution:**

DS: Concept and data analysis.

LC: Data collection and interpretation.

KY: Data analysis, interpretation and design.

QH: Data collection and analysis.

NW: Finalising, proofread, analysis and revision.