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Review Article

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The Role of Platelet-Rich Plasma in Bone Regeneration in Patients with Osteoporotic Fractures: A Literature Review

Alyssa Cevetello[1], Kyle Taylor[2], Janae Rasmussen[3*], Layla Aljoudi[4], Jacob Ritter[5], Rachel Yim[6], Donia Javidi[7] and Behzad Maher[7]

[1]*Touro College of Osteopathic Medicine, Middletown, NY, USA*
[2]*Kansas City University College of Osteopathic Medicine, Kansas City, MO, USA*
[3]*Valley Consortium for Medical Education, Modesto, CA, USA*
[4]*Tbilisi State Medical University, Georgia*
[5]*Campbell University College of Osteopathic Medicine, Lillington, NC, USA*
[6]*A.T. Still University School of Osteopathic Medicine, Mesa, AZ, USA*
[7]*California Health Sciences University College of Osteopathic Medicine, Clovis, CA, USA*

[*]Corresponding author
Janae Rasmussen DO, Valley Consortium for Medical Education, Modesto, CA, USA.

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ABSTRACT

Platelet-rich plasma (PRP) is an innovative biologic therapeutic treatment used in orthopedics to enhance tissue repair and accelerate the healing process. PRP promotes the release of growth factors and cytokines involved in wound healing. It has extensive clinical applications and has become increasingly prevalent in the treatment of various orthopedic-related injuries. Osteoporosis is an increasingly common comorbidity in orthopedics and is a significant factor that increases susceptibility to fractures. The risk of developing osteoporosis rises with age, making it more prevalent in the geriatric population. Since osteoporotic fractures are a frequent consequence of osteoporosis, selecting appropriate treatment modalities remains a critical aspect of patient care in this population. As PRP continues to gain traction in orthopedics, it is necessary to study its therapeutic effects on bone regeneration in osteoporotic fractures. This literature review aims to evaluate whether PRP provides clinical benefits in treating osteoporotic fractures based on recent investigations.

Keywords: Platelet-Rich Plasma, Orthopedic Surgery, Osteoporosis, Bone Regeneration, Osteoporotic Fractures

List of Abbreviations:

PRP	:	Platelet-rich plasma
NSAIDs	:	nonsteroidal anti-inflammatory drugs
β-TCP	:	β-tricalcium phosphate
CPC	:	calcium phosphate cement
BMPs	:	bone morphogenetic proteins
TGF-β	:	transforming growth factor-β
FGFs	:	fibroblast growth factors
IGF	:	insulin-like growth factor
MSCs	:	mesenchymal stem cells
BMSCs	:	bone marrow mesenchymal stem cells
I-PRF	:	injectable platelet rich fibrin

Introduction

Osteoporosis is a common bone disease that affects millions of people globally, particularly among the geriatric population and postmenopausal women [1]. Osteoporosis is attributed to an imbalance between osteoblasts producing new bone and osteoclasts resorbing old bone. Changes in bone homeostasis seen in osteoporosis results in lower bone mineral density,

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compromised structural integrity, and an increased risk of fracture [2]. In postmenopausal women, decreased estrogen levels stimulates bone resorption, increases cortical porosity, and causes trabecular thinning [3]. Therefore, postmenopausal women are at an increased risk of osteoporosis and subsequent osteoporotic fractures. Osteoporosis can also be caused by aging, chronic inflammation, nutritional deficiencies, or certain drugs [4]. Such changes can also be seen at the cellular level, such as decreased osteoblastic activity, impaired osteocyte signaling, and altered synthesis of key cytokines and growth factors required for effective osseous remodeling [5]. As a result, osseous repair is severely limited, particularly after a fracture.

Multiple studies suggest that platelet-rich plasma (PRP) is a potential treatment modality to manage osteoporotic fractures [6, 7]. PRP is a concentration of autologous platelets, which includes a composition of various growth factors and cytokines necessary for tissue repair and regeneration by promoting osteogenesis and angiogenesis [8, 9]. Release of these mediators promotes healing and recruitment of other immune cells in the body to a target area. To obtain PRP, a portion of the patient's blood is collected and concentrated by techniques like centrifugation that separate the blood into layers where platelet-poor plasma (PPP) is removed and PRP is obtained [10]. Among PRP's previously demonstrated benefits, it has also been shown to promote fracture healing [11]. Therefore, PRP has become a promising adjunctive therapy for promoting healing of various orthopedic conditions outside of fracture healing.

The benefits of PRP have been increasingly observed in clinical practices. A systematic review of thirteen clinical studies discovered that PRP treatment led to a greater healing rate in long-bone delayed fracture union and fracture nonunion [12]. Beyond musculoskeletal fractures, PRP has also shown therapeutic potential in various non-orthopedic fields, such as dermatology, for treating hair loss and chronic wounds, and dentistry for enhancing healing after oral surgery [13, 14].

This broad range of PRP treatment offers potential benefits, particularly in individuals with osteoporosis. However, further research is necessary to determine the effectiveness of PRP applications in patients with osteoporotic fractures. Maximizing PRP treatment benefits requires an understanding of its specific effects on bone healing pathways in this patient group. This literature review presents an analysis of existing studies about PRP application in osseous repair for patients with osteoporotic fractures. It examines clinical efficacy assessments and suggests future approaches to enhance PRP therapy for patients who experience osteoporotic fractures.

Methods

A comprehensive literature review was conducted to examine the role of Platelet-Rich Plasma (PRP) in bone regeneration in patients with osteoporotic fractures. This review aimed to investigate the impact of PRP on healing outcomes, bone density, and fracture repair in patients with osteoporotic fractures. The potential risks, benefits, challenges, and alternatives associated with PRP utilization in osteoporosis and osteoporotic fractures were also assessed. This review identified relevant studies through a systematic search of PubMed, Google Scholar, and other scientific databases. Key search terms included "Platelet-Rich Plasma," "Bone Regeneration," "Osteoporotic Fractures," "Osteoporosis," "Fracture Healing," "Bone Density," and combinations of these keywords. The search conducted by the authors was restricted to peer-reviewed journal articles, clinical trials, literature reviews, and meta-analyses published in English from 1990 to 2025. The data synthesized by these studies provided a comprehensive understanding of the potential role of PRP in bone regeneration for patients suffering from osteoporotic fractures, while also focusing on identifying gaps in the current research, and areas for future investigation.

Clinical Implications and Outcomes

Prevalence and Other Treatment Options

As more people reach advanced age worldwide, osteoporotic fractures become more prevalent. Osteoporosis typically affects multiple regions of the body, with higher risk of fractures to the hips, wrist, and spine [15]. Due to the pathogenesis of osteoporosis, minimal trauma, such as a ground level fall, can result in these pathologic fractures. While surgical intervention is a possible treatment modality for osteoporotic fractures, non-surgical alternatives are also seen in practice. According to Larsson, the preservation of excellent vascularity together with acceptable osseous alignment makes non-surgical management an appropriate choice for stable fractures [16]. Some osteoporotic fractures can be managed conservatively utilizing bracing with pain medication and physiotherapy treatment. However, extended periods of inactivity, such as a non-weight bearing extremity, can lead to further weakening of the bones, soft tissues, and stiffness. This can result in a higher risk of future falls or other osteoporotic fractures.

Some osteoporotic fractures, particularly hip fractures, are treated with surgery to improve mobility and decrease potential sequelae of the initial fracture, such as pneumonia [17]. As discussed by Yaacobi et al., surgical intervention for osteoporotic fractures focuses on achieving optimal mechanical stability through limited surgical disruption to start rehabilitation programs and return to function [17]. Geriatric hip fractures are often treated using intramedullary implants like cephalomedullary nails to help promote immediate weight bearing, but the fixation method varies depending on factors like fracture morphology [18].

Vertebral body fractures are classically seen in geriatric patients with osteoporosis. A recent systematic review and network meta-analysis by Alimy et al. supports conservative treatment as the standard of care, showing that nonsteroidal anti-inflammatory drugs (NSAIDs) and anabolic agents, like teriparatide, can significantly reduce pain, while the benefits of bracing remain less conclusive [19]. However, in select cases with severe pain or functional limitations, vertebroplasty may be considered [16]. This minimally invasive procedure involves percutaneous injection of bone cement into the fractured vertebra to provide pain relief and mechanical stability [16]. While kyphoplasty may also be considered, Alimy et al. found that conservative measures outweigh kyphoplasties when considering contradictory findings of kyphoplasties [19]. The medical application of novel biologically compatible cements exists, but remains under restricted clinical utilization, highlighting a gap in current clinical practice.

Platelet-Rich Plasma for Osteoporotic Fracture Management

Platelet-rich plasma (PRP) is a potential treatment solution for osteoporotic fractures. The high incidence of osteoporotic fractures poses critical concern for geriatric patients, as they frequently have poor healing capability compared to younger patients. PRP delivers important growth factors including PDGF, TGF-β, and VEGF, which can help improve biologic repair mechanisms [8, 20]. PRP provides on-site delivery of growth factors to fracture sites, which has the potential to increase the repair process. PRP's side effects that should be considered include, but are not limited to, wound infections, inflammatory reactions, ectopic bone growth, or increased bone resorption [12]. PRP promotes tissue repair by enhancing the endogenous healing pathways through the localized delivery of growth factors [20].

However, the benefits of PRP have demonstrated inconsistent outcomes throughout studies. The inconsistency in PRP effects stems from various approaches in its preparation and application including variations in the amount of platelets in a concentration and ratios of other cells included [8]. The procedural variability in preparation methods for PRP have demonstrated biological promise as a tool for healing osteoporotic fractures, but requires continued investigation.

Several studies have demonstrated the effects of platelet-rich plasma in osteoporotic fractures [6, 21-28]. All included studies were performed in ovariectomized animal models, including rats, mice, or rabbits. Most studies were performed utilizing PRP in addition to additional interventions rather than with PRP alone. For instance, studies evaluated PRP with mesenchymal stem cells, performed by Wei et al. and Rocha et al., additional biomaterials as seen by Rocha et al., Sakata et al., and Cho et al., and implant osseointegration, studied by Jiang et al. and Sun et al. [21-23, 26, 27]. The primary outcomes of platelet-rich plasma administration in each study can be found in Table 1.

Table 1: Summary of Studies on the Administration of PRP

Reference	Animal Model	Study Groups	Site of Application	Evaluation Methods	Main Outcomes
[6]	OVX rats	I: PPP II: High concentration PRP III: Medium concentration PRP IV: Low concentration PRP	Artificial defect of the femur	I: Radiology II: Histology II: Three-point load bearing	Medium concentration PRP exhibited best performance in enhancing bone healing and stiffness
[21]	OVX rats	I: PRP II: BMSCs III: PRP and BMSCs	Artificial defect of tibia	I: Micro CT II: Histology III: Gene expression (RT PCR)	Groups treated with PRP with BMSC exerted best results with improved bone volume and mineralization
[22]	OVX rabbits	I: PRP with collagen sponge II: MSCs with collagen sponge III: PRP and MSCs with collagen sponge	Artificial defect of tibia	I: Radiographic optical densitometry II: Histology	MSC alone demonstrated the best outcome with highest densitometric indices and histological evidence
[23]	OVX rats	I: PRP with gelatin with β-TCP II: PBS with gelatin with β-TCP	Defect in lumbar vertebral body	I: Micro CT II: Histology III: Biomechanical testing	PRP combined with gelatin β-TCP sponge exerted greatest osteogenesis and increased stiffness
[24]	OVX mice	I: Young OVX mice with PRP and PBS (1 month-old) II: Old OVX mice with PRP and PBS (10 months-old)	Bone marrow cavity of femur	I: Immunohistochemistry II: BMD III: Micro CT IV: Gene expression	PRP and PBS treatment enhanced osteogenic differentiation while suppressing adipogenesis in bone marrow
[25]	OVX mice	I: NIH3T3 cells II: PRP III: PRP/NIH3T3 cells	Bone marrow cavity of tibia	I: Osteogenic differentiation II: RT-PCR III: In vivo fluorescence imaging IV: BMD V: SEM VI: Immunohistochemistry	Bone marrow transplantation of NIH3T3 cells treated with PRP induced proliferation and osteoblastic differentiation, in addition to an extended life span

[26]	OVX rats	I: Control implant without any other treatment II: Anodized TiO2 nanoporous implant III: Control implant with PRP treatment IV: Anodized TiO2 nanoporous implant with PRP treatment	Bone marrow cavity of tibia	I: Micro-CT II: Histology III: Biomechanical testing IV: SEM V: Gene expression	Group IV implants exerted significant enhancement of osteogenesis with improved biomechanical stability
[27]	OVX rats	I: Implant with CaP II: Implant with PRP III: Implant with CaP and PRP	Bone marrow cavity of tibia	I: Micro CT II: Biomechanical testing III: Histology	Application of implant with CaP and PRP improved osteoinductive effects and implant stabilization
[28]	OVX rats	I: PMMA II: CPC III: CPC with PRP	Artificial defect in vertebral body	I: Micro-CT II: Histology	CPC with PRP group exhibited significantly greater trabecular bone volume fraction and bone regeneration

Abbreviations: OVX, ovariectomized; PRP, platelet-rich plasma; BMSCs, bone marrow mesenchymal stem cells; Micro CT, microcomputed tomography; MSCs, mesenchymal stem cells; β-TCP, β-tricalcium phosphate; PPP, platelet-poor plasma; PBS, phosphate-buffered saline; BMD, bone mineral density; PRP/NIH3T3-G, NIH3T3-G pre-differentiated into osteoblast-like cells using PRP; SEM, scanning electron microscope; PMMA, polymethyl methacrylate; CPC, calcium phosphate cement

The regenerative capabilities of PRP in osteoporotic fractures are evident throughout the studies referenced in Table 1. Although there are differences in the conduction and evaluation of studies, researchers remain keen to evaluate histology, gene expression, biomechanics, and microcomputed tomography among other factors. Furthermore, the application of PRP can be conducted in multiple ways, including with biomaterials, implants, and other cell types. While the administration of PRP alone was infrequent, Chen et al. demonstrated that medium-concentration PRP (2.65±0.2×109 /mL) exerted the best ability to enhance osseous healing [6]. Many studies have found similar results regarding the usage of PRP. For instance, biomaterials, such as gelatin β-tricalcium phosphate (β-TCP) and calcium phosphate cement (CPC), both displayed improved trabecular bone volume and osteogenesis when combined with PRP [23, 28]. Three additional studies noted enhanced osteogenesis when PRP was administered. Liu et al., Lo et al., and Jiang et al. all saw an up-regulation of osteogenic markers (Runx2 and Col1) with down-regulation of adipogenic markers (PPAR-γ2 and leptin) [24-26]. This is particularly relevant as there is usually an increase in adipogenic markers in osteoporosis [24]. Thus, a reversal of this osteoporotic trend allows for additional bone formation. There is a resultant increase in bone morphogenetic proteins (BMPs), transforming growth factor-β (TGF-β), fibroblast growth factors (FGFs), and insulin-like growth factor (IGF) secondary to osteogenic markers [29]. These growth factors are essential in the setting of osteoporotic fractures to maintain a supportive microenvironment that favors bone regeneration.

The versatility of PRP is apparent through its utilization in fracture care as well as surgical procedures involving implantation. Titanium and its alloys have commonly been used in endosseous implantable materials because of their mechanical properties [26]. However, low bone mass associated with osteoporosis can affect their long-term stable performance [26]. To address the low bone mass, researchers have explored the usage of PRP intraoperatively. According to Jiang et al., anodized titanium dioxide (TiO2) nanoporous implants with PRP treatment resulted in significant improvement in biomechanical stability [26]. More specifically, the group containing the anodized TiO2 nanoporous implant with PRP demonstrated a 95% higher force and 55% higher shear strength when compared to the next best performer [26]. This is critical as stabilization and osseous stiffness play a substantial role in the success of implants and healing. Chen et al., Sakata et al., and Sun et al. each concluded that the addition of PRP alone, with an implant, or with a biomaterial, enhanced the stiffness and strength of bone [6, 23, 27]. Chen et al. discovered a 50% increase in peak failure load and a 70% increase in bone stiffness with medium-concentration PRP compared to the control group [6]. The improved stiffness is likely secondary to osteogenic markers, which enhance bone formation and remodeling, improving the outcomes of patients with osteoporotic fractures.

Although most studies demonstrated the superiority with PRP application, one study reported better results with mesenchymal stem cells (MSCs) [22]. More specifically, Rocha et al. noted radiographic consolidation with mature and immature bone tissue with allogeneic MSCs compared to PRP and other groups [22]. The improved outcome with MSCs implies that PRP is limited in its use as an adjunctive treatment. In contrast, Wei et al. exhibited improved bone volume and mineralization with bone marrow mesenchymal stem cells (BMSCs) and PRP [21]. Nevertheless, most studies identified enhanced osteogenic markers, bone regeneration, bone stiffness, and strength when utilizing platelet-rich plasma for osteoporotic fracture treatment.

Challenges and Limitations

Current Gaps in Research

Platelet-rich plasma (PRP) has become a promising adjunctive treatment for osteoporotic fractures. Recent studies suggest positive results in bone regeneration through the administration

of platelet derivatives [6, 21, 24, 30, 31]. Most studies on the usage of PRP for osteoporosis are in vitro or through animal models. While these studies are beneficial, they highlight a substantial concern regarding the limited amount of studies conducted involving human subjects [30]. In addition, there is a lack of long-term studies evaluating the efficacy of PRP. Thus, limited long-term rigorous clinical trials on human subjects may raise concerns regarding translation into clinical settings [30]. Further research must be performed through high-quality, long-term clinical trials in human subjects to evaluate the effectiveness and safety of platelet-rich plasma for osteoporotic fracture treatment.

Financial Barriers

PRP is often not covered by insurance companies and can be difficult to access, especially for patients in the United States with Medicare or other government-assisted programs [32]. Orthopedic surgeons often do not have access to PRP supplies outside of their outpatient offices, so offering inpatient PRP could result in increased costs to the patient, and require resources from device representatives to be delivered. These logistical barriers provide considerable issues for the possibility of incorporating PRP into patient care for osteoporotic fractures.

Variations in Preparations of Platelet-Rich Plasma

The use of PRP in bone regeneration has several limitations due to inconsistencies in preparation, application, and assessment techniques [31]. PRP is typically prepared by centrifuging blood with a predetermined centrifugal force and duration. Evaluation of studies suggests there is a lack of standardization regarding centrifugal force and duration. For example, Wei et al. centrifuged blood at 215 g for 10 minutes to remove red blood cells and then at 863 g for 10 minutes to obtain PRP [21]. Meanwhile, Chen et al. centrifuged blood at 220 g for 15 minutes to separate the plasma portions and again at 980 g for 10 minutes to obtain PRP [6]. The considerable variation in preparation of PRP may lead to differing concentrations of platelets and growth factors that can have unexpected biological effects. Regarding platelet concentration, Chen et al. reported that "medium-concentration PRP (2.65±0.2×109 /mL) seemed to be the optimal concentration" [6]. However, there appears to be continued variation in the concentrations utilized. Given the inconsistencies between preparation and concentration, this can complicate direct comparisons between studies leading to limited generalizability.

Variations in Delivery of Platelet-Rich Plasma

PRP can be administered alone or with osteoinductive and osteoconductive biomaterials on a local or systemic level [30]. The addition of biomaterials enhances bone regeneration and makes it difficult to compare and evaluate the efficacy of PRP alone. Systemic application of PRP involves intravenous administration, which can improve bone microstructure on a broader scale throughout the skeletal system [30]. The local application involves tissue-targeted administration, which leads to tissue-specific regeneration through the direct application of PRP [30]. There is no strict rationale in selecting between local or systemic administration. However, the local administration has shown notable benefits in promoting bone regeneration and stimulation of osteogenic differentiation [30]. Given the variability for application, there are likely differing results based on the use of additional biomaterials and choice of administration, further complicating comparisons between studies.

Variations in Assessment of Bone Regeneration

Assessment of bone regeneration can be performed through a variety of techniques. For instance, evaluations have been made using radiographic optical densitometry seen by Rocha et al., histology studied by Wei et al., Rocha et al., and Sakata et al., micro-CT by Wei et al. and Sakata et al., biomechanical testing performed by Sakata et al., and gene expression studied by Wei et al. [21-23]. The utilization of various techniques exemplifies the vast approaches available to determine bone regeneration. There does not appear to be a single superior method for evaluation. However, most studies in a systematic review by Amiri et al. included histological analysis [30]. There seems to be an attempt to create a standardized evaluation, but ultimately there is too much variability in interpretation. This leads to difficulties in drawing conclusions. A standardized protocol for platelet-rich plasma preparation, delivery, and evaluation for osseous healing could help compare its efficacy in clinical trials.

Future Directions

Cellular and Molecular Mechanisms

While knowledge on the mechanism of fracture healing is continuing to improve, there are still many gaps in understanding. One of which is the underlying cellular and molecular mechanisms of platelet-rich plasma (PRP) on osseous healing in non-osteoporotic bone. This lack of understanding is amplified in the context of the mechanisms of PRP on osteoporotic bone [33]. PRP has demonstrated positive impacts on osseous health, specifically after fractures, through activating angiogenesis and providing growth factors, such as VEGF, PDGF, TGF-β, and IGF [34]. In addition, PRP was found to inhibit the maturation of preadipocytes while also promoting osteogenesis, which aids in preventing osteoporotic fractures [35]. With greater understanding of PRP's mechanisms, investigators can tailor formulations to specific patient characteristics, which has the potential to help with treatment options for osteoporotic fractures.

Clinical Models

The benefit of platelet concentrations, such as PRP, has been shown in a variety of studies to improve the healing process of bone and improve overall osseous stability following osteoporotic fractures. However, many of these studies have demonstrated these advantageous findings in animal models alone [21-23, 25, 28, 36-39]. As such, the extrapolation of these findings should be viewed with caution. Further randomized control trials evaluating the effects of PRP on accelerating union rates, functional outcomes, and complication rates in patients with osteoporotic fractures are essential in bridging the gap when evaluating the efficacy and safety of PRP in patients with osteoporotic fractures. Furthermore, there is a lack of investigation in comparing the efficacy of PRP against more conventional treatment options, such as bisphosphonates, which are known to have considerable adverse effects, such as osteonecrosis of the jaw or other fractures [40]. Conversely PRP, being an autologous compound, is considered safe and has a minor adverse effect profile limited primarily to minor blood

loss and local skin infections [41, 42]. A comparison between different treatment options could allow for improved shared decision making with patients and their orthopedic surgeon.

Optimal Dosing

Determining the optimal dosage for PRP is an area of research that requires further investigation. This review identified one study that demonstrated that medium concentrations of PRP were superior in the promotion of fracture healing in osteoporotic models when compared to low and high concentrations [6]. No additional studies have been recorded to date that have shown similar findings. Therefore, additional studies comparing dosing concentrations are required. To date, no studies have explored the optimal number of injections of PRP for osteoporotic fractures. However, for conditions like osteoarthritis, research has demonstrated that three injections of PRP are superior to one injection in relation to pain relief, but the specific dosing recommendations are not elucidated [43]. As such, more research into PRP dosing for osteoporotic fracture adjunctive treatment is critical in the development and refining of treatment protocols to ensure maximum therapeutic efficacy.

Variety of Platelet Concentrates

A new generation of liquid platelet concentrates called platelet rich fibrin (PRF) could potentially be a more effective platelet-derived factor to aid in the generation of healthy bone in patients with osteoporotic fractures. PRF was created with the intention of removing anticoagulation through the formation of a dense fibrin network [44]. The fibrin network of PRF traps growth factors resulting in an extended release of growth factors over 10-28 days compared to PRP, which releases growth factors over eight hours after preparation [44]. This extended release of growth factors has resulted in superior performance of PRF in stimulating cell proliferation and mineralization of osteoblasts when compared to PRP [45]. An additional generation of platelet concentrates known as injectable platelet rich fibrin (I-PRF) was found, not only to have an extended-release time, but to also have higher levels of growth factors when compared to other platelet concentrates [46, 47]. Studies to date have not yet explored the effects of prolonged release of growth factors through products like PRF on osteoporotic fractures. Therefore, additional studies focusing on using PRF in the treatment of osteoporosis in vitro and in vivo studies are required.

Conclusion

Platelet-rich plasma (PRP) has become a potential therapeutic agent in enhancing bone regeneration in osteoporotic fractures. PRP is rich in growth factors and cytokines that can stimulate osteogenic differentiation and improve fracture healing by promoting cellular proliferation, angiogenesis, and extracellular matrix production. By delivering concentrated growth factors and cytokines directly to fracture sites, PRP may support osteogenesis and improve healing outcomes in patients with compromised osseous quality. However, its clinical effectiveness remains an area of active research and debate. Despite encouraging clinical observations and its broad applicability across medical disciplines, the effectiveness of PRP remains inconsistent due to variations in preparation methods and treatment protocols. As osteoporosis significantly contributes to fracture risk and impaired recovery, further research is essential to standardize PRP application and fully understand its role in bone healing. Optimizing PRP therapy leads to more effective, personalized treatment strategies for patients with osteoporotic fractures. Some studies have noted no significant improvement in bone healing with PRP application. Thus, future research will be critical in clarifying PRP's role in bone regeneration for patients with osteoporotic fractures. Furthermore, high-quality, randomized controlled trials will be essential to establish standardized protocols and assess their clinical efficacy, providing more precise guidance for their integration into clinical practice. This comprehensive review underscores that while PRP has promise, the full extent of its benefits in patients with osteoporotic fractures remains uncertain, and more data are required to determine its optimal use.

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