Journal of Pharmacological Biomolecules and Therapeutics

ETERNO PRESS

Review

Platelet-Rich Plasma Drug Delivery System for the Treatment of Osteoporosis

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Abstract

Osteoporosis affects millions of people worldwide and presents significant challenges for treatment, characterized by decreased bone density and increased fracture risk. While conventional treatments such as hormone replacement therapy can alleviate symptoms, they often fail to reverse bone loss and are associated with long-term side effects. Platelet-rich plasma (PRP), known for its regenerative potential, has emerged as a promising approach for the treatment of osteoporosis. This review evaluates the efficacy of PRP-based drug delivery systems for the treatment of osteoporosis and presents key findings from clinical, in vitro, and in vivo studies. PRP has been shown to improve bone regeneration and fracture healing in patients, enhancing bone mineral density and structural integrity. In vitro studies have shown that PRP promotes osteoblast proliferation and differentiation, thereby supporting bone formation. In vivo animal models have further confirmed the ability of PRP to increase bone volume and trabecular thickness, highlighting its therapeutic promise. We analyze the biological mechanisms driving the effects of PRP, including growth factor release and cell signaling, and explore innovative PRP formulations, such as hydrogels and scaffolds, designed for targeted delivery. Despite these advances, challenges such as standardization of PRP preparation and long-term safety remain. This article reviews these results, emphasizes the potential of PRP to transform osteoporosis treatment through a regenerative strategy, and proposes future studies to improve its clinical applicability and efficacy.

Keywords

Osteoporosis, Treatment system, Platelet derivatives, Hydrogels, Biomaterials

Highlights

1. PRP-Based Regenerative Potential: PRP's natural healing properties offer a promising alternative for osteoporosis treatment, with the potential to enhance bone regeneration and increase bone density.

2. Innovative Drug Delivery Systems: Advances in PRP-based drug delivery systems show potential for more targeted and effective therapeutic approaches to combat osteoporosis compared to traditional therapies.

3. Biological Mechanisms of PRP: PRP promotes bone healing through biological pathways that enhance osteoblast activity, improve bone matrix deposition, and modulate inflammation, contributing to bone tissue regeneration.

4. Challenges and Future Directions: Despite promising results, further research is needed to address challenges related to the standardization, safety, and long-term efficacy of PRP-based treatments for osteoporosis.

Article History

Received: 27 January 2025 Revised: 17 March 2025

Accepted: 19 March 2025 Available Online: 22 August 2025

1. Introduction

Osteoporosis represents a significant public health issue, affecting an estimated 200 million people worldwide. This condition is characterized by a decrease in bone density and microarchitectural deterioration of bone tissue, leading to increased fragility and risk of fractures, particularly in postmenopausal women and older adults [1-3]. Currently, osteoporosis treatment relies on drugs such as bisphosphonates to slow bone loss. In addition, existing treatments often fail to fully restore bone strength or prevent fractures in all patients, highlighting their limitations. These shortcomings underscore the ongoing need to develop new drugs that can more effectively and safely treat this disease [4,5].

The quest for better therapeutic strategies has led to the exploration of regenerative medicine, specifically the use of platelet-rich plasma (PRP). PRP is an autologous preparation that concentrates platelets from the patient's own blood. Rich in growth factors like platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), and insulin-like growth factor 1 (IGF-1), PRP has shown promising results in promoting tissue repair and regeneration in various fields such as orthopedics, dentistry, and dermatology [6-8]. The mechanism behind PRP's effectiveness lies in its ability to enhance the recruitment, proliferation, and differentiation of cells involved in tissue regeneration. For bone, this means attracting osteoblasts and stimulating them to produce new bone matrix and mineralize old bone structures. This biological mechanism provides a compelling rationale for the use of PRP in treating osteoporosis, which inherently involves the impairment of bone-building cells and their activities.

Recent studies have demonstrated the potential of PRP to not only prevent further bone loss but also to enhance the density of already weakened bones [9-11]. Clinical trials have reported improvements in bone mineral density (BMD) and reductions in pain associated with osteoporotic fractures following PRP treatments [12]. However, despite its potential, the use of PRP in osteoporosis is not without challenges. Standardization of PRP preparations is a major issue, as variations in concentration, cellular content, and activation protocols can affect treatment outcomes [13,14].

The integration of platelet-rich plasma (PRP) with innovative biomaterials and technologies, such as scaffolds and 3D-printed bone matrices, heralds a transformative approach to osteoporosis treatment [15-17]. This synthesis aims to exploit the synergistic effects of PRP’s biological activity with the structural benefits provided by these materials, enhancing the overall therapeutic outcomes for bone regeneration. Scaffolds, which serve as artificial structures that support tissue formation, can be imbued with PRP to create bioactive platforms for bone growth. These scaffolds are typically fabricated from materials like polycaprolactone (PCL), hydroxyapatite, or bioglass, which are biocompatible and support the adhesion and proliferation of osteoblasts [18,19]. When PRP is added, the scaffold not only provides a physical matrix to guide bone growth but also becomes a reservoir of growth factors that continuously stimulate the bone healing process. Meanwhile, the advent of 3D printing technology offers customized solutions to osteoporosis treatment by allowing for the precise fabrication of bone scaffolds that match the patient's specific anatomical needs. These 3D-printed structures can be designed to mimic the complex architecture of bone tissue, providing an optimal environment for bone growth and integration. Incorporating PRP into these 3D-printed scaffolds enhances their functionality by infusing them with bioactive compounds that accelerate the healing process [20,21].

The combination of PRP with 3D-printed scaffolds can be particularly effective in treating osteoporotic fractures, which often require complex geometries for optimal healing. The ability to customize the scaffold’s structure to fill specific bone voids while simultaneously delivering PRP-derived growth factors directly to the site of injury represents a significant advancement over traditional bone grafts or synthetic implants. Moreover, the dynamic field of tissue engineering continues to evolve with the exploration of novel bioinks that can be used in 3D bioprinting [22,23]. These bioinks, which can be formulated with a mixture of hydrogels and PRP, enable the printing of living tissues that can integrate seamlessly with the existing bone.

This review aims to comprehensively evaluate the efficacy of platelet-rich plasma (PRP)-based drug delivery systems as regenerative strategies for the treatment of osteoporosis. This work investigates the biological mechanisms of PRP action, such as growth factor release and cell signaling, while exploring innovative formulations for targeted delivery, such as hydrogels and scaffolds. In addition, this review aims to identify current challenges such as standardization of PRP preparation and long-term safety, and propose future research directions to improve its clinical applicability and therapeutic efficacy. By addressing these objectives, this review aims to highlight the transformative potential of PRP in the treatment of osteoporosis and guide the integration of PRP with other regenerative approaches to optimize patient outcomes (Figure 1).

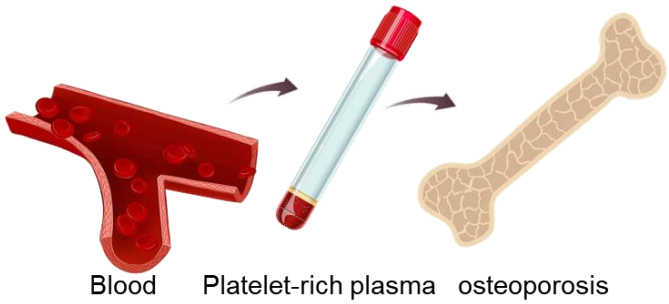

Figure 1. PRP is separated from the blood for bone thinning treatment.

2. PRP and Bone Metabolism

Platelet-rich plasma (PRP) is a concentrated autologous preparation of platelets and their associated growth factors, which plays a significant role in bone metabolism and osteogenesis (Figure 2) [24,25]. The efficacy of PRP in promoting bone repair and regeneration is largely attributed to its high concentration of growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and insulin-like growth factor (IGF). These growth factors are crucial in mediating cellular processes that contribute to bone healing and homeostasis [26].

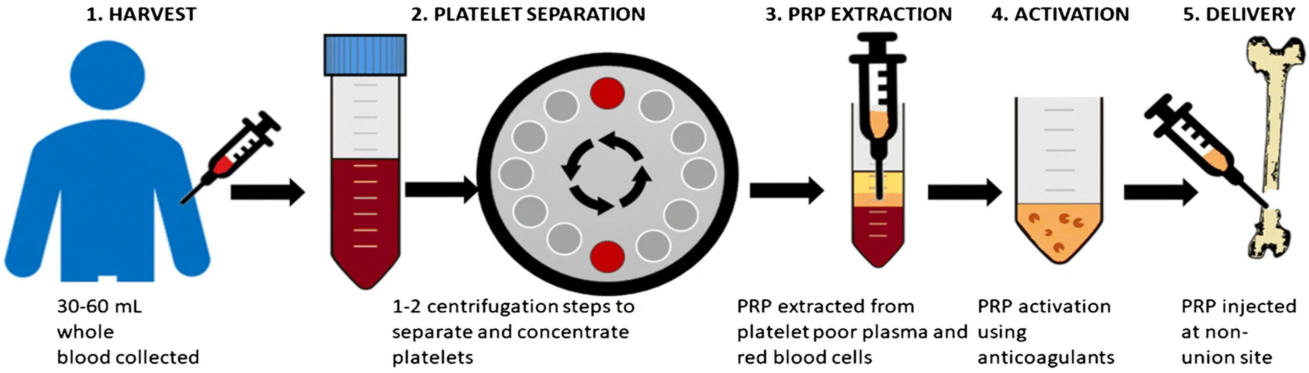

Figure 2. A generalised overview of the PRP process (Copyright acquired from Ref [24]).

PDGF, one of the key components of PRP, is instrumental in the recruitment and proliferation of osteoblasts and mesenchymal stem cells at the site of bone injury [27]. It also stimulates angiogenesis, which is essential for providing the necessary blood supply for bone regeneration. The role of PDGF in bone healing has been well documented in various studies, which show enhanced recovery in bone defects and fractures when PDGF is applied locally [28,29].

TGF-β is another potent growth factor in PRP that plays a multifaceted role in bone metabolism. It promotes the proliferation and differentiation of osteoblasts into mature osteoblasts and regulates the deposition of extracellular matrix proteins that are essential for bone tissue structure. TGF-β also modulates the immune response at the injury site, reducing inflammation and enabling the proper healing environment [30]. Additionally, TGF-β is involved in the formation of cartilage by chondrocytes, often acting as a precursor to bone formation in the healing process.

VEGF is essential for blood vessel formation during bone repair. It promotes the migration and proliferation of endothelial cells, leading to the formation of new blood vessels. This vascularization is essential for transporting oxygen, nutrients and repair cells to the site of bone injury, thus facilitating the healing process. The role of VEGF in bone regeneration, particularly in vascularized or low-vascular tissue, has been highlighted in recent clinical trials in which VEGF supplementation significantly improved the outcome of bone repair [31,32].

In addition to promoting osteoblastic activity and vascularization, PRP plays a role in regulating bone resorption. It affects osteoclast formation and activity, primarily through molecules such as osteoprotegerin found within the plasma. This regulation ensures a balanced bone remodeling process, crucial for maintaining bone density and structural integrity over time [33,34]. In addition, the effects of PRP extend to enhanced extracellular matrix (ECM) production. ECM components, such as collagen, glycoproteins, and proteoglycans, are essential for forming the scaffolders necessary for bone mineral deposits. PRP promotes the secretion of these components, thereby enhancing the mechanical properties of newly formed bone tissue.

The utilization of PRP in clinical settings has shown promising results in speeding up recovery times and improving the quality of bone repair, especially in cases of non-union fractures and osteoporotic lesions. Studies demonstrate the potential of PRP in reducing the incidence of complications in bone surgery and improving the outcomes of bone graft procedures. PRP's diverse array of growth factors makes it an invaluable tool in the management and treatment of bone-

related disorders. By harnessing the natural healing capabilities of these growth factors, PRP therapy presents a viable option for enhancing bone regeneration and repair, making it a focus of ongoing research and application in orthopedics and regenerative medicine.

3. PRP Drug Delivery Systems

Platelet-rich plasma (PRP) has evolved from a simple clinical adjunct to a sophisticated drug delivery system that leverages its inherent biological properties to enhance therapeutic outcomes, particularly in the field of osteoporosis. PRP's natural ability to release growth factors and other healing molecules has been harnessed to develop drug delivery systems that offer controlled release, enhanced bioactivity, and reduced side effects of osteoporosis treatments.

Osteoporosis is a chronic disease characterized by loss of bone mass and deterioration of bone tissue, leading to fragility and an increased risk of fracture. Traditional treatments include bisphosphonates, calcitonin and hormone replacement therapy, which, while effective, can cause serious side effects and do not address the root cause of bone loss. Prp-based drug delivery systems that promote bone regeneration and repair by binding bioactive molecules into biocompatible vectors represent a new therapeutic approach (Figure 2) [35].

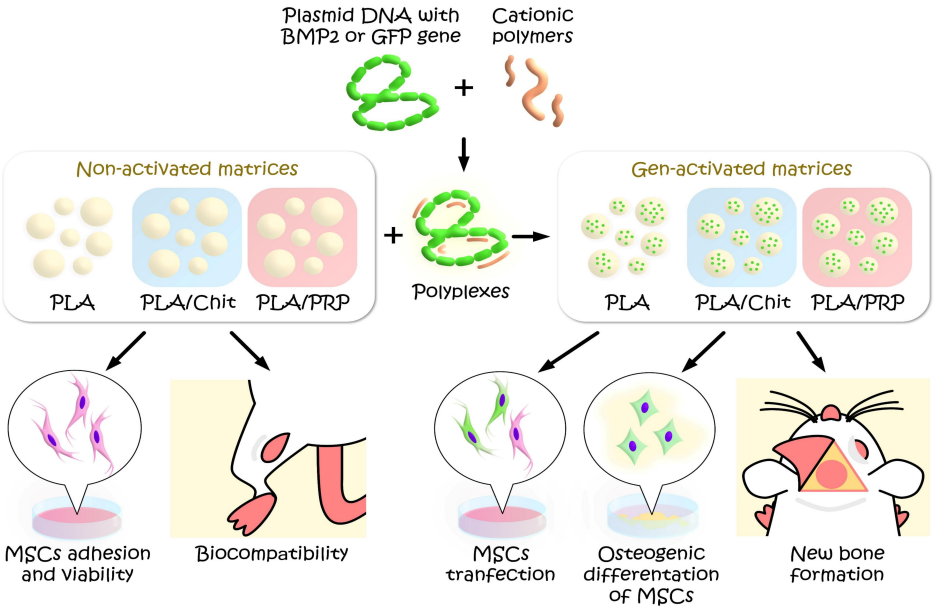

Figure 3. PRP-mediated drug delivery systems are used to promote bone repair (Copyright acquired from Ref [35]).

PRP-based systems typically utilize the plasma as a natural scaffold to encapsulate drugs, thereby providing sustained release at the site of bone degeneration [36]. This method significantly enhances the bioavailability of drugs and allows for lower dosages, reducing the potential for systemic side effects. Recent advancements have seen the development of PRP gels and fibrin matrices that can be loaded with osteogenic drugs and placed directly into bone lesions or areas of osteoporotic bone to stimulate bone growth and healing [37,38]. For instance, researchers have encapsulated simvastatin within PRP gels, which release the drug in response to natural bone resorption processes, thereby enhancing the drug's efficacy and reducing its side effects [39]. Another innovative approach involves integrating PRP with biodegradable polymeric scaffolds, which can be implanted into osteoporotic sites to provide structural support and simultaneous drug delivery [40].

The use of PRP also facilitates the co-delivery of multiple therapeutic agents, such as osteogenic peptides and bone morphogenetic proteins, which can synergistically enhance bone regeneration [41]. These combinations have been shown to effectively stimulate osteoblast proliferation and differentiation while inhibiting osteoclast activity and promoting a balanced bone remodeling process. In addition, the combination of nanotechnology and PRP systems opens up new ways to enhance the delivery of osteoporosis drugs. Nanoparticles can be embedded within PRP to improve the delivery of hydrophobic drugs, protect drugs from premature degradation, and target them to specific sites within the bone [42,43]. This nanocomposite approach has been particularly effective in targeting drugs to micro-fractures within osteoporotic bones, where they can exert maximum therapeutic effects.

PRP drug delivery systems are also being developed for non-invasive routes, such as transdermal patches infused with PRP and osteoporosis drugs, offering a pain-free alternative to injections or surgical implantation [44-46]. These systems utilize micro-needles or iontophoresis to enhance the penetration of PRP and drugs through the skin, targeting the underlying bone tissue. In clinical trials, PRP-based drug delivery systems have demonstrated significant improvements in bone density and structural integrity, along with a reduction in fracture incidence among osteoporosis patients [47,48]. In addition, these systems have shown good compatibility and safety, with minimal adverse reactions reported. Despite these promising developments, challenges remain in optimizing the formulation, stability, and

scalability of PRP drug delivery systems. Current research focuses on improving drug encapsulation efficiency, controlling release kinetics, and ensuring long-term stability of PRP preparations.

The integration of PRP technology with advanced drug delivery systems holds significant promise for transforming the treatment landscape of osteoporosis. By providing targeted, sustained, and biologically synergistic therapeutic options, PRP-based systems could potentially reduce the reliance on systemic drugs and offer a more effective, patient-friendly approach to managing osteoporosis.

4. Clinical Applications and Efficacy

The utilization of platelet-rich plasma (PRP) in the clinical setting has gained considerable traction due to its potential to improve outcomes in osteoporosis-related conditions, particularly in the healing of fractures and enhancement of bone density. A multitude of clinical trials and observational studies have elucidated the efficacy of PRP, revealing its capacity to not only speed up the healing processes of fractures but also to augment bone mass and facilitate recovery of function.

The effective application of PRP in orthopedics is mainly due to its rich growth factors, such as PDGF, TGF-β, VEGF, etc., which have a significant promoting effect on the regeneration of bone tissue. These growth factors stimulate angiogenesis, enhance the proliferation and differentiation of osteoblasts, and regulate the activity of osteoclasts, thereby creating an environment conducive to bone repair and growth. In clinical trials, PRP has been shown to accelerate fracture healing by promoting the formation and maturation of callus, thereby significantly shortening recovery time [49-51]. For instance, a trial by Andrew et al. reported that Lewis rats with vertebral fractures treated with PRP injections showed a 30% or 40% faster healing rate compared to those who received standard care [52]. Furthermore, these rats exhibited improved pain scores and functional outcomes.

Additionally, PRP's role in increasing bone mass is particularly beneficial for patients with osteoporosis, who are susceptible to fractures even with minimal trauma. In a study, osteoporotic patients undergoing PRP therapy showed a marked increase in bone mineral density at the lumbar spine and femoral neck over a six-month period. An increase in bone density is associated with a reduced risk of subsequent fractures, which is a potential indication for PRP as a treatment for osteoporosis. PRP has also been successfully used for surgical intervention of osteoporotic fractures. By combining PRP with bone grafts or synthetic bone substitutes, surgeons have observed enhanced bone graft integration and stability [53]. For example, in surgeries involving the use of bone substitutes, the application of PRP has been found to stimulate faster and more robust bone ingrowth, thus improving the structural stability of the implant. Moreover, the use of PRP is not limited to fracture healing. It has also been applied in preventive treatments to strengthen areas of bone that are at high risk of fracture in osteoporotic patients. By injecting PRP into these high-risk areas, clinicians have been able to locally enhance bone density, potentially averting the occurrence of fractures.

Despite promising results, clinical use of PRP faces challenges, including variability in preparation methods and a lack of standardized protocols, which may impact treatment outcomes. Ongoing research aims to address these issues by developing standardized, reproducible PRP preparation techniques to ensure consistent quality and therapeutic potential. PRP offers a versatile and effective treatment modality for osteoporosis and related conditions. It provides a synergistic approach by enhancing the body's natural healing process and providing a bioactive scaffold that supports bone regeneration. Future research focused on optimizing PRP formulation and administration methods is expected to further establish PRP as a cornerstone therapy for osteoporosis treatment.

5. Challenges and Future Directions

The clinical application of platelet-rich plasma (PRP) as a drug delivery system provides a broad prospect for the treatment of osteoporosis. However, to fully exploit its potential, a number of major obstacles must be overcome. Major challenges include the lack of standardized protocols for PRP preparation, variability in growth factor concentrations, and the lack of established guidelines for optimal dosing and dosing schedules. These factors contribute to inconsistent clinical outcomes and complicate the widespread use of PRP therapy.

Standardization of PRP preparation is crucial as variations in platelet concentration and the presence of other cellular components can significantly influence the therapeutic efficacy of PRP [13]. The method of PRP activation and the formulation used can alter the profile and activity of the released growth factors, which are critical for bone regeneration. Research highlights the need for standardized extraction techniques that ensure a consistent yield of bioactive compounds critical for effective treatment outcomes. Understanding the long-term effects of growth factor release from PRP is another area that requires extensive investigation. While the short-term benefits of PRP in enhancing bone healing and density are well documented, the long-term consequences of sustained growth factor exposure remain poorly understood. Studies suggest that prolonged exposure to certain growth factors could potentially lead to adverse effects, such as unwanted bone overgrowth or ectopic bone formation [54]. Establishing the optimal dosing regimen is critical to maximize the therapeutic benefits of PRP while minimizing the potential risks. The effective dose can vary depending on the characteristics of the individual patient, the severity of osteoporosis, and the specific formulation of the PRP used. The study highlights the importance of tailoring treatment approaches, taking into

account patient-specific factors, to optimize treatment outcomes and safety. Regulatory considerations also play a key role in the clinical translation of PRP therapies. As with any new medical approach, PRP must undergo rigorous regulatory review to ensure its safety, effectiveness, and quality before it can be widely adopted. This includes costly and time-consuming approval processes that can limit the availability of PRP treatments. Cost-benefit analysis is also critical to ensure that PRP treatments offer a good value proposition compared to existing treatments.

Future directions for research should focus on addressing these challenges through the development of standardized PRP preparation protocols, detailed studies on the pharmacokinetics and long-term impacts of growth factor release, and the establishment of clinical guidelines for PRP use. Additionally, exploring the combinational use of PRP with other osteogenic agents may offer synergistic effects that enhance the overall treatment efficacy. Conducting large-scale, randomized clinical trials will be essential to validate the benefits and safety of PRP treatments, paving the way for their integration into standard clinical practice for osteoporosis management.

6. Conclusion

Platelet-rich plasma (PRP) emerges as a transformative approach in the treatment of osteoporosis, tapping into the body's innate regenerative capabilities. As a cutting-edge therapeutic option, PRP-based drug delivery systems show substantial promise in revolutionizing osteoporosis management. By harnessing the concentrated growth factors inherent in platelets, PRP therapies facilitate enhanced bone regeneration and repair, thus addressing the limitations of conventional treatments that largely focus on symptom management and disease progression control. The development of complex PRP formulations could lead to more targeted and effective interventions specifically designed to improve bone density and structural integrity. In addition, the patient-centered nature of PRP treatment - utilizing autologous blood products - reduces the risk of adverse reactions and increases patient acceptance of the treatment. This innovative approach not only promises to improve the mechanical properties of bones, but also significantly improve the overall quality of life for patients with osteoporosis, making it a key advance in orthopedic medicine.

Funding

Not applicable.

Author Contributions

YC and JW conceived the idea and wrote the reviews.

Conflict of Interest Statement

The author(s) declare(s) that there are no conflicts of interest regarding the publication of this review.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Acknowledgements

Not applicable.

Reference

[1] Akkawi I, Zmerly H. Osteoporosis: Current Concepts. Joints. 2018, 6(2), 122-127. DOI: 10.1055/s-0038-1660790

[2] Hennemann A. Osteoporosis: prevention, diagnosis and therapy. Medizinische Monatsschrift für Pharmazeuten. 2002, 25(5), 164-167. PMID: 12050922

[3] Pisani P, Renna MD, Conversano F, Casciaro E, Di Paola M, et al. Major osteoporotic fragility fractures: Risk factor updates and societal impact. World Journal of Orthopedics. 2016, 7(3), 171-181. DOI: 10.5312/wjo.v7.i3.171

[4] Reid IR. Short-term and long-term effects of osteoporosis therapies. Nature Reviews Endocrinology. 2015, 11(7), 418-428. DOI: 10.1038/nrendo.2015.71

[5] Ukon Y, Makino T, Kodama J, Tsukazaki H, Tateiwa D, et al. Molecular-Based Treatment Strategies for Osteoporosis: A Literature Review. International Journal of Molecular Sciences. 2019, 20(10), 2557. DOI: 10.3390/ijms20102557
[6] Fioravanti C, Frustaci I, Armellin E, Condo R, Arcuri C, et al. Autologous blood preparations rich in platelets, fibrin and growth factors. ORAL & Implantology. 2015, 8(4), 96-113. DOI: 10.11138/orl/2015.8.4.096
[7] Kartika RW, Alwi I, Suyatna FD, Yunir E, Waspadji S, et al. The role of VEGF, PDGF and IL-6 on diabetic foot ulcer after Platelet Rich Fibrin + hyaluronic therapy. Heliyon. 2021, 7(9), e07934. DOI: 10.1016/j.heliyon.2021.e07934
[8] Lubkowska A, Dolegowska B, Banfi G. Growth factor content in PRP and their applicability in medicine. Journal of Biological Regulators and Homeostatic Agents. 2012, 26(2 Suppl 1), 3S-22S. PMID: 23648195
[9] Lucarelli E, Fini M, Beccheroni A, Giavaresi G, Di Bella C, et al. Stromal stem cells and platelet-rich plasma improve bone allograft integration. Clinical Orthopaedics and Related Research. 2005, 62-68. DOI: 10.1097/01.blo.0000165736.87628.12
[10] Schlegel KA, Zimmermann R, Thorwarth M, Neukam FW, Klongnoi B, et al. Sinus floor elevation using autogenous bone or bone substitute combined with platelet-rich plasma. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics. 2007, 104(3), e15-25. DOI: 10.1016/j.tripleo.2007.04.021
[11] Xie Y, Zhang LC, Xiong Q, Gao YP, Ge W, et al. Bench-to-bedside strategies for osteoporotic fracture: From osteoimmunology to mechanosensation. Bone Research. 2019, 7, 25. DOI: 10.1038/s41413-019-0066-7
[12] Albanese A, Licata ME, Polizzi B, Campisi G. Platelet-rich plasma (PRP) in dental and oral surgery: from the wound healing to bone regeneration. Immunity Ageing. 2013, 10(1), 23. DOI: 10.1186/1742-4933-10-23
[13] Fadadu PP, Mazzola AJ, Hunter CW, Davis TT. Review of concentration yields in commercially available platelet-rich plasma (PRP) systems: a call for PRP standardization. Regional Anesthesia Pain Medicine. 2019. DOI: 10.1136/rapm-2018-100356
[14] Kramer ME, Keaney TC. Systematic review of platelet-rich plasma (PRP) preparation and composition for the treatment of androgenetic alopecia. Journal of Cosmetic Dermatology. 2018, 17(5), 666-671. DOI: 10.1111/jocd.12679
[15] Bahraminasab M, Doostmohammadi N, Talebi A, Arab S, Alizadeh A, et al. 3D printed polylactic acid/gelatin-nano-hydroxyapatite/platelet-rich plasma scaffold for critical-sized skull defect regeneration. BioMedical Engineering OnLine. 2022, 21(1), 86. DOI: 10.1186/s12938-022-01056-w
[16] Chang SH, Hsu YM, Wang YJ, Tsao YP, Tung KY, et al. Fabrication of pre-determined shape of bone segment with collagen-hydroxyapatite scaffold and autogenous platelet-rich plasma. Journal of Materials Science: Materials in Medicine. 2009, 20(1), 23-31. DOI: 10.1007/s10856-008-3507-1
[17] Zhu LB, Li P, Qin YH, Xiao BW, Li JN, et al. Platelet-rich plasma in orthopedics: Bridging innovation and clinical applications for bone repair. Journal of Orthopaedic Surgery. 2024, 32(1), 10225536231224952. DOI: 10.1177/10225536231224952
[18] Liu F, Kang HL, Liu ZW, Jin SY, Yan GP, et al. 3D Printed Multi-Functional Scaffolds Based on Poly(epsilon-Caprolactone) and Hydroxyapatite Composites. Nanomaterials (Basel). 2021, 11(9), 2456. DOI: 10.3390/nano11092456
[19] Mancuso E, Shah L, Jindal S, Serenelli C, Tsikriteas ZM, et al. Additively manufactured BaTiO(3) composite scaffolds: A novel strategy for load bearing bone tissue engineering applications. Materials Science & Engineering. C, Materials for Biological Applications. 2021, 126, 112192. DOI: 10.1016/j.msec.2021.112192
[20] Jiang GY, Li S, Yu K, He B, Hong JQ, et al. A 3D-printed PRP-GelMA hydrogel promotes osteochondral regeneration through M2 macrophage polarization in a rabbit model. Acta Biomaterialia. 2021, 128, 150-162. DOI: 10.1016/j.actbio.2021.04.010
[21] Li JD, Chen ML, Wei XY, Hao YS, Wang JM. Evaluation of 3D-Printed Polycaprolactone Scaffolds Coated with Freeze-Dried Platelet-Rich Plasma for Bone Regeneration. Materials (Basel). 2017, 10(7), 831. DOI: 10.3390/ma10070831
[22] Keshavarz M, Jahanshahi M, Hasany M, Kadumudi FB, Mehrali M, et al. Smart alginate inks for tissue engineering applications. Materials Today Bio. 2023, 23, 100829. DOI: 10.1016/j.mtbio.2023.100829
[23] Zhang X, Cheng F, Islam MR, Li HB. The fabrication of the chitosan-based bioink for in vitro tissue repair and regeneration: A review. International Journal of Biological Macromolecules. 2024, 257(Pt 2), 128504. DOI: 10.1016/j.ijbiomac.2023.128504
[24] Andersen C, Wragg NM, Shariatzadeh M, Wilson SL. The use of platelet-rich plasma (PRP) for the management of non-union fractures. Current Osteoporosis Reports. 2021, 19, 1-14. DOI: 10.1007/s11914-020-00643-x
[25] Latalski M, Elbatrawy YA, Thabet AM, Gregosiewicz A, Raganowicz T, et al. Enhancing bone healing during distraction osteogenesis with platelet-rich plasma. Injury. 2011, 42(8), 821-824. DOI: 10.1016/j.injury.2011.03.010
[26] Smith OJ, Talaat S, Tomouk T, Jell G, Mosahebi A. An Evaluation of the Effect of Activation Methods on the Release of Growth Factors from Platelet-Rich Plasma. Plastic and Reconstructive Surgery. 2022, 149(2), 404-411. DOI: 10.1097/PRS.0000000000008772
[27] Niu WT, Lim TC, Alshihri A, Rajappa R, Wang LS, et al. Platelet-Derived Growth Factor Stimulated Migration of Bone Marrow Mesenchymal Stem Cells into an Injectable Gelatin-Hydroxyphenyl Propionic Acid Matrix. Biomedicines. 2021, 9(2), 203. DOI: 10.3390/biomedicines9020203
[28] Graham S, Leonidou A, Lester M, Heliotis M, Mantalaris A, et al. Investigating the role of PDGF as a potential drug therapy in bone formation and fracture healing. Expert Opinion on Investigational Drugs. 2009, 18(11), 1633-1654. DOI: 10.1517/13543780903241607
[29] Shah P, Keppler L, Rutkowski J. A review of platelet derived growth factor playing pivotal role in bone regeneration. The Journal of Oral Implantology. 2014, 40(3), 330-340. DOI: 10.1563/AAID-JOI-D-11-00173
[30] Patil AS, Sable RB, Kothari RM. An update on transforming growth factor-beta (TGF-beta): sources, types, functions and clinical applicability for cartilage/bone healing. Journal of Cellular Physiology. 2011, 226(12), 3094-3103. DOI: 10.1002/jcp.22698
[31] García JR, Clark AY, García AJ. Integrin-specific hydrogels functionalized with VEGF for vascularization and bone regeneration of critical-size bone defects. Journal of Biomedical Materials Research. Part A. 2016, 104(7), 1845. DOI: 10.1002/jbm.a.35777
[32] Tobiume S, Kaji Y, Nakamura O, Yamaguchi K, Oka K, et al. Effects of VEGF on Prefabricated Vascularized Bone Allografts in Rats. Journal of Reconstructive Microsurgery. 2021, 37(5), 405-412. DOI: 10.1055/s-0040-1718394
[33] Chen LW, Yang XB, Huang G, Song DW, Ye XS, et al. Platelet-rich plasma promotes healing of osteoporotic fractures. Orthopedics. 2013, 36(6), e687-694. DOI: 10.3928/01477447-20130523-10
[34] Ogino Y, Ayukawa Y, Kukita T, Atsuta I, Koyano K. Platelet-rich plasma suppresses osteoclastogenesis by promoting the secretion of osteoprotegerin. Journal of Periodontal Research. 2009, 44(2), 217-224. DOI: 10.1111/j.1600-0765.2008.01109.x
[35] Nedorubova IA, Bukharova TB, Mokrousova VO, Khvorostina MA, Vasilyev AV, et al. Comparative Efficiency of Gene-

Activated Matrices Based on Chitosan Hydrogel and PRP Impregnated with BMP2 Polyplexes for Bone Regeneration. International Journal of Molecular Sciences. 2022, 23(23), 14720. DOI: 10.3390/ijms232314720

[36] Kazakos K, Lyras DN, Thomaidis V, Agrogiannis G, Botaitis S, et al. Application of PRP gel alone or in combination with guided bone regeneration does not enhance bone healing process: An experimental study in rabbits. Journal of Cranio-Maxillo-Facial Surgery. 2011, 39(1), 49-53. DOI: 10.1016/j.jcms.2010.03.005

[37] Delgado D, Beitia M, Mercader Ruiz J, Sánchez P, Montoya-Alzola M, et al. A Novel Fibrin Matrix Derived from Platelet-Rich Plasma: Protocol and Characterization. International Journal of Molecular Sciences. 2024, 25(7), 4069. DOI: 10.3390/ijms25074069

[38] Liu W, Huang Y, Liu DQ, Zeng T, Wang JZ, et al. The Combination of Platelet Rich Plasma Gel, Human Umbilical Mesenchymal Stem Cells and Nanohydroxyapatite/polyamide 66 Promotes Angiogenesis and Bone Regeneration in Large Bone Defect. Tissue Engineering and Regenerative Medicine. 2022, 19(6), 1321-1336. DOI: 10.1007/s13770-022-00471-3

[39] Zhang Y, Yu J, Zhang JF, Hua YX. Simvastatin With PRP Promotes Chondrogenesis of Bone Marrow Stem Cells In Vitro and Wounded Rat Achilles Tendon-Bone Interface Healing In Vivo. The American Journal of Sports Medicine. 2019, 47(3), 729-739. DOI: 10.1177/0363546518819108

[40] Aoki K, Ideta H, Komatsu Y, Tanaka A, Kito M, et al. Bone-Regeneration Therapy Using Biodegradable Scaffolds: Calcium Phosphate Bioceramics and Biodegradable Polymers. Bioengineering (Basel). 2024, 11(2), 180. DOI: 10.3390/bioengineering11020180

[41] Park EJ, Kim ES, Weber HP, Wright RF, Mooney DJ. Improved bone healing by angiogenic factor-enriched platelet-rich plasma and its synergistic enhancement by bone morphogenetic protein-2. The International Journal of Oral & Maxillofacial Implants. 2008, 23(5), 818-826. PMCID: PMC2847851

[42] Rothe R, Hauser S, Neuber C, Laube M, Schulze S, et al. Adjuvant Drug-Assisted Bone Healing: Advances and Challenges in Drug Delivery Approaches. Pharmaceutics. 2020, 12(5), 428. DOI: 10.3390/pharmaceutics12050428

[43] Shang HT, Gu H, Zhang N. From traditional to novel treatment of arthritis: a review of recent advances in nanotechnology-based thermal therapy. Nanomedicine (Lond). 2021, 16(23), 2117-2132. DOI: 10.2217/nnm-2021-0182

[44] Gentile RD. Easy Platelet-Rich Fibrin (Injectable/Topical) for Post-resurfacing and Microneedle Therapy. Facial Plastic Surgery Clinics of North America. 2020, 28(1), 127-134. DOI: 10.1016/j.fsc.2019.09.011

[45] Li Y, Ju XJ, Fu H, Zhou CH, Gao Y, et al. Composite Separable Microneedles for Transdermal Delivery and Controlled Release of Salmon Calcitonin for Osteoporosis Therapy. ACS Applied Materials & Interfaces. 2023, 15(1), 638-650. DOI: 10.1021/acsami.2c19241

[46] Sim J, Kang G, Yang H, Jang MY, Kim Y, et al. Development of Clinical Weekly-Dose Teriparatide Acetate Encapsulated Dissolving Microneedle Patch for Efficient Treatment of Osteoporosis. Polymers (Basel). 2022, 14(19), 4027. DOI: 10.3390/polym14194027

[47] Laver L, Marom N, Dnyanesh L, Mei-Dan O, Espregueira-Mendes J, et al. PRP for Degenerative Cartilage Disease: A Systematic Review of Clinical Studies. Cartilage. 2017, 8(4), 341-364. DOI: 10.1177/1947603516670709

[48] Roffi A, Di Matteo B, Krishnakumar GS, Kon E, Filardo G. Platelet-rich plasma for the treatment of bone defects: from pre-clinical rational to evidence in the clinical practice. A systematic review. International Orthopaedics. 2017, 41(2), 221-237. DOI: 10.1007/s00264-016-3342-9

[49] Alsousou J, Thompson M, Hulley P, Noble A, Willett K. The biology of platelet-rich plasma and its application in trauma and orthopaedic surgery: a review of the literature. The Journal of Bone and Joint Surgery. British Volume. 2009, 91(8), 987-996. DOI: 10.1302/0301-620X.91B8.22546

[50] Komatsu DE, Warden SJ. The control of fracture healing and its therapeutic targeting: improving upon nature. Journal of Cellular Biochemistry. 2010, 109(2), 302-311. DOI: 10.1002/jcb.22418

[51] Li S, Xing F, Luo R, Liu M. Clinical Effectiveness of Platelet-Rich Plasma for Long-Bone Delayed Union and Nonunion: A Systematic Review and Meta-Analysis. Frontiers in Medicine. 2021, 8, 771252. DOI: 10.3389/fmed.2021.771252

[52] Simman R, Hoffmann A, Bohinc RJ, Peterson WC, Russ AJ. Role of platelet-rich plasma in acceleration of bone fracture healing. Annals of Plastic Surgery. 2008, 61(3), 337-344. DOI: 10.1097/SAP.0b013e318157a185

[53] Roffi A, Filardo G, Kon E, Marcacci M. Does PRP enhance bone integration with grafts, graft substitutes, or implants? A systematic review. BMC Musculoskeletal Disorders. 2013, 14, 330. DOI: 10.1186/1471-2474-14-330

[54] Rose LF, Rosenberg E. Bone grafts and growth and differentiation factors for regenerative therapy: a review. Practical Procedures & Aesthetic Dentistry. 2001, 13(9), 725-734; quiz 736, 721-722. PMID: 11862923