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Review

Platelets as Regenerative Cells, Hundreds of Opportunities in Sight

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Special Issue: Prospects of Platelet Rich Plasma in Regenerative Medicine

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Abstract

Platelets were the last to be discovered of the three formed blood elements. Several scientists have been interested in them, recognizing them as cells other than leukocytes and erythrocytes. Its job in hemostasis and thrombosis is currently known. Platelets contain growth factors and secrete cytokines, which have roles in inflammation and tissue regeneration processes. This is why platelet concentrates have been widely used in regenerative medicine, an emerging field that involves biomolecules, cells, and scaffolds. Due to their chemotactic, angiogenic, immunomodulatory, and cell differentiation-generating properties, platelets have been used to promote the regeneration of tissues such as bones, tendons, ligaments, and wounds. The efficacy and safety of platelet-rich plasma (PRP) have been demonstrated in various medical scenarios. However, it is essential to implement standardized protocols for each population's conditions and conduct clinical studies based on the available evidence. It must be considered that, as a biological product, the number of

platelets used, the number of growth factors, and the way of application will lead to results that will depend on each patient.

Keywords
Platelet-rich plasma; growth factors; regenerative medicine; tissue engineering; clinical applications

1. Introduction

The study of platelet function began over 100 years ago, when researchers identified unique characteristics crucial for hemostasis and thrombosis. In the context of biochemical research aimed at countering cellular aging processes, tissue regeneration, and wound healing, platelet-rich plasma (PRP) has been studied and utilized for its modulating and stimulating properties on various cell and tissue types.

There is no standardized production or preparation protocol, nor has a specific dosage been established. The method of application varies significantly and depends on the condition being treated. Nevertheless, positive effects have been observed in dentistry, orthopedics, dermatology, reconstructive medicine, ophthalmology, sports medicine, and vascular medicine. In this literature review, we explore the history of platelets' discovery, function, and the growth factors they contain to provide an update on their application in tissue regeneration. This allows us to recognize the properties and some indications of this preparation, which can improve the characteristics of many cells in our body.

2. Discovery of Platelets Physiology and Function

Of blood cells, platelets were the last to be discovered. This can be explained by their small size, limitations regarding chromatic aberration of the microscopes of past centuries, and the agglutination during the taking of the sample; aspects that prevented them from being observed as independent particles.

The German Friederich Arnold was the first anatomist to recognize and illustrate platelets in his book “Handbuch der Anatomie des Menschen”, published in 1845, and called them “elementary granules”, with the characteristic of having one-third the size of erythrocytes. Later, in 1862, anatomy professor Max Schultze described colorless corpuscles that tended to clump together and called them “little elements”. He also thought they were the remains of leukocytes after their destruction. Riess, in 1872, supported the same hypothesis as Schultze and called them "disintegration bodies" [1].

Edme Felix Alfred Vulpian discovered in 1873 that these colorless blood bodies could adhere to glass and form aggregates. Around the same time, Louis Antoine Ranvier observed that during coagulation, fibrous matter appears with granulations, as well as morphology and staining characteristics different from those of erythrocytes and leukocytes [2].

At the end of the 19th century, the Italian scientist Giulio Bizzozero recognized platelets as cells, different from leukocytes and erythrocytes, and acquired a better understanding of platelets by recognizing that hemostasis and thrombosis are analogous processes [3].

Nowadays, platelets are known as enucleated cells that are generated in the bone marrow by fragmentation of the edges of megakaryocytes. Their size is 1-2 μm, and they can accumulate where the endothelium is dysfunctional or damaged within the arterial wall, which initiates thrombus formation [4].

Physiologic platelet count ranges from 150 to 400 × 10^9/L of blood. The life expectancy of platelets is 7 to 10 days. They have no nucleus and lack gene transcription. In a physiological environment, platelets circulate in an inactive form and express on their surface a relatively small proportion of the molecules that can express in an activated state, facilitating their interaction with other platelets and other cells in their environment. Platelets contain different granules (dense granules, α granules, and lysosomes). When these cells are activated, they release various growth factors stored, which stimulate the activity of the platelet itself. However, they also have biological effects on other cells of the injured environment [5].

Platelets are one of the first cells to accumulate at sites of tissue damage, releasing growth factors that initiate an inflammatory cascade that attracts leukocytes, activates target cells, and stimulates the growth and repair of damaged vessels [6].

The platelet's work is well known today thanks to the new Omics developments. After endothelium damage, platelet adhesion occurs through compounds such as collagen via calcium ion platelet entrance. Then follows the formation of a clump made up of many of them, a process known as platelet aggregation because of pseudopod formation, cell surface receptor interactions and release of compounds like fibrin, thromboxane A2, platelet factor four, and fibronectin, among others; that allows the formation and stability of the clot. Additionally, they can take different shapes, depending on the type of signal received and its duration, which permits them to form other structures, such as free thrombi (emboli) and platelet plugs [7].

Different receptors mediate the interaction between platelets with themselves, and with other cells. They have four types of receptors: integrins, selectins, glycoproteins, and immunoglobulin-like receptors. Namely, the cellular adhesion to the extracellular matrix proteins collagen is mediated mainly by integrin αIIbβ3, also known as GPIIb-IIIa, employing different agonists, such as adenosine diphosphate (ADP), thromboxane A2, fibrinogen, and thrombin, in turn, synthesized and released by activated platelets, which results in more platelets being attracted and becoming part of the thrombus [7]. Each agonist/receptor binding activates a different signaling pathway, e.g., interaction through ADP allows the calcium entry favoring the platelet shape change, the release of thromboxane A2, and binding of platelets to other extracellular matrix proteins like vitronectin and osteopontin. Interaction through fibrinogen activates kinase pathways, resulting in the rise of intracellular calcium levels and thus favoring the cytoskeletal reorganization of platelets, their contact with the vessel walls, and the release of growth factors. Finally, all these responses lead to the start of the coagulation cascade, which aims to obtain a fibrin network that stabilizes the clot and maintains the platelet aggregate [8].

3. Beyond Their Role in Hemostasis and Thrombosis

Platelets also play an essential role as immunomodulators since they secrete proinflammatory molecules such as interleukin-1β, RANTES, and Monocyte Chemoattractant Protein-1 (MCP-1), among others. This modulation can occur through granules, noncoding RNA species, and exosomes. Furthermore, they can be affected by different immune molecules because they express a variety

of chemokine and cytokine receptors, and other immune receptors. Their interaction with not only endothelial but also immune cells possible. Activated platelets also release CD40L (CD154), a glycoprotein that favors the inflammatory and thrombotic response and antibody production [9]. Additionally, the expression CD40L (CD154) can stimulate T cells, acting as antigen-presenting cells. Platelets also interact with vascular cells [10, 11].

On the other hand, platelets can modulate the innate immune response against pathogens through the expression of receptors such as Fc gamma receptor IIA, through which platelet and leukocyte aggregates immobilize microorganisms. Platelet pattern recognition receptors (PRR), for example, Toll-like receptors (TLRs), bind pathogen-associated molecular patterns (PAMPs) from infectious agents, leading to the release of proinflammatory molecules that activate the phagocytic cells and thus ending the innate immune response. TLR-4 increases the platelet-neutrophil aggregates [12].

In addition to modulating cellular responses, inflammatory activation, or apoptosis; recent studies have shown that platelets can influence the extent of tissue injury after ischemia. They carry considerable amounts of cytokines and growth factors in their secretory granules, and the large number of platelets that circulate in the bloodstream makes them an essential force in the immune response in health and disease processes [13].

4. Platelets and Tissue Regeneration

In recent years, the key role of platelets in tissue regeneration has been revealed. When tissue and vascular damage occurs, platelets are activated, inducing the formation of a platelet plug and a blood clot whose function is to achieve hemostasis. As explained before, platelets contain secretory cytoplasmic and lysosomal granules, microparticles, and exosomes, which release growth factors, cytokines, adhesive molecules, chemokines, and other signaling molecules that accelerate the healing of both soft and hard tissues [14, 15].

Biochemical investigations that have delved into the physiology of platelets have elucidated their modulating and stimulating properties of the proliferation of cells derived from stem cells of mesenchymal origin, such as fibroblasts, osteoblasts, endothelial cells, epithelial cells, adipoblasts, myocytes, and chondrocytes, mainly; resulting in collaborative work to improve tissue regeneration. During the initial stages of tissue repair, some growth factors contained in the alpha granules of platelets, such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), insulin-like growth factor (ILGF) and transforming growth factor beta 1 (TGF-β1) are released to fulfill different roles in the process of regeneration. For example, PDGF functions as a chemoattractant molecule for fibroblasts, neutrophils, and macrophages, promotes the release of other growth factors and favors extracellular matrix synthesis. TGF-β1 acts as pro-inflammatory and modulates the keratinocyte migration during the remodeling phase. FGF and VEGF stimulate angiogenesis by contributing to endothelial cell migration, proliferation, and differentiation. In general, they all promote the migration and proliferation of mesenchymal and epithelial cells, increasing the production of extracellular matrix proteins and helping form fibrous connective tissue [15].

Another of the main functions of growth factors is the external control of the cell cycle through the abandonment of cell quiescence (G0) and the entry of the cell into the G1 phase. Growth factors stimulate the increase in cell size by increasing protein synthesis in the cells on which they act.

Considering the properties of platelets, autologous and heterologous platelet concentrates have been used in regenerative medicine and tissue engineering strategies in applications of many branches of medicine, dentistry, and other allied sciences because of their role in wound healing and repair [16].

This is why platelet concentrates have been widely used since 1970. They are characterized by having a higher concentration of platelets and other living cells, releasing growth factors, chemoattractant and immunomodulator molecules, and undertaking as a scaffold [17].

5. Characteristics of Platelet-Rich Plasma

Platelet-rich plasma (PRP) is a biological product composed of a fraction of plasma with a platelet concentration higher than baseline, obtained after centrifugation of whole blood. It can be autologous or heterologous. It is rich in growth factors that come from the alpha granules of platelets (Table 1). Indeed, platelet-rich plasma contains a high concentration of chemokines, cytokines, adhesion molecules like fibrin, fibronectin, metalloproteinases, vitronectin, and many other growth factors released by activated platelets, including platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF), fibroblastic growth factor (FGF), an insulin-like growth factor (IGF), as previously mentioned [18, 19].

Table 1 Main molecules stored in the α-granules of platelets and some of their roles in tissue regeneration [20, 21].

Molecule	Main functions
Epidermal growth factor (EGF)	Stimulates migration, cell growth, and differentiation of keratinocytes
Platelet-derived growth factor (PDGF)	Chemoattractant, stimulates the synthesis of various proteins and proangiogenic factors.
Fibroblast growth factor (FGF)	Stimulates angiogenesis, epithelialization, and granulation tissue formation.
Vascular endothelial growth factor (VEGF)	Stimulates angiogénesis
Insulin-like growth factor I (IGF-I)	Stimulates cell differentiation, proliferation, and collagen synthesis
Platelet-derived epithelial cell growth factor (PDEGF)	Promotes angiogénesis
Transforming growth factor-beta (TGF-β)	Chemotactic, induces fibroblast differentiation, and endothelial cell proliferation, and formation of the Extracellular Matrix (ECM)
Interleukins such as: IL-1 β, IL-4, IL-6, IL-10, Tumor necrosis factor alpha (TNF-α)	Inflammatory and pro-inflammatory activity
Fibronectin, fibrinogen, vitronectin, von Willebran factor	Induce thrombus formation, stimulate cell adhesion, and participate in cell division.
Interleukin (IL) 1 receptor antagonist (IL-1ra)	Blocks the IL-1 receptor, inhibiting its activity

Interferon-gamma	Promotes the inhibition of IL-18, a pro-inflammatory and chemotactic factor
Fibrinogen	It forms a matrix that offers a growth factors reservoir and environment for cell adhesion, proliferation, and migration.

The preparation of PRP by centrifugation, starting from anticoagulated whole blood, must be done under sterile conditions, handled in a biological safety cabinet, and at room temperature (20-24°C). Various protocols are available to obtain platelet-rich plasma, ranging from laboratory techniques (single or double centrifugation) to commercial kits. Regarding the type of anticoagulant used when taking the blood sample, acid citrate dextrose (ACD) is one of the anticoagulants that best maintains the optimal pH (7.2) conditions of the platelets [22, 23].

6. PRP Classification

In 2009 Ehrenfest et al, qualitatively classified PRP according to cellular content and fibrin architecture into 4 groups Pure platelet-rich plasm (P-PRP), Leukocyte and platelet-rich plasm (L-PRP), Pure platelet-rich fibrin (P-PRF) and Leukocyte and platelet-rich fibrin (L-PRF) [24].

Later, in 2012, DeLong et al, added a quantitative element and proposes the PAW classification (Platelets concentration, Activation and White blood cell count) [25]. For 2015, Mautner et al recommended the PLRA classification (Platelet count, Leukocyte presence, Red blood cell presence, and use of Activation) [26].

In 2016, Malagón and collaborators published the DEPA classification (Dose of injected platelets, Efficiency of production, Purity of the PRP, and Activation of the PRP), which added evaluation elements related to the PRP preparation process [27].

The latest proposed classification system is the MARSPILL (Method, Activation, RBCs, Spin, Platelet concentration, Image-guided, Leukocyte concentration, Light activation), developed by Lana et al., in 2017. These researchers considered it essential to evaluate the concentration of leukocytes and incorporated the activation of platelets with light and reference images that facilitate classification [28].

Currently, work continues incorporate new parameters and generate subclassifications. However no international classification system has been adopted [29].

7. PRP from Autologous or Allogeneic Platelets?

Autologous platelets from the patient do not lead to immunogenic reactions, disease transmission, or rejection. The blood draw is proportional to the PRP needed [30]. On the other hand, the effectiveness and safety of allogenic PRP have been proposed in different studies to manage wound healing. Shan G-Q et al. treated 21 patients suffering refractory diabetic lower extremity ulcers with ABO- compatible allogenic PRP, they found that ulcer size and pain were decreased in two weeks after treatment, and 85.7% of the patients had healed wounds without side effects and HLA class I antibodies production [31].

Even though these results are promising, a lack of control or placebo groups limits their interpretation. He M et al., in a case-controlled study, showed that autologous and ABO- compatible allogenic PRP, used topically, are comparable concerning decrease in healing time and safety for the

treatment of refractory diabetic lower extremity ulcers. In both studies, quality assurance of hemocomponents, includes examination of infectious markers such as human immunodeficiency virus, hepatitis B and C virus, before starting the treatment [32].

In another randomized study involving 60 patients with refractory wounds located in different body parts, Liao X et al, assigned the volunteers to the allogenic PRP group, where the PRP was obtained from close relatives of the patient screened for transfusion transmissible infections as negatives, or to the control group, which were treated employing regular wound cleaning methods. After the treatment with allogenic PRP from the first week, healing percentages were observed approximately 2 times better than in the control group. Therefore, this shortens the healing time of wounds with no adverse reactions [33].

The use of autologous platelets significantly reduces the risks of immunological rejection reactions. The choice between allogeneic and autologous platelets depends on the clinical context and the patient's specific needs.

8. PRP for Musculoskeletal Management

Trauma is the damage caused by the sudden exposure of the organism to sources or concentrations of mechanical, chemical, thermal, or radiant energy that exceed its tolerance margin, and it is associated with high increasing morbimortality rates worldwide [34].

After aggression that involves loss of tissue, the body responds with a process of restoration of the affected tissue, which begins with the appearance of a blood clot, where platelets appear during the first hours and, in cooperation with fibrin, they form bruises, later fibrous tissue, which fills the defect [35, 36].

Up to 70% of the growth factor content of activated PRP can be released in the first 10 minutes. Bone healing is generated with the physiological activation of platelets and the release of growth factors and various cytokines. It modulates the formation of soft and hard calluses and bone remodeling [37].

Al-Hamed, Faez et al. show how differences in PRP obtaining protocol can influence the bone healing outcome, finding that leukocyte and platelet-rich plasma (L-PRP) obtained after two centrifugations protocol significantly reduces the size of bone defects in rats, compared to that obtained through centrifugation or after filtration. This result can result from the major concentration of platelets in the double spin protocol [38].

PRP has been widely used in maxillofacial surgery and regenerative dentistry. Mandibular fractures are among the most frequent in facial trauma. González-Ojeda et al, conducted a controlled clinical trial with 20 patients with mandibular angle fracture. The study group underwent fracture reduction, internal fixation, and PRP application, and the control group underwent the same procedure without PRP administration. The PRP used was autologous and obtained using a commercial kit. Radiographic intensity and density in the first month and at 3 months were higher in the group that applied PRP compared to the control group ($p < 0.005$). Regeneration time was 3.7 ± 0.48 and 4.5 ± 0.52 weeks, respectively ($p = 0.002$). The authors concluded that PRP increased the intensity and bone density in the fracture lines and recovery in less time, in contrast to the control group [39].

PRP has been used in dentistry (including endodontics, periodontics, and maxillofacial surgery) for several years due to its regenerative properties on both soft and hard tissues. A review on

regenerative dentistry explains that PRP reinforces cell proliferation and differentiation in the root canal, promotes revascularization, and revitalizes and regenerates oral tissues. In endodontics, PRP serves as a tool for regeneration. Although contradictory results have been published in periodontics, PRP has shown improvement in treating intrabony defects. For maxillofacial surgery, growth factors in PRP contribute to postoperative pain reduction and prevention of osteitis development, making its use advisable before or during implant placement. However, the review emphasizes the need for further research with standardized protocols despite the reported benefits of clinical PRP use [40].

Recent evidence highlights the growing importance of PRP as an adjunct in bone healing. *In vitro* studies demonstrate PRP's regenerative potential at the cellular level by stimulating cell types and promoting proliferation, gene expression, and migration. Pre-clinical animal research confirms positive effects on radiographic, histopathologic, and biomechanical aspects of bone regeneration. Clinical studies support PRP's role in bone healing but emphasize the need for rigorous methodologies. Bacevich et al., mention that it is impossible to recommend the routine use of PRP for the healing of fractures and the treatment of pseudarthrosis. Further exploration is warranted regarding dose-dependent effects and PRP formulations. PRP offers advantages like enhanced cellular responses and accelerated tissue restoration, but integration into evidence-based practice requires standardized clinical investigations [41].

Laver L et al. reviewed 29 studies on using PRP in treating cartilage degeneration, finding clinical benefits in all studies, regardless of the methodology for obtaining PRP, especially in young patients and patients with early osteoarthritis. Likewise, according to the studies by Chang et al., pure platelet-rich plasma (P-PRP) is more suitable for intra-articular use [42].

The study by Calori et al. supports using rhBMP-7, a recombinant bone morphogenetic protein, as a superior treatment for stimulating bone healing compared to PRP in patients with non-unions of long bone fractures. The promising results of rhBMP-7 suggest it could influence clinical practice by offering a more practical alternative for patients with difficult-to-heal fractures [43]. Arya and colleagues found that platelet-rich growth factor (PRGF) is promising in dental procedures, particularly in accelerating bone regeneration and improving soft tissue healing. It offers advantages such as reduced waiting times for further treatments, cost-effectiveness, and minimal donor site morbidity compared to traditional graft materials [44]. Further research into platelet derivatives is promising for advancing techniques in bone regeneration, potentially transforming dental care practices in the future [43].

9. Use of PRP in Alterations of Tendons and Ligaments

In a case report published by our research group, we applied autologous PRP to a 50-year-old soccer player with an injury at the origin of the hamstring muscle of the right thigh. Ultrasound (US) guided PRP injection was done 13 days after injury. Control by the US and nuclear magnetic resonance (NMR) was performed two weeks after the application of PRP, showing recovery of the injury and resolution of the hematoma. The patient returned to sports activities at week 12 after treatment, without pain and with improvement in muscle strength and healing of the hamstring muscles. PRP treatment could be an option to avoid surgical procedures [45].

In another systematic review and meta-analysis published in 2018, including 268 patients with grade I and II acute hamstring muscle injuries, they compared the time to return to sport and the

rate of new injuries after the use of physical therapy or injection of placebo versus platelet-rich plasma injection. Five randomized controlled trials were included. Results showed a significantly earlier return to sport for the PRP group compared with the control group (mean difference, -5.57 days [95% confidence interval, -9.57 to -1.58]); (P = 0.006). There were no differences related to time to return to sport when PRP and control therapy were compared in grade I and II hamstring strains. The use of PRP could mean an earlier return to sport in patients with grade I or II acute muscle strains without significantly increasing the risk of re-injury at 6-month follow-up [95% confidence interval, -9.57 at -1.58]; (P = 0.006) [46].

A systematic review of the literature by Madhi et al., determined the efficacy of platelet-rich plasma as a treatment option in chronic Achilles tendinopathy. They included 5 randomized controlled trials, 4 prospective and 2 retrospective cohort studies, 406 patients were treated for non-insertional Achilles tendinopathy, and 230 patients received local injections of PRP under ultrasound guidance. This study showed promising results fromusing platelet-rich plasm, which was demonstrated by a significant improvement in the VAST-A score. It also highlighted the need for well-designed randomized controlled trials to show accurate results [47].

Kwong et al. conducted a clinical study in patients with rotator cuff tendinopathy and partial-thickness rotator cuff tears (PTTRCT) using platelet-rich plasma compared with standard corticosteroid (CS) injection, both ultrasound-guided procedures. They included 99 patients (47 in the PRP group and 52 in the CS group). The researchers found an improvement in pain relief, assessed with the visual analog scale (VAS). Other functional outcomes included changes in American Shoulder and Elbow Surgeons (ASES) and Western Ontario Rotator Cuff Index (WORC) scores. Three months after injection, the PRP group had more significant improvement in VAS (-13.6 vs. 0.4, P = 0.03), ASES (13.0 vs. 2.9, P = 0, 02), and WORC (16.8 vs. 5.8, P = 0.03) scores. There were no differences in the results at 6 weeks or 12 months [48].

Epicondylitis is the pathology where more evidence exists on the use of PRP [49]. In a review carried out in 2018, a group of researchers mentioned that platelet-rich plasma had been used in different musculoskeletal disorders, which have included controlled and randomized studies trying to demonstrate that its use can repair tendons, ligaments, muscles, and cartilage and that there is currently level 1a evidence supporting its use for lateral epicondylitis, knee osteoarthritis, plantar fasciitis, and rotator cuff tendinopathy; and level 1b for patellar tendinopathy and hip osteoarthritis. Promising results have also been shown in retrospective cohort studies and case series with PRP for treating other musculoskeletal disorders [50].

Several studies and meta-analyses are mentioned, comparing PRP to conservative treatments such as rehabilitation exercises and placebo. The results suggest that PRP may be beneficial in reducing pain and encouraging an accelerated return to sports activities without increasing the risk of new injuries. The cited studies show promising results, such as improvements in muscle strength and injury recovery without surgery. However, PRP production and application protocol variability and a lack of consensus on dosing highlight the need for more controlled and standardized research to validate its efficacy and optimize its clinical use.

10. PRP in Wound Healing

Wound healing is a physiological event that begins with blood coagulation. Catabolic cleansing processes are activated, then the regeneration of new filler tissue, and ends with the structuring of

new tissue cicatricial. The wound healing process is an active, dynamic, and involuntary process in which the different phases that compose it overlap in time without being able to separate one from the other. These phases are inflammatory/exudative, proliferative, and differentiation or remodeling [51].

Various strategies are used in the search for wound healing, ranging from different types of dressings and negative pressure therapy to aloe vera. Other techniques include biological treatment, where amniotic membranes and cadaveric allografts, which are temporary, are used. Other biologics such as: Apligraft®, Matriderm®, and Alloderm® [52, 53] are permanent.

Various factors affect physiological tissue regeneration, generating clinical difficulties such as abnormal healing (hypertrophic, keloid, and atrophic), bleeding, ulcers, pain, pruritus, infection, and amputation [54].

In a case series, patients with chronic wounds were studied, 39 men and 21 women (57 ± 10 years). The researchers used allogeneic PRP, donated by a relative, which was processed using double centrifugation and activated with calcium gluconate. After 30 days of treatmen the wound closure was faster in the group treated with PRP. Between the first and the third week of treatment, they observed bright red granulation tissue, without signs of rejection or necrotic tissue, compared with the control group, which received conventional skin graft treatment [33].

A randomized controlled study conducted in 2018 compared the use of activated PRP in gel form vs hydrogel treatment in patients with chronic non-healing ulcers of different etiologies. They included 60 patients: 30 received a placebo with hydrogel, and 30 were treated with allogeneic platelet gel. Platelets were centrifuged once at 1,500 g for 8 min and activated using thrombin and calcium. Treatment was repeated weekly for 3 weeks and followed up 6 months after starting treatment. The investigators found that wound size decreased to 35.01% compared to 89.95% in controls ($p < 0.001$) at 6 months. No adverse reactions were observed. The researchers found more excellent stability of the platelet gel and prolongation of the effect; the patients who received the platelet gel apart from their wounds healed quickly and returned to everyday life [55].

Qin et al, conducted a study in 2019 on 90 patients with diabetic foot ulcers, applying autologous platelet-rich plasma, the patients were divided into three groups, 30 cases per PRP injection group; group A, PRP was injected, and a hydrogel dressing covered the wounds, group B, they used PRP gel and a hydrogel dressing covering the scars, and the control group, group C, they were covered only with a hydrogel dressing. The frequency of treatments in groups A, B, and C was (10.2 ± 0.8), (11.4 ± 0.6), (12.5 ± 0.5) times, respectively. They found statistically significant differences in the days of hospitalization of groups A, B, and C; (40.5 ± 1.8), (62.1 ± 2.3) and (88.6 ± 1.4) days, respectively. Group A patients showed better results than groups B and C. Wound areas, exudation, and necrosis were gradually reduced. The clinical application of PRP can improve and accelerate the healing of diabetic foot ulcers. The effectiveness of local injection of PRP is superior to local coverage with hydrogel [56].

Two treatment groups were compared in a study involving 52 spinal cord-injured patients with grade 3 or 4 sacral pressure ulcers. Group A received a hydrogel bandage covered with sterile cotton gauze. In contrast, Group B received a freshly prepared platelet-rich plasma (PRP) injected into the ulcer margin and base, followed by sterile cotton. After 6 weeks of follow-up, both groups showed improvement in ulcer area, PUSH score, and volume. However, the PRP group significantly enhanced epithelialization, granulation, and neovascularization. These findings suggest that PRP could be an alternative treatment for pressure ulcers [57].

Platelets contain growth factors that impact cell viability, proliferation, migration, angiogenesis, tissue repair, and inflammatory responses. In a study, human keratinocytes exposed to 10% PRP showed increased proliferation and migratory properties. Transcriptome analysis revealed induction of MMP9, fibronectin 1, collagen 1, and collagen XXII in PRP-treated keratinocytes. Beyond clotting, platelets play a crucial role in immunity, recognizing harmful microorganisms and contributing to wound healing. They may influence skin health by interacting with the microbiome [58].

11. PRP in Alopecia

Alopecia is abnormal hair loss resulting from a pathological process. The causes of alopecia are diverse and pose a challenge for both physicians and patients. It occurs in both men and women. Studies have shown that elevated levels of 5-alpha-reductase and dihydrotestosterone (DHT) play a role in androgenetic alopecia. Both hormonal and genetic factors contribute to its development. Testosterone is converted into DHT by the enzyme 5-alpha-reductase, which is present in hair follicles and other tissues throughout the body [59].

A study aimed to determine the clinical efficacy of platelet-rich plasma (PRP) in treating non-scarring alopecia. The study assessed the time required to demonstrate a reduction in hair loss, promote healthy hair growth, observe increased hair density, and measure patient satisfaction. It involved 261 patients with male androgenetic alopecia (AGA) up to grade IV and AGA in women up to grade II. The study found that hair loss reduction occurred at approximately 4.56 weeks, hair growth at 10.8 weeks, and increased density was evident in males at 4.6 months and in females at 7.25 months. Patient satisfaction was measured using a visual analog scale (average 7.6 in women and 7 in men). The study concluded that growth factors can reduce hair loss in non-cicatricial lesions, prolong follicle life, enhance quality, increase density, and result in high patient satisfaction [60].

Balasundaram et al. compared standardized non-activated PRP to topical minoxidil in men with AGA. The study included 64 participants aged 20-50 with Grade III and IV AGA. Although differences between the groups were not statistically significant, PRP effectively treated moderate AGA in men. Adverse events occurred in 53% of the PRP group and 37% of the minoxidil group, with higher patient satisfaction reported for minoxidil. Additional research and clinical trials are needed to compare PRP's effectiveness with FDA-approved treatments for moderate AGA [61].

In a randomized, double-blind, split-head comparative study, researchers investigated the effect of an activator in platelet-rich plasma and baseline platelet count on the treatment of androgenetic alopecia. The study included 80 patients. The activated PRP significantly improved hair density and thickness six months after four months. Increasing platelet count led to significant improvements in both parameters. The study concluded that the activator and platelet count significantly affect hair density and thickness [62].

Stem cells in hair follicles are believed to reside in the bulge area. Akiyama et al. focused on regulating the hair cycle and the growth factors involved. They observed intense labeling for growth factors such as transforming growth factor alpha (TGF-α), EGF receptors, and PDGF in bulge cells of human fetal stem cells. It was also found that the β1 factor protects the proliferative potential of basal keratinocytes by inhibiting cell growth and differentiation [63].

In a review of 27 controlled trials involving 1,117 subjects, researchers investigated the use of PRP for androgenetic alopecia and alopecia areata (AA). The studies included various PRP types and

administration schedules. PRP was compared to saline injections, local steroid injections, and other treatments. The most reported outcomes were hair density and regrowth. PRP injections increased hair density over the medium term compared to saline injections (mean difference: 25.6 hairs/cm^2; 95% CI: 2.62-48.57), but the evidence quality was low due to inconsistency and bias. For AA, it remains unclear whether PRP injections improve hair regrowth compared to triamcinolone injections [64].

In the case of the randomized controlled studies for AA selected by Paichitrojjana et al., they found that intralesional injection of PRP induces hair regrowth to the same extent as the application of triamcinolone acetonide. Still, less efficacy is observed compared to the use of the steroid. Therefore, it is considered that the use of PRP in this entity is indicated in patients who do not respond to conventional therapy [65].

Recent research suggests that PRP injections can increase hair growth and density in people with hereditary hair thinning or baldness. However, PRP therapy typically requires multiple sessions for optimal results, and maintenance treatments may be necessary.

In participants with AGA, the PRP treatment increased hair density but not diameter. PRP has more potent effects on male patients in terms of hair density. A trend in the direction of differing treatment effects by gender with PRP injection calls for further research, particularly in women. Table 2 summarizes the reviewed studies on the uses of PRP.

Table 2 Summary of reviewed studies on different uses of PRP.

BONE REGENERATION AND OSTEOARTRITIS			
AUTOR	**YEAR**	**TYPE STUDY**	**CONCLUSIONS**
Calori GM, et al	2008	A randomized clinical study. 60 patients	Consolidation fracture occurred in 86.7% cases in the rhBMP-7 group compared to 68.3% cases in the PRP group. The conclusion is that the use of rhBMP-7 as a bone-stimulating agent is superior to that of PRP.
Lavert L, et al	2017	Systematic review. 29 studies	Clinical benefits in all cases.
Castillo-Cardiel G, et al	2017	Controlled clinical trial. 20 patients	The PRP group increased the intensity and bone density in the fracture lines and recovered in less time, in contrast to the control group.
Arya V, et al	2019	Controlled clinical trial. 20 patients	Mean bone density 13 weeks after extraction was higher in the PRP treated socket.
Bacevich BM, et al	2024	Narrative review	Pre-clinical data support the therapeutic potential of PRP but clinical trials don't demonstrate unequivocally benefits.
WOUND HEALING			
Semenič D, et al	2018	A randomized controlled clinical study. 60 patients	The wound size in the PRP group decreased to 35.01% compared to 89.95% in controls ($p < 0.001$) at 6 months.
Qin X, et al	2019	Randomized controlled clinical study. 90 patients	The clinical application of PRP can improve and accelerate the healing of diabetic foot ulcers. The effectiveness of local injection of PRP is superior to local coverage with hydrogel.
Muñoz AL, et al	2019	Pilot study. 4 patients	The use of autologous PRP gel combined with biocompatible porous membranes produced with the polysaccharides chitosan and alginate led to the complete reduction of the area of the ulcers and a decrease in pain for a mean of 5.4 months.
Liao X, et al	2020	Case series. 52 patients	The closure of the wounds was faster in the group treated with PRP

Meznerics FA, et al	2022	Systematic review. 29 studies	The odds of achieving complete wound closure were markedly higher in the PRP group than in the control Group. Injected PRP showed greater improvement than topically applied PRP.
ALOPECIAS			
Cruciani, et al.	2021	Systematic review. 27 studies (18 AGA and 9 AA)	On average, the use of PRP injection compared with saline infusion may increase hair density over a medium-term follow-up. On average, it is unclear whether using PRP injection compared with triamcinolone injection increases the rate of subjects with hair regrowth over a follow-up period of 3-12 months.
Paichitrojjana A, et al	2022	Systematic review 13 studies (7 AGA, 6 AA)	Significant improvement in clinical symptoms in both groups (PRP vs Triamcinolone acetonide), but there was no significant difference between these two groups SALT score showed statistically significant improvement from baseline in both groups. Steroid group showed the most hair regrowth, followed by PRP group.
Abdin R, et al	2022	Systematic review 17 studies AGA	The study found that hair loss reduction occurred at approximately 4.56 weeks, hair growth at 10.8 weeks, and increased density was evident in males at 4.6 months and in females at 7.25 months.
Balasunderam M, et al	2023	Randomized clinical trial 64 patients AGA	PRP is effective in the treatment of moderate grades of androgenetic alopecia in men, although perhaps not different from minoxidil. The difference between the groups was not statistically significant. Adverse events occurred in 53% and 37% of the PRP and minoxidil groups, respectively. Patient satisfaction was better with Minoxidil.
Singh SK, et al	2023	Randomized, double-blind split-head comparative clinical study. 80 patients AGA	Activated PRP produced significant improvement of hair density after four months and hair thickness at 6 months. There is a significant effect of activator and platelet count of the platelet-rich plasma on hair density as well as hair thickness.
TENDINITIS/EPICONDYLITIS			

Pas HI, et al	2015	Systematic review and meta-analysis. 10 randomized controlled trials, only 3 studies used PRP injections.	The application of PRP was compared with physiotherapy programs, with a placebo, with injections of platelet-poor plasma, or without injection. The study found superior efficacy for rehabilitation exercises compared to PRP injection.
Shelth U, et al	2018	Systematic review and meta-analysis. 5 studies	significantly earlier return to sport for the PRP group compared with the control group (mean difference, -5.57 days [95% confidence interval, -9.57 to -1.58]; (P = 0.006).
Madhi MI, et al,	2020	Systematic review. 6 randomized controlled trials	PRP group demonstrated a significant improvement in the VAST-A score, as well as highlighting the need for well-designed randomized controlled trials to show accurate results.
Kwong CA, et al	2021	Clinical study 99 patients	The patients with rotator cuff tendinopathy and partial-thickness rotator cuff tears in the PRP group had greater improvement in VAS (-13.6 vs. 0.4, P = 0.03), ASES (13.0 vs. 2.9, P = 0, 02), and WORC (16.8 vs. 5.8, P = 0.03) scores. There were no differences in the results at 6 weeks or 12 months.
Gómez LA, et al	2021	Case report 1 patient	Two weeks after the application of PRP, recovery of the injury and resolution of the hematoma were observed. The patient returned to sports activities at week 12 after treatment, without pain and with improvement in muscle strength and healing of the hamstring muscles.

AGA. Allogenic alopecia. AA. Alopecia areta. SALT. Severity of Alopecia Tool Score. VISA-A. Victorian Institute of Sports Assessment – Achilles Questionnaire. VAS. visual analog scale for pain. ASES. American Shoulder and Elbow Surgeons Score. WORC. Western Ontario Rotator Cuff Index.

12. Discussion

Repair and regeneration are the goal of treating damaged tissues or organs. Although synthetic materials have been considered for enhancing healing, their avascular nature, mechanical properties, and immunogenic potential have made it necessary to improve and develop other biomaterials.

Due to their ability to orchestrate the cellular and molecular response at the injured environment, platelet concentrates have emerged as a tool to restore these defects safely and non-invasively. PRP has been used for more than 40 years, showing favorable results in applications such as bone regeneration, chronic wounds, alterations in tendons and ligaments, dentistry, and alopecia and we have seen technological changes in obtaining protocols and technologies during this time.

However, although there are many publications about it, there is a lot of disparity in the published results. Factors include variation in centrifugation parameters (device type, speed, and time conditions), hematocrit, PRP doses, application protocols, combined therapies, and duration of follow-up time. Furthermore, there are some studies in which low statistical power of the sample [30, 33], or lack of control or placebo groups are observed, which ultimately translates into a lack of standardization that at the same time may influence the quality of the PRP [57].

Another aspect to consider is the possibility of the presentation of adverse events after the use of PRP. Although its use is relatively safe, it has recently been associated with postoperative infections because of contamination with microbes during the PRP obtaining or application [66].

It is vital that treatment involving PRP use be carried out by trained personnel with strict quality procedures.

In general, the use of platelet-rich plasma shows fewer side effects than those of the control groups. The treatment is considered practically innocuous. Further randomized clinical trials and extensive prospective studies are needed to establish future indications and confirm efficacy, safety, and long-term stability as a therapy of choice in regenerative medicine.

13. Conclusions

Despite the advances in the procurement and application of PRP, there is currently no consensus on PRP formulations. The outcome of this therapy may be related to the number of platelet-derived growth factors, the cell-cell interactions, and the interactions between everyone's innate and adaptive immune systems. There is high quality evidence supporting the use of PRP in musculoskeletal disorders, reducing pain and encouraging an accelerated return to sports and physical activities. PRP is also considered a safe, effective, steroid-sparing, and alternative treatment for alopecia areata. PRP promoted the healing of patients with wounds, improving the healing rate and healing time.

PRP has been applied for various therapeutic purposes, and the efficiency of its use as regenerative therapy continues to be discussed due to the lack of consensus regarding its preparation techniques and dosage. In this sense, they could standardize the protocols based on the particularities of each country. For example, The Indian Association of Dermatologists, Venereologists, and Leprologists (IADVL) has formed a task force to prepare recommendations for the preparation and use of PRP in AGA. [58].

Platelet-rich plasma PRP is a treatment method for various medical conditions. The variability in the preparation and application of PRP can significantly affect the results. We consider that well-

designed clinical studies with sufficient statistical power are necessary to determine the therapeutic potential of PRP.

14. Limitations of Current PRP Research

Platelet-rich plasma (PRP) is a blood-derived product rich in signaling peptides, cytokines, and growth factors. Although it has been used in various fields of medicine, there are limitations and essential considerations:

1. Lack of Standard Protocol: No universal PRP production or preparation protocol exists. Additionally, a specific dosage for application has not been established.
2. Variability in Application: PRP application methods vary based on the condition being treated, making it challenging to compare results across studies.
3. International Regulation Differences: Regulations regarding PRP use differ across countries.
4. Limited Robust Clinical Trials: Despite expectations, robust clinical trials are insufficient to validate routine PRP use for specific conditions.
5. Difficulty Comparing Results: Variability in preparation methods and heterogeneity in treated lesions hinder comparison between studies.

In summary, while PRP shows promise, more rigorous research is needed to establish standardized protocols and demonstrate its effectiveness in various clinical conditions.

Author Contributions

The authors confirm contribution to the paper as follows: Elga J. Vargas: Study conception and design; data collection, analysis and interpretation of results, draft manuscript preparation. Ana L. Muñoz: Study conception and design, data collection, analysis and interpretation of results, draft manuscript preparation. Lina A. Gómez: Study conception and design, data collection, analysis and interpretation of results, draft manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

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Competing Interests

The authors have no conflicts of interest.

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