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REVIEW ARTICLE

Major clinical approaches on the bone regeneration with bone morphogenetic protein and platelet-rich plasma: a systematic review

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Abstract

Introduction: The production or regeneration of any tissue is a complex biological process in itself, since it requires intrinsically regulated interactions between cells, the action of systemic hormones, the participation of extracellular matrix components, and the local action of so-called growth factors. **Objective:** It was to review the concepts related to growth factors, as well as in relation to platelet rich plasma and bone morphogenetic protein as an adjuvant in bone regeneration therapies directed to implant dentistry. **Methods:** The systematic review rules of the PRISMA Platform were followed. The search was conducted from January to March 2026 across the Embase, Scopus, PubMed, Web of Science, and Google Scholar databases. The quality of the studies was assessed using the GRADE instrument, and the risk of bias was evaluated according to the Cochrane instrument. **Results and Conclusion:** According to the GRADE instrument, most studies presented homogeneous results, with X^2=81.7% > 50%. A total of 134 articles were found and submitted for eligibility analysis, with 45 final studies selected to compose the results of this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 14 studies with a high risk of bias and 22 studies that did not meet GRADE and AMSTAR-2 standards. It was concluded that the greatest advantages of the use of platelet-rich plasma are its ability to accelerate the process of bone regeneration by increasing the number of growth factors present in human platelets. On the other hand, it is observed that one of its major disadvantages is the low life expectancy of these platelets in the recipient or graft bed. However, it is also known that the PRP technique would only accelerate a process of bone regeneration that normally already occurs, and this process follows its path until the formation of mature bone.

Keywords: Bone regeneration. Bone Remodelation. PRP. BMP. Implant dentistry. Dental implant.

Introduction

Science has evolved at an accelerated pace in recent decades, due to the need to know more and more about the human being and the environment that surrounds it [1,2]. In the search for this knowledge, aiming to improve the quality of life and the treatment of diseases previously considered incurable, research, especially in the field of biotechnology, has transformed the dayto-day health professionals [3,4].

Concern about the healing process and / or repair of the various tissues of the human body, the progressive identification of components from the organic and inorganic matrix of the bone tissue, as well as the *in vitro* manufacturing capacity of the same, has been a constant target of a new research field called tissue engineering [4]. The production or regeneration of any tissue is a complex biological process in itself, since it requires intrinsically regulated interactions between cells, the action of systemic hormones, the participation of extracellular matrix components, and the local action of so-called growth factors [4].

The application of this biotechnology related to growth factors can be exemplified in the use of platelet-rich plasma (PRP), a gel capable of modulating and accelerating some repair processes, both bone and gingival, since this technique has been used in dentistry juntamente com células tronco mesenquimais and bone morphogenetic protein (BMP), in the areas of bucomaxillofacial surgery, implantology, and periodontics [4,5]. The simple strategy of obtaining the PRP gel is one of the success factors of this new technology, since in a few minutes we can have a ready-to-use concentrate containing inside the various growth factors usually present in the platelets. In addition, this gel obtained can be considered non-toxic and non-immunoreactive [5].

Regarding one of the indications for the use of PRP in dentistry, in implant dentistry, it is known that the technique of implant osseointegration presents a high predictability of success when the bone remnant is favorable in relation to its quantity and quality [5,6] . These initial conditions would be able to provide initial stability and optimal positioning of the implant to perform the posterior prosthetic step. The use of autogenous bone associated with platelet gel in the previous grafts would then be an excellent option in those cases where the requirements previously mentioned could not be filled [6,7].

The objective of this study was to review the concepts related to growth factors, as well as in relation to platelet rich plasma and bone morphogenetic protein as an adjuvant in bone regeneration therapies directed to implant dentistry.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed at: 01/24/2026. The AMSTAR 2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed at: 01/24/2026.

Search Strategy and Search Sources

The literature search process was carried out from January to March 2026 and developed based on Embase, Scopus, PubMed, Web of Science, and Google Scholar, covering scientific articles from various periods to the present day. The following descriptors were used in health sciences (DeCS/MeSH terms): *"Bone regeneration. Bone Remodelation. PRP. BMP. Implant dentistry. Dental implant"*, and the Boolean "and" was used between the MeSH terms and "or" between the historical findings. This study focuses on the treatment of bone regeneration through platelet-rich plasma and bone morphogenetic protein (BMP).

Main Predictors Continuous and Categorical

The main predictors are PRP and BMP.

Main Predictors Answer

The main predictor of response was bone regeneration.

Results and Discussion

Summary of Findings

A total of 134 articles were found and submitted to eligibility analysis, with 45 final studies selected to compose the results of this systematic review. The listed studies were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as metaanalysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=81.7%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 14 studies with a high risk of bias and 22 studies that did not meet GRADE and AMSTAR-2.

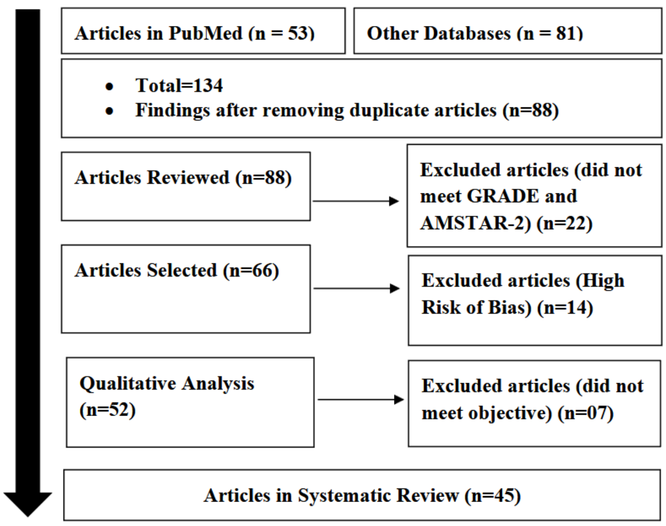

Figure 1. Flowchart showing the article selection process. Source: Own Authorship.

Major Clinical Findings

Platelets are viable cytoplasmic fragments of blood that are incorporated into each trauma or surgical wound. After millions of years of evolution, extremely important functions for platelets related to hemostasis and healing have been proven [1-5]. Some authors have observed that regenerative cells of the bone tissue, also called undifferentiated mesenchymal cells, occur only in small amounts when compared to other functional and structural cells [5-12].

The number of mesenchymal cells varies greatly from the newborn to the elderly. Mean values range from 1: 10000 in the newborn, 1: 100,000 at 15 years, 1: 250000 at 35 years, 1: 400000 at 50 years, and finally 1: 2000000 in the elderly, around 80 years of age. These mesenchymal cells represent the tissue's ability to regenerate, and, despite their small amount, they are capable of being induced by special cytokines or growth factors, increasing in number and undergoing cell differentiation. In addition, they are also able, under certain conditions, to produce regulatory factors [13-17].

The process of bone regeneration is initiated by successive mitoses of mesenchymal and endothelial cells, as well as activation of osteoblasts and vascular proliferation guided by PDGFs and TGF-β. These growth factors also promote matrix formation and osteoblast differentiation [18-30]. Besides these factors, for there to be bone regeneration is essential to the presence of certain viable cells and biological or synthetic matrix. Local conditions of vascularization and anatomy of the recipient bed also directly influence this process [31-35].

The bone formation phase in the remodeling process of this tissue involves a series of complex events that include chemotaxis of cells to the injured site, reabsorption, differentiation of lineage of pre-osteoblastic cells, and proliferation and production of extracellular matrix [2-4]. These processes are monitored by so-called regulatory factors. Among the producing sources are the activated monocytes that secrete, among others, growth factors derived from platelets, interleukin-1, and fibroblast growth factors. Platelets are another source of factors that include transforming beta factors, platelet-derived growth factors, and epidermal growth factors. Platelets, by their own location in the bloodstream, serve as an efficient vehicle for distributing the factors to injured tissues [5,6,17].

Among the regulatory factors, growth factors are proteins that can act locally or systemically, altering the growth and function of cells in various ways [5]. They may have an increased growth rate in order to accelerate the repair of a tissue, or even control the rate of production of a certain component of the extracellular matrix, such as collagen [13], as shown in Table 1.

Table 1. Activity of growth factors.

	Proliferation Of fibroblasts	Proliferation of osteoblasts and pre-osteoblasts	Matrix synthesis Extracellular	Differentiation of mesenchymal cells	Vascularization
PDGF	++	++	–	–	+ a
IGF	+	++	++	–	–
BMP	–	+	+	++	++ a
TGF-β	+ OR -	+ OR -	++	–	+ a
FGF	++	++	–	–	++

Legends: PDGF - platelet-derived growth factor; IGF - Insulin growth factor; BMP - Bone morphogenetic protein; TGF-β - transforming growth factor -β; FGF- Fibroblast growth factor. Results: ++ = greatly increased, + = increased, + or - = slightly increased, - = no effect or negative effect. Note: a = indirect effect. Source: [5,6,13].

These factors may, as previously stated, transform inactive precursor cells such as undifferentiated mesenchymal cells into mature functional cells such as osteoblasts. Depending on the case, these cells may or may not be influenced by the factors that produced them [13]. These inactive precursor cells, as well as osteoblasts, then produce an immature and poorly mineralized bone, which progressively will be able to receive functional load [30].

Platelet-derived growth factors (PDGF) are glycoproteins with a molecular mass of 30,000 daltons and an isoelectric point in the range of 10.2. Although it is the main factor of platelets, it can also be synthesized and secreted by other cells, such as macrophages, endothelial cells, monocytes, and fibroblasts, according to Table 2. It can be considered a stable polypeptide at elevated temperatures up to 100 ° C [5,8,28].

Table 2. Sources of growth factors in the surgical wound.

FACTORS GROWTH	MAIN SOURCES OF OBTAINMENT
PDGF	Platelets, macrophages, bone matrix, endothelial cells, Epithelial cells and smooth muscle cells.
TGF-β	Platelets, macrophages, osteoblasts, bone matrix T lymphocytes, immature chondrocytes.
EGF/TGF-β	Platelets, macrophages, epithelial cells, eosinophils
IGF-I	Platelets, epithelial cells, endothelial cells, fibroblasts, smooth muscle cells, osteoblasts, bone matrix.
FGF	Macrophages, endothelial cells, osteoblasts, mature and immature chondrocytes, bone matrix.

Source: [5,8,28].

Platelet-derived growth factors have two main roles. The first of the reserve site for other growth factors, and the second is a hemostasis factor. This would probably be related to a mechanism of survival, since in a situation of bone fracture, for example, the injured site would be readily occupied by PDGFs, facilitating not only haemostasis, but also revascularization, fibroblast proliferation, collagen synthesis, an increase in the production of granulation tissue, and bone regeneration [36-40]. There is also a consensus that these growth factors increase the proliferation rate of mesenchymal cells [41,42].

Their molecular structure consists of dimers, which may have the same or different amino acid chains (A-A or B-B) (A-B). The former is called homodimeric, and the latter are called heterodimeric [13,29]. The A and B chains have similarities in the order of 60%, whereas the A chain is formed by 121 amino acids, while the B chain has 125 amino acids [8]. The so-called PDGF-BB have the highest potential for activation of osteoblast-like cells, while PDGF-AA is the one with the lowest potential. The PDGF-AB is in intermediate values [43].

The important role of platelet-derived growth factors (PDGFs) as autocrine or paracrine factors for human bone cells has been demonstrated through the work of Graves et al. (1989) [17]. Paracrine defines the growth factor that is secreted by one cell and exerts its effect on an adjacent cell; In autocrine factors this action also occurs in its own cell [29].

Due to their ability to act on a large number of cells (fibroblasts, muscle cells, bone cells, etc.), they have been considered to have high specificity. When present at the wound site, it seeks to target target cells by adhering to two types of receptors (alpha and beta) of the cell membrane and establishing tyrosine-kinase protein bindings 8 29. Only beta receptors stimulate chemotaxis, although both induce mitogenesis [8]. This binding to alpha receptors is influenced by proinflammatory cytokines such as Interleukin-1 (II-1) and tumor necrosis factor (TNF-ɑ) that are present in destructive inflammatory processes [20].

Despite the high rate of mitogenesis induced by this growth factor, accelerating the healing process, they occur in small amounts (about 0.06 ng of PDGF to one million platelets or 6 x 10 17 of PDGF per Platelet) [29]. In addition, it has been found that the maintenance of therapeutic concentrations of PDGF in periodontal wounds is very difficult, with a half-life of less than 5 hours [43]. These would then be some of the reasons why the addition of growth factors associated with biological carriers, such as methylcellulose or even the collection of platelet concentrates (differential centrifugation), could accelerate the properties of these growth factors [43,44].

In addition to the platelet-derived factors themselves (PDGF), others are also found in platelet-rich plasma (PRP). The beta-transforming growth factors and insulin-like growth factors type I have been described in a number of published papers and play an important role in the remodeling of bone and periodontal tissues [8,18,29,45]. Beta-transforming factors (TGF-β) encompass a superfamily of factors in which bone morphogenetic proteins (BMPs) are inserted. They received this designation due to the fact that they were first described in pathological tissues (sarcomas) [8,29].

Of the various TGF-β groups, the so-called TGF-β1 and TGF-β2 are the most common and are involved in the processes of soft tissue healing and bone remodeling. Both have a dimeric structure with two subunits and an average molecular mass of around 25.0 kDa; each subunit is formed by 112 amino acids and approximately 12,500 daltons in mass. The types β1 and β2 present about 72% similarity, whereas the β1-type is most commonly found in platelets, lymphocytes, and neutrophils, whereas β2-types are more prevalent in bone tissue, platelets, lymphocytes, and neutrophils (Table 2) [8]. TGF-β1 are also recognized as activators of fibroblasts to form precollagen, which in turn will result in collagen, essential in the repair process [24].

When released by platelet degranulation or secreted by macrophages, these factors act on other cells such as fibroblasts, totipotent mesenchymal cells, and pre-osteoblasts. These cells, however, also have the ability to produce their own TGFs that will act not only on themselves but also on other cells, sustaining and enhancing the entire process of bone remodeling [29]. Some authors even mention that TGF-β would have the capacity to inhibit the activation of osteoclasts, as well as bone resorption [32].

The insulin-like growth factors types I and II (IGF-1 and IGF-2) are secreted by osteoblasts during the formation of bone tissue to accelerate the process of deposition of mineralized tissue, according to Table 2 [11]. The presence of IGF in platelets could be understood as a way of acting on the precursors of osteoblasts and even on osteoblasts of the endosteum, which are the cells responsible for producing bone in the initial phase of the bone grafts. They are small molecules (7.5 kDa) [29].

Despite this recognized mitogenic capacity for the osteoblast lineage, its chemotactic activity for fibroblasts and bone matrix deposition, insulin-like growth factors do not seem to have the same ability to guide differentiation into bone tissue as do bone morphogenetic proteins (BMPs) [29]. Compared to platelet-derived growth factors (PDGF), insulin-like growth factors have ten-fold mitogenic capacity, since IGF-1, for example, only reaches its mitogenic capacity at concentrations greater than 1.0 ng / ML [31].

Several researches have been published proving the participation of all these growth factors in the capacity to induce a greater capacity of repair or regeneration. In 1989, a combination of PDGF / IGF-I was used in dogs with the purpose of stimulating periodontal regeneration, and the results indicated that these agents were mitogenic and chemotactic for fibroblasts and osteoblasts [27].

The use of an autologous platelet-based compound was used in 32 patients, aiming at the healing of chronic ulcers. The results indicated that the epithelization time of the wounds was 8.6 weeks, unlike the control group which presented a time of 15 weeks [19]. Through many researches and works published in the last years and the fact that the first tissue to have contact with an endo-osseous implant is the blood, it has been observed that the early interactions of this blood with the implants and the cells present in the region May play a key role in the osteoconduction stage of the healing response of the peri-implant bone around the rough surface implants [34].

With the established bone / implant contact and the presence of platelets in this direct contact, they are assumed to undergo biochemical and morphological changes typical of their responses to extraneous surfaces. These changes include adhesion, distribution, aggregation, and other intracellular biochemical changes such as phosphotyrosine induction, intracellular Ca +2 increase, and phospholipid hydrolysis [10].

The scientific finding that the use of growth factors could stimulate osteoprogenitor cells to cell differentiation was suggested in another work where 40 implants were installed in 8 dogs, and in the test group, a PDGF / IGF-I association was used simultaneously Implants. The results were positive regarding bone regeneration around them [26].

In another work with implants, where an association of the use of ePTFE membranes, lyophilized particulate bone, and a combination of PDGF-BB / IGF-I was performed in 24 implants installed in dogs, the best results in relation to the bone density rates and Areas of bone growth corresponded to the group in which the membranes were associated with growth factors [9]. Research multiplied at an accelerated pace in the 1990s. Several studies on periodontal regeneration confirmed the action of growth factors. The use of PDGF associated with dexamethasone and collagen matrix generated alveolar bone growth in interdental areas in monkeys [14,36].

The use of recombinant PDGF-BB was tested in bone defects produced in the calvaria of 16 rabbits in order to evaluate the remodeling of mineralized tissues. Teflon membranes were used as barriers to maintain the growth factors in place. The results after 8 weeks indicated that the growth of new bone into the defect was 52% in area compared to 30.0% in the control group. Another interesting feature showed that in the experimental group, the new bone presented a more trabecular aspect when compared to the more compact bone of the control group [43].

The search for an ideal hemostatic agent to be used in surgical wounds in soft and hard tissues resulted in the development of fibrin glues [24]. Fibrin adhesives also began to be related to a greater ability to repair surgical wounds after work performed where these adhesives or adhesives were obtained from the patient's own peripheral blood collection prior to surgery. As an alternative for this fibrin glue, the use of platelet gel was suggested for use in oral and maxillofacial surgery, with the advantages of greater safety against infections and greater support for wound healing, due to the presence of a greater number of factors of Growth [44].

A 1998 study using several growth factors, including those found in platelets, demonstrated in vitro and in vivo the effectiveness of osteoblastic cells in osteotomies. The results were enthusiastic regarding the clinical use of these substances [23]. In the same way, bone grafts associated to the use of PRP were performed in 44 patients whose defects were greater than 5 cm in the mandible, and the results showed a regeneration twice as fast and with a higher density in the groups where PRP was associated. This density reached 20.0% higher, showing that the quality of the newly formed bone would stimulate the use of this new technique [28]. This work was a milestone in the attempt to develop a methodology for the use of platelet rich plasma. Multicentric studies began to be performed, and methods of collection and processing became frequent concerns of researchers [29].

The use of inorganic bovine bone collagen matrix was tested in association with PDGF-BB in order to evaluate the interaction between them and also to determine if there would be a greater increase of osteoblastic cell proliferation when compared to the matrix without PDGF-BB. The results showed that both hypotheses could be confirmed [40]. Another study of the same year evaluated the results of the application of platelet-rich plasma collected and processed from patients' own blood in periodontal bone defects. This was the first published work associating this new methodology with the periodontal surgical therapy. The results showed a significant reduction in depth of probing, as well as neoformed bone was observed radiographically around 2 months postoperatively [33].

Many studies have evaluated that the time and manner of contact of growth factors in relation to their respective sites could influence the final regenerative capacity. Some biodegradable natural polymers (chitosan®) associated with inorganic materials such as tricalcium phosphate were tested as spongy carriers for PDGF-BB. Chitosan® has been assigned hemostatic properties, inducing bone formation and regulating the release of bioactive agents as antibiotics and anti-inflammatories. The results of this work, performed in rat calvaria, indicated statistically significant improvements in the groups in which PDGF-BB was added. Evidence of carrier material encapsulated by fibrous tissue was found in the regenerated bone area [21].

Still in relation to the time, it would be important to emphasize that although the beginning of the regenerative process of bone provoked by the action of platelet factors is immediate, its duration does not exceed 7 to 10 days, life time of these cells. After 5 to 7 days and it is these macrophages that will secrete more growth factors giving continuity to the process [30]. The results indicated that in the 3-week period, there was a greater difference between the experimental groups (associated with growth factors) in relation to the control groups. The comparative result in the group analyzed after 8 and 12 weeks did not present statistically significant differences in the percentage area of bone / implant contact. The high values found for the analysis of neoformed bone in the group of 3 weeks in relation to the other times could also well exemplify this initial osteoblastic activity [40].

Similar results were found using bovine osteogenic protein (OP-1) and immediate implants when they were evaluated over a 3-week period [37]. In the same study, the results in longer periods (8 and 12 weeks) also do not show statistically significant differences. The same results can also be observed in Cook et al., 1995 [14]. In a comparative analysis between the use of expanded polytetrafluoroethane membrane alone or associated with rh-PDGF, rhIGF-1, or lyophilized bone (DFDBA), in areas around immediate implants, it showed significant results even in the group analyzed after 18 weeks [9]. The use of platelet-rich plasma has been indicated and used in other areas of buco-maxillofacial surgery that do not involve the therapy associated with dental implants. In a study published in 2002, the authors report a clinical case where a 13-year-old patient, with an alveolar cleft, needed correction aimed at the end of orthodontic treatment.

The closure of the alveolar cleft is indicated for the prevention of constriction and collapse of the maxilla, closure of buconasal fissures, irruption of the canine or lateral incisor through good bone anchorage, and the periodontal support to the teeth adjacent to the cleft. In this case, the patient had complete left unilateral pre-foramen cleft, which was reconstructed with autogenous bone graft from the limb and branch, associated with PRP. As a result, the authors achieved faster healing of the mucosa and graft. The use of PRP, according to the authors, allowed the use of an excellent donor area, but it had the only drawback of limiting the quantity to be removed, a fact that was, to a certain extent, compensated by the use of PRP [16].

Therefore, the use of PRP, which would accelerate the rate of bone formation, with BMP, recombinant or autogenous, should be quite important and elucidative. The development of new research, seeking to use all known technology, will always be the best way for the short future to recognize what should be incorporated into the daily routine of medical and dental clinics, differing from what, for various reasons, whether it was just a marketing procedure or something.

Conclusion

It was concluded that the greatest advantages of the use of platelet-rich plasma are its ability to accelerate the process of bone regeneration by increasing the number of growth factors present in human platelets. On the other hand, it is observed that one of its major disadvantages is the low life expectancy of these platelets in the recipient or graft bed. However, it is also known that the PRP technique would only accelerate a process of bone regeneration that normally already occurs, and this process follows its path until the formation of mature bone.

CRediT

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Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate@.

Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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