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RATIONALE FOR THE USE OF PRF, PRP, PDGF AND BMPS GROWTH FACTORS IN BONE TRANSPLANTS

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Abstract: Bone tissue has an unquestionable capacity to constantly renew itself and simultaneously regenerate. These processes are conducted through a complex cascade of biological events, influenced by various growth factors secreted by bone cells and reactive cells present at the site of injury. Growth factors are a class of natural biological agents that regulate the main cellular events involved in tissue repair, such as cell proliferation, chemotaxis, differentiation and matrix synthesis, through interaction with specific receptors on the cell surface. In the face of considerable bone loss, the field of implantology has several techniques for reconstructing bone tissue prior to the placement of dental implants. The scientific literature extensively details the advantages of autologous bone grafts over alloplastic and xenogenous bone grafts, due to their osteoinduction, osteoconduction and osteogenesis properties. Autologous bone grafts release a variety of molecules, including growth factors, which can direct the mesenchymal cells involved in bone regeneration. The aim of this study is to evaluate the clinical and histological outcomes of the growth factors PDGF and BMP and the platelet concentrates PRF and PRP in bone regeneration, taking into account in vitro, animal and human studies. To this end, searches were conducted for articles published in English or Portuguese in the PubMed and Medline databases, among others, using the terms "growth factors", "bone regeneration", "tissue engineering", "bone graft", "PRF", "PRP", "PDGF" and "BMPs". The literature review reveals that PDGF plays an important role in bone regeneration when combined with other materials, while BMPrh-2 improves and accelerates the bone regeneration process. On the other hand, PRP does not seem to favor significant results in bone regeneration, while PRF has shown promising results in bone regeneration in maxillary sinuses. However, more studies are needed to justify its use in implant dentistry clinical practice.

Keywords: Growth factors. Implant dentistry. PGDF. PRP. PRF. BMPs. Bone regeneration. Bone grafting. Tissue engineering.

INTRODUCTION

Since the first studies published by Branemark in the late 1960s, the adoption of osseointegrated implants has grown significantly (Loureiro, 2020). Bone tissue has a recognized ability to constantly remodel and regenerate at the same time. These processes are governed by a complex and multifactorial cascade of biological events (cell migration, proliferation, adhesion and differentiation, as well as vascular neoformation), regulated by distinct growth factors secreted by bone cells and reactive cells present in the damaged area. However, large bone defects, whether congenital or the result of disease, trauma or surgery, do not regenerate spontaneously and often represent a clinical challenge in orthopaedic and dental practices. Such situations may benefit from the use of strategies capable of replacing lost bone or stimulating bone formation (Lamano; Peres, 2021).

In the face of significant bone loss, the field of implantology has several techniques for reconstructing bone tissue prior to the installation of dental implants. The most common approaches include autologous, allogenic and xenogenic grafts, guided bone regeneration, osteogenic distraction, among others. However, these techniques have some limitations, such as morbidity, graft resorption and post-operative complications. Through the manipulation of cells, matrices and molecular signaling, tissue engineering seeks to improve these existing techniques and develop new, more effective and less invasive approaches (Cury; Guimarães, 2022).

Scientific literature widely highlights the advantages of autologous bone grafts compared to alloplastic and xenogenous grafts, due to their osteoinduction, osteoconduction and osteogenesis properties. Autologous bone grafts release a variety of molecules, including growth factors, which can direct the mesenchymal cells involved in bone regeneration (Caballé-Serrano *et al.,* 2016). In this context, the aim of this study is to describe growth factors, their mechanisms of action and their effects on bone regeneration. To achieve this objective, the following specific objectives were outlined: to describe the mechanisms of action of growth factors: PRF, PRP, PDGF and BMP; to analyze the histological and clinical results of using these growth factors in bone regeneration; to identify the most relevant growth factor for bone regeneration.

METHODOLOGY

For the studies included in this review, electronic searches were conducted in the Medline database, using the Pubmed search platform (Digital Archive of Biomedical and Life Sciences Literature of the US National Institutes of Health), the Capes Portal and scientific publications on Google Scholar. To establish the search parameters, terms such as "growth factors", "bone regeneration", "tissue engineering", "bone graft", "PRP", "PDGF", "BMPs" and "PRF" were used. Due to the importance of the information contained in classic articles and the progression of the studies carried out, there was no specific time delimitation. In addition, only articles published in Portuguese and English were considered.

The selection criteria used to include the articles were those that dealt with in vitro studies, clinical studies on animals and clinical studies on human beings related to the use of growth factors for the recovery of bone tissue defects. The data obtained was analyzed and used to prepare this literature review.

LITERATURE REVIEW

GROWTH FACTORS

Growth factors represent a category of natural biological agents that regulate the main cellular processes involved in tissue repair, including cell proliferation, chemotaxis, differentiation and matrix synthesis, mediated by interaction with specific receptors present on the cell surface. These elements are found in various tissues, highlighting their importance during periods of repair or remodeling, where they play a fundamental role (Howell *et al.,* 2017).

These factors play a crucial role in bone formation, influencing the chemotaxis of osteoblasts and contributing to angiogenesis (Anitua, 2019). Among the growth factors tested in the field of implantology are insulin--like growth factor-1 (IGF-I), platelet-derived growth factor (PDGF) and bone morphogenetic proteins (BMP). It has been observed that the use of these factors favors osseointegration. These are applied using platelet-rich plasma (PRP) and recombinant human bone morphogenetic protein 2 (rhBMP-2) (Shmidt, 2016).

The remodeling cycle includes the resorption of bone matrix by osteoclasts, followed by the formation and mineralization of a new matrix, under the responsibility of osteoblasts, which control the degradation of bone matrix through the production of cytokines that stimulate osteoblast precursors, then osteoclasts release acids and proteases to dissolve the mineral and degrade the organic matrix, releasing the stored growth factors (Anitua, 2019). Bone growth factors, mainly platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs), transforming growth factor-β (TGF-β), insulin-like growth factors (IGFs), vascular endothelial growth factor (VEGF) and bone morphogenetic proteins (BMPs), regulate the differentiation and functional activity of osteoblastic lineage cells (Peres; Lamano, 2021).

PDGF - PLATELET-DERIVED GROWTH FACTOR

Platelet-derived growth factor (PDGF) was first identified in 1974 as a potent mitogenic agent for mesenchymal cells present in serum (Childs *et al.,* 1982). It plays a fundamental role as a primary mitogen for cells of mesodermal origin. It is a 30 kDa dimeric protein, made up of A or B type polypeptide chains, which are associated through disulfide bridges, and can exist in vivo both as a homodimer (PDGF-AA or -BB) and as a heterodimer (PDGF-AB) (Nevins *et al.,* 2023). This protein is predominantly stored in platelet α-granules and is released during coagulation and the platelet adhesion process in vascular lesions (Lynch *et al.,* 2021). Its mitogenic activity has been observed in various cell types, especially in osteoblasts and periodontal ligament fibroblasts (Dennison *et al.,* 2024).

Activation of the target cells occurs through their α and β receptors, which are structurally related to the protein tyrosine kinase and express intense myogenic signals, where this activation results from the homodimerization or heterodimerization of the receptors, forming A and B peptide chains (Marx; Carlson, 2016). Among the various PDGF isoforms, PDGF-BB has been shown to be the most effective in all cellular parameters, including mitogenesis and cell chemotaxis, and is therefore the most suitable form for reconstructive therapy of craniofacial tissues. The PDGF--AB isoform showed an intermediate response, while PDGF-AA was the least effective (Boyan *et al.,* 2024). PDGF is a glycoprotein whose activities include mitogenesis, angiogenesis, macrophage activation and chemotaxis promotion (Marx; Carlson, 2016).

PDGF is an important molecular signaling agent that has been highlighted since a human clinical trial in which it was shown that the use of 0.15 mg/ml PDGF-BB and IGF-1 resulted in a significant increase in the filling of periodontal bone defects when compared

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to the flap alone (Howell *et al.,* 2017). rhPDGF-BB was approved by the FDA (Food and Drug Administration), under the trade name GEM 21S, following the publication of a prospective, multicenter, randomized, triple-blind study involving 180 patients, which demonstrated that the use of rhPDGF-BB was safe and effective in the treatment of periodontal bone defects (Nevins *et al.,* 2015).

Simion, Rochietta and Dellavia (2017) reported a clinical case in which two patients with extensive bone defects underwent three-dimensional ridge augmentation using a xenograft in combination with rhPDGF-BB. The first patient had an atrophic alveolar ridge in the edentulous site. He received a block of bovine matrix infused with PDGF which was fixed by two screws, with the aim of augmenting the ridge horizontally.

After 5 months, a radiograph was taken to evaluate the graft, which showed a satisfactory appearance, then, after 5 months, re-entry was carried out and three implants were successfully installed, where the radiographic image of the implants after loading, 6 months after installation, showed positive results as well as the histological ones (Simion; Rochietta, Dellavia, 2017).

Subject 2 was diagnosed with a vertical bone deficiency in which a vertical ridge expansion procedure was performed, combining deproteinized bovine bone particles saturated in a collagen matrix containing PDGF-BB, in which three implants were inserted, and the clinical and radiographic results showed excellent healing of both soft and hard tissues after 5 months (Simion; Rochietta, Dellavia, 2017).

Histological success was observed, with complete bone regeneration in the affected area and incorporation of the xenograft particles into the bone, accompanied by resorption gaps adjacent to areas of ongoing bone formation, indicating that significant physiological remodeling was taking place in the grafted areas (Simion; Rocchietta; Dellavia, 2017).

It is therefore recommended that the use of rhPDGF-BB in conjunction with a deproteinized bovine graft may have the potential to regenerate large three-dimensional alveolar defects in human subjects. Geurs *et al*. (2024) evaluated the healing of alveoli submitted to grafts and non-grafts, as well as the effect of PRP and rhPDGF-BB on the initial remodeling process. The study involved 41 patients who underwent extraction of anterior and premolar teeth and were randomized into four groups. After 8 weeks, a sample of the 41 alveoli was taken.

Significant differences were observed in the tissue distribution between the groups and in the different thirds of the harvested core and in the sites where the bone graft was combined with growth factors, the presence of residual particles was lower compared to the sites where the bone graft was used alone, coming to the conclusion that the inclusion of the bone replacement graft suppressed new bone formation during the initial healing phase (Simion; Rocchietta; Dellavia, 2017). The inclusion of PRP and rhPDGF-BB resulted in less residual bone, indicating faster bone graft turnover, and all treatments achieved a significant amount of vital new bone within 8 weeks (Geurs *et al*. 2024).

In another study, Ntounis *et al.* (2015) evaluated the clinical, histological and histomorphometric bone quality of human alveoli after extraction, using mineralized freeze-dried bone allograft (FDBA), associated or not with growth factors. The study was conducted with the same forty-one patients as the aforementioned study. After 8 weeks of healing, the implants were installed. The clinicians assessed bone quality according to the Misch classification. The inclusion of the allograft resulted in an improvement in quality from D4 to D3, although it did not completely eliminate the incidence of D4. However, the addition of PRP (platelet-rich plasma) and rhPDGF-BB (platelet-derived growth

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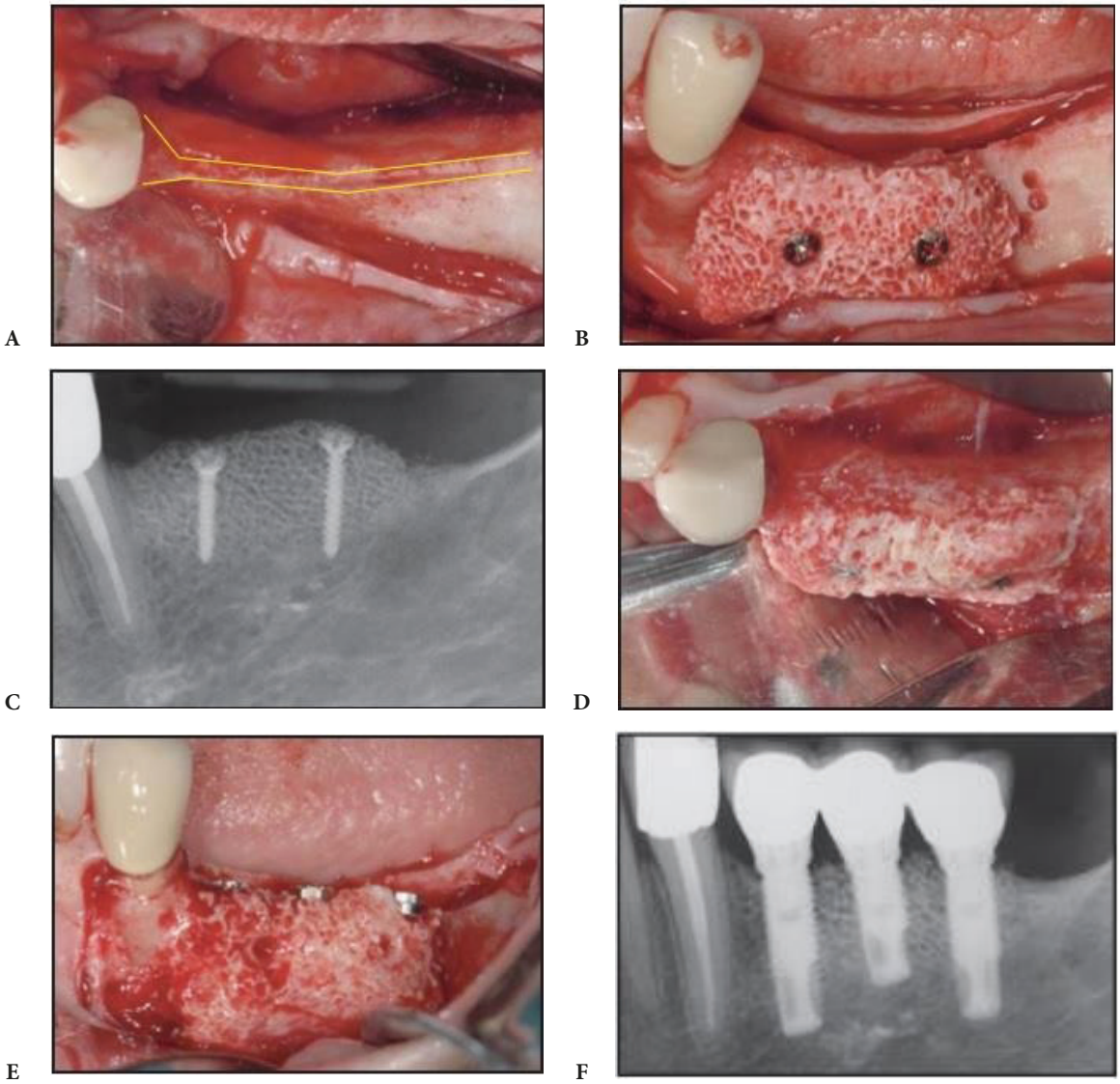

Figure 1 - Lateral expansion of the ridge. Clinical and radiographic aspects (PATIENT 1) - (A) The atrophic alveolar crest of the edentulous site in patient 1. (B) Deproteinized bovine block implant infused with rhPDGF-BB. (C) Radiographic image during re-entry (5 months). (D) Occlusal view during re-entry. (E) Three implants are inserted in the left posterior quadrant of the mandible. (F) Radiographic appearance of the three implants after loading (6 months after implant installation).

Source: SIMION; ROCCHIETTA; DELLAVIA, (2017)

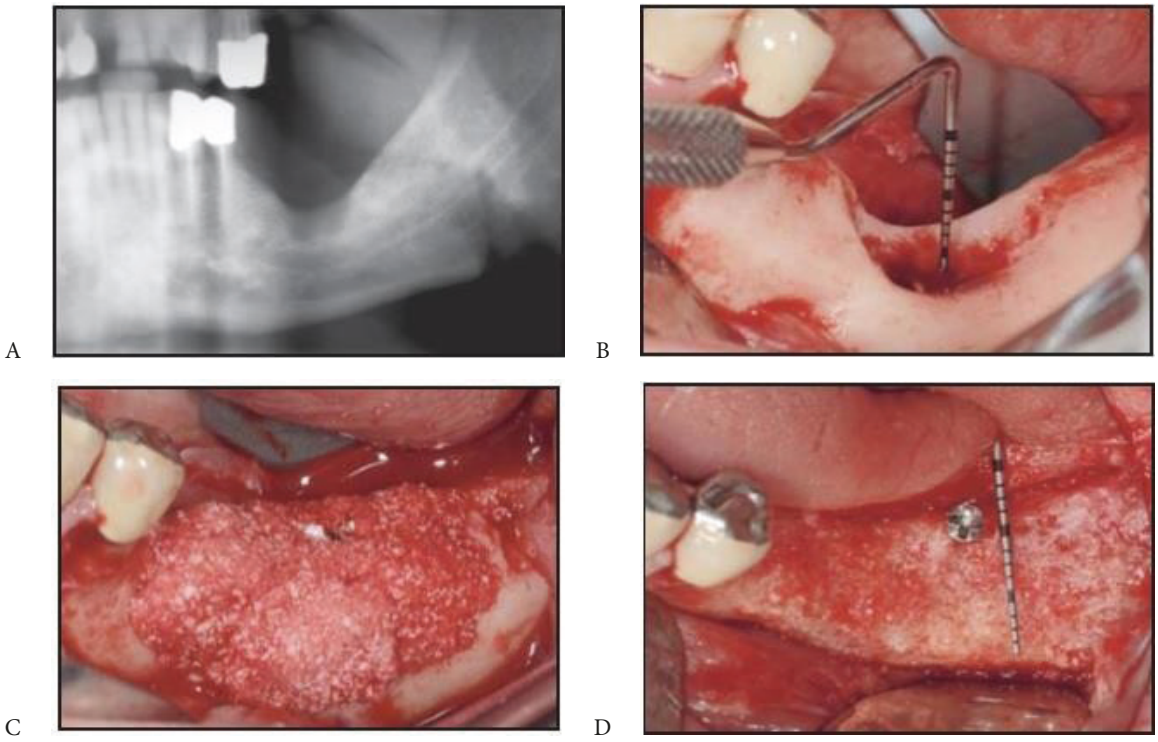

Figure 2 - Vertical ridge expansion. Clinical and radiographic aspects (PATIENT 2): (A) Radiographic representation of the deep vertical bone defect in the left posterior mandible before grafting. (B) Clinical observation of the vertical bone defect (depth 11 mm.) (C) Deproteinized bovine bone particles embedded in a collagen matrix and impregnated with rhPDGF-BB, positioned over the defect. (D) Clinical aspect of the site after 5 months of healing. The bone defect was completely filled with hard tissue, clinically similar to bone, with a total vertical gain of around 8 mm. (E) Radiographic aspect after the installation and restoration of three titanium dental implants placed in the regenerated area.

Source: SIMION; ROCCHIETTA; DELLAVIA, (2017)

factor) increased bone quality, eliminating the incidence of D4. Furthermore, it was concluded that the use of PRP and rhPDGF-BB improves and reduces healing time prior to the installation of implants.

BMPS - BONE MORPHOGENETIC PROTEINS

Bone morphogenetic proteins (BMPs) are polypeptides that belong to the transforming growth factor β (TGF-β) super family, and are found in human bone-derived and recombinant forms. These proteins are produced by osteoblasts and play a crucial role in bone neoformation. Mainly, they stimulate the differentiation of mesenchymal and bone marrow cells into chondrocytes, leading to ossification of the endochondral type, or by stimulating the proliferation of osteoprogenitor cells that differentiate into mature odontoblasts, which are responsible for producing bone matrix proteins. BMP-2 is recognized for recruiting, differentiating and multiplying osteogenic cells (Hollinger *et al*. 2018).

The main clinical relevance of their application lies in their ability to reduce the time it takes to start the prosthetic phase, and they are recommended for cases of major bone loss (Gonçalves *et al.,* 2018). BMPs are supplied with a vehicle to protect the bone defect against the invasion of fibrous and muscular tissues, facilitating the presence of blood vessels and mesenchymal cells. Absorbable collagen sponges (ACS) have been identified as

the best vehicle option (Shmidt, 2016). BMPs are available on the market in the form of a lyophilized powder and are associated with the vehicle using sterile water before being applied to the surgical bed (Block; Achong, 2016).

Through extensive genetic engineering research, it was possible to isolate the main protein for bone regeneration, BMP-2, and subsequently synthetically derive this protein, called Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2). In March 2017, rhBMP-2 (INFUSE® Bone Graft), associated with a collagen sponge as a vehicle, had its commercial approval regulated by the U.S. Food and Drug Administration (FDA) for dental use, with an indication for maxillary sinus lift, localized alveolar ridge grafts and defects associated with extraction sockets (Smith *et al.,* 2018).

Osteoblasts are the main cells involved in bone formation and repair. Mesenchymal stem cells (MSCs) are their precursors and are undifferentiated, multipotent cells found in bone marrow, periosteum and smaller muscle tissues. They have the ability to differentiate into various cell types, including osteoblasts and chondroblasts. Osteoblasts produce new bone on a collagen matrix and initiate the release of biological signals that direct bone formation and remodeling.

These signals attract MSCs and other bone-forming cells to the site of bone formation and induce the differentiation of MSCs into osteoblasts (Meditronic package insert, 2017). BMPs-2 have the ability to induce the migration, proliferation and differentiation of mesenchymal cells in vitro and can therefore be involved in every stage of bone formation in vivo.

The recombinant version of BMP is a highly purified commercial solution of a single BMP. Human recombinant bone morphogenetic protein-2 (rhBMP-2) is a proven osteoinductive protein produced by expressing the gene encoding human BMP-2 (Smith *et al.,* 2018).

The combination of rhBMP-2/ACS in appropriate quantities has the capacity to initiate a series of cellular events involved in the bone induction process. This is initiated by the undifferentiated mesenchymal cells adjacent to the tissues, which are the first to infiltrate the implanted rhBMP-2/ACS sponge. Subsequently, the sponge degrades and the mesenchymal cells differentiate into bone-forming cells, initiating the process of bone and/or cartilage trabeculae formation, accompanied by simultaneous vascular invasion (angiogenesis). Bone formation progresses from outside the rhBMP-2/ACS implant towards the center, culminating in replacement by trabecular bone (Meditronic package insert, 2017).

Undifferentiated mesenchymal cells and osteoblasts present in bleeding bone, muscle and periosteum infiltrate the rhBMP-2/ACS implant. In vitro studies have shown that rhBMP-2 can stimulate the specific chemotactic migration of bone-forming cells (Meditronic package insert, 2017).

The undifferentiated mesenchymal cells then proliferate within the rhBMP-2/ACS implantation site. rhBMP-2 has the ability to increase the proliferation of multipotent cell lines, which are capable of differentiating into osteoblasts. Through specific receptors present on undifferentiated mesenchymal cells, rhBMP-2 binds to MSCs, promoting their differentiation into bone-forming cells.

Smith *et al*. (2018) stated that BMP-2 are osteoinductive, regulating substances that initiate tissue development and are also involved in mediating the condensation of mesenchymal cells that appear before mature bone structures, both in intramembranous and endochondral ossification.

Howell *et al*. (2017) demonstrated that the use of rhBMP-2/ACS for extraction socket preservation and lateral ridge augmentation in localized defects is safe and feasible. The study, conducted over 24 months, involved twelve patients, six with extraction socket preservation and six with lateral ridge augmentation. The study was divided into two parts: the first assessed safety and the short-term bone induction period after 4 months; the second assessed osseointegration, functional restoration and long-term safety with the use of rhBMP-2/ACS.

Patient safety was monitored through clinical and radiographic examinations and the collection of blood samples to measure antibody formation. Technical feasibility was assessed by collecting information related to the properties of rhBMP-2/ACS. The clinical results indicated that rhBMP-2/ACS was well tolerated locally and systemically, with no adverse events. The device was easily manipulated and adapted to the ridge in the extraction sockets. All sites showed hardness and filling on palpation in the first four weeks, although a loss of volume was observed in some areas between the fourth and eighth weeks. There was bone filling in all the extraction sockets.

Cochram *et al*. (2020) and colleagues conducted a study that demonstrated the safety of using rhBMP-2/ACS in human patients. In a pilot study involving 12 patients, with follow-up over 3 years, the first and main objective was to evaluate the long-term safety of these patients treated with rhBMP-2 associated with ACS, applied to extraction sockets or lateral ridge augmentation, followed by evaluation of the implants installed at the sites of these grafts.

Four months after placement of the sponges, implantation of rhBMP-2/ACS (0.43 mg/ml) was considered safe, as assessed clinically, by periapical radiographs and monitoring of adverse events. During the 3-year follow-up period, implants were installed in the areas treated with rhBMP-2/ACS, and bone biopsy samples were taken for histological analysis.

After two years of rhBMP-2/ACS implantation, no adverse, negative or unexpected events were observed. The implants installed in the 10 patients (6 in extraction sockets and 4 in lateral ridge augmentation) showed clinical stability in all evaluations and all were functionally restored.

The histological study showed the formation of normal bone tissue, identical to the native bone tissue, around the graft. After three years of clinical follow-up, all implants showed normal marginal bone levels and healthy peri-implant tissues. The results indicate that rhBMP-2/ACS at 0.43 mg/mL can be safely used in extraction sockets and lateral ridge augmentation, allowing these sites to receive implant therapy and be functionally loaded without complications (Cocharan *et al.,* 2020).

Jung *et al.* (2023) conducted a clinical study to investigate whether the addition of rhBMP-2 to a mineral bone substitute (Bio-Oss®) could improve bone regeneration therapy in terms of volume, density and maturation. Thirty-four implants were installed in 11 partially edentulous patients in need of lateral ridge augmentation. All defects were grafted with xenogeneic bone substitutes and resorbable collagen membrane (Bio guide®), and in the test group, the xenogeneic grafts were added to rhBMP-2. The peri-implant bone defects were measured from the implant shoulder to the first bone-implant contact, and after an average period of six months, the residual defects were measured again. Twenty-two biopsies were taken with a trephine drill.

In the first assessment, the height of the bone defect was 7 mm in the test group and 5.8 mm in the control group. In the second assessment, the defect decreased to 0.2 mm in the test group and to 0.4 mm in the control group, showing a statistically significant

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result. Histometric analysis showed an average density of 37% of new bone formed in the test group and 30% in the control group.

The fraction of mineralized bone identified as mature lamellar bone was 76% in the test group and 56% in the control group. In the sites treated with rhBMP-2, 57% of the surface of the bone substitute particles was in direct contact with the newly formed bone, while only 30% of the control group had this contact. It was concluded that the combination of mineral xenogeneic bone (Bio-Oss) with rhBMP-2 can accelerate the maturation process of bone regeneration and increase the bone contact of the graft with the native bone in humans, showing the potential of rhBMP-2 to predictably improve guided bone regeneration therapy (Jung *et al.,* 2023).

Subsequently, Fiorellini *et al.* (2015) conducted an investigation into the efficacy of two dosages of rhBMP-2/ACS in 80 patients who required grafting after tooth extraction. The participants were divided into three groups: a group with no graft (control), a group that received only the ACS sponge (placebo), and another group that received two concentrations of rhBMP-2/ACS (0.75 mg/cc or 1.5 mg/cc).

The results indicated that the sites treated with 1.5 mg/cc of rhBMP-2/ACS had approximately double the amount of bone compared to the control groups, maintaining the height of the ridge and significantly increasing the width and length of the alveolus after extraction. Bone maturation for the installation of dental implants was approximately twice as good in the rhBMP-2/ACS-treated group as in the control groups. In addition, histological analysis of bone biopsies revealed no differences between rhBMP-2-induced bone and native bone (Fiorellini *et al.,* 2015).

In 2017, Medtronic conducted a randomized pilot study to evaluate the safety and efficacy of INFUSE® Bone Graft in the maxillary sinus lift grafting procedure. This study involved 160 patients, of whom 82 received rhBMP-2/ACS at 1.5 mg/cc and 78 received conventional bone grafts or some combination associated with allogenic bone. The patients were followed up for a period of 4 to 12 months during the bone formation process, followed by 12 months during osseointegration and a further 12 months after the installation of the prosthesis.

Tomographic and histological analyses were carried out. After six months, the average bone height was 7.83 for the INFUSE® grafts and 9.46 for the conventional autogenous bone grafts. In the histological analysis, both groups showed the formation of new bone trabeculae that were biologically and structurally similar to the native bone tissue. After six months of functional loading, the group using INFUSE® had an implant success rate of 79%, exceeding the expected rate of 73%. After 12 months of loading, the success rates of both groups were similar (Meditronic package insert, 2017).

PRP - PLATELET-RICH PLASMA

Subsequently, Fiorellini *et al.* (2015) carried out an analysis of the efficacy of two dosages of rhBMP-2/ACS in 80 patients who required grafting after tooth extraction. The participants were divided into three groups: a group without a graft (control), a group that received only the ACS sponge (placebo), and another group that received two concentrations of rhBMP-2/ACS (0.75 mg/cc or 1.5 mg/cc).

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The study conducted by Khairy *et al.* (2023) consisted of a randomized clinical trial (RCT) to investigate the beneficial potential of adding platelet-rich plasma (PRP) to autogenous bone used in the maxillary sinus lift (MSL) procedure and to determine whether there is a significant difference in the bone quality of sinuses grafted using autogenous bone with or without PRP.

The study sample included 15 healthy patients, of both sexes, aged between 22 and 54 years (average 38 years), partially edentulous in the unilateral or bilateral posterior maxilla, and with an indication for LSM followed by dental implant insertion. These patients were divided into two groups: Group I, made up of 5 patients who underwent LSM with autogenous bone graft and implant insertion 6 months after grafting; Group II, made up of 10 patients who underwent LSM with autogenous bone graft mixed with PRP obtained from the patient's own blood, with implant insertion 4 months (Group IIB) or 6 months (Group IIA) after grafting. Patients were randomly allocated to the study groups using the concealed allocation technique, ensuring that the investigator responsible for recruiting the participants had no prior knowledge of the group to which the next patient would be assigned.

The grafted sites were assessed using panoramic radiography in all cases. Cases with a bone height of 5 mm or less were included in the study. A study model, a surgical guide and a vacuum-formed transparent acrylic model containing metal spheres of known diameter were used as radiographic markers to determine image magnification. The clinical results showed normal healing after the first and second surgeries, with no significant complications.

The study found that PRP improves the handling properties of the grafted material, facilitating its placement and stability. Although enrichment with PRP did not show a significant improvement in bone density or morphometric values at 3 months after grafting, it was observed that the bone graft enriched with PRP showed a higher bone density at 6 months after grafting.

Bae, Kim, and Myung (2021) conducted a meta-analysis with the aim of evaluating the efficacy of platelet-rich plasma (PRP) in sinus bone grafts combined with bone grafting materials for bone regeneration. The authors searched the PubMed and EMBASE databases, covering the period from 2020 to January 2020, as well as the Cochrane Central Register of Controlled Trials in the Cochrane Library, covering the period from 2022 to January 2020.

Only controlled clinical studies in humans that addressed the effects of PRP grafts on dental implants were selected. Of the 61 articles reviewed, 8 studies were included, of which 6 were randomized controlled clinical trials and 2 were non-randomized controlled clinical trials. These studies reported 352 sinus bone grafts in 191 patients, 178 of which were sinus bone grafts with PRP combined with other factors and 174 sinus bone grafts without PRP as a control group.

In the four studies that looked at implant survival, no significant differences were observed between the implants made in the intervention group treated with PRP and the control group, using a fixed effects model. Similarly, no significant differences were identified in bone--implant contact. However, with regard to bone formation, the PRP-treated group showed significantly better results than the control group, using a random effects model.

Based on the meta-analysis and the results obtained, there is favorable evidence for the use of PRP in bone formation, since it reduces healing time in sinus bone grafts and facilitates the bone formation process in the early stages. However, no evidence was found that the use of PRP influences long-term implant durability.

PRF - FIBRIN-RICH PLASMA

Platelet Rich Fibrinogen (PRF) was conceived in France by Choukroun for a specific purpose in oral and maxillofacial surgery. It represents a new generation of platelet concentrates, with a simplified process and without the need to manipulate biochemical blood. During the PRF process by means of centrifugation, platelets are activated and their massive degranulation results in a significant release of cytokines. Studies have indicated that the gradual polymerization of fibrin during the PRF process leads to the intrinsic incorporation of platelet cytokines and glycan chains into the fibrin structure, which suggests that PRF, unlike other platelet concentrates, could release cytokines progressively during the remodelling of the fibrin matrix. This mechanism may explain the clinically observed healing properties of PRF.

The three main platelet cytokines play a crucial role in the initial healing processes, due to their ability to stimulate cell migration and proliferation (particularly platelet-derived growth factors - PDGFs) and induce fibrin matrix remodeling, as well as promoting the secretion of a scar collagen matrix (especially transforming growth factor β - TGFβ).

Insulin-like growth factors (IGFs) I and II act as positive regulators of proliferation and differentiation for most cell types. Although these cytokines mediate cell proliferation, in general, they constitute the main axis of the programmed regulation of cell death (apoptosis), signaling cell survival and protecting them against various matrix apoptotic stimuli (Dohan *et al.,* 2016).

To obtain PRP, it is not necessary to use anticoagulants or bovine thrombin (or any other gelling agent). The technique described by Dohan *et al*. (2016) in their article "Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part I Technological concepts and evolution" is quite simple: a blood sample is collected without anticoagulant in 10 mL tubes, which are then immediately centrifuged at 3000 rpm for 10 minutes.

The absence of anticoagulant results in the activation of most of the platelets in the blood sample within a few minutes, when they come into contact with the tube walls, triggering the coagulation cascade. Fibrinogen is initially concentrated at the top of the tube, before being transformed into fibrin by circulating thrombin. A fibrin clot is then formed in the center of the tube, between the red corpuscles at the bottom and the acellular plasma at the top. The platelets are theoretically trapped in the fibrin meshes.

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Serum must be removed before the autologous fibrin membrane is ready for use. In the study conducted by Dohan *et al.* (2016), entitled "Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part V: Histologic evaluations of PRF effects on bone allograft maturation in sinus lift", an investigation was carried out into the effectiveness of PRF in conjunction with freeze-dried bone allograft (FDBA) in improving bone regeneration during sinus floor lift. The experiment involved nine sinus lift procedures, in which six used PRF added to FDBA particles (test group), while in three procedures only FDBA was used (control group).

After four months for the test group and eight months for the control group, bone samples were taken from the augmented region during implant insertion for histological analysis. The results revealed the presence of residual bone surrounded by newly formed bone and connective tissue in both conditions. After four months of healing, histological maturation in the test group was comparable to that of the control group after eight months. In addition, the amounts of newly formed bone were similar between the two protocols. Therefore, it is suggested that sinus lift with FDBA and PRF reduces healing time before implant placement. Despite the promising results, large-scale studies are needed to confirm these initial findings.

In a study conducted by Tajima *et al.* (2023), patients undergoing maxillary sinus lift with simultaneous implant installation using only PRF as the grafting material were evaluated. The study was carried out between July 2019 and January 2021 at the Department of Oral and Maxillofacial Surgery at Nagasaki University Hospital. For each patient, radiographs and CT scans were taken pre- and post-surgery (6 months after).

The density of the newly formed bone and the height of the bone were measured using implant planning software. The study involved nine maxillary sinus lifts and 17 implants placed in six patients. Before surgery, the average residual bone height was 4.28 ± 1.00 mm, while after surgery it was 11.8 ± 1.67 mm. The average density of new bone gain around the implants was 323 ± 156.2 HU. All implants were clinically stable at the time of abutment insertion, six months after the procedure. The results indicate that maxillary sinus lift with simultaneous implant placement using PRF as the sole grafting material can effectively promote bone regeneration.

DISCUSSION

In vitro studies have shown that platelet-derived growth factor (PDGF) associated with grafting materials improves their effectiveness. Jiang *et al.* (2019) investigated the interaction of bovine bone matrix with PDGF-BB and IGF-I. Through experiments, they found that PDGF-BB was significantly adsorbed to the bovine bone matrix, increasing the proliferation of cultured osteoblastic cells compared to the matrix alone, thus improving the osteogenic capacity of this bone graft material.

Similar results have been observed with the use of PDGF associated with alloplastic materials, as demonstrated by Bateman *et al.* (2015) in an in vitro study with osteoblastic bone cell cultures. In this study, PDGF-BB was associated in different concentrations with β -TCP or CaSO4, resulting in an improvement in the regenerative biological response. The association also promoted a significant increase in osteoblast proliferation, as well as greater osteoid matrix formation compared to β-TCP alone. Therefore, these results suggest that the association of alloplastic materials with the growth factor PDGF-BB makes this grafting material more efficient and improves its osteogenic capacity.

PDGF-BB is also capable of promoting cell chemotaxis of osteoblasts, as demonstrated in an in vitro study by Sanchez-Fernandez *et al.* (2018), and of mesenchymal progenitor cells, as evidenced in a cell study by Krattinger *et al.* (2021).

Considering the results of two dog studies conducted by Schwarz *et al.* (2020) and Schwarz *et al.* (2019), which initially evaluated the influence of rhPDGF-BB on initial bone formation after lateral ridge augmentation using BCP (biphasic calcium phosphate) and guided bone regeneration, in combination with a native collagen membrane (CM), and subsequently the initial pattern of angiogenesis and bone formation after lateral ridge augmentation, using rhPDGF and guided bone regeneration, it is assumed that the association of BCP + rhPDGF-BB has the potential to assist the initial stages of guided bone regeneration in chronic lateral ridge defects, as does rhPDGF-BB soaked in NBM (natural bone mineral).

The findings and hypotheses raised in the in vitro and animal studies were of significant importance, as they gave impetus to human research. From a clinical trial conducted by Howell *et al.* (2017), it was determined that the use of PDGF and IGF at a concentration of 0.15 mg/ml resulted in a significant increase in the filling of periodontal bone defects when compared to the flap alone.

In 2015, after a multicenter RCT study involving 180 patients by NEVINS *et al.* (2015), the safety and efficacy of PDGF in the treatment of periodontal bone defects were proven. Following this study, the FDA approved its use under the trade name GEM 21. Clinically, it appears that the use of rhPDGF-BB in combination with a deproteinized bovine graft may have the potential to regenerate large three-dimensional alveolar defects in humans, according to a clinical case report by Simion *et al.* (2017), in which two patients with extensive bone defects underwent three-dimensional ridge augmentation using a xenograft in combination with rhPDGF-BB. The clinical and histological findings showed excellent soft and hard tissue healing.

The combination of PRP and rhPDGF-BB results in less residual bone, indicating faster turnover of the bone graft, as shown in a study published by Geurs *et al.* (2024), which involved 41 patients, with the aim of evaluating the healing of grafted and non-grafted alveoli and the effect of this combination on initial remodeling. Furthermore, in another study involving these same patients, carried out by the authors in 2015, it was shown that this PRP/rhPDGF-BB association in human alveoli after extraction, using mineralized lyophilized bone allograft (FDBA), increases bone quality and reduces healing time before the installation of implants.

Cell culture studies suggest that rhBMP-2 is involved, at least in vitro, in inducing the differentiation of osteoblast precursor cells into more mature osteoblastic cells, as reported by Yamaguchi *et al.* (2021) and Kawasaki *et al.* (2018), and may be a potent stimulator of osteoblast differentiation and bone formation in human cells. In addition, the study by Yamaguchi *et al.* (2021) demonstrated that rhBMP02 also appears to participate in the inhibition of myogenic differentiation.

Several studies have documented the positive effects of certain bone morphogenetic proteins (BMPs) on bone regeneration. The use of rhBMP-2 with PLPG-sponge has been shown to increase BIC (bone-implant contact) and BD (bone density) in maxillary sinus lift procedures in sheep, when compared to autologous bone; as reported by Gutwal *et al.* (2020).

A study conducted by Howell *et al.* (2017) showed that the use of rhBMP-2/ACS is safe and viable for preserving extraction sockets and for lateral ridge augmentation in localized

defects. The clinical findings of this study showed that rhBMP-2/ACS was well tolerated locally and systemically, without presenting any adverse events, and that the device is easily manipulated and adapted to the ridge and extraction sockets. Another pilot study in humans, involving 12 patients with long-term follow-up (3 years), conducted by Cochran *et al*. (2020), also demonstrated that rhBMP-2/ACS can be used safely in human patients, in extraction sockets or in lateral ridge augmentation, and that these sites can receive implant therapy and be functionally loaded without complications.

Similar results were found in another clinical study conducted by Howell *et al*. (2015), in which the efficacy of two doses of rhBMP-2/ACS was tested in 80 patients who required socket filling after exodontia. The results showed that the sites treated with 1.5 mg/cc of rhBMP-2/ACS had approximately double the amount of bone compared to the control groups, preserving the height of the crest and significantly increasing the width and length of the extraction socket. Bone maturation for the placement of dental implants was approximately twice as good in the rhBMP-2/ACS--treated group as in the control groups. In addition, histological analysis of bone biopsies showed no difference between rhBMP-2-induced bone and native bone.

In 2017, the randomized pivotal study carried out by Medtronic also confirmed the safety and efficacy of INFUSE Bone Graft in maxillary sinus lift grafting procedures. This study included 160 patients, 82 of whom were treated with rhBMP-2/ACS at 1.5 mg/cc and 78 with bone grafts alone, or with some combination associated with allogenic bone (Meditronic package insert, 2017).

The combination of mineral xenograft bone (Bio-Oss) with rhBMP-2 can increase the maturation process of bone regeneration and the bone contact of the graft with the native bone in humans, and has the potential to predictably improve and accelerate guided bone regeneration therapy, as demonstrated in a clinical study published by Jung *et al*. (2023).

A study conducted by Barbosa *et al*. (2018) in dogs compared the radiopacity in the region of dog tibial defects (unfilled defect, defect with autogenous bone graft, defect with PRP and defect with PRP + autogenous bone graft) and showed that PRP associated with the graft determined greater precocity and uniformity of radiopacity, when compared to the defect filled only by PRP and grafts alone, both determining better filling results when compared to the untreated defect.

However, comparative in vitro studies between PRP and PRF were conducted by He *et al*. (2019) to assess the impact of the biological characteristics of each on the proliferation and differentiation of osteoblasts in rats over 14 days, demonstrating that PRF is superior to PRP in terms of ALP expression and mineralization induction. This is possibly due to the fact that PRF releases autologous growth factors gradually, exerting a more robust and lasting effect on the proliferation and differentiation of rat osteoblasts in vitro. The results indicated that PRP released the highest amounts of TGF-1 and PDGF-AB on the first day, followed by a significantly reduced release at later time points. On the other hand, PRP released the highest amount of TGF-1 on day 14 and the highest amount of PDGF-AB on day 7.

Similar results on the release of CFs by PRP were found in an animal study in which PRP was considered an important tool for bone regeneration, especially in the first few days after application, carried out by Monteiro *et al*. (2020) in 32 mice. It was clear that the effects of PRP gel were more noticeable in the first few days after application, when there was a greater release of growth factors present in the plasma.

Among the components of PRP that were most important in this process were cytokines and growth factors, which are essential for healing, increased vascularization and tissue regeneration. However, at the end of the 90-day observation period, the results of the treatment were not satisfactory, as the defects were not completely filled and the repair process was not sufficient to complete it.

In an RCT study involving 15 patients, conducted by Khairy *et al*. (2023) to assess the potential benefit of adding a PRP mixture to autogenous bone used for maxillary sinus augmentation and to detect whether there is a significant difference in the bone quality of augmented sinuses using autogenous bone with or without PRP, the following results were observed: PRP enrichment did not significantly improve bone density or morphometric value at 3 months after grafting, but PRP-enriched bone grafting was associated with higher bone density at 6 months post-grafting. PRP was found to improve the handling properties of the associated graft material, facilitating graft placement and stability.

According to the results of a meta-analysis published by Bae *et al*. (2021), with the aim of evaluating the efficacy of using PRP in sinus bone grafts associated with bone grafting materials, in four of the studies analyzed that reported on implant survival, no significant differences were found between the implants made in the intervention group treated with PRP and the fixed-effect control group.

No significant differences were found in bone-implant contact. However, with regard to bone formation, the group treated with PRP showed significantly better results than the control group. It therefore appears that the use of PRP is justified for bone formation, since it reduces the healing time of sinus bone grafts and aids the bone formation process in the early stages, although no evidence was found that the use of PRP influences the long--term durability of the implant.

Positive results in relation to PRF were observed by Dohan *et al*. (2020) in an in vitro study involving human bone mesenchymal stem cells (BMSCs). According to these authors, it seems that PRF significantly stimulates the proliferation and differentiation of BMSCs. However, the authors consider that more studies are needed on this subject.

Animal studies have also supported the use of LPRF. Research conducted by Öncü *et al*. (2016) showed that LPRF increased both the amount and rate of bone formation during the initial healing period, as well as providing faster osseointegration around implants. Similar results were observed in a study involving sheep carried out by Bölükbaş *et al*. (2023) to evaluate the effects of combining PRF with BCP. This study revealed a histomorphometric increase in bone formation with the addition of PRF to BCP in the defects created in the animals' tibias, resulting in higher rates of new bone.

The association of PRF with FDBA (freeze-dried bone allograft) in maxillary sinus lifts seems to reduce healing time to 8 months, as evidenced in a study conducted by Dohan *et al*. (2016). The results of this study indicated that after a 4-month healing period, the histological maturation of the group treated with the PRF+FDBA association was similar to that of the control group after a period of 8 months. In addition, the amount of bone formed was equivalent. However, the authors stress the need for further large-scale studies to validate these results. PRF, when used as the sole grafting material, also seems to promote bone regeneration, as indicated by Tajima *et al*. (2023), who conducted a study including patients undergoing maxillary sinus lift with simultaneous implant installation.

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CONCLUSION

The scientific literature reviewed provides a solid basis for the use of growth factors such as Fibrin-Rich Plasma (FRP), Platelet--Rich Plasma (PRP), Platelet-Derived Growth Factor (PDGF) and Bone Morphogenetic Proteins (BMPrh-2) in bone transplants. The effectiveness of these factors in bone regeneration has been widely documented in in vitro studies, in animals and in clinical trials.

The studies reviewed indicate that PRF has shown significant results in bone regeneration in maxillary sinuses, while PRP has shown less consistent results in this context. On the other hand, PDGF and BMPrh-2 have been consistently associated with an improvement in bone regeneration, both in terms of quality and speed of the process.

Platelet-derived growth factor (PDGF) makes a crucial contribution to bone regeneration when combined with other materials. Recombinant human Bone Morphogenetic Protein type 2 (BMPrh-2) has been shown to enhance and accelerate the bone regeneration process. On the other hand, Platelet Rich Plasma (PRP) does not seem to provide significant results in bone regeneration. On the other hand, Fibrin Rich Plasma (FRP) has shown promising results in bone regeneration in maxillary sinuses. However, more studies are needed to fully justify its use in implant dentistry.

However, it is important to note that there are still gaps in scientific knowledge, and more studies are needed to fully validate the efficacy and mechanisms of action of these growth factors in bone transplants. Furthermore, additional considerations, such as the standardization of protocols for the preparation and application of these factors, are essential to guarantee consistent and replicable results.

Despite the open questions, the rationale for using PRF, PRP, PDGF and BMPrh-2 in bone transplants is robust, and these factors continue to represent promising tools for improving clinical results and speeding up recovery in bone reconstruction procedures.

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