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REVIEW ARTICLE

Main processes of bone formation and regeneration through molecules and cells as biostimulators in buccomaxillofacial surgery: a systematic review

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Abstract

Introduction: At a cellular and molecular level, tissue engineering offers numerous advantages that meet the needs of the injured tissue or organ for the bone regeneration process in buccomaxillofacial surgeries. To achieve this, it is necessary to understand the chemical, physical, and biological processes of both the biological material and the target biological niche. **Objective:** It was to carry out a concise systematic review of the main processes of bone formation and regeneration using molecules and cells as biostimulators in buccomaxillofacial surgeries. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from December 2023 to February 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 182 articles were found, 60 articles were evaluated in full and 36 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 12 studies with a high risk of bias and 20 studies that did not meet GRADE and AMSTAR-2. Most studies did not show homogeneity in their results, with X^2=54.7%>50%. The bone regeneration process occurs through the activation of osteoblasts and vascular control guided by PDGFs and TGF-β. These growth factors also promote matrix formation and osteoblast differentiation. Some biodegradable natural polymers (chitosan®) associated with inorganic materials such as tricalcium phosphate were tested as spongy carriers for PDGF-BB. Chitosan® has been attributed to hemostatic properties, inducing bone formation and regulating the release of bioactive agents. The use of platelet-rich plasma and mesenchymal stem cells (exosomes and microRNAs) has been indicated and used in other areas of oral and buccomaxillofacial surgery, accelerating a process of bone regeneration that normally already occurs and this process continues its path until the formation of bone mature.

Keywords: Buccomaxillofacial surgery. Bone regeneration. Adipose-derived stem cells. Exossomes. Platelet-rich plasma.

Introduction

At a cellular and molecular level, tissue engineering offers numerous advantages that meet the needs of the injured tissue or organ for the bone regeneration process in buccomaxillofacial surgeries. For this, it is necessary to understand the chemical, physical, and biological processes of both the biological material and the target biological niche [1-3].

In this sense, biological microenvironments enable cellular recognition and signaling cascades for neovascularization and bone graft stabilization. Another advantage is the minimally invasive surgical intervention, which allows the use of faster surgical techniques that cause less risk to the patient. Furthermore, adult stem cells, such as adipose-derived stem cells (ADSC), are pointed out as an alternative for cell therapy and human tissue engineering, since it has been found that they have a high degree of plasticity, with the capacity of self-renewal and differentiation into specialized progenitors [1,4].

In this context, aiming to improve the quality of life and the treatment of diseases previously considered incurable, research has transformed the daily lives of health professionals [3,4]. The concern with the healing and/or repair process of the various tissues of the human body, and the progressive identification of components of the organic and inorganic matrix of bone tissue is part of tissue engineering [4-7]. The production or regeneration of any tissue is a complex biological process in itself, as it requires intrinsically regulated interactions between cells, the action of systemic hormones, the participation of components of the extracellular matrix, and the local action of so-called growth factors [8-11].

In this sense, the application of biotechnology related to growth factors can be exemplified in the use of platelet-rich plasma (PRP), ADSC, vesicles such as exosomes, and molecules such as microRNAs, since this technique has been used in dentistry in the areas of oral and buccomaxillofacial surgery, implantology and periodontics [11,12].

Regarding one of the indications for the use of PRP in buccomaxillofacial surgery, it is known that the osseointegration technique has a high predictability of success when the bone remnant is favorable in terms of quantity and quality [12,13]. These initial conditions would be capable of providing initial stability and ideal positioning of the implant for the subsequent prosthetic stage. The use of autogenous bone associated with platelet gel in anterior grafts would therefore be an excellent option in those cases in which the previously mentioned requirements could not be met [13,14].

Therefore, this study aimed to carry out a concise systematic review of the main processes of bone formation and regeneration using molecules and cells as biostimulators in buccomaxillofacial surgeries.

Methods

Study Design

The present study followed the international systematic review model, following the rules of PRISMA (preferred reporting items for systematic reviews and meta-analysis). Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 08/14/2023. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 08/14/2023.

Data Sources and Research Strategy

The literary search process was carried out from December 2023 to February 2024 and was developed based on Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various to the present. The descriptors (MeSH Terms) were used: *"Buccomaxillofacial surgery. Bone regeneration. Adipose-derived stem cells. Exossomes. Platelet-rich plasma"*, and using the Boolean "and" between the MeSH terms and "or" between historical discoveries.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low in terms of risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using the Cohen test (d).

Results and Discussion

Summary of Findings

A total of 182 articles were found that were subjected to eligibility analysis, with 36 final studies being selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with X^2=54.7%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 12 studies with a high risk of bias and 20 studies that did not meet GRADE and AMSTAR-2.

Figure 1. Article selection and exclusion process.

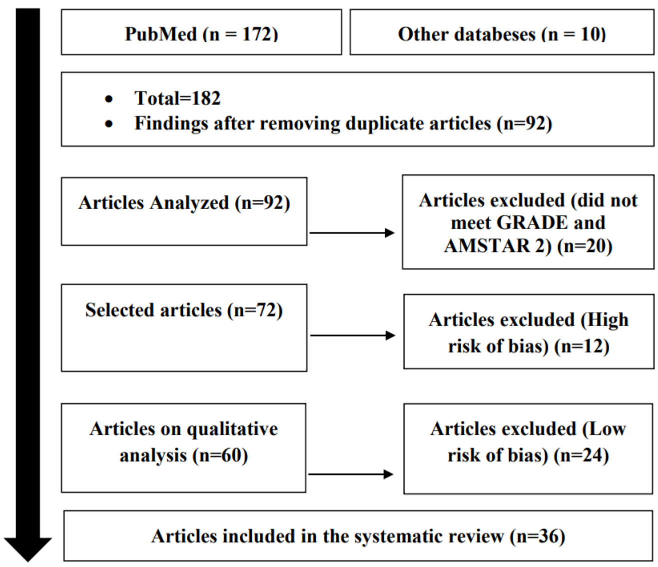

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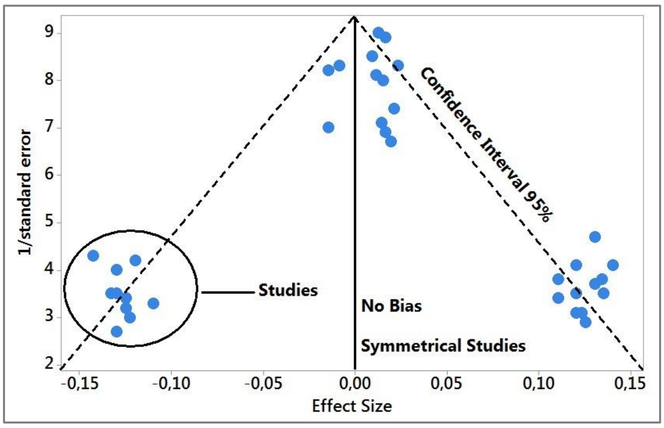
Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the bottom of the graph and in studies with a large sample size that are presented at the top.

Figure 2. The symmetric funnel plot suggests no risk of bias among the small sample size studies that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n=36 studies).



Source: Own authorship

Major Clinical Outcomes

The bone regeneration process occurs through the activation of osteoblasts and vascular proliferation guided by PDGFs and TGF-β. These growth factors also promote matrix formation and osteoblast differentiation [15]. Furthermore, the presence of certain viable cells and a biological or synthetic matrix is essential. The local vascularization conditions and the anatomy of the receptor bed also directly influence this process [1].

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, resorption, differentiation of pre-osteoblastic cell lineage, and proliferation and production of extracellular matrix [9-11]. These processes are monitored by so-called regulatory factors. Among the producing sources are activated monocytes that secrete, among others, platelet-derived growth factors, 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, due to their location in the bloodstream, serve as an efficient vehicle for distributing factors to injured tissues [15].

Growth factors are proteins that can act locally or systemically, altering cell growth and function in several ways [16]. They may have increased the growth rate to accelerate tissue repair, or even control the production rate of a certain component of the extracellular matrix such as collagen [6-8], as shown in Table 1.

Table 1. Activity of growth factors [6-8].

Factors/ Functions	Proliferation Of fibroblasts	Proliferation of osteoblasts and pre-osteoblasts	Matrix synthesis Extracellular	Differentiation of mesenchymal cells	Vascularization	Sources
PDGF	++	++	–	–	+ a	Platelets, macrophages, bone matrix, endothelial cells, Epithelial cells and smooth muscle cells.
IGF	+	++	++	_	_	Platelets, macrophages, osteoblasts, bone matrix T lymphocytes, immature chondrocytes.
BMP	_	+	+	++	++ a	Platelets, macrophages, epithelial cells, eosinophils
TGF-β	+ OR -	+ OR -	++	_	+ a	Platelets, epithelial cells, endothelial cells, fibroblasts, smooth muscle cells, osteoblasts, bone matrix.
FGF	++	++	_	_	++	Macrophages, endothelial cells, osteoblasts, mature and immature chondrocytes, bone matrix.

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.

In the setting of ADSC, exosomes change the biochemical characteristics of recipient cells through the delivery of biomolecules and play a role in cellular communication, showing that ADSC-derived exosome (ADSC-EXO) exhibits similar functions to ADSC with low immunogenicity and no tumorization [17]. Studies have shown that exosomes participate in intercellular communication and play a fundamental role in osseointegration. Authors Zhang et al. (2021) [18] found that exosomes can promote osteogenic differentiation and mineralization of cells.

Several types of research 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 to stimulate periodontal regeneration and the results indicated that these agents were mitogenic and chemotactic for fibroblasts and osteoblasts [19].

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. Through many types of research 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 [20-22].

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 [6,7]. 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 the test group, a PDGF / IGF-I association was used simultaneously Implants. The results were positive regarding bone regeneration around them [19].

In another study, 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 concerning the bone density rates and Areas of bone growth corresponded to the group in which the membranes were associated with growth factors [16]. Research multiplied at an accelerated pace in the 1990s. Several studies on periodontal regeneration came to confirm the action of growth factors. The use of PDGF associated with dexamethasone and collagen matrix generated alveolar bone growth in interdental areas in monkeys [21,23,24].

The use of recombinant PDGF-BB was tested in bone defects produced in calvaria of 16 rabbits to evaluate the remodeling of mineralized tissues. Teflon membranes were used as barriers to maintain the growth factors in place [25-30]. The results after 8 weeks indicated that the growth of new bone into the defect was 52% in an 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 [31].

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 [32]. 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 peripheral blood collection before surgery. As an alternative for this fibrin glue, the use of platelet gel was suggested for use in oral and buccomaxillofacial 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 [33].

Also, a 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 [6-8]. In the same way, bone grafts associated with 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. 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 [6,7].

The use of inorganic bovine bone collagen matrix was tested in association with PDGF-BB 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 [28]. Another study of the same year evaluated the results of the application of platelet-rich plasma collected and processed from patients' blood in periodontal bone defects. This was the first published work associating this new methodology with periodontal surgical therapy. The results showed a significant reduction in the depth of probing as well as the neoformed bone was observed radiographically around

2 months postoperatively [21].

Many studies have evaluated that the time and manner of contact of growth factors concerning 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 [34].

Still, concerning 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, a lifetime of these cells. After 5 to 7 days it is these macrophages that will secrete more growth factors giving continuity to the process [35]. The results indicated that in the 3 weeks, there was a greater difference between the experimental groups (associated with growth factors) concerning 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 [28]. The high values found for the analysis of neoformed bone in the group of 3 weeks concerning the other times could also well exemplify this initial osteoblastic activity.

Similar results were found using bovine osteogenic protein (OP-1) and immediate implants when they were evaluated over 3 weeks [25]. 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 [36]. On the other hand, a comparative analysis between the use of expanded polytetrafluoroethylene membrane alone or associated with rh-PDGF, rhIGF-1, or lyophilized bone (DFDBA), in areas around immediate implants, showed significant results even in the group analyzed after 18 Weeks [19]. The use of platelet-rich plasma has been indicated and used in other areas of bucomaxillofacial 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-yearold 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, an irruption of the canine or lateral incisor through the good bone anchorage and the periodontal support to the teeth adjacent to the cleft. In this case, the patient had a complete left unilateral pre-foramen cleft, which was reconstructed with an 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 [19].

Therefore, the use of PRP, which would accelerate the rate of bone formation, with bone morphogenetic proteins (BMPs), 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 [7,8].

Conclusion

The bone regeneration process occurs through the activation of osteoblasts and vascular control guided by PDGFs and TGF-β. These growth factors also promote matrix formation and osteoblast differentiation. Some biodegradable natural polymers (chitosan®) associated with inorganic materials such as tricalcium phosphate were tested as spongy carriers for PDGF-BB. Chitosan® has been attributed to hemostatic properties, inducing bone formation and regulating the release of bioactive agents. The use of platelet-rich plasma and mesenchymal stem cells (exosomes and microRNAs) has been indicated and used in other areas of oral and buccomaxillofacial surgery, accelerating a process of bone regeneration that normally already occurs and this process continues its path until the formation of bone mature.

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Ethical Approval

Not applicable.

Informed consent

Not applicable.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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