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Major approaches to bucomaxillofacial bone regeneration and remodeling with the use of biomaterials: a systematic review

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Abstract

Introduction: The number of dental implants in the world has increased, totaling more than one million procedures per year. The development of biomaterials has represented an important therapeutic tool in the correction of bone defects. The bone regeneration process is initiated by successive mitosis of mesenchymal and endothelial stem cells, as well as by activation of osteoblasts and vascular proliferation guided by platelet-derived growth factors (PDGF) and TGF-β. **Objective:** To present, through a systematic review, the main results involving bone formation and remodeling in the maxillofacial system using biomaterials, cells and molecules in the appropriate biological niche of human bone. **Methods:** The research was carried out from July 2021 to August 2021 and developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, following the Systematic Review-PRISMA rules. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results:** A total of 225 articles were found. After the selection process, 95 articles were recruited for analysis, 44 articles were selected and 43 articles were used in this study to compose the textual part. The selected articles had moderate quality in their clinical trials. The bias risks found do not affect the reliability of the results. As main findings, it was found that the osteoinduction process is influenced by several factors, requiring the presence of inducers, which include β-glycerolphosphate, ascorbic acid and dexamethasone. Mesenchymal cells acquire the morphology and components of osteoblastic membranes and start to express alkaline phosphatase to deposit extracellular matrix rich in calcium and certain proteins, such as osteopontin and osteocalcin. Bone morphogenetic proteins function as growth factors with a specific role in the proliferation and differentiation of mesenchymal stem cells present in the lesion's niche. Platelet-rich fibrin (PRF) stimulates bone regeneration more efficiently. Studies have reported that the addition of PRF with bone graft is associated with positive clinical results and is a good method of manipulating the bone graft during insertion into the maxillary sinuses and it stimulates bone regeneration. **Conclusion:** Optimized bone regeneration is a matter of great research to accelerate the osseointegration process, leading to reduced waiting time before any subsequent procedure. The balance between the biomaterial, mesenchymal stem cells, fibrin formation and platelet activation are responsible for the process and performance of bone regeneration or formation.

Keywords: Biomaterials. Bone regeneration. Cells. Cytokines. Bone morphogenetic protein.

Introduction

In recent decades, the number of dental implants has increased in the world, totaling more than one million procedures per year [1]. In this scenario, the development of biomaterials has represented an important therapeutic tool in the correction of bone defects [2,3]. Many patients, elderly or not, sought implant-supported rehabilitation, but there is a need for

some adjustments that lead to the consequent demand for regenerative procedures for maxillary reconstructions [4,5].

These patients can often present pathological changes, or use medication, which can alter bone healing [6]. As an example for neovascularization, materials such as hydroxyapatite and calcium phosphate had the highest expression rates of vascular growth factors (VGF) and microvascular density; while polymer grafts had the lowest rates [7]. In this sense, the search for a solution for large bone defects started studies based on guided tissue regeneration therapy or guided bone regeneration. These studies promote the use of fillers and epithelial barriers that aid in treatment as an adjunct to bone grafting techniques. Thus, they favor greater predictability in alveolar and peri-implant reconstructions and have a good prognosis [8].

In this context, the main problem is with non-absorbable membranes, because they require a second surgery, they provide infections if there is any type of exposure; they have a firm consistency, which makes it difficult to adapt to the bone defect and, thus, impairs the blood supply and can cause dehiscence and tissue necrosis [7-9]. Guided bone regeneration (ROG) favors the formation of new bone tissue and prevents the invagination of the gingival tissue into the space between the bone and the implant [10].

In this aspect, filler biomaterials are highlighted by Platelet-rich fibrin (PRF) and platelet-rich plasma (PRP), hydroxyapatite, lyophilized and ground demineralized bone marrow, autogenous bone (another pattern), and Bio-Oss® [4]. In conjunction with fillers, it is most often necessary to use characteristics to isolate the implant using biological membranes, which are epithelial barriers that guide tissue regeneration, work as a mechanical barrier that separates periodontal tissues from the bone surface or implant, thus promoting a formation of new bone, containment of the filling material and stability of the graft [11-17].

In this sense, the bone regeneration process is initiated by successive mitosis of mesenchymal and endothelial stem cells, as well as by activation of osteoblasts and vascular proliferation guided by platelet-derived growth factors (PDGF) and TGF-β. These growth factors also promote matrix formation and osteoblast differentiation. Furthermore, the presence of viable cells and a biological or synthetic matrix is essential. The local conditions of vascularization and anatomy of the receiving bed also directly influence this process [18].

Furthermore, the bone formation phase in the remodeling process of this tissue involves a series of complex events that include chemotaxis of cells to the injury site, resorption, differentiation of the pre-osteoblastic cell lineage, and proliferation and production of extracellular matrix, strongly influenced by the morphogenetic protein BMP-2 [19]. Among the producing sources are activated monocytes that secrete, among others, platelet-derived growth factors, interleukin-1, and fibroblast growth factors.

In this context, monocytes, macrophages, and endothelial cells contribute to bone remodeling, either through contact with osteogenic cells or through the release of soluble factors, such as cytokines and growth factors. In the skeletal system, TNF-α stimulates bone and cartilage resorption and inhibits collagen and proteoglycan synthesis. IL-1 induces the expression of a wide variety of cytokines. LIF and IL-6 are two such molecules that are known to stimulate the differentiation of mesenchymal progenitor cells into the osteoblastic lineage, they are also potent anti-apoptotic osteoblast agents. In bone, the main sources of IL-6 are osteoblasts and not osteoclasts. Prostaglandin E2 (PGE2) is also directly related to the expression of the cytokine IL-6 [20].

Based on this information, this study aimed to present, through a systematic review, the main results involving the bone formation and remodeling in the maxillofacial system with the use of biomaterials, cells, and molecules in the appropriate biological niche of human bone.

Methods

Study Design

The present study was followed by a systematic literature review model, according to the PRISMA rules [21].

Data sources and research strategy

The search strategies for this review were based on the descriptors: “Biomaterials. Bone regeneration. Cells. Cytokines. Bone morphogenetic protein". The research was carried out from July 2021 to August 2021 and developed based on Google Scholar, Scopus, PubMed, Scielo, and Cochrane Library.

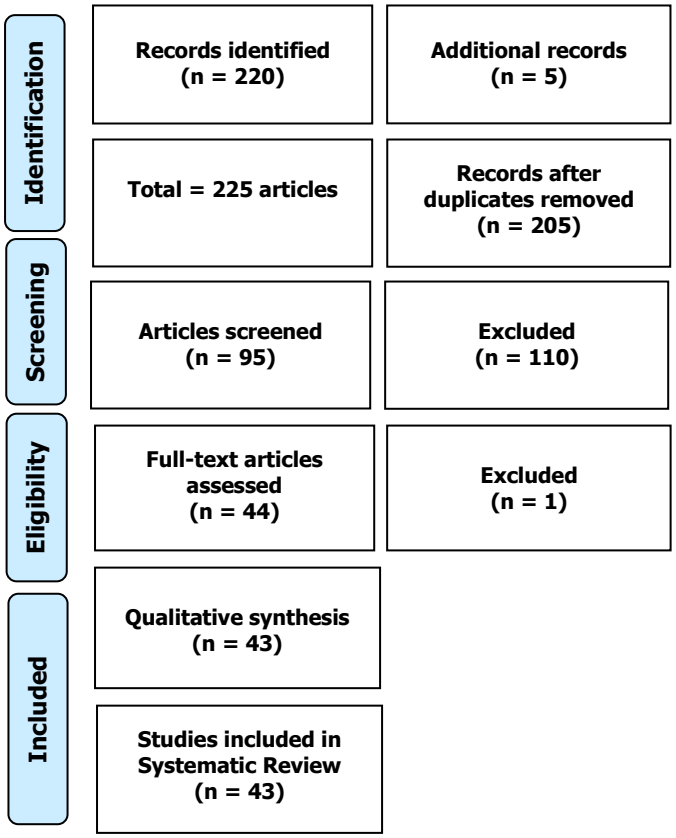
Study quality and risk of bias

The quality of the studies was based on the GRADE instrument, with randomized controlled clinical studies, prospective controlled clinical studies, and studies of systematic review and meta-analysis listed as the studies with the greatest scientific evidence. The risk of bias was analyzed according to the Cochrane instrument.

Results and Discussion

In total, 225 articles were found. After the selection process, 95 articles were recruited for analysis, 44 articles were selected and 43 articles were used in this study to compose the textual part (**Figure 1**). The selected articles had moderate quality in their clinical trials. The bias risks found do not affect the reliability of the results. As main findings, it was found that in the scenario of bone regeneration and remodeling, the lack of bone in the alveolar crests has been a major problem in the functional esthetic recovery in patients who suffered dentoalveolar trauma, traumatic tooth extractions, congenital tooth absence, maxillary and mandibular, in addition to infections due to emotional and the possibility of deformity and also the economic impact they cause on the National Health System [22]. Furthermore, bone loss can also occur due to periodontal disease, traumatic surgeries, and physiological reasons [23].

Figure 1. Study selection scheme.



Still, maxillofacial trauma due to accidents or oncology represents other reasons for the improvement of bone regenerative processes [22,23]. The microscopic bone structure consists of osteoprogenitor cells, support cells (osteoblasts and osteocytes), remodeling cells (osteoclasts), and a non-mineralized extracellular matrix called osteoid, composed of type I collagen proteins and osteonectin, osteocalcin, bone morphogenetic protein (BMP), glycosaminoglycans and bone sialoproteins [24]. Osteoprogenitor cells are small spindle cells found on all non-resorbable bone surfaces and are derived from mesenchymal stem cells that differentiate into more specialized cells such as osteoblasts and osteocytes [24].

Osteoblasts are responsible for the production of bone matrix, rich in collagen (mainly type I) and essential for subsequent mineralization, by adhering calcium, magnesium, potassium, sodium, and carbonate hydroxyapatite crystals to collagen fibrils [25]. Osteoblasts are also rich in alkaline phosphatase, which is of high value during periods of bone formation. The osteoblast-mediated process of new bone formation is called osteogenesis [26]. It is known that osteoblasts bind directly to collagen through integrin-RDG interaction sites (-Arg-Gly-Asp-).

In this sense, the osteoinduction process is influenced by several factors, requiring the presence of inducers, which include β-glycerolphosphate, ascorbic acid, and dexamethasone [27]. In the presence of these substances, mesenchymal cells acquire the morphology and components of osteoblastic membranes and start to express alkaline phosphatase, to deposit extracellular matrix rich in calcium and certain proteins, such as osteopontin and osteocalcin. Also, organic phosphates, such as β-glycerolphosphate, promote osteogenesis due to their role in mineralization and modulation of osteoclast activity [28]. Thus, free phosphates can induce mRNA and protein expression, exemplified by the protein osteopontin. If organic phosphate, eg β-glycerolphosphate is present, a mineral content, hydroxyapatite, is formed between the collagen fibers [29]. Other compounds, such as phosphoric ascorbic acid, are also used in osteogenic induction, in the involvement of increased alkaline phosphatase activity, and in promoting the production of osteocalcin and osteopontin [29].

Bone morphogenetic proteins (BMP) function as growth factors with a specific role in the proliferation and differentiation of mesenchymal stem cells present in the lesion niche [30]. BMP-2 is involved in the early stages of osteogenesis; furthermore, it was shown that the differentiation of human mesenchymal stem cells into the osteogenic lineage requires the presence of BMP-2 in the first days of culture and that these cells after 21 days express specific proteins of the osteogenic lineage, such as osteonectin, osteocalcin, and osteopontin [29].

In the scenario of cell orchestration, monocytes, macrophages, and endothelial cells contribute to bone remodeling, either through contact with osteogenic cells or through the release of soluble factors such as

cytokines and GF [31]. In the skeletal system, TNF-α stimulates bone and cartilage resorption and inhibits collagen and proteoglycan synthesis. IL-1 induces the expression of a wide variety of cytokines. LIF and IL-6 are two of these molecules that are known to stimulate the differentiation of mesenchymal progenitor cells into the osteoblastic lineage, they are also potent anti-apoptotic agents for osteoblasts. In bone, the main sources of IL-6 are osteoblasts and not osteoclasts. Prostaglandin E2 (PGE2) is also directly related to the expression of the cytokine IL-6 [32].

Platelet-rich fibrin (PRF) as an autologous biomaterial was developed in France by Choukroun et al. (1993) [32] for specific use in oral and maxillofacial surgery. This biomaterial has the majority of leukocytes, platelets, and growth factors, forming a fibrin matrix, with a three-dimensional architecture. It is the second generation of platelet concentrate with a high potential for wound repair [33]. PRF is based on protecting growth factors from proteolysis that can maintain their activity for a longer period and stimulate bone regeneration more efficiently [33,34].

The most critical phase of the sinus membrane elevation procedure after maxillary sinus lateral wall osteotomy is its detachment [35]. At this stage, Schneider's membrane ruptures may occur, in around 15.0% of the cases, which, depending on the size of the perforation, may make the graft unfeasible, mainly due to the containment character of the graft material that the membrane exerts. The most frequent causes of these perforations are inadequate osteotomies, incomplete membrane detachments with lack of bone support for lifting curettes, exerting excessive pressure on the membrane, and the presence of septa [36].

If sinus membrane perforations are present, this should be quantified as small perforations do not require treatment as membrane folds obliterate the perforation. In case of ruptures larger than 5.0 mm, the use of collagen membranes is indicated. Another study indicated the use of fibrin membranes obtained from PRF to seal the perforations. In the presence of perforations larger than 10.0 mm, the surgery should be aborted and re-entry performed after 60 to 90 days [37].

Thus, authors documented for the first time that the combination of biomaterial and PRF significantly improved bone regeneration in the peri-implant area [38]. The placement of the implant with the simultaneous use of the PRP creates a good relationship between the hard tissue and the soft tissue, in addition to the advantage of the psychological relationship with the patient. Cell migration and proliferation on the surface of the implants are essential to initiate the tissue regeneration process [39].

Authors such as Zhang and his colleagues have analyzed the combined effect of PRF in a bovine bone without xenograft in maxillary sinus elevation, promoting bone regeneration [40]. Ten patients with atrophic maxilla were selected for this study; the test group consisted of six maxillary sinus elevations that were treated with Bio-Oss® mixed with PRF and the control group consisted of five atrophic sinuses treated with Bio-Oss® alone. Over the next six months, healing occurred without complications for all patients; postoperative radiographs revealed the presence of mineralized tissue in adequate quantity and density in all cases. Biopsies were performed and bone characteristics were analyzed histologically: both PRF and control biopsies showed very similar composition and distribution of histological structures and no significant signs of inflammatory reaction. Still, to the formation of new bone, the percentage in the group that used PRF was 1.4 times higher when compared to the control group. Regarding the amount of Bio-Oss® residue present, as well as the size of the contact between the Bio-Oss® and the newly formed bone, there was no statistically significant difference [40].

In addition, other studies report that the addition of PRF to a bone graft is associated with positive clinical outcomes and is a good method of manipulating the bone graft during insertion into the maxillary sinuses and stimulates bone regeneration around the implants placed in the graft [41].

In this context, a study of 60 patients investigated clinically and histologically the potential use of PRF associated with Bio-Oss® deproteinized bovine bone for sinus graft with severe maxillary atrophy compared to a control group with only Bio-Oss®. Thus, the use of PRF, together with the "piezosurgery" technique, reduced the healing time to before 150 days, as described in the literature, favoring bone regeneration. In 106 days it was already possible to obtain good primary stability of endosteal implants [42]. Another study with 82 patients analyzed the biomechanical stability of enlarged sites in the maxillary bone when using a new class of moldable biomaterials with self-levelling calcium phosphate, with and without the addition of PRF in the subperiosteal, also with the use of "piezosurgery". ". There have been significant improvements, with almost double mechanical stability, with the addition of PRF [43].

In addition, a study with 50 patients, aged between 36 and 69 years, evaluated changes in the height of the alveolar bone, using radiographic examination and Straumann implant, with a survival rate after increased maxillary height and sinus elevation with autogenous bone in combination with platelet-rich plasma from venous blood (SV), with n=25 for each group. Panoramic radiographs were taken preoperatively,

immediately, at 6 months and 1 year postoperatively. The results showed a difference in the mean values of bone height between the groups, with p = 0.001. Thus, significant differences were also observed between the "immediate", "postoperative" and "six months" phases, p<0.01, for the use of PRF. In the SV group, there were also significant differences (p=0.0280) between "postoperative", "immediate" and "six months". Therefore, both groups showed a reasonable increase in alveolar bone height after sinus augmentation, with no significant difference. However, in one year after surgery, the PRF group had a significant difference to the SV group, with more predominant results [44].

Conclusion

Optimized bone regeneration is a matter of great research to accelerate the osseointegration process, leading to a reduction in waiting time before any subsequent procedure. Cell migration and proliferation on the implant surface is necessary to initiate the tissue regeneration process, while modifications on the implant surface incorporating biological growth and differentiation mediators can enhance tissue regeneration. The balance between the biomaterial, mesenchymal stem cells, fibrin formation and platelet activation are responsible for the process and performance of bone regeneration or formation.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

It was applied by Ithenticate@.

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