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Major clinical outcomes of cellular and molecular regulation in maxillofacial bone regeneration: a systematic review

Bruna Maria Vital dos Anjos[1,2], Leandro Gotardello Alves[1,2], Fabio Alarcon Idalgo[1,2], Silvio Antonio dos Santos Pereira[1,2], Alexandre Gomes Nunes[1,2], Elias Naim Kassis[1,2], Alvaro José Cicareli[1,2]*, Igor Mariotto Beneti[1,2]

[1] UNORTE - University Center of Northern São Paulo, Dentistry department, São José do Rio Preto, São Paulo, Brazil.
[2] UNIPOS - Post graduate and continuing education, Dentistry department, São José do Rio Preto, São Paulo, Brazil.

*Corresponding author: Prof. Me. Álvaro José Cicareli.
Unorte/Unipos – Graduate and Postgraduate education, Dentistry department, São José do Rio Preto, São Paulo, Brazil. E-mail: alvarocicareli@gmail.com

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Abstract

Introduction: The importance of knowing the constitution of this epithelium is because these hair cells play a fundamental role in the physiology of the maxillary sinus. When a dental element is lost in the posterior region of the maxilla, there is natural reabsorption of the alveolar process and, at the same time, pneumatization of the maxillary sinus will occur. **Objective:** It was to demonstrate, through a systematic review, the main clinical outcomes of cellular and molecular regulation in maxillofacial bone regeneration. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from September to October 2022 in 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. A total of 110 articles were found, 41 articles were evaluated and 31 were included in this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 31 studies at high risk of bias and 25 studies that did not meet the GRADE. Most studies showed homogeneity in their results, with I2 =98.9% >50%. **Results and Conclusion:** It was found that the search for a solution to large bone defects guided the studies for regeneration therapy tissue or bone regeneration. These studies can promote the use of fillers and epithelial barriers that help in the treatment as an adjuvant to bone graft techniques, favoring greater predictability in alveolar and peri-implant reconstructions and with a good prognosis. The main filler biomaterials can be fibrin-rich plasma (FRP), Bio-Oss®. It is necessary to understand the chemical, physical and biological processes of both the biological material and the biological niche of the host. Crossing compatible information between microenvironments allows cell recognition and signaling cascades for neovascularization and regeneration and bone filling.

Keywords: Maxillofacial surgery. Cell regulation. Bone regeneration. Biomaterials.

Introduction

The importance of knowing the constitution of this epithelium is because these hair cells play a fundamental role in the physiology of the maxillary sinus [1,2]. While the calciform cells produce mucus, these cilia generate movements that cause this mucus to be directed to the drainage site of the maxillary sinus [3-6]. The maxillary sinus drains through its ostium into the nasal cavity, which usually occurs in the middle meatus. Around 25% of all maxillary sinuses, there is an accessory bone that is located in a lower portion than the main ostium, and all the mucus produced and the particles trapped in this mucus are directed through the ciliary beat to the ostium [7].

In this context, when a dental element is lost in the posterior region of the maxilla, there is natural reabsorption of the alveolar process and, at the same time, pneumatization of the maxillary sinus will occur. It will increase its volume towards the place where the roots existed and this will often make it difficult or impossible to restore implants at the site. For this reason, the maxillary sinus floor elevation procedure should be performed, or short implants when possible [8].

In this sense, when grafting procedures are needed, the focus is often on the type of biomaterial to be used and the success and predictability of results do not depend only on the biomaterial. It is also necessary to consider the type of defect to be treated, and its morphology. The morphology will have an impact mainly because the defects have different vascularization capacities, different osteogenic cell recruitment capacities, and different graft natural stabilization capacities, therefore, the characteristics of the biomaterials that we should use, but also the characteristics, must be considered. bed and bone defect for treatment [9,10].

Also, several surgical techniques can be used to reconstruct the atrophic alveolar ridge, isolated techniques or associated with autogenous, allogeneic, xenogeneic, and alloplastic biomaterials. The autogenous bone graft is the only one capable of presenting three important biological properties (osteogenesis, osteoinduction, and osteoconduction) guaranteeing a self-regenerative potential [11].

Further, platelet concentrates have been proposed as regenerative materials in tissue regeneration procedures. Among the platelet concentrates proposed in the literature, there is PRP (platelet-rich plasma) and FRP (fibrin-rich plasma) which act as autogenous platelet aggregates with osteoinductive properties. These biomaterials, due to their low morbidity and possible regenerative potential, have been indicated for use in combination with other biomaterials or even alone. FRP is a second-generation

concentrate, that is, no anticoagulant is used for its acquisition. The patient's blood, after being collected, is subjected to a specific centrifugation force, and thus, the figured elements are separated according to their density. From then on, the part corresponding to the red blood cells is discarded and the resulting platelet concentrate is used for regenerative purposes. Leukocytes and platelets synthesize and release a variety of cytokines and growth factors that act on chemotaxis, angiogenesis, cell differentiation, and inhibition [10-12].

Besides, animal derivatives are the most used in guided bone regeneration (GBR), especially deproteinized sterilized bovine medullary bone, which has been extensively researched and demonstrated to have similarities with human medullary bone [13]. deproteinized sterilized bovine medullary bone is an excellent osteoconduction, providing a favorable framework for bone formation. Its slow resorption contributes a lot to maintaining the graft volume. It has good wettability and a good surface contact angle, favoring contact with the blood clot. Elevations of the floor of the maxillary sinus performed using exclusively deproteinized sterilized bovine medullary bone demonstrate good osteoconductive capacity and excellent biological integration, which facilitates bone neoformation. A study with deproteinized sterilized bovine medullary bone used alone or mixed with autogenous bone at different percentages in maxillary sinus floor elevation demonstrated bone formation similar to that of autogenous bone after 9 months [13,14].

Therefore, the present study sought to demonstrate, through a systematic review, the major clinical outcomes of cellular and molecular regulation in maxillofacial bone regeneration.

Methods

Study Design

The present study followed a systematic review model, following the rules of systematic review - PRISMA (Transparent reporting of systematic review and metaanalysis, access available in: http://www.prisma-statement.org/).

Search Strategy and Search Sources

The literary search process was carried out from September to November 2022 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, addressing scientific articles from various eras to the present day. The descriptors (MeSH Terms) were used “Maxillofacial surgery. Cell regulation. Bone regeneration. Biomaterials”, and using Boolean "and" between MeSH terms and "or" between historical discoveries.

Study Quality and Risk of Bias

Quality was rated as high, moderate, low, or very low for risk of bias, clarity of comparisons, accuracy, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analysis 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 through the analysis of the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

Results and Discussion

Summary of Findings

As a corollary of the literary search system, a total of 110 articles were found that were submitted to the eligibility analysis, and, then, 31 of the 41 final studies

were selected to compose the results of this systematic review. The listed studies showed medium to high quality (**Figure 1**), considering in the first instance the level of scientific evidence of studies in types of study such as meta-analysis, consensus, randomized clinical trial, 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 I2=98.9%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 31 studies with a high risk of bias and 25 studies that did not meet GRADE.

Figure 1. Flowchart showing the article selection process.

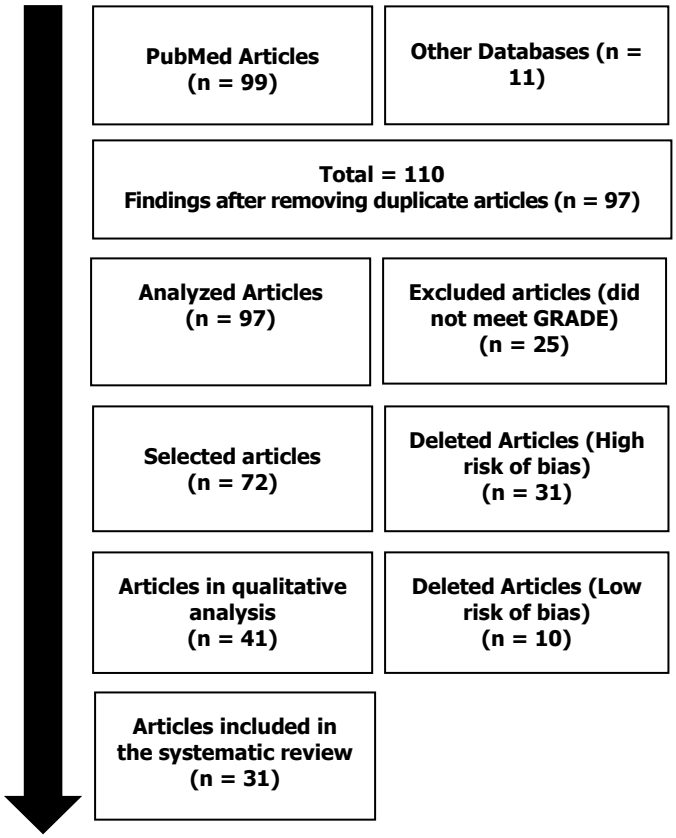
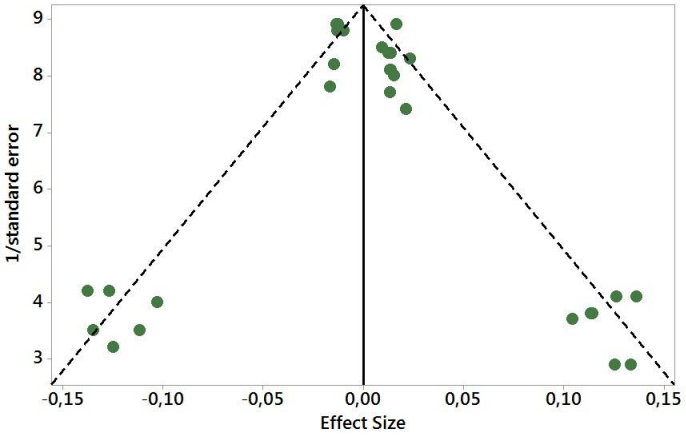


Figure 2 presents the results of the risk of bias of the studies through the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was indirectly determined by the inverse of the standard error (1/Standard Error). This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

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (n=31 studies).



Source: Own authorship.

Major Clinical Findings

Normal bone formation and tissue repair involve coordinated interaction between bone-forming cells and biological signals [15,16]. The main force in this process is the osteoblasts and their precursors [17]. Osteoblasts can produce new bones along with biomaterials and can initiate the release of biological signals that guide the bone formation and remodeling [18].

These biological signals attract bone-forming cells to the recipient site. Growth factors and other proteins are some biological signs that may be involved in bone neoformation and tissue remodeling. Furthermore, through chemotaxis, there is a migration of bone-forming cells to the application area, as the stimulation of cell migration occurs in response to chemical stimuli [19].

In this sense, 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 [19]. 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 [20,21].

In this aspect, for the success of the surgery practice, osseointegration is essential. However, it is a complex process with many factors interfering in the formation and maintenance of bone tissue around the

implant, such as topography and surface roughness, biocompatibility, and loading conditions. In addition, a healthy, compatible host bone layer that allows for primary stability is needed [22-25].

In this sense, after extraction, the repair process occurs in the inner region of the alveolus, together with the formation of a clot rich in cells and growth factors, promoting neoformation, bone remodeling, and soft tissue epithelialization [25]. During this process, the alveolar ridge undergoes relevant changes, both in height and thickness, which influence the possibility of installing the implants. Thus, the optimized processes of implantology and biomaterials allow the installation of implants in areas of thin bone thickness, width, and height, with simpler surgeries and greater success rate and patient comfort [26].

The lack of bone in the alveolar crests has been a major problem in the functional aesthetic recovery of patients who have suffered dentoalveolar trauma, traumatic tooth extractions, congenital tooth loss, and maxillary and mandibular pathologies [27,28]. To fill large bone defects, the development of bone regeneration improves the epithelial barriers for the bone graft, favoring greater predictability in alveolar and peri-implant reconstructions and presenting a good prognosis [29]. In this sense, filling biomaterials can be fibrin-rich plasma (FRP), Bio-Oss®, hydroxyapatite, lyophilized and ground demineralized bone marrow, autogenous bone, which is considered the gold standard, among others [22].

Thus, FRP as an autologous biomaterial for use in oral and maxillofacial surgery has the majority of leukocytes, platelets, and growth factors, forming a fibrin matrix, with a three-dimensional architecture [30]. The Bio-Oss® (Geistlich) biomaterial, as it is biodegradable, biocompatible, non-toxic, and has low immunogenicity and bio stimulators, can act in the regeneration of bone tissue, as it establishes, with adenomatous mesenchymal stem cells, the appropriate biological niche for bone growth and, thus, allowing the dental implant as effectively as possible [14].

Based on this, two important studies reported results on the combined use of BioOss® and FRP. Thus, the first study investigated clinically and histologically the potential of FRP as a graft material in pre-implant reconstructive surgeries for severe maxillary atrophy after sinus lift procedures in 106-120-180 days, to determine whether the use of FRP can accelerate the bone regeneration process, which is essential to promote implant stability. This study also includes a control group, in which only deproteinized bovine bone (Bio-Oss®) was used as reconstructive material. As a result, the use of FRP optimized bone formation [31].

The second study compared the use of Bio-Oss® mixed with FRP and Bio-Oss® with Tisseel® to improve bone regeneration. After elevating the sinus membrane in both maxillary sinus cavities, an implant was placed in the sinus cavity. In one of the sinus cavities, the FRP/Bio-Oss® composite was grafted and the Tisseel®/Bio-Oss® composite was grafted in the other sinus cavity. After a 6-month healing period, bone formation at the graft sites and bone-implant contact were assessed. The mean rate of osseointegration was 43.5 ± 12.4% and the rate of new bone formation was 41.8 ± 5.9% at the FRP/Bio-Oss® composite sites. In the composite sites Tisseel® / Bio-Oss® were 30.7 ± 7.9% and 31.3 ± 6.4%. There were statistically significant differences between groups. The findings of this study suggested that when FRP is used as an adjuvant to BioOss® particles for bone augmentation in the maxillary sinus, bone formation at the graft sites is significantly greater than when Tisseel® is used [14].

Conclusion

It was found that the search for a solution to large bone defects guided the studies for regeneration therapy tissue or bone regeneration. These studies can promote the use of fillers and epithelial barriers that help in the treatment as an adjuvant to bone graft techniques, favoring greater predictability in alveolar and peri-implant reconstructions and with a good prognosis. The main filler biomaterials can be fibrin-rich plasma (FRP), Bio-Oss®. It is necessary to understand the chemical, physical and biological processes of both the biological material and the biological niche of the host. Crossing compatible information between microenvironments allows cell recognition and signaling cascades for neovascularization and regeneration and bone filling.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

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