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Systematic review of biomaterials for bone regeneration: clinical findings in bucomaxillofacial

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Abstract

Introduction: In the bone engineering scenario and the molecular and cellular constituents, 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. **Objective:** It was performed a systematic review of bone regeneration processes using biomaterials and the main molecular and cellular constituents for bone regeneration. **Methods:** The present study was followed by a systematic review model (PRISMA). The search strategy was performed in the PubMed, Cochrane Library, Web of Science and Scopus, 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:** The total of 132 articles were found involving implantology and biomaterials. A total of 62 articles were fully evaluated and 17 were included in the systematic review. A total of 34 studies were excluded because they did not meet the GRADE and AMSTAR-2 criteria, and 6 studies were excluded because they had a high risk of bias. The symmetric funnel plot does not suggest a risk of bias between the small sample size studies. According to the aim of this study on bone regeneration processes with the use of biomaterials and the main molecular and cellular constituents for bone regeneration, the symmetric funnel plot does not suggest a risk of bias between the small sample size studies. 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 plasma rich-fibrin or Bio-Oss®. However, 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: Bone regeneration. Biomaterials. Cellular processes. Bucomaxillofacial surgery.

Introduction

In the bone engineering scenario and the molecular and cellular constituents, 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 [1]. It will increase its volume toward the place where the roots existed and this will often make it difficult or

impossible to restore implants at the site [2-4]. For this reason, the maxillary sinus floor elevation procedure should be performed, or short implants when possible [5-7].

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 [2]. 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 [8,9].

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. As a disadvantage to autogenous bone graft, the need for second surgical access in the donor area is highlighted, resulting in longer surgical time, morbidity, and a consequent greater resistance of the patient to the proposed treatment [10].

In this context, allogeneic, xenogenous, and alloplastic bone grafts are an alternative for the treatment of bone deficiencies in the jaws, as they avoid the need for a second surgical approach. But due to the need for processing to eliminate antigenic components, these grafts are uniquely osteoconductive with a lower bone formation potential compared to the autogenous bone graft. To increase the bone formation potential of these grafts, combinations have been proposed to obtain better regenerative conditions through volume preservation (osteoconduction) and induction of cell migration differentiation (osteoinduction) [10,11].

Over the past 20 years, 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 PRF (plasma rich-fibrin) 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. PRF 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 [9-11].

Also, 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 [10]. 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 [12].

Also, the most used xenograft in guided bone regeneration procedures is deproteinized bovine bone mineral, commercially known as Bio-Oss®, it is the most researched product in regenerative dentistry worldwide. It is a bone of bovine origin processed to produce natural bone minerals without organic elements [13]. After thermal and chemical treatments, the inorganic phase of bovine bone consists mainly of hydroxyapatite (HA) which retains the porous architecture. The excellent osteoconductive properties of Bio-Oss® lead to predictable and efficient bone regeneration, Bio-Oss® particles become an integral part of the newly formed bone structure and conserve its volume in the long term [13,14].

Besides, due to its 'great' resemblance to the human bone, the 'Bio-Oss®' is 'incorporated' into the 'natural' process of 'shaping' and 'reshaping'. The highly porous structure of the Bio Oss® offers space for the formation of blood vessels (angiogenesis) and the deposit of neoformed bone (osteogenesis) [13]. The 'microstructure' of the 'surface' of Bio-Oss® supports the 'excellent growth' of osteoblasts, which are 'responsible' for 'bone' formation. In this way, the 'Bio-Oss'® particles become an integral part of the structure of the 'new 'bone' in formation and the 'low speed' of

'conversion into proper 'bone' (remodeled) from Bio-Oss®, stabilizes the structure and allows the volume of the graft to maintain over the long term. These biofunctional processes make Bio-Oss® unique [14,15].

Although the results do not seem to confirm that PRF is better than other biomaterials, it is suggested that its use can result in a decrease in the total healing time, around 104 days, and improve the handling of the graft material. Furthermore, the use of PRF associated with Bio-Oss® seems to illustrate high success rates with minimal costs, which can reduce the amount of bone graft needed to fill the sinus cavity, reducing procedure costs [7].

Therefore, the present study performed a systematic review of bone regeneration processes using biomaterials and the main molecular and cellular constituents for bone regeneration.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed at: 11/11/2024. The AMSTAR 2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed at: 11/11/2024.

Search Strategy and Search Sources

The literature search process was carried out from November 2024 to January 2025 and developed based on Web of Science, Embase, Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following descriptors were used in health sciences (DeCS/MeSH): *Bone regeneration. Biomaterials. Cellular processes. Bucomaxillofacial surgery*, and the Boolean "and" was used between the MeSH terms and "or" between the historical findings.

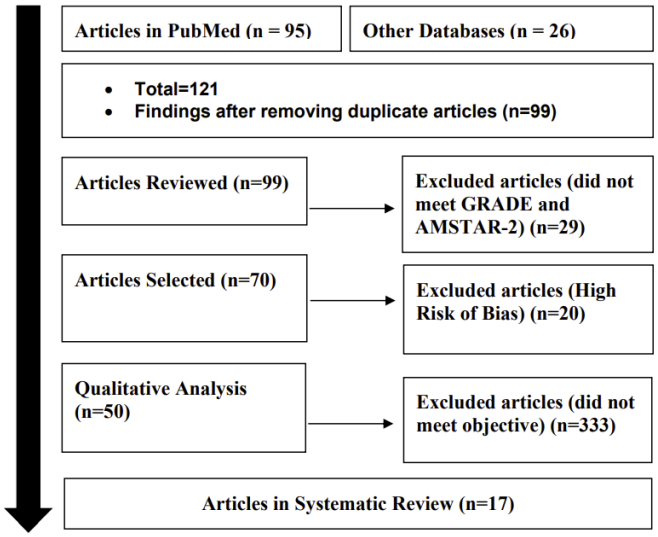
Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low regarding the 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. 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 Cohen's test (d).

Summary of Findings

A total of 121 articles were found and submitted to eligibility analysis, with 17 final studies selected to compose the results of this systematic review. The listed studies were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=72.7%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 20 studies with a high risk of bias and 29 studies that did not meet GRADE and AMSTAR-2.

Figure 1. Flowchart showing the article selection process.

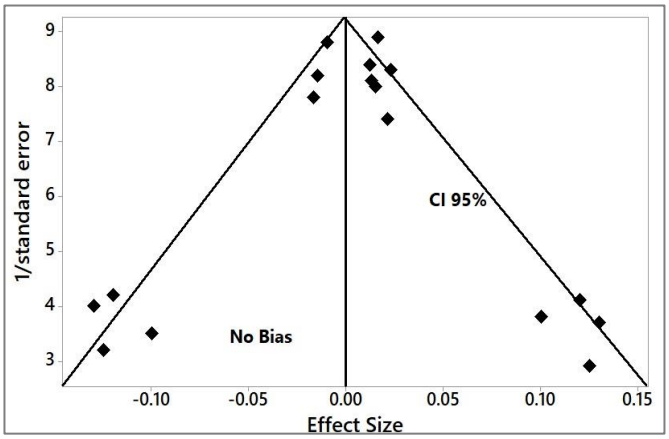


Source: Own Authorship.

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 Cohen's 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 among studies with small sample sizes (lower precision) that are shown at the base of the graph and in studies with large sample sizes that are presented at the top.

Figure 2. The symmetrical funnel plot suggests no risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. High confidence

and high recommendation studies are shown above the graph (n=17 studies).



Source: Own Authorship.

Major Clinical Results – Bone Graft and Regeneration

In recent decades, biomaterials in implant therapy have promoted bone response and biomechanical capability, which is long-term from surgical equipment to final prosthetic restoration. Biomaterials play a crucial role in the rehabilitation of damaged tooth structures and in providing acceptable results correlated with clinical performance. There are some challenges in implantation such as bleeding, mobility, peri-implant infections, and the solution associated with modern strategies that refer to biomaterials. Biomaterials must be biodegradable and biocompatible. Furthermore, biomaterials have important roles in prosthetic conditions, such as dental pulp regeneration, the healing process, and antibacterial and anti-inflammatory effects [16].

Normal bone formation and tissue repair involve coordinated interaction between bone-forming cells and biological signals. 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 dental implant 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].

Dental implants are being used more and more due to the high success rates. However, a large number of patients do not have sufficient minimum bone conditions for the installation of implants, therefore, previous bone reconstructive surgery is necessary. Dentists must master the knowledge of the healing process of post-extraction alveoli, to provide correct planning of cases [26,27].

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. 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 [28].

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. 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 (PRF), Bio-Oss®, hydroxyapatite, lyophilized and ground demineralized bone marrow, and autogenous bone, which is considered the gold standard, among others [22].

Thus, PRF 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 Bio-Oss® and PRF. Thus, the first study investigated clinically and histologically the potential of PRF 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 PRF 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 PRF optimized bone formation [31].

Finally, the second study compared the use of Bio-Oss® mixed with PRF 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 PRF/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 PRF/Bio-Oss® composite sites. In the composite sites, Tisseel® / Bio-Oss® was 30.7 ± 7.9% and 31.3 ± 6.4%. There were statistically significant differences between groups. The findings of this study suggested that when PRF is used as an adjuvant to Bio-Oss® particles for bone augmentation in the maxillary sinus, bone formation at the graft sites is significantly greater than when Tisseel® is used [14].

Conclusion

According to the aim of this study on bone regeneration processes with the use of biomaterials and the main molecular and cellular constituents for bone regeneration, the symmetric funnel plot does not suggest a risk of bias between the small sample size studies. 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 plasma rich-fibrin or Bio-Oss®. However, 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.

CRediT

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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@.

Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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