



Bone regeneration processes with the use of biomaterials and molecular and cellular constituents for dental implants

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Abstract

Introduction: When a dental element is lost in the posterior region of the maxilla, there is a natural reabsorption of the alveolar process and, at the same time, pneumatization of the maxillary sinus will occur. For this reason, the maxillary sinus floor elevation procedure should be performed, or short implants when possible. Often the focus is on the type of biomaterial to be used and the success and predictability of our results does not depend only on the biomaterial. It is also necessary to consider the type of defect to be treated, its morphology. The characteristics of the biomaterials to be used must be considered, as well as the characteristics of the bed and the bone defect for treatment. **Objective:** It was to carry out a concise systematic review of bone regeneration processes using biomaterials and the main molecular and cellular constituents for subsequent dental implantation. **Methods:** The present study 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 Cochrane Instrument was used to assess the risk of bias of the included studies. **Results and Conclusion:** 152 articles involving implantology and biomaterials were found. A total of 64 articles were fully evaluated and 28 were included in the present study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 5 studies with high risk of bias (studies with small sample size) and 3 studies with uncertain risk (studies with results without statistical significance). The search for a solution for large bone defects directed studies to tissue regeneration therapy 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, 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 for successful posterior dental implant.

Keywords: Bone regeneration. Biomaterials. Molecular and cellular processes. Dental implants.

Introduction

The maxillary sinus is the largest of the paranasal sinuses and its function is to contribute to phonation resonance, conditioning the air we breathe and aiding in the production of mucus in the nasal cavity. It also acts to equalize barometric pressures in the nasal cavity, which is covered by a membrane called Schneider's membrane. This membrane consists of a cylindrical pseudostratified epithelium with calciform cells that produce mucus [1,2].

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. 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]. 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 is directed through the ciliary beat to the ostium [4].

In this context, when a dental element is lost in the posterior region of the maxilla, there is a 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 [5].

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 does not depend only on the biomaterial. It is also necessary to consider the type of defect to be treated, its morphology. The morphology will have an impact mainly because the defects have different vascularization capacity, different osteogenic cell recruitment capacity, different graft natural stabilization capacity, therefore, the characteristics of the biomaterials that we should use, but also the characteristics, must be considered. bed and bone defect for treatment [6,7].

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 a 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 [8].

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) [8,9].

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 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 [7-9].

Xenografts are bone minerals derived from animals or algae and corals. The organic component is removed to eliminate the risk of immunogenic responses or disease transmission. 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 osteoconductor, 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 [10].

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 mineral without organic elements [11]. 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 [11,12].

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 much for the formation of blood vessels (angiogenesis) and the deposit of neoformed bone (osteogenesis) [11]. 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 allowsthevolume of the graft to maintain overlong term. These biofunctional processes make Bio Oss® unique [12,13].

Therefore, although the results do not seem to confirm that FRP 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 FRP 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 [5].

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

Methods

Study Design

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

Data Sources

The search strategy was performed in the PubMed, Cochrane Library, Web of Science and Scopus, and Google Scholar databases, using scientific articles from 2009 to 2021.

Descriptors (MeSH Terms)

The main descriptors (MeSH Terms) used were "Bone regeneration. Biomaterials. Molecular and cellular processes. Dental implants". For greater specification, the description "bone regeneration" for refinement was

added during the searches, following the rules of the word PICOS (Patient; Intervention; Control; Outcomes; Study Design).

Selection of studies and risk of bias in each study

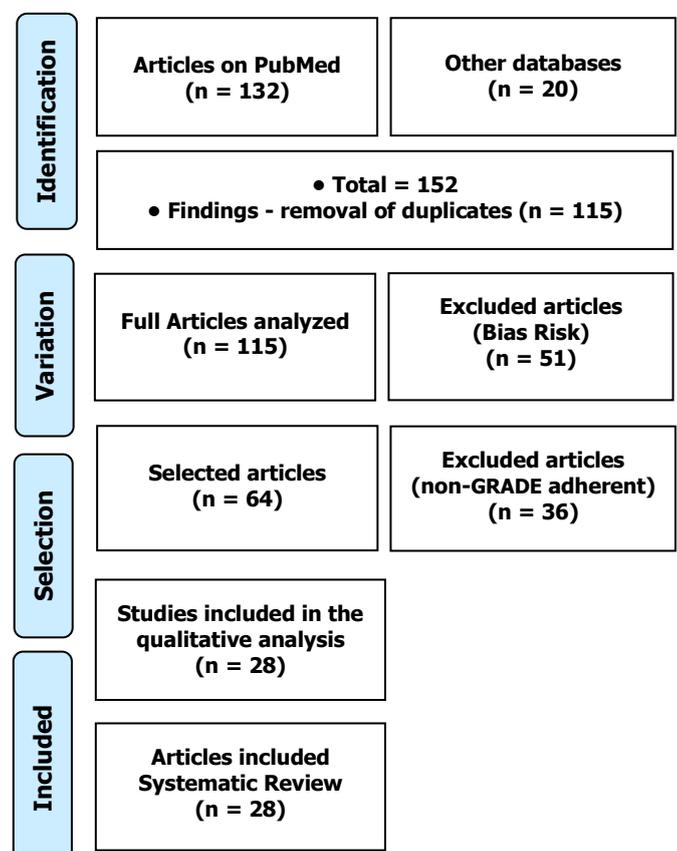
Two independent reviewers (1 and 2) performed research and study selection. Data extraction was performed by reviewer 1 and fully reviewed by reviewer 2. A third investigator decided some conflicting points and made the final decision to choose the articles. Only studies reported in Portuguese and English were evaluated. The Cochrane Instrument was used to assess the risk of bias of the included studies.

Results

Article Series and Eligibility

The total of 152 articles were found involving implantology and biomaterials. Initially, the duplication of articles was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing the articles that did not include bone regeneration using Biomaterials and/or fibrin-rich plasma. A total of 64 articles were fully evaluated and 28 were included in this study (Figure 1).

Figure 1. Flowchart showing the article selection process.



Considering the Cochrane tool for risk of bias, the overall assessment resulted in 5 studies with high risk of bias (studies with small sample size) and 3 studies with uncertain risk (studies with results without statistical significance). The domains that presented the highest risk of bias were related to the number of participants in each study addressed, and the uncertain risk was related to the bone maturation time for implantation. In addition, there was a lack of funding source in 4 studies and 3 studies did not disclose information about the declaration of conflict of interest.

Molecular and Cellular Processes

Normal bone formation and tissue repair involve coordinated interaction between bone-forming cells and biological signals. The main force in this process are the osteoblasts and their precursors [14]. Osteoblasts can produce new bones along with biomaterials, and can initiate the release of biological signals that guide bone formation and remodeling [15].

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 neof ormation and tissue remodeling. Furthermore, through chemotaxis, there is migration of bone-forming cells to the application area, as the stimulation of cell migration occurs in response to chemical stimuli [16].

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 [16]. 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 [17,18].

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 [19-22].

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 in the healing process of post-extraction alveoli, to provide a correct planning of cases [1,23,24].

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 neof ormation, bone remodeling and soft tissue epithelialization. During this process, the alveolar ridge undergoes relevant changes, both in height and in 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 [25].

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, 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 [26]. 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 [19].

Thus, fibrin-rich plasma (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 [27]. The Bio-Oss® (Geistlich) biomaterial, as it is biodegradable, biocompatible, non-toxic and has low immunogenicity and biostimulators, 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 [11].

Based on this, two important studies reported results on the combined use of Bio-Oss® 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 [28].

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 $43.5 \pm 12.4\%$ and the rate of new bone formation was $41.8 \pm 5.9\%$ at the FRP/Bio-Oss® composite sites. In the composite sites Tisseel® / Bio-Oss® were $30.7 \pm 7.9\%$ and $31.3 \pm 6.4\%$. There were statistically significant differences between groups. The findings of this study suggested that when FRP 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 [11].

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 subsequent dental implantation, 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®. 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 for successful posterior dental implant.

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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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