



Molecular, cellular and surgical processes of osseointegration for dental implants: a systematic review

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Abstract

Introduction: The maxillary sinus floor elevation procedure should be performed based on the cellular and molecular process of osseointegration. In this sense, when grafting procedures are necessary, the success and predictability of the results do not depend only on the biomaterial, but as well as the morphology of the bone defect. Combinations have been proposed to obtain better regenerative conditions through volume preservation (osteoconduction) and induction of cell migration differentiation (osteinduction). The surface microstructure of Bio Oss® supports the growth of osteoblasts, which are responsible for bone formation.

Objective: To carry out a concise systematic review of the molecular and surgical processes of osseointegration for dental implants. **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 Cochrane Instrument was used to assess the risk of bias from the included studies. **Results and Conclusion:** In line with the objective of this study, it was observed that the understanding of bone bioengineering, understanding the entire bioprocess of bone formation through the main cells (mesenchymal stem cells and osteoblasts) and molecules (BMPs, PRP, PRF, cytokines and growth factors), can promote the use of biomaterials and epithelial barriers that help in the treatment as an adjuvant to bone grafting-techniques, favoring greater predictability in alveolar and peri-implant reconstructions and with a good prognosis.

Keywords: Osseointegration. Biomaterials. Molecular processes. Cellular processes. Dental implants.

Introduction

In the scenario of implantology and osseointegration process, the maxillary sinus is the largest of the paranasal sinuses with fundamental functions for phonatory resonance, conditioning the air, to equalize the pressures in the nasal cavity that is covered by Schneider's membrane [1-3]. 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 [4-6].

In this context, when a tooth is lost in the posterior region of the maxilla, there is natural resorption of the alveolar process and, at the same time, pneumatization of the maxillary sinus will occur. Thus, there will be an increase in volume toward the place where the roots existed and this will often make it difficult or impossible to restore implants in place. For this reason, the maxillary sinus floor elevation procedure should be performed, based on the cellular and molecular process of osseointegration [7].

In this sense, when grafting procedures are necessary, 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 [8,9]. In this aspect, several surgical techniques can be used to reconstruct the atrophic alveolar ridge, isolated techniques, or associated with autogenous, allogeneic, xenogenic, and alloplastic biomaterials. The autogenous bone graft is

the only one capable of presenting the properties of osteogenesis, osteoinduction, and osteoconduction [10].

Furthermore, allogeneic, xenogeneic, 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. 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]. In this scenario, PRP (platelet-rich plasma) and PRF (fibrin-rich plasma) stand out as they act as autogenous platelet aggregates with osteoinductive properties [9-11].

Also, deproteinized sterilized bovine medullary bone is an excellent osteoconduction, providing a favorable framework for bone formation. Its slow resorption contributes greatly to the maintenance of graft volume. Maxillary sinus floor elevations performed with exclusively deproteinized sterilized bovine bone marrow demonstrate good osteoconductive capacity and excellent biological integration, which facilitates bone neoformation [12]. In this sense, deproteinized bovine bone (Bio-Oss®) stands out [13,14].

In this context, Bio-Oss® is similar to human bone and its porous structure offers a lot of space for the formation of blood vessels (angiogenesis) and the deposit of newly formed bone (osteogenesis) [13]. The surface microstructure of Bio Oss® supports the growth of osteoblasts, which are responsible for bone formation [14,15].

Therefore, the present study aimed to carry out a concise systematic review of the molecular and surgical processes of osseointegration for dental implants.

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. The present study was carried out from February to June of 2022.

Descriptors (MeSH Terms) And Search Strategy

The main descriptors (MeSH Terms) used were

“*Osseointegration. Biomaterials. Molecular processes. Cellular processes. Dental implants*”. The rules of the word PICOS (Patient; Intervention; Control; Outcomes; Study Design) were followed.

Selection Process, Risk of Bias and Quality of Studies

Two independent reviewers 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. 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, and the risk of bias was analyzed according to the Cochrane instrument.

Results and Discussion

Summary of Findings

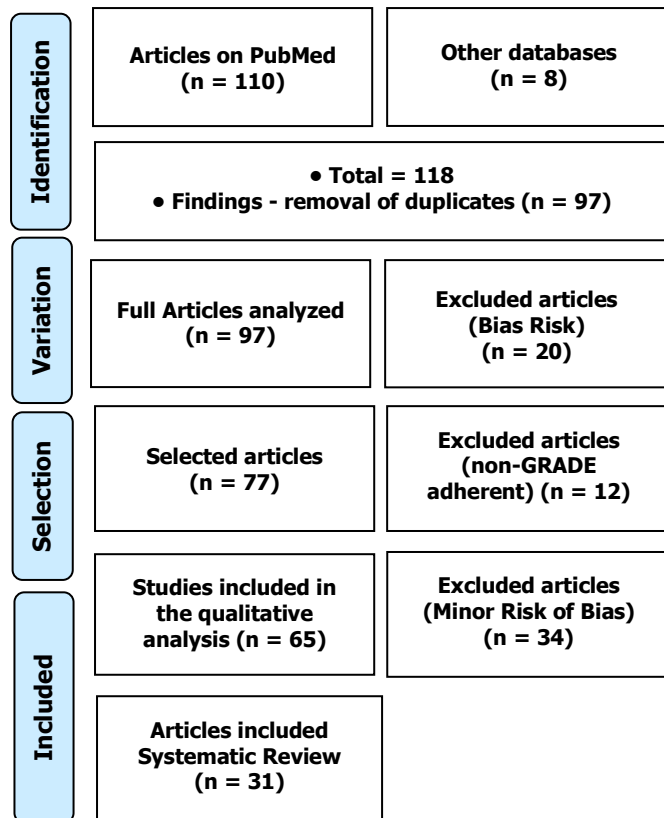
A total of 118 articles were found. Initially, duplicate articles were excluded. After this process, the abstracts were evaluated and a new exclusion was performed based on the GRADE Instrument and Risk of Bias. A total of 65 articles were fully evaluated and 31 were included and discussed in this study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 20 studies that were excluded with a high risk of bias (studies with small sample size). Also, 12 studies were excluded because they did not meet the GRADE (**Figure 1**).

Major Findings

Osseointegration was originally defined as a direct functional and structural connection between organized living bone tissue and the surface of an implant under load. Currently, it is permissible for an implant to be considered osseointegrated when there are no relative and progressive movements between this same implant and the bone with which it is in direct contact [16]. Moreover, it is possible to cite that in practice, in osseointegration, there is an anchoring mechanism in which non-vital components can be reliably and predictably incorporated into living bone, and from that anchorage can remain under all conditions and normal loads [17]. Osseointegration is also described as a series of remodeling phenomena and/or bone regeneration, which will result in the formation of new bone, organized around the implant installed [18].

In the process of bone formation, there is coordination between bone-forming cells and biological

Figure 1. Flowchart showing the article selection process.



signals (paracrine, autocrine, and endocrine effects) with cytokines and growth factors. The main force in this process are osteoblasts and their precursors [19]. Osteoblasts together with morphogenetic proteins (BMPs) can produce new bones together with biomaterials and mesenchymal stem cells.

These biological signals attract bone-forming cells to the receptor site. Growth factors and other proteins are some biological signals that may be involved in bone neoformation and tissue remodeling. In addition, 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 such molecules that are known to stimulate the differentiation of mesenchymal progenitor cells in 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 regard, for the success of dental implant practice, osseointegration is essential. However, it is a complex process with many factors that interfere 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 and compatible host bone layer is required that allows for primary stability [22-26].

Dental implants are being increasingly used due to high success rates [1,2]. However, a large number of patients do not have sufficient minimum bone conditions for implant placement, requiring previous bone reconstructive surgery. The dentist must master the knowledge of the healing process of post-extraction sockets, to provide correct planning of the cases [27,28].

In this sense, after extraction, the repair process takes place in the internal 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 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 ridges has been a major problem in the functional aesthetic recovery of patients who have suffered dentoalveolar trauma, traumatic extractions, congenital tooth loss, and maxillary and mandibular pathologies. For filling large bone defects, the development of bone regeneration improves the epithelial barriers to the bone graft, favoring greater predictability in alveolar and peri-implant reconstructions and presenting a good prognosis [27]. In this sense, the filling biomaterials can be fibrin-rich plasma (FRP), Bio-Oss®, hydroxyapatite, freeze-dried and ground demineralized bone marrow, and autogenous bone, which is considered the gold standard, among others [24,29].

Also, specific immune cells such as macrophages play a crucial role in the dynamics of osseointegration. Infiltrating macrophages and resident macrophages contribute to achieving an early pro-regenerative peri-implant environment. In addition, multinucleated giant cells at the bone-implant interface and their polarization capacity maintain a peri-implant immunological balance to preserve the integrity of osseointegration. Thus, to prevent bone loss from implants, a better understanding of the osteoimmunology of the peri-implant environment would lead to the development of new

therapeutic approaches [25].

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 [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 [13].

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 [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 $43.5 \pm 12.4\%$ 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® was $30.7 \pm 7.9\%$ 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 [13].

Conclusion

According to the objective of this study, it was observed that the understanding of bone bioengineering, understanding the entire bioprocess of bone formation through the main cells (mesenchymal stem cells and osteoblasts) and molecules (BMPs, PRP, PRF, cytokines, and growth), can promote the use of biomaterials and epithelial barriers that help in the treatment as an adjuvant to bone grafting-techniques,

favoring greater predictability in alveolar and peri-implant reconstructions and with a good prognosis.

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Ethics approval

Not applicable.

Informed consent

Not applicable.

Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

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