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Biomaterials, surgical processes and bone formation for dental implants: a systematic review

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Abstract

Introduction: Several factors have been reported related to implant success, such as the development and maintenance of healthy peri-implant soft tissues. The development of biomaterials for use in dental clinics in recent years has represented a powerful therapeutic tool in the correction of bone defects. **Objective:** The present study aimed to carry out a systematic review of the main approaches to the use of biomaterials, surgical methods, and bone regeneration for dental implants. **Methods:** The systematic review rules of the PRISMA Platform were followed. The search was carried out from January to March 2023 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases, using articles from 1991 to 2022. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed accordingly, according to the Cochrane instrument. **Results and Conclusion:** A total of 204 articles were found, 78 articles were evaluated and 66 were included and developed in this systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 96 studies with a high risk of bias and 20 studies that did not meet GRADE. For a successful 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. The dental surgeon must master the knowledge of the healing process of the post-extraction sockets, to provide correct planning of the cases. The optimized processes of implant dentistry and biomaterials allow the installation of implants in areas of low bone thickness, width, and height, with simpler surgeries and greater success rates and patient comfort.

Keywords: Biomaterials. Bone bioengineering. Bone regeneration. Surgical techniques. Dental implants.

Introduction

Several factors have been reported related to implant success, such as the development and maintenance of healthy peri-implant soft tissues. The traditional method involves implant placement with a submerged protocol, followed by second-stage surgery after the osseointegration period. A two-piece implant with a smooth transmucosal hyperbolic neck present with platform switching and a smooth transmucosal neck projecting through the peri-implant soft tissue was shown to reduce marginal bone loss in a 3-year prospective cohort study. Another method to avoid two-stage surgery and create peri-implant soft tissue is with an immediate connection of a transmucosal healing abutment [1,2].

In this context, the number of dental implant procedures has been increasing worldwide, reaching about one million dental implants per year [3,4]. In Brazil, in the last decades, there has been a very rapid evolution in implant dentistry with high success rates

[5]. The development of biomaterials for use in dental clinics in recent years has represented a powerful therapeutic tool in the correction of bone defects. However, despite the proven benefits, its use requires the professional to take care of clinical and ethical criteria in the analysis of the risks and benefits that each biomaterial can present [1,5].

A study with 123 dental surgeons using biomaterials showed that professionals are not aware of the risks and benefits of biomaterials, nor their biological principles since 45.0 % believe there is no risk to the patient and 56.0 % do not consider biomaterial as medicine. About 70.0 % felt safe concerning the origin. Despite this, 96.0 % of the interviewees said that there should be greater control of health authorities. More than half of the interviewees (51.0 %) reported little or no patient participation in the process of therapeutic choice [5].

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 [1,2,6]. These patients can often present pathological changes, or make use of medications, which may alter bone healing [7]. Several materials can be used as a bone graft, each with different properties; for example: for neo-vascularization, materials such as hydroxyapatite and calcium phosphate showed the highest expression rates of vascular growth factors (VGF) and microvascular density; while the grafts of polymer, showed the lowest rates [8-10].

The search for a solution for large bone defects has begun 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 present a good prognosis [6]. The main problem is with non-absorbable membranes because they require a second surgical act, they provide infections if there is any type of exposure; have a firm consistency, which makes it difficult to adapt to the bone defect and thus impairs blood supply and can cause dehiscence and tissue necrosis [7-9].

Also, guided bone regeneration (GBR) favors the formation of new bone tissue and prevents the gingival tissue from invaginating into the space between the bone and the implant [5,6]. Covani et al [11], in a prospective 10-year study comparing patients who received the GBR technique with patients who did not receive indicated the possibility of gingival retraction in the group that did not receive the technique when compared to the group that received [6].

Besides, the filling biomaterials can be fibrin-rich plasma (FRP), hydroxyapatite, lyophilized and milled demineralized bone marrow, and autogenous bone, which is considered the gold standard, among others. In conjunction with the fillers, it is often necessary to use features to isolate the implant by using biological membranes, which are epithelial barriers that guide tissue regeneration, and function as a mechanical barrier separating the periodontal tissues from the bone surface or implant, thus promoting a new bone formation, containment of the filling material and stability of the graft [8,10].

Therefore, the present study aimed to carry out a systematic review of the main approaches to the use of biomaterials, surgical methods, and bone regeneration for dental implants.

Methods

Study Design and Data Sources

This was followed by a systematic literature review model, according to the PRISMA rules. The literary search process was carried out from January to March 2023 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, using scientific articles from 1991 to 2022, using the descriptors (MeSH Terms): *Biomaterials. Bone bioengineering. Bone regeneration. Surgical techniques. Dental implants,* and using the Booleans "and" between the descriptors (MeSH Terms) and "or" between the historical findings.

Study Quality and Risk of Bias

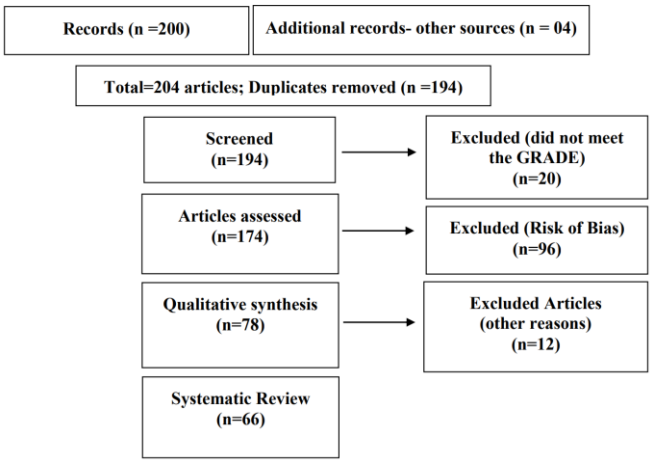
The quality of the studies was based on the GRADE instrument, with randomized controlled clinical studies, prospective controlled clinical studies, and studies of systematic review and meta-analysis listed as the studies with the greatest scientific evidence. The risk of bias was analyzed according to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

Results and Development

Summary

A total of 204 articles were found. Initially, 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 the theme of this article, resulting in 174 articles. A total of 78 articles were evaluated and 66 were included and developed in this systematic review study (**Figure 1**). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 96 studies with a high risk of bias and 20 studies that did not meet GRADE.

Figure 1. Selection of studies.



Source: Own authorship.

Major Clinical Findings

For a successful 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 host bone layer that is healthy, compatible, and allows primary stability is required [12].

Dental implants are being used more and more due to high success rates. However, a large number of patients do not have enough minimum bone conditions for the installation of implants, therefore, previous reconstructive bone surgeries are necessary. The dental surgeon must master the knowledge of the healing process of the post-extraction sockets, to provide correct planning of the cases [13].

In this sense, after a tooth 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 epithelialization of soft tissues. During this process, the alveolar ridge undergoes significant changes, both in height and thickness, which influence the possibility of installing implants [1,2]. Thus, the optimized processes of implant dentistry and biomaterials allow the installation of implants in areas of low bone thickness, width, and height, with simpler surgeries and greater success rates and patient comfort [1].

The lack of bone in the alveolar ridges has been a major problem in functional aesthetic recovery in patients who have suffered dentoalveolar trauma, traumatic tooth extractions, congenital tooth absence, and maxillary and mandibular pathologies. For the filling of large bone defects, the development of bone regeneration improves epithelial barriers to bone grafting, favoring greater predictability in alveolar and peri-implant reconstructions and presenting a good prognosis. In this sense, filling biomaterials can be fibrin-rich plasma (PRF), Bio-Oss®, hydroxyapatite, freeze-dried and ground demineralized bone marrow, autogenous bone, which is considered the gold standard, among others [12].

Thus, fibrin-rich plasma (FRP) as an autologous biomaterial for use in oral and maxillofacial surgery presents most of the leukocytes, platelets, and growth factors, forming a fibrin matrix with three-dimensional architecture [13]. The Bio-Oss® (Geistlich) biomaterial, as it is biodegradable, biocompatible, non-toxic, and has low immunogenicity and biostimulation, 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 to be performed with the greatest possible efficiency [14].

Based on this, two important studies reported results on the combined use of Bio-Oss® and PRF. Thus, the first study clinically and histologically investigated the potential of PRF as a grafting material in pre-implant reconstructive surgery for severe maxillary atrophy after sinus lift procedures at 106-120-180 days, to determine whether the use of PRF is capable of accelerating 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 the reconstructive material. As a result, the use of PRF optimized bone formation [14].

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 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 evaluated. The mean rate of osseointegration was 43.5 ± 12.4% and the rate of new bone formation was 41.8 ± 5.9% in PRF/Bio-Oss® composite sites. In Tisseel® / Bio-Oss® composite sites they 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 PRF is used as an adjunct to BioOss® particles for bone augmentation in the maxillary sinus, bone formation at the graft sites is significantly greater than when Tisseel® is used [15].

In this scenario, the lack of bone in the alveolar ridges has been a major problem in functional aesthetic recovery in patients who have suffered dentoalveolar trauma, traumatic dental extractions, congenital dental

absence, maxillary and mandible pathologies, as well as infections due to the emotional and the possibility of deformity and also the economic impact they cause in the National Health System (NHS) [16-18]. Bone loss can also occur due to periodontal disease, traumatic surgeries, or even physiological reasons due to lack of adequate or inadequate prosthetic load. The trauma in the face region can reach both the soft tissues (skin, muscles, nerves) and hard tissues (bones, teeth), so these lesions can affect the quality of life as well as the health of the victim [19].

The trauma maxillofacial injury can be considered one of the most devastating aggressions found in traumatology and oncology due to the emotional consequences and the possibility of deformity and also the economic impact they cause in the National Health System (NHS) [20-23]. The face, more than any other region of the body, is affected by aesthetic changes, since it is always visible, and damages are perceived immediately [24]. For this reason the trauma of the face deserves to be highlighted in the treatment of polytrauma due to its high incidence and severity.

Bone Tissue Engineering

The microscopic bone structure consists of osteoprogenitor cells, support cells (osteoblasts and osteocytes), remodeling cells - osteoclasts - and a non-mineralized extracellular matrix called the osteoid, composed of type I collagen and non-collagen proteins such as osteonectin, osteocalcin, bone morphonetic protein (BMP), glycosaminoglycans and bone sialoproteins [24,25]. The osteoprogenitor cells are small spindle cells found on all non-resorbable bone surfaces, derived from primitive mesenchymal cells and form a population and precursor cells that can differentiate into more specialized cells such as osteoblasts and osteocytes [20].

Osteoblasts are responsible for the production of bone matrix, rich in collagen (mainly type I) and essential for subsequent mineralization, by adherence of calcium hydroxyapatite crystals, magnesium, potassium, sodium and carbonate ions in collagen fibrils [20]. Osteoblasts are also rich in alkaline phosphatase, which has a high value in periods of bone formation. The process of formation of new bone mediated by osteoblasts is called osteogenesis [26-29]. It is known that osteoblasts bind directly to collagen through integrin-RDG (-Arg-Gly-Asp-) sites of interaction.

The osteoinduction process is influenced by several factors, requiring the presence of inducers, which include β-glycerolphosphate, ascorbic acid and dexamethasone. In the presence of these substances mesenchymal cells acquire the morphology and components of osteoblast membranes and begin to express alkaline phosphatase, to deposit extracellular matrix rich in calcium and certain proteins, such as osteopontin and osteocalcin [30].

Organic phosphates, such as β-glycerolphosphate, promote osteogeny by their function in mineralization and modulation of osteoblast activity [30]. Thus, free phosphates can induce mRNA and protein expression, exemplified by the osteopontin protein. If organic phosphate, for example β-glycerolphosphate is present, the formation of a mineral content occurs, hydroxyapatite that is formed between the collagen fibers [31]. Other compounds such as phosphoric ascorbic acid are also used in osteogenic induction, in the involvement of increased alkaline phosphatase activity and in the promotion of the production of osteocalcin and osteopontin [32-34].

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 . BMP-4 is involved in the early stages of osteogenesis; in addition, it has been demonstrated that the differentiation of human mesenchymal stem cells into the osteogenic lineage requires the presence of BMP-4 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].

There are three fundamental parameters in bone tissue engineering that will determine the ability of osteoinduction are the presence of soluble osteoinductive signals, the viability of the undifferentiated mesenchymal stem cells to respond, the ability to differentiate into bone-forming cells and the production of extracellular matrix adequate [35-40].

Tissue engineering encompasses numerous advantages that meet the needs of the injured tissue or organ for the regeneration process [1,2,41]. For this, it is necessary the understanding of chemical, physical and biological processes both biological material and the biological niche of the host [21]. The cross-referencing of compatible information between the microenvironments allows cellular recognition and signaling cascades for neovascularizations. Another advantage is the minimally invasive surgical intervention, that is, it allows the use of surgical techniques that are faster and cause less risk to the patient [42-44].

Thus, tissue engineering is a tool that makes possible through a suitable biological niche the construction and regeneration of any tissues and organs. For this, xenografts, autografts and allografts are used, with and without the use of cells [45]. According to the Conference of the National Institute for the Development of Health Consensus in 1982,

biomaterials are beneficial organic compounds, or combinations thereof, that can be used for a period of time, wholly or partially as part of a system that treats, replace any tissue, organ or function of the human body [46-48]. The great challenge is to understand that the science of biomaterials is multidisciplinary and its application needs adjustments of its processing, sterilization and structural modifications to favor the interaction with the tissue of interest [49,50].

Also, bioengineering and cell therapy act jointly for Regenerative Medicine, favoring and improving biological conditions to accelerate repair and tissue regeneration and thus maintaining tissue homeostasis [51]. This condition is maintained because the required cellular elements, cell proliferation and differentiation factors, and supramolecular structures are provided which guarantee the functional stereochemical organization of the generated tissues and their systemic integration [52-54].

Mechanism Of Action - Bone Regeneration

Normal bone formation and tissue reestablishment involve coordinated interaction between bone-forming cells and biological signals. The main force in this process are the osteoblasts and their precursors [34]. Osteoblasts can produce new bone along with biomaterials, and can initiate the release of biological signals that guide the formation and remodeling of bone [1].

These biological signals attract bone-forming cells to the receptor site. Growth factors and other proteins are some biological signs that may be involved in new bone formation and tissue remodeling. Moreover, through chemotaxis, there is migration of bone-forming cells to the application area, as stimulation of cell migration occurs in response to chemical stimuli [29].

Monocytes, macrophages and endothelial cells contribute to bone remodeling, either by contact with osteogenic cells or by the release of soluble factors such as cytokines and GF [36]. In the skeletal system, TNF-α stimulates bone and cartilage reabsorption and inhibits the synthesis of collagen and proteoglycans. 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, are also potent anti-apoptotic agents of 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 cytokine IL-6 [37].

Biomaterials

Fibrin-rich plasma (FRP) as an autologous biomaterial was developed in France by Choukroun et al. (2006) [39] for specific use in oral and maxillofacial surgery. This biomaterial presents the majority of leukocytes, platelets and growth factors, forming a fibrin matrix, with three-dimensional architecture. It is the second generation of platelet concentrate with high potential for repair of lesions.

In addition, obtaining FRP follows an easy and simple protocol. A blood sample is obtained without anticoagulant in 10.0 mL tubes that are immediately centrifuged at 3000 rpm (approximately 400.0 g) for 10.0 minutes [55]. After initiation of centrifugation in the absence of anticoagulant, the activation of most of the collected blood platelets begins, from the contact with the walls of the tube and the release of the coagulation cascades. As the end product of this process we have fibrinogen, which is a soluble protein, transformed into fibrin insoluble by thrombin. The fibrin gel constitutes the first scar matrix of the injured sites7. The fibrinogen is concentrated in the upper part of the tube, before the circulating thrombin converts it into fibrin. A fibrin clot is then obtained in the middle of the tube, between the red blood cells at the bottom and acellular plasma at the top [56-59].

Besides, FRP has the characteristic of polymerizing naturally and slowly during centrifugation. The fibrin network thus formed presents, in particular, a homogeneous threedimensional organization, more coherent than natural fibrin clots [60]. In this context, with the progressive polymerization, the incorporation of circulating cytokines increases in the fibrin network, implying a longer life for these cytokines, because they will be released and used only when remodeling the initial cicatricial matrix, which is long term. Cytokines are thus kept available in situ for a convenient period when the cells begin scar remodeling of the matrix [61,62].

Furthermore, FRP is based on the protection of proteolysis growth factors that can maintain its activity for a longer period and stimulate bone regeneration more efficiently. The most critical phase of the sinus membrane elevation procedure after osteotomy of the lateral wall of the maxillary sinus is its detachment [63]. In this phase Schneider membrane ruptures can occur, around 15.0 % of the cases, that depending on the size of the perforation, can make the grafting unfeasible, mainly due to the containment character of the grafting 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 presence of septa [64].

If sinus membrane perforations are present, this should be quantified3, since small perforations do not

require treatment, since the membrane folds themselves obliterate the perforation. In the case of ruptures greater than 5.0 mm, the use of collagen membranes is indicated. Another study8 indicates the use of fibrin membranes obtained from the FRP for the sealing of the perforations. In the presence of perforations greater than 10.0 mm, surgery should be aborted and reentry performed after 60 to 90 days [65].

The development of optimized implant surfaces is a reason for great research with the aim of accelerating the osseointegration process, leading to a reduction in the waiting period before loading, as well as making the immediate loading of the implant safer [66]. Moreover, Lynch et al. (1991) [46] documented for the first time that the combination of biomaterial and FRP significantly improved bone regeneration in the peri-implant zone. Placement of the implant with the simultaneous use of PRP creates a good relationship between hard tissue and soft tissue beyond the advantage of the psychological relationship to the patient.

Also, migration, adhesion and cell proliferation on the surface of the implants are required to initiate the tissue regeneration process, whereas modifications in the surface of the implants incorporating biological mediators of growth and differentiation may potentiate tissue regeneration at implant placement. The balance between fibrin formation and platelet activation are responsible for the PRP process and performance [1,2].

Thus, tissue engineering is a tool that makes possible through the creation of a suitable biological niche the construction and regeneration of any tissues and organs [1]. For this, xenografts, autografts and allografts are used, with and without the use of cells. Thus, the Bio Oss® (Geistlich) biomaterial, because they are biodegradable, biocompatible, nontoxic and present low immunogenicity and biostimulators can act in the regeneration of bone tissue, since they establish with the adenomatous mesenchymal stem cells the appropriate biological niche (favorable microenvironment) for the bone growth [4-6].

Some data show that Guided Tissue Regeneration (GTR) its better for treatment of periodontal intra-bony defects and furcation defects [55-57]. In general, RTG is more efficient than DRA in reducing:> horizontal open furcation depths,> horizontal and vertical insertion levels, and> alveolus depths for class II furcation defects in the mandible or maxilla . With the use of Bio-Oss®, it is possible to achieve orthodontic movement in patients after treatment with GTR [58,59]. Moreover, the resorbable membranes proved to be superior to the non-resorbable membranes with regard to generation of vertical bone filling [60].

Conclusion

For a successful 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. The dental surgeon must master the knowledge of the healing process of the postextraction sockets, to provide correct planning of the cases. The optimized processes of implant dentistry and biomaterials allow the installation of implants in areas of low bone thickness, width, and height, with simpler surgeries and greater success rates and patient comfort.

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Ethical Approval

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Informed consent

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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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