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Major aspects of mesenchymal stem cell signaling and differentiation into osteoblasts in the optimization of bone formation for dental implant: a systematic review

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Abstract

Introduction: In recent decades, the number of dental implant procedures has shown significant growth worldwide, reaching about one million dental implants per year. In Brazil, in recent decades, there has been a very rapid evolution in implant dentistry with high success rates. Several materials can be used as a bone graft, each with different properties, for example, regarding neovascularization. Guided bone regeneration favors the formation of new bone tissue. When grafting procedures are required, the focus is often on the type of biomaterial to be used and the success and predictability of the results. **Objective:** It was to carry out a concise systematic review of bone regeneration processes using biomaterials and the main molecular and cellular constituents for implant dentistry. **Methods:** The survey was carried out from January to February 2023 in the Scopus, PubMed, Science Direct, and Scielo databases, using older scientific articles with a gold standard reference up to 2022. The quality of the studies was based on the GRADE instrument and the risk of bias by the Cochrane instrument. **Results and Conclusion:** It was founded on 128 studies that underwent eligibility analysis. The final sample had 34 eligible studies that were described in the systematic review. Most studies showed homogeneity in their results, with X^2=89.8.8% <50%. Due to bone regeneration and biological barriers in graft surgeries, there has been a technological growth of these materials as they point to potential tools for treating bone loss. The greater potential of guided bone regeneration was associated with the graft material due to the higher grade of vital bone and the lower percentage of residual graft particles. All studied bone substitute materials resulted in efficient bone formation for dental implants and alveolar ridge preservation procedures.

Keywords: Bone regeneration. Biomaterials. Biological membranes. Dental implants.

Introduction

In recent decades, the number of dental implant procedures has shown significant growth worldwide, reaching about one million dental implants per year [1,2]. In Brazil, in recent decades, there has been a very rapid evolution in implant dentistry with high success rates [3]. The development of biomaterials for use in clinical dentistry in recent years has represented a powerful therapeutic instrument in the correction of bone defects [3]. However, despite the proven benefits, its use requires careful clinical and ethical care from the professional, especially in the analysis of the risks and benefits that each biomaterial may present [4].

In this sense, several materials can be used as bone grafts, each one with different properties, for example, regarding neovascularization, materials such as hydroxyapatite and calcium phosphate showed the highest expression rates of vascular growth factors (VEGF) and microvascular density; while polymer grafts showed the lowest rates [5-8]. In the search for a solution for large bone defects, studies based on guided tissue regeneration therapy or guided bone regeneration were initiated. These studies promote the use of filling materials and epithelial barriers that help in the treatment as an adjunct to bone grafting techniques. Thus, they favor greater predictability in alveolar and

peri-implant reconstructions and present a good prognosis [4].

In this regard, the main problem is with non-absorbable membranes, as they require a second surgical procedure, they favor infections if there is any type of exposure, they have a firm consistency, which makes it difficult to adapt to the bone defect and thus impair blood irrigation and may cause dehiscence and tissue necrosis [5-7]. Membranes can be nonabsorbable, such as expanded polytetrafluoroethylene (e-PTF), non-expanded polytetrafluoroethylene (PTF), calcium phosphate, titanium mesh or foil; or absorbable, such as collagen, polylactic acid and polyglactin, fibrin and elastin monomers and Vicryl membrane [6].

Also, guided bone regeneration (GBR) favors the formation of new bone tissue and prevents the gingival tissue from invading the space between the bone and the implant [5,6]. Covaniet al [9], in a prospective study of 10 years, compared patients who received the GBR technique with patients who did not, indicating the possibility of gingival recession in the group that did not receive the technique when compared to the group that received it [4].

In this context, the filling materials can be hydroxyapatite, freeze-dried and ground demineralized medullary bone, and autogenous bone, which is considered the gold standard, among others. Together with the filling materials, it is often necessary to use resources to isolate the implant using biological membranes, which are epithelial barriers that guide tissue regeneration, work as a mechanical barrier separating the periodontal tissues from the bone or implant surface, thus promoting bone neoformation, filling material containment and graft stability [6,8].

Moreover, when a dental element 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. It will increase its volume towards the place where the roots existed and this will often make it difficult or impossible to restore the implants in place. 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 necessary, 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 natural graft stabilization capacities, therefore, the characteristics of the biomaterials that we must use, but also the characteristics, must be considered bed and bone defect for treatment [6,7].

As a corollary of this, 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 able to present three important biological properties such as osteogenesis, osteoinduction, and osteoconduction guaranteeing a self-regenerative potential. As a disadvantage of autogenous bone graft, the need for second surgical access in the donor area is highlighted, resulting in longer surgical time, morbidity, and consequent greater resistance. patient's response to the proposed treatment [8].

In this context, 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. But due to the need for processing to eliminate antigenic components, these grafts are exclusively osteoconductive with less potential for bone formation 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) [8-10].

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 minerals without organic elements [11]. After thermal and chemical treatments, the inorganic phase of bovine bone consists mainly of hydroxyapatite (HA) which maintains 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 [11-13].

In addition, platelet concentrates have been proposed as regenerative materials in tissue regeneration procedures. Among the platelet concentrates proposed in the literature, PRP (platelet-rich plasma) and FRP (fibrin-rich plasma) stand out, 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 formed elements are separated according to their density. From there, 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 in chemotaxis, angiogenesis, cell differentiation, and inhibition [7-9].

Therefore, the present study carried out 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 the international model of systematic review and metaanalysis, following the rules of PRISMA (preferred reporting items for systematic reviews and meta-analysis) [27]. Table 1 shows the main variables of the present study that were addressed, according to the designation of the literature search strategy PICOS (Patients; Intervention; Control; Outcomes, and Study Design).

Table 1. Literary search strategy - PICOS.

PATIENTS	Patients with maxillofacial bone loss
INTERVENTIONS	Bone grafts and/or biological membranes
CONTROL	Bone graft only, no growth factors, and mesenchymal stem cells
EXPECTED RESULTS	Satisfactory bone elevation for dental implant and alveolar bone regeneration
TYPES OF STUDIES SEARCHED	Randomized, prospective, retrospective observational clinical studies and case series

Instruments for the Eligibility of Studies

Studies that rigorously presented the results of the search process in Table 1 and that presented scientific quality according to the GRADE classification, and that did not present a risk of significant bias, that is, that could compromise the safety of the results, were chosen. according to the Cochrane instrument.

Quality of Studies, Eligibility Criteria, and Risk of Bias

According to GRADE recommendations [28], the quality of scientific evidence in the studies addressed was classified as high, moderate, low, or very low, according to the risk of evidence bias, sample size, clarity of comparisons, precision, and consistency in the effects of the analyses. High-quality evidence was assigned using four criteria: 1) Randomized or prospective controlled clinical trials; 2) Retrospective clinical trials or case series; 3) Sample size greater than 15 participants; 4) Studies with statistically well-prepared results; 5) Studies published in indexed journals with a significant impact factor; 6) descriptive (identification of studies that show the surgical technique), interpretative (identification of the advantages and disadvantages of biomaterials), theoretical (credibility of methods) and pragmatic (application of the use of each type of biomaterial) validity. Articles that did not report the technique employed were excluded.

Data Sources, Research Strategy, and Study Timing

The search strategies for the present study were based on the keywords (MeSH Terms): Bone regeneration. Biomaterials. Biological membranes. Dental implants (Bone regeneration. Biomaterials. Biological membranes. Dental implants). Search filters designated as clinical studies were used. The search was carried out from January to February 2023 in Scopus, PubMed, OVID, Science Direct, LILACS, and EBSCO databases, using gold-standard reference scientific articles up to 2022. In addition, a combination of keywords with booleans "OR", AND, and the "NOT" operator were used to direct scientific articles of interest. The title and abstracts were screened under all conditions. Table 2 presents an example of the search structure in PubMed. The same search strategy was used in the other databases.

Table 2. Example of the search structure in PubMed, the same search strategy was used in the other databases.

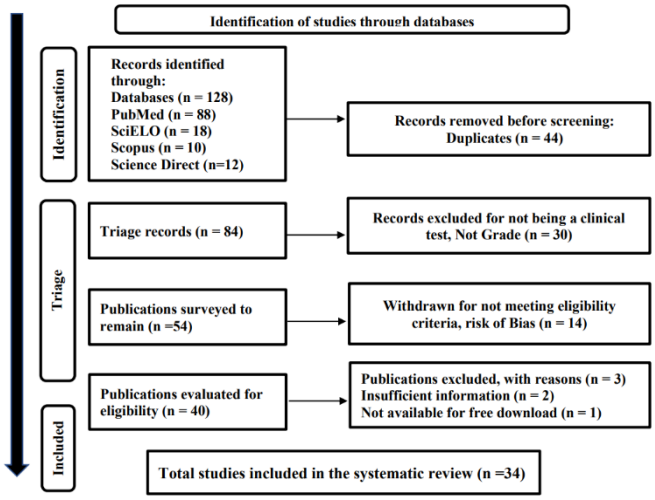
PubMed	*Bone regeneration* ***OR*** *Biomaterials*
	AND
PubMed	*Biological membranes* ***OR*** *Dental implants*
	AND
PubMed	*Prospective Clinical studies* ***OR*** *Retrospective Clinical studies* ***OR*** *Randomized clinical trials* ***OR*** *Clinical case series*
	NOT
PubMed	*Review studies* ***OR*** *Editorials* ***OR*** *Short communications* ***OR*** *Case Report*

Summary of Literary Findings

A total of 128 articles were found. Initially, duplicate articles were 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 54 articles. A total of

34 articles were fully evaluated and included in this study (Figure 1). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 14 studies with a high risk of bias and 30 studies that did not meet GRADE. According to the GRADE instrument, the 34 studies that made up the systematic review showed homogeneity in their results, with X^2=89.8.8% <50%.

Figure 1. Flowchart showing the article selection process.



Main Findings of Clinical Studies

The authors Zampara et al. 2022 clinically evaluated the potential of guided bone regeneration (GBR) of allograft, xenograft, and alloplastic materials in combination with resorbable membranes in extraction sockets. Qualitative and quantitative assessments of this prospective study were performed using histological and histomorphometric analyses. Three experimental groups and one control group for comparison (n=8) received an allograft (lyophilized human cancellous bone, Deutsches Institut für Zell und Gewebeersatz, Berlin, Germany), xenograft (BioOss, Geistlich Pharma AG, Wolhusen, Switzerland), or alloplastic (biphasic calcium sulfate, Bondbone, MIS Implants Technologies Ltd., Charlotte, NC). The negative control group did not receive regenerative material. Tissue samples were then evaluated qualitatively and quantitatively for a percentage of vital new bone, graft particle content, soft tissue, and bone marrow over time. All 3 study groups had adequate bone volume for the successful placement of a dental implant. The xenograft group yielded significantly less vital bone compared to the allograft and alloplastic groups. When comparing the percentage of residual graft particles, there were significantly greater amounts associated with the xenograft group as opposed to the allograft and alloplastic groups. Likewise, a significantly increased amount of soft tissue percentage was observed in the xenograft group relative to all other groups. No significant differences were observed in the percentage of residual graft particles between the allograft and alloplastic groups. There were also no significant differences detected in the percentage of vital bone between the allograft, alloplastic, and control groups. When evaluating the percentage of bone marrow, the only significant difference detected was between the xenograft and alloplastic materials. Overall, no complications (ie, fever, malaise, purulence, or fistula) were observed throughout the clinical trial among all patients. The highest GBR potential was associated with the graft material due to the higher grade of vital bone and the lower percentage of residual graft particles. All studied bone substitute materials resulted in bone apposition for efficient use in alveolar ridge preservation procedures [14].

Also, a randomized clinical study carried out by the authors Galindo-Moreno et al. 2022 compared the effectiveness of two xenografts for maxillary sinus floor augmentation in terms of clinical, radiographic, histological, and molecular results. A total of 10 consecutive patients in need of two-stage bilateral maxillary sinus floor augmentation were included. Each patient received both biomaterials (porcine bone mineral and inorganic bovine bone), which were randomly assigned to bilateral breast augmentation. Autogenous maxillary bone scraped from the sinus access window was mixed with each xenograft in a 20:80 ratio. After a 6-month healing period, bone biopsies were taken with trephine during implant placement in the regenerated area. The resulting anatomical features were similar between the two groups. After six months of graft healing, graft resorption rates were similar between the two biomaterials. Histological, histomorphometric, and immunohistochemical results did not show statistical differences between groups. Therefore, inorganic bovine bone and porcine bone mineral combined with maxillary autogenous cortical bone showed similar biological and radiological characteristics in terms of biomaterial resorption, osteoconduction, and osteogenesis when used for maxillary sinus floor augmentation [15].

Added to this, the authors Meschi et al. 2021, through a multicenter controlled clinical trial, evaluated the impact of platelet-leukocyte-rich fibrin (LPRF) in regenerative endodontic procedures (REPs) of immature permanent teeth in terms of periapical bone repair (PBH) and subsequent development (DR). Healthy patients aged 6-25 years with an inflamed or necrotic immature permanent tooth were included and divided into test (= REP + LPRF) and control (= REP-LPRF) groups. After receiving REP ± LPRF, patients were recalled after 3, 6, 12, 24, and 36 months. At each recall

session, the teeth were evaluated clinically and radiographically (employing a periapical radiograph [PR]). A cone-beam computed tomography (CBCT) scan was performed preoperatively and 2 and 3 years after surgery. PBH and DR were evaluated quantitatively and qualitatively. Twenty-nine teeth with necrotic pulp were included, of which 23 (9 test and 14 control) were analyzed. Three teeth in the test group reacted within the first year after the REP. Except for 2, all analyzed teeth survived up to 3 years after REP and, in case of failure, apexification preserved them. Complete PBH was obtained in 91.3% and 87% of cases based on qualitative and quantitative assessments of PR, respectively, with no significant difference between groups from baseline. Quantitative change in PR in RD at the last recall session from baseline was not significant (all p-values>0.05) in either group. The qualitative assessment of the REP healing type was not uniform. In the test group, 55.6% of the teeth did not show DR or apical closure. Only 50% of the 14 teeth evaluated with CBCT showed complete PBH. Concerning volumetric measurements in RD 3 years after REP for change from baseline in root hard tissue volume, mean root hard tissue thickness, and apical area, the control group performed significantly in favor of the RD than the test group (p= 0.03, 0.003, and 0.05, respectively). For volumetric change 3 years after REP from baseline in root length and maximum root hard tissue thickness, no significant differences (p=0.72 and 0.4, respectively) were found between groups. The correlation between PR and CBCT variables assessing RD was weak (root elongation) to very weak (root thickening). Therefore, REP-LPRF appears to be a viable treatment option to obtain PBH and aid in the DR of necrotic immature permanent teeth [16].

Bone Regenerative Dentistry

The bone's microscopic structure is made up of osteoprogenitor cells, support cells (osteoblasts and osteocytes), remodeling cells – osteoclasts – and a non-mineralized extracellular matrix called osteoid, composed of type I collagen and non-collagen proteins such as osteonectin, osteocalcin, bone morphogenetic protein (BMP), glycosaminoglycans (GAG) and bone sialoproteins [14,15,17]. Osteoprogenitor cells are small spindle-shaped cells found on all non-resorbable bone surfaces, derive from primitive mesenchymal cells, and form a population of precursor cells that can differentiate into more specialized cells such as osteoblasts and osteocytes [18].

The regeneration of composite tissues such as periodontal tissue has also been demonstrated, proving that adipose mesenchymal stem cells associated with platelet-rich plasma can regenerate alveolar bone, cementum, and periodontal ligament eight weeks after implantation [19,20]. Clinically, there is a combined study of bone grafting with fibrin glue, a biodegradable biomaterial, and adipose mesenchymal stem cells for the reconstruction of a large bone defect in the skull of a seven-year-old trauma victim [19].

Also, osteoblasts are derived from undifferentiated mesenchymal stem cells, being 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 ions, and carbonate in collagen fibrils [22]. Osteoblasts are also rich in alkaline phosphatase, which is elevated during periods of bone formation. The process of formation of new bone mediated by osteoblasts is called osteogenesis [21]. It is known that osteoblasts bind directly to collagen through integrin-RDG (Arginine-Glycine-Aspartate) interaction sites.

The osteoinduction process is influenced by several factors and consists of the induction of mesenchymal stem cells from adipose tissue into osteoprogenitor cells [18,23]. Osteogenic differentiation requires 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, deposit extracellular matrix rich in calcium, and certain proteins, such as osteopontin and osteocalcin [23].

Organic phosphates, such as β-glycerolphosphate, provide osteogenesis due to their role in mineralization and modulation of osteoblast activity [18]. Thus, free phosphates can induce mRNA and protein expression, exemplified by the osteopontin protein. If organic phosphate, for example, β-glycerolphosphate, is present, mineral content, hydroxyapatite, is formed between the collagen fibers. Other compounds, such as phosphate ascorbic acid, are also used in osteogenic induction, involving increased alkaline phosphatase activity and promoting the production of osteocalcin and osteopontin [23-25].

Besides, BMP function as growth factors with a specific role in the proliferation and differentiation of mesenchymal stem cells from adipose tissue [26,27]. BMP-4 is involved in the initial stages of osteogenesis, in addition, it was 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 [27]. Three fundamental parameters in bone tissue engineering that

will determine the osteoinduction capacity are the presence of soluble osteoinductive signals, the viability of undifferentiated mesenchymal stem cells in responding, the ability to differentiate into bone-forming cells, and the production of extracellular matrix adequate [27].

Moreover, tissue engineering contemplates numerous advantages that meet the needs of the injured tissue or organ for the regeneration process [26,28]. For this, it is necessary to understand the chemical, physical and biological processes, both biological material and the biological niche of the host [29]. Crossing compatible information between microenvironments enables cell recognition and signaling cascades for neovascularizations [30]. Another advantage is the minimally invasive surgical intervention, that is, it allows the use of faster surgical techniques that cause less risk to the patient [31].

Thus, tissue engineering is a tool that enables the construction and regeneration of any tissues and organs through an adequate biological niche [24,32]. For this, xenografts, autografts, and allografts are used, with and without the use of cells [29,30]. According to the Conference of the National Institute for Consensus Development in Health in 1982, biomaterials are beneficial organic compounds or a combination thereof, that can be used over some time, completely or partially as part of a system that treats, enhances or replace any tissue, organ or function of the human body [24,32,33]. The great challenge is to understand that the science of biomaterials is multidisciplinary and their application requires adjustments in their processing, sterilization, and structural modifications to favor interaction with the tissue of interest.

Bioengineering and cell therapy work together for Regenerative Medicine, favoring and improving biological conditions to accelerate tissue repair and regeneration and, thus, naturally maintaining tissue homeostasis [34]. This condition is maintained because the required cellular elements are provided, the cell proliferation and differentiation factors, and supramolecular structures that guarantee the functional stereochemical organization of the generated tissues and their systemic integration [24,33].

Bone Remodeling

Normal bone formation and tissue healing involve coordinated interaction between bone-forming cells and biological signals [19]. The main force in this process are osteoblasts and mesenchymal stem cells from adipose tissue [17]. Osteoblasts can produce new bone, along with biomaterials, and can initiate the release of biological signals that guide the bone formation and remodeling [26].

These biological signals attract mesenchymal cells and other bone-forming cells to the receptor site, stimulating the differentiation of mesenchymal cells into osteoblasts [27]. Growth factors and other proteins are some of the biological signals that may be involved in new bone formation and tissue remodeling.

In addition, through chemotaxis, there is a migration of bone-forming cells to the area of application, as there is stimulation of cell migration in response to chemical stimuli. Mesenchymal stem cells, and osteoblasts from bleeding bone, muscle, and periosteum infiltrate the biomaterial implanted in the grafted area. BMP binds to specific receptors located on the surface of mesenchymal stem cells and promotes their differentiation into bone-forming cells [25,26].

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 [17]. In the skeletal system, tumor necrosis factor (TNF-α) stimulates bone and cartilage resorption and inhibits the synthesis of collagen and proteoglycans. Interleukin 1 (IL-1) induces the expression of a wide variety of cytokines. IL-6 are molecules that are known to stimulate the differentiation of mesenchymal progenitor cells to the osteoblastic lineage, they are also potent anti-apoptotic agents of osteoblasts. In bone, the main sources of IL-6 are osteoblasts and non-osteoclasts. Prostaglandin E2 (PGE2) is also directly related to the expression of the cytokine IL-6 [28].

Conclusion

It was concluded that due to bone regeneration and biological barriers in graft surgeries, there was a technological growth of these materials as they point to potential tools for the treatment of bone loss. The greater potential of guided bone regeneration was associated with the graft material due to the higher grade of vital bone and the lower percentage of residual graft particles. All studied bone substitute materials resulted in efficient bone formation for dental implants and alveolar ridge preservation procedures.

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Ethical 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.

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