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# Enhancing Bone Regeneration: A Systematic Review of Osteoinductive Agents Combined with Alloplastic Biomaterials

## Mejora de la Regeneración Ósea: Una Revisión Sistemática de Agentes Osteoinductores Combinados con Biomateriales Aloplásticos

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**SUMMARY:** Bone grafts and biomaterials are commonly used to enhance bone volume. To achieve this objective, they are often combined with additional systems that confer osteogenic, osteoinductive, and osteoconductive properties. The aim of this study was to analyze the characteristics of osteoinductive agents used in combination with alloplastic biomaterials, as well as the survival rates of the implants placed. A systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A comprehensive literature search was performed using MeSH terms and Boolean operators (AND/OR) in English, Portuguese, and Spanish, covering publications up to December 2024. The databases consulted included Medline, Embase, Scopus, and Web of Science. Additionally, gray literature was explored through Google Scholar and Open Access Theses and Dissertations (OATD). Eight studies met the inclusion criteria. Among the grafted sites, maxillary sinus augmentation was the most frequently reported, followed by post-extraction sockets in premolar and molar regions, and the maxillary incisor area. The average healing period prior to implant placement ranged from 4 to 6 months. A total of 428 implants were placed, with follow-up periods ranging from 9 months to 10 years. In the longest follow-up study, a survival rate of 94.8 % was reported for 160 implants. In conclusion, the combination of synthetic biomaterials with osteoinductive agents appears essential to promote new bone formation both on the internal surfaces of the biomaterial and in the surrounding tissue.

**KEY WORDS: Alloplastic grafts; Bone regeneration; Osteoinductors; Dental implants.**

## INTRODUCTION

Tooth extraction triggers an inflammatory response that leads to alveolar bone resorption and a reduction in mucosal volume due to physiological atrophy. On average, this process results in a loss of 3.87 mm in alveolar ridge width and 1.67 mm in height within the first three months (Canullo *et al*., 2022). Other studies have reported that bone resorption within the first six months can range from 7.20 % (±1.4 %) to 46.9 % (±23.3 %) (Riachi *et al*., 2012; Mordenfeld *et al*., 2014; Gultekin *et al*., 2016; Jing & Su, 2024). The use of certain biomaterials has been shown to help reduce this loss in volume. Biomaterial application after extraction has demonstrated significantly better outcomes for alveolar ridge preservation compared to spontaneous healing through physiological clot formation alone (Avila-Ortiz *et al*., 2019). These findings support the routine use of biomaterials in post-extraction reconstructive procedures.

Autologous bone remains the only graft material that possesses all three essential properties for bone regeneration: osteogenesis, osteoinduction, and osteoconduction (Zhao *et al*., 2021). Although alternative biomaterials have been explored to replicate these characteristics, their results have been inconsistent, prompting the integration of osteoinductive agents to enhance their performance. When

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autogenous bone is used, graft survival rates reach 98.7 % ± 3.7, and implant survival rates after a 92-month follow-up are reported at 93.8 % (Moraschini *et al*., 2024). In contrast, outcomes with synthetic or alternative biomaterials remain variable and, in some cases, minimal (Fernandez de Grado *et al*., 2018). However, given the limited availability of autogenous bone and the invasive procedures required for its harvesting, it is essential to consider other options—such as allogenic, xenogenic, and alloplastic materials—that may offer comparable results with reduced morbidity (Papageorgiou *et al*., 2016).

Alloplastic materials offer several advantages over biologically derived grafts, including high biocompatibility, consistent osteoconductive properties, and the ability to be produced on a large scale. Their therapeutic potential can be significantly enhanced by incorporating growth factors, pharmacological agents, or osteoinductive compounds that support the adhesion, proliferation, and differentiation of bone forming cells, thereby improving the overall efficacy of the reconstructive technique (Al-Moraissi *et al*., 2020; Ferraz, 2023).

Naturally derived materials have also demonstrated favorable outcomes in minor reconstructive procedures (McKenna *et al*., 2022); however, concerns remain regarding their organic components. Despite the existence of standardized protocols for harvesting and processing these materials for clinical use, a small percentage of cases may still contain residual collagen proteins or multinucleated cells encapsulated within inorganic bovine bone particles. These remnants carry a potential risk for disease transmission and other biological complications (Bannister *et al*., 2008).

The aim of this study was to analyze the characteristics of osteoinductors used with alloplastic biomaterials and the survival of the implants placed.

## MATERIAL AND METHOD

A systematic review was conducted in accordance with the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (Page *et al*., 2021), to address the following research question: Which osteoinductive agents are combined with alloplastic biomaterials to promote bone regeneration in patients requiring dental implant placement? P: Subjects over 18 years old, totally or partially edentulous; I: Bone regeneration followed by implant placement; C: Comparison of different osteoinductors combined with synthetic grafts; O: Evaluation of clinical and/or radiographic parameters.

Clinical trials and quasi-experimental studies published from 1996 onward were included, as this marks the year the U.S. Food and Drug Administration (FDA) began approving the clinical use of alloplastic materials in reconstructive procedures. Eligible studies involved human subjects who underwent bone regeneration using synthetic biomaterials in combination with osteoinductive agents, defined as autologous bone, pharmacological agents, receptor agonists, autologous platelet concentrates, recombinant growth factors, mesenchymal stem cells, or bone morphogenetic proteins. To ensure methodological rigor, only studies with a sample size of 10 or more participants presenting with partial or complete edentulism—and requiring maxillary sinus augmentation or bone grafting for subsequent dental implant placement in the maxilla and/or mandible—were selected. Diagnostic assessments and outcome evaluations were conducted using cone-beam computed tomography (CBCT) and/or histological analysis. The following types of publications were excluded: case reports, literature reviews, animal studies, and human studies involving patients with a history of prior surgical interventions in the area of interest.

A systematic literature search was conducted using Medical Subject Headings (MeSH) and Boolean operators (AND/OR) in English, Portuguese, and Spanish,covering publications up to March 2025. The search was performed across four major databases: Medline, Embase, Scopus, and Web of Science. In addition, gray literature was explored through Google Scholar and the Open Access Theses and Dissertations (OATD) repository. The review protocol was prospectively registered in the PROSPERO database (CRD420251011428).

Data selection was conducted independently by two calibrated investigators (V.R. and G.O.), achieving a Kappa coefficient of 0.74 over a two week calibration period. After applying the search terms, duplicates were removed using Mendeley software (version 2.90.0; Reference Management, Elsevier, London, England). The investigators independently screened titles and abstracts according to predefined inclusion and exclusion criteria. In cases of disagreement, consensus was reached through discussion or consultation with a third reviewer (S.O.). Full texts of articles that met the inclusion criteria were subsequently reviewed by the same investigators. Throughout the screening process, reviewers remained blinded to the authorship and journal of the studies to minimize bias.

Two calibrated reviewers independently extracted data and evaluated the methodological quality of the included studies using a predefined, standardized data collection form. A pilot test was conducted to ensure

consistency between reviewers. Reviewers were not blinded to the authors or journals of the studies. The risk of bias for non-randomized studies was independently assessed using the ROBINS-I tool (Sterne *et al*., 2019). The risk of bias was evaluated across seven domains: (1) confounding, (2) selection of study participants, (3) measurement of exposure, (4) deviations from intended interventions, (5) missing data, (6) measurement of outcomes, and (7) reporting of results. Each domain was rated as having low, moderate, serious (critical) risk of bias, or no information.

## RESULTS

The systematic search across Medline, Embase, Scopus, and Web of Science databases identified a total of 3,671 articles. After removing 983 duplicates, 2,688 records were screened by title and abstract, resulting in 16 articles selected for full-text review (Fig. 1). The gray literature search retrieved 1,172 documents, of which 1,141 were excluded after title and abstract screening. Among the 31 articles assessed in full text, 29 were excluded for not meeting the inclusion criteria.

A total of 18 studies were initially selected for full-text analysis. However, based on the predefined inclusion and exclusion criteria, 9 studies were excluded for the following reasons: four studies (Steigmann & Garg, 2005; Kher *et al*., 2014; Saito *et al*., 2021; Machado *et al*., 2023) did not use osteoinductive agents in combination with alloplastic grafts; four studies (Pereira *et al*., 2015; dos Santos-Pereira *et al*., 2016; Arumugam *et al*., 2021; Tzur *et al*., 2021) did not perform implant placement following the use of alloplastic grafts combined with osteoinductors, preventing assessment of functional success; one study did not report the use of cone-beam computed tomography (CBCT) for diagnostic evaluation (Wach & Kozakiewicz, 2021); and one study included fewer than 10 subjects (Alves *et al*., 2024). Consequently, eight studies were included for descriptive analysis and risk of bias assessment (Lee *et al*., 2008; Manso & Wassal, 2010; Trautvetter *et al*., 2011; Santana *et al*., 2015; Baena *et al*., 2017; Maître *et al*., 2020; Han *et al*., 2022; Mekcha *et al*., 2023).

Among the eight selected studies (Table I), five were clinical trials (Lee *et al*., 2008; Manso & Wassal, 2010; Santana *et al*., 2015; Baena *et al*., 2017; Han *et al*., 2022), while the remaining three were quasi-experimental studies (Trautvetter *et al*., 2011; Maître *et al*., 2020; Mekcha *et al*., 2023). Together, these studies encompassed a total of 200 participants, with ages ranging from 19 to 73 years. Regarding sex distribution, 91 participants were male and 86 were female, although one study (Santana *et al*., 2015) did not report the sex of the participants.

Regarding the graft site, maxillary sinus elevation was the most commonly performed procedure, followed by post-extraction sockets of premolars and molars, and the incisor region of the maxilla. In the pre-surgical stage for sinus elevation, patients exhibited a residual vertical bone height ranging from 4 to 6 mm (Lee *et al*., 2008; Manso & Wassal, 2010; Trautvetter *et al*., 2011; Han *et al*., 2022). For posterior tooth sockets, a buccal defect

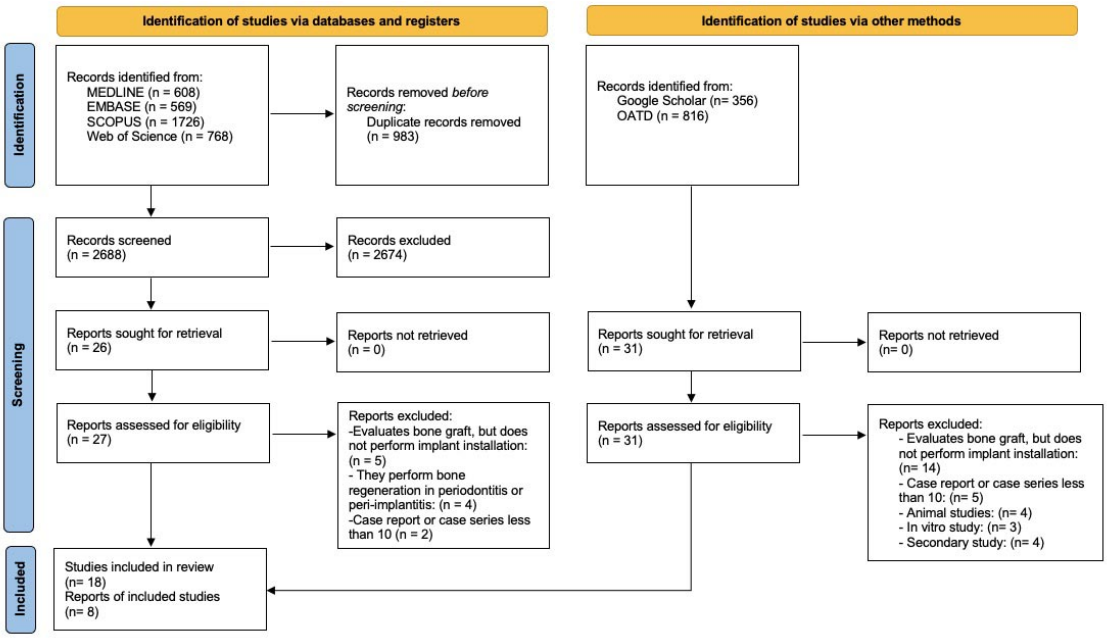


Fig. 1. Flow chart of the systematic review.

Table I. Description of the objectives and designs of the 8 selected studies.

| Author | Objetive | Country | Design |
|---|---|---|---|
| Lee *et al*., 2008 | Evaluate the histological and clinical outcomes of macroporous biphasic calcium phosphate alone and combined with other grafts for maxillary sinus floor augmentation. | South Korea | Clinical Trial |
| Manso & Wassal, 2010 | Evaluate clinical and imaging parameters, and long-term predictability of osseointegrated implants inserted with sinus lift in atrophic maxillae using a synthetic bioactive resorbable graft and an autogenous bone graft. | Brazil | Clinical Trial |
| Trautvetter *et al*., 2011 | Evaluate long-term bone regeneration quality of tissue-engineered bone using periosteal cells in fibrin and resorbable polymer structures in atrophic maxillae. | Germany | Quasi-experimental |
| Santana *et al*., 2015 | Evaluate the efficacy of recombinant human platelet-derived growth factor BB (incorporated into _-TCP/HA) compared with autologous bone.en comparación con hueso autólogo. | Brazil | Clinical Trial |
| Baena *et al*., 2017 | Evaluate the ability of micrografts derived from autologous periosteum combined with PLGA and hydroxyapatite to induce bone augmentation in sinus lift procedures via clinical investigation, radiographs, and histological analysis. | Italy | Clinical Trial |
| Maitre *et al*., 2020 | Analyze short-term clinical characteristics of horizontal reconstruction with BMP-2 and porous hydroxyapatite of the alveolar ridge. | Chile | Quasi-experimental |
| Han *et al*., 2022 | Evaluate clinical and radiographic outcomes after implant installation and functional loading in patients undergoing maxillary sinus lift using rhBMP-2/HA. | South Korea | Clinical Trial |
| Mekcha *et al*., 2023 | Describe a workflow for customized 3D-printed HA block grafts combined with osteoinductors to determine the clinical efficacy of alveolar ridge augmentation. | Thailand | Quasi-experimental |

exceeding 4 mm was observed preoperatively (Santana *et al*., 2015). In the anterior maxillary region, residual bone width was 4 mm or less, with height measuring 2 mm or less (Maître *et al*., 2020). The study by Mekcha *et al*. (2023), did not report specific measurements in millimeters, noting only that horizontal bone support was less than 50 % of the implant diameter.

The graft materials used varied across studies, but the most prevalent components were hydroxyapatite, followed by calcium phosphate in its biphasic and b-tricalcium phosphate (β-TCP) forms. In the study by Santana *et al*. (2015), a mixture of hydroxyapatite and b-tricalcium phosphate was used, while Trautvetter *et al*. (2011), did not specify the polymer used. Regarding the osteoinductor used, two studies employed particulate autogenous bone (Lee *et al*., 2008; Manso & Wassal, 2010); one study used periosteum extracted from the outer layer of the flap (Baena *et al*., 2017), and another used osteogenic cells obtained from the lateral region of the mandible at the level of the third molar (Trautvetter *et al*., 2011). The studies by Santana *et al*. (2015), and Mekcha *et al*. (2023), used platelet-derived growth factors, while the studies by Maitre *et al*. (2020), and Han *et al*. (2022), used bone morphogenetic protein (BMP) (Table II).

Among the 8 studies analyzed, the average waiting period for bone consolidation and subsequent implant placement ranged from 4 to 6 months. A total of 429 implants were placed, with a minimum follow-up of 9 months and a maximum of 10 years. The longest follow-up reported a survival rate of 94.8 % out of 160 implants placed. When evaluating implant survival in the selected studies, survival rates ranged from 83.3 % to 100 %, with follow-up periods of 9 months, 12 months, 5 years, and 10 years (Table III).

Regarding the risk of bias (Fig. 2), all eight studies exhibited a moderate risk of confounding bias due to the absence of sample randomization. In the domains of participant selection and selection of reported outcomes, all studies demonstrated a low risk of bias. Three studies reported postoperative complications, which led to treatment protocol modifications and participant dropout, resulting in a moderate risk of bias in the domains of deviations from intended interventions and missing data. A serious risk of bias was identified in three studies within the outcome measurement domain, attributed to the lack of control groups and absence of investigator blinding. Notably, none of the studies were rated as having a low risk of bias in outcome measurement. Overall, five studies were classified as having a moderate risk of bias, while three presented a serious risk.

The included studies encompassed a variety of surgical procedures. Four studies performed vertical sinus lift procedures in edentulous areas (Lee *et al*., 2008; Manso & Wassal, 2010; Trautvetter *et al*., 2011; Baena *et al*., 2017). One study (Santana *et al*., 2015) involved tooth extractions in the premolar and molar regions followed by alveolar ridge preservation. Another study (Maître *et al*., 2020) applied biomaterials combined with osteoinductive agents in a single anterior edentulous site, while Mekcha *et al*. (2023), focused on multiple edentulous sites spanning the anterior, premolar, and molar regions. Variations were also noted in the residual bone criteria among participants: sinus lift studies reported only vertical bone measurements, whereas studies involving alveolar or anterior sites assessed residual bone width or both height and width. Alloplastic biomaterials and osteoinductive agents varied across the included studies.

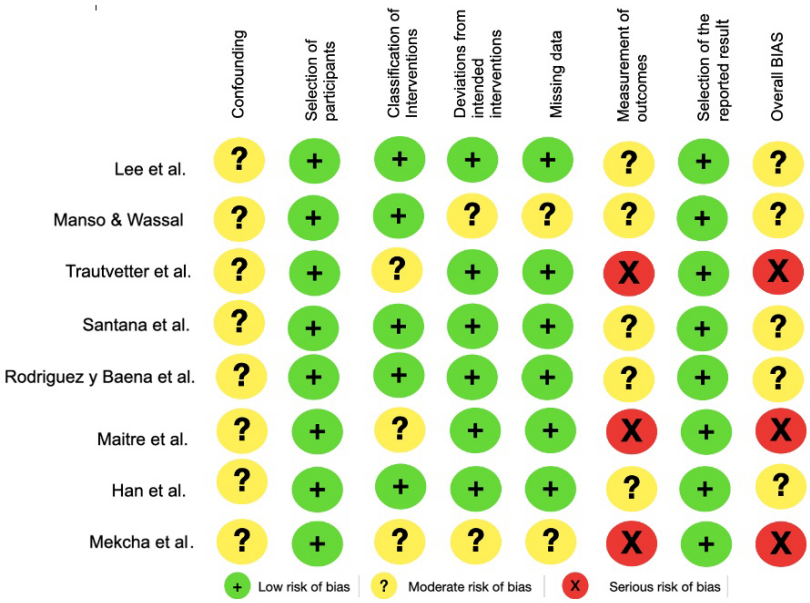


Fig. 2. Summary of risk of bias of the included studies (green: strong; yellow moderate; red: weak).

Table II. Descriptive analysis regarding the location, length, and type of biomaterials used prior to implant placement.

| Author | N | Sex (M/F) | Age (Years) | Graft Site | Graft Site Length | Alloplastic Bone Graft | Osteoinductor | Graft Follow-Up |
|---|---|---|---|---|---|---|---|---|
| Lee *et al*., 2008 | 52 | 28 - 24 | 30 - 73 | Maxillary sinus elevations | Residual vertical sinus bone < 6 mm | Macroporous biphasic calcium phosphate | Irradiated cancellous bone and cancellous bone from tuberosity or mandibular ramus | Average 6.78 months |
| Manso & Wassal, 2010 | 45 | 16 - 29 | 26 - 80 | Maxillary sinus elevations | Residual vertical sinus bone < 5 mm | Bioactive resorbable calcium HA | Particulate bone from mandibular retromolar area | 6 months |
| Trautvetter *et al*., 2011 | 10 | 6 - 4 | ND | Maxillary sinus lift | Residual vertical bone of 4 mm and horizontal of 6 mm | Biodegradable polymer | Osteogenic cells from lateral mandible near third molar | 6 months |
| Santana *et al*., 2015 | 14 | ND | ND | Sockets of upper and lower molars | Vestibular defect > 4 mm | β–TCP / HA | Recombinant human platelet-derived growth factor | Not described |
| Baena *et al*., 2017 | 24 | 12 - 12 | 45 - 64 | Maxillary sinus elevations | Not described | 20 % PLGA and HA | Periosteum extracted from outer layer of the flap | 6 months |
| Maitre *et al*., 2020 | 13 | 7 - 6 | 19 - 28 | Central and lateral incisor region of the maxilla | Residual width ≤ 4 mm and height ≤ 2 mm | HA | BMP-2 | 4 to 5 months |
| Han *et al*., 2022 | 27 | 19 – 8 | 40 - 60 | Maxillary sinus lift | 4.48 ± 2.69 mm | HA | BMP-2 | 3 to 6 months |
| Mekcha *et al*., 2023 | 10 | 6 - 6 | 38 - 65 | 5 anterior, 3 premolar and 2 molar regions | Horizontal bone support < 50% of implant | 3D-printed HA | Growth factors and platelet-rich fibrin | 6 months |

Table III. Descriptive analysis of the methods used to evaluate bone consolidation and survival of the placed implants.

| Author and year | N | Analysis | Implants Installed | Implant Size | Implant Survival / Follow-Up |
|---|---|---|---|---|---|
| Lee *et al*., 2008 | 52 | CT and histology | 130 | 4 to 5 mm diameter | 128 implants (98.47 %) / 12 months |
| Manso & Wassal, 2010 | 45 | CT in 20 subjects over 5 years | 160 | ND | 149 implants (94.8 %) / 10 years |
| Trautvetter *et al*., 2011 | 10 | CT and histology | 21 | 13 to 18 mm length and 4 to 6 mm diameter | 21 implants (100 %) / 5 years |
| Santana *et al*., 2015 | 14 | CT | 28 | 6.5 mm diameter | 28 implants (100 %) / 12 months |
| Baena *et al*., 2017 | 24 | CT and histology | 24 | ND | 24 implants (100 %) / 2 years |
| Maitre *et al*., 2020 | 13 | CBCT | 13 | 3.5 mm diameter and 10 to 11 mm length | 13 implants (100 %) / 9 months |
| Han *et al*., 2022 | 27 | CBCT | 43 | 4.0 mm diameter and 11.5 mm length | 39 implants (90.7 %) / 12 months |
| Mekcha *et al*., 2023 | 12 | CBCT and histology | 10 | 3.2 to 4.5 mm diameter and 8 to 10 mm length | 10 implants (83.3 %) / 9 months |

## DISCUSSION

Bone grafts are intended to promote regenerative processes that increase bone volume, thereby creating a suitable environment for dental implant placement (Shah *et al*., 2022). Currently, there is growing interest in replacing autologous bone with biomaterials capable of mimicking the osteoinductive signals provided by growth factors and osteogenic cells. Key factors to evaluate for these materials include microstructure particularly porosity mechanical stability, controlled degradation, and ultimately the ability to support bone remodeling comparable to that of autologous bone (Zhao *et al*., 2021).

Karl *et al*. (2008), in a clinical study involving 385 implants placed without grafts or biomaterials, demonstrated that primary stability values vary depending on the implant site. Implant Stability Quotient (ISQ) values ranged from 69.41 ± 9.3 to 69.89 ± 8.5 in the maxilla, and from 71.92 ± 7.8 to 75.98 ± 5.9 in the mandible. In contrast, Vallecillo-Rivas *et al*. (2021), compared ISQ values between native bone and biomaterials using implants of 10 mm length and diameters between 3.7 and 4.1 mm, reporting significantly higher initial ISQ values in native bone (75.40 ± 12.80) compared to xenografts (67.17 ± 11.47). Meanwhile, Han *et al*. (2022), evaluated mean ISQ values between an alloplastic graft combined with the osteoinductive agent BMP-2 and a xenograft group. The rhBMP-2/hydroxyapatite (HA) group presented a mean ISQ of 70.5 ± 3.4, while the xenograft group showed 75.3 ± 2.6, with no statistically significant differences between the groups.

Shah *et al*. (2022), through a systematic review and meta-analysis, demonstrated that bone defects treated with autogenous bone grafts, xenografts, and synthetic biomaterials combined with platelet-rich fibrin (PRF) as an osteoinductive agent showed implant survival rates of 96.9 % at six months post-placement. These findings highlight that, regardless of the biomaterial used, primary stability can be achieved, with ISQ values varying but implant survival rates consistently exceeding 90 %. The role of residual bone is critical, as mature bone beneath the graft serves as the primary anchor for the implant. Thus, the biomaterial must facilitate new bone formation laterally to support osseointegration and improve long-term implant survival.

Jing & Su (2024), noted that a residual bone height of 5 mm or greater contributes significantly to the vertical stability of bone grafts, especially in the posterior region, where stability remains consistent after the first year. Among the studies included in this review, subjects presented with residual ridge heights between 4 and 6 mm at baseline. Following the application of bone substitutes, vertical bone gains sufficient for implant placement and rehabilitation were observed, with survival rates ranging from 94.8 % to 100 %. Santana *et al*. (2015), combined platelet-derived growth factors with b-TCP/HA, achieving vertical gains of 3 to 4 mm. Meanwhile, Trautvetter *et al*. (2011), reported a vertical gain of 7 mm in the posterior region, starting with a residual bone height of 4 mm, by using a bioresorbable alloplastic biomaterial and osteogenic cells as the osteoinductive agent.

The primary function of osteoinductive agents is to stimulate the differentiation of osteoprogenitor cells into mature osteoblasts, thereby enhancing bone regeneration. When incorporated into biomaterials, these agents enable the controlled and sustained release of growth factors, maintaining their bioactivity throughout the therapeutic window (Ozdemir *et al*., 2013; Zhao *et al*., 2021). For instance, platelet-rich fibrin (PRF) not only facilitates the aggregation of biomaterials but also promotes revascularization through its neoangiogenic properties, which guide the migration of osteoprogenitor cells toward the graft material (Choukroun *et al*., 2006). The combination of PRF with bone substitutes allows for the gradual release of autologous growth factors, exerting prolonged effects on cell proliferation anddifferentiation—with a peak activity observed around day 14 (He *et al*., 2009). Several authors (Pichotano *et al*., 2019; Trimmel *et al*., 2021) have highlighted that the incorporation of osteoinductive agents not only enhances early bone formation within the biomaterial but also enables earlier implant placement, reducing the required osseointegration period to approximately four months.

Histological findings from studies included in our review show that at six months post-grafting, inflammatory processes are absent. Active resorption of autogenous material and new bone formation with blood vessels within the connective tissue are still evident. A distinct interface between the augmented bone layer and native bone is clearly identifiable. Additionally, osteocytes are embedded within the lacunae of trabecular bone, and osteoblasts are observed in active areas adjacent to or within the alloplastic material.

The study by Manso & Wassal (2010), reported the highest number of implants placed, with a survival rate of 94.8 %. They noted that all implants achieved osseointegration at placement, and implant failures were attributed to peri-implant disease that developed five years after rehabilitation. Although maintenance and follow-up protocols are crucial for implant stability, these were not consistently reported across the studies (Carra *et al*., 2023). Feng *et al*. (2020), evaluated risk factors for peri-implant bone loss over a 10-year period, identifying autoimmune diseases, heavy smoking, and bisphosphonate use as significant contributors. They also reported a peri-implantitis prevalence of 11.7 % at 8 to 10 years, primarily affecting the anterior region followed by the posterior molar area. While all studies documented favorable primary stability with insertion torque values around 30 N·cm, only Mekcha *et al*. (2023), assessed implant stability quotient (ISQ), reporting an average value of 65 ± 4.08 Hz.

Autologous bone remains widely used due to its inherent biological advantages and its ability to initiate the inflammatory processes necessary for cellular differentiation and bone formation (Karl *et al*., 2008; Guler *et al*., 2013). However, Mackenna *et al*. (2022), in a systematic review, highlighted not only the benefits of autologous bone but also postoperative complications associated with donor site morbidity. These include pain and sensory disturbances following harvesting from the chin or mandibular ramus, as well as gait disturbances or walking difficulties when grafts are taken from the hip. In our review, several studies reported combining autologous bone with synthetic biomaterials such as hydroxyapatite, calcium phosphate, or their composites in varying proportions. Among osteoinductive agents, bone morphogenetic protein-2 (BMP-2) was the most commonly used, followed by osteogenic cells isolated from the patient and platelet-derived growth factors.

To achieve successful osseointegration and subsequent definitive restoration, it is necessary to obtain at least 1 mm of alveolar bone on both the buccal and palatal/lingual sides. Although bone substitutes contribute to an increase in horizontal tissue volume, a reduction in the volume of the biomaterial itself occurs over time, resulting in differences between initial and final volumes within a 4 to 6 month period (Hameed *et al*., 2019; Smeets *et al*., 2022). Some studies (Zhou *et al*., 2020) have reported rapid and significant alveolar bone resorption in the anterior maxillary region during the first 5 to 6 months, predominantly in the horizontal dimension. Consequently, a minimum horizontal bone width of 4.1 to 4.5 mm is required for implant placement. Maître *et al*. (2020), evaluating anterior ridge width with an initial thickness of 2.75 ± 0.9 mm, achieved a horizontal gain of 4.15 mm between 4 and 5 months. Similar results were reported by Mekcha *et al*. (2023), who observed a horizontal bone gain of 4.53 ± 1.80 mm at 6 months using hydroxyapatite. In contrast, Deeb *et al*. (2021), evaluated horizontal alveolar ridge augmentation in the anterior region using biological agents and found only a slight improvement in bone density, with no significant effect on bone gain or volume adequate for implant placement.

3D printing of bone scaffolds facilitates the adhesion, attachment, and proliferation of osteoinductive cells on their surfaces, thereby promoting bone remodeling (Brachet *et al*., 2023). This technology enables the fabrication of synthetic materials with excellent biocompatibility, osteoconductive properties, and stable mechanical strength, while allowing for personalized treatment tailored to the size and shape of the defect site (Feng *et al*., 2020). Among the most commonly used

materials in 3D printing are b-tricalcium phosphate (b-TCP), followed by polycaprolactone (PCL) and hydroxyapatite (HA), which are frequently printed using extrusion-based techniques (Francisco *et al*., 2023).

In a clinical trial, Kim *et al*. (2024), compared commercially available blocks composed of 60 % HA and 40 % b-TCP with personalized 3D-printed blocks. Both graft types supported new bone formation, with no significant differences observed in bone volume, bone volume percentage, bone surface, or bone density. Therefore, the main advantage of 3D printing lies in the ability to plan and customize the graft according to the defect's specific size, thickness, and shape. These findings align with those reported by Kijartorn *et al*. (2022), who conducted a similar comparison between printed and commercially available grafts, observing that at four months post-grafting in extraction sockets, both groups exhibited comparable results.

Additionally, during implant placement, both groups achieved insertion torque values exceeding 35 N·cm, with no significant differences in Implant Stability Quotient (ISQ) between the control group ($70 \pm 2.7$) and the 3D-printed graft group ($69.2 \pm 1.9$). Within our review, only the study by Mekcha *et al*. (2023), utilized 3D printing to fabricate a personalized nanohydroxyapatite block graft. This study also incorporated osteoinductive agents, demonstrating that combining alloplastic grafts with platelet-rich fibrin (PRF) results in greater bone volume compared to the use of alloplastic grafts alone. Despite these promising findings, at six months postoperatively, an interface remained visible between the augmented bone layer and the native bone, along with new bone formation surrounding the graft particles in all biopsy cores.

## CONCLUSION

We conclude that alloplastic grafts exhibit favorable osteoconductive properties and effectively increase ridge or residual bone volume in maxillary sinus augmentation. However, to stimulate new bone formation throughout the grafted material, these biomaterials must be combined with osteoinductive agents. Although all included studies reported positive outcomes in implant placement and survival, they generally involved sites with a favorable baseline bone matrix for implant installation. This suggests that the grafted materials may not be fully engaged in the entire osseointegration process required for long-term implant viability. Consequently, the true capacity of these grafts to support functional load and ensure lifelong implant success remains uncertain. Further research is needed to better elucidate the functional performance of these biomaterials in clinical reconstruction.

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**RAVELO, V.; OLATE, G.; PARRA, M.; VALDIVIA, J.; OTERO, J. J. & OLATE, S.** Osteoinductores utilizados junto con biomateriales aloplásticos para regeneración ósea: Una revisión sistemática. *Int. J. Morphol., 43(6)*:2032-2041, 2025.

**RESUMEN:** El injerto óseo y los biomateriales se utilizan para conseguir aumentos del volumen óseo y para llegar al objetivo, muchas veces se combina con otros sistemas para obtener características osteogénicas, osteoinductoras y osteoconductoras, El objetivo de este estudio fue analizar las características de los osteoinductores utilizados en biomateriales aloplásticos y la supervivencia que presentaron los implantes instalados. Se realizó una revisión de sistemática siguiendo las recomendaciones descritas en el informe de transparencias de revisiones sistemáticas y meta-análisis. Se realizó una búsqueda sistemática de la literatura mediante el registro de términos MeSH y términos boléanos AND/ OR en los idiomas inglés, portugués y español hasta diciembre del 2024, utilizando las bases de datos Medline, Embase, Scopus y Web of Science. Se incorporó una búsqueda de literatura gris en las bases de datos Google Scholar y Open Access Theses and Dissertations (OATD). Se incluyeron 8 estudios; en relación a la zona de reconstrucción, existió mayor prevalencia de elevación de seno maxilar, seguida de alveolos de premolares y molares posterior a exodoncia y región incisiva del maxilar. El rango promedio de espera para la consolidación ósea y posterior instalación del implante fue entre los 4 a 6 meses. Se instalaron un total de 428 implantes, en donde el seguimiento mínimo fue 9 meses y el máximo fue de 10 años, en donde este último seguimiento presentó una supervivencia del 94.8 % de un total de 160 implantes instalados. Podemos concluir que es necesario combinar los biomateriales sintéticos con agentes osteoinductores para poder inducir neoformación ósea en sus superficies internas como a su alrededor.

**PALABRAS CLAVE: Injerto aloplásticos; Regeneración ósea; Osteoinductores; Implantes dentales.**

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