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Systematic Review

Three-Dimensional Scaffolds Designed and Printed Using CAD/CAM Technology: A Systematic Review

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Abstract: The objective of this work is to review the literature on the use of three-dimensional scaffolds obtained by printing for the regeneration of bone defects in the maxillofacial area. The research question asked was: what clinical experiences exist on the use of bone biomaterials manufactured by CAD/CAM in the maxillofacial area? Prospective and retrospective studies and randomized clinical trials in humans with reconstruction area in the maxillofacial and intraoral area were included. The articles had to obtain scaffolds for bone reconstruction that were designed by computer processing and printed in different materials. Clinical cases, case series, in vitro studies and those that were not performed in humans were excluded. Six clinical studies were selected that met the established inclusion criteria. The selected studies showed heterogeneity in their objectives, materials used and types of regenerated bone defects. A high survival rate was found for dental implants placed on 3D-printed scaffolds, with rates ranging from 94.3% to 98%. The materials used included polycaprolactone, coral-derived hydroxyapatite, biphasic calcium phosphate (BCP) and bioceramics. The use of CAD/CAM technology is seen as key for satisfying variations in the shapes and requirements of different fabrics and size variations between different individuals. Furthermore, the possibility of using the patient's own stem cells could revolutionize the way bone defects are currently treated in oral surgery. The results indicate a high survival rate of dental implants placed on 3D-printed scaffolds, suggesting the potential of this technology for bone regeneration in the maxillofacial mass.

Keywords: systematic review; CAD/CAM; polycaprolactone; beta-TCP; hydroxyapatite

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1. Introduction

It is anticipated that about two million bone grafts are performed worldwide each year [1,2] to repair significant bone defects caused by severe trauma, tumor excision, absence of union after a fracture, infections or congenital illnesses [3].

Autografts (microvascularized free grafts) are the gold standard for bone grafts, but due to their limited availability, high morbidity, need for intraoperative modification, and structural differences between bones, alternatives like allografts and xenografts have been developed. Allografts enable scaffolds to be generated in a wide range of forms and sizes; nevertheless, this type of graft is linked with restricted revascularization, can elicit an immunological response in the recipient patient, can transmit infections, and can induce long-term mechanical failures [2–4].

For this reason, various possibilities have been presented, such as sintered calcium phosphates (beta-tricalcium phosphate) or hydroxyapatite, which are utilized as bone substitutes in orthopedic surgery since their properties are remarkably similar to those of organic apatite crystals from natural bone. However, these types of materials are limited to not-too-large bone defects and to the regeneration of bones that do not have to bear too much load as their biomechanical properties are poor [2,3].

One of the major obstacles in the creation of bone substitutes is that there is substantial anatomical heterogeneity across patients, and bone abnormalities vary based on the type of defect and the mechanism that caused it [3].

The concept of prosthesis-guided bone reconstructive surgery is particularly important for reconstructing bone structures involved in masticatory function. This is because, at times, the mandibular bone grafts are so thin that the implants emerge too low at the level of the floor of the mouth [4].

All of this justifies the use of additive manufacturing (AM) in conjunction with computer-aided design (CAD) for the purpose of designing scaffolding and personalized grafts for each patient based on CBCT (cone beam computed tomography), CT (computed tomography) or magnetic resonance imaging [3,4].

The intricate design of face bone structures complicates scaffolding material research, as does the requirement to produce biocompatible, osteoinductive and osteoconductive materials with appropriate mechanical qualities. New printing methods enable the combination of biomaterials made of synthetic or natural polymers (degradable or not) or hydrogels [4].

Biopolymers are the most recent trend in bone scaffolding materials development. Microbial polyhydroxyalkanoates (PHAs) are thermoplastic biopolymers that accumulate in the cytoplasm of cultivated bacteria. They are regarded the most promising biopolymers because of their sustainability, biodegradability, and biocompatibility qualities [4].

Printed dental scaffolds for bone regeneration represent a potential field of research. The materials currently being used are:

- Hydroxyapatite-based scaffolds: these scaffolds have been discovered to be better suited for mechanically demanding bone regeneration due to their microporosity [5].
- Biphasic and triphasic scaffolds: they have been designed for the regeneration of periodontal ligaments and cementum, as well as alveolar bone tissue [6].
- GelMA/PEGDA/F127DA scaffolds: these scaffolds have proven to be beneficial in the treatment of bone deformities [7].
- Oxygen-releasing scaffolds: incorporating oxygen supply into 3D-printed scaffolds has been shown to promote bone repair in mice [8].
- Icariin-releasing scaffolds: icariin-encapsulated scaffolds have been designed to promote bone regeneration in situ [9].
- Polycaprolactone scaffolds with nanosilicates: these biomaterials customized using 3D printing technology have the ability to address the needs of oral and maxillofacial bone repair and regeneration [10].

1.1. Advantages of 3D-Printed Scaffolds for Bone Regeneration

1. Customization: three-dimensional printing enables the production of patient-specific scaffolds that are suited to the individual's requirements in terms of histocompatibility, transplant size and bone growth pace [11].
2. High porosity: three-dimensional-printed scaffolds have high porosity, allowing for the penetration of cells and nutrients, which promotes tissue regeneration [11,12].
3. Controlled release of biomolecules/drugs: three-dimensional-printed scaffolds can be configured to release biomolecules and medications in a controlled manner, potentially improving bone regeneration [13].
4. Mechanical strength: adequate mechanical strength ensures integrity after implantation. Bone scaffolds must have temporary mechanical stability, and 3D printing enables the fabrication of scaffolds with mechanical qualities similar to those of real bone [14].
5. Bioprinting technology enables the insertion of living cells and/or growth factors into scaffolds with the goal of emulating the structure and function of natural bone [15].

Additive manufacturing offers the advantage of enabling the creation of scaffolds with a variety of micro- and macrostructures. This is significant because the size and direction

of the material's pores, as well as its composition at the microscopic level, influence the formation of the vascular and bone structures of the tissue to be regenerated [3,4,13].

1.2. Objectives of Scaffolding

The objectives of these scaffolds are as follows [4]:

1. Promote quick cell adherence to the substrate in order to create new bone tissue with scaffold-predetermined morphologies (osteoinduction).
2. Provide solid support for cell osseoconduction.
3. Using CAD/CAM technologies, ensure that the scaffold fits perfectly to the morphology of the defect.
4. Avoid bacterial infection of the graft and superinfection of the surgical site in the oral cavity.

To achieve the first two objectives, PHA polymers containing osteoinductive bioactive nanofillers are employed. To achieve the third objective, both the microanatomy and macroanatomy of the scaffolds will be tailored using 3D printing technology to resemble the microstructure of actual human bone while also improving the mechanical and hydrodynamic qualities of the scaffold. The latter objective can be met by incorporating specialized antibacterial inorganic fillers into the scaffold in a hyaluronic acid hydrogel foundation. All of this is expected to replace the present gold standard of maxillary bone restorations in the future [4].

The purpose of this research is to examine the literature on the use of three-dimensional scaffolds produced by printing for the regeneration of bone abnormalities in the maxillofacial area.

2. Materials and Methods

The following research PICO question was asked: what clinical experiences exist on the use of bone biomaterials manufactured by CAD/CAM in the maxillofacial area?

Problem (P): need for bone regeneration for the reconstruction of defects in the maxillofacial area.

Intervention (I): three-dimensional graft printing.

Comparison (C): different types and materials that can be produced through additive manufacturing and customization.

Outcome: what are the clinical experiences so far with these materials?

For the writing of this systematic review, the PRISMA guidelines were followed [16], from the search strategy development to the writing of the manuscript.

2.1. Eligibility Criteria

2.1.1. Inclusion Criteria

We included prospective and retrospective studies and randomized human clinical trials. Works had the maxillofacial and intraoral area (upper jaw and mandible) as a reconstruction area. The included works had to obtain computer-designed scaffolds for bone reconstruction (CAD/CAM) and were printed on different materials.

2.1.2. Exclusion Criteria

Clinical cases and case series were excluded. We excluded in vitro studies and those not conducted in humans. Also, those who used preformed grafts that were cut intraoperatively and not adapted by CAD/CAM were excluded.

2.2. Sources of Information and Search

A literature search was carried out in Web Of Science (WOS) with the following terms: (TS = (custom-made bone graft) OR TS = (biomaterial bone grafts) OR TS = (CAD/CAM bone graft) OR TS = (computer-aided design computer-aided manufacturing bone graft) OR TS = (3D-printed bone graft) OR TS = (polycaprolactone) OR TS = (beta-tricalcium

phosphate) OR TS = (hydroxyapatite) OR TS = (scaffold)) AND (TS = (maxillofacial) OR TS = (dental)).

We limited the search to the last 10 years (2013–2023), and the last search was performed in March 2024.

Figure 1 shows the diagram of the search performed [16].

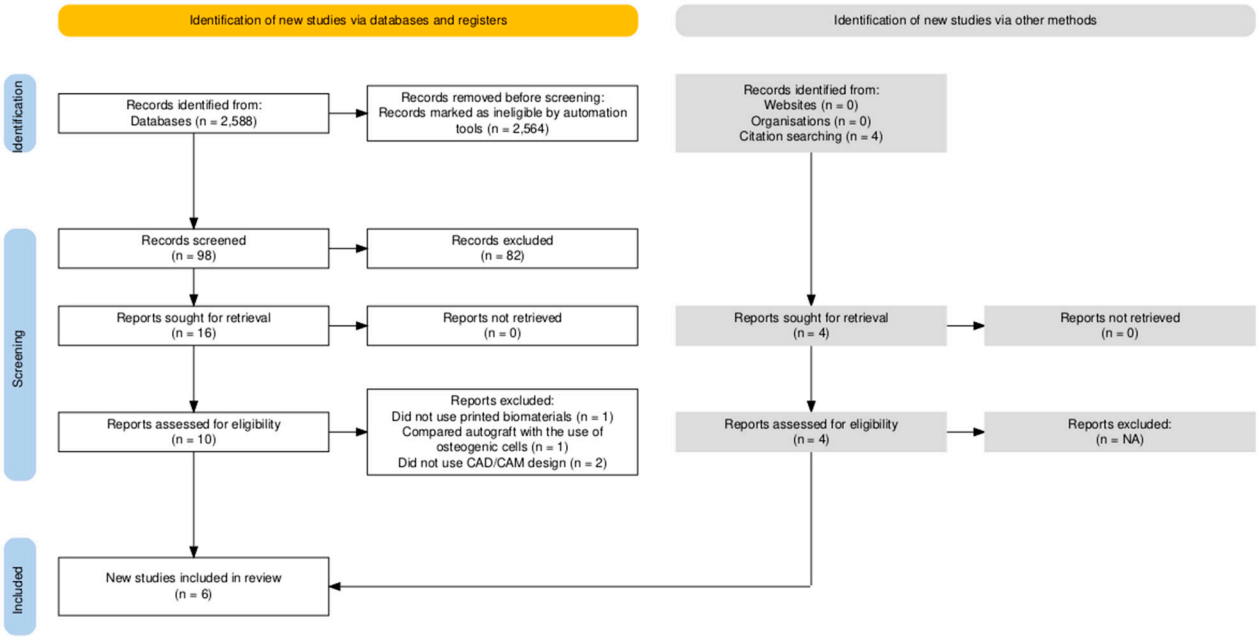


Figure 1. PRISMA diagram of the included studies.

2.3. Study Selection

Only papers that met the described inclusion criteria were selected for this systematic review. Two authors (B.P.P. and C.G.P.) identified and selected the studies that would be read in full text and ultimately selected those that would be included in the systematic review based on the eligibility criteria.

The study by Zhu et al. [17] was excluded as it did not involve printed biomaterials; rather, it was a comparison of guided surgery for obtaining autografts versus freehand collection. It compared the outcome and effectiveness of the computer-aided intraoral block bone grafting procedure with those of the conventional technique for the augmentation of horizontal ridge defects.

The study by Kadry et al. [18] was excluded because it was a comparison between the use of an iliac crest particulate bone graft (control) and the use of a collagen scaffold with cultured cells differentiated into osteogenic cells from the bone marrow (test).

The work of Naik et al. [19] was eliminated because, while it employed PCL blocks, it did not use computer design; they cut these blocks to the size of the flaw, but this does not imply that the design was accomplished by a computer.

Finally, the work by Wang et al. [20] was omitted because, although it used CAD/CAM, the block material it used was allogeneic iliac crest bone rather than a biomaterial.

Goh et al. [21] were excluded as well because they used manufactured polycaprolactone scaffolds that the surgeon manually cut with a scalpel. The authors believe that cutting the scaffolds with a scalpel diminishes precision.

2.4. Data Collection Process

Data were extracted from the selected papers and sorted in an Excel table. Data were extracted on the material used, the type of system used for its fabrication, whether a study on bone volume gain was conducted or not, whether a histological analysis of the obtained bone was performed or not, whether the survival and marginal bone loss of implants placed

in the regenerated bone using scaffolds were evaluated and whether the complications experienced by the patients were recorded.

2.5. Summary of Results

A meta-analysis was not conducted due to the heterogeneity of the included studies in terms of objectives, outcomes and materials. We have conducted a qualitative synthesis of the results obtained, which means that a quantitative study has not been carried out due to the difficulty of unifying criteria and quantitative data.

2.6. Quality Assessment

The Risk Of Bias In Non-randomized Studies assessment tool (ROBINS-I) (available on https://methods.cochrane.org/robins-i accessed on 12 October 2024) was used to assess the risk of bias in five studies. It was not studied in de Almeida's [22] work because this is merely a protocol for a future study. ROBINS-I is structured into a fixed set of domains of bias, where each domain is a series of questions ('signaling questions') that aim to obtain information on the risks of bias (RoBs) in each study. The judgment can be 'Low', 'Some concerns (Unclear)' or 'High' risk of bias. The final judgement is described as: high risk of bias: if the study has a high RoB in at least one domain; unclear risk of bias: if the study is unclear in at least one domain; and low risk of bias: if the study has a low risk of bias in all domains. In cases of disagreement, the reviewers resolved the disagreement by consensus (B.P.P., C.G.P.). If no agreement was achieved, an independent third reviewer (J.M.) was invited to resolve and make the final decision.

3. Results

3.1. Study Selection and Study Characteristics

Six studies that met the established inclusion criteria were selected, one protocol for conducting a randomized clinical trial [22] and five prospective studies [23–27]. There were no randomized clinical trials that met the inclusion criteria (Table 1).

Table 1. Characteristics of the included studies.

Author/Year	Type of Study	N Patients	N Males	N Women	Middle Ages	Follow-Up (Months)	Implant Placement Times (Months)	Second Phase Times (Months)
Mangano et al., 2013 [26]	Prospective study	5	NE	NE	45–57 years	24	6	3–4
Mangano et al., 2014 [27]	Prospective study	10	5	5	56.5 (52–66)	12	8	4
Luongo et al., 2016 [24]	Multicenter retrospective study	15	6	9	54.2 ± 5.5 median 55 CI 51.5–56.9)	8	8	2–3
de Almeida et al., 2022 [22]	RCT (project)	20	NE	NE	>18 NE	14	8	6
Jeong et al., 2022 [23]	Prospective study	8	NE	NE	NE	6	NE	NE
Mangano et al., 2022 [25]	Retrospective study	26	11	15	58.6 ± 8.9 MEDIAN 58 CI 55.2–62.0	72	8	2–3
Total		97						

CI: confidence interval; N: number; NE: not specified; RCT: randomized controlled trial.

3.2. Results of Individual Studies

The total number of patients studied was 84, with the study with the smallest sample size being 5 patients [26] and the one with the largest sample size being 26 patients [25].

The age range of the patients studied ranged from 29 [21] to 66 years old [27], and in most of the works, this parameter is reflected as a range or mean. The study by Jeong et al. does not specify the age of the patients [23].

Follow-up time ranged from 6 months [23] to 3 years [25].

In relation to the objectives pursued by these studies, they are different as they also use and compare different types of materials. Table 2 shows the material used in each study.

Table 2. Materials used.

Author/Year	Material	Membrane
Mangano et al., 2013 [26]	Coral-derived hydroxyapatite (Biocoral, Leader-Novaxa, Milan, Italy)	NO
Mangano et al., 2014 [27]	Coral-derived hydroxyapatite (Biocoral, Biocoral Inc, Le Garenne Colombes, France)	NE
Luongo et al., 2016 [24]	Biphasic calcium phosphate (BCP) (70% beta-tricalcium phosphate and 30% hydroxyapatite) (BTK, Dueville, Vicenza, Italy).	YES
de Almeida et al., 2022 [22]	Beta-tricalcium phosphate (Plenum® Oss 3Dβ fit, Plenum Bioengenharia, Jundiaí, Brazil)	YES
Jeong et al., 2022 [23]	Polycaprolactone (Evonik Industries, Essen, Germany) and β-TCP tricalcium phosphate (Foster corporation, Putnam, CT, USA)	NE
Mangano et al., 2022 [25]	Biphasic calcium phosphate (BCP) (70% beta-tricalcium phosphate and 30% hydroxyapatite) (RIGENERA 3D, Biotec-BTK, Dueville, Vicenza, Italy).	NO

NE: Not specified.

Mangano et al. [26,27] employed coral-derived hydroxyapatite from several commercial brands in their 2013 and 2014 research, respectively. In the 2013 study [26], a customized block graft for sinus lift was employed in such a way that the graft was generated by computer using software, and then a hydroxyapatite block (15 × 15 × 30 mm) was used and cut to the exact three-dimensional shape. The graft was introduced en bloc after the lateral window and sinus membrane elevation had been completed. In the 2014 study [27], coralline hydroxyapatite was employed to regenerate anterior or posterior maxillary abnormalities. As in the previous investigation, prefabricated hydroxyapatite blocks were cut to the exact size of the 3D pattern. In both cases, the scaffolds were sterilized before surgery.

Regarding the findings of Luongo et al. [24] and Mangano et al. in 2022 [25], they employed synthetic micro-/macroporous blocks of biphasic calcium phosphate (BCP) composed of 70% beta-tricalcium phosphate and 30% hydroxyapatite.

Luongo et al. [24] created a computer design of the needed block based on the geometry of the bone defect, and the block was then trimmed to match that design. The bespoke blocks were then sterilized. Mangano et al. [25] used 3D modeling software (Rhinoceros, Robert McNeel & Associates, Seattle, WA, USA) to develop a custom anatomically shaped onlay graft, which was subsequently machined on a five-axis milling machine. In this case, they also employed a polyurethane replica to ensure that the subsequent adjustment was adequate and to ready the bed for the set screw.

Almeida et al. [22] conducted a randomized split-mouth clinical trial to compare bone regeneration in the anterior jaw using autologous bone grafting and a bioceramic graft (Patient-specific Plenum® Oss 3Dβ fit) manufactured by additive manufacturing on a ceramic 3D printer (CeraFab 7500 LITHOZ, Lithoz, Troy, NY, USA). It will then be sintered at 1000 °C in a muffle furnace before being sterilized using gamma irradiation.

Jeong et al. [23] used polycaprolactone (PCL, Evonik Industries, Essen, Germany) and beta-tricalcium phosphate (β-TCP, Foster Corporation, Putnam, CT, USA) at an 8:2 ratio to cure zygomatic maxillary deformities. The PCL was melted at 110 °C for 15 min, then

combined with β-TCP powder for 10 min. This mixture was then manufactured on a 3D printer with CAM software. The 3D printing program (3-Matic Research 9.0, Materialise, Leuven, Belgium) calculated a porosity of 50% by 500 microns. The scaffolds were dried at −85 °C for 24 h before sterilization with a 450 W UV lamp for 4 h.

Table 3 shows the complications presented by the patients in each of the studies.

Table 3. Complications.

Author/Year	Complications
Mangano et al., 2013 [26]	No
Mangano et al., 2014 [27]	Scaffolding breakage during fixation (2/10) Dehiscence (1/10)
Luongo et al., 2016 [24]	Pain/Swelling (2/15) Scaffolding exhibition (3/15) Partial flap necrosis dehiscence (1/15)
de Almeida et al., 2022 [22]	No; it is a protocol
Jeong et al., 2022 [23]	Partial flap necrosis (1/8)
Mangano et al., 2022 [25]	Pain and swelling (2/26) Bone graft exposure (3/26) Graft loss (1/26) Peri-implant mucositis (1/26) Abutment fracture (1/26)

In the 2013 study by Mangano et al. [26], There were no surgical problems, no clinical evidence of sinus disease, and no patients demonstrated symptoms of maxillary sinusitis. A total of 19 implants were inserted. At the end of the research, following two years of functional loading, all implants were operational, with no clinical or prosthetic problems. Radiographic examination demonstrated a low tendency for marginal bone resorption and high stability of peri-implant bone tissue.

In the 2014 publication of Mangano et al. [27], the scaffolds fractured in two patients when attempting to fix them with mini-screws; nevertheless, they were repositioned and the screws were fastened in another area. No further issues or failures of the augmentation surgery were reported in these patients. One patient developed a dehiscence two months following surgery. The implants that were implanted had a 100% survival rate. None of the implants had discomfort, suppuration, mobility, radiolucency or prosthetic problems.

In the study of Luongo et al. [24], three incidents of scaffold exposure occurred one, three and five months following surgery. In these situations, a new flap was used to remove a portion of the scaffold using a piezoelectric device, resulting in two exposures being resolved with complete re-epithelialization of the regions and soft tissue closure in 2–3 weeks. The third case involved an infection and complete graft failure. One example of wound dehiscence was caused by partial flap necrosis, necessitating the adoption of a local flap for coverage. This latter issue was also reported in a patient by Jeong et al. [23].

In the instance of Mangano et al. in 2022 [25], three cases of dehiscence and graft exposure were successfully treated by opening a new full-thickness flap and removing the most coronal component of the scaffold using a piezoelectric device. Treatment with chlorhexidine gel and a rinse was recommended. An exposure resulted in infection, graft extraction, and surgery failure. A significant rate of postoperative complications, including graft exposure, was documented (11.5%). There was one incidence of peri-implant mucositis and another of abutment fracture.

3.3. Risk of Bias of Included Studies

The risk of bias (RoB) of the included studies was mainly low; three of them presented a low RoB [23,24,27], and two presented an unclear RoB [25,26]. Based on the domains, in Domains 1, 2, 3 and 4 (bias due to confounding, the bias in selection of participants into the

study, classification of interventions and deviations from interventions) none of the studies presented risk of bias. One study had some concerns regarding bias of missing data [25] and two in the measurement of outcomes [25,26] (Figure 2).

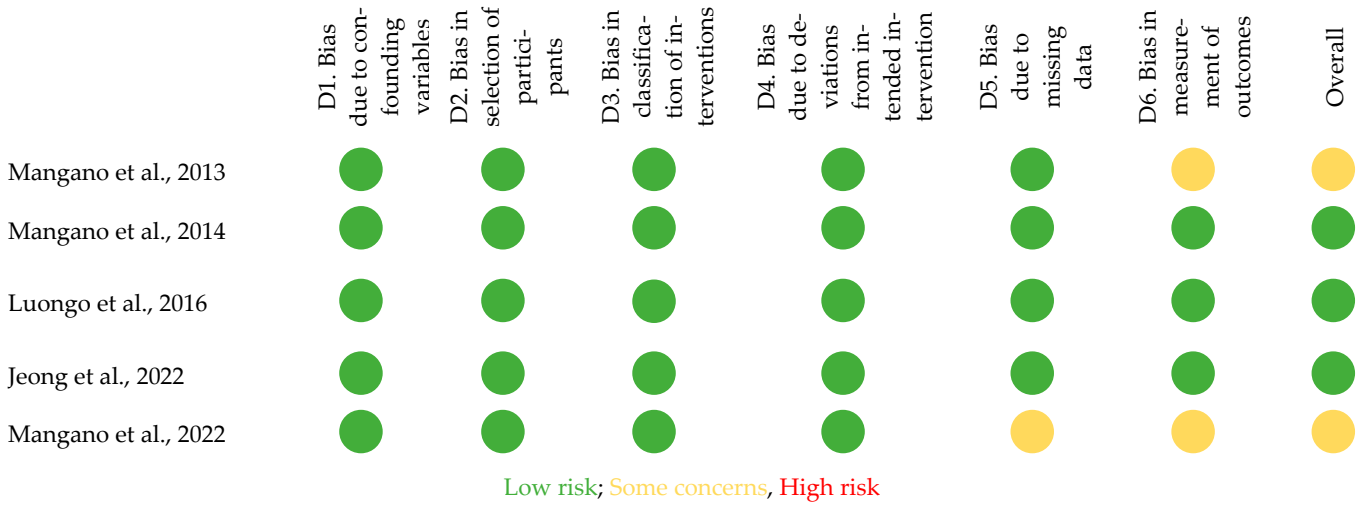


Figure 2. Risk of bias (RoB-I). The risk of bias by domain is presented in seven domains (columns) and specified by studies (lines) [23–27].

4. Discussion

Six studies that met the established inclusion criteria were selected [22–27].

It should be noted that there is heterogeneity between the selected studies as their objectives are different, as well as the regenerated bone defects and the materials used for regeneration.

All cases were prospective studies except for one case that was a project for a clinical trial that is currently underway [22].

In many of the studies, bone regeneration was performed using scaffolds designed and printed using CAD/CAM in order to subsequently place dental implants on this scaffolding [24–27]. In the case of the work by Jeong et al., it is not specified whether dental implants were placed or when they were placed if they were [23].

4.1. Materials Used and Their Properties

Synthetic grafts are usually ceramics based on calcium phosphates, such as hydroxyapatite (HA), beta-tricalcium phosphate (β-TCP) or a combination of both [22].

4.1.1. Polycaprolactone (PCL)

Only one job used polycaprolactone scaffolding [23]. In this case, it combined PCL with β-TCP.

Polycaprolactone (PCL) is one of the polymers prepared by ε-caprolactone ring-opening polymerization using a series of catalysts. It safely degrades into carbon dioxide and water over 2–3 years and provides a suitable scaffold for guided bone regeneration [23].

The PCL/β-TCP scaffolds used in this study were three-dimensional in shape, moderately rigid and relatively high elastic and were manufactured with a patient-specific design [23].

The Young's modulus of elasticity of the scaffold that had a porosity of 50% was 162.7 ± 12. 8 MPa, which is a level similar to that of human mandibular trabecular bone (6.9 to 199.5 MPa). This scaffolding was strong enough to maintain the three-dimensional shape, and it also had adequate elasticity to be carved [23].

This scaffold has an internal structure in which pores with a size of several hundred micrometers are completely interconnected by a layer-by-layer manufacturing method.

These pores favor the penetration of surrounding cells and help the grafting of regenerated tissue into the artificial scaffold as the blood vessels connect [23].

On the other hand, the addition of β-TCP to PCL was shown to improve the mechanical performance of the scaffold and increase osteogenic cell proliferation and differentiation. By increasing the concentration of β-TCP in the scaffolds, significantly higher mineralization was achieved compared with pure PCL.

In this case, the PCL/β-TCP scaffold with an 80:20 ratio and a pore size of 500 µm was used to strike a balance between β-TCP content and print speed [23].

According to these authors, the combined use of virtual surgical simulations, 3D printing techniques and biodegradable grafts can replace traditional non-resorbable grafts as the method is more precise and the materials more biocompatible. [23].

4.1.2. Coral-Derived Hydroxyapatite (HA)

Mangano et al. in 2013 and 2014 used coral-derived hydroxyapatite [26,27].

In both works, a porous HA block was used, a material that has excellent osteoconductivity and mechanical properties suitable for machine cutting. This block was cut three-dimensionally based on preoperative simulation using CAD/CAM technologies. In addition, a custom osteotomy template was designed and manufactured prior to surgery [26].

In the case of the sinus lift, the dimensions of the custom-made block are related to the dimensions of the demarcated lateral bony window, making it difficult to entirely fill the space between the old and new floors with the CAD/CAM block alone, and there is a possibility of minor flaws. However, it might readily be addressed by employing particulate bone in combination with the custom-made CAD/CAM block [26].

4.1.3. Beta-Tricalcium Phosphate (β-TCP)

The protocol by de Almeida et al. and the work by Luongo et al. and Mangano et al. in 2022 used beta-tricalcium phosphate (β-TCP) [22,24,25].

In the case of Luongo et al. and Mangano et al. 2022 [24,25], biphasic tricalcium phosphate is used, which has a composition of 70% beta-tricalcium phosphate and 30% hydroxyapatite (HA).

β-TCP has stood out as a bone graft substitute material due to its resorption by osteoclasts, which end up causing slight local acidification, leading to the dissolution of β-TCP. This process converts β-TCP into a resorbable compound, allowing for rapid replacement with new bone. In addition, bioceramic β-TCP can be obtained through various production methods. One of these processes, additive manufacturing or 3D printing, has been attracting attention thanks to the numerous advantages derived from the production method [22].

4.2. Analysis of the Bone Volume Obtained

In the work of Jeong et al. [23], bone regeneration of large maxillary zygomatic defects was performed in eight patients, and a measurement of the volume gain achieved after grafting was performed. The mean volume of the preoperatively planned graft was 11.32 mm^3, ranging from 2.16 mm^3 to 30.37 mm^3. The mean postoperative volume of the actual graft was 10.21 mm^3, ranging from 1.84 mm^3 to 28.22 mm^3. After superimposing the two images using software, the average volume was 79.71%, ranging from 70.89% to 86.31%. In the postoperative period, the formation of new bone was calculated and the mean was 2.15 mm^3 (0.22 mm^3 to 7.15 mm^3). The bone volume fraction was obtained as the ratio between the bone volume measured after healing and the graft volume measured postoperatively, and a mean volume gain of 23.34% (7.81% to 66.21%) was obtained. The mean bone density in the grafted areas was 188.84 HU (151.48 HU to 291.74 HU), indicating type IV bone quality according to the Lekholm and Zarb classification [28].

In the study by Luongo et al. [24], there was a mean vertical bone gain of 2.1 ± 0.9 mm (range 0–3.3 mm, median 2.4 mm, 95% CI: 1.7–2.5 mm) and a mean horizontal bone gain

of 3.0 ± 1.0 mm (range 0–4.5 mm, median 3.2 mm, 95% CI: 2.5–3.5 mm).The 2022 study by Mangano et al. [25] assessed vertical and horizontal bone gain 8 months after graft placement with radiographic evaluation, revealing mean vertical and horizontal bone gains of 2.10 mm (±0.35) and 2.96 mm (±0.45), respectively. They also found a statistically significant difference between vertical and horizontal bone gain ($p < 0.001$). This work also evaluated crestal bone loss in implants placed in the regenerated area.

The 2014 study by Mangano et al. [27] evaluated the reduction in the size of the defect in height and width 8 months after graft placement through the use of a periodontal probe, observing a bone increase in height of up to 5 mm in two of the patients and in width of up to 3 mm in two of the patients. However, they do not perform any type of statistical analysis of the bone gain achieved, nor evaluation with CBCT. In this paper, a result of improved maintenance of crestal bone height was obtained after 6 months in those alveoli in which scaffolding was placed compared with those in which nothing was placed.

The 2013 study by Mangano et al. [26] did not assess bone volume gain. They simply performed a CBCT 6 months after the graft and verified that the bone volume gained was sufficient for the placement of the implants without performing any quantitative measurement.

4.3. Implant Survival and Marginal Bone Loss

Peri-implant marginal bone loss (MBL) was measured with intraoral periapical radiographs in those studies in which it was measured.

In the 2022 study by Mangano et al. [25], 11 maxillary implants were placed (5 in the anterior maxilla, of which 1 implant failed) and 15 implants were placed in the mandible (11 in the anterior sector), and a statistically significant difference was found between vertical (1 year/3 years) and horizontal (1 year/3 years) bone gain ($p < 0.001$). Comparison between the sites before and after 1 year ($p = 0.885$) and 3 years ($p = 0.508$) revealed no statistically significant differences [25].

Overall, the results suggest that dental implants placed on 3D-printed scaffolds have a high survival rate and may be a successful option for oral rehabilitation [25].

Mangano et al.'s 2013 study [26] shows that radiographic examination of implants implanted on 3D bone grafts demonstrated a trend toward reduced marginal bone loss and good peri-implant bone stability, but no additional data were provided.

The rest of the studies do not provide information on marginal bone loss.

4.4. Complications

Regarding complications, the dehiscence and exposure of the scaffold that occurred in eight patients stood out. In all but two cases, the incidence could be resolved by preserving the graft.

Complete graft loss only occurred in two patients, one in the 2022 study by Mangano et al. [25] and another in the work of Jeong et al. [23].

The advantage of custom CAD/CAM blocks over preformed blocks is that the former type does not require a manual adaptation by the surgeon to the defect at the time of surgery. The need to adapt and trim the graft intraoperatively is difficult for the surgeon and can lead to various risks, such as unsatisfactory stabilization/integration of the biomaterial block with the native bone, mobility and failure of the entire procedure. In addition, manual adaptation of the graft greatly increases the surgery time. Surgically, the custom-made synthetic scaffolds were of satisfactory size, shape, and appearance. They conformed to the area of the defect, were tailored to the surgeon's requirements and were easily implanted [24].

Regardless of the material employed, the use of onlay blocks has always offered a challenge: they must be adjusted intraoperatively to fit the residual anatomy. Such adaptation is difficult for the surgeon because it necessitates extended manipulation of the scaffold with the danger of contamination, and it always ends in incomplete adaptation, inadequate adjustment and insufficient stabilization. Improper correction can compromise

the scaffold's biological integrity, increasing the likelihood of failure; if surgery takes too long, there is a considerable risk of infection [25].

4.5. Histological Study of the Specimens

In the 2014 publication by Mangano et al. [27], samples were collected 8 months following graft insertion. There was evidence of newly created trabecular bone and biomaterial, particularly in the middle area. The new bone was in close contact with the remaining material. Wide gaps in osteocytes were found in close proximity to and in touch with the graft material, as well as an osteoid matrix that was mineralizing. Bone neoformation was also found within remaining HA particles, with a newly created osteoid matrix being mineralized. According to histomorphometric assessments of bone nuclei recovered 8 months after augmentation, the average percentages of new bone, biomaterial and medullary spaces were 34.9%, 26.3% and 38.8%, respectively.

On the other hand, the 2022 study by Mangano et al. indicates that a histological study was performed 8 months after the placement of the scaffold but does not provide further information [25].

The remaining studies do not include histology examinations. De Almeida et al. [22] include it in their clinical trial protocol.

4.6. Protocol

The CAD/CAM procedure for the fabrication and application of custom-made synthetic scaffolds can be divided into three different steps: the virtual planning and design of the scaffold, the milling of the scaffold into the exact size/shape from a preformed synthetic bone block, and finally reconstructive surgery.

Virtual scaffold planning and design involves taking a CBCT of the maxillomandibular area and putting the exploration data into 3D reconstruction software. This software allows the surgeon to assess the area of the defect. With the help of additional tools, the virtual reconstruction is accomplished.

Virtual scaffold files are then sent to a milling machine, and the manufacturing process begins with a preformed, standardized synthetic bone block. The scaffold is then sterilized [24].

4.7. Limitations of the Study

In relation to the limitations of this work, the scarcity of studies on patients using computer-designed and manufactured materials (CAD/CAM) stands out, which may be related to the fact that this is a novel topic that is under development. On the other hand, the absence of randomized clinical trials, the small sample size of the available studies and the heterogeneity in the protocols, regenerated areas and materials used are also striking.

All studies concur that the application of CAD/CAM technology may be the key to satisfying variances in the forms and needs of different tissues, as well as size differences between individuals.

In the near future, it could even be possible to use the patient's own stem cells, which could revolutionize the way bone defects are currently treated in oral surgery [26].

All this makes it necessary to review the literature in the future to assess whether there is an increase in the publication of randomized clinical trials with protocol standardization that allows for a better evaluation of the results.

At the moment, de Almeida's protocol has been in process since February 2023, and Mangano et al. in their 2014 paper indicated that they would conduct a clinical trial on the use of a composite scaffold composed of polycaprolactone and beta-tricalcium phosphate for alveolar preservation, although no randomized trial of this group on this topic has been published at the moment [22,27].

5. Conclusions

In relation to the objective of this study, it can be concluded that additional studies with a larger sample size and appropriate design (randomized clinical trials on patients) are needed to draw specific conclusions about the reliability of the new techniques, standardizing the protocols and interventions performed on patients.

It is also necessary to study the bone gain obtained with this type of scaffolding compared with the grafts currently used (autograft and xenograft) to verify the advantage of one over the other.

It is also important to carry out a cost study as in many cases this is decisive for the patient.

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