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Systematic Review

Multidimensional 3D-Printed Scaffolds for Ridge Preservation and Dental Implant Placement: A Systematic Review

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Featured Application: This present systematic review aimed to provide new insights into the development of 3D-printed scaffolds to promote dental implant placement.

Abstract: Background: Regenerative medicine in dentistry involves tissue engineering applications suitable for the unique oral environment. In this regard, advances in computer-aided technology have facilitated the creation of 3D scaffolds using cone beam computed tomography (CBCT). This review aimed to investigate whether 3D-printed scaffolds can be effectively used to achieve ridge preservation and/or predictable vertical and horizontal bone augmentation, ensuring successful outcomes for dental implant placement. Methods: A comprehensive search was conducted across six electronic databases (PubMed, Scopus, ScienceDirect, Google Scholar, Web of Science, Ovid) to identify relevant studies according to specific eligibility criteria, following the PRISMA guidelines. Two independent reviewers screened and selected studies, performed data extraction, and assessed the risk of bias using the Cochrane tool for randomized clinical trials and the Newcastle–Ottawa Scale for non-randomized clinical trials. Results: The initial search yielded 419 articles, which were subsequently screened to remove duplicates. After evaluating 293 articles based on title and abstract, 10 studies remained for full-text assessment. Ultimately, only three studies met all the pre-established eligibility criteria. Conclusions: The studies included in this systematic review showed that the use of multidimensional customized scaffolds appears to promote dental implant placement. Nevertheless, despite the positive reported effects, further well-designed randomized clinical trials are necessary to determine the special characteristics of the optimal 3D-customized scaffold.

Keywords: 3D printing; scaffolds; dental implant; ridge preservation; bone augmentation

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1. Introduction

Osseointegration as a concept was introduced several decades ago [1]. During these decades, implant dentistry has advanced, and today, it is a common, predictable, and successful treatment option in the rehabilitation of partially or completely edentulous patients, providing reliable long-term results [2]. Opposed to other treatment procedures, dental implants have gained popularity because they can maintain adjacent tooth shape and

bone formation [3]. Furthermore, implant treatment apparently enhances the masticatory function and quality of life for edentulous and partially edentulous patients [3,4]. Due to alveolar bone diversity and morphology, implants of varying dimensions have been fabricated in an attempt to manage this problem. However, the correct placement of dental implants can be more complex or even impossible in certain cases due to alveolar atrophy and extensive bone defects resulting from various reasons, such as tooth extraction and periodontal disease [5]. Following tooth extraction, a sequence of events arises regarding modeling and remodeling processes during socket healing. This chronic irreversible process leads to qualitative and quantitative changes at the edentulous site and an almost 50% reduction of the alveolar ridge within the first 6 months [6].

In such conditions, setting the location of dental implants in the precise three-dimensional (3D) role is nearly impossible due to substantial adjustments in the vertical and horizontal bone dimensions, thus negatively affecting right prosthetic reconstruction [6]. Several techniques and bone grafting substances have been proposed to overcome this problem by increasing the width and height of the atrophic alveolar ridge. Guided bone regeneration (GBR) is a well-established method among these approaches [7–10]. Onlay/inlay bone grafting [11,12], distraction osteogenesis [12], and nerve transposition have also been proposed. Although it has been shown that augmentation of the alveolar ridge following most of these distinctive techniques is feasible, the chance of complications or potential loss of the bone grafting material is always possible [13].

While various substitutes for bone grafting in ridge augmentation are now available, including allogenic, xenogenic, or synthetic substances [14], autografts remain widely recognized as the "gold standard" in oral and maxillofacial surgical treatment for bone augmentation [15]. This preference is attributed to their osteogenic, osteoinductive, and osteoconductive properties. Nevertheless, challenges such as site morbidity and limited availability persist [16].

Various "biologic principles" have been proposed as essential factors for achieving predictable horizontal or vertical bone augmentation. Ensuring the stability of the graft, achieving primary wound closure without tension on the flaps, and preserving the grafted area are crucial for the infiltration and proliferation of osteogenic cells [17–19]. The primary function of bone grafting substances is to act as scaffolds, creating space for the immigration of osteogenic cells and facilitating the transport of nutrients and growth factors, both integral to the reparative process. Consideration of factors influencing bio-absorbability and the maintenance of bone volume should involve replacing the implanted material at the site with newly formed bone tissue through bone remodeling.

During the bone formation phase, the rate of bio-absorption is associated with space-making capability and biocompatibility, predominantly mediated by passive chemical dissolution of the bone substitute [20,21]. The surrounding bone walls of the defect play an essential role in the bone regeneration of the atrophic alveolar ridge. As such, the morphology of the bone defects can affect the choice of the bone grafting material and the technique. Extensive atrophy of the alveolar ridge with fewer surrounding osseous walls is more demanding and requires substances and techniques that provide more space maintenance, graft balance, and biological activity. It is obvious that the understanding of the morphology of the atrophic alveolar ridge before surgery is verified to be pivotal for selection, making on flap design and perhaps at the biomaterials for use. In recent years, there has been a trend for new therapeutic options and strategies due to the progressive scientific advances in scaffolds, biomaterials, cell therapy, and growth factors. It is a fact these tissue engineering strategies today involve the customization of the scaffolds to the bone defects and also the enrichment with living cells or growth factors, aiming at mimicking the cascades of wound healing events and the clinical outcomes of conventional autogenous grafts.

In the last decade, cone beam computed tomography (CBCT) has been introduced in oral and implant dentistry as a helpful and non-invasive device, supplying notably unique 3D imaging of hard tissues. Mozzo et al. [22] first presented it to dentists and

maxillofacial surgeons in 1998. In contrast to the traditional computed tomography (CT) generation, CBCT delivers high-resolution 3D images, ranging from 0.4 mm to as low as 0.076 mm, and at the same time, CBCT has a reduced effective radiation dose and reduced cost [23]. Studies comparing the application of 3D volumetric images to 2D images for detecting artificial bone defects revealed that CBCT achieves a sensitivity of 80–100% in detecting and classifying bone defects, whereas intraoral radiographs offer a sensitivity of 63–67%. In contrast to periapical and panoramic pictures, CBCT shows a lack of distortion and overlapping, presenting a consistency to the actual size [24]. Because of these advantages, the usage of CBCT has increased, especially within the preoperative assessment and planning of surgical approaches in complex cases in dentomaxillofacial surgery, implantology, orthodontics, and endodontics. [25]

In recent years, computer-aided design/computer-aided manufacturing (CAD/CAM) technology, facilitated by cone beam computed tomography (CBCT) datasets, has played a pivotal role in the production of personalized dental materials like polymethyl methacrylate or allogenic bone blocks [26–28]. The bone block graft material is tailored based on the digital data obtained from CBCT, ensuring a precise fit within the morphology of the alveolar defect. This customization significantly reduces the space between the block graft and the host bone, enhancing space maintenance and graft stability, and ultimately promoting a more effective and predictable regenerative outcome [29–32].

Since promising therapeutic implications could be provided by a better understanding of these mechanisms, a systematic review was performed to address the most important findings to answer the following focus question: Are 3D printed scaffolds effective in the regeneration of alveolar ridge promoting dental implant placement?

2. Materials and Methods

The current systematic review adhered to the PRISMA guidelines [33]. The research question was formulated as follows: "Do 3D printed scaffolds demonstrate effectiveness in achieving ridge preservation and/or predictable vertical and horizontal bone augmentation, ensuring successful outcomes for dental implant placement?"

2.1. Eligibility Criteria

The PICOS framework was used as the basis of inclusion and exclusion criteria, as shown in Table 1.

Table 1. The PICOS framework for inclusion and exclusion criteria.

	Inclusion Criteria	**Exclusion Criteria**
Population	Partially or completely edentulous humans.	Patients with no need for implants, animals, experimental studies.
Intervention	3D-printed scaffolds and implant placement.	No 3D-printed scaffolds and implant placement.
Comparison	No 3D scaffolds.	
Outcome	Ridge preservation, bone augmentation.	No data ridge preservation, bone augmentation.
Study design	Randomized controlled clinical trials, case-control observational studies, cohort studies, prospective controlled clinical trials.	Unsupported opinion of expert, editor's choices, replies to the author/editor, interviews, commentaries, summaries, narrative/systematic reviews, meta-analyses.

Respectively, according to the exclusion criteria, experimental in vitro studies, animal studies, editor's choices, replies to the author/editor, interviews, commentaries, books' or

conferences' abstracts, summaries, case reports, narrative reviews, systematic reviews, and meta-analyses were also excluded.

2.2. Search Strategy

Two authors searched independently and systematically in six electronic databases (PubMed, Scopus, Science Direct, Google Scholar, Web of Science, Ovid) of articles published up to 30 October 2023. The principal search strategy was ("dental implants"[MeSH Terms] OR ("dental"[All Fields] AND "implants"[All Fields]) OR "dental implants"[All Fields]) AND ("3D"[All Fields] AND ("scaffold"[All Fields] OR "scaffold s"[All Fields] OR "scaffolded"[All Fields] OR "scaffolder"[All Fields] OR "scaffolders"[All Fields] OR "scaffolding"[All Fields] OR "scaffoldings"[All Fields] OR "scaffolds"[All Fields])). No limitations were set regarding language or publication date.

2.3. Study Selection

The screening process was independently conducted, with two reviewers managing the selection based on title and abstract. Clinical trials and case series that met the inclusion criteria at each screening stage, or those with missing information, were kept for final full-text evaluation. Discrepancies between the two reviewers were discussed, and in cases where consensus could not be reached, a third review author was consulted to make the final decision.

Following the completion of full-text screening, reasons for studies not meeting eligibility requirements were documented. Subsequently, all studies that met the eligibility criteria underwent data extraction and quality assessment.

2.4. Data Extraction

Clinical and radiographic variables indicating ridge preservation and bone augmentation were set as primary outcomes.

2.5. Quality Assessment

The quality assessment of included clinical trials was conducted by two reviewers using either the revised Cochrane risk of bias assessment tool for randomized trials [34] or the Newcastle–Ottawa scale tool for cohort studies [35]. The revised Cochrane risk of bias assessment tool [34] allows for the evaluation of seven distinct domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Each domain was assessed as either low risk, high risk, or unclear risk of bias. On the other hand, the Newcastle–Ottawa scale tool for cohort studies [35] enables the evaluation of three separate domains (Selection, Comparability, and Outcome), with subsequent questions in each domain. Each question can provide one or two stars, and the final evaluation can be categorized as Good, Fair, or Poor quality based on the number of stars obtained in each domain.

3. Results

The search strategy initially identified 419 articles for screening. After eliminating duplicates, this number was reduced to 293 articles. Upon screening based on title and abstract, only 10 articles remained for the subsequent stage of the process. Screening at the full-text level resulted in just three articles [36–38], one pilot randomized clinical trial [36], one prospective case series study [37], and one case series study [38] that fulfilled all eligibility criteria. The flowchart of the screening and selection process, according to the PRISMA guidelines, is presented in Figure 1. The primary characteristics of the included articles are summarized in Table 2.

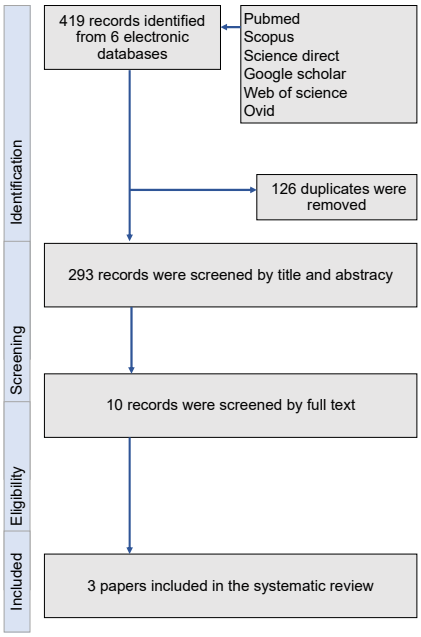

Figure 1. Flowchart of the screening and selection process, according to the PRISMA guidelines.

Table 2. Main characteristics of the included studies.

Author (Year)	Study Design	Sample	Intervention	Follow Up	Outcome Criteria	Main Results
Falisi et al. (2013) [38]	Case series	18 patients	3D scaffold for sinus augmentation and implant placement	6 and 12 months	Implant stability via RFA at day of surgery (T0), 6 months (T1), and 12 months (T2).	Implant stability was increased over time from day 1 to 12 months postsurgically.
Goh et al. (2014) [36]	RCT	13 patients	Test group: 3D scaffold for socket preservation Control group: No space filler for socket preservation	6 months	Bone resorption, implant stability via RFA, degree of radiopacity via RGS, bone regeneration via micro-CT.	Test group: Less vertical ridge resorption (Sig. dif. in the mesio-buccal aspect, P = 0.008). Less implant stability and more horizontal resorption (no sig. dif.). In both groups: Micro-CT and histological observations revealed mainly mineralized bone formation.
Mangano et al. (2014) [37]	Prospective study	10 patients	3D HA scaffolds and graft for ridge augmentation and implant placement	12 months	Presence of pain, suppuration, or exudation. Histological and histomorphometric evaluation.	Scaffolds were of satisfactory size, shape, and appearance. Good match to the defect. Easy handling. Less surgery time. Good healing of the defects.

(3D): three-dimensional; (RCT): randomized clinical trial; (HA): hydroxyapatite; (RFA): resonance frequency analysis; (RGS): radiopacity grading scale; (CT): computerized tomography; (sig. dif.): significant difference; (P): level of statistical significance.

Across all the studies, there existed notable diversity in the types of 3D scaffolds employed, as outlined in Table 3. More specifically, one study [36] used a polycaprolactone scaffold, the second one [37] used a porous hydroxyapatite block scaffold, and the third [38] combined a porcine antigen-free cartilage scaffold with collagen-based antigen-free bovine filling material. Falisi et al. [38], in their case series study, examined the effectiveness of 3D scaffolds in sinus lift procedures. They reported that implant stability increased through the follow-up period, while only two implants were lost, one due to temporary prosthesis and one due to postsurgical infection. Goh et al. [36], in their RCT study, tested the healing of fresh sockets with or without the use of polycaprolactone 3D scaffolds. No adjunct agent was applied in the test group, whereas the sockets of the control group were merely sutured in order to achieve primary closure directly after tooth extraction. They concluded that the sockets healed with 3D scaffolds showed less vertical resorption compared to the control group. Nevertheless, the horizontal resorption was more evident in the test

group combined with less implant stability. Albeit, the last data showed no statistically significant difference between the two groups. Mangano et al.'s prospective study [37] revealed that the use of 3D scaffolds contributed to good healing of bone defects following an 8-month period. In more detail, the histomorphometric measurements of bone cores after 8 months reported 34.9% (±4.2) new bone, 26.3% (±2.8) biomaterial, and 38.8% (±4.7) marrow spaces.

Table 3. Type of 3D scaffold and adjunct agents used for each included study.

Author (Year)	Type of 3D Scaffold	Adjunct
Falisi et al. (2013) [38]	Porcine antigen-free cartilage	Collagen-based antigen-free bovine bone filling material
Goh et al. (2014) [36]	PCL	-
Mangano et al. (2014) [37]	Porous HA block	-

(3D): three-dimensional; (HA): hydroxyapatite; (PCL): polycaprolactone.

A quality assessment of the included studies is presented in Tables 4 and 5 for the RCT study and the case series studies, respectively. In the included randomized clinical trial [36], the domains related to blinding of participants and personnel, and outcome assessment were characterized with a high risk of bias. Moreover, the case series studies [33,34] were both assessed as poor quality for the comparability domain.

Table 4. Risk of bias of the included studies according to the revised Cochrane risk of bias assessment tool for randomized trials.

Author (Year)	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias	Overall Bias
Goh et al. (2014) [36]	+	+	–	–	+	+	+	–

Table 5. Risk of bias of the included studies according to the Newcastle–Ottawa Scale for non-randomized clinical trials.

Author (Year)	Selection	Comparability	Outcome	Overall Evaluation
Falisi et al. (2013) [38]	⋆⋆⋆⋆	-	⋆⋆⋆	poor
Mangano et al. (2014) [37]	⋆⋆⋆	-	⋆⋆⋆	poor

Good quality: three or four stars in the selection domain AND one or two stars in the comparability domain AND two or three stars in the outcome/exposure domain. Fair quality: two stars in the selection domain AND one or two stars in the comparability domain AND two or three stars in the outcome/exposure domain. Poor quality: zero or one star in the selection domain OR zero stars in the comparability domain OR zero or one star in the outcome/exposure domain.

Conducting a meta-analysis was unfeasible due to several reasons. Not a single study included was categorized as having a low risk of bias, and there was variability in the study design, unit of observation, type of 3D scaffolds, type of adjunct biomolecule (if used), follow-up times, and outcome criteria.

4. Discussion

Bone regeneration constitutes an attractive therapeutic method for the customized treatment of bone defects following tooth extraction. The development of CAD/CAM technology can provide new options in this direction by manufacturing personalized scaffold patterns that precisely match the lesion. To the best of the authors' knowledge, this is the first systematic review aimed at evaluating the efficacy of 3D scaffolds in the bone regeneration of jaw defects in humans, ensuring adequate bone volume for dental implant placement. In this present review, we systematically evaluated only three human

studies: one randomized clinical study, one case study, and one prospective study [36–38]. Due to the relatively recent nature of this therapeutic approach, there is a limited number of clinical studies on humans that meet the pre-established inclusion criteria. In total, our results revealed that 3D-printed scaffolds are easy to handle by clinicians, can fit precisely into the defect, contribute to uneventful healing, and generally yield better outcomes in terms of ridge preservation, bone augmentation, and implant stability. Unfortunately, we encountered a high degree of heterogeneity across all domains in the included studies, including experimental protocols, study designs, and the small sample size. Furthermore, variations within humans, influenced by factors such as age, gender, overall systemic health, and biomechanical constraints, contributed to the complexity of the data.

The examination of the international literature reveals numerous published case reports on the utilization of customized CAD/CAM scaffolds for bone augmentation and dental implant placement. Tallarico et al. (2020) [39] presented a clinical case involving severe anterior maxillary atrophy in a younger female patient. The treatment comprised a titanium mesh scaffold customized using computer-aided design/computer-aided manufacturing (CAD/CAM), simultaneous implant placement, and a fully digital workflow. After an uncomplicated 4-month healing period, a second-stage surgery removed the titanium mesh. The study concluded that a fully digital approach for addressing aesthetic, complex bone defects in the anterior maxilla can yield satisfactory results. It is crucial to recognize the need for a proper learning curve and a well-trained team, given the broad applications associated with new digital technologies.

On the same note, Figliuzzi et al. [40] reported a case introducing a novel protocol for manufacturing custom-made CAD/CAM hydroxyapatite scaffolds to augment posterior mandibular bone and reduce the extent of surgery in a case of severe atrophy. At the 1-year follow-up examination, the implant-supported restorations exhibited favorable functional and aesthetic integration. In 2020, Mangano et al. [41] assessed the healing and resorption process associated with a 3D-printed Biphasic Calcium Phosphate Ceramic (BCP) scaffold in a bone augmentation procedure. The patient underwent maxillary buccal plate bone regeneration using a 3D-printed biphasic-HA block. After a 7-year period, a specimen of the regenerated bone underwent harvesting and processing for micro-CT and histomorphometric analyses. Their findings indicated that in cases where jaws remained unloaded, the microarchitecture typically resembled osteoporotic features after one year without loading. In contrast, the utilization of BCP contributed to the preservation of correct microarchitecture even after 7 years. The conclusion drawn was that BCP 3D-printed scaffolds offer a viable solution for bone regeneration, facilitating straightforward and less time-consuming surgery while promoting bone preservation.

Another notable case report by Lee et al. (2023) [42] validated successful outcomes through the utilization of particulate bone grafts placed within a 3D-printed, patient-specific polycaprolactone/bioactive glass-7 scaffold (PCL/BGS7) for augmenting the mandibular alveolar ridge with severe bone atrophy for dental implant placement. While these studies offer interim reports, they underscore the feasibility of creating anatomically shaped custom-made scaffolds through the integration of computed tomographic scans and CAD/CAM techniques. Subsequent studies are warranted to validate and build upon these initial findings.

In recent years, tissue engineering has emphasized bone reconstruction techniques employing 3D scaffolds for comprehensive biological and mechanical tissue rehabilitation [30]. The fundamental principles governing these bone grafting materials encompass low immunogenicity, bioactive behavior, and the capacity to interact seamlessly with host tissues [39]. It is imperative that the 3D scaffold not only provides temporary skeletal support until the formation of new bone tissue but also ensures structural integrity and porosity for the rapid dissemination of cells and nutrients throughout the entire structure. Additionally, the manufactured 3D scaffold must be biodegradable, eliminating the necessity for surgical removal. Simultaneously, the resorption speed rate should be slow, ensuring degradation occurs while new tissue formation is ongoing. Notably, there is

a divergence in the types of bioprinted scaffolds observed in the included studies. For instance, one study [37] utilized porous hydroxyapatite (HA) blocks. Hyaluronic acid (HA) emerges as a promising material for bioprinting applications due to its natural presence in the extracellular matrix (ECM) and distinct characteristics, including high viscoelasticity, biocompatibility, and degradability. Significantly, HA constitutes 11% of the total polymer distribution employed in bioink preparation. Nevertheless, it is crucial to acknowledge that the heightened hydrophilicity of HA may compromise the stability of its bioprinted constructs, thereby restricting its application scope [43]. Goh et al. [36] used polycaprolactone (PCL) scaffolds. PCL, a biodegradable synthetic polyester employed in bioprinting, exhibits enhanced stiffness and elasticity. It facilitates the growth of human chondrocytes, preserving their cell morphology, viability, gene expression, and matrix production potency [44]. Falisi et al. [38] used a porcine antigen-free cartilage as a 3D scaffold. This type of scaffold falls within the category of natural polymers, specifically in the subgroup of gelatins. Gelatin has proven to be highly effective in the formulation of bioink for bioprinting materials due to its distinctive properties, such as high biocompatibility, biodegradability, significant cross-linking potential, and improved thermal stability in physiological environments [45]. However, despite the extensive advantages offered by advanced fabrication techniques, bioprinting currently faces numerous obstacles and challenges that limit its wide-ranging applications. Further studies are necessary to explore and identify the ideal type for optimal functionality.

The potential to engineer anatomically accurate biomaterials holds tremendous promise for alveolar bone reconstructions. This systematic review uncovered that, across all the examined studies, a notable enhancement in bone augmentation and implant stability was observed with the utilization of multidimensional customized scaffolds. In general, each scaffold aims to mimic the natural extracellular matrix of bone tissue for a specific time period, both in terms of structure and mechanics. The limitations of all scaffolds are often associated with imaging resolution and, in most cases, inadequate mechanical properties. Moreover, the lack of cell viability for long time periods in these anatomic fields remains a problem to be solved. Subsequent investigations should leverage the insights gained from our analysis to formulate preclinical and clinical research protocols characterized by improved consistency. The combination of multiple components will result in a significant variability of materials, comprising various cell types, and an enhanced control over the delivery of bioactive agents. Future advancements may prioritize enhancing the accuracy and precision of 3D-printing development. High-resolution CT scanners will enable quantitative analysis of scaffolds and monitoring of the mineralization process. Improved CT scanners will also allow operators to thoroughly evaluate any failures and comprehend the overall micro- and macro-mechanical properties of the applied materials. Such an approach would facilitate more meaningful comparisons and enhance the overall quality of foundational data, thereby contributing to the strategic advancement of future clinical studies. In the future, enhancing custom-made scaffolds with stem cells or bioactive agents could expedite vascular invasion and promote bone regeneration.

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