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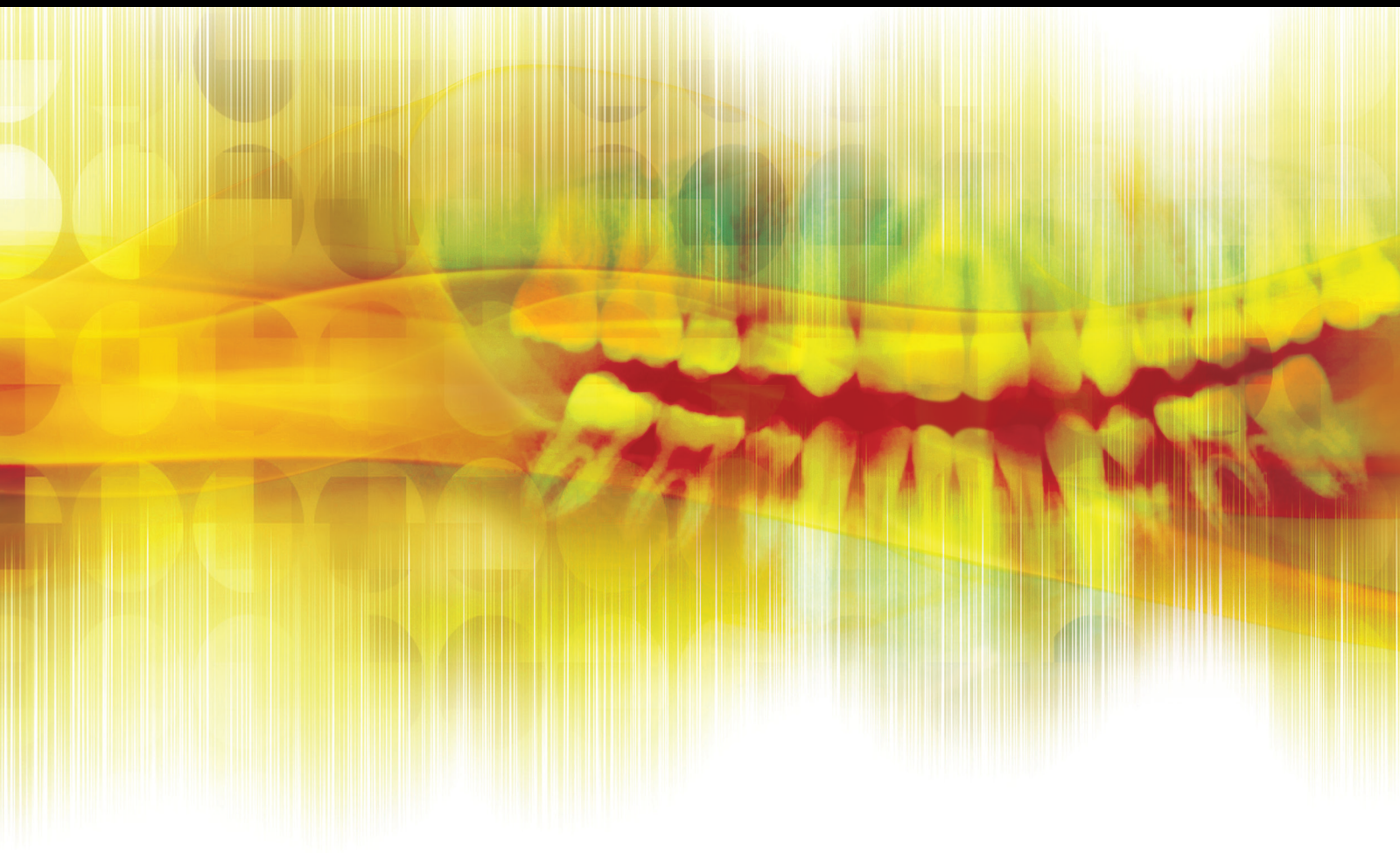

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*Review Article*

# Advances in Tissue Engineering of the Temporomandibular Joint Disc: An Overview of Current Status and Future Directions

**Ashutosh Kumar Singh**,[1] **Nikita Khanal**,[2] **and Rajib Chaulagain**[3]

[1]*Department of Oral and Maxillofacial Surgery, Tribhuvan University Teaching Hospital, Maharajgunj Medical Campus, Institute of Medicine, Kathmandu, Nepal*
[2]*Ek Ek Paila Foundation, Kathmandu, Nepal*
[3]*Department of Oral Biology, Chitwan Medical College, Bharatpur, Nepal*

Correspondence should be addressed to Ashutosh Kumar Singh; dr.ashutosh@cmsnepal.edu.np

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Advances in tissue engineering have progressed to potentially offer a solution to temporomandibular joint disc (TMJ) disorders not amenable to conservative therapies. Conclusive treatment options for patients with end-stage disc disorders requires discectomy and reconstruction of the articular disc with various materials. Tissue engineering TMJ disc is a promising alternative to the limited and sometimes inadequate clinical options in the management of such disorders. However, tissue engineering is far from completion for the TMJ disc regeneration. This review briefly discusses the properties of native disc, the mechanism by which TMJ disorders manifest, and how a tissue engineered disc could assuage the problems inherent in the management of such disorders. Furthermore, the review addresses and provides updates to relevant themes of tissue engineering in regards to the TMJ disc, namely, the scaffolds, cells and biomarkers, hurdles in tissue engineering of the disc, and its application in translation to the clinical practice and future directions.

## 1. Introduction

The temporomandibular joint (TMJ) is a synovial joint between the mandibular condyle and the glenoid fossa of the cranium. The temporomandibular disc is a fibrocartilaginous tissue with a biconcave shape that allows it to fit the bony anatomy and divide the joint into a superior and inferior compartment [1]. It is viscoelastic because of its composition of water (73%) and ground substance (glycosaminoglycans) in a thick collagen matrix, which allows it to expel and imbibe fluid during compression and relaxation, thus allowing smooth loading and unloading of the joint [2]. At the same time, it allows frictionless motion and maintains joint stability and congruity during motion. Morphologically, it has three distinct zones, where the anterior and posterior bands are thicker (4 mm) compared to the thinnest intermediate zone (1 mm) [2].

In a normally functioning TMJ, the continuous wear and tear of joint surfaces and the disc are repaired by the reparative cells present in the synovial fluids and the joint surfaces, but this intricate and delicate balance is oftentimes disrupted by unusual loading due to micro or microtrauma to the joint, the result of which is displacement, elongation, and fragmentation of the disc which bears the brunt of initial forces before it gives way and the joint surfaces are exposed to trauma [3]. Symptoms of disc disorders like clicking, pain on chewing, and difficulty opening the mouth are very common in adults around the world, and most of these are managed by noninvasive techniques like physiotherapy, diet restrictions, pharmacotherapeutic agents, splints, topical agents, lasers, and lavage [4–6]. The prevalence of TMDs has been reported to be anywhere between 6 and 93%, a majority of which is asymptomatic clicking [7–9]. The severe symptoms of trismus along with pain during mouth opening and chewing is reported by around 3–7% of patients, which

typically occurs after the disc is perforated, and there are osteoarthritic changes in the condylar head of the mandible. These severe symptoms not amenable to conservative procedures require surgical interventions, the endpoint of which is discectomy and reconstruction with one of available alloplastic or autogenous grafts [10]. Alloplasts have fallen out of favor because they fragment under load and incite foreign body reactions, so the current favorites are the local pedicled temporalis myofascial flap (TMF) [11, 12], the pedicled buccal fat pad flap (PBFP) [13], and free dermis fat graft (DFG) [14–16]. These grafts all have some lingering complications associated with them; TMF is thin, friable, and may fragment or fibrose, thus contributing to trismus and pain on function, PBFP and DFG gradually lose the transplanted fat volume, and long-term results are not available [10, 17]. Moreover, these grafts necessitate second-site surgery which may result in some donor site morbidity and complications.

Tissue engineering (TE) in its essence tries to solve the inherent problems associated with autogenous grafts, namely, donor site morbidity, the inability of autografts to be a replica of the desired tissue anatomically, morphologically and histologically, and lack of mechanical properties required to rehabilitate the organ to its prediseased functional state [18, 19]. In this brief overview, we will present the latest advances in tissue engineering, a TMJ disc implant, limitations that have hindered its development and current technologies that may assuage the current limitations. We will also discuss results from contemporary preclinical studies reporting real-world outcomes from which clinical implications, applicability in humans, and future trends of its application can be derived.

## 2. Materials and Methods

*2.1. Search Strategy.* We searched PubMed and Google Scholar with the following search algorithm: "tissue engineering" AND "temporomandibular disc. Only recent articles published after 2010 were considered to present recent advances in the field. This is a scoping review to update the scientific advancement on this topic; hence, protocol registration was not performed.

*2.2. Results.* Multiple reviews on the topic were analyzed, each reporting on different themes concerning TMJ disc tissue engineering. Recent in vitro and preclinical animal studies were analyzed which presented outcome data of in vivo TMJ disc implants generated with various materials as scaffolds, cell sources, and signaling biomarkers. These findings are presented according to these themes: scaffolds, cell sources and biomarkers, hurdles in tissue engineering of TMJ disc, and future directions.

## 3. Results

*3.1. Scaffolds.* Scaffolds are natural, synthetic, or combination structures that act as a template and carrier of cells and biosignals for the neoformation of a tissue [20, 21]. An ideal scaffold material is yet to be determined for TMJ disc TE, as various conventional scaffold materials were investigated in in vitro studies and were compromised by their limitations [22].

The first used natural scaffolds were collagen fibrous mesh which showed promising results with spontaneous extracellular matrix (ECM) and cartilage formation but was limited by foreign body reaction around the implant. Fibrin, agar, and alginate gels are used as hydrogel which exhibits excellent water retention capacity and encloses seeded cells uniformly, but lack the mechanical strength, shrink in volume, and rapidly degrade; thus, they are disqualified as an ideal scaffold material for TMJ disc TE [23–25]. Autogenous ECM-based bioscaffolds from other organs like the urinary bladder mucosa (UBM) have shown satisfactory collagen and ECM deposition and adequate function in a 6-month follow-up study; however, it lacks the mechanical properties of the native disc, and a major limitation is a difficulty in obtaining an appropriate pore size which is essential for diffusion-based differentiation of seeded cells [26].

Synthetic materials provide freedom and flexibility, as they can be modified in most parameters, processing capacity, mechanical stability, biocompatibility, biodegradability, pore size, and geometry [27, 28]. An ideal scaffold could be fine-tuned based on available biomechanical studies of the human TMJ disc based on its three-dimensional geometry, histological variations, and mechanical properties. Yet an ideal synthetic scaffold eludes for TMJ TE, not only in part of the limitations inherent in the scaffold materials themselves but also because of the complex and unique composition and biomechanics of the TMJ disc compared to other joints like the knee [29, 30]. PGA (polyglycolic acid) scaffolds can support the growth and differentiation of human umbilical cord cells. However, PGA resorbs rapidly and is mechanically weak for adequate strength. PLLA (poly-L-lactic acid) has a slower degradation rate, and studies showed that seeding with TGF-$\beta$1 results in improved mechanical properties and higher collagen and ECM deposition compared with the PGA control [27]. PLGA (poly-L-lactic-co-glycolic acid) is versatile enough for the modulation of mechanical properties; nonetheless, a study failed to show good interaction with native TMJ disc collagen [31].

A way forward to compensate for the limitations of individual scaffolds is to fabricate composite scaffolds, utilizing multiple materials, each with different desired properties, to end up with an ideal material close to the native disc [32]. A composite scaffold of natural polymers, chitosan, and alginate cross-linked with calcium chloride ($CaCl_2$) allowed cell adhesion and upregulation of fibrocartilage formation. Additionally, the composite scaffolds showed similar storage modulus and elastic response comparable to the native TMJ disc.

The combination of synthetic polymers, PLGA, and polycaprolactone (PCL) seeded with recombinant human bone morphogenetic protein 2 (rhBMP-2), connective tissue growth factor, and TGF-$\beta$3 can be 3D printed mimicking spatially distributed collagen of TMJ disc. Histologically accurate tissue similar to native TMJ disc with a full recovery of the perforated disc was observed in vivo. A study used

PCL, photopolymerized hydrogel polyethylene glycol diacrylate (PEGDA), and a combination of the two materials. The combination material showed the best results, as the slow degradation of PCL was congruent with the slow growth rate of the TMJ disc. Moreover, PCL with its relative rigidity provided adequate mechanical properties which could be advantageous during surgery, whereas PEGDA hydrogel promoted cellular adhesion and lubrication. Thus, a reduction of joint friction and the distribution of the functional load allowed by PEGDA and scaffold geometry and mechanical properties of PC demonstrated that the combination of materials could lead to a desired progress in the TMJ disc TE.

3D printing of scaffolds can achieve high precision and accuracy, with the ability to fabricate complex geometric shapes with close to native spatial cell distribution and mimic the native ECM [19, 33]. A layered fabrication process allows cells and growth factors to be included, which offers better control of desired tissue architecture. Tarafder et al. reported spatiotemporal bioprinting systems with PLGA microspheres and growth factors, seeding mesenchymal stem cells (MSCs) onto the printed scaffold with geometry and contour to a native TMJ disc [34].

In a study using nanoassembly and nanocoating technologies, titanium dioxide surface modification was implemented with TMJ disc cells which showed a proportional increment in cell proliferation and extracellular matrix (ECM) deposition with increasing thickness of nanofilms [35] layered nanoassembly with single or composite scaffold materials such as polycaprolactone (PCL) or polylactic acid (PLA) may enhance the results of the TE disc.

To bypass the complications of scaffold-based TE, the scaffold-free self-assembling process has been reported to generate a functional disc resembling the native disc which is mechanically robust [36]. However, the scaffold-free processes lack the flexibility of scaffold-based approaches like scaffold functionalization with biomolecules. Nevertheless, exogenous stimulation has shown promise with increased mechanical properties without biomolecular signaling [37]. Self-assembled scaffold-free disc implants have approached native values in mechanical properties due to the synergism of biochemical and exogenous mechanical stimuli [38, 39].

In a randomized controlled preclinical trial on interpositional TMJ discs in the black merino sheep model (TEMPOJIMS) [40], the authors compared three 3D tailored TMJ disc implants: polyglycerol sebacate (PGS) scaffold reinforced with electrospun polycaprolactone (PCL) fibers on the outer surface (PGS + PCL), PCL and polyethylene glycol diacrylate (PEGDA) (PCL + PEGDA), and PCL only. None of the implants could regenerate a new autologous disc; however, PGS + PCL was safe and was not observable in multiorgan analysis, demonstrated rapid resorption in 6 months, and prevented further condyle degenerative changes in the sheep TMJ. The PCL + PEGDA and PCL implants showed detrimental changes when compared to the discopexy controls [41]. The results reimpose that we should rather not interpose any material in the joint than to use an unsafe and unreliable material.

*3.2. Cell Sources and Growth Factors.* The success of TMJ-related tissue engineering is dependent upon selection of cell source that are utilized for seeding the scaffolds. The primary cell source in TMJ tissue engineering include autologous TMJ disc cells, articular chondrocytes, costal chondrocytes, and allogenic cells. The native TMJ disc cells have been of great interest of many researchers; however, the challenges associated with healthy tissue such as donor site morbidity and degenerative changes have also been reported [42]. Due to these reasons, other alternatives to TMJ disc cells were explored. In this instance, the use of cocultures of articular chondrocytes and meniscus cells when treated with two exogenous stimuli resulted into formation of collagen fibrils similar native tissue [43]. Further to address the issue of cell scarcity and donor site morbidity, costal chondrocytes were also utilized [44, 45]. To minimize the issue of donor site morbidity, many other options were explored such as use of nonautologous cells. However, even with the use of non-autologous cells, the problem of immunogenicity was still debatable. A ray of hope was then observed with the use of stem cells [46].

Stem cells (mesenchymal and embryonal stem cells) have been successfully used in TMJ tissue engineering. The mesenchymal stem cells (MSCs) have self-renewal property and have capacity for differentiation into various cell lineages. The MSCs have been explored to a great extent for the treatment of medical problems due to their potential role in tissue repair and reduction of inflammation [47]. They have been obtained from many sources for TMJ articular disc tissue engineering including adipose tissue, bone marrow, synovial fluid, muscle, dermis, blood, and dental pulp. Among these, the MSCs derived from TMJ were promising in TMJ tissue engineering as they were associated in repair and regeneration [46].

Notably, MSCs derived from synovial fluid and synovium have stemness trilineage differentiation, self-renewal capacity, and immunosuppressive properties [48]. Both synovial membrane and synovial fluid derived mesenchymal cells isolated from TMJs when induced to proliferate and differentiate in vitro, the cells displayed fibroblast like, spindle-shaped morphology [48]. In addition, these cells differentiated into other cell lineages such as osteogenic, chondrogenic, adipogenic, and neurogenic lineages [49–51]. The MSCs also release growth factors, cytokine, exosomes, and extracellular vesicles. These are called as "secretome" and are said to fluctuate with physiological and pathological conditions. They are said to exert the paracrine effect and also play an important role in transfer of protein, lipid, and genetic material to the recipient cells [52].

The use of type I collagen matrix isolated from rabbit tendon favored the regeneration of TMJ articular disc in rabbit [53]. In another study to observe the changes in the extracellular matrix in partial discectomized rabbit, the reconstituted collagen template favored regeneration of articular disc suggesting the role of type I and type II collagen in regeneration [54]. A unique property of cartilage is that it has limited capacity to repair and small injuries can eventually lead to progressive damage to TMJ. Hence, new approaches, such as use of biological signals, to regenerate

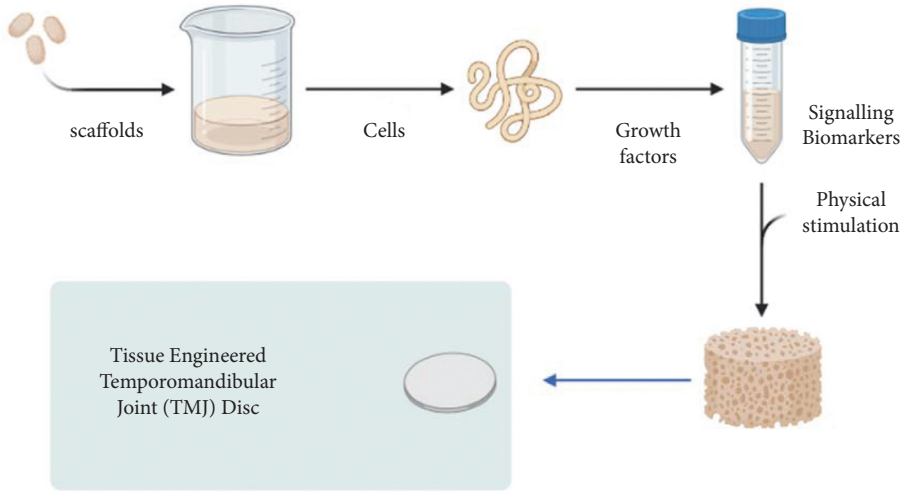


Figure 1: Steps and components of tissue engineering the TMJ disc.

and repair the injured cartilage have gained special interest. In case of TMJ tissue engineering, the potential role of biological signals is to activate signaling pathways that initiate the extracellular protein production. The prominent growth factors that regulate growth and function of introduced cells and host cells are fibroblast growth factor 2 (FGF-2), transforming growth factor $\beta$1 (TGF-$\beta$1), and insulin like growth factor (IGF) [55].

It has been well documented that laser treatment modulates cellular properties. Photobiomodulation have been used to decrease inflammation and promote wound healing. Photobiomodulation with low-level laser therapy has shown to reduce pain sensation in rats [56]. Studies using photobiomodulation and adult stem cells have shown differentiation of stem cells. Adipose-derived stem cells are component of mesenchymal cell lineage and have qualities to restore and renew tissues [57]. Using photobiomodulation, the differentiation of adipose-derived stem cells into fibroblastic and chondrogenic phenotype was shown suggesting a treatment option for degenerative joint disorders patients [58].

In addition, various growth factors such as bone morphogenetic protein 2 (BMP-2), connective tissue growth factor (CTGF), and platelet-rich plasma (PRP), epidermal growth factor, interleukin 1, and tumor necrosis factor alpha used alone or in combination with cells and/or scaffolds have a role in proliferation and production of collagen and glycosaminoglycans (GAG), and hence, they have been used to regenerate TMJ discal tissues too [31]. Among these growth factors, PRP has been widely used due to the presence of various growth factors in it [59]. In a study to explore the role of PRP, the regeneration of hyaline and fibrocartilage was higher in surgical defects treated with PRP than in the control group [60].

Apart from this, other factors such as platelet derived growth factor, epidermal growth factor, interleukin-1, and tumor necrosis factor alpha also have role in proliferation, production of collagen, and glycosaminoglycans (GAG) [61]. In a recent study, Chen et al. reported inhibition of TNF-$\alpha$/Nf-$\kappa$B promoted fibrocartilage stem cell's chondrogenic potential [62]. Kang et al. in their study reported that TGF-$\beta$1 and IGF-1 induced increase in type 1 collagen and GAG synthesis and cells proliferation [63]. In a study by Wang et al., it was observed that the concentrated growth factor leads to repair of goat TMJ. It assisted in cell proliferation and induced tissue repair [64]. Figure 1 shows the steps and components of tissue engineering the TMJ disc.

*3.3. Hurdles in Tissue Engineering of the TMJ Disc.* Scaffolding material for TMJ disc TE remains a challenge because these materials exhibit differential contraction, insufficient mechanical strengths for load-bearing, degradation of the products, stress-shielding, and material-induced immunologic responses [31]. Novel techniques like nanoassembly and nanocoating are yet to be studied in detail, and self-assembling scaffold-free approaches have yet to be studied widely in TMJ disc regeneration [27, 65]. Furthermore, preclinical studies on smaller animal models fail to scale to the size and function of human TMJ, thereby limiting the application of smaller constructs in reparative surgeries of small disc perforation and thinning, but exclude their translation to an implantable disc after a discectomy or larger defects [66, 67]. In contrast to the knee joint, a complete understanding of TMJ biomechanics is still lacking to support preclinical studies. Treatment guidelines and studies specific to TMJ should bring forward additional knowledge of TMJ to levels of other diarthrodial joints like the knee [68]. Additionally, the proximity of the TMJ to the brain is another issue where an engineered disc will have to go through stringent scrutiny compared to TE implants for the knee joint which is not closely approximated to a high-stake tissue as the brain [69]. Caution must be exercised to ensure strict safety with regards to the brain when translating the engineered implantable disc from preclinical studies to clinical applications and to not repeat the conundrum associated with alloplastic Teflon-Proplast implants of the yesteryears [70, 71]. Figure 2 shows the hurdles in developing a practically useable TE TMJ disc.

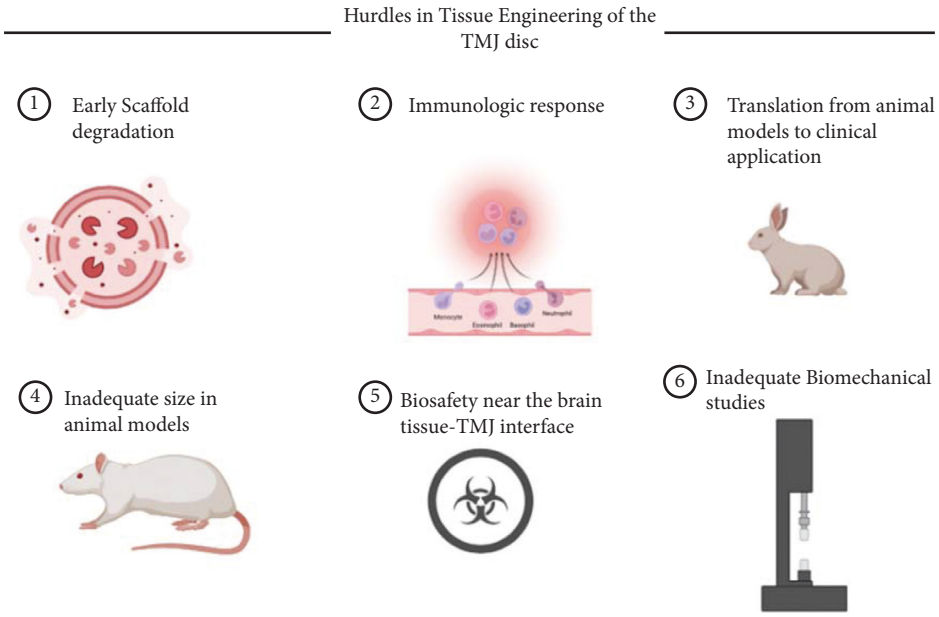


Figure 2: Hurdles in developing a practically useable TE TMJ disc.

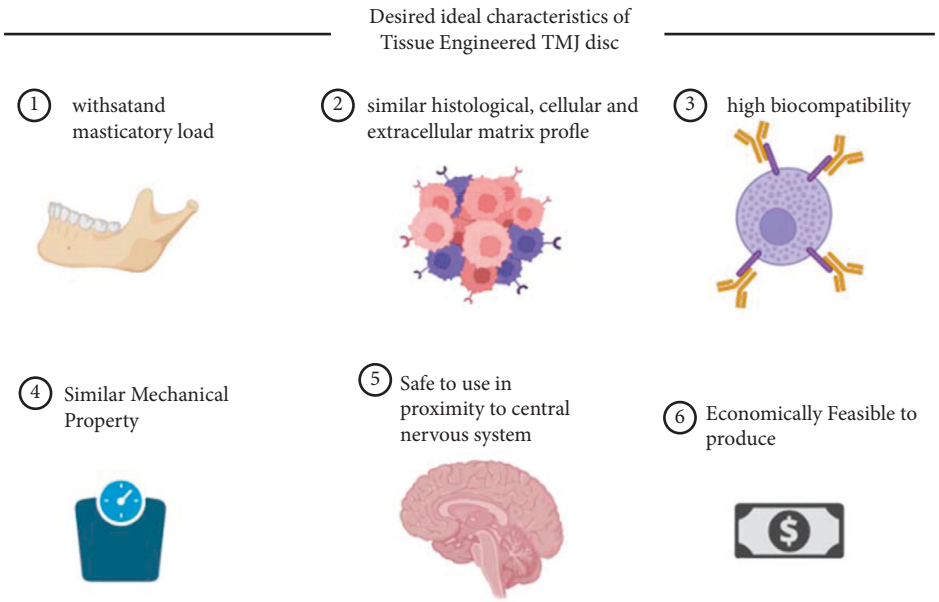


Figure 3: Ideal desired characteristics of a TE TMJ disc.

*3.4. Recent Advances and Future Directions.* In a recent study on minipigs, TE discal implants were compared to empty controls. The tissue engineered discal implants restored "disc integrity by inducing 4.4 times more complete defect closure, formed 3.4-fold stiffer repair tissue, and promoted 3.2-fold stiffer intralaminar fusion. The osteoarthritis score (indicative of degenerative changes) of the untreated group was 3.0-fold of the implant-treated group." These encouraging findings support that theoretically TE TMJ discs can one day supplant current grafts and alloplasts as the most convenient and effective treatments [72]. Bioprinting TMJ disc cells along with the ECM components representing the native TMJ disc with critical biosignaling molecules incorporated into the printed scaffolds may mimic the biomechanics and functions of the native disc. This combination of 3d bioprinting, appropriate signal markers, and exogenous mechanical stimulation could be the future in completing the advanced biomimicry required to end up with an engineered disc closer in function to the replaced disc. Self-assembling biochemical stimuli along with exogenous mechanical stimuli can be used to augment the mechanical properties of engineered discs to withstand the dynamic force in vivo. Scaling up of animal models closer to human TMJ is essential, and ensuring adequate thickness

and size of the preclinical implants in animal models is paramount. Figure 3 shows the ideal desired characteristics of a TE TMJ disc.

## 4. Conclusion

An ideal TMJ disc implant should have a few desirable properties; first, it should be able to withstand masticatory functional loads for a considerable long period or loading cycles; second, it should have a similar histological, cellular, and extracellular matrix profile, should have high biocompatibility and feasible to produce, and have familiar mechanical properties of the native disc. Current limitations of tissue engineering strategies for implantable TMJ disc analogue are not near completion; nevertheless, they represent a promising future in the disc replacement strategies for the clinicians. Safety issues related to immunologic response towards the brain tissue is critical in formulating indications for the application of TE TMJ disc in clinical practice.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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*Review Article*

# Chewing Gums as a Drug Delivery Approach for Oral Health

**Morteza Banakar**,[1,2,3] **Sedigheh Moayedi**,[4] **Erfan Shamsoddin**,[5] **Zahra Vahedi**,[6] **Mohammad Hasan Banakar**,[7] **Seyyed Mojtaba Mousavi**,[8] **Dinesh Rokaya**,[9] **and Kamran Bagheri Lankarani**[2]

[1]*Dental Research Center, Dentistry Research Institute, Tehran University of Medical Sciences, Tehran, Iran*
[2]*Health Policy Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Iran*
[3]*Department of Pediatric Dentistry, Faculty of Dentistry, Shahed University, Tehran, Iran*
[4]*Department of Orthodontics, Mashhad University of Medical Sciences, School of Dentistry, Mashhad, Iran*
[5]*Cochrane Iran Associate Centre, National Institute for Medical Research Development (NIMAD), Tehran, Iran*
[6]*School of Dentistry, Islamic Azad University Tehran Medical Sciences, Tehran, Iran*
[7]*School of Dentistry, Yasuj University of Medical Sciences, Yasuj, Iran*
[8]*Department of Chemical Engineering, National Taiwan University of Science and Technology, Taipei, Taiwan*
[9]*Department of Clinical Dentistry, Walailak University International College of Dentistry, Walailak University, Bangkok 10400, Thailand*

Correspondence should be addressed to Dinesh Rokaya; dinesh.ro@wu.ac.th

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*Background*. Drug delivery approaches with the shortest therapeutic period and the lowest side effects have always been considered a sublime target in the medical sciences. Among many delivery methods, chewing gum could be perceived as a promising drug carrier that can carry several types of drugs for oral health. These drug carriers could represent optimal therapeutic time and lower side effects due to their sustained release capability and lower required thresholds for the drug compared with other delivery approaches. The convenient use in the oral cavity's local environment and the ability to locally carry multiple drugs are considered the main advantages of this delivery approach. *Aim*. This review aimed to explore chewing gum as a promising drug carrier that can carry several types of drugs for oral health. *Materials and Methods*. Articles were searched for on PubMed, ISI, SCOPUS, Google Patents, the Royal Society of Chemistry website, and electronic databases using MESH terms and the following keywords: ("Gum" OR "Chewing gum") and ("Drug delivery OR Drug delivery systems") in the English language. No time limit was applied, and all documents as of August 30th, 2020 were retrieved. *Results*. Gum-drug interactions, mechanisms of release, and formulations of the drugs might all play a role in this versatile delivery method. Accordingly, chewing gum-based carriers may be presented as a plausible candidate for drug delivery in oral diseases. *Conclusion*. Gum-driven drugs could be introduced as promising candidates for treating oral diseases due to their ability to deliver the proper local dosages of active ingredients, short contact time, biocompatibility, and biodegradable chemical structures.

## 1. Introduction

The field of drug delivery is one of the most fascinating ones in medicine. Numerous medication delivery methods have been developed, sharing several advantages. The delivery process could make many advantages for patients, from the low period of therapy to less side effects due to their low usage dose [1]. Typically, the delivery approaches the target drug-loaded carriers and the routes for drug transmission. In recent decades, many families of carriers and their routes in the human body have been appropriately delineated and their advantages and disadvantages have been illuminated [2–4]. The polymeric and nanomaterial-based carriers with appropriate biocompatibility [5] and drug loading efficiency have attracted much attention for *in vivo* delivery in various cancer types. Noticeably, their toxicity is an issue that has

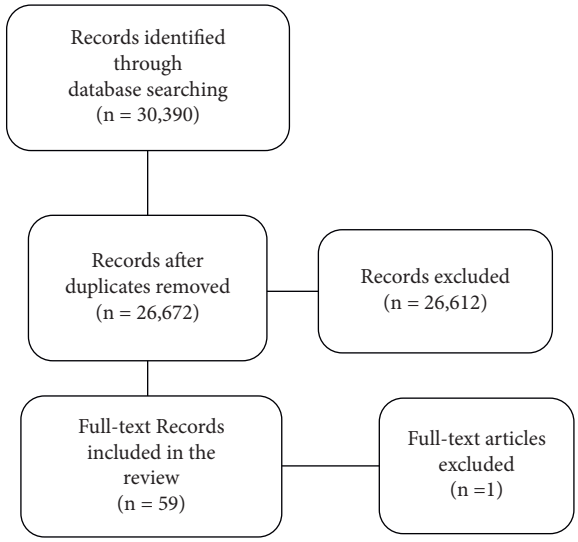


Figure 1: Study selection flow diagram.

remained in debate for many years. This challenge using delivery methods with a safe route is certainly promising [5–7]. Among the routes of administration, the oral types are attractive, mostly because of their comfortable appliances. As a result, approaches based on chewable carriers, such as drug-loaded gums and tablets, show some promise for many oral, esophageal, and GI-related diseases [8, 9]. Considering its unique characteristics, oral-based chewy delivery is highlighted as a promising candidate. Rapid onset of action, facile administration, low side effects, and appropriate local impact on oral diseases are all major factors contributing to this salience [9–11]. In this study, we discussed the characteristics of oral conditions for the effect of medications and the application of chewing gums in drug delivery for oral health. Additionally, medically applicable chewing gum types are further scrutinized in more detail.

## 2. Materials and Methods

In this narrative review, we searched PubMed, SCOPUS, Google Patents, the Royal Society of Chemistry website, and electronic databases using MESH terms and the following keywords: ("Gum" or "Chewing gum") and ("Drug delivery" OR "Drug delivery systems") with a language filter (English). No time limit was applied and all documents by August 30$^{th}$, 2020 were retrieved. We did not use other filters. All articles and patents that satisfied our selection criteria were retrieved. After omitting the duplicates, we identified 30390 papers. Three independent reviewers assessed the article titles and abstracts, applying eligibility criteria. Articles were omitted if they were deemed irrelevant based on our keyword research. We defined the following criteria for inclusion using the PICO model:

Population: There is no identifiable reference population.

Intervention: Chewing gums are a vehicle for drug delivery in clinical trials, animal studies, and in vitro investigations.

Comparison: Placebo-controlled or intra-individual pre-post comparison.

Outcome: Cavity fighters, antibiotics, antibacterial, antifungal, antiviral, antiplaque, and remineralization are some clinical effects.

References to these articles were also reviewed. Figure 1 illustrates the procedure for conducting a literature search. After removing the duplicates, 26671 papers were obtained, of which only 60 studies made it through the eligibility assessments. One study was excluded after full-text reading and was deemed irrelevant to our inclusion criteria.

This study followed the recommendations of SANRA (a scale for the quality assessment of narrative review articles) to ensure internal consistency and proper presentation of the manuscript.

## 3. Results

### 3.1. Influencing Parameters in Chewing Gum-Based Drug Delivery

*3.1.1. Saliva Flow Rate.* The accessibility of drug delivery is an essential factor in designing carriers. The oral cavity potentially provides systemic and local delivery accessibility. Saliva, a complicated multifunctional mixture that can solve the drug and delivery process's ability from the gum to the oral mucosa cells, acts as an intermediate platform. The saliva flow rate, which has been stimulated by chewing gum, has a positive impact on delivery; for instance, a study showed the beneficial effect of saliva flow on xerostomia [12]. Some reports have considered a plateau phase for saliva secretion rate while is being stimulated by chewing gum [11–13].

*3.1.2. Local Effect.* Drug molecules released into the mucosal membranes during an equilibrium that occurred in minutes could be absorbed from the oral cavity microenvironment [14]. The buccal epithelium cells with a 20-40-cell thickness and a turnover of two weeks could play a vital role in the delivery process [15]. In the oral cavity, highly vascularized mucus membranes can provide an active drug circulation in jugular veins and act as a suitable drug reservoir [14]. The results showed that clearance is better in sublingual parts than in the labial vestibule. The main reason for these observations is the difference in the anatomy of the oral cavity [16–18]. The extended delivery time in the mouth causes the appropriate drug release rate and the maintenance of drug concentration for better therapy. Additionally, the local effects of therapeutic agents could be altered by the quality of drug distribution in the oral mucosa. The residence time of sublingual tablets showed the best time activity while chewing gum was better than the lozenge [19].

*3.1.3. Contact Time.* Contact time is a significant determinant of the therapeutic period and side effects of the treatment regime. During chewing, the dissolution of ingredients occurs in the first few minutes of the process. Nevertheless, there is no standard time for chewing in general, but some case studies have suggested a 30-minute-period as a reasonable means of chewing time [20].

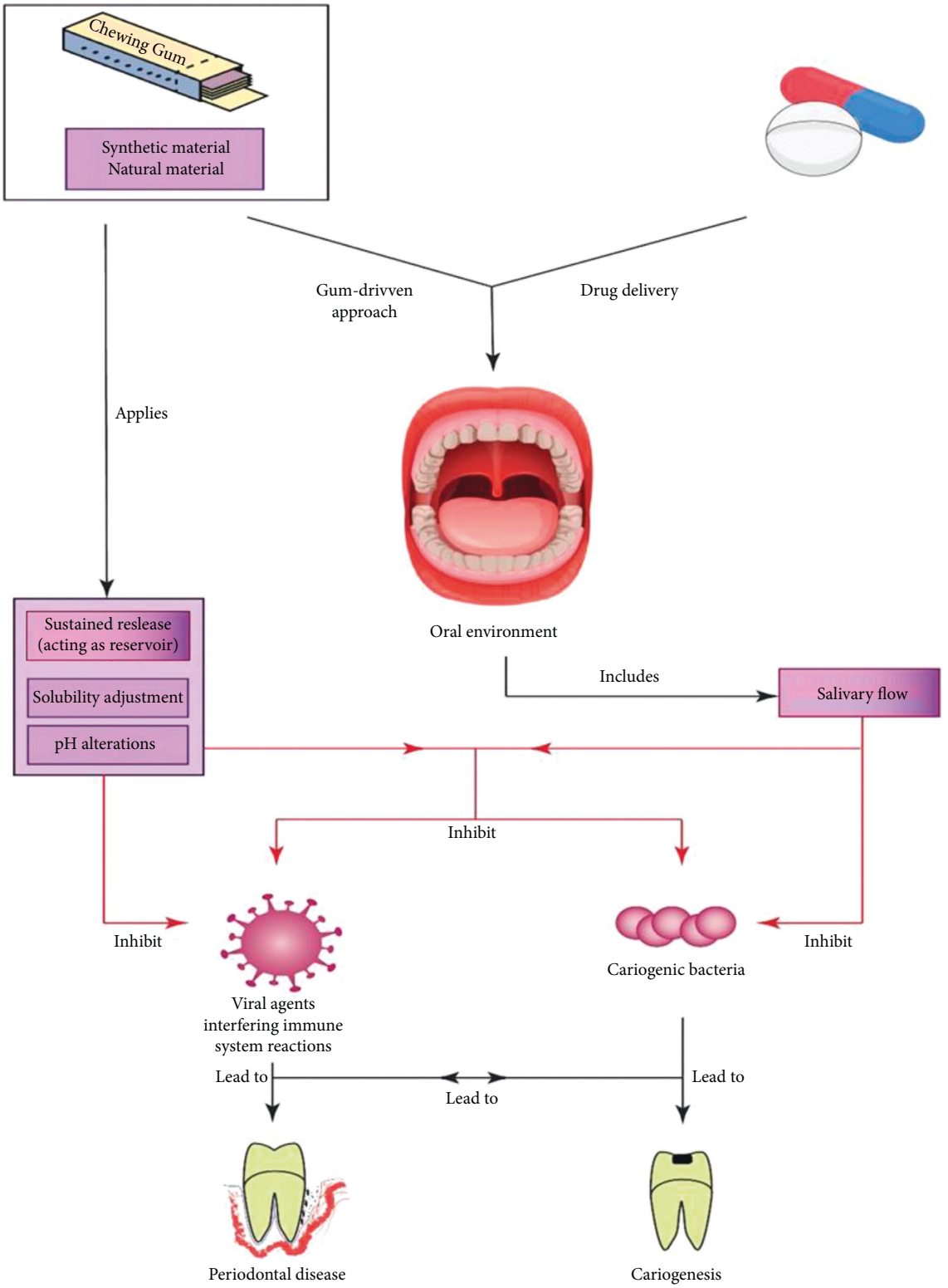


Figure 2: Schematic diagram of the gum drug delivery approach and factors affecting it.

*3.1.4. Ingredients and Formulation.* When noticing drug formulation and active ingredients, hydrophobicity, stiffness, chemical structure, and interaction types are essential. The hydrophobicity/hydrophilicity of gum influences the drug-gum interactions and reflects the quality of interactions between the drug and gum structures [21]. The hydrophilicity of carriers in delivery could be mentioned as one of the most important physical properties that potentially control the drug release rate and mechanism. Furthermore, for chewing gums, this parameter could be

impressive because the release process closely depends on the hydrophilicity state of the drug-containing carrier [22]. The cyclic oligosaccharides with dual hydrophobic and hydrophilic structures provide excellent opportunities for loading hydrophobic drugs. This could boost the drug's solubility in saliva by its hydrophilic entity. Agglomeration and encapsulation with biocompatible polymers could be other approaches to the formulation [21, 23]. The interaction between drugs and gum structures influences the release time and the mechanism of drug delivery. While water-soluble drugs need 10–15 minutes for a significant release, some lipid-soluble drugs may require more time. Finally, the pH of saliva is another important property that could greatly impact how drugs are released [21, 23]. Figure 2 shows the schematic diagram of the gum drug delivery approach and the factors affecting it.

*3.2. Chewing Gum Material Base.* Masticatory resins, which resemble chewing gum, date all the way back to the Bronze Age, some 5000 years. In Finland and Sweden, resin particles have even been found with teeth evidence [24]. Chicle from the Sapodilla tree was sold like chewing gum for the first time in 1848. In 1869, Ohio doctor William F. Semple patented chewing gum as a sweet and a medication to protect teeth. Aspergum®, the first medicated chewing gum introduced in the United States in 1924, was the first to gain acceptance as a drug delivery system through the market release of nicotine chewing gum [11, 25]. On the other hand, modern chewing gums are frequently made from synthetic resins, as opposed to the natural latex basis used by Thomas Adams, who obtained the first patent for a chewing machine to produce chicle kneaded and smoothness. In 1991, the European Communities Commission allowed the word "chewing gum" as a medicinal dosage form in guidelines [11, 26, 27].

With extensive usage in the pharmaceutical and food industries, polyol sweeteners are generally used as substitutes for sugar and alcohol. Because of their laborious metabolizing processes in the body, they could not act as a calorie source. They could be used in food and as a drug carrier when treating oral diseases. Xylitol and sorbitol have been broadly evaluated as noncariogenic gum-based materials and agents for preventing lactic acid production by bacteria in the mouth environment. Preventing lactic acid formation could decrease dental and oral diseases such as dental caries [28]. These protective results are partially attributed to the fact that chewing xylitol and sorbitol-based gums, even for five minutes per day, could significantly reduce plaques and *S. mutans* levels [29,30]. *Streptococcus mutans* could not metabolize xylitol, which could result in bacterial accumulation in intercellular spaces and competition for sucrose, a critical substrate in bacterial metabolic pathways [31–33].

Alginate-based gums are another candidate. The cross-linking process using calcium ions can control drug release profiles in these gums. Other than altering the release rate, this further could increase the interactions between the alginate and the drug [34]. Nowadays, natural and synthetic substances with significant therapeutic properties, such as xanthan, chitosan, and gellan, have been considered for chewing gum [35]. Some of these materials are listed in Table 1.

*3.3. Types of Medicaments That Can Be Used in Chewing Gums.* To date, various drugs and substances with various therapeutic properties have been introduced for use in chewing gum, some of which and their therapeutic properties are listed in Table 2. These materials based on the source are divided into synthetic and natural, which are mentioned below.

*3.3.1. Synthetic Material.* Various types of synthetic gum-driven agents have been suggested so far. The ingredients that fight cavities include Ca phosphate [36–39] and bicarbonate [40, 41]. They also include chlorhexidine [42] and copper chlorophyllin [43]. Hydrogen peroxide [44] and zinc [45] are antibacterial and antiviral agents, as are pycnogenol [46], stannous EDTA [47], sulfathiazole [11], urea [48, 49], zirconium silicate [50–52], and also fluoride [53–56]. Among these drugs, chlorhexidine, hydrogen peroxide, sulfathiazole, and zinc have more potential to be loaded in chewing gum and as an oral disease remedy [11]. Chlorhexidine was used in nanocapsules to treat dentin substrates that had been decalcified. Gum could be used as a carrier for this drug [57].

*3.3.2. Natural Material.* Some natural ingredients can be used in chewing gum with medical properties. Garlic, for instance, shows antiviral, antibacterial, and antifungal properties [58]. Ginger can also counteract respiratory viruses [59]. Oregano has powerful antiviral properties. In high concentrations, it could inactivate viral agents within one hour of exposure [60]. Lemon balm and green tea have antiviral properties and effectively against various viruses, including influenza, herpes, adenovirus, and HIV [61, 62]. Elderberry exhibits antiviral and antibacterial effects and is considered a remedy for the common cold in traditional medicine [63]. Coconut oil has also shown strong antiviral properties. It can either eradicate or inactivate harmful bacteria in the body [64]. Black walnut has antiviral, antifungal, antimalarial, and antiparasite properties [65]. Turmeric could inhibit viral replication and interfere with the virus-cell binding process [66].

*3.4. Chewing Gums as Drug Carriers for Oral Health.* Chewing gum can be used to provide a controlled dose of an active component to the mouth. Chewing gum active compounds are released in a variety of ways, depending on parameters such as chewing speed, gum base concentration, and active ingredient solubility in water, allowing them to remain in the mouth for a longer period of time. Chewing gums could transport chlorhexidine, calcium, and carbamide-based medications such as captopril, nitroglycerin, methadone, antihistamines, and antifungal-based compounds as drug carriers [67–69]. Figure 3 illustrates some of

Table 1: Carriers that can be used in chewing gum and their properties.

| Carriers | Origin/components | Properties |
|---|---|---|
| *Acacia* | Stems of tree *acacia arabica* | Antimicrobial activity |
| Alginic acid | Natural polysaccharides isolated from the brown seaweed | Antianaphylaxis effect, immunomodulatory activity, and antioxidant activity |
| Dextrin | Produced by the hydrolysis of starch and glycogen | Applications as a targetable carrier and bioadhesive |
| Gelatin | Linear anionic high molecular weight exopolysaccharide, commercially produced by microbial fermentation | Antibacterial drug delivery systems |
| Guar | Biopolymer extracted from the seeds of *Cyamopsis tetragonolobus* beans (*Leguminosae* family) | Sustained-release systems |
| Lecithin | The mixture of fats that are essential to cells, derived from sunflower seeds, eggs, or soybeans | Oral and aerosol delivery systems |
| Sodium alginate | Brown seaweeds (*Phaeophyceae*) | pH-sensitive carrier |
| Xanthan | Hydrophilic, anionic-bacterial heteropolysaccharide, derived from the fermentation of gram-negative bacteria *Xanthomonas campestris* | Antioxidant, anti-inflammatory, antibacterial, and biofilm inhibitor |
| Gellan | Exocellular polysaccharide secreted by *Pseudomonas elodea* | Anti-inflammatory |
| Rosin | Clear, pale yellow to dark amber thermoplastic resin present in oleoresins of the tree *Pinus roxburghii* and *Pinus taeda* | Film-forming, coating properties, and sustained and controlled drug release systems |
| Chitosan | Invertebrates, insects, and yeast | Antifungal, wound healing acceleration, and immune system stimulation |
| Tamarind seed polysaccharide | Galactoxyloglucan, tamarind seed polysaccharide | Noncarcinogenicity, mucoadhesive nature |
| Carrageenan | Extract from a red seaweed commonly known as Irish moss | Immunomodulatory and antioxidant activity |
| *Terminalia catappa* | *Terminalia catappa* leaves | Antimicrobial, antioxidant, anticancer, antiviral, anti-inflammatory properties |
| Pectin | Methoxyester of pectic acid derived from plant cell walls | Anticancer, immunostimulation, anti-inflammatory, antibacterial, antiadhesive effects |

Table 2: Therapeutic effects and materials used in chewing gum on oral health.

| Therapeutic effect | Material used |
|---|---|
| Analgesic | Aspirin, benzocaine, and eugenol |
| Acid neutralization | Antacid, calcium carbonate, carbamide, bicarbonate, xylitol |
| Antiplaque (biofilm control) | Chlorhexidine gluconate, eucalyptus, mastic, xylitol, sorbitol sulfonamides, neomycin, gramicidin, hydrogen peroxide, zinc, sulfathiazole, magnolia bark extract, fluoride, and propolis |
| Anticalculus formation | Vitamin C and polyphosphates |
| Antioxidant, antiseptic, and healing | Green tea and aloe vera |
| Dental caries prevention | Fluoride, calcium phosphate, bicarbonate, copper, chlorophyllin, and xylitol |
| Antibacterial agent | Chlorhexidine gluconate, sulfonamides, neomycin, gramicidin, hydrogen peroxide, zinc, sulfathiazole, fluoride, and propolis |
| Antiallergy | Cetirizine, diphenhydramine hydrochloride |
| Gingival inflammation | Green tea, amyloglucosidase combined with glucosidase, egg-white lysozyme, and rhozyme P-11 |
| Deficiency of vitamin C | Vitamin C |
| Plaque removal | Zirconium silicate, decapeptide-based antiseptic, and sodium bicarbonate |
| Dental enamel strengthening agent | Potassium aluminum sulfate, calcium, CPP-ACP, and fluoride |
| Oral candidiasis | Miconazole, nystatin |
| Periodontal disease | Sodium bicarbonate/sorbitol |
| Vincent disease | Metronidazole |
| Reduction of planktonic bacteria in saliva | Chlorhexidine, xylitol, chitosan, mastic, magnolia bark extract, and propolis |
| Mitigation in a volatile sulfur compound | Eucalyptus, zinc, and magnolia bark extract |
| Tooth stain prevention | Polyphosphates and hydrogen peroxide |

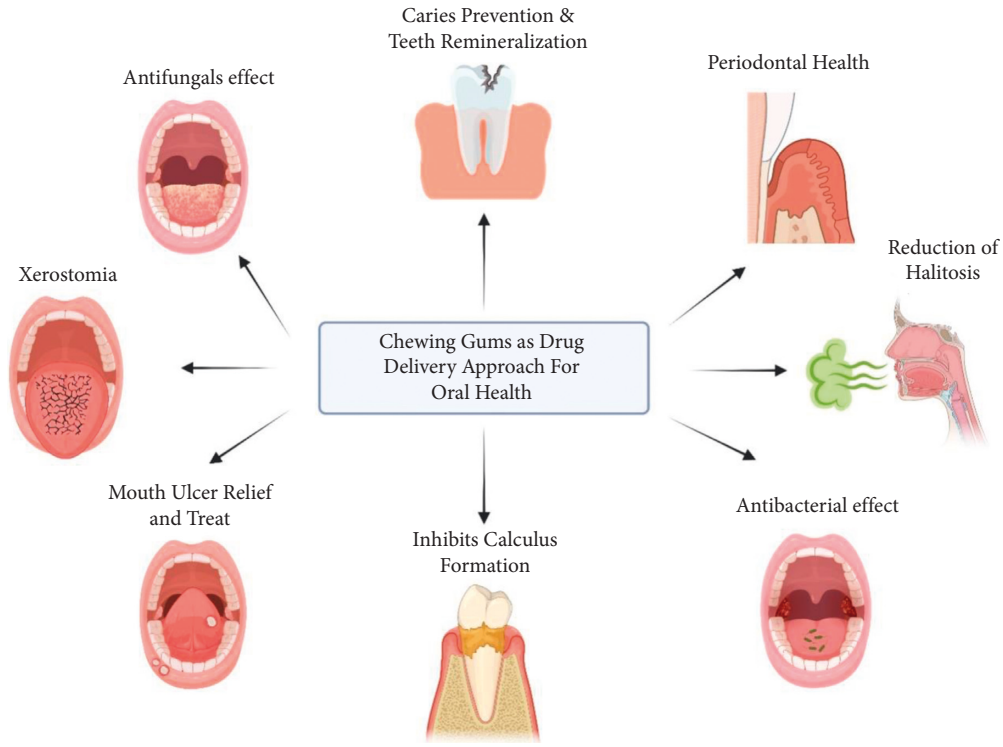


Figure 3: Chewing gums as a drug delivery approach for oral health.

the uses of chewing gum as a drug delivery approach for oral health.

Mouth dryness, also known as xerostomia, is a condition that occurs when salivary glands do not produce enough saliva to keep the mouth moist. Chewing gum has long been recognized to increase saliva production. The first five minutes of chewing generate a 10-fold increase in salivary flow over unstimulated salivation [70]. Since gum chewing has been shown to alleviate the symptoms of xerostomia in certain conditions, such as Sjogren's syndrome, various clinical experiments have been conducted to support this claim. With pilocarpine added to the chewing gum, salivary secretion can be boosted to an even greater extent. Saliva has a buffering capacity and may be able to lower the acidity of the stomach juice. Gum without active ingredients has been shown to prevent postprandial reflux in clinical trials. In order to get the most out of this, an antacid should be added to the gum.

Gum chewing stimulates the flow of saliva. Mechanical mastication is considered a key element in this boosting effect. Findings show that chewing gum could potentially decrease gingivitis and carious lesions. Additionally, calcium-containing gums could remineralize incipient caries [71]. Tooth plaques are the most critical risk factor affecting dental and periodontal health. Periodontal disease could be partly treated by sodium bicarbonate/sorbitol mixture-based gums. These types of gum could increase the pH of saliva and reduce dental plaque accumulation [72]. Patients with weakened immune systems are more likely to develop bacterial or fungal infections of the mouth. Dental and oral infections can be alleviated by chewing chlorhexidine gum. Dental plaques can be treated with chlorhexidine and decapeptide-based antiseptic gums. Chlorhexidine/xylitol-based gums have the potential to significantly lower the load of S. mutans and lactobacilli in the mouth. [73–76]. Since the harsh taste of chlorhexidine in mouthwash is easily disguised by the sweet flavor of chewing gum, it is a better choice for daily oral hygiene than a chlorhexidine mouthwash [77].

Chewing gums with antibacterial actions in the oral cavity, such as gramicidin and neomycin, are similar to sulfathiazole chewing gums. For Vincent's illnesses, metronidazole gums could substitute penicillin-loaded gums in terms of bacterial resistance. The miconazole chewing gum has been demonstrated to be at least as effective as a miconazole oral gel in treating oral candidiasis in clinical trials involving patients. In addition, patients favored chewing gum over oral gel since it was more convenient and had fewer adverse effects [78–80]. Namibian chewing gum, which contains *Diospyros lycioides,* indicates an antibacterial effect on *Streptococcus mutans* and *Streptococcus sanguis* [81, 82]. Another natural ingredient used in gum is the magnolia bark extract, which shows an antibacterial effect against *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *S. mutans* [83].

Bacterial colonization has long been claimed to be prevented by fluoride-containing chewing gums. For example, fluoride ions block the metabolism of plaque bacteria when used in a dental therapy, as might other chemicals with therapeutic applications that act locally or are absorbed through the oral and buccal capillaries. Patients with xerostomia and children in fluoride-deficient areas, as well as adults with a high incidence of dental caries, may benefit from chewing fluoride-containing gum. Adults can also benefit from its use in preventing dental cavities [53–56].

Other commercially available options include vitamin C chewing gums and tablets. Chewing vitamin C-fortified gum at least five times a day for three months reduced the production of supragingival calculus in comparison to a control gum and no chewing gum at all. Calcium phosphate deposits are thought to be reduced because of the acidic characteristics of vitamin C [84]. However, dental enamel damage due to high local vitamin C concentrations is the main drawback of these gums [85]. Chewing gum with pyro/triphosphate supplementation showed similar benefits after six weeks of use, which may be due to the calcium-sequestering activities of polyphosphates on the enamel. However, the reduction in calculus formation was only observed on supragingival surfaces [86].

Oral health is becoming more and more concerned with appearance, notably the appearance of white teeth. Stains caused by chromogens from food, drink, or smoking can be extrinsic or intrinsic, depending on the source (or calculus). Polyphosphates have been added to sugar-free chewing gums to help prevent and remove extrinsic stains. In short-term (2 days) trials, a sugar-free gum containing sodium hexametaphosphate outperformed a control gum at reducing stain formation [87, 88].

Oral malodor is caused by anaerobic gram-negative bacteria adhering to the tongue or associated with periodontitis, which produces VSCs such as hydrogen sulfide and methyl mercaptan [89]. Gums that contain active compounds that target bacteria that cause bad breath have been shown to reduce the amount of VSCs in the mouth and the amount of VSCs in the mouth. To reduce VSC levels after chewing, the zinc-allyl isothiocyanate combination works particularly well because of zinc's affinity for sulfur compounds [90, 91]. To reduce oral odor, chewing gum with the magnolia bark extract or eucalyptus essential oil has been successful when paired with zinc, which inhibits the viability of the bacteria that produce VSC [91, 92].

Probiotics (*L. reuteri, L. salivarius, and L. plantarum*) have been studied to minimize dysbiosis and maintain a balanced microbiota in the form of chewing gum. Because of the prevention of antibiotic adverse effects, probiotics are also indicated as a supportive treatment alongside scaling and root planning [93].

Minor pain treatment can benefit from the use of chewing gums as a drug delivery mechanism because of its rapid onset of action and reduced risk of digestive side effects. Up to 63% of the normal dose of acetylsalicylic acid can be delivered by chewing an acetylsalicylic gum for 15 minutes. Drug absorption rates are faster in the liquid form compared to a tablet form with the same dosage of the same medications. Toothaches could possibly be relieved faster if drugs had a faster absorption rate [94–96].

There are various limitations to using chewing gum as a medicine delivery device, including the fact that it prevents you from eating, drinking, and conversing while you have a delivery system in your mouth. Due to saliva dilution, the mouth cavity always shrinks, and the medicine secreted in saliva soon disappears as a result of the swallowing process. When it comes to the release of drugs from chewable formulations, chewing habits have been shown to have a substantial impact.

*3.5. Future Trends.* The science of using different carriers as a drug delivery system is advancing daily. Chewing gum, mousse [97], exosomes [98], and micro- and nanorobot [99] have been considered. More attempts will be made in the future to develop drugs that use chewing gum as a drug delivery mechanism. The treatment of fungal infections, prevention of cavities and other dental health problems, remineralization of teeth, cold relief, increased energy, antinausea, and a slew of other benefits of this novel drug delivery technique are all likely to play a key role in future research. Chewing gum does, in fact, take some time to gain acceptance as a method of drug delivery. Alternative delivery mechanisms for administering pharmaceuticals locally to the oral cavity may be replaced by medications incorporated into chewing gums. The reason is simple: the chewing gum administration system is convenient, easy to deliver anywhere, at any time, and its pleasant taste encourages patient compliance, particularly among children.

## 4. Conclusions

Gum-driven drugs could be introduced as promising candidates for treating oral diseases. This is due to their ability to deliver the proper local dosages of active ingredients, short contact time, biocompatibility, biodegradable chemical structures, and ability to maintain a state of eubiosis. These benefits have spurred many people to research to make a lot of different kinds of medicated chewing gum commercials.

## Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

## Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

## Authors' Contributions

Conceptualization or design of the work was done by M.B. and K.BL. Acquisition of data was carried out by E.S, K.BL., and S.M. Analysis and interpretation of data were done by M.B., SM.M., Z.V., and E.S. The draft was written by M.B., D.R., S.M, and Z.V. Revision of the manuscript for important intellectual content was done by MH.B., D.R., Z.V, M.B, K.BL, SM.M., and S.M. All authors gave final approval and agreed to be accountable for all aspects of the work.

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*Review Article*

# Bone Augmentation for Implant Placement: Recent Advances

**Van Viet Dam**,[1,2] **Hai Anh Trinh**,[1,2] **Dinesh Rokaya**,[3] **and Dinh Hai Trinh**[2]

[1]*Department of Implantology, Ha Noi National Hospital of Odonto-stomatology, Hanoi, Vietnam*
[2]*VNU School of Medicine and Pharmacy, Vietnam National University, Hanoi, Vietnam*
[3]*Walailak University International College of Dentistry, Walailak University, Bangkok 10400, Thailand*

Correspondence should be addressed to Hai Anh Trinh; trinhhaianh88@mail.ru

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There are various advancements in biomaterials and methods for bone augmentation. This article aims to review the recent advances in bone augmentation for dental implants. Relevant articles on bone augmentation for dental implants were searched in PubMed/Medline, Scopus, Google Scholar, and Science Direct published in English literature published between January 1996 and March 2021. Relevant studies on bone grafts for dental implants were included and critically analyzed in this review. Various biomaterials can be used to augment bone for implant placement. Each graft procedure has advantages and disadvantages in each clinical application and needs to choose the graft material with a high success rate and less morbidity.

## 1. Introduction

Dental aesthetics is one of the prime objectives of prosthodontic treatment. Facial aesthetics as macroaesthetics and that of peri-oral and dental tissues understood, respectively, as micro- and miniaesthetics play a fundamental role in the preliminary aesthetic and functional evaluation of the patient [1–4]. The dental implant has played an important role in oral rehabilitation, restorative dentistry, and maxilla-facial reconstruction. Currently, the use of dental implants has increased due to their high success and survival rates [5–7]. According to Straumann, approximately 10.7 million implants are placed annually all over the world [8]. Dental implants are used in the replacement of missing teeth or provide retention and support for prostheses [9, 10]. In particular, prosthetically guided approaches to implant insertion, fully digital, are currently a possible and recommended alternative [11, 12]. Composition and roughness play an important role in implant-tissue interaction and osseointegration [13–15]. But due to insufficient bone or bone defects in the maxilla and mandible, it is often difficult for implant placement. In such situations, bone grafts play a vital role in the restoration of bone.

Bone regeneration is rapidly evolving to treat various defects in the human body. There are various advancements in biomaterials and methods for bone augmentation. The outcome of the biodegradable scaffold is dependent on the interdisciplinary collaboration among clinicians, bioengineers, and materials scientists [16]. The use of different scaffold material types, stem cells, and growth factors shows promise in regenerative treatment interventions for maxillofacial defects [16–19]. This article aims to review the recent advances in bone augmentation for dental implants. Articles on bone augmentation for dental implants were searched in PubMed/Medline, Scopus, Google Scholar, and Science Direct published in English literature published between January 1996 and March 2021 (Figure 1). Relevant studies on bone grafts for dental implants were included and critically analyzed in this review.

## 2. Bone Grafts and Their Types

Biomaterials are natural or synthetic substances and help to repair, augment, or replace any tissue or organ of the body [20, 21]. Bone grafts are the type of biomaterials that are used to substitute bone defects and recover atrophic bone regions

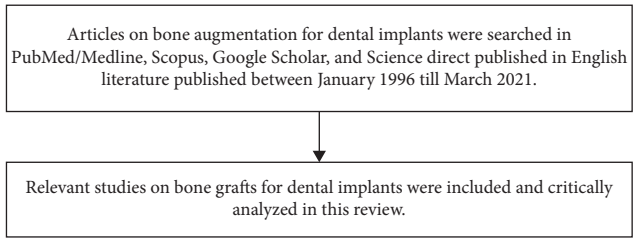


Figure 1: Schematic diagram of the method for the selection of articles.

[22]. They are major components in maxillofacial surgery and implantology. A bone graft is also needed for 1 of every 4 implants [23]. They are generally used as scaffolds and fillers to accelerate bone augmentation as they act as a reservoir for new bone formation. They are bioresorbable with no antigen-antibody reaction [24, 25]. It is important to have a clear and detailed understanding of the fundamentals in regenerative science for successful outcomes in bone grafting [26].

Different bone grafts are used in clinical practice, and the classifications are based on composition, physical properties, and other parameters [4]. Classification of bone grafts based on composition is shown in Table 1 [27] which are based on allograft, factor, cell, ceramic, and polymer. Above gone grafts can be used alone or in combination with other grafts. The chronological classification divides the bone substitutes into 5 divisions: xenograft, allograft, and autogenic bone; allogenic bone; natural bone matrix containing growth factors; tissue-engineered; and gene-activated bone grafts [28]. Autogenous bone is regarded as the gold standard because of its biocompatibility, osteoconductive, osteoinductive, and osteogenic properties [28–33].

## 3. Fibula Free Flap and Iliac Crest Flap

Segmental or partial mandibular defects from trauma or resective surgery result in various degrees of skin, mucosa, or soft tissue loss [34]. The use of free bone flaps such as the fibula, iliac crest, and scapula has revolutionized the maxillofacial rehabilitation in extensive mandibular defects [35]. Well-vascularized bone with soft tissues is used in repairing and reconstructing maxilla-mandibular defects achieving morphological and functional goals [36]. Ideally, the ideal flap should be vascularized bone with adequate height and length that can be shaped to match the original mandible.

Figure 2 shows the rehabilitation of mandibular defects with a fibula graft in a female patient following the resection of ameloblastoma. A fibula free flap (FFF) was done to restore the bone defect and receive the prostheses. The advantages of FFF for the reconstruction of the mandible include an adequate length of bone, the possibility of using a skin paddle, and donor site low morbidity [35]. However, the disadvantage is that it is difficult to reconstruct large soft tissue defects and reduction of bone vascularization following many osteotomies.

In a clinical study by Yilmaz et al. [34], they performed 37 mandibular reconstructions involving skin and/or mucosa: 16 out of 24 patients with iliac crest flap and 3 out of 13 patients with FFF. They found that FFF showed better oral continence, aesthetic facial appearance, and social activities with less complication rate compared to the iliac crest flap.

Lonie et al. [37] did a systematic review of iliac free flaps versus FFFs for mandibular defect reconstruction. There was a significant delay in healing and breakdown of the suture line in the iliac flap group but higher donor site complications in FFF. Osseointegrated dental implant loss in FFF (5.3%) was higher than in iliac flaps (1.7%). The flap loss in FFF and the iliac free flap showed no significant difference. Although they concluded that both iliac free flaps and FFF can be considered in the reconstruction of the mandible, the iliac crest can be considered as the 1st choice for the reconstruction of the body or angle defects in the mandible or defects needing greater thickness of soft tissue, whereas the FFF can be considered as the 1st choice when the bony length is essential as in the case of total or subtotal mandibulectomy.

In addition, a mandibular reconstruction should support the dental implants for total prosthetic rehabilitation [34, 38]. Vascularized fibula grafts are appropriate primary and secondary implantation for prosthetic restoration of the mandibular defects [39, 40]. Wei et al. [40] mentioned that inserting dental implants after some months following mandibular reconstruction using vascularized bone grafts is successful. Hypothetically, primary placement of implants in the mandible presents higher success in a shorter period in oral rehabilitation. Still, the success of a dental implant depends on the condition of the mandible and the history of radiotherapy. In addition, soft tissue and bone needs, the use of implants, and several surgeries are important for the planning.

The FFF contains thick cortical bone with a fatty marrow, but the marrow limits bone stock. Recently, bone-impacted FFF (BIFFF), a novel technique, has been used in which the autologous bone is compacted into the FFF marrow space which increases the density of implant site for the dental implant and this increases the long-term success rate of a dental implant with no or less risk of complications [41, 42]. In addition, bone marrow can be centrifuged to generate mesenchymal stem cell concentrates for better osseointegration. Furthermore, in vitro culture can produce progenitor cells [43]. In maxillofacial rehabilitation, both the iliac crest and FFF are commonly used to harvest bone for a dental implant or the reconstruction of jaw defects [22].

The bone grafts can be ordinary or activated as shown in Figure 3 based on their composition and biological effects. The osteoinductivity and osteogenicity of activated osteoplastic biomaterials allow the replacement of large bone defects.

## 4. Combination of Bone Grafts

The combination of autogenous bone graft with deproteinized bovine bone has shown better results because of its osteogenic property [44–48]. Kim et al. [24] assessed the bone formation and stability of grafts with autogenous bone and Bio-Oss at different amounts in rabbit calvaria. They concluded that the Bio-Oss either alone or with the 25%

Table 1: Classification of bone grafts based on the composition.

| SN | Types of bone graft | Description and examples |
|---|---|---|
| 1 | Allograft based | Allograft bone, such as grafton and orthoblast |
| 2 | Factor based | Natural and recombinant growth factors, such as transforming growth factor-beta (TGF-beta), platelet-derived growth factor (PDGF), bone morphogenic protein (BMP), and fibroblast growth factors (FGF) |
| 3 | Cell based | Cells generate new tissue, such as mesenchymal stem cells |
| 4 | Ceramic based | Calcium phosphate, calcium sulphate, and bioglass, such as Osteograf, Osteoset, and Proosteon |
| 5 | Polymer based | Biodegradable and nondegradable polymers, such as open porosity polylactic acid polymer |

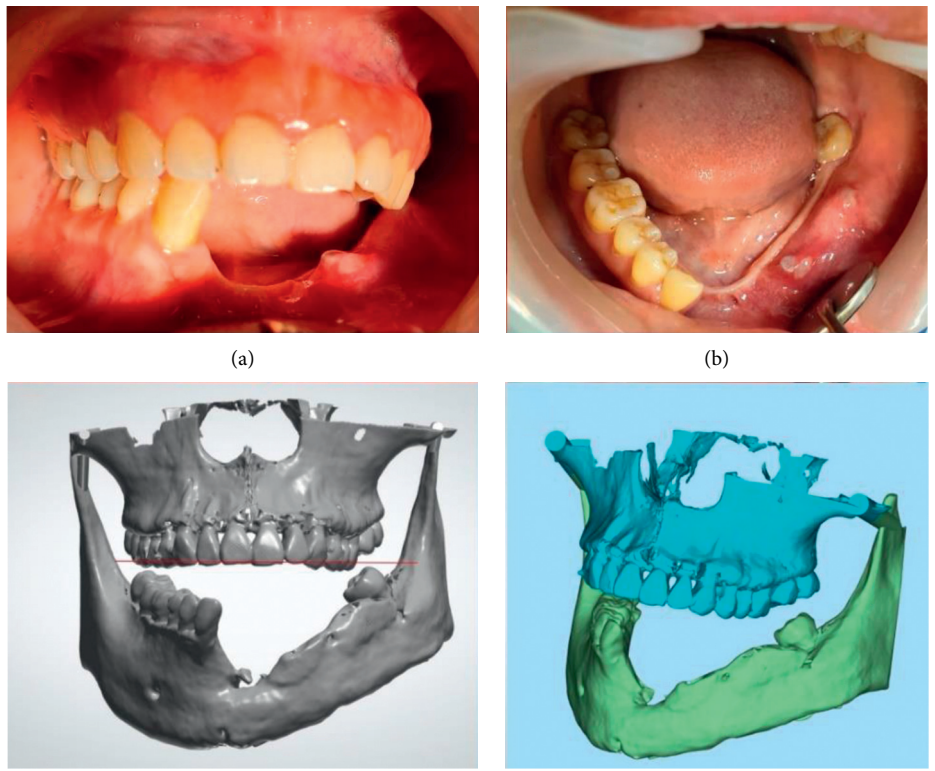


Figure 2: Fibula free flap in the mandibular arch: clinical pictures (a, b) and 3D views (c, d).

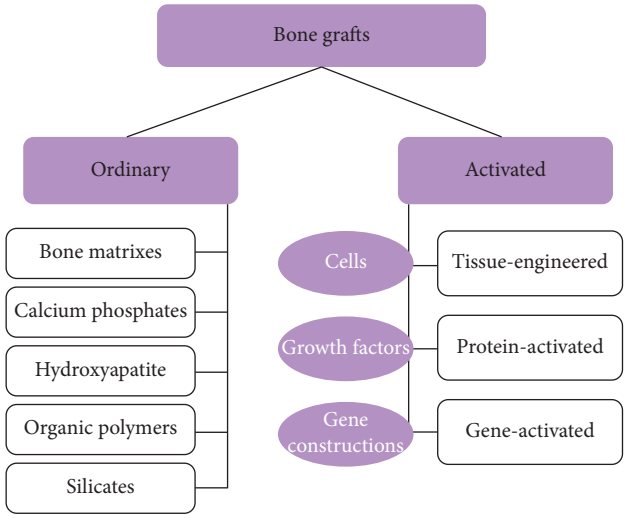


Figure 3: Types of ordinary or activated bone grafts [22].

autogenous bone showed better stability compared to autogenous bone alone. Similarly, another study [29] compared the histology of bone filled with Bio-Oss, PerioGlas, or Ostim-Paste in the rabbit tibiae defect. They found that the implants placed in all 3 grafting materials presented better osseointegration due to osteoconductive because of the formation of the mineralized bone bridge extending from the cortical plate to the surface of the implant compared to the nongrafted bone.

Thuaksuban et al. [47] compared the clinical outcomes of composite autogenous bone + deproteinized bone from bovine and autogenous bone alone to repair a cleft palate. Group I consisted of autogenous cancellous bone grafts harvested from the anterior iliac crests. Group II consisted of a composite of deproteinized bovine bone and autogenous cancellous bone (1 : 1 proportion by volume). The operation time, blood loss, postoperative pain, hospital stay, and recovery time were more in Group I than in Group II.

Table 2: Various growth factors used with bone grafts.

| Growth factor | Main constituent | Producer |
|---|---|---|
| Emdogain | Enamel matrix proteins | Straumann, Germany |
| OP-1 | Recombinant BMP-7 | Stryker Biotech, USA |
| Infuse | Recombinant BMP-2 | Medtronic, USA |
| GEM21S | Bone graft with recombinant PDGF-BB | BioMimetic Therapeutics Inc., USA |
| i-Factor putty | Protein P-15 (ligand for integrins $\alpha 2\beta 1$) | Cerapedalloics, USA |

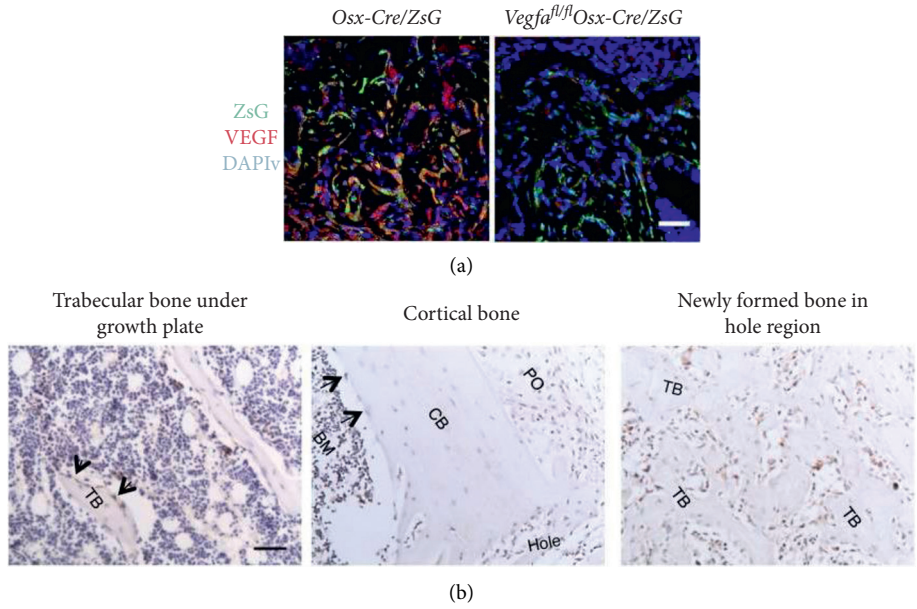


Figure 4: Osteoblastic lineage cells at the bone-repair site as a source of VEGF at postsurgery day 7 in WT mice. (a) A low density of anti-VEGF staining (red) in $Vegfa^{fl/fl}$ Osx-Cre/ZsG mice (6.1%) compared with Osx-Cre/ZsG mice (15.5%). (b) VEGF in cortical bone, trabecular bone, and the newly formed bone within cortical defects. Black arrows show the VEGF-expressing osteoblast lining. TB = trabecular bone and CB = endosteum of cortical bone [52].

Various materials and techniques are being used to create the structural base of osseous tissue to support dental implants. Aghaloo and Moy [33] did a systematic review to identify the successful technique to provide the alveolar bone for the success of the dental implant. They mentioned that the bone augmentation in the alveolar ridge is technique-sensitive and does not have detailed documentation or long-term follow-up studies, except for GBR.

## 5. Bone Grafts Containing Growth Factors

At present, bone grafts with scaffold and growth factors can provide a successful osteoinductive effect. Such various products for clinical use are shown in Table 2 [22].

Various bone substitutes with growth factors are being developed such as recombinant BMP-2 [49, 50] or VEGF [51, 52]. The osteoblastic lineage cells are an important source of VEGF at the bone-repair site (Figure 4).

The combination of bone substitutes with growth factors with several factors such as angiogenic and osteogenic in the scaffold, for example, VEGF and BMP-2, [53] causes a prolonged release of therapeutic proteins from the matrix with biodegradation [54, 55] or the growth factors' encapsulation into polymer microspheres [56]. The structure of growth factors can be changed using site-directed mutagenesis creating "mutant" molecules causing osteogenesis. Kasten et al. modified the differentiation factor-5 (GDF-5) by binding BMP-2 with specific receptors in its sequence and the GDF-5 molecule showed the properties typical of BMP-2 [57, 58]. Their action is long term than the bone substitutes with growth factors due to the expression of gene constructions being delivered to target cells.

## 6. Gene-Activated Bone Grafts

The active agent of gene-activated grafts is nucleic acids, and they are directly related to gene therapy, such as gene-therapeutic drugs [22]. In addition, gene-activated bone substitute is combined using chemical binding, adjuvants, or fusion of nucleic acids into the graft scaffold [59]. The efficacy of these products is determined by the osteoinduction by gene construction and osteoconduction by scaffold.

There are 2 stages in the osteoinductive action of gene-activated bone grafts: specific and nonspecific. The specific

action contains protein regulatory molecules produced by transfected cells which act as bioreactors of therapeutic proteins. The nonspecific action is associated with the release of nucleic acids from the graft scaffold, delivery to the cells, and expression. The gene-activated bone graft presents significantly higher efficacy compared to the substitutes containing growth factors [60].

## 7. Limitations and Future Perspectives

Bone grafts have certain shortcomings, especially which have growth factors. Firstly, protein molecules in the body undergo rapid biodegradation from exudation and proteolytic enzymes limiting their osteoinductive action [22]. Second, the therapeutic protein acts short term, and it is difficult for controlled release. In addition, newer technologies such as growth factors using recombinant growth factors also have limitations in using such biomaterials in surgery for early release in wound healing. Another emerging technique for the delivery of growth factors is gene therapy [61], where genetic material is transferred into the genome to produce specific action through a functional protein, such as BMP. The biodegradable scaffolds are developed to maintain space to promote vascular ingrowth, and cell adhesion [43]. Various techniques can be used to study the bone structures, such as cell staining, infrared absorption spectroscopy, and CBCT [52, 62–65]. In addition, it is important to consider technological evolution to reduce the damage and side effects of necessary diagnostic tests. This can be done by specifying the difference between radiation-free and non-radiation in evaluating the effects [66]. The use of ultrasound in dentistry can represent a radiation-free alternative to the other most used exams.

Similarly, digital technologies are at the forefront for integrating 3D and 4D printing with other technologies that can be applied in implant dentistry. A CBCT of the jaw can produce virtual planning of the reconstruction using software and can produce a 3D model of the jaw for reconstruction [62, 63]. Furthermore, allogeneic graft and xenograft block bone grafts may be milled to make custom-fit [67]. In addition, custom-made resorbable scaffolds or custom titanium meshes can be fabricated containing growth factor-enhanced grafts routinely using a 3D printer [43, 68].

## 8. Conclusion

There are various advancements in biomaterials and methods for bone augmentation. Various biomaterials can be used to augment bone for implant placement. No single biomaterial or clinical technique is ideal, and the clinicians need to decide the suitable approach which can provide suitable results with less complication. Each graft procedure has advantages and disadvantages and should use the material with a high success rate and less morbidity. The use of different scaffold material types, stem cells, and growth factors show promise in regenerative treatment interventions for maxillofacial defects.

## Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

## Conflicts of Interest

The authors declare no conflicts of interest.

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*Research Article*

# Quantitative Fit Test of a 3D Printed Frame Fitted Over a Surgical Mask: An Alternative Option to N95 Respirator

**Suchada Kongkiatkamon**,[1] **Norachai Wongkornchaowalit**,[1] **Valailuck Kiatthanakorn**,[1] **Somkiat Tonphu**,[2] **and Chaiyos Kunanusont**[2]

[1]*Bangkok Hospital Dental Center, Bangkok Hospital, Bangkok 10310, Thailand*
[2]*Bangkok Health Research Center (BHRC), Bangkok Dusit Medical Services Public Company Limited (BDMS), Bangkok, Thailand*

Correspondence should be addressed to Suchada Kongkiatkamon; suchada.kongkiatkamon@gmail.com

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*Background*. COVID-19 has spread worldwide and caused severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) led to numerous dead cases. However, with the new COVID-19 outbreaks, there is a shortage of personal protective equipment (PPE) especially N95 masks worldwide including Thailand. This issue had placed the health professional in great need of an alternative mask. *Aim*. This study aimed to measure the fit factor of 3D printed frames by quantitative fit testing (QNFT) to find an alternative facemask by using a mask fitter together with 2 different kinds of the American Society for Testing and Materials (ASTM) level 1 surgical mask. *Materials and Methods*. Two commonly used surgical masks (Sultan Com-Fit Super Sensitive Ear Loop Mask or "White Mask Group," not water-resistant, and Sultan Blue Com-Fit Super High Filtration Ear Loop Mask or "Blue Mask Group," water-resistant) with and without 3D printed frame covering. The fit performance was measured by a quantitative fit test (QNFT) device (PortaCount, model 8048, TSI Incorporated, Minnesota, USA) accepted by the Occupational Safety and Health Administration (OSHA). The PortaCount device, which is based on a miniature continuous flow condensation nucleus counter (CNC), assesses the respiratory fit by comparing the concentration of ambient dust particles outside the surgical mask to the concentration that has leaked into the surgical mask. The ratio of these two concentrations ($C_{out}/C_{in}$) is called the fit factor. A fit factor of a 3D printed frame of at least 100 is required and considered as a pass level. *Results*. We found that the mask fitter improves the overall performance of surgical masks significantly. The improved performance is comparable to that of N95. *Conclusion*. The mask fitter improves the performance of surgical masks. The authors suggested that further study on frame material, shape, and expanded sample size would be beneficial to society.

## 1. Introduction

COVID-19 is considered a pandemic disease in this era and rapidly spread worldwide, causing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and numerous dead cases [1, 2]. The spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurs mainly via respiratory droplets [3, 4]. During dental treatment procedures, many droplets and aerosols are generated, and the standard protective measures are not effective enough to prevent the spread of COVID-19 in dental clinics and hospitals [3, 5, 6].

One of the essential personal protective equipment (PPE) for healthcare practitioners is respiratory protective equipment (RPE) [7]. The standard surgical face mask is one of the RPE designed to protect the nasal and oral mucosa from splashes and droplets. Even though the filter efficiency test is carried out and evaluated by the manufacturers according to the FDA regulations, the fit performance plays a great role that we should not ignore.

Because the surgical mask fits loosely to the wearer's face, perimeter leakage during the procedure may carry aerosol particles from dental aerosol-generating procedures. A total

of 10% to 40% of particles penetrate the facial seal as a result of poor fit [8]. Since it is found that the coronavirus can survive in the air for hours, the World Health Organization (WHO) and the United States Centers for Disease Control and Prevention (US CDC) recommended a new "airborne precaution" for medical professionals [7]. Thus, only filtration performance is not enough to protect the clinical practitioners from airborne substances, and a respiratory protective device should have high filtration efficiency with sufficient fit as well.

However, with the new COVID-19 outbreaks, there is a shortage of PPE especially N95 masks worldwide including Thailand. This issue had placed the health professional in great need of an alternative mask. The research also shows that the effectiveness of N95 is sometimes not different from that of a surgical mask [9].

Recently, the Bellus3D team has been collaborating with the researcher at Loma Linda University School of Dentistry to develop a mask fitter by simply performing a 3D facial scan by using an application such as Bellus3D Face App and Bellus3D Dental Pro [10]. From the facial scan, a customized mask fitter is designed and can be printed easily from a 3D printer. The covering of a customized mask fitter is designed to improve the peripheral seal of the surgical mask. The fit performance was qualitatively tested by comparing the American Society for Testing and Materials (ASTM) level 1, 2, and 3 surgical masks to N95 ASTM F2100-11 (2011) [11]. They found that ASTM level 2 and 3 masks with the personalized frame had a better seal and prevented the aromatics from being detected inside the mask.

This study aimed to test the fit factor of a 3D printed frame by quantitative fit testing (QNFT) to find an alternative facemask by using a mask fitter together with 2 different kinds of ASTM level 1 surgical masks.

## 2. Materials and Methods

Five dentists ranging in age from 37 to 55 years were recruited in this study to test the two commonly used surgical masks (Sultan Com-Fit Super Sensitive Ear Loop Mask or "White Mask Group," not water-resistant and Sultan Blue Com-Fit Super High Filtration Ear Loop Mask or "Blue Mask Group," water-resistant) with and without 3D printed frame covering. The fit performance was measured by a quantitative fit test (QNFT) device (PortaCount, model 8048, TSI Incorporated, Minnesota, USA) accepted by the Occupational Safety and Health Administration (OSHA) [12]. The PortaCount device (Figure 1), which is based on a miniature continuous flow condensation nucleus counter (CNC), assesses the respiratory fit by comparing the concentration of ambient dust particles outside the surgical mask to the concentration that has leaked into the surgical mask [13]. The ratio of these two concentrations ($C_{out}/C_{in}$) is called the fit factor [8, 13]. A fit factor of at least 100 is required and is considered as a pass level. The 3D facial scan and designed mask fitter from Bellus3D Face App and Bellus3D Dental Pro. Similarly, we used polylactic acid (PLA) following the Bellus3D recommendation.

The adaptor is attached to one side of the surgical mask then connect the tube from PortaCount to the adaptor port. Subjects performed 2 minutes and 29 seconds of exercises in the bending over position, talking, head side-to-side position, and head up-and-down position (Table 1) in a 25°C air-conditioned room. The QNFT was performed in three groups: blue mask, blue mask with a frame, and white mask with a frame.

## 3. Results

Although the five testers were different in terms of age and gender, we found a consistent improvement in terms of fit factors when face frames were applied. The type of mask also played an important role in passing the 100 fit factor threshold (Figure 2 and Table 2). Only when a blue mask (water-resistant) was used with a face frame, fit factors were above the 100 thresholds. On the contrary, when either (a) a blue mask (water-resistant) without a face frame was tested, or (b) a white mask (not water-resistant) was used with a face frame, fit factors were below 100.

## 4. Discussion

Medical and dental practices are severely affected by COVID-19 [14, 15]. Due to the shortages or limited PPE especially N95, leaving doctors, nurses, and other frontline workers dangerously ill-equipped to care for COVID-19 patients, a reusable PPE-like facemask was recommended. In addition, people are psychologically affected from COVID-19 [16, 17].

There has also been discussion about the reuse of N95 respirators after sterilization with ionizing radiation, UV, or heat. Following sterilization, it can cause in decline in their filtering efficiency due to damage to the respirators [18]. Disposable N95 masks pass the qualitative fit-test but have decreased filtration efficiency after cobalt-60 gamma irradiation [19]. Ideally, healthcare workers in true need of N95 respirators should be using them as they are designed and disposing of them when appropriate.

Quantitative fit tests are considered valid measures and normally tested in tight-fitting respirators; however, the same principle is applied to measure the fit performance of surgical masks and surgical masks covered with mask fitter in this study [20, 21]. Even if the mask fitter tightens the surgical mask, the user-seal-check may be unreliable for detecting leakage. In some cases, users reported that the respirator fitted well, but the fit factor was very low, and the overall quantitative fit test failed [22]. Thus, the leakage between the face and the respirator is not easily detected by the user. The QNFT is the gold standard used to determine this fit objectively. In this study, the authors tested the fit factor by QNFT PortaCount to find an alternative facemask by using a mask fitter together with 2 different kinds of ASTM level 1 surgical masks.

In this study, the customized 3D printed mask fitter improves the quantitative fit performance of the surgical mask. But differences can be seen between groups 1 and 2. Group 1 (Sultan Com-Fit Super Sensitive Ear Loop Mask or

(a) (b)

Figure 1: PortaCount and Face Frame. (a) PortaCount respirator fit tester, (b) 3D facial scan, and designed mask fitter from Bellus3D Face App and Bellus3D Dental Pro.

Table 1: Modified ambient aerosol CNC quantitative fit testing (PortaCount) protocol for filtering facepiece respirators [12].

| Exercises | Exercise procedure | Measurement procedure | Duration (seconds) |
|---|---|---|---|
| Bending over | The test subject shall bend at the waist as if going to touch his/her toes for 50 sec and inhale 2 times at the bottom | A 20-sec ambient sample, followed by a 30-sec mask sample | 50 |
| Talking | The test subject shall talk out loud, slowly and loud enough to be heard clearly by the test conductor for 30 sec. He/she will either read from a prepared text such as the rainbow passage, count backward from 100, or recite a memorized poem or song | A 30-sec mask sample | 30 |
| Head side-to-side | The test subject shall stand in place, slowly turning his/her head from side-to-side for 30 sec and inhale 2 times at each extreme | A 30-sec mask sample | 30 |
| Head up-and-down | The test subject shall stand in place, slowly moving his/her head up and down for 39 sec and inhale 2 times at each extreme | A 30-sec mask sample followed by a 9-sec ambient sample | 39 |
| | Total duration | | 2 min and 29 sec |

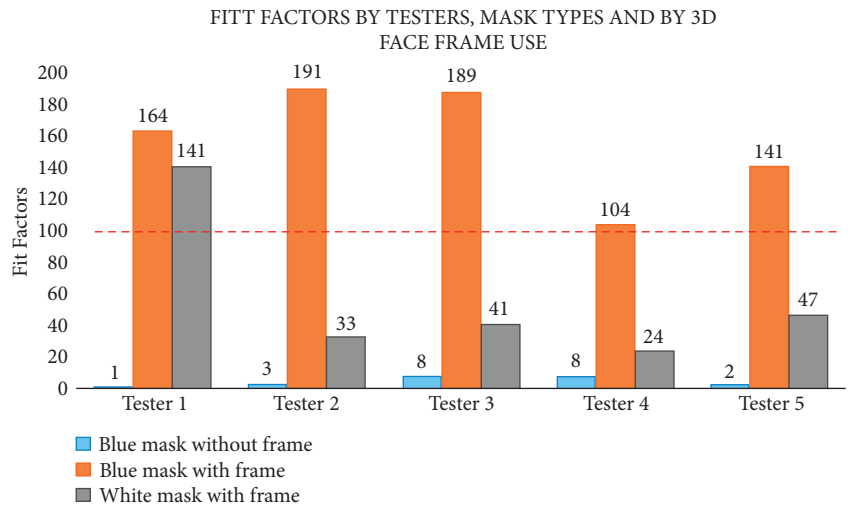


Figure 2: Summarized quantitative fit test results with interpretation. Describe "Head Tilt" results specifically for dentists—(5/5 tests) passed.

"White Mask Group") is the ASTM mask level 1 in white color which the outer facing is made of polypropylene and an aluminum strip was incorporated at the nose piece. However, group 2 (Sultan Blue Com-Fit Super High Filtration Ear Loop Mask or "Blue Mask Group") is the ASTM mask level 1 in blue color which the outer facing is a double layer (fractured film and cellulose) and aluminum with synthetic foam support was incorporated at the nose

Table 2: Quantitative fit factors by testers and types of masks and framing.

| SN | Mask type | Tester | Fit factor |
|---|---|---|---|
| 1 | Blue | Female | 1 |
| 2 | Blue | Female | 3 |
| 3 | Blue | Male | 8 |
| 4 | Blue | Male | 8 |
| 5 | Blue | Female | 2 |
| 6 | Blue + frame | Female | 164 |
| 7 | Blue + frame | Female | 191 |
| 8 | Blue + frame | Male | 189 |
| 9 | Blue + frame | Male | 109 |
| 10 | Blue + frame | Female | 250 |
| 11 | White + frame | Female | 141 |
| 12 | White + frame | Female | 33 |
| 13 | White + frame | Male | 41 |
| 14 | White + frame | Male | 24 |
| 15 | White + frame | Male | 47 |

piece. The authors believe that nasal support played a great role in the fitting [23]. From this study, head tilt, which is the usual position of dental practice, did not compromise performance. However, talking showed the most compromised results. It was worth pointing out that the fit factor of Tester 4 was lower than the other testers. We had taken note that, during the talking position, Tester 4 talked at a fast speed. This might have contributed to the accumulation of particles inside (Cin), thus decreasing the overall fit factor.

Recently, a study by Liu et al. [24] mentioned that 90% of subjects passed the minimum requirement of QNFT by using mask fitters over the ASTM mask level 3 which has higher bacterial filtration efficiency (BEF) than the ASTM level 1. However, in our study, we used mask fitter over ASTM level 1 which provides a good fit and comparable result to N95. So, it is possible that the design of the mask, cellulose lining material, or sponge antifog nose bridge pad would have a high potential effect on the fit than BFF properties.

Similarly, we used polylactic acid following the Bellus3D recommendation. However, the other materials that could be used should be environmentally friendly, biodegradable, flexible physical property, and economical. Elastic tightening can be done to hold the fitter in place around the head [25]. Although Bella3D recommends using a chain of thin rubber bands, it can be possible to use elastic cloth or string.

Some other alternatives to disposable N95 respirators can be reusable stop-gap respirators as alternatives made from 3D printing, silicone molding, and plastic extrusion [26–28]. Anwari et al. [26] developed and did the preliminary testing of an open-hardware-licensed device, the "simple silicone mask" (SSM). The respirator originally included a cartridge for holding filter material; this was modified to connect to standard heat-moisture exchange (HME) filters (N95 or greater) after the cartridge showed poor filtration performance due to flow acceleration around the filter edges, which was exacerbated by high filter resistance. All 8 HME-based iterations provided an adequate seal by user seal checks and achieved a pass rate of 87.5% ($N = 8$) on quantitative testing, with all failures occurring in the first iteration. The overall median fit-factor was 1662 (100 = pass). The estimated unit cost for a production run of 1000 using distributed manufacturing techniques is CAD $15 in materials and 20 minutes of labor. Small-scale manufacturing of an effective, reusable N95 respirator during a pandemic is feasible and cost-effective. Required quantities of reusables are more predictable and less vulnerable to supply chain disruption than disposables. With further evaluation, such devices may be an alternative to disposable respirators during public health emergencies. The respirator described previously is an investigational device and requires further evaluation and regulatory requirements before clinical deployment. The authors and affiliates do not endorse the use of this device at present. Similarly, Ng et al. [25] developed one such device, the "SSM." They evaluated the qualitative fit test (QNFT), comfort, breathability, and communication. The SSM scored 3.5/5 and 4/5 for comfort and breathability. The median overall harmonic mean fit factors of disposable N95 and SSM were 137.9 and 6316.7, respectively. SSM scored significantly higher than disposable respirators in fit-test runs and overall fit-factors ($p < 0.0001$). Overall passing rates in disposable and SSM respirators on QNFT were 65% and 100%. During dynamic runs, passing rates in disposable and SSM respirators were 68.1% and 99.4%, respectively; harmonic means were 73.7 and 1643. They validated the reusable N95 stop-gap filtering face piece respirator that can match existent commercial respirators which can be used in an emergency.

The mask fitter designed in this study is customized and has a better fit, but the N95 is not customized. But the N95 has its importance as it offers good prevention. In addition, the mask fitter is reusable. The mask filters themselves are not reusable to the same degree, but their use can be prolonged. To clinically evaluate such fitting devices, more clinical studies are needed. Aesthetic and pragmatic human performance considerations are equally important including comfort and breathability which were not carried out in our study. Further study on frame material, shape, and expanded sample size would be beneficial to society. This study can be expanded to include these factors in more sample sizes in a larger population.

## 5. Conclusion

From this study, we found that the 3D printed frame fitted over a surgical mask offers advantages comparable to those offered by N95 respirators. However, the fit and seal of the mask would be decreased once the speech pace increases. Also, the surgical mask brand or even design would affect the result too. So, the author suggested that minimizing conversation and slow-speed talking would be very beneficial.

The custom mask fitter requires further investigation to test its effectiveness through quantitative means and further design adjustments to improve its comfort, user-friendliness, and everyday feasibility. In its current state, it cannot replace the N95 respirator but may provide an alternative PPE solution when N95 supplies are limited.

## Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

## Ethical Approval

All experimental protocols were approved by the Bangkok Hospital Institutional Review Board (IBR number: BHQ-IRB 2020-08-28).

## Consent

Informed consent was obtained from the participants for this study.

## Conflicts of Interest

The authors declare that there are no conflicts of interest.

## Authors' Contributions

SK, NW, and VK designed the experiments. SK supervised the experiment. KS supervised corrosion testing. SK performed the analysis and prepared the draft of the manuscript. SK and VK corrected the manuscript. All the authors discussed the results and approved the publication of this manuscript. P.T. contributed to the conceptualization of the study, developed methodology, carried out formal analysis and investigation, curated the data, and prepared the original draft; P.A. and A.P. contributed to the validation of the study; P.A. and P.S. reviewed and edited the manuscript; and A.P. supervised the study. All authors have read and agreed to the published version of the manuscript.

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*Research Article*

# Effects of Three Novel Bracket Luting Agents Containing Zirconia Primer on Shear Bond Strength of Metal Orthodontic Brackets Attached to Monolithic Zirconia Crowns: A Preliminary In Vitro Study

**Milad Shamohammadi Heidari**,[1] **Mehrnaz Moradinejad**,[2] **Hamed Tabatabaei**,[3] **and Vahid Rakhshan**[4]

[1]*Orthodontic Department, Dental School, Shahed University of Medical Sciences, Tehran, Iran*
[2]*Department of Orthodontics, Dental School, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
[3]*Dental School, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
[4]*Department of Anatomy, Dental School, Azad University of Medical Sciences, Tehran, Iran*

Correspondence should be addressed to Hamed Tabatabaei; hamed_tabatabaie20@yahoo.com

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*Background*. The increased use of zirconia crowns in adult orthodontic patients warrants the establishment of methods and materials to adhere orthodontic brackets properly to zirconia crowns. However, studies in this regard are scarce, and many materials remain untested. This preliminary study aimed to examine three new adhesives containing zirconia primers for the first time. *Methods*. Sixty identical monolithic zirconia crowns were fabricated and randomly divided into 4 groups of 15 each (Panavia SA Cement Plus, G-CEM, TheraCem, and Transbond XT Composite (control)). After glaze removal with a diamond bur, a metal orthodontic bracket was attached to the surfaces of the crowns using the respective adhesive. Specimens were incubated at 37°C and then thermocycled for 2000 cycles. Shear bond strengths (SBS) of brackets in different groups were estimated using a universal testing machine. Mean SBS values were compared with the values 6, 8, and 10 (as acceptable SBS values) and 13 MPa (as the maximum SBS tolerable by zirconia) using the one-sample *t*-test. They were also compared with each other using the one-way ANOVA and Tamhane post hoc test ($\alpha = 0.05$). *Results*. The ANOVA indicated a significant overall difference; the Tamhane test showed that the difference between the control group and all test groups was significant ($P < 0.0005$); however, the 3 test groups were not significantly different from each other ($P > 0.30$). The SBS of the control group was significantly lower than the minimum acceptable SBS (6 MPa, $P < 0.0005$). The mean SBS of the TheraCem was not significantly different from 10 MPa ($P = 0.902$), while the mean SBS values of Panavia SA Cement Plus and G-CEM were significantly greater than 10 MPa ($P < 0.05$). None of the three zirconia adhesives had mean SBS values higher than 13 MPa. *Conclusion*. All novel zirconia adhesives (Panavia SA Cement Plus, G-CEM, and TheraCem) generated SBS values adequate to attach metal orthodontic brackets to zirconia prostheses (at or greater than 10 MPa) without damaging the zirconia during bracket removal (not above 13 MPa).

## 1. Introduction

Esthetics is an ever-increasing demand of dental patients, especially adult ones; the number of adults who have esthetic dental restorations and seek orthodontic treatment is increasing [1, 2]. Orthodontists increasingly face adult patients with various esthetic dental restorations such as porcelain, reinforced ceramics, and zirconia [1–5]. This has highlighted the importance of bonding in orthodontics, and orthodontists should be able to bond brackets not only to the enamel but also to various restorative materials, including zirconia. Nevertheless, it is difficult to properly bond

brackets to nonenamel surfaces [3]. In orthodontics, bracket adhesive systems should meet high standards; they should provide shear bond strengths (SBSs) of about 6 to 10 megapascals (MPa) in order to constantly keep the bracket attached to the tooth or dental restoration, yet not to be excessively strong to damage the tooth or crown surface while debonding the bracket [3, 6–8].

Zirconia has recently gained a lot of attention due to its esthetics and durability [3, 9]. Previously, zirconia crowns were formed of zirconia core coated with porcelain veneer; however, they are now used more as monolithic zirconia crowns to avoid the fracture of the outer porcelain veneer [4, 10, 11]. After improving the esthetics of monolithic crowns, monolithic zirconia crowns are now used frequently in the esthetic zone as well [4, 12].

Despite its advantages, zirconia is a challenge for orthodontists. It cannot be easily etched, even using hydrofluoric acid, and therefore does not provide proper bracket bonds [3, 4, 13]. In restorative dentistry and prosthodontics, different studies have tested methods and materials to increase the zirconia bond, including surface treatments using alumina or silica [12, 14–16] and zirconia primers [4, 12, 17–19], which usually contain 10-methacryloyloxydecyl dihydrogen phosphate (10-MDP), the phosphate group of which reacts chemically with zirconium oxide, increasing the bond strength [4].

Not many studies have assessed methods to improve the bond strength of orthodontic brackets bonded to zirconia [1–4, 20–23]. Moreover, the effects of different zirconia primers have been investigated merely in a few studies [4, 23]. Therefore, the efficacy of primers in bonding metal brackets (as the most common type of brackets) to zirconia remains unaddressed. Hence, this study aimed to investigate the SBS of brackets bonded to monolithic zirconia crowns using three other primers. The null hypothesis was the lack of any difference among the shear bond strengths of the four groups.

## 2. Materials and Methods

An acrylic tooth was selected and trimmed. An impression was taken from the acrylic tooth. A die was fabricated from that impression, and it was duplicated until fabricating 60 similar dies. Then, 60 monolithic zirconia crowns were manufactured using CAD-CAM technology. The zirconia block in use was Sirona, and blocks were cut using a Sirona CAD-CAM device (CAD/CAM milling machine inLab MC X5, Dentsply Sirona, Versailles, France). Afterward, the surface treatment of glaze removal was carried out using a diamond bur. Next, the crowns were embedded in the heat-cured acrylic blocks. Finally, buccal tubes (Ortho Technology, Lutz, Florida, USA) with different cement materials in 4 groups were bonded to monolithic zirconia crowns. In terms of resin cement used, the samples were randomly divided into four groups: Group 1: Panavia SA Cement Plus (Kuraray, Okayama, Japan); Group 2: G-CEM (GC); Group 3: TheraCem (Bisco, Schaumburg, Illinois, USA); Group 4 (as the control group): Transbond XT Composite (3M UniTek, Monrovia, USA). The sample size was predetermined as 15 specimens per group by augmenting the sample sizes of previous studies [4].

After 24 hours of storage at 37°C, all samples were thermocycled for 2000 cycles. Next, a Universal Testing Machine (Zwick, Z020, Berlin, Germany) with a rod moving at 1 mm/min crosshead speed was used to measure the shear force (in Newton). The SBS was measured in megapascal (MPa) by dividing the shear force (in Newton) by the surface area of the bracket attached to the crown (in $mm^2$). The authors asked the manufacturer for the surface area of the bracket in use. However, the manufacturer declined to give information beyond what was presented in the catalog. Therefore, the authors themselves estimated the bracket base surface area using a digital image editing program as 17.854 $mm^2$ (Figure 1). For estimating the surface area, the maximum width and length of the surface of the bracket base, which had been provided in the manufacturer's catalog, were used to calculate the surface area of a square with those maximum dimensions. The bracket base was not a square, but a composite shape looking like a trapezoid with round corners (Figure 1). Therefore, we put a digital image of this bracket base tightly within a square frame (with those maximum measurements). Then, we counted the pixels within the trapezoidal shape of the bracket base and also those within the rectangular frame tightly surrounding it. The surface area of the square was measured as the maximum width × the maximum length. The ratio of the number of pixels within the bracket base to the number of pixels within the framing square was used to calculate the surface area of the bracket base (Figure 1).

*2.1. Statistical Analysis.* Descriptive statistics and 95% confidence intervals (CIs) were calculated for each group. Data were normally distributed (Shapiro–Wilk and Kolmogorov–Smirnov, $P > 0.05$). Groups were compared with each other using one-way analysis of variance (ANOVA) and the Tamhane post hoc test. They were also compared with the value of 10 MPa (as the highest value in the range of clinically acceptable SBS) using a one-sample *t*-test. Since the value of TheraCem was not significantly different from 10 MPa, it was also compared with another recommended clinically acceptable SBS value, 8 MPa, which is the median of the clinically acceptable range. Also, the SBS of the control group was compared with 6 MPa, which is the minimum acceptable SBS. The mean SBS values of all experimental groups were compared with the value of 13 MPa, above which can be damaging to zirconia [3, 24]. All tests were done using SPSS 25 (IBM, Armonk, NY, USA). The level of significance was predetermined as 0.05.

## 3. Results

The control group showed the lowest mean SBS, while Panavia and G-CEM had the highest mean SBS values (Table 1, Figure 2). The one-way ANOVA showed that there was a significant difference among the 4 groups ($P < 0.0000005$). The Tamhane post hoc test showed that the mean SBS of the control group was significantly lower than

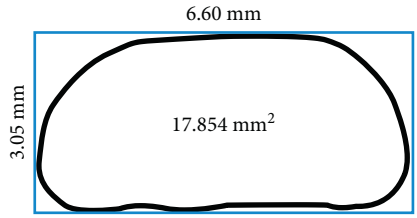


Figure 1: A schematic view of the shape of the bracket base. The surface area of the rectangle is 20.13 $mm^2$ according to the length (6.60 mm) and the width (3.05 mm) of the rectangle specified in the manufacturer's catalog. The area of the bracket base was calculated as follows: the percentage of the rectangle area occupied by the bracket base was determined by counting the pixels within the rectangle (both within the bracket base and outside it). After the application of that percentage, the surface area of the bracket base was calculated as 17.854 $mm^2$.

that of the other groups, but the experimental cements had mean SBS values that were not significantly different from each other (Table 2).

The one-sample *t*-test showed that the control group had a mean SBS significantly smaller than 10 MPa and also significantly smaller than 6 MPa (both $P$ values < 0.000001). The mean SBS of the TheraCem was not significantly different from 10 MPa ($P = 0.902$), while the mean SBS values of Panavia SA Cement Plus and G-CEM were significantly greater than 10 MPa ($P < 0.05$, Table 1). The mean SBS of TheraCem was significantly higher than 8 MPa ($P = 0.029$, one-sample *t*-test).

Compared with the SBS value of 13 MPa, TheraCem had a value significantly lower than 13 MPa ($P = 0.005$), while the values of Panavia SA Cement Plus ($P = 0.877$) and G-CEM ($P = 0.839$) were not significantly different from 13 MPa.

## 4. Discussion

The success of fixed orthodontic treatment depends on the proper bonding of orthodontic brackets to the teeth. Repeated debonding of orthodontic brackets can accompany limitations. For example, it can disrupt the treatment process, increase the duration of treatment, and waste considerable chair time in the clinic. Therefore, a great deal of research has been done to improve the properties of dental materials and treatment techniques, hoping to create more stable and long-lasting bracket bonds [25–28]. The findings of this study indicated that all three experimental adhesives produced adequate shear bond strengths to attach the bracket to a monolithic zirconia crown. However, two of the materials (G-CEM and Panavia) produced bond strengths that might be considered slightly excessive. The ideal SBS needed for attaching orthodontic brackets is not necessarily the maximum bond strength. Instead, the SBS should also be weak enough to allow convenient and safe bracket debonding, without inflicting damage to the underlying restoration. The control group lacking primer had the lowest SBS that was significantly lower than the minimum acceptable SBS value of 6 MPa [7, 23, 29]. It is suggested that optimum SBS values for orthodontic brackets range from 6 to 10 MPa [3, 4, 6–8, 30]. In this study, there was not a significant difference among the three experimental primers. Therefore, the ones with higher SBS values can still be considered acceptable, although they produce SBS values significantly higher than 10 MPa. Besides, it is shown that SBS values slightly greater than 10 MPa can still be harmless: Our results were in line with the findings of other primers generating SBS values of about 13 to 14 MPa, which did not damage the ceramic surface after bracket removal [3, 31]. In the case of zirconia, SBS values greater than 13 MPa might cause ceramic fracture during bracket removal [3, 24], and none of the tested primers in this study had SBS values above this threshold. Our results were achieved without hydrofluoric acid pretreatment and after thermocycling, which makes these materials proper clinical candidates, since hydrofluoric acid is toxic and contraindicated in the clinic [3, 32].

MDP-containing primers can provide proper SBS by improving chemical bonding with zirconium oxide even after thermal cycling [4, 33–35]. The adhesion between zirconia and resin cement can be improved by combining different treatments such as silane, silica-coating, and MDP [36, 37]. Other forms of materials might not need primers: multimode or universal adhesives usually contain 10-MDP and therefore allow bonding to zirconia without zirconia primers [4, 20, 22, 23].

We thermocycled the specimens for 2000 cycles. This was considerably greater than many other studies evaluating bond strengths between ceramics and brackets that had implemented either no thermocycling at all [38, 39] or merely up to 500 cycles [40, 41]. A higher number of thermal cycles can better reflect the oral environment conditions and the deterioration of mechanical properties due to aging [3, 9]. In this regard, two studies used 10000 thermal cycles with and without hydrofluoric acid [3, 32].

This study was limited by some factors. The results of in vitro studies cannot be easily generalized to in vivo situations full of thermal, chemical, and mechanical shocks and alterations. Moreover, the results of these tested materials cannot be generalized to other brands. We used a rather large sample per group in order to ensure proper test power, which was confirmed by the statistical results obtained. Also, we used a rather high number of thermal cycles to better simulate the oral environment. At first look, there might seem a large difference among standard deviations (SDs) of SBS in different groups, with some groups having much greater SDs than others. However, it should be noted that standard deviations should be assessed in light of mean values. This is why we have also calculated and reported coefficients of variation (CVs), which are calculated by dividing the standard deviation by the mean. The CV values of different groups did not change considerably across groups. Future studies should assess the efficacy of these materials and methods in clinical conditions.

Table 1: Descriptive statistics and 95% CI for SBS values (MPa) and the results of the one-sample *t*-test comparing each group with 10 MPa.

| Material | Mean | SD | CV (%) | 95% CI | | Min | Q1 | Med | Q3 | Max | *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| TXT (control) | 2.24 | 0.86 | 38.6 | 1.76 | 2.71 | 1.25 | 1.57 | 1.93 | 3.10 | 4.33 | <0.0005 |
| TheraCem | 10.11 | 3.37 | 33.3 | 8.24 | 11.98 | 5.55 | 7.39 | 10.12 | 11.61 | 17.35 | 0.902 |
| G-CEM | 13.28 | 5.27 | 39.7 | 10.36 | 16.20 | 4.42 | 9.97 | 12.80 | 17.91 | 22.91 | 0.030 |
| Panavia | 12.84 | 3.99 | 31.1 | 10.63 | 15.05 | 3.90 | 10.89 | 12.61 | 15.40 | 20.91 | 0.016 |

SD, standard deviation; CV, coefficient of variation; CI, confidence interval; Min, minimum; Q1, first quartile; Med, median; Q3, third quartile; Max, maximum; TXT, Transbond XT.

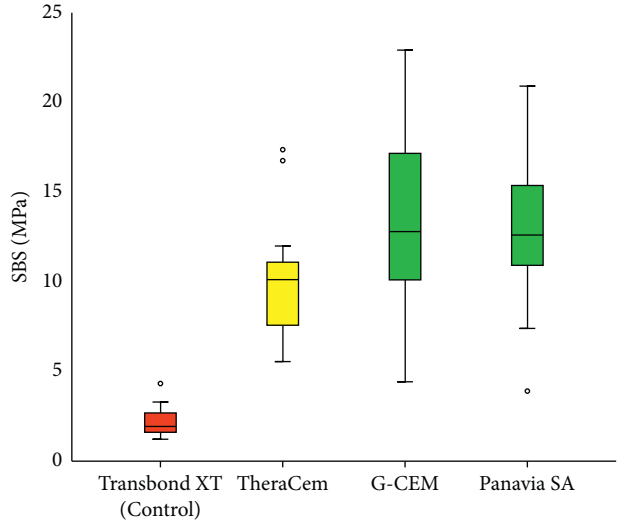


Figure 2: Box plots showing descriptive statistics for SBS values (MPa) in each group.

Table 2: The results of the Tamhane test comparing all groups with each other.

| Compared groups | | Diff (MPa) | SE | *P* | 95% CI | |
|---|---|---|---|---|---|---|
| TXT (control) | TheraCem | −7.87 | 0.90 | 0.000001 | −10.57 | −5.18 |
| TXT (control) | G-CEM | −11.05 | 1.38 | 0.000006 | −15.23 | −6.86 |
| TXT (control) | Panavia | −10.60 | 1.05 | <0.0000005 | −13.79 | −7.42 |
| TheraCem | G-CEM | −3.17 | 1.61 | 0.316 | −7.80 | 1.46 |
| TheraCem | Panavia | −2.73 | 1.35 | 0.279 | −6.55 | 1.10 |
| G-CEM | Panavia | 0.44 | 1.71 | 1.0 | −4.41 | 5.30 |

Diff, difference between mean SBS of groups; SE, standard error; CI, confidence interval for the difference; TXT, Transbond XT.

## 5. Conclusions

All three cements containing zirconia primers (Panavia SA Cement Plus, G-CEM, and TheraCem) were able to generate shear bond strengths adequate to attach metal orthodontic brackets to zirconia prostheses (at or greater than 10 MPa). At the same time, the bond strengths were not excessive (not above 13 MPa) to damage zirconia prostheses during bracket debonding. The control group did not produce adequate shear bond strengths to bond brackets to zirconia (below 6 MPa).

## Data Availability

Data are available from the authors upon request.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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*Review Article*

# Vitamin *D* Supplementation for Prevention of Dental Implant Failure: A Systematic Review

**Alaa Makke**

*Oral and Maxillofacial Department, Umm AlQura University, Faculty of Dentistry, Makkah 24225, Saudi Arabia*

Correspondence should be addressed to Alaa Makke; azmakki@uqu.edu.sa

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*Background*. Many factors play a significant role in osseointegration and healing after dental implant insertion and restoration. Some factors are related to dental biomaterials, such as the dental implant, prosthesis, and grafting materials. Other factors can be connected to operator skills and accumulated experience. Local and systemic patient-related factors are crucial in determining the success of the dental implant. Thorough examination and analysis of local factors using available examination tools are vital to prepare the implant candidate for such treatment. The patient's systemic condition directly affects the healing of the dental implant. One of the most overlooked systemic factors is the patients' vitamin *D* level, which influences bone formation around the implant and subsequent osseointegration. The current review examined the available literature regarding the association between vitamin *D* supplementation and dental implant osseointegration. *Methods*. Data of this review were derived from recent research available on PubMed, Google Scholar, and Scopus. Inclusion criteria were the relation between the vitamin *D* serum and dental implant osseointegration or failure. The Systematic Reviews and Meta-Analyses (PRISMA) checklist was followed to perform the review. The study's outcome was the need for vitamin *D* supplementation to prevent implant failure. *Results*. Five human studies (including case reports, case series, and retrospective studies) and six animal studies. All included studies discussed the relationship between vitamin *D*, early dental implant failure, and bone implant contact. Three retrospective studies found no significant relationship between vitamin *D* supplementation and EDIFs in humans. On the other hand, one retrospective study showed a significant relationship in humans. A case report and case series claimed that the implant was successfully placed after vitamin *D* supplementation. A total of four animal studies showed a significant relationship between vitamin *D* supplementation and osseointegration of the dental implant. Two animal studies showed no significant association. *Conclusion*. To ensure optimal treatment outcomes, it is recommended to supplement the patient with vitamin *D* if the serum level is not within the normal range. Further clinical studies and case reports are needed to confirm the association between serum vitamin *D* levels and osseointegration.

## 1. Introduction

Osseointegration is the key to dental implant success and is required to achieve direct structural and functional bone formation. For this to occur, many integrated factors should be thoroughly assessed, such as surgical techniques, type of prosthesis, biomaterials, and operator- and patient-related factors [1]. Implant failures are classified according to the timing of the loss to early dental implant failure (EDIF) or late dental implant failure (LDIF). Early implant failure occurs due to improper implant placement and restoration, low bone volume or density, systemic conditions, or smoking [2, 3].

The primary goal for any oral implantologist is to obtain satisfactory healing and long-term treatment success. Most researchers and manufacturing companies pursue innovations through new implant designs and surface treatment to increase stability and accelerate the osseointegration process. Often, systemic health is a significant factor that is not adequately considered. The human skeleton derives its vitality from key minerals, such as calcium, fluoride, magnesium, potassium, vitamin B6, vitamin *D*, and zinc [4]. The European Register of Nutrition and Health described 18 items that directly affect bone and teeth, including vitamin *D* [5], one of the most necessary micronutrients for dental implant osseointegration. Therefore, adequate exposure to

sunlight and optimal dietary habits support the maintenance of satisfactory vitamin *D* levels [6].

Vitamin *D* insufficiency is defined as any serum level ranging between 21 and 29 ng/ml, deficiency is when levels are less than 20 ng/ml, and severe deficiency is less than 10 ng/ml (Table 1). Vitamin D3 is the basic form of the vitamin *D* family, and it is activated by hydroxylation in the liver. Vitamin *D* stimulates osteoclastic activity and the production of extracellular matrix proteins by osteoblasts. Moreover, it increases calcium absorption in the intestines [7–11]. Some studies proposed that a low vitamin *D* level might be associated with EDIF [2, 12]. Therefore, the purpose of the current review is to investigate the available literature regarding vitamin *D* supplementation and dental implant osseointegration.

Table 1: Vitamin *D* levels.

| *Serum 25(OH) vitamin D levels* | |
|---|---|
| Optimal | 30 ng/mL |
| Insufficiency | 10–30 ng/mL |
| Deficiency | 10 ng/mL |

## 2. Materials and Methods

The most recently published English research was reviewed, including animal studies, in vitro studies, case series, case reports, cohort studies, and clinical studies. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was followed to perform the review. Data were collected using the following keywords: vitamin *D*, dental implant, implant failure, osseointegration. A database such as Google Scholar, PubMed, Scopus, or ResearchGate was used to explore recent research. Inclusion criteria were studies investigating the vitamin *D* serum and dental implant osseointegration or failure. Exclusion criteria were incomplete data and irrelevant or duplicated studies. Data were reviewed according to the patient age and sex of the patient, the year of the study, and the number and location of the study.

## 3. Role of Vitamin *D* on Dental Implant Osseointegration

Sunlight vitamin *D* synthesis begins from cholesterol in the skin converted into pre-vitamin D3 and then isomerized to vitamin D3. Subsequently, 25-hydroxyvitamin D3 resulting after vitamin D3 is hydrolyzed in the liver [13]. Primarily, vitamin *D* stimulates the osteoclastic activity and production of extracellular matrix proteins by osteoblasts and increases the Ca absorption in the intestines [7–11]. Likewise, there is a microbicidal effect on monocytes affected by vitamin *D* levels, which increase the body's resistance to bacteria, fungi, and viruses [14]. There was a significant correlation between infection rate and vitamin *D* levels <20 ng/ml [15]. Therefore, the optimal vitamin *D* level might be one of the most critical systemic factors in preventing infection and providing an optimal environment for successful osseointegration.

## 4. Retrospective Studies and Case Reports

A retrospective study on 1,740 implants placed in 885 patients showed no significant relationship between low vitamin *D* levels and increased risk of EDIFs [16]. In patients with serum levels of vitamin $D < 10$ ng/ml, there were 11.1% EDIFs before loading the prosthetic part. In comparison, when the serum level of vitamin *D* was between 10 and 30 ng/ml, the EDIFs was 4.4%, and when the serum level of vitamin *D* was >30 ng/ml, there was a 2.9% EDIF rate. The retrospective study by Wagner et al. showed a significant and positive effect of vitamin *D* on marginal bone loss at the mesial and distal aspects of the dental implants [17].

Similarly, a retrospective study of 1,625 implants placed in 822 patients showed an increase in the incidence of EDIFs in patients with compromised vitamin *D* levels, but statistically, it was not significant. The study described 9% EDIF for those with a serum level of vitamin $D < 10$ ng/ml and 3.9% EDIFs for those with a serum level of vitamin *D* between 10 and 30 ng/ml. Surprisingly, a 2.2% EDIF rate was noted in patients with a serum level of vitamin $D > 30$ ng/ml [18].

A case series examined implants that were successfully osseointegrated in two patients with a history of EDIFs after vitamin *D* supplements [19]. Another case report claimed EDIFs occurred after immediate implant placement due to severe vitamin *D* deficiency [20] (Table 2).

## 5. Animal Studies

Kelly et al. found exposed implant surfaces in vitamin D-deficient rats and bone fracture between the implant and surrounding bone after 14 days of implant placement when subjected to a lower push-in test and lower bone to implant contact (BIC) [21]. On the contrary, vitamin *D* supplementation increased bone density by 1.2-fold and osseointegration by 1.5-fold and extrusion force resistance by 2.0-fold in osteoporotic rats. The trabecular bone amount was increased by 96%, and osseointegration was elevated up to 94.4%, while the trabecular number was elevated by 112.5% and 51.8% in connective tissue [22].

Wu et al. used vitamin *D* and insulin on diabetic rats to improve osseointegration. The study claimed that bone volume, osseointegration, trabecular bone number and thickness, connective tissue density, BIC, and push-out force were enhanced [23]. Another study on diabetic rats showed no significant effect of vitamin *D* on osseointegration. In a different study, vitamin *D* combined with insulin was administered to diabetic rats, and histological analysis was conducted during the third week after implant placement. A BIC level of 44 was measured in the diabetic rats and 57 for rats in the vitamin *D* + insulin group. Six weeks later, the BIC level was 70 for the control group and 65 for the vitamin *D* group 5 [24]. Dvorak et al. observed no significant rescission of BIC in the medullar and periosteal compartment among rats that received vitamin *D* in their diet compared to those which did not receive it [25].

Table 2: Data from case reports, case series, and retrospective studies.

| Author | Title | Study type | Results |
|---|---|---|---|
| Mango et al., 2018 | Low serum level vitamin *D* and early dental implant failure | Retrospective study | No significant relationship between low vitamin *D* levels and an increase in the risk of EDIF |
| Wagner et al., 2017 | Does osteoporosis influence the marginal peri-implant bone level in female patients? A cross-sectional study in a matched collective | Retrospective parallel-group | A significant and positive effect of vitamin *D* on marginal bone loss at the *M* and *D* aspect of the dental implants |
| Mangano et al., 2016 | Is low serum vitamin *D* associated with early dental implant failure? A retrospective evaluation of 1625 implants placed in 822 patients | Retrospective study | Increase in EDIF with compromised levels of vitamin *D*, but statistically not significant |
| Fretwurst et al., 2017 | Vitamin *D* deficiency in early implant failure: Two case reports | Case series | The implant was successful after administration of vitamin D |
| Bryce and macbeth, 2014 | Vitamin *D* deficiency as a suspected causative factor in the failure of an immediately placed dental implant: A case report | Case report | The EDIFs occurred after immediate implant placement due to severe vitamin *D* deficiency |

A significant difference was observed when vitamin *D* supplements were administered to rats with chronic kidney disease (CKD) compared to those with CKD without supplementation. BIC levels were significantly higher among the supplementation group [26] (Table 3).

## 6. Discussion

The current review aimed to investigate the association between vitamin *D* levels and the osseointegration process of a dental implant. The United States Centers for Disease Control and Prevention's National Health and Nutrition Survey claimed an insufficient intake of vitamin *D* for more than 25% of the US population. This deficiency is shared outside the US, with more than 2 billion people worldwide also showing vitamin *D* deficiency. Thus, vitamin *D* deficiency directly affects the skeleton of the human body, including the jawbone [27], and therefore, it may play a critical role in dental implant treatment outcomes. Accordingly, a stable vitamin *D* level will assist in maintaining a healthy body, and ideal daily amounts are 2,000 IU (50 mcg) for most people and up to 4,000 IU [27] during pregnancy.

The current review included five human studies (including case reports, case series, and retrospective studies) and six animal studies. All included studies discussed the relationship between vitamin *D*, EDIFs, and BIC.

A significant relationship was found between vitamin *D* and osseointegration in four animal studies when BIC was examined. A lower push-in test was performed 14 days after implant insertion in rats. Kelly et al. found that, after scanning electron microscopy (SEM) analysis, all rats with vitamin *D* deficiency showed exposed implant surfaces, which occurred because of bone fracture between the implant and the surrounding bone [21]. Likewise, an investigation conducted to determine the effect of 1,25(OH)2D3 on implant osseointegration in osteoporotic rats indicated that vitamin *D* supplementation resulted in significant bone formation around the implant [22].

Other animal studies showed that bone volume increased when vitamin *D* was used with insulin in diabetic rats after implant placement [24]. The mean bone volume and osseointegration outcomes of the studies were very similar to those of healthy rats. Similarly, Liu et al. proved that CKD rats that received vitamin *D* supplementation showed greater BIC and bone volume than CKD rats that did not receive vitamin *D* supplementation [23]. The studies, as mentioned earlier, showed the importance of vitamin *D* supplementation, especially for compromised rats. The findings of these studies demonstrated the significance of supplemental vitamin *D* in the short- and long-term outcomes after dental implant treatment.

Two animal studies showed no significant correlation between vitamin *D* supplementation and dental implant osseointegration [24, 25]. Akhavan et al. showed that vitamin *D* supplementation did not significantly affect osseointegration, although the study did not mention if the experimental rats received diabetes medication [24]. Dvorak et al. showed that there no significant difference when rats were fed a standard vitamin *D* diet [25]. However, the study did not mention the vitamin *D* blood levels of the rats after diet administration.

There has been a lack of human studies examining the association between vitamin *D* serum levels and osseointegration. In 2018, Mango et al. investigated vitamin *D* serum levels and EDIFs in a retrospective clinical study that included 885 patients, with specified inclusion and exclusion criteria [16]. Their findings showed 35 EDIFs (3.9%) reported, with no significant relationship between the EDIFs and patient gender, smoking, history of periodontal disease, or vitamin deficiency. Three EDIFs were noted in 27 patients with vitamin *D* serum levels <10 ng/ml, 20 EDIFs in 448 patients with groups of 10–30 ng/ml, and 12 EDIFs in 410 patients with serum levels >30 ng/ml. Limitations of the study included the sample size of the patients with low serum levels of vitamin *D* and the retrospective design.

One case report found severe vitamin *D* deficiency correlated with immediate implant placement [20]. A case series confirmed this hypothesis when the implant was successfully osseointegrated after *D* supplementation, although there was a previous implant failure [19]. Interestingly, the results of the retrospective studies, case reports, and case series concluded that the serum level of vitamin *D* seems to influence dental implant osseointegration. The limitation of the study includes a limited number of available data and sample size and few clinical studies.

Table 3: Data from animal studies.

| Author | Title | Study type | Results |
|---|---|---|---|
| Kelly et al., 2008 | Vitamin *D* and bone physiology: Demonstration of vitamin *D* deficiency in an implant osseointegration rat model | Animal study | Exposed implant surface in vitamin D-deficient rats |
| Zhou et al., 2012 | 1,25-Dihydroxy vitamin D3 improves titanium implant osseointegration in osteoporotic rats | Animal study | Increased bone density by 1.2-fold, osseointegration by 1.5-fold, and extrusion force resistance by 2.0-fold in osteoporotic rats. The trabecular bone amount was elevated by 96%, and osseointegration was elevated up to 94.4%. Trabecular number was elevated by 112.5% and 51.8% connective tissue |
| Wu et al., 2012 | Vitamin D3 and insulin combined treatment promotes titanium implant osseointegration in diabetes mellitus rats | Animal study | Bone volume, osseointegration, trabecular bone number and thickness, connective tissue density, BIC, and push-out force were improved |
| Akhavan et al., 2012 | The effect of vitamin *D* supplementation on bone formation around titanium implants in diabetic rats | Animal study | No significant effect of vitamin *D* on osseointegration in diabetic rats |
| Dvorak et al., 2012 | Impact of dietary vitamin *D* on osseointegration in the ovariectomized rat | Animal study | No significant rescission of the BIC in the medullar and periosteal compartment among rats that received vitamin *D* when compared to those that did not |
| Liu et al., 2014 | Vitamin *D* supplementation enhances the fixation of titanium implants in CKD mice | Animal study | A significant difference was observed when vitamin *D* supplements were given to rats with CKD |

## 7. Conclusions

Additional prospective clinical studies and case reports are required to determine the association between serum vitamin *D* levels and osseointegration. Some studies showed a clear association in terms of osseointegration and EDIFs. Additional studies with specific inclusion and exclusion criteria are necessary to isolate vitamin *D* levels as the only factor tested. If a patient's vitamin *D* level is severely compromised according to the level mentioned in this review, the recommendation is to supplement with vitamin *D* to ensure optimal treatment outcomes.

## Abbreviations

BIC: Bone to implant contact
EDIFs: Early dental implant failures.

## Data Availability

The data supporting this review are from previously reported studies and datasets, which have been cited.

## Conflicts of Interest

The author declares no conflicts of interest.

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