

Review Article

Bone Augmentation for Implant Placement: Recent Advances

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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

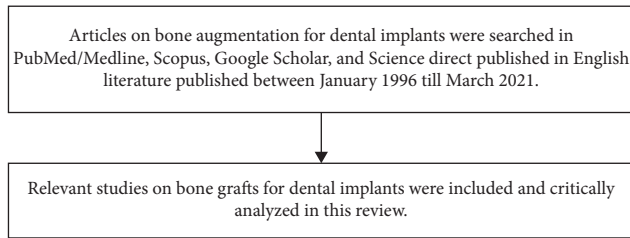


FIGURE 1: Schematic diagram of the method for the selection of articles.

[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 Osteograft, Osteoset, and Proosteon
5	Polymer based	Biodegradable and nondegradable polymers, such as open porosity polylactic acid polymer

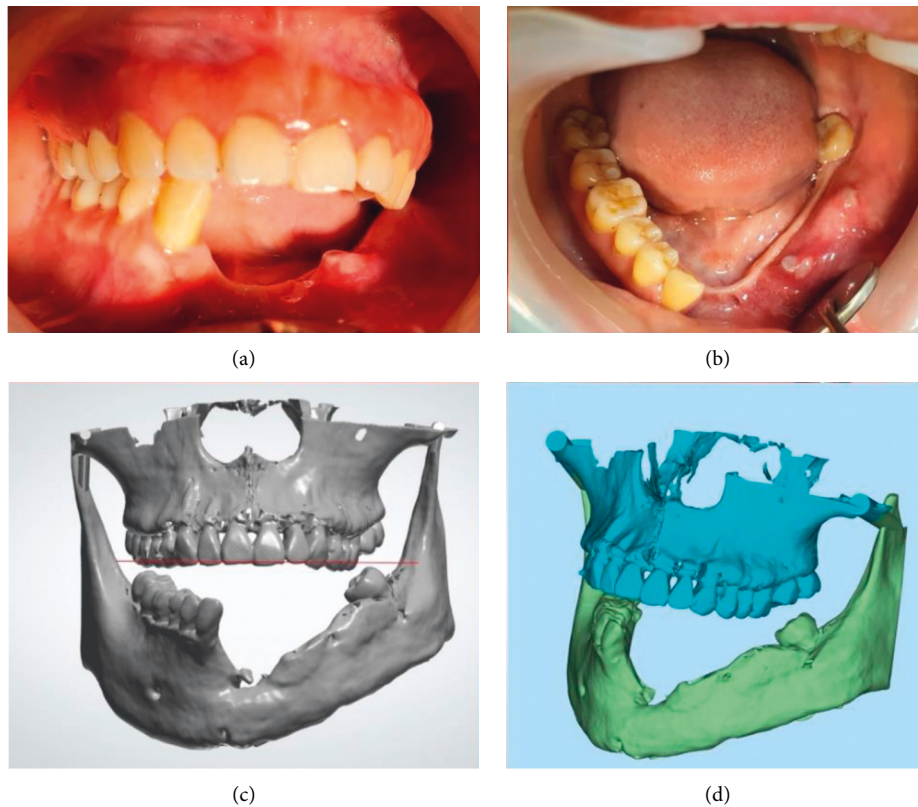


FIGURE 2: Fibula free flap in the mandibular arch: clinical pictures (a, b) and 3D views (c, d).

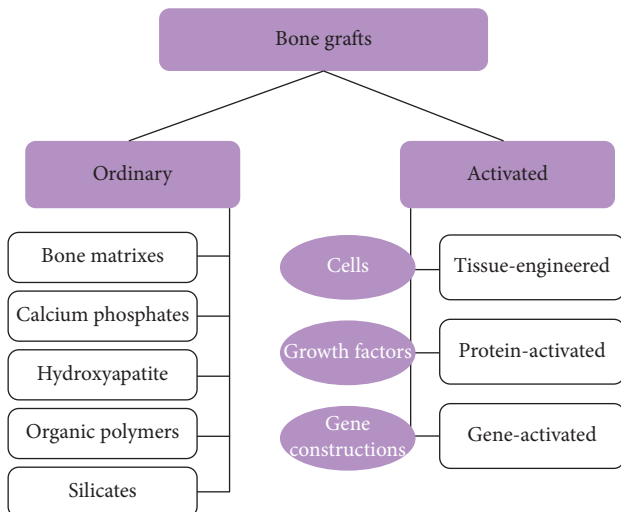


FIGURE 3: Types of ordinary or activated bone grafts [22].

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

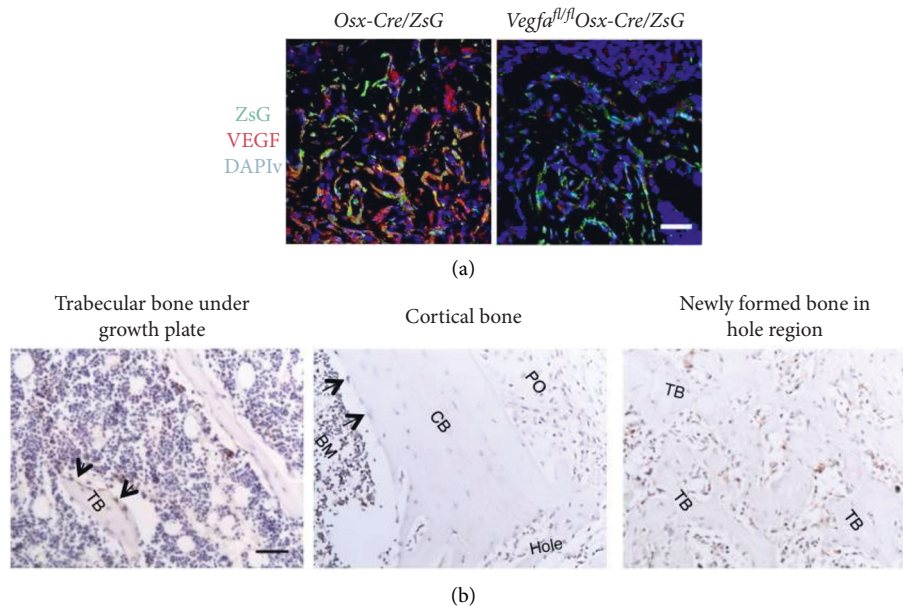


FIGURE 4: Osteoblastic lineage cells at the bone-repair site as a source of VEGF at postsurgery day 7 in WT mice. (a) A low density of anti-VEGF staining (red) in $Vegfa^{fl/fl}$ $Osx-Cre/ZsG$ mice (6.1%) compared with $Osx-Cre/ZsG$ mice (15.5%). (b) VEGF in cortical bone, trabecular bone, and the newly 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.

References

- [1] M. S. Alhammadi, A. A. Al-Mashraqi, R. H. Alnami et al., "Accuracy and reproducibility of facial measurements of digital photographs and wrapped cone beam computed tomography (CBCT) photographs," *Diagnostics*, vol. 11, no. 5, p. 757, 2021.
- [2] D. Rokaya, K. Suttagul, B. Sapkota, and S. K. Maharjan, "Gender based comparison of the relationships of maxillary anterior teeth and facial measurements," *Journal of International Dental Medical Research*, vol. 11, no. 1, pp. 465–469, 2018.
- [3] D. Rokaya, B. Bhattarai, K. Suttagul, D. Kafle, and M. Humagain, "Mentolabial sulcus: an esthetic-based classification," *Journal of Datta Meghe Institute of Medical Sciences University*, vol. 13, no. 1, pp. 16–19, 2018.
- [4] M. Humagain, D. Rokaya, R. Sree, S. Dixit, and D. Kafle, "Gender based comparison of gingival zenith esthetics," *Kathmandu University Medical Journal (KUMJ)*, vol. 14, no. 54, pp. 148–152, 2016.
- [5] E. Papatheoanis, M. Finkelman, J. Hanley, and A. O. Parashis, "Prevalence, etiology and treatment of peri-implant mucositis and peri-implantitis: a survey of periodontists in the United States," *Journal of Periodontology*, vol. 87, no. 5, pp. 493–501, 2016.
- [6] Annual report 2013, turning a new page, Straumann, 2013, <http://www.straumann.com/content/dam/internet/straumanncom/Resources/investor-relations/annual-report/2013/STMN-2013-Annual-Report.pdf>.
- [7] D. Rokaya, V. Srimaneepong, W. Wisitrasameewon, M. Humagain, and P. Thunyakitpisal, "Peri-implantitis update: risk indicators, diagnosis, and treatment," *European Journal of Dermatology*, vol. 14, no. 4, pp. 672–682, 2020.
- [8] S. M. Kurtz and J. N. Devine, "PEEK biomaterials in trauma, orthopedic, and spinal implants," *Biomaterials*, vol. 28, no. 32, pp. 4845–4869, 2007.
- [9] P. Amornvit, D. Rokaya, S. Bajracharya, K. Keawcharoen, and W. Supavanich, "Management of obstructive sleep apnea with implant retained mandibular advancement device," *World Journal of Dentistry*, vol. 5, no. 3, pp. 184–189, 2014.
- [10] H. A. Trinh, V. V. Dam, B. Le, P. Pittayapat, and P. Thunyakitpisal, "Indirect sinus augmentation with and without the addition of a biomaterial: a randomized controlled clinical trial," *Implant Dentistry*, vol. 28, no. 6, pp. 571–577, 2019.
- [11] J. D. Lee, S. Jung, C.-W. Wang, and S. J. Lee, "Integrated digital and conventional treatment workflow in guided complete mouth implant rehabilitation: a clinical case report," *Dentistry Journal*, vol. 7, no. 4, p. 100, 2019.
- [12] P. P. Poli, A. K. Mukhtadar, F. A. Souza, C. Maiorana, and M. Beretta, "Computer-guided implant placement associated with computer-aided bone regeneration in the treatment of atrophied partially edentulous alveolar ridges: a proof-of-concept study," *Journal of Dental Science*, vol. 16, no. 1, pp. 333–341, 2021.

- [13] A. Wennerberg and T. Albrektsson, "On implant surfaces: a review of current knowledge and opinions," *The International Journal of Oral & Maxillofacial Implants*, vol. 25, no. 1, pp. 63–74, 2010.
- [14] Y. Wu, J. P. Zitelli, K. S. TenHuisen, X. Yu, and M. R. Libera, "Differential response of staphylococci and osteoblasts to varying titanium surface roughness," *Biomaterials*, vol. 32, no. 4, pp. 951–960, 2011.
- [15] V. Srimaneepong, "Different surface topography of dental implant," *Chulalongkorn University Dental Journal*, vol. 24, pp. 51–56, 2001.
- [16] H. E. Jazayeri, M. Tahriri, M. Razavi et al., "A current overview of materials and strategies for potential use in maxillofacial tissue regeneration," *Materials Science and Engineering: C*, vol. 70, no. Pt 1, pp. 913–929, 2017.
- [17] E. García-Gareta, M. J. Coathup, and G. W. Blunn, "Osteoinduction of bone grafting materials for bone repair and regeneration," *Bone*, vol. 81, pp. 112–121, 2015.
- [18] M. E. Sayed, M. H. Mugri, M. A. Almasri et al., "Role of stem cells in augmenting dental implant osseointegration: a systematic review," *Coatings*, vol. 11, 2021.
- [19] S. Bhandi, A. Alkahtani, R. Reda et al., "Parathyroid hormone secretion and receptor expression determine the age-related degree of osteogenic differentiation in dental pulp stem cells," *Journal of Personalized Medicine*, vol. 11, no. 5, 2021.
- [20] K. Tappa and U. Jammalamadaka, "Novel biomaterials used in medical 3D printing techniques," *Journal of Functional Biomaterials*, vol. 9, no. 1, 2018.
- [21] S. Derakhshanfar, R. Mbeleck, K. Xu, X. Zhang, W. Zhong, and M. Xing, "3D bioprinting for biomedical devices and tissue engineering: a review of recent trends and advances," *Bioactive Materials*, vol. 3, no. 2, pp. 144–156, 2018.
- [22] R. V. Deev, A. Y. Drobyshev, I. Y. Bozo, and A. A. Isaev, "Ordinary and activated bone grafts: applied classification and the main features," *BioMed Research International*, vol. 2015, Article ID 365050, 19 pages, 2015.
- [23] M. Chiapasco, P. Casentini, and M. Zaniboni, "Bone augmentation procedures in implant dentistry," *The International Journal of Oral & Maxillofacial Implants*, vol. 24, pp. 237–259, 2009.
- [24] Y. J. Kim, C. E. T. Saiki, K. Silva et al., "Bone formation in grafts with bio-oss and autogenous bone at different proportions in rabbit calvaria," *International Journal of Dentistry*, vol. 2020, Article ID 2494128, 6 pages, 2020.
- [25] P. Kumar, B. Vinitha, and G. Fathima, "Bone grafts in dentistry," *Journal of Pharmacy & bioallied sciences*, vol. 5, pp. S125–S127, 2013.
- [26] N. Moussa, Y. Fan, and H. Dym, "Maxillofacial bone grafting materials," *Dental Clinics of North America*, vol. 65, no. 1, pp. 167–195, 2021.
- [27] C. Laurencin, Y. Khan, and S. F. El-Amin, "Bone graft substitutes," *Expert Review of Medical Devices*, vol. 3, no. 1, pp. 49–57, 2006.
- [28] N. T. Moussa and H. Dym, "Maxillofacial bone grafting materials," *Dental Clinics of North America*, vol. 64, no. 2, pp. 473–490, 2020.
- [29] D. Carmagnola, S. Abati, S. Celestino, M. Chiapasco, D. Bosshardt, and N. P. Lang, "Oral implants placed in bone defects treated with bio-oss, ostim-paste or perioglas: an experimental study in the rabbit tibiae," *Clinical Oral Implants Research*, vol. 19, no. 12, pp. 1246–1253, 2008.
- [30] H. Browaeys, P. Bouvry, and H. De Bruyn, "A literature review on biomaterials in sinus augmentation procedures," *Clinical Implant Dentistry and Related Research*, vol. 9, no. 3, pp. 166–177, 2007.
- [31] S. Chavda and L. Levin, "Human studies of vertical and horizontal alveolar ridge augmentation comparing different types of bone graft materials: a systematic review," *Journal of Oral Implantology*, vol. 44, no. 1, pp. 74–84, 2018.
- [32] C. Maiorana, P. P. Poli, A. Mascellaro, S. Ferrario, and M. Beretta, "Dental implants placed in resorbed alveolar ridges reconstructed with iliac crest autogenous onlay grafts: a 26-year median follow-up retrospective study," *Journal of Cranio-Maxillofacial Surgery*, vol. 47, no. 5, pp. 805–814, 2019.
- [33] T. L. Aghaloo and P. K. Moy, "Which hard tissue augmentation techniques are the most successful in furnishing bony support for implant placement?" *The International Journal of Oral & Maxillofacial Implants*, vol. 22, pp. 49–70, 2007.
- [34] M. Yilmaz, H. Vayvada, A. Menderes, C. Demirdover, and A. Kizilkaya, "A comparison of vascularized fibular flap and iliac crest flap for mandibular reconstruction," *Journal of Craniofacial Surgery*, vol. 19, no. 1, pp. 227–234, 2008.
- [35] J. Ferri, B. Piot, B. Ruhin, and J. Mercier, "Advantages and limitations of the fibula free flap in mandibular reconstruction," *Journal of Oral and Maxillofacial Surgery*, vol. 55, no. 5, pp. 440–448, 1997.
- [36] D. Fasano, F. M. Montanari, R. Cocchi, and C. Marchetti, "Free-flap fibula for the reconstruction of composite mandibular defects," *Acta Otorhinolaryngologica Italica*, vol. 16, no. 1, pp. 25–29, 1996.
- [37] S. Lonie, P. Herle, A. Paddle, N. Pradhan, T. Birch, and R. Shayan, "Mandibular reconstruction: meta-analysis of iliac-versus fibula-free flaps," *ANZ Journal of Surgery*, vol. 86, no. 5, pp. 337–342, 2016.
- [38] S. Y. Patel, D. D. Kim, and G. E. Ghali, "Maxillofacial reconstruction using vascularized fibula free flaps and endosseous implants," *Oral and Maxillofacial Surgery Clinics of North America*, vol. 31, no. 2, pp. 259–284, 2019.
- [39] R. S. Jackson, D. L. Price, K. Arce, and E. J. Moore, "Evaluation of clinical outcomes of osseointegrated dental implantation of fibula free flaps for mandibular reconstruction," *JAMA Facial Plastic Surgery*, vol. 18, no. 3, pp. 201–206, 2016.
- [40] F.-C. Wei, E. Santamaria, Y.-M. Chang, and H.-C. Chen, "Mandibular reconstruction with fibular osteoseptocutaneous free flap and simultaneous placement of osseointegrated dental implants," *Journal of Craniofacial Surgery*, vol. 8, no. 6, pp. 512–521, 1997.
- [41] B. R. Barber, P. T. Dziegielewski, R. Chuka, D. O'Connell, J. R. Harris, and H. Seikaly, "Bone-impacted fibular free flap: long-term dental implant success and complications compared to traditional fibular free tissue transfer," *Head & Neck*, vol. 38, pp. E1783–E1787, 2016.
- [42] P. T. Dziegielewski, A. M. Mlynarek, J. R. Harris et al., "Bone impacted fibular free flap: a novel technique to increase bone density for dental implantation in osseous reconstruction," *Head & Neck*, vol. 36, no. 11, pp. 1648–1653, 2014.
- [43] R. Dimitriou, E. Jones, D. McGonagle, and P. V. Giannoudis, "Bone regeneration: current concepts and future directions," *BMC Medicine*, vol. 9, no. 1, p. 66, 2011.
- [44] M. Yildirim, H. Spiekermann, S. Handt, and D. Edelhoff, "Maxillary sinus augmentation with the xenograft bio-oss and autogenous intraoral bone for qualitative improvement of the implant site: a histologic and histomorphometric clinical study in humans," *The International Journal of Oral & Maxillofacial Implants*, vol. 16, no. 1, pp. 23–33, 2001.
- [45] L. Cordaro, D. D. Bosshardt, P. Palattella, W. Rao, G. Serino, and M. Chiapasco, "Maxillary sinus grafting with bio-ossor

- straumannbone ceramic: histomorphometric results from a randomized controlled multicenter clinical trial,” *Clinical Oral Implants Research*, vol. 19, no. 8, pp. 796–803, 2008.
- [46] L. Meijndert, G. M. Raghoobar, P. Schüpbach, H. J. A. Meijer, and A. Vissink, “Bone quality at the implant site after reconstruction of a local defect of the maxillary anterior ridge with chin bone or deproteinised cancellous bovine bone,” *International Journal of Oral and Maxillofacial Surgery*, vol. 34, no. 8, pp. 877–884, 2005.
- [47] N. Thuaksuban, T. Nuntanarant, and P. Pripatnanont, “A comparison of autogenous bone graft combined with deproteinized bovine bone and autogenous bone graft alone for treatment of alveolar cleft,” *International Journal of Oral and Maxillofacial Surgery*, vol. 39, no. 12, pp. 1175–1180, 2010.
- [48] D. B. Kamadjaja, Z. Z. Abidin, R. Diana et al., “In vivo analyses of osteogenic activity and bone regeneration capacity of demineralized freeze-dried bovine bone xenograft: a potential candidate for alveolar bone fillers,” *International Journal of Dentistry*, vol. 2021, Article ID 1724374, 10 pages, 2021.
- [49] R. Medikeri, V. Meharwade, and K. Sinha, “Effects of recombinant human bone morphogenetic protein-2 compared to other biomaterials in the treatment of intrabony defects in periodontitis patients: a systematic review,” *Journal of Indian Society of Periodontology*, vol. 23, no. 4, pp. 311–315, 2019.
- [50] Z. Sheikh, M. Javaid, N. Hamdan, and R. Hashmi, “Bone regeneration using bone morphogenetic proteins and various biomaterial carriers,” *Materials*, vol. 8, no. 4, pp. 1778–1816, 2015.
- [51] K. Hu and B. R. Olsen, “The roles of vascular endothelial growth factor in bone repair and regeneration,” *Bone*, vol. 91, pp. 30–38, 2016.
- [52] K. Hu and B. R. Olsen, “Osteoblast-derived VEGF regulates osteoblast differentiation and bone formation during bone repair,” *Journal of Clinical Investigation*, vol. 126, no. 2, pp. 509–526, 2016.
- [53] W. Zhang, C. Zhu, Y. Wu et al., “VEGF and BMP-2 promote bone regeneration by facilitating bone marrow stem cell homing and differentiation,” *European Cells and Materials*, vol. 27, pp. 1–11, 2014.
- [54] J. L. Holloway, H. Ma, R. Rai, and J. A. Burdick, “Modulating hydrogel crosslink density and degradation to control bone morphogenetic protein delivery and in vivo bone formation,” *Journal of Controlled Release*, vol. 191, pp. 63–70, 2014.
- [55] Y.-R. Yun, J. H. Jang, E. Jeon et al., “Administration of growth factors for bone regeneration,” *Regenerative Medicine*, vol. 7, no. 3, pp. 369–385, 2012.
- [56] P.-C. Chang, A. S. Dovban, L. P. Lim, L. Y. Chong, M. Y. Kuo, and C.-H. Wang, “Dual delivery of PDGF and simvastatin to accelerate periodontal regeneration in vivo,” *Biomaterials*, vol. 34, no. 38, pp. 9990–9997, 2013.
- [57] P. Kasten, I. Beyen, D. Bormann, R. Luginbühl, F. Plöger, and W. Richter, “The effect of two point mutations in GDF-5 on ectopic bone formation in a β -tricalciumphosphate scaffold,” *Biomaterials*, vol. 31, no. 14, pp. 3878–3884, 2010.
- [58] K. Kleinschmidt, F. Ploeger, J. Nickel, J. Glockenmeier, P. Kunz, and W. Richter, “Enhanced reconstruction of long bone architecture by a growth factor mutant combining positive features of GDF-5 and BMP-2,” *Biomaterials*, vol. 34, no. 24, pp. 5926–5936, 2013.
- [59] F. Wegman, A. Bijenhof, L. Schuijff, F. C. Oner, W. J. Dhert, and J. Alblas, “Osteogenic differentiation as a result of BMP-2 plasmid DNA based gene therapy in vitro and in vivo,” *European Cells and Materials*, vol. 21, pp. 230–242, 2011.
- [60] C. H. Evans, “Gene delivery to bone,” *Advanced Drug Delivery Reviews*, vol. 64, no. 12, pp. 1331–1340, 2012.
- [61] A. I. Caplan, “Mesenchymal stem cells and gene therapy,” *Clinical Orthopaedics and Related Research*, vol. 379, pp. S67–S70, 2000.
- [62] L. K. Chow and L. K. Cheung, “The usefulness of stereomodels in maxillofacial surgical management,” *Journal of Oral and Maxillofacial Surgery*, vol. 65, no. 11, pp. 2260–2268, 2007.
- [63] A. M. Pham, A. A. Rafii, M. C. Metzger, A. Jamali, and B. E. Strong, “Computer modeling and intraoperative navigation in maxillofacial surgery,” *Otolaryngology-Head and Neck Surgery*, vol. 137, no. 4, pp. 624–631, 2007.
- [64] M. Butu, S. Rodino, M. Pentea, N. Adina, P. Petrache, and M. Butnariu, “IR spectroscopy of the flour from bones of European hare,” *Digest Journal Nanomater Biostructures*, vol. 9, no. 4, pp. 1317–1322, 2014.
- [65] M. Butnariu, P. Negrea, L. Lupa et al., “Remediation of rare earth element pollutants by sorption process using organic natural sorbents,” *International Journal of Environmental Research and Public Health*, vol. 12, no. 9, pp. 11278–11287, 2015.
- [66] R. Reda, A. Zanza, A. Cicconetti et al., “Ultrasound imaging in dentistry: a literature overview,” *Journal of Imaging*, vol. 7, no. 11, p. 238, 2021.
- [67] M. Schlee and D. Rothamel, “Ridge augmentation using customized allogenic bone blocks,” *Implant Dentistry*, vol. 22, no. 3, pp. 212–218, 2013.
- [68] N. Casap, Z. Laster, A. Laviv et al., “Recombinant human bone morphogenetic protein-2 confined by an impermeable titanium shell over high-profile dental implants in rabbit tibiae: a pilot bone augmentation study,” *The International Journal of Oral & Maxillofacial Implants*, vol. 28, no. 6, pp. e349–e356, 2013.