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Review Article

Biomaterials in Guided Bone and Tissue Regenerations: An Update

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Purpose. Guided tissue reconstruction can be performed to restore the supporting structure of a previously lost tooth, which, in addition to maintaining beauty, preserves the function of the tooth in the patient. *Materials and Methods*. In this review, Scopus, PubMed, and MEDLINE databases were searched using the keywords "biocompatible materials," "membrane," "bone regeneration," "tissue reconstruction," and "dental biomaterials." Overall, 150 articles were reviewed, and finally, 107 articles published during 2000–2021 were included in the final paper. *Results*. Studies have been conducted on a variety of membranes in both clinical and experimental settings. The first half of this article explores the different kinds of membranes and diverse classes of biomaterials used in these procedures. Secondly, biomaterials are examined for their therapeutic uses such as growth factors, stem cells, and gene delivery vehicles. *Conclusion*. If a tooth has been extracted or if the gums have been infected with periodontal disease, guided bone regeneration procedures may be used to restore the lost bone. Recent years have seen a variety of approaches to regenerating these tissues. To prevent nonossifying cells from entering, membranes are heavily employed during guided rebuilding.

1. Introduction

Today, one of the most critical topics in periodontology is the repair of periodontal lesions and the reconstruction of lost jawbone through proliferating bone cells. A fundamental prerequisite for successful implant treatments is the adequate volume of hard bone tissue [1]. On the other hand, for the successful repair of damaged tissue, it is necessary to prevent the invasion of cells with high-speed migration to the damaged tissue and guide sedentary cells to the lesion site.

In recent years, tissue engineering using biocompatible polymers has introduced new methods for repairing damaged tissues [2]. Guided bone regeneration (GBR) and guided tissue regeneration (GTR) are the most important conventional reconstruction methods. The GBR is used to regenerate alveolar bone in toothless areas, and GTR is utilized to repair damaged periodontal tissue [3, 4]. In general, GTR and GBR are surgical techniques that use a porous polymer membrane to physically prevent the migration of undesirable tissues and cells to the lesion site [4]. As a result, a suitable space and substrate are provided for

repairing damaged tissue by proliferating the cells in question [5]. The GBR can maintain and strengthen the alveolar bulge, regenerate alveolar bone, correct contractions around the implant or fenestration, and regenerate the bone around the implant [6]. In contrast, GTR refers to periodontal ligament (PDL) regeneration, bone regeneration, and cementum around the tooth [7].

Although porous membranes in the GBR technique seem necessary, repairing and growing damaged bone require osteogenic cells, as well as osteoconductive and bone-inducing (osteoinductive) materials [8]. The ideal membrane used in guided bone tissue repair should have unique properties, such as good biocompatibility and functional stability over the required time. In addition, the membrane must maintain the space and biomechanical stability of the lesion area by filtering out the disturbing cells and tissues and protecting the newly formed tissue [9].

Generally, membranes used in GTR and GBR techniques may fall into the following categories: (1) bioabsorbable based on natural polymers, including collagen, chitosan, and gelatin, or synthetic polymers; (2) nonresorbable membranes, including expanded polytetrafluoroethylene, titanium-reinforced e-PTFE, and dense-PTFE [10]; and (3) metals and inorganic compounds considered as another group of guided membranes, which will be discussed in detail.

2. Materials and Methods

Based on the institutional regulations, this research was granted an exemption regarding approval since it was a literature review. A comprehensive search of the Scopus, PubMed, and MEDLINE databases was performed. All relevant articles published during 2000–2021 were obtained using the keywords "biocompatible materials," "membrane," "bone regeneration," "tissue reconstruction," and "dental biomaterials." Afterwards, articles were reviewed by titles and abstracts. The papers that were less relevant to the subject of study were excluded. The remaining full-text articles were evaluated, and those unrelated to the subject were removed. The filtered papers were further analyzed by the team of authors, and this review was structured.

3. Bioabsorbable

A significant advantage of this type of membrane is that it does not have to be removed by secondary surgery, that it has a better repair and healing ability, that it is biocompatible, and that it reduces the risk of inflammation and infection [11]. However, there are several limitations to these structures, the most important of which is the low ability to make a suitable space for new tissue growth and the high destruction rate. These structures are destroyed in the body much faster than expected and leave the damaged area before completing the tissue formation process [12, 13]. The two kinds of adsorbable membranes consist of natural polymers and synthetic polymers [14].

3.1. Natural Adsorbable Membranes. The application of natural polymers has expanded due to their properties in the GTR and GBR processes. In other words, inherent bioactivity and the ability to provide active sites for cell attachment are among the most important advantages of natural polymers over synthetic polymers [15]. However, some problems related to the intrinsic bioactivity of polymers, including strong immune responses, complications associated with the purification of these polymers, and the possibility of disease transmission, restrict the use of these polymers [16]. Table 1 summarizes the disadvantages and advantages of various types of membranes.

3.1.1. Collagen Membranes. Collagen is the hardest filament in the connective tissue. This membrane has significant advantages, such as good tissue integrity, fast vascularization, biodegradability without external reactions, weak immunogenicity, hemostatic property, biocompatibility, and wound healing capacity [42]. In addition, collagen is a chemotactic factor for fibroblasts and accelerates cell migration. Collagen membranes may secondarily increase tissue thickness as a result of enzymatic degradation and replacement by surrounding connective tissue [43]. Such properties have led to collagen-based membranes in GTR and GBR research. This type of membrane is degradable and adsorbable by enzymatic degradation, carried out by collagenases and proteases [44, 45]. Porcine collagen fiber types I and II are incorporated into Bio-Gide, one of the most commonly used commercial collagen membranes. Soft tissue invasion and development into a defect may be limited by the smooth surface of Bio-Gide, which may also act as a scaffold for the attachment of fibroblasts [46–50]. The rough, porous side of Bio-Gide functions as a framework for the migration and proliferation of blood vessels and bone cells [43, 46].

Disadvantages of collagen membranes have rapid biodegradability and reduced membrane capability in maintaining the space and biomechanical stability of the lesion area in wet conditions. The destruction time of these membranes is about 4–8 weeks, which is not enough for the full regeneration of bone tissue [51, 52]. To improve the mechanical properties and decrease the rate of deterioration of collagen membranes, several approaches have been investigated [42, 53]. There are a number of possibilities for treatment with UV light or chemical therapies with genipin (Gp) [54, 55].

Moreover, various physical, chemical, and biological crosslinking methods effectively strengthen the mechanical characteristics and augment the stability of collagen membranes against biodegradability. The most common chemical crosslinking agents are glutaraldehyde, 3-dimethyl-aminopropyl, carbodiimide, and polypoxy [45, 55]. Crosslinking is accompanied by pros and cons. Its advantage is improving the tensile strength of collagen and delaying the breakdown time [56]. Drawbacks entail limiting the use of membranes by creating potential toxic effects by the remaining crosslinking agent or the formation of byproducts during collagen degradation, which can lead to severe inflammation at the

Table 1: Advantages and disadvantages of various membranes.

Membrane type	Membrane materials	Advantage	Disadvantage	References
Natural polymers	Collagen, gelatin, chitosan	• High biocompatibility • Improved cellular Interaction •Hydrophilicity •Antibacterial effect •Cell/drug containing •Enhancement of wound healing •No surgical removal	• Lack of bioactivity • Rapid degradation rate •Low mechanical strength •Residual crosslinking agents •Possible disease transmission •Questionable barrier function •Hard to control biodegradation •Few studies	[17–27, 51, 52, 57, 60]
Synthetic polymers	PLA/PLGA, PCL, PEG	• Mechanical strength can be processed • Able to seed mesenchymal cells/growth factors •Favorable biocompatibility •Favorable barrier function •High reproducibility •Manageable biodegradability and mechanical properties •No surgical removal needed	• Slow degradation rate • Hydrophobic (PCL) •Low cell affinity •Poor cellular response •Not suitable for a drug delivery system •Acidic byproducts	[28–34]
Nonresorbable	e-PTFE, d-PTFE, TR-ePTFE	• Many studies demonstrate their success • Could be titanium-reinforced •Remain intact until removal •Easily fixed with titanium or resorbable tacks •Greater bone fill if the membrane is not exposed •Minimal tissue response if the membrane is not exposed •High chemical stability •High biocompatibility •High barrier function	• Require a second surgery for removal • Increase patient morbidity •If exposed, must be removed in most cases •Could be technique sensitive •Membrane exposure	[12, 35–38, 87]
Metals	Titanium, titanium alloy	• High biocompatibility • High barrier function •Mechanical strength, durability	• Surgical removal required • Expensive	[39–41, 91]

implant site [51, 57]. Crosslinking, in addition to reducing the rate of degradation, greatly diminishes tissue integration and angiogenesis and also affects the biocompatibility of the final structure. Increasing the percentage of crosslinker decreases the adhesion and proliferation of PDL fibroblasts and osteoblasts [58, 59]. Therefore, the success of the operation by collagen membrane, in addition to the source of the collagen, depends on the preparation and processing stages, including decellularization, sterilization, and crosslinking methods. The Gp and D-ribose, as two natural safe and nontoxic compounds, have been proposed to raise the mechanical strength of collagen and diminish its degradation rate [51, 60, 61].

3.1.2. Gelatin-Based Membrane. Gelatin is a protein that is soluble and is made from collagen. Improved cell adhesion, suitable biocompatibility, reasonable price, and flexibility of this protein have made it a favorable biomaterial for tissue engineering, GTR, and GBR [62, 63]. Protein membranes have poor mechanical properties, and they degrade rapidly. A method for improving stability and mechanical properties is crosslinking glutaraldehyde and N-hydroxyl succinamide using heat treatment [64]. However, crosslinking can reduce the modulus of elasticity under humid conditions, even though it improves the tensile properties of gelatin fiber membranes. Because of this, gelatin can sometimes be used alone in GTR and GBR [65, 66].

3.1.3. Chitosan-Based Membranes. Studies showed that chitosan is well adapted to cells in vitro and facilitates bone regeneration at the site of rat skull lesions [67]. Chitosan is also a suitable membrane for GTR and GBR because of its reasonable price, high biocompatibility, good degradation rate, antibacterial properties, wound healing potential, and flexibility in humid environments. Chitosan membranes deteriorate at different rates depending on their molecular weight and manufacture method [68]. One of the ways to boost mechanical strength and reduce the rate of chitosan degradation is chemical crosslinking. Gp-crosslinked chitosan membranes produce fewer inflammatory reactions than glutaraldehyde-crosslinked membranes, accelerating lesion healing [69]. Chitosan-based electrospinning membranes crosslinked with Gp have a much lower degradation rate than nonlattice membranes. Due to the high cost of Gp and the toxicity of glutaraldehyde, ionic crosslinking with sodium tripolyphosphate has been proposed as an alternative for crosslinking [70].

3.2. Synthetic Adsorbable Membranes

3.2.1. PLA and PLGA. The PLA is among the most important and common synthetic polymers applied in the GTR and GBR processes. This polymer has high mechanical and biocompatible properties. To control the hydrophilicity of PLA and its degradation rate, its copolymers are synthesized based on lactide, caprolactone, and glycolide [71]. Polyglycolic acid (PLGA), in orthopedic applications, is an excellent alternative to PLA. Despite the biodegradability and nontoxicity of PLA and PLGA-based membranes, there are limitations to using these membranes. One of these problems is the possibility of inflammatory reactions and reactions to an external object in vivo when oligomers and acidic byproducts are released during degradation [72]. Their hardness is another problem that limits the medical applications of these membranes. One effective solution for the hardness is to add emollients, such as N-methyl-2-pyrrolidone (NMP). The NMP softens PLGA membranes, thereby accelerating bone regeneration and osteoblast growth [73].

3.2.2. Poly-Caprolactone (PCL). A low-cost polymer is also biocompatible and possesses excellent mechanical strength. Therefore, it has received much attention in bone tissue engineering. There are still few studies on PCL-based GTR membranes. One of the advantages of this polymer over PLA and PLGA polymers is that PCL degradation does not increase environment acidity [74]. The complete bioabsorption of the PCL membrane in the body takes about 3 years, which is long for use in the GBR and GTR methods. On the other hand, the hydrophobicity of its pure membranes reduces adhesion and cell proliferation. Consequently, it is always combined with other polymers or as a copolymer for medical applications [75, 76].

3.2.3. Polyethylene Glycol (PEG). This polymer is remarkably biodegradable and biocompatible, making it a suitable option for use in GTR and GBR membranes [77]. The main positive points of this polymer membrane are regulated biodegradation, manageability, processability, and the ability to encapsulate the medicine [75, 78]. In contrast, poor instability and high degradation rates produce a robust inflammatory response that affects the outcome of bone regeneration and leads to regenerated bone resorption [79, 80].

4. Nonresorbable

The first used membranes were nonresorbable and able to keep the bone lesion separate from other tissue cells for a long time. In these membranes, reoperation is often required to remove the membrane. The repair will not occur spontaneously if these membranes are exposed. In addition, there is a possibility of bacterial contamination of the exposed membrane resulting in infection [81].

4.1. Expanded Polytetrafluoroethylene (e-PTFE). The e-PTFE membranes are the first synthetic polymer used for GBR with cavities of 0.02–20 μm and are an excellent candidate to cover the defect opening around the implant and repair or maintain the bone around the implant in the area [82–85]. Due to its high chemical stability, this membrane is biologically considered the most stable polymer, which resists degradation caused by host tissues and does not lead to immunological reactions [80]. They also prevent bone and

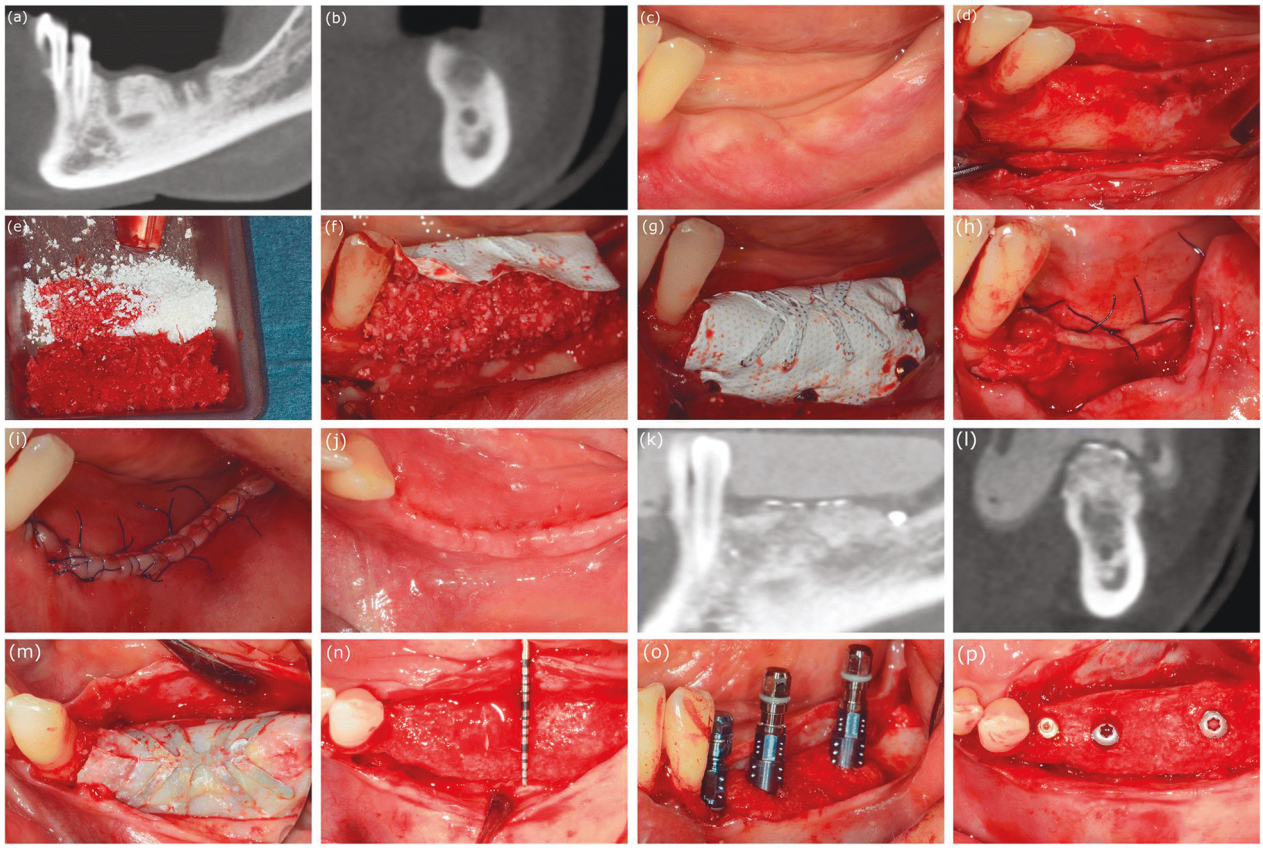

Figure 1: Bone augmentation with a titanium-reinforced d-PTFE membrane. (a) Primary CBCT scan, parasagittal section showing the horizontal and vertical bone defect. (b) Primary CBCT scan, frontal section showing the horizontal and vertical bone defect. (c) Clinical photograph of the edentulous mandible. (d) Flap preparation with the split-thickness method. (e) Bovine-derived xenograft (Geistlich Bio-Oss) and particulate autogenous bone graft. (f) Adaptation of nonresorbable titanium-reinforced d-PTFE membrane (Osteogenics Cytoplast) over the graft. (g) Fixing the membrane with titanium pins. (h) Suturing. (i) Closure of the mucosal layer with horizontal mattress and noninterrupted sutures. (j) Healing two weeks post-op. (k) Postoperative CBCT scan after nine months: parasagittal section. (l) Postoperative CBCT scan after nine months: frontal section. (m) Reentry for removing the membrane. (n) Good quantity of bone tissue for implant placement. (o) Guided implant surgery (Straumann bone level). (p) Final positioning of implants through a prosthetically driven technique [92].

other connective tissue cells from migrating to the lesion [86]. As a result, bone marrow cells, which migrate less rapidly, are more likely to be present at the lesion site. Despite the expansion of tetrafluoroethylene membranes, osteogenesis without interfering with other tissues leads to repairing damaged bone tissue in an average period of three months. In contrast, osteogenesis occurs incompletely in control samples without membrane because of connective tissue interference [87].

4.2. Dense Polytetrafluoroethylene (D-PTFE). The porosity of the e-PTFE membrane can allow germs to migrate. This problem was addressed through the creation of d-PTFE membranes with pores smaller than 0.3 m. Clinical studies have found that d-PTFE does not generate bacterial colonies as rapidly as e-PTFE [88, 89]. The d-PTFE membranes used in the mouth cavity may prevent bacteria from passing through, but they do allow oxygen to enter and tiny molecules to pass through. On the other hand, e-PTFE membranes have larger holes and can interact more strongly with soft tissue. This results in membrane separation being significantly more challenging and requiring deeper incisions following hard tissue regeneration. As there is no development or attachment to soft tissues, d-PTFE membrane separation is straightforward [90].

4.3. Titanium-Reinforced Expanded Polytetrafluoroethylene (TR-ePTFE). Flexible titanium mesh-reinforced polytetrafluoroethylene membranes allow the membrane to be ductile to fit the shape and size of the defect in the desired area and provide adequate structural stability in bone defects around the implant [91]. Figure 1 demonstrates an implant surgical procedure using a titanium-reinforced d-PTFE membrane [92]. Clinical and experimental studies on nonabsorbable membranes have shown good therapeutic results in GTR and GBR applications. However, one of the most important disadvantages of these membranes is the need for secondary surgery to remove them after bone growth. In addition to raising the cost to patients, this sometimes leads to the loss of a part of the regenerated tissue. Stiffness and rigidity are

other weaknesses of nonabsorbable membranes that screws are used in most cases to make them more stable [56].

4.4. Metals. A frequent medical material used in maxillofacial surgery and orthopedics, titanium, is highly biocompatible, strong, corrosion-resistant, dense, and light [93]. In addition to bone grafts, titanium mesh has been shown to improve the localized deficiency of the alveolar ridge prior to or after implant placement [94, 95]. Studies have shown that titanium causes less lasting inflammation compared with PTFE [96]. When considering chronic inflammation connected to titanium micro/nanoparticles, there is a well-established mechanism by which metal nanoparticles cause inflammation via their immunomodulatory properties, which mostly act at the macrophage level [97, 98]. A number of factors increase with increasing oxidative stress, including DNA damage, protein carbonylation, lipid peroxidation, and superoxide dismutase activity, while catalase and total glutathione are all declining. In addition, they result in macrophage activation that is aberrant, which is associated with an increase in inflammation and a decrease in innate immunity [99, 100]. Ti nanoparticles were investigated in vitro to determine their effects on MSC physiology, ROS generation, and phenotyping of osteogenic and adipogenic cells. Activating PKC beta, which is implicated in MSC commitment to adipocyte lineage, also causes ROS production, and metal particles are not degradable, so ROS production causes abnormal neutrophil recruitment. The bone regeneration function of VEGF is reduced by a genetic abnormality. This imbalance affects the osteogenic commitment [101]. Another used metal is cobalt-chromium (CoCr), which has suitable mechanical properties, but less biocompatibility than titanium. One study found that placing a CoCr membrane on the tibial defect of a rabbit created enough space for bone regeneration [102].

5. Inorganic Components

Calcium sulfate (CaS) is a substance used to form significant GBR membranes because it is osteoconductive, biocompatible, and bioresorbable [103, 104]. It is possible to make solid substances with relatively stable and less absorbable crystals by hydrating CaS hemihydrate powder [105, 106]. It is a calcium phosphate of the hydroxyapatite type. HA is frequently used in bone applications due to its resemblance to bone minerals and biocompatibility. The biocompatibility and osteoconductivity of HA make it a common material used in bone treatments. Membranes with strong mechanical properties can withstand soft tissue static pressure while allowing bone to regenerate more readily [107]. When combined with nonabsorbable and absorbable membranes, membranes that are mixed with HA have been shown to enhance osteoblast-like cell activity in vitro [108–113].

6. Biomaterial-Based Delivery

6.1. Growth Factor Delivery. Signal molecules such as growth factors control how cells grow and develop. Several cell functions are affected by growth factors, including proliferation, migration, and extracellular matrix (ECM) formation. Some of them play a role in cell differentiation [114]. Growth factors include VEGFs, FGFs, PTHs, PDGFs, and IGFs. When cells begin to repair themselves, PDGF is released, which is chemotactic and mitogenic. Angiogenesis is induced by FGF, and cells such as fibroblasts, periodontal ligaments, osteoblasts, and endothelium are proliferated and differentiated by this growth factor [115]. Similarly, FGF signaling contributes to the development of the cranial skeleton [116]. Figure 2 illustrates a method developed to deliver growth factors to scaffolds [117]. The combined use of PDGF and grafts results in bone regeneration of up to 5 mm, whereas grafts alone result in bone regeneration of about 1-2 mm. Therefore, it is expected that growth factors will enhance the results of grafting materials [114]. To maintain skeletal health and growth, IGFs are necessary [118]. The mesenchyme also plays a role in vascularization, proliferation, and bone formation in the skull and maxilla [119]. Periodontal lesions are treated with plasma-rich plasma (PRP) derived from one's own centrifuged blood. This can be used alone or with grafting materials. Although there is insufficient evidence to suggest a relation between PRP and maxillary sinus floor elevation, it appears to have benefits in treating periodontal lesions [120, 121]. The PDGFs are known to contribute to bone repair, wound healing, and regeneration following trauma or infection by stimulating osteoblastic progenitor cells to multiply [122]. There is histological evidence that the enamel matrix derivative (EMD), Emdogain, can regenerate periodontal lesions due to its high amelogenin content and small amounts of enamel and other proteins. Additionally, angular periodontal lesions can be treated with it [123, 124]. In addition, EMD contains growth factors that stimulate the production of growth factors, such as bone morphogenetic proteins (BMPs), and enhance angiogenesis. In addition, EMD contains growth factors that encourage angiogenesis and enhance bone morphogenetic proteins (BMPs). In several studies, the combination of demineralized freeze-dried bone allograft (DFDBA) with EMD has been studied and found to be successful in regenerating periodontal lesions [125, 126].

Bone matrix proteins, or BMPs, play an important role in bone development at all stages. In addition to their contribution to the formation of the neural crest, rhBMP-7 and rhBMP-2 are also involved in the development of the teeth, lips, palates, and facial primordia, as well as creating soft and hard calluses [116, 127]. In the process of creating it, orthopedics, periodontics, and dentistry were considered. By interacting with the ECM, growth factors are stabilized and maintained in vivo. To achieve steady and local release of one or several GFs, selecting the right biomaterial delivery method is crucial [128]. To capture GFs physically or chemically, sponges, micro/nanoparticles, nanofiber membranes, and hydrogels are being used as delivery vehicles [129]. In addition to maintaining release kinetics, the GFs in the biomaterial provide a porous scaffold that facilitates internal bone growth [118, 130]. The following examples demonstrate two effective strategies. According to Jung, recombinant BMP-2 has the potential to enhance and expedite gingival resorption in humans, as well as for a wide

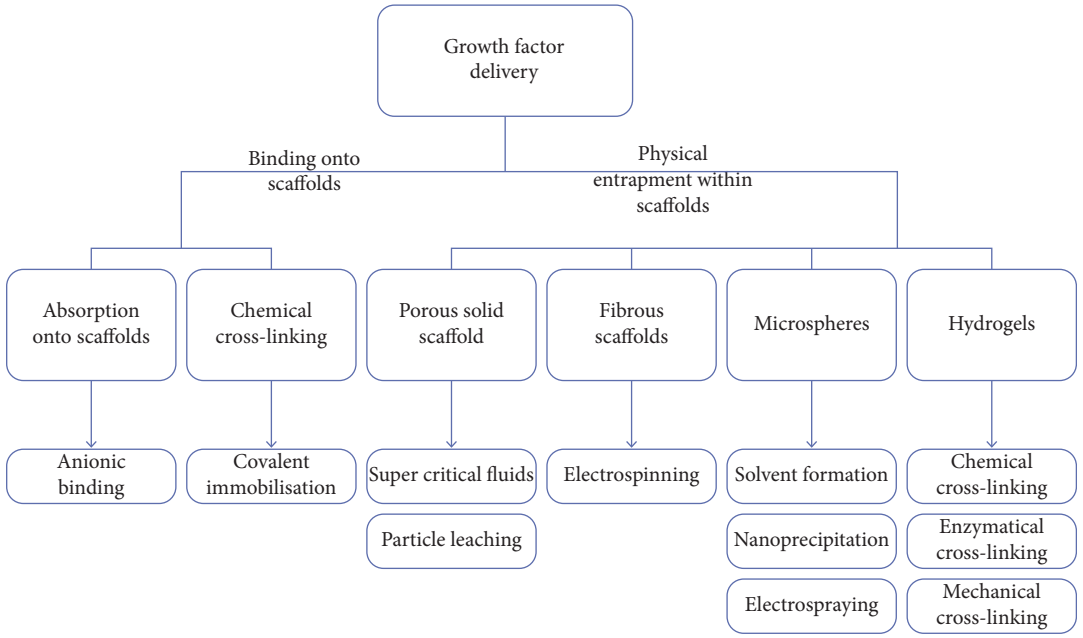

Figure 2: Current methods for fabrication of growth factor-loaded scaffolds [117].

range of bone defects. These include (1) rhBMP-2 injected into absorbable collagen for sinus lift and local augmentation of alveolar ridges, (2) OP-1 putty and rhBMP-7 for nonbonded fractures, and (3) TCP injected with rhPDGF for periodontal tissue [131]. Another study revealed that human periodontal ligament cells developed early osteoblasts when recombinant BMP-7 was added [132]. In bone development, bone production, and homeostasis, BMPs function in tandem with transforming growth factor-beta (TGF-beta) by activating signaling pathways [133].

6.2. Stem Cell Delivery Vehicles. Biomaterials can also be used for the delivery of stem cells. Embedded cells can be connected and developed using biomaterials rather than native ECM, avoiding ankylosis. In many cases, biomaterials can be altered to activate the cellular processes required for tissue regeneration and to prevent a host immune response [134, 135]. Hydrogels allow stem cells to be delivered minimally invasively to the face and jaw to repair deformities and disorders of the skull. Adipose tissue, dental pulp placenta, bone marrow, and limbus adult progenitor and stem cells were utilized in clinical studies [136]. Only a few commercially accessible materials based on mesenchymal stem cells are available for clinical uses such as DBM, Trinity Evolution Matrix™, Map3™, Osteocel Plus®, and AlloStem® [137]. A report by Soe and others indicated that mesenchymal stem cells existed in the periodontal ligament [138]. Overall, stem cell administration via biomaterials appears to help regenerate and restructure the oral cavity. Nevertheless, further research is required to evaluate the safety of the medication and its effectiveness in the long run [139].

6.3. Gene Delivery. The short half-lives of many growth factors used in tissue engineering restrict their availability at the right time and in the right amount. Recently, genes have been used to stimulate cells to create growth factors. Biomaterials have been preferred over other virus vector systems for their safety and ease of modification and mutagenesis [118]. A study by Giannobile et al. successfully transferred BMP-7 and PDGF genes to fibroblast, cementoblasts, and other periodontal cells [140]. Transplantation of cells expressing these genes into periodontal wounds stimulated bone and cement regeneration in rats [141]. Using this technology, periodontal repair simulations can be simulated, although additional studies on the efficiency and safety of the method are necessary [142].

6.4. Scaffold and Cell-Free Technologies. To diagnose prognostic human illness, scientists continually develop new models for diseases, detect early indicators, and experiment with new treatments. Humans are capable of curing a variety of illnesses through multipotent stem cells. Cells of the mesenchymal stem cell line may differentiate into a variety of cell types and function as paracrine glands that secrete endogenous chemicals that affect the immune response and aid tissue repair [143]. It is difficult to safely use MSC banking for rapid regenerative applications due to the unique challenges specific to each MSC type, including technical, legal, and ethical issues. EVs are a group of small vesicles that are released from a different cell types and heterogeneous cultures by budding from the plasma membrane. There are many different vesicles that are seen in EVs, such as exosomes, shed vesicles, nanoparticles, and apoptotic bodies [144]. The terms ectosome, microparticle, and nanoparticle refer to single vesicles released directly from the plasma membrane. The origin of exosomes has been implicated in numerous studies; however, reliable information regarding EV origins is often lacking. Nano- or microvesicles are classified according to their size. The secretome of a cell includes extracellular vesicles. The major

components of exosomes are nucleic acids, proteins, cytokines, enzymes, and misfolded proteins [143]. In light of their many features to be utilized for diagnosing, prognosticating, and therapeutic purposes, EVs are regarded as new and clever theranostic instruments [144]. Studies have examined how MSC-derived exosomes can be used in the regeneration of kidney, liver, hearts, and neurological damage in a variety of model illnesses and conditions. Scientists have recently focused on ESC-MSCs. Several methods were employed for examining the components in the conditioned medium, including multidimensional protein identification technologies, gene microarrays, and cytokine antibody arrays [144]. Based on computational analysis of the acquired data, computational analysis of the gene products involved in immune response and tissue differentiation was predicted [145]. According to Zhang et al., exosomes produced from human embryonic MSCs can be used to heal cartilage and subchondral bones and can therefore be considered a "cell-free" therapeutic method for osteochondral disorders [146].

6.5. Other Potential Biomaterials. These days, smart material research focuses on allotropic materials that have unique properties including medicinal applications that make them valuable components. Smart two-dimensional materials are being studied mainly due to their unique allotropic properties, which have shown potential in a number of applications. Two-dimensional materials that are nanometer scalable can be used to enhance the interaction between cells and human tissue. Biocompatible and bioactive interfaces are needed between cells and biomaterials. Recent studies have demonstrated the effectiveness of MoS2, WSe2, and h-BN as biomedical device fabrication materials [147]. It has been consistently found that two-dimensional materials exhibit distinct physical, chemical, electrical, and optical properties. The antimicrobial and physical properties of graphene have been widely reported in recent years, but the material also has certain limitations. In the coming years, black phosphorene (BP) could replace graphene as a potential material for biomedical applications due to its material structure and biological properties. In the same way as other 2D materials, BP may be used to make colorimetric and fluorescence detectors and biosensors. Furthermore, BP produces nontoxic byproducts in the body after in vivo biodegradation. The property of this material could be beneficial for pharmaceuticals, prosthetic coatings, and scaffolds. Because BP is a low cytotoxic agent, there are no local effects [147].

Inzana and others focused their 2014 research on creating calcium phosphate scaffolds using low-temperature 3D printing. Biolinking these scaffolds to bone tissue chemicals is possible because these scaffolds showed good cytocompatibility and osteoconductive properties [148]. There is already BP in bone, but in tiny amounts, comprising 1% (slightly more than 660 grams) of the total body weight [149]. A biolinkage may use this characteristic to combine with chemicals that enhance osteoconduction [148]. The role of calcium and phosphate in bone healing is well known in tissue engineering. The researchers focused on bioglass-based scaffolds made from BP nanosheets. A variety of scaffolds can be created using bio-printing. A 3D printing technique that uses biomaterials that have been doped or coated with BP might be a viable way of improving osteosarcoma therapy [150]. Wang et al. created experimental scaffolds that mimicked medullary bone by creating reticular damage to promote and enhance cellular attachment and colonization. Nanosheets of BP (200–400 nm) were applied to the scaffolds to bind them safely and effectively. Based on results from in vitro testing, the coated scaffolds were very capable of promoting bone formation due to increased cell proliferation on their surfaces, which may have been explained by their unique shape. The BP-BG scaffolds have been demonstrated to be more effective at treating post-oncological bone abnormalities in a mouse model of osteosarcoma [150]. The BP coating was also applied to hydrogels. In particular, gels were created by photo-reticulation of gelatin containing methacrylamide with ultraviolet light (GelMA). GelMA and BP were coated with arginine and poly(ester amide). A functionalized hydrogel facilitated bone development. The hydrogel's compression modulus and biodegradability time were measured in vitro, where BP submerged in mimicked physiological fluids produced a positive response. In addition, BP-based hydrogels promoted the proliferation of human dental pulp stem cells (hDPSCs) when differentiation into osteoblasts occurred. Based on the results of this study, BP-coated hydrogels may be suitable for use in dentistry if they provide the optimal environment for hDPSCs [151]. Then, 2D boron sheets have been grown on Ag substrates to produce two-dimensional triangular structures known as borophene (BO). As with graphene, boreophene regularly exhibits anisotropic properties. Because of its simple 3D structure, borons are classified as metalloids because neither metals nor nonmetals can be formed from their structure. Several semiconductors are fabricated using this material. The metal properties of boron are more apparent when it is arranged in a two-dimensional structure. This is comparable to allotropes such as graphene [152]. A borophene ridge's form and size are determined by how strongly boron atoms bond together. Because of this, the surfaces of graphene and borophene are significantly different. Borophene is a polymorphous and anisotropic compound due to its structural feature [153]. The properties of borophene make it a fascinating material for biomedical applications. This material is known as the "chameleon" of biomedical materials because it exhibits a variety of chemistry and physical properties that are suitable for both medical devices and customized biomedicine, exhibiting a variety of behavior and existence in many phases.

7. Conclusion

To place a suitable implant, doctors have examined the tissue and bone repair to put a crown/root ratio that is ideal, as well as long-term stability of soft tissue. The epithelium is separated from the damaged tissue with the help of different kinds of degradable septic membranes in GTR and GBR

treatments. Because e-PTFE membranes are indestructible, additional surgery is required to remove them. They have the greatest flaw of all. Despite their biodegradability and cell adhesion, natural polymer-based membranes have poor mechanical strength and short degradation cycles. Synthetic polymer-based membranes can be controlled for their biodegradability and mechanical strength. They, however, have a lower biological activity than natural polymers. Additionally, their decomposition products might trigger inflammatory responses outside the body. Despite some drawbacks, the importance and irreplaceability of biodegradable polymers cannot be overstated in GTR and GBR procedures, while periodontal biomaterials have become increasingly popular over the past several decades, owing to their many benefits ranging from testing membranes to everyday use. Biomaterials will be determined by factors found in genes and stem cells that control cell growth. Furthermore, membrane ossification activity needs to be studied to maintain a balance between their mechanical and biological features.

Abbreviations

GTR: Guided tissue reconstruction/regeneration
PDL: Periodontal ligament
GBR: Guided bone regeneration
PLA: Polylactic acid
PLGA: Polyglycolic acid
NMP: N-methyl-2-pyrrolidone
PCL: Poly-caprolactone
FGF: Fibroblast growth factor
PEG: Polyethylene glycol
PTFE: Polytetrafluoroethylene
e-PTFE: Expanded polytetrafluoroethylene
d-PTFE: Dense polytetrafluoroethylene
TR-ePTFE: Titanium-reinforced expanded polytetrafluoroethylene
CoCr: Cobalt-chromium
CaS: Calcium sulfate
HA: Hydroxyapatite
PDGF: Platelet-derived growth factor
PTH: Parathyroid hormone
BMP: Bone morphogenetic proteins
PRP: Platelet-rich plasma
IGF: Insulin-like growth factor
EMD: Enamel matrix derivative
ECM: Extracellular matrix
VEGF: Vascular endothelial growth factor
DFDBA: Demineralized freeze-dried bone allograft
GFs: Growth factors
DBM: Demineralized bone matrix
Gp: Genipin
TGF-β: Transforming growth factor-beta
MSCs: Mesenchymal stem cells
EVs: Extracellular vesicles
ESC-MSCs: Human embryonic stem cell-derived MSCs
2D: Two-dimensional
BP: Black phosphorene
GelMA: Methacrylamide gelatin
U-Arg-PEAs: Arginine and poly (ester amide)
hDPSCs: Human dental pulp stem cells.

Data Availability

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

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