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Regeneration of mandibular and alveolar bone defects: the role of biomaterials and biological scaffolds

(review article)

Abstract

Regeneration of the hard tissues of the mandibular and alveolar bones, which are damaged and resorbed due to severe physical trauma, oral and gingival diseases or tooth extraction, has been a key area of focus for oral and maxillofacial surgeons as well as dental researchers. Thanks to innovative approaches and advanced materials, that are progressively entering the market, many bone defects have been effectively repaired and regenerated. Natural materials such as autografts, allografts, and xenografts, which have been utilized for repairing mandibular and alveolar bone defects for a long time, are now commercially offered in various shapes, sizes, and as cancellous or cortico-cancellous types. Recently, the use of fibrin clots, derived from a patient's own plasma (Platelet-Rich fibrin) also called PRF, has shown remarkable success for jawbone ridge augmentation.

Meanwhile, with the progress in tissue engineering and biomaterials science, new biological composites and scaffolds have been developed that overcome the limitations of previous materials like poor osteogenesis induction and immunologic reactions. These advancements, particularly in maxillary sinus-lift surgeries and crest bone augmentation, have demonstrated remarkable results. For Examples materials such as calcium phosphate-based compounds, biocompatible and biodegradable polymers like polylactic-co-glycolic acid (PLGA) and polylactic acid or polylactide (PLA), bioactive glass composites, and advanced biological membranes are currently being used .Moreover , by integrating these materials with biological factors such as stem cells, osteogenic molecules, and growth factors, more efficient and effective approaches for regenerating of mandibular and alveolar bone defects are now accessible to patients. This highlights the significance of researching and comprehending biomaterials and their compositions to improve their performance in the mentioned bone regeneration.

Keywords: Biomaterials, Tissue Scaffolds, Mandibular Bone Defects Regeneration, Osteogenesis.

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Introduction

Based on information and experiences derived from periodontology and periodontitis, most injuries and bone resorption around the jaw and teeth are caused by atrophies following tooth extraction, trauma, wounds, tumor removal, congenital diseases, pathological conditions, and progressive complications such as cleft lip and palate(1). The field of regenerative medicine or bone tissue engineering has emerged to control and compensate for these injuries with the goal of replacing or reconstructing lost tissues to restore their natural structure and function. Bone regeneration refers to the intrinsic growth and reformation of some of the lost or damaged bone tissue to its original structure, whereas bone remodeling refers to the physiological formation of bone through a continuous process of activation, resorption, and bone formation processes(2).

Maxillofacial bone Regeneration often involves a range of medical procedures focused on cell recruitment and guidance, as well as cellular grafting and gene therapy. Periodontal regeneration, as an important part of this broad field, includes the regeneration of the cementum, periodontal ligament (PDL), and alveolar bone around the teeth. Most work in this area is related to the treatment of bone defects prior to implant placement, the regeneration of alveolar defects aimed at augmenting hard tissue for implant placement, and maxillary sinus-lift surgeries(3).

The main strategies for reconstructing mandibular and periodontal bone rely on the use of growth factors or signaling molecules, biological scaffolds, and stem cells to stimulate osteogenesis.These methods are employed either independently or in combination to achieve the best outcomes, where osteogenesis induction, angiogenesis, and inflammation control are carefully considered. In this multi-stage process, efforts are made to encourage osteogenic cells to migrate to the injured or defective area. To this end, various biocompatible materials and methods are utilized(4). The use of growth factors derived from the tissues of living organisms (humans or animals) stimulates and differentiates bone cells, thereby accelerating the repair process and promoting the growth of new bone tissue. In guided bone regeneration techniques, the goal is to create a stable physical space in the bone defect area for the migration and entry of osteoblasts and osteoclasts. Under injury conditions, these two types of cells play a crucial role in bone formation and resorption, forming a clot that subsequently serves as a natural scaffold for new bone formation(4,5). Available information suggests that the morphology of the defect (i.e., the number of walls, dimensions, depth, width, and volume), its location (such as sockets from tooth extractions or the cartilaginous junctions and ramus of the lower jaw), and whether the area under treatment is open or closed, fundamentally affect the bone regeneration process success rate(6). To achieve a better and faster regeneration environment, tissue engineering has emerged, aiming to produce biofunctional tissues to replace with lost or damaged mandibular and alveolar bones(2,4). In Figure 1, the most common regions of the jawbone that are typically regenerated are shown. Autologous bone grafts from the mouth or from the patient's own body remain the golden standard method for bone Regeneration due to their tissue integration, minimal immune system stimulation, and lack of disease transmission. This method has achieved excellent results, especially in repairing areas like the mandibular symphysis and maxillary tuberosity. While small defects can be reconstructed with autografts in cases requiring surgery and where there are no unknown diseases and the patient's body is healthy, for large defects caused by pathological fractures, underlying bone diseases, or bone infections from periodontal issues, the use of allografts, typically sourced from the skull or pelvis, provides an effective solution(7-9). However, accessibility limitations have posed challenges to their application(9). Another type of grafts is xenografts, derived from animals such as cows, horses, pigs, etc., which possess bone-guiding properties to promote the growth and development of osteogenic cells(11).

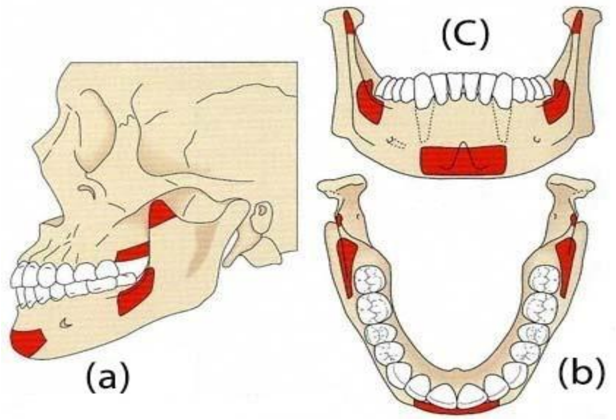

Figure 1: Representation of the mandibular symphysis, maxillary tuberosity, and the angles of the ramus process, which are commonly exposed to injury and require tissue regeneration. (a) Lateral view, (b) Superior view, and (c) Anterior view of the mandibular defect areas(10)

One of the most common bone defects or resorption issues that surgeons encounter involves the resorption of the mandibular and alveolar bones before the placement of dental implants. Another concern is the preservation of the bone socket after tooth extraction, which is addressed in implantology(12). During implantation, the alveolar ridge bone must have sufficient height, width, and volume to support the implant base adequately(13). Moreover, the bone of the socket or canal wall, which remains on the ridge or edge of the mandible after tooth extraction, is prone to resorption and the infiltration of surrounding soft tissues, which must be prevented. This is why periodontists use methods of bone resorption regeneration with the help of natural and synthetic biomaterials, to not only stimulate osteogenesis in the defect site but also provide optimal conditions for new bone formation over a specified period(14). Additionally, in sinus-lift surgery, after lifting the maxillary sinus membrane, periodontists use bone grafts to fill the resulting void, ultimately forming a sufficient volume of new bone to accommodate the implant(15). In guided bone regeneration (GBR), a type of membrane is used as a barrier to prevent the rapid invasion of soft tissue cells. This membrane has a highly porous surface, allowing small molecules and nutrients to enter and nourish the regenerating cells while blocking soft tissue cells from entering the defect site(16). Typically, GBR uses barrier membranes in conjunction with bone grafts(14,17).

This paper first briefly reviews the common grafts, scaffolds, and biomaterials used in mandibular and alveolar bone regeneration, along with their advantages and limitations, and explains several commercial types. A general summary of the role of each in the repair and regeneration of lost jaw and periodontal bones is then provided.

Types of Grafts Used in the Regeneration of Mandibular and Alveolar Bone Defects

In addition to autografts, several other materials are used to replace or repair mandibular and alveolar bone defects. The use of these materials depends on various factors such as tissue viability, size, shape, and volume of the defect(18).

Allografts are available as demineralized bone matrix (DBM) or freeze-dried bone allografts (FDBA)(19). These types of grafts are available in different shapes and sizes, including cortical (dense), cancellous (spongy), or cortico-cancellous (dense-spongy). They may contain osteogenic cells and have the ability to synthesize new bone, functioning as a biologically active scaffold with osteoinductive properties. However, these grafts also have disadvantages and are typically used for small to medium-sized defects(8,20). The evaluation of bone grafts is based on several key criteria:

1. Unlimited availability without harm to the donor
2. Promotion and stimulation of osteogenesis
3. Absence of immune rejection
4. Rapid revascularization
5. Induction of osteogenic stimulation
6. Promotion of osteoinductive properties
7. Complete replacement of lost bone with equivalent quantity and quality of the original tissue(9,21).

Wardani et al. along with Saliba et al. have examined the use of allografts and xenografts, respectively, in alveolar bone Regeneration, reporting significant results related to allografts. Additionally, Saliba has demonstrated not only the significant effect of xenografts in wound healing but also their successful use in bone regeneration(25).In comparison with allografts, which have a higher risk of disease or infection transmission from the donor to the recipient, xenografts, due to the complex standards they undergo during the manufacturing process, are safer(18). However, Saliba's research indicated that the use of xenografts is associated with higher pain levels than allografts(22-25). Table 1 shows several commercial grafts along with their advantages and disadvantages(9,26,27).

Table 1: Introduction of characteristics, advantages, and disadvantages of some commercial grafts (9,25,27)

No.	Commercial Name	Graft Type	Source	Advantages	Disadvantages
1	DBX®	Allograft	cadaver	Bone induction property, Bone conduction property, Medium availability	Risk of disease transmission, Immune system stimulation
2	Dynagraft®				
3	Grafton™				
4	OsteoSponge®				
5	Puros®				
6	Raptos®		cadaver		
7	Algipore®	Xenograft	algae	Bone conduction property, High availability	
8	Smartgraft®		Porcine		
9	Cerabone®		bovine		
10	Gen-Os®		bovine		
11	CollaBone®		equine		
12	BonePlast®	Synthetic Bone Substitute	Calcium Phosphate	Bone conduction property, High availability	Requires precise sterilization
13	Cortoss®		Hydroxyapatite		

14	Eurobone®		Calcium Carbonate		
15	PerioGlass®		Bioactive Glass		
16	OsteoBiol®		Calcium Phosphate (Biphasic)		
17	Straumann®		Calcium Phosphate (Biphasic)		

Synthetic Biomaterials Used in Alveolar and Jaw Bone Regeneration

The main role of synthetic biomaterials is to stimulate or support the bone regeneration process. These materials are widely used among surgeons due to their characteristics, including biocompatibility, bone induction and conduction properties, injectability at defect sites, moldability, wide compatibility with other biological additives, variability in mechanical and chemical properties, availability, minimal risk of infection and disease transmission, reduced wound formation (since only the specific defect area is operated on and only one surgical stage is required), easy reproducibility, and more(28). Among ceramic materials, calcium phosphates have gained significant attention due to their structural similarity to bone and their bone-conducting properties, and have been used since 1980(29).

In terms of applications, they are divided into two categories: those known as brushite, which harden in a short period, and those known as apatite, which require more time to solidify. The reason for this difference is that brushite varieties absorb more water during mixing, while apatite absorbs very little or no water at all. Although their use is limited in the regeneration of large jaw defects due to the lack of bone-inducing properties, they are still widely used(9,30). Calcium-phosphate ceramics are another type of material that can be used in block or granule form, either with or without pores. These ceramics include hydroxyapatite (HA), tricalcium phosphate (α-TCP and β-TCP), biphasic calcium phosphate (BCP), and amorphous calcium phosphate (ACP). A study comparing the effects of β-TCP and a type of xenograft bone powder over 8 weeks in a guinea pig model showed that β-TCP induced a higher amount of new bone formation than the xenograft(31).

The main advantage of using calcium phosphate cements and ceramics is their compatibility with anti-resorptive molecules and osteoclast-inhibiting properties. These materials can be used as carriers for growth factors, antibiotics, or drugs, helping to prevent the activity of osteoclasts (the bone-resorbing cells)(32).

Bioactive Glasses are another group of materials with bone-conducting properties. They include silica, calcium phosphate, and sodium oxide. When calcium and silicate ions are released from these materials, they interact with the surrounding tissue cells, causing the cells to attach to the bone(9,34). In other words, bioactive glasses release ions through bone conduction and their ability to adhere to bone surfaces, ultimately leading to the formation of an apatite layer(35).

Biodegradable polymers are another category of materials used in scaffolds for bone regeneration in the jaw. Most of these are based on glycolic acid and lactic acid, known as polylactic acid (PLA) and polyglycolic acid (PLGA), and recently, polycaprolactone (PCL) has also been added to them. Their main advantage is their biodegradability, but their limitation is the lack of bone-conducting properties(37).

In dentistry, these synthetic materials are used in various jaw surgeries, such as sinus lifts, periodontal defects, and bone crest augmentation, to increase the quantity and quality of jawbone for implant placement(9). In a clinical analysis conducted in 2022, led by the Tokyo University School of Dentistry, regarding ridge bone regeneration before implantation, 288 patients were observed over 3 to 60 months. Ultimately, it was found that 26 out of 274 cases (9.5%) experienced negative complications or issues related to bone repair operations, while the majority (93.7%) were satisfied with the success of the implant surgery and surrounding bone regeneration without any issues(14). In another research study on alveolar ridge bone in 108 patients, following immediate implant placement, it was observed that 41% of 308 patients who had previously undergone implant surgery used deproteinized bovine mineral cements for ridge bone augmentation(38).

Biological Scaffolds Used in Jawbone and Alveolar Regeneration

Regeneration of jawbone and peri-dental tissues has always been considered challenging due to their anatomical complexity and tissue diversity. Generally, bone possesses a limited self-healing capacity, necessitating the use of three-dimensional volumes of biomaterials to assist in the regeneration process. Synthetic biomaterials lack osteoinductive properties (a key factor in forming new bone); therefore, materials or factors that stimulate osteogenesis are required for this approach(39). Growth factors, osteogenic cells, autografts, and therapeutic elements are among the materials that can be combined with these biomaterials in the form of a biological scaffold to accelerate the biological regeneration of the jawbone and alveolar regions(40). Today, various types of biological scaffolds have been designed and made available for this purpose, either through cell integration or the combination of biocompatible and bioactive materials. Biological scaffolds provide the necessary mechanical support and create an environment where osteoblasts and bone progenitor cells can adhere, proliferate, and differentiate to form new bone(27,41).

One of the natural materials successfully used to fill and repair small defects in the jawbone and alveolar regions is Platelet-Rich Fibrin (PRF), derived from the patient's own blood plasma. Due to its properties in bone regeneration, angiogenesis, and wound healing, PRF has gained significant acceptance among surgeons (Figure 2). In a study conducted by Laham et al., it was found that three months after the use of PRF for socket preservation, bone resorption within and around the socket was minimized(42). Furthermore, incorporating growth factors and bioactive additives can enhance its socket preservation capability and bone regeneration properties. In another study conducted by Santos Pereira and colleagues on the application of advanced PRF in jawbone surgery, it was reported that this material successfully maintained the ridge bone profile, increased bone density, and improved tissue repair following surgical procedures(45).

Application of the GBR Technique for Regeneration of Alveolar and Periodontal Bone Defects

Guided Bone Regeneration (GBR) is a dental surgical method aimed at increasing bone volume in areas with bone resorption or deficiency by using a biological membrane placed over the bone defect. It is commonly employed in fields such as dental implants, orthodontics, and prosthodontics(46). GBR utilizes barrier membranes with or without granular bone grafts(47).

This method was first introduced in 1959 by Harley and colleagues for experimental treatment of spinal fusion. In 1960, a research team led by Bowen and Basset employed laboratory-grade cellulose acetate filters (Millipore brand) to treat cortical defects in long bones and to reconstruct facial bones. These filters were used to create an environment conducive to osteogenesis by preventing connective tissue cells from invading the bone defects(48). However, clinical studies involving membranes were not recognized until the early 1980s, when a research team led by Nyman and Karring applied barrier membranes in both laboratory and clinical studies for periodontal tissue regeneration. A few years later, laboratory studies expanded the use of membranes for bone Regeneration. With promising results from these studies, clinical trials began in late 1988 to use membranes in patients requiring implants(46,48).

Continuous studies conducted by Dahline et al. in 2004 on a specific type of surgical membrane demonstrated that if a barrier membrane is placed in direct contact with the surrounding bone surface and creates a closed physical space, only cells from adjacent regions or bone marrow progenitors are permitted to migrate into the bone defect. This occurs without invasion by competitive soft tissue cells, such as those from the gingiva and its surroundings, which typically exhibit higher proliferation and growth rates(49).

After performing GBR procedure, bone regeneration undergoes a series of specific transformations. Within 24 hours of the bone graft, the space created by the barrier membrane is filled with a blood clot. Subsequently, growth factors (derived from platelets or Platelet Derived Growth Factors (PDGFs)) and cytokines (such as IL-8) are released to attract neutrophils and macrophages. The clot is then absorbed and replaced by granulation tissue, which is rich in newly formed blood vessels. Through these vessels, nutrients and mesenchymal stem cells, which are osteogenic, are transported and participate in the formation of osteoid. The mineralization of osteoid forms a woven bone structure that later serves as a template for the deposition of lamellar bone(Figure 3). All these processes occur over a period of 3 to 4 months(46,48,50).

The characteristics of several commercial membranes are presented in Table 2.

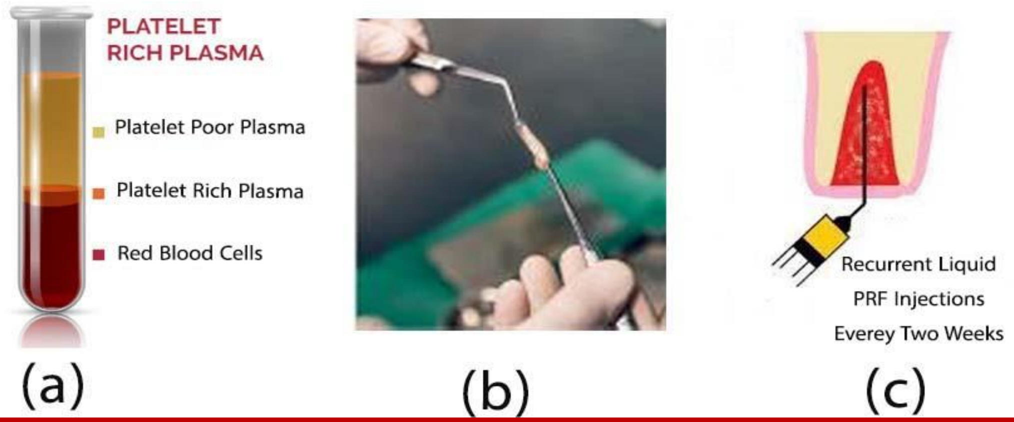

Figure 2: (a) Processing of the PRF clot from human blood, (b) isolation of the fibrin clot, and (c) injection into a maxillary bone defect(43,44).

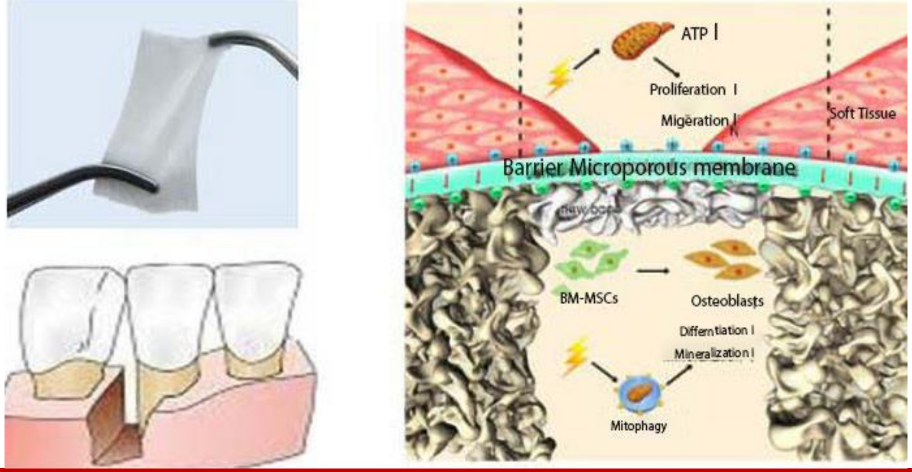

Figure 3: Illustration of the use of a barrier membrane in bone defect regeneration, showcasing its biological role in the differentiation and proliferation of osteogenic cells(51). (Reproduced with permission from Chunhua et al.)

Table 2: Physical and structural properties of various commercial barrier membranes(50,52,53)

Row	Membrane Type	Commercial Brand	Manufacturer	Composition	Application	Membrane Thickness (µm)	Stability Period Without Degradation	Bio-Absorption Duration

1	Non-resorbable	Cytoplast TXT 200	Osteogenics Biomedical Co. (USA)	PTFE	GBR	200–300	Unlimited	Non-resorbable
2	Non-resorbable	Surgitime	Bioinnovation Co. (Brazil)	PTFE	GTR	250	Unlimited	—
3	Resorbable	Bio-Gide	Geistlich Biomaterials Co. (Switzerland)	Porcine collagen	GTR/GBR	730	4–6 weeks	—
4	Resorbable	Botiss-Jason	Botiss Biomaterials Co. (Germany)	Cross-linked collagen	GTR/GBR	200	12 weeks	12–28 weeks
5	Resorbable	Regen Allograft	Iranian Tissue Products	Human cadaver collagen	GTR	300–1800	—	—
6	Resorbable	Guidor	Sunstar Americas (USA)	PLA	GBR	600–750	4–6 weeks	6–8 weeks
7	Resorbable	Tisseos	Biomedical Tisseos (France)	PLGA	GBR	650	8 weeks	16-24 weeks

Unique Features of Synthetic Biomaterials and Challenges Compared to Common Allografts

Biomaterials and the biological scaffolds derived from them offer significant relative advantages compared to allografts. They typically possess high osteoinductive and osteoconductive properties, whereas allografts generally exhibit osteoconductivity alone. Osteoinductive properties are created and enhanced through growth factors, stem cells, progenitor cells, and cytokines embedded in synthetic biological scaffolds. Bone healing, especially for fractures, heavily relies on osteoinduction; thus, scaffolds made from synthetic biomaterials have garnered significant attention. Another advantage is their minimal risk of infection transmission and disease spread compared to allografts(9,54). They involve less invasive surgical procedures, leading to reduced wound occurrences. Furthermore, their mechanical strength, physical shape, and reactivity can be controlled by altering the components and through chemical processes. These materials can be fabricated into gels or hydrogels and injected directly into the defect site, or synthesized into powders for molding purposes(26).

Unlike autografts, allografts, and xenografts, which often face supply limitations, synthetic biomaterials are highly accessible and can be easily produced on a large scale(55). In dentistry, the application of synthetic biomaterials has become popular in several strategies, including maxillary sinus lifts, periodontal defects, and crest bone augmentation(26,55).

Methods for Synthesizing and Fabricating Synthetic Biomaterial Scaffolds

The methods used to create scaffolds or composites from biomaterials must be capable of forming porous structures with pore sizes greater than 100 µm to allow for the migration of bone cells and angiogenesis. These scaffolds mimic the structure of bone tissue and significantly enhance the results of bone regeneration(56,57). In addition, the integration of osteoinductive molecules and factors, such as Bone Morphogenetic Protein 2 (BMP-2), Fibroblast Growth Factor 2 (FGF-2), Insulin-like Growth Factor (IGF), and Platelet-derived Growth Factor BB (PDGF-BB), which play essential roles in the bone regeneration process, is possible(58).

Over the past decade, freeze-drying techniques, often combined with electrospinning, 3D bioprinting, and particle leaching techniques, have gained significant popularity. Among these, 3D printing and freeze-drying have found more widespread commercial applications(56,57,58).

3D printing, also known as additive manufacturing, has been widely used in bone tissue engineering. This method is fast, precise, and offers repeatability, with controllable parameters. Complex shapes and volumes of bone defects, even with porous structures, can be easily designed and fabricated layer by layer through a software design system connected to the printing machine. Furthermore, growth factors, osteogenesis-stimulating molecules, and stem cells can be added through this technique (Figure 4). Moreover, biodegradable polymers with low melting points, such as PLA, PLGA, PCL, and others, can also be printed in porous forms using this method(59).

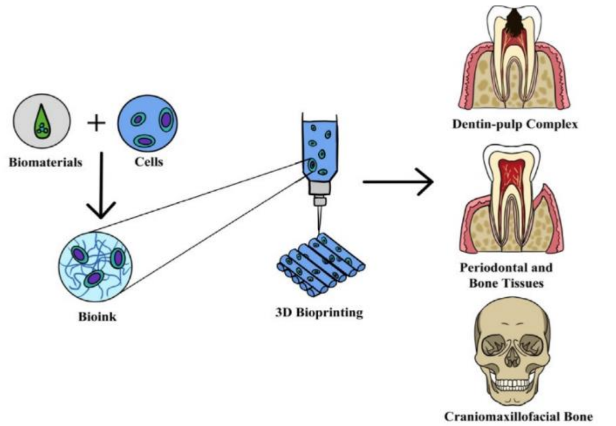

Figure 4: Schematic of the use of cells and biomaterials in 3D printing methods with bioinks for the regeneration of bone tissues around the teeth, jaw, and skull(60).

Freeze-drying is another method for producing highly porous polymeric and ceramic scaffolds. In this process, a polymer solution is frozen, causing the organic solvent within it to freeze. Then, through the freeze-drying process, the solvent is removed from the structure, leaving behind pores in its place. Temperature directly affects the size and distribution of the pores within the scaffold. Ultimately, a porous structure is formed where the pores are interconnected internally. However, scaffolds produced using this method may lack sufficient mechanical strength, necessitating additional modification processes to improve this property(61).

Biological Scaffold Compositions

Commonly used biological scaffolds in the field of alveolar and mandibular defect regeneration are primarily based on calcium-phosphate cements and ceramics. However, another category has been developed based on biocompatible and biodegradable polymers(62). Calcium phosphate cements, which form a paste when combined with water, come in various types, with the composition percentage and reaction temperature determining the type and properties of the material. For example, with a calcium-to-phosphate ratio of 1.3 (Ca/P=1.3) at temperatures between 900-1100°C, β-tricalcium phosphate (β-TCP) or $Ca_3(PO_4)_2\beta$ forms. On the other hand, if the calcium-to-phosphate ratio is 1.5, at temperatures above 1125°C, tetracalcium phosphate (TTCP) or α-TCP (α-$Ca_3(PO_4)_2$) will form(63,64). Both materials are widely used in alveolar and mandibular bone defect repair. α-TCP is more reactive in aqueous solutions compared to β-TCP, producing an apatite product, while β-TCP is more stable and produces a product called brushite ($CaHPO_4 \cdot 2H_2O$)(63,65). Brushite absorbs more water compared to apatite, resulting in faster setting and hardening. In clinical applications, the setting time of calcium phosphate cements based on brushite is longer, while that of apatites is shortened to control the hardening process(66). Hydroxyapatite (HA), which is formed from apatite ($Ca_{10}(PO_4)_6(OH)_2$), is one of the most widely used calcium phosphate compounds due to its close resemblance to the mineral portion of human bone. Clinical reports indicate its excellent osteoconductivity without causing inflammation, cytotoxicity, or immune system stimulation(67). Nano-hydroxyapatite particles, with a size of less than 100 nanometers, exhibit a much closer functional resemblance to the mineral particles found in bone tissue due to increased surface activity between the ultra-fine particles(68).

Calcium phosphate ceramics, another group of biomaterials, are processed into granules or blocks with or without porosity, unlike cements that form a paste. They are composed of hydroxyapatite (HA), tricalcium phosphate (α-TCP and β-TCP), biphasic calcium phosphate (BCP), which is a combination of HA and tricalcium phosphate, amorphous calcium phosphate (ACP), etc.(69).

Natural and synthetic biocompatible and biodegradable polymers form another category of biomaterials widely used in research for creating biological scaffolds. Examples of natural polymers include alginate, chitosan, gelatin, collagen, glucosamine glycan, hyaluronic acid, etc., which have biochemical and structural properties similar to the organic matrix of natural bone. A key feature of these natural polymers is their ease of forming hydrogels, which can absorb large amounts of liquid and be injected into defects. The most important synthetic biocompatible polymers with hydrolytic or enzymatic degradation properties within the body include polylactic acid (PLA), polyglycolic acid (PGA), polylactic-co-glycolic acid (PLGA), polyethylene glycol (PEG), polycaprolactone (PCL), and polyurethane (PU)(70).

According to research reports, PLA and PLGA have gained the most interest in bone tissue engineering scaffolds. The advantages of biodegradable synthetic polymers include their cost-effectiveness, physical stability, minimal immune system stimulation, and controllable degradation rate(70,71). Biodegradable polymers are also of significant interest in the production of GBR membranes, and various types of these biological membranes are commercially produced and used in jawbone regeneration for augmentation, sinus lifts, flap surgeries, etc. However, there are still some limitations and challenges associated with them, and researchers are continuously working on optimizing their mechanical, chemical, and biological properties(48,50,72).

Biomaterial Composites with Enhanced Properties

While ceramic and polymer biomaterials each offer unique advantages for biological scaffold construction, they also have limitations. Researchers have therefore sought to create composite biomaterials that exhibit exceptional properties unattainable through individual components alone(9,26).

The combination of various ceramics and calcium phosphate cements is commercially well-established. Hydroxyapatite (HA), in particular, can be integrated with numerous natural and synthetic polymers, cells, and growth factors to better mimic the natural bone structure. This approach enhances osteoinductive and osteoconductive properties, facilitating bone formation and tissue regeneration(73).

For instance, commercial enterprises have developed biphasic materials containing both HA and β-TCP in varying proportions for specific applications. One such product, EasyGraft™ Crystal, consists of 60% HA and 40% β-TCP, to take benefits of HA's stability and β-TCP's solubility simultaneously. This composite is particularly suitable for periapical dental procedures(9,74).

Collagen, a critical factor in the mineralization of the bone matrix, has demonstrated significant osteogenic results when combined with calcium phosphates. An example is the Integra Mozaik™ product, which contains 80% β-TCP and 20% type I collagen(9,75). In the category of polymers, combining natural and synthetic polymers is widely applied to achieve both mechanical and biological benefits. A notable example is Fisiograft®, which includes hyaluronic acid and the biodegradable polymer PEG(9).

Hydrogels have also garnered special attention due to their liquid-absorbing capacity and 3D structure. These materials provide an ideal environment for embedding bone cells and growth factors, allowing for straightforward injection into complex mandibular bone defects(76).

Efforts to improve the mechanical, rheological, and biological properties, as well as the ease of application of biomaterial composites, continue. Many composites that combine ceramics with polymers, cells, and osteogenic factors are currently undergoing human clinical trials and are poised for commercialization(77).

Future Perspectives and Challenges

The growing demand for solutions to mandibular and alveolar bone regeneration, alongside advancements in surgical techniques and tools, underscores the critical need for grafts and biomaterials that facilitate and accelerate new bone formation. Efforts to optimize the processing of allografts and xenografts aim to eliminate the risk of infection and disease transmission, driving continuous development in this field.

Synthetic biomaterials, with their versatility, reproducibility in production, injectability, self-setting properties, and tunable mechanical and chemical characteristics, remain a focus of extensive research. These materials are being studied to maximize their biological performance in stimulating and supporting osteogenesis.

Given the high success rates of xenografts in bone regeneration, future advancements are expected to involve combining them with biomaterials and novel, more efficient biological molecules. This integration holds great promise for further progress in the Regeneration of mandibular and alveolar bone.

In the coming years, the development of synthetic biomaterials will likely prioritize enhancing their capability to regenerate bone defects larger than 5 mm. Achieving this goal will require materials or composites with significantly higher mechanical strength and stability(78).

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