Lobat Tayebi *Editor*

Applications of Biomedical Engineering in Dentistry

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Chapter 1
Introduction to Application of Biomedical Engineering in Dentistry

Lobat Tayebi

"Good fences make good neighbors" …"Why do they make good neighbors?"… "Something there is that doesn't love a wall"…."He says again, Good fences make good neighbors" [1].

These are scattered verses from an American poet Robert Frost (1874–1963) in his famous poem *Mending Wall* (published in 1914, North of Boston by David Nutt). In this poem, there is a stone wall between two farms. Farmer 1 asked his neighbor in the spring mending-time to reconstruct the wall. Farmer 2 wondered if he should. The dialogue continued between them with repeating the verse by Farmer 2 "Something there is that doesn't love a wall" followed by the insisting of Farmer 1 relying on the proverb of "Good fences make good neighbors!"

It is interesting that the story still continues between groups of Farmer 1 and Farmer 2 after more than a hundred years. Do we need a wall? "That is the question." We don't know who is right in farms and livestock grazing, but we do know that in today's dentistry. "Something there is that doesn't love a wall" [1].

More broadly, in today's science, technology, and medicine, each field is trying to touch the concept of interdisciplinary. Do we *need* the interdisciplinary approach to succeed? Perhaps not. Do we *need* the interdisciplinary approach to be modern, progressive, and advanced? Definitely yes.

Modern dentistry tries its best to take advantage of linking with other fields, especially biomedical engineering. This book aims to present some of these efforts. Biomedical engineering, itself, is known as an exceedingly multidisciplinary field spanning biology, material science, physics, chemistry, engineering, and medicine. The recent progress in biomedical engineering significantly impacts many relevant areas. Such impacts on dentistry are the focus of this book, in which an interdisciplinary document is presented, that relates biomedical engineering

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and dentistry by introducing the recent technological achievements in engineering with applications in dentistry.

The book will begin by studying the biomaterials in dentistry and materials used intraoperatively during oral and maxillofacial surgery procedures. Next, it will consider the subjects in which biomedical engineers can be influential, such as three-dimensional (3D) imaging, *laser and photobiomodulation,* surface modification of dental implants, and bioreactors. Hard and soft tissue engineering in dentistry will be discussed, and some specific and essential methods such as 3D printing will be elaborated. Presenting particular clinical functions of regenerative dentistry and tissue engineering in the treatment of oral and maxillofacial soft tissues is the subject of a separate chapter. Challenges in the rehabilitation handling of large and localized oral and maxillofacial defects are severe issues in dentistry, which will be considered to understand how bioengineers help with treatment methods in this regard.

Recent advances in nanodentistry will be discussed followed by a chapter on the applications of stem cell-encapsulated hydrogel in dentistry.

Periodontal regeneration is a challenging issue in dentistry and, thus, is going to be considered separately to understand the efforts and achievements of tissue engineers in this matter.

Oral mucosa grafting is a practical approach in engineering and treatment of tissues in ophthalmology, which is the subject of another chapter. Microfluidic approaches became more popular in biomedical engineering during the last decade; hence, one chapter will focus on the advanced topic of microfluidics technologies using oral factors as saliva-based studies. Injectable gels in endodontics is a new theme in dentistry that bioengineering skills can advance its development, specifically by producing clinically safe and effective gels with regeneration and antibacterial properties. Engineered products often need to be tested in vivo before being clinical in dentistry; thus, one chapter is dedicated to reviewing applicable animal models in dental research. The last chapter will cover the progress on the whole tooth bioengineering as a valuable and ultimate goal of many dental researchers.

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Chapter 2
Biomedical Materials in Dentistry

Fahimeh Sadat Tabatabaei, Regine Torres, and Lobat Tayebi

1 Introduction

Biomedical materials are biomaterials intended to be in long-term contact with biological tissues. Based on the American National Institute of Health definition, a biomaterial is "any substance or combination of substances, other than drugs, synthetic or natural in origin, which can be used for any period, which augments or replaces partially or totally any tissue, organ or function of the body, to maintain or improve the quality of life of the individual" [1]. This definition does not comprise materials such as orthodontic brackets, impression materials, gypsum, waxes, investment materials, finishing materials, irrigants, bleaching materials, or instruments.

The biomaterials used in dentistry can be classified into metals, ceramics, polymers, and composites (Fig. 2.1), which will be the focus of this chapter.

2 Metallic Biomaterials

Due to the inherent characteristic of metallic bonds, metals and alloys have high density, thermal and electrical conductivity, strength, and hardness.

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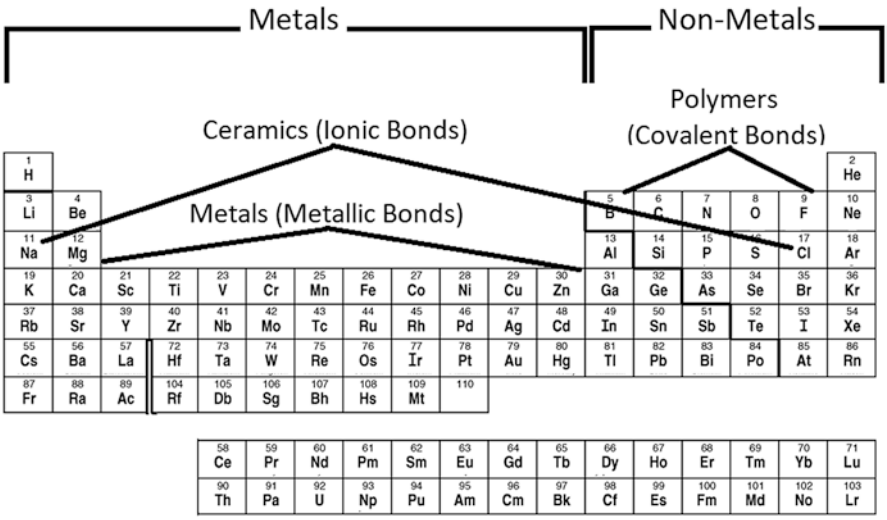

Fig. 2.1 Metals, ceramics, and polymers in the periodic table

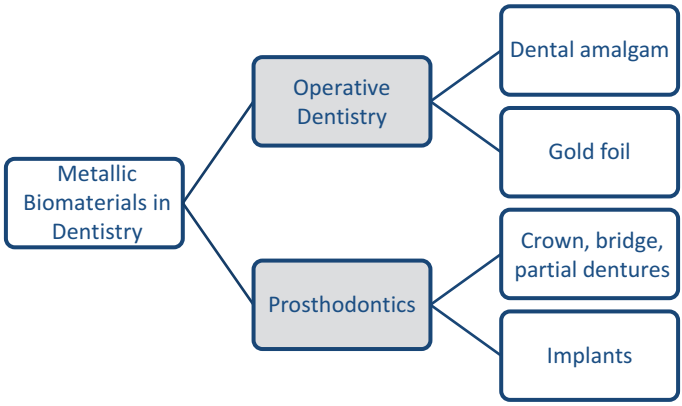

Fig. 2.2 Metallic biomaterials used in operative dentistry and prosthodontics

In dentistry, metals and their alloys are used for direct restorations as dental amalgams or for indirect restorations as casting alloys or dental implants (Fig. 2.2).

2.1 Dental Amalgam

The primary goals of dental restorative treatment are to replace diseased or damaged tooth structure and to restore function. Interest in the use of amalgam for the restoration of teeth dates back to the 1800s onward. *Amalgam* is a *metal* alloy, of

which one of the components is *mercury*. Dental amalgam is the result of mixture of liquid mercury with amalgam alloy powder composed *principally* of silver, tin, and copper. Amalgam alloy is derived from the intermetallic compound Ag_3Sn, and the powder can be lathe-cut (irregular-shaped) particles, spherical particles, or a combination of these. When the powder is mixed with mercury (about 40–50% by weight), it can be packed or condensed into a prepared tooth cavity. In the setting reactions of dental amalgam, a series of intermetallic compounds are formed. The reaction products of Hg with pure γ-phase (Ag_3Sn) alloy are Ag_4Hg_5 (γ_1) and $Sn_{7\text{-}8}Hg$ (γ_2). The γ-phase does not react completely with mercury, and some of the original Ag_3Sn remains as unreacted particles, which is the source of strength in dental amalgam. The γ_2-phase is very weak, is prone to corrosion, deforms readily, and contributes to the static creep of amalgam. Because of these properties, extra copper (Cu) is incorporated either in the form of a second alloy powder mixed with the first (admixed alloy) or by coating of Ag_3Sn alloy with Cu alloy (unicompositional alloy). These new generations are referred to as high-copper amalgams, in which the copper content of the alloy particles may be as high as 30% by weight. Increase in the copper content, which results in decrease of silver content, has a direct influence on the cost of product. It is of relevance to note that no γ_2-phase is present in these new generations. At the end of the amalgamation reaction, little or no unreacted mercury remains, and reacted mercury is not easily released from the amalgam. Dental amalgam restorations are easy to manipulate and place, are able to withstand normal occlusal forces, and have a low cost. Some disadvantages, however, are that the material is silver-colored, sensitive to mixing technique, and subject to corrosion and does not have bonding properties. Additionally, amalgam restorations usually require larger cavity preparation to provide sufficient mechanical retention, and there are regulatory concerns about amalgam disposal in the wastewater. Due to these disadvantages, especially the emerging concerns over its potential neurotoxic effects and environmental issues associated with waste amalgam disposal, clinical use of amalgam continues to decline [2, 3].

2.2 Alloys for Metallic Restorations

Besides dental amalgams, other alloys used in dentistry are casting dental alloys, wrought alloys, and solders. Cast alloys are melted and cast into the shape of a wax-up. These alloys could be in the form of noble metals, which are resistant to corrosion, or base–metal alloys like cobalt–chromium, nickel–chromium, stainless steel, titanium, and titanium alloys [4].

Wrought alloys—like those used in dental wire, endodontic posts and instruments, orthodontic brackets, and stainless steel crowns and implants—are alloys that have been worked or shaped after casting by mechanical force, compression, or tension into a serviceable form for an appliance. Cold working applied during the shaping process results in a fibrous microstructure, increase in tensile strength and hardness, and decrease in ductility and resistance to corrosion in comparison to

corresponding cast structures. One of the promising biomaterials in this category is Ni–Ti, which has huge application in endodontics and orthodontics. This material possesses special characteristics, like shape-memory and superelasticity. Shape-memory permits shaping at a higher temperature, followed by deformation at a lower temperature, and a return to the original shape upon reheating. On the other hand, superelasticity is characterized by an extensive region of elastic activation and deactivation at a nearly constant bending moment [5–7].

Solders, which are used for joining metals together or repairing cast restorations, are gold-based or silver-based.

Alloys used as bases for porcelain have special formulations because they need to provide a firm bond to the applied porcelain via an oxide layer on the alloy surface. Another important property is the thermal expansion of ceramic and alloy. A high difference in the coefficient of thermal expansion results in more expansion on heating and more contraction on cooling, which could increase the risk of fracture of ceramic during service [8].

Metal and alloys used in different fields of dentistry include inlays, onlays, and crowns in operative dentistry; crowns, bridges, implants, clasp wires, and solders in prosthodontics; wires and brackets in orthodontics; and files and reamers in endodontics.

2.3 Titanium in Implant Dentistry

The use of titanium dental implants rather than dentures or fixed bridges has changed the rehabilitation of patients in modern dentistry. Dental implants protrude through the mucosa as a suitable structure for supporting a denture, crown, or bridge. The rigidity of the implant structure is related to its dimensions, and the modulus of elasticity has an important role in its function. In fact, we can use materials with a high modulus of elasticity with smaller cross-sectional bulk, but these materials also are at risk of stress shielding. Currently, most dental implants are fabricated from titanium and its alloys, which are light and have adequate strength. The interfacial condition when bone grows to within 100 Å of the titanium surface without any fibrous tissue in this space is called osseointegration. Osseointegration would result in non-mobility of the implant and should be maintained over the long term. Attempts have been made to improve the efficacy and rate of osseointegration by techniques such as different designs and microtextures on the surface of the implant, coating the surface with hydroxyapatite, as well as coating with a layer of protein-containing drugs. The degradation of coatings over time could jeopardize the stability of the interface in the long term [9, 10].

3 Polymeric Biomaterials

Polymers, which are long chain molecules consisting of many small repeating units (*monomers*), represent the largest class of biomaterials in dentistry and play a major role in most areas of dentistry. Covalent bonding along the backbone and the amount of cross-linking is responsible for the properties of polymers, such as low density, insulation, and flexibility. Figure 2.3 represents the polymeric biomaterials in different fields of dentistry.

3.1 Bonding Agents

Bonding agents (adhesive systems) are used with composites to obtain a strong and durable bond to dentin and enamel. Three important components of bonding agents are etchant (conditioner), primer, and adhesive. Etchants are 30% to 40% phosphoric acid gels used for the demineralization of tooth structure. Primers are hydrophilic monomers, oligomers, or polymers and act to improve wetting and penetration of the treated dentin. Adhesives have hydrophobic groups that polymerize and form a bond with the composite; they also contain a small amount of a hydrophilic monomer to diffuse into the hydrophilic, primer-wetted dentin. These components can be combined to simplify the application of bonding agents. Bonding agents are classified as light-cured and dual-cured multi-bottle systems (fourth generation);

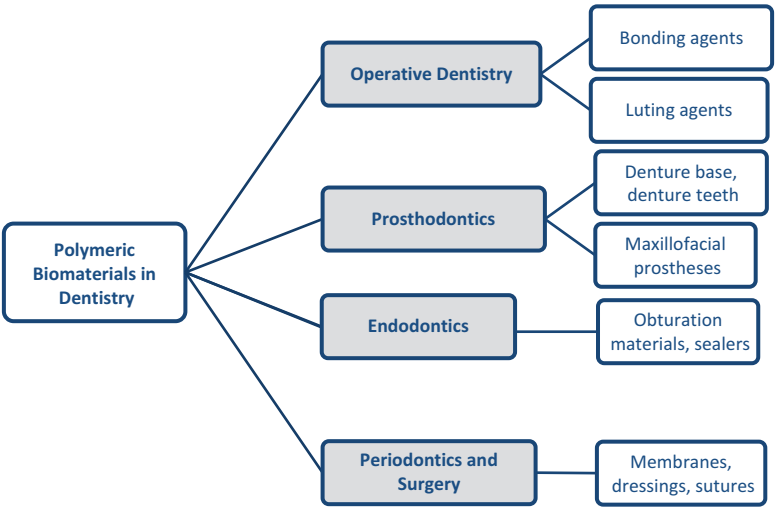

Fig. 2.3 Polymeric biomaterials in different fields of dentistry

light-cured single-bottle systems (fifth generation); and self-etching systems (sixth and seventh generation). Fourth- and fifth-generation bonding agents are called total-etch (etch-and-rinse) systems. Universal bonding agents can be either total-etch or self-etch systems. Bonding agents may also contain fluoride to prevent secondary caries, chlorhexidine to prevent collagen degradation, antimicrobial ingredients like MDPB and paraben, or desensitizers such as glutaraldehyde [11, 12].

Bonding of resins to enamel involves its penetration into the porous surface of the etched enamel. This micromechanical bond results from adequate etching and drying of the surface. Composite resins may be applied directly to the etched enamel surface without using bonding agent. However, using unfilled resin may enhance the adhesive bond strength. Bonding to moist enamel could be achieved by using an enamel bonding resin containing primers and solvents. Bonding to dentin occurs through a complex mechanism involving wetting, penetration, and the formation of a layer of bound material at the interface between the restorative material and the substrate. Dentin bonding agents have an affinity for calcium or the organic collagenous component of dentin [13, 14].

3.2 Luting Agents

Luting agents are either provisional or permanent. Provisional cements (like zinc oxide–eugenol and noneugenol cements or calcium hydroxide pastes) have a relatively low strength. Permanent cements should seal the tooth/restoration interface, have a low film thickness, be resistant to disintegration and dissolution, have good esthetics, have high strength (both static and fatigue) and fracture toughness, and have good wear resistance. These cements can be divided into those that set through an acid–base reaction (glass ionomer, resin-modified glass ionomer, zinc oxide–eugenol, zinc polycarboxylate, and zinc phosphate) and those that set by polymerization (resin cements, compomers, and self-adhesive resin cements). Resin-modified glass ionomers and compomers may undergo both reactions. Some of the cements (like glass ionomer cements) are self-adhesive materials that bond to tooth structure via micromechanical and chemical bonding; therefore, there is no need for the application of bonding agents when placing GICs in cavities. Release of fluoride from cements and the capacity to recharge them could inhibit the progression of initial proximal caries in adjacent teeth. Calcium aluminate/glass ionomer cement is a new cement which was shown to be bioactive due to its calcium content and high pH [15–17].

3.3 Prosthetic Polymers and Resins

The part of the denture that rests on the soft tissues is termed the acrylic denture base. Denture-based material should be capable of matching the appearance of the natural oral soft tissues, should have a value of glass transition temperature (Tg) to prevent softening and distortion during use, should have good dimensional stability, and should have a low value of specific gravity and high value of thermal conductivity. Polymeric denture-based materials can be heat-processing polymers, autopolymerized polymers, thermoplastic blank or powder, light-activated materials, or microwave-cured materials. The major component is polymethylmethacrylate (PMMA). The set material can be considered a composite system in which residual PMMA particles are bound in a matrix of freshly polymerized material. Resin or acrylic teeth have good bonding with acrylic denture-based material. Occasionally, hard reline materials, tissue conditioners, or soft lining materials may be applied to the fitting surface of the denture base in order to improve the fit of the denture or enable traumatized soft tissues to recover. These materials also contain polymethylmethacrylate in combination with some monomers and plasticizers to perform their functions. Silicone elastomers and polyphosphazine fluoroelastomers are also available for use as denture soft lining materials. Hydrogels, which are biopolymers containing poly(N-substituted methacrylamides), can also be used as soft tissue conditioners. Acrylic resins and other polymers and copolymers—like latex, polyurethane, and silicone—are used for maxillofacial prostheses. New-generation color-stable resins, incorporation of antimicrobial agents, and nanoparticle-reinforced PMMA are recent advances in prosthetic materials [18–20].

3.4 Endodontic Obturation Materials

Endodontic biomaterials obturate the root canal system of teeth when the pulp tissuehas been destroyed.

Bulk-filling materials are based on a modified natural rubber gutta-percha or a polyester resin-based material. Gutta-percha is derived from latex as an isomer of trans-polyisoprene and can be produced in two crystalline forms, which are interchangeable depending on the temperature of the material. Currently there are different forms of gutta-percha:

- Gutta-percha pellets or bars (e.g., Obtura system)
- Pre-coated core carrier gutta-percha (e.g., Thermafil)
- Syringe systems (use low viscosity gutta-percha) (e.g., Alpha Seal)
- Gutta flow: gutta-percha powder incorporated into a resin-based sealer
- Gutta-percha dissolved in chloroform/eucalyptol (e.g., Chloropersha and Eucopercha)
- Medicated gutta-percha (e.g., calcium hydroxide, iodoform, or chlorhexidine-containing GP points)

Polyester resin (Resilon) based on a thermoplastic synthetic polyester may contain bioactive glass fillers and claims to release calcium and phosphate ions from its surface, stimulating bone growth [21].

Sealer cement fills the spaces between increments of the bulk-fill material and maintains the seal around the root filling. The most commonly used sealers are zinc oxide–eugenol and calcium hydroxide-based cements. There are also resin-based products, such as AH26, which are based on epoxy resins, contain formaldehyde, have antimicrobial action, and provide a good seal. Photocuring resin sealers are also used as sealants with the polyester bulk-fill materials and are typically a mixture of hydrophilic difunctional methacrylates [22].

Castor oil polymer (COP) extracted from plants is a new material for use in dentistry as a biocompatible retrograde filling material. The chemical composition of this biopolymer consists of a chain of fatty acids. The body does not recognize it as a foreign body. In comparison to MTA and GIC, COP displays excellent sealing ability as a root-end filling material [23].

3.5 PEEK in Dentistry

PEEK, or polyether ether ketone (-C6H4-OC6H4-O-C6H4-CO-)n, is a tooth-colored semi-crystalline linear polycyclic aromatic polymer with mechanical properties close to human bone, enamel, and dentin. This biomaterial has many potential uses in dentistry as fixed restorations, dental implants, individual abutments, and removable prostheses. Due to its low Young's (elastic) modulus, it may exhibit lower stress shielding than titanium dental implants although some literature reported nonhomogeneous stress distribution to the surrounding bone. Moreover, its poor wetting properties limit its osteoconductivity. Improving its bioactivity without compromising its mechanical properties is challenging [24, 25].

3.6 Membranes and Polymeric Periodontal Biomaterials

Periodontitis can lead to the destruction of interfaces between the root cementum and alveolar bone, which constitute the periodontium. Isolation of periodontal defects through the use of a barrier to avoid epithelial and connective tissue migration into the defect led to the development of GTR/GBR membranes. The membrane must also support bone cell infiltration from the bone defect side. A GTR/GBR membrane should have proper physical properties and an acceptable degradation rate matching that of new tissue formation. According to degradation feature, GTR/GBR membranes can be divided into two groups: resorbable (such as polylactic acid (PLA) and its copolymers, in addition to tissue-derived collagen) and nonresorbable (like titanium membranes, polytetrafluoroethylene (PTFE) reinforced with or without a titanium framework). The most commonly used membranes are

collagen-based or derived from the human skin, porcine skin, or bovine Achilles tendon. They are available in various forms, such as sheets, gels, tubes, powders, and sponges. Nevertheless, improvement of the biomechanical properties and matrix stability of native collagen is necessary. Research on new bioactive and multilayered membranes with the aim of biomolecule delivery (e.g., antimicrobials and growth factors) is underway. Polypeptide growth factors—such as platelet-derived growth factor (PDGF), enamel matrix proteins (Emdogain of porcine origin), and bone morphogenetic proteins (BMPs)—can mediate the periodontal regeneration. Nowadays, sustained drug delivery can be used in the periodontal regeneration process. Arestin (PLGA microspheres containing minocycline) and Periochip (gelatin chip containing 2.5 mg of chlorhexidine (CHX) gluconate) are two examples of these products [26, 27].

Periodontal pack or dressing is another biomaterial used for wound protection in periodontal surgery to facilitate healing. Wonder Pak is a eugenol dressing containing antiseptic additives, such as thymol or septol, whereas Coe-pack does not contain eugenol. Cyanoacrylates have also been used as periodontal dressings but are not very popular. Light-cured elastomeric resin is also available as a periodontal dressing material. Incorporation of antimicrobials into the unset gel is a method of delivering these agents in situ [28].

3.7 Sutures and Alternatives

Suture materials should have good physical and biological properties. The source of suture material can be natural (silk, collagen fibers from the intestine of healthy sheep or cows) or synthetic (polyglactin, polyglecaprone, polydioxanone (PDS)). Based on degradability, the sutures are either absorbable (catgut, PDS) or non-absorbable (silk). Hydrolysis of synthetic absorbable sutures does not cause any adverse tissue reactions. If hemostasis cannot be managed by sutures, fibrin glue can be used to arrest bleeding. It consists of fibrinogen and thrombin and acts faster than sutures. The fibrin sealant kit contains sealer protein concentrate (human) freeze-dried, fibrinolysis inhibitor solution, thrombin (human) freeze-dried, and calcium chloride solution. Liquid stitches, skin adhesives, or cyanoacrylates can be used as an alternative to sutures. Polymerization of the adhesive on contact with tissue fluids results in the formation of a thin layer that adheres to the underlying surface [29].

4 Ceramic Biomaterials

Ceramics are brittle, and inorganic/nonmetallic biomaterials, composed of metal–oxygen ionic bonds. As they have no free electrons to conduct heat or electricity, they are poor thermal conductors. They have also excellent biocompatibility.

4.1 Dental Ceramics

Due to their excellent *esthetic* value, ceramics have been used widely in restorations. Dental ceramics can be classified into four major types: (1) traditional feldspathic (glassy or porcelain), (2) predominantly glass (glass dominated), (3) particle-filled glass (crystalline dominated), and (4) polycrystalline, which has no glass phase. Feldspathic ceramics (dental porcelain) are the most esthetic but weakest of the ceramics. They are made by mixing kaolin (hydrated aluminosilicate), quartz (silica), and feldspars (potassium and sodium aluminosilicates) and composed principally of an amorphous phase with embedded leucite crystals. These ceramics are primarily used as veneers for porcelain fused-to-metal (PFM) and all-ceramic restorations. Ceramic–metal restorations (PFM) consist of several layers of ceramic (core [opaque], dentin [body], enamel) bonded to an alloy substructure. Figure 2.4 shows different techniques for fabrication of dental ceramics. In the dental laboratory, the physical process of fabrication of dental porcelains is sintering or stacking. In sintering, slurry of porcelain powder in water is applied to the alloy surface or ceramic core, and after condensation (the green state), the ceramic is fired (heating without melting). Glass-dominated ceramics (particle-filled glass) contain crystals like leucite or fluoroapatite. They have more strength than glassy ceramics and sufficient translucency, but they cannot be used for posterior crowns or bridges. Pressing techniques (heat-pressing) are used in the dental laboratory for fabrication of these ceramics. In this technique, after wax-up, investing, and lost-wax process, a viscous mass of molten ceramic will be forced into the mold to get the desired final form. The composition of crystalline-dominated ceramics is crystalline 70% by volume. They

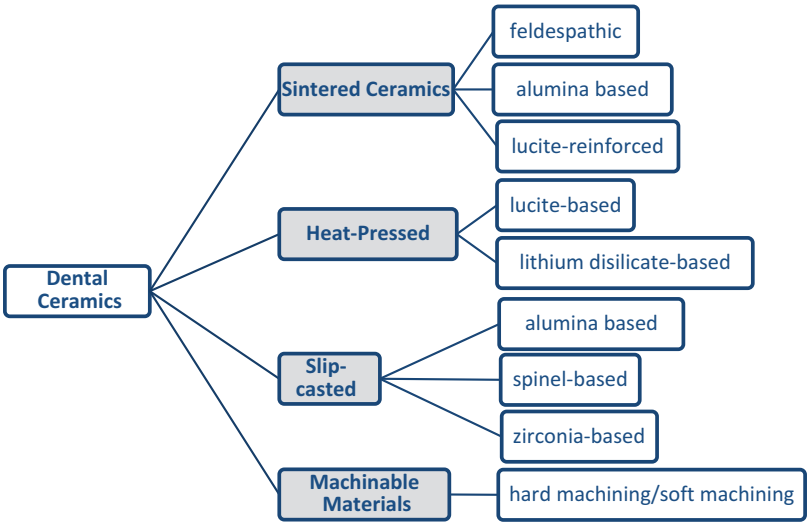

Fig. 2.4 Different techniques used for fabrication of dental ceramics

contain crystals like spinel ($MgAl_2O_4$), zirconia (ZrO_2), alumina (Al_2O_3), or lithium disilicate. Although not highly esthetic, they can be used as cores for anterior or posterior all-ceramic crowns. The fabrication method of these ceramics is heat-pressing (for lithium disilicate) or infusion (slip casting). In slip casting, ceramic slurry is sintered, then a silica glass is infiltrated in the porous sintered ceramic, and the restoration is sintered again. Today, this technique has been replaced by machining. The newest and strongest ceramics are the polycrystalline ceramics (ceramic oxides), which are formed from alumina or zirconia (Procera). They cannot be used as esthetic veneers on alloys or teeth; however, because of their high strength, they can be used in posterior crowns and bridges. These ceramics are prepared from blocks by CAD/CAM. Ceramic blocks for CAD/CAM can be conventional feldspathic porcelains, glass ceramics, and heat-pressed or infiltrated with glass [30–34].

4.2 HA and Other Bioceramics

Hydroxyapatite (HA) [$Ca_{10}(PO_4)_6(OH)_2$], tricalcium phosphate (TCP) [$Ca_3(PO_4)_2$], and biphasic calcium phosphate (consisting of HA with TCP) are common brittle materials used for craniofacial defects. Although porosity in these ceramics allows faster bony ingrowth, it also weakens them. HA is a natural component of enamel, dentin, cementum, and bone. This non-resorbable material could be applied in different situations, like periodontal osseous defects, ridge augmentation/implant placement, sinus elevation surgeries, etc. Substitution of strontium, carbonate, zinc, or silicates in the structure of HA could favor its dissolution and bioactivity or increase the strength of porous ceramics. Tricalcium phosphate (TCP) is similar to HA, but it is not a natural component of hard tissues, as it is converted in part to crystalline HA in the body. The resorption period of TCP is 3–24 months. Cerasorb is a commercial product of TCP, but there are also some products that are prepared from combinations of HA and TCP. These materials, based on porosity, could be dense, macroporous, or microporous. Based on crystallinity, these materials are classified as crystalline, amorphous, granular, or molded. Calcium phosphate material, derived from calcium-encrusted sea algae, has the hexagonal structure of HA and high bioactivity. Interconnected microporosity in this material guides hard and soft tissue formation. Coraline is another ceramic material derived from the calcium carbonate skeleton of coral that has a three-dimensional structure similar to the bone. Calcium sulfate, or plaster of Paris, is a salt used for bone implantation. The resorption of calcium sulfate is rapid, and this drawback limits the application of the material in the oral and maxillofacial region. The addition of HA to this material provides osteoconductivity and sufficient strength. Cements based on calcium salts, phosphates, or sulfates have excellent biocompatibility and bone-repair properties without the need for delivery in prefabricated forms [35–37].

4.3 Bioactive Glass

Bioactive glasses are materials consisting of a three-dimensional network structure of *silica* that have the capacity to form chemical bonds with apatite crystals in bone tissue and teeth via formation of apatite crystals on their surface. This material has appropriate strength, stiffness, and hardness but—like other glasses—is brittle and cannot be used in load-bearing areas. However, it can be used in some areas as powder, particles, or small monoliths. There are three different types of bioactive glass: (1) glasses based on silicates (SiO_2), (2) glasses based on phosphates (P_2O_5), and (3) glasses based on borates (B_2O_3). Bioactive glass is a promising material in dentistry, since it has the ability to support bonding to biological tissue, to regenerate tissue, and to inhibit bacterial growth. Therefore, there are many studies on its ability to prevent loss of bone after tooth extraction, to regenerate tissue in periodontal disease (as PerioGlass), to induce bone regeneration before denture replacement, to reduce dental hypersensitivity, and to remineralize damaged dentin in combination with glass ionomer cement. Coating of titanium implants and fiber-reinforced polymer composites for dental prosthetic devices is also considered in some studies. In addition, the formulation of toothpastes with bioactive glass could be helpful in the release of antibacterial, remineralizing, or desensitizing agents. All of the commercial products available in dentistry are based on the 45S5 Bioglass formulation [38, 39].

4.4 Endodontic Obturation Materials: MTA and Others

Calcium hydroxide [$Ca(OH)_2$] is a strong base with a high pH that has been used in endodontics as an intracanal medication, sealer, and pulp-capping agent. This biomaterial is antibacterial, aids in the dissolution of necrotic pulp tissue, promotes dentinal bridge formation, and preserves the vitality of the pulp. Some of the $Ca(OH)_2$ formulations with lower pH values (9–10) produce a more uniform dentin bridge in comparison to higher pH (11–13) calcium hydroxide. As this material is used for a wide range of applications, it has various forms with different setting times: fast setting and controlled setting (light cure) as a liner, slow setting as a pediatric obturating material or sealer, and non-setting as an intracanal medicament [40].

Mineral trioxide aggregate (MTA), which is chemically identical to Portland cement, is a strongly alkaline material. In its set condition, it is biocompatible and antimicrobial, can induce cementogenesis, and can provide a good seal at the root–material interface. The effects of calcium hydroxide and MTA on stem cells are the subject of many studies. Other materials based on MTA include endo CPM sealer, viscosity enhanced root repair material (VERRM), and calcium-enriched mixture (CEM) cement. Bioaggregate, which is the modified version of MTA, is aluminum-

free and contains ceramic nanoparticles. Biodentin is another material containing calcium chloride and hydrosoluble polymer to shorten setting time. In addition, calcium phosphate cement (CPC) is a mixture of two calcium phosphate compounds, one acidic and the other basic, and is under study as root-end filling and root repair material [41].

Minerals (ceramic in nature), like MTA, have good biocompatibility but also potentially contain toxic heavy metals. It seems that bioceramics (chemically bonded ceramic) are the future of root-end filling materials [42].

4.5 Zirconia in Dentistry

Zirconia, or zirconium dioxide (ZrO_2), is a special ceramic that has been used in single-crowns, long-span fixed dentures, and root canal posts and as a subgingival implant material in dentistry. This ceramic is a white biomaterial, with reduced plaque affinity and resistance to chemical attacks. It is one of the best currently known biocompatible ceramic biomaterials. Zirconia consists of different crystallographic forms at different temperatures: monoclinic (M) phase, tetragonal (T) phase, and cubic (C) phase. Addition of some amount of metal oxide, like yttria (yttrium trioxide, Y_2O_3) and ceria (cerium trioxide, Ce_2O_3), to zirconia can transform pure zirconia into a partially stabilized zirconia called "tetragonal zirconia polycrystal (TZP)," which has high flexural strength and fracture toughness. Under stress, transformation of the tetragonal phase to the monoclinic phase, which is called transformation toughening, could inhibit crack propagation. However, it makes the implant susceptible to aging. Addition of higher amounts of yttrium oxide increases the amount of cubic phase, which results in zirconia ceramics with increased translucency. Restorations made of TZP are prepared by CAD/CAM (soft machining of pre-sintered blanks followed by sintering or hard machining of fully sintered blocks). Evidence shows that Y-TZP implants have osseointegration comparable to titanium implants and superior biocompatibility and esthetics. Nevertheless, high elastic modulus of zirconia (210 GPa) could result in even higher stress shielding than titanium implants. Moreover, there is not enough scientific clinical data for recommendation of ceramic implants for routine clinical use [43, 44].

5 Composite Biomaterials

Composites are biomaterials consisting of two or more constituents, which when combined leads to a material with properties different from those of its individual components. Enamel, dentin, and bone are some examples of composites in the body.

5.1 Resin-Based Composites

Resin composites are a mixture of resin phase and inorganic filler. The resins used are composed of methacrylate monomers. Depending on the resin matrix used, there are Bis-GMA-based, UDMA-based, and silorane-based dental composites. Fillers commonly used are quartz, fused silica, and many other types of glasses. Ormocers (organically modified ceramics) are fillers with molecule-sized hybrid structures that are used in the formulation of several commercial composites. Polyhedral oligomeric silsesquioxane (POSS) is another molecule-sized hybrid compound, which, like ormocer, provides a reinforcing function, but filler particles must also be included in the composite. Incorporation of fillers in resin composite materials will linearly affect the properties like coefficient of thermal expansion, setting contraction, and surface hardness. A coupling agent will enhance bonding between the filler and resin matrix. Polymerization in resin composites occurs through free radical addition or a ring-opening mechanism. The method used to activate polymerization can be chemical (in self-curing composites) or through a visible light source (in light-cured composites). Dual-cure materials have a self-curing mechanism but are also cured by light or heat. Based on the particle size distribution of fillers, there are different types of resin composites. Conventional composites contain 60–80% (by weight) of filler in the particle size range of 1–50 μm. Microfilled composites contain fillers in the range of 0.01–0.1 μm (30–60% by weight). Hybrid composites that contain a blend of both conventional filler (75% by weight, 1–50 μm) together with some submicron fillers (8%, 0.04 μm average) enable filler loading of up to 90% by weight to be achieved. There are also nanocomposites with particles of less than 1 μm average diameter and filler loading of up to 79.5%. Highly viscous resin composites are classified as “packable” composites, while more fluid products are referred to as “syringeable” composites. Laboratory composites may be used to indirectly prepare crowns, inlays, veneers bonded to metal substructures, and metal-free bridges. Pre-cured composites for in-office milling are also available. Low-viscosity composite materials with adjusted filler distribution can be used as resin cements [45, 46].

5.2 Modified Composites and GIOMERS

Modified composites are resin–matrix composites in which the usual filler has been replaced by a glass that exhibits fluoride release. Setting of these biomaterials is the same as usual composites (often light-activated). In polyacid-modified composites or compomers, there is also the possibility of an acid–base reaction with the filler component, which may help in liberating fluoride. In these materials, the first reaction is still a polymerization reaction. In GIOMERS, the acid–base reaction is

completed before blending the filler with resin. Partially or fully reacted fillers are blended with resin to form a composite structure. GIOMERS are single paste materials that set through light-activated free radical addition polymerization [47, 48].

5.3 Bone Augmentation Materials

Hard tissue grafts—such as autografts, allografts, xenografts, and alloplasts—are composite biomaterials used for bone regeneration. Allografts (like mineralized or demineralized freeze-dried bone allografts (FDBA)) refer to grafting between genetically dissimilar members of the same species. Generally, they are frozen, freeze-dried (lyophilized), demineralized freeze-dried, and irradiated. In contrast, xenografts (like Bio-Oss (bovine bone grafts)) are taken from a donor of another species. Studies show dentin as another composite biomaterial that could be used for bone augmentation [49].

A different composite of calcium hydroxide and polymer (like Bioplant) can be used for ridge preservation and augmentation [50].

6 Conclusion

Material science is an integral part of dentistry, and during the last decades, dental biomaterials have advanced rapidly. Some of these advances include biomimetic materials with the ability of mimicking nature; smart materials with the capability of showing different responses to change in temperature, pH, etc.; nanostructured materials with the capacity of modification of surface properties of different materials; and tissue engineering through the use of biomaterials and cells for tissue regeneration.

The common feature of first-generation dental biomaterials was biological inertness. The second generation intended to be bioactive and recruit specific interactions with surrounding tissue. But these two generations of biomaterials could not change with physiological load and biochemical stimuli. It seems that repair and regeneration of tissues require a more biologically based method, and the third generation of biomaterials are cell- and gene-activated materials designed to regrow, rather than replace, tissues.

Interaction between biomaterials and new technologies like biotechnology, nanotechnology, and tissue engineering will have a huge impact on the future of dentistry.

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Chapter 3
Materials Used Intraoperatively During Oral and Maxillofacial Surgery Procedures

Mina D. Fahmy, Anish Gupta, Arndt Guentsch, and Andre Peisker

1 Introduction

The methods that currently exist for treating maxillofacial defects are not as robust as they could be. Moreover, large contributors to success are the surgeon's skill and the patient's own bodily reactions to materials used intraoperatively [1]. Often, patients are left with oral and maxillofacial defects or fractures, which range in size due to such things as congenital anomalies, acquired pathologies, and trauma. For instance, complete or partial resection in the midface or mandible due to oncologic surgery or following trauma requires the use of grafting materials, whether natural or synthetic, to resolve the void created. Further, bone graft materials are applied to congenital defects such as cleft palate, facial clefts, and facial asymmetries [2]. To enhance the effectiveness of such grafts, growth factors are used. Growth factors are steroid hormones or proteins that aid in cellular differentiation, proliferation, growth, and maturation. Growth factors may also have both inhibitory and stimulatory effects and have been shown to aid in the regeneration of bodily hard and soft tissues. Growth factors are also involved in a multitude of processes including mitogenesis, angiogenesis, metabolism, and wound healing [3]. In this chapter, we place

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emphasis on BMP, TGF, FGF, and PDGF. Within the realm of oral and maxillofacial surgery, oral implantology is becoming more popular among patients hoping to bridge gaps within their dentition for improvement in form, function, and esthetics. As will be discussed later in the chapter, there are a multitude of different implant systems and numerous types of implant materials, shapes, and coatings that are used at the surgeon's preference and skill level [4]. This chapter will also explore different options concerning inter-maxillary and mandible fractures and how to fixate with plates, and screws, either biodegradable or permanent, in an effort to speed healing and recovery.

2 Grafting and Growth Factors

2.1 Grafting

Recovery and maintenance of natural structures has been a great challenge within the realm of oral and maxillofacial surgery. For a number of years, autogenous bone has been the gold standard for grafting due to its osteogenic, osteoinductive, and osteoconductive properties. However, there are several drawbacks to using autogenous bone including morbidity, availability, and inability to customize shape and potential resorption [5–8]. To date, the perfect grafting material has not been identified, as this may be very patient specific. This section focuses on autografts; however, properties of various bone grafts and bone substitutes will be discussed later in this chapter.

Autogenous grafts may include cortical, cancellous, or cortico-cancellous bone with multiple factors determining successful incorporation. The healing process of these grafts requires both osteoconduction and osteoinduction. Embryonic origin, extent of revascularization, biomechanical features, type of fixation, and availability of growth factors are all factors of significant importance for incorporation of autogenous bone grafts [9]. Albrektsson and colleagues used a rabbit model to investigate the survivability of both cortical and cancellous bone grafts. It was found that trauma to the graft compromised cell viability in addition to a lag in the revascularization time, whereas the carefully handled graft revascularized and remodeled faster [10]. Furthermore, it was found that the cancellous bone grafts demonstrated a faster rate of revascularization than the cortical grafts [11–13]. More regarding grafting techniques will be discussed later in this chapter.

With regard to healing, it has been suggested that soft tissue pressure applied by the periosteum and/or the flap covering the graft may in fact increase the osteoclastic activity [14, 15]. As will be discussed in more detail later in the chapter, rigid fixation, a technique often used in the operating room, is important for healing. Several studies have concluded that rigid fixation (Figs. 3.1 and 3.2) increases the survival rate of the graft [16, 17].

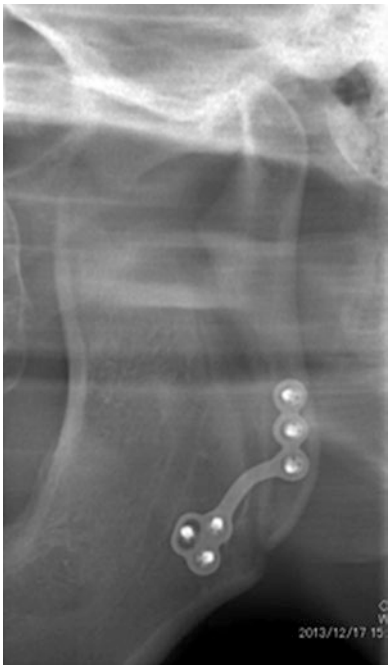

Fig. 3.1 Mandibular angle fracture with rigid fixation [18]

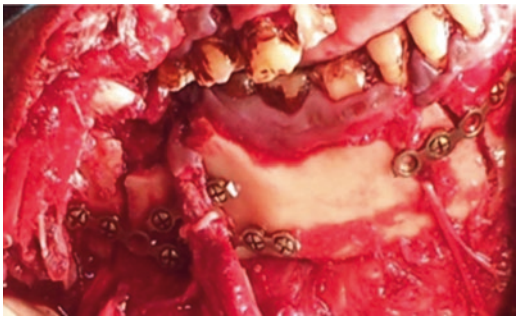

Fig. 3.2 Rigid fixation of mandibular fracture using plates and screws [19]

2.2 Growth Factors Relevant to Surgery

Currently, researchers are investigating proteins and carriers for the delivery of growth factors (GFs): however, there are questions that exist with regard to the efficacy of these materials [20]. GFs are present in bone matrix and plasma, albeit in low concentrations [21]. GFs are biological mediators that have been shown to help in the regeneration of the natural periodontium. They are key factors in cellular differentiation, proliferation, and maturation. In addition, these GFs have been shown to have both stimulatory and inhibitory effects [3].

2.2.1 Bone Morphogenetic Protein

In 1971, it was shown that protein extracted from demineralized bone matrix induced the formation of the bone. This extracted protein was named BMP [22]. BMPs can provoke local immediate action, bind to extracellular antagonists, or interact with the extracellular matrix proteins and, subsequently, target cells. Interestingly, BMPs can regulate morphogenesis during development while also inducing bone and cartilage formation [23]. In their work, Karsenty and Kingsley describe how BMPs form a large group of proteins, which affect migration, differentiation, and cell growth. This protein group is the TGF-β superfamily [24, 25]. The TGF-β superfamily includes a number of proteins such as BMPs, osteogenic proteins, cartilage-derived morphogenic proteins, and growth differentiation factors [26]. Mesenchymal stem cells exhibit several BMP receptors [27] while also synthesizing the BMP antagonists noggin, gremlin, follistatin, and sclerostin. The osteoconductive biomaterial BMP/hydroxyapatite has been used in oral and maxillofacial surgery for contour augmentation by means of a macroporous delivery system [28].

2.2.2 Transforming Growth Factor

TGF-β increases the chemotaxis as well as the mitogenesis of the osteoblast precursors while also acting to stimulate osteoblast deposition of collagen matrix for wound healing and the regeneration of the bone [29]. TGF-β is produced by osteoblasts and is found at the highest concentration in platelets [30]. This growth factor stimulates the expression of bone matrix proteins [31] and moderates the breakdown activity of matrix metalloproteinases, among others [32]. The differentiation and proliferation of osteoblastic cells, along with the inhibition of osteoclast precursor formation, may be attributed to TGF-β [33]. Unlike BMP, TGF-β does not have the capacity to induce ectopic bone formation [34]. During the healing of bone fractures, the release of TGF-β, BMP 1–8, and growth differentiation factors (GDFs) 1, 5, 8, and 10 are plentiful [35]. Signaling molecules that are released after a bone fracture and during the progression of healing include pro-inflammatory cytokines, TGF-β superfamily, and other growth factors like PDGF, fibroblast growth factor, and insulin-like growth factors, as well as angiogenic factors such as vascular endothelial growth factor, angiopoietins 1 and 2, and matrix metalloproteinases [36]. TGF-β is found in high amounts in PRP which will be discussed in a later section.

2.2.3 Platelet-Derived Growth Factor

PDGF has the important biological activity of initiating connective tissue healing while also increasing mitogenesis and macrophage activation [29]. PDGF is produced by monocytes, macrophages, osteoblasts, endothelial cells, and platelets [37]. There are three types of PDGF, including PDGF AB, AA, and BB, with PDGF BB

being the most biologically potent. In the early stages of fracture healing, PDGF plays a key role in acting as a chemotactic agent for inflammatory cells and as an inducer for osteoblasts and macrophages [34]. Hock and Canalis proposed that PDGF acts as a stimulant for osteoblasts, as well as osteoclast lineages, which may allow for decreased healing time [38]. As mentioned previously, PRP, which on its own will be discussed in a following section, is an autologous source of PDGF and TGF-β. Moreover, both of these growth factors play a primary role in the creation of platelet gels that, unlike fibrin glue, have a high concentration of platelets that release bioactive proteins necessary for tissue repair and regeneration .

2.2.4 Fibroblast Growth Factor

FGF may be produced by macrophages, mesenchymal cells, monocytes, chondrocytes, and osteoblasts. FGF is essential in the process of bone resorption and chondrogenesis [39]. Of the two isoforms that exist, α-FGF plays a key role in chondrocyte proliferation, while β-FGF is significant in the maturation of chondrocytes and bone resorption during the process of fracture healing, which often occurs after oral and maxillofacial surgery. Basic fibroblast growth factor (bFGF) is a growth factor that may be isolated from the pituitary glands of bovine [40]. bFGFs have also been isolated from a number of cells and tissues in tumors [3]. FGF-2 is considered a mitogen that has an effect on angiogenesis, thereby inducing a differentiation stimulus for mesodermal cells. In the short term, FGFs prevent the mineralization of the bone; however, in the long term, they act to speed and support bone development [41]. This was shown in a study by Takayama and colleagues where topical application of FGF-2 had a healing effect on bone fractures [42].

3 Growth Factor Enhancements

At the foundation of any surgical discipline is the science of wound healing. The oral and maxillofacial surgeon is usually blessed to work in an environment with rich vasculature; surgical and traumatic wounds tend to heal. But there will be compromised patients and ambitious reconstructive goals, and the surgeon will take any advantage given to assist his patient's natural healing process.

As discussed previously, growth factors with cytokine-mediated healing have been shown to assist in the biological healing process. Many of these growth factors can be resultant from platelets, including PDGF, TGF, VEGF, and EGF [43]. Platelet-derived products have been used as early as the 1970s, starting with fibrin glue [44]. Fibrin adhesives are still commercially available today (e.g., Tisseel from Baxter Healthcare) and are primarily used for hemostasis of diffuse microvascular bleeding. Its use is well documented in multiple surgical specialties, including oral and maxillofacial surgery [45]. Fibrin glue evolved into other autologous platelet concentrates including PRP [46], platelet gel, and platelet-rich fibrin (PRF) [47].

The literature reveals multiple studies with favorable treatment effects, not only in dentistry but also in orthopedics, dermatology, and ophthalmology [48]. Unfortunately, the literature has not come up with any consensus in terminology for platelet derivatives [49], and even less uniformity in their preparations, which likely accounts for inconsistencies in reported therapeutic effects.

3.1 The Biology of Wound Healing

Injury to tissue, whether surgical or traumatic, starts a cascade of events to allow wound healing. There are overlapping phases of inflammation, proliferation, and remodeling. The initial priority is to prevent hemorrhage, then prevent infection, and ultimately, restore the injured tissue [50]. The immediate reaction to injured tissue is vasoconstriction to limit bleeding. Coagulation factors are activated and multiple cascades are set into motion. A fibrin matrix is formed at the injured vasculature, and circulating platelets aggregate at the exposed subendothelium, creating a platelet plug. This plug functions not only for hemostasis but also orchestrates subsequent healing [51]. Activated platelets in the plug degranulate and create cellular signals through cytokines and growth factors.

Entire chapters can be devoted to each individual component of the wound healing process. We will limit and simplify our discussion to the roles of fibrin and platelets.

Platelets are anuclear structures arising from bone marrow precursors. The platelet membrane contains receptors for many molecules, including thrombin, and the cytoplasm contains granules that are released on activation [52]. Fibrin is a fibrous protein, which is activated by thrombin. Activated platelets and resulting thrombin allow fibrin to form a cross-linked mesh with the platelet plug to finalize a blood clot.

3.2 Collection and Preparation of Platelet Derivatives

Platelet derivatives have few contraindications, specifically in patients with platelet counts less than 10^5/microliter, hemoglobin level less than 10 g/dL, or presence of active infections [53]. PRP has shown great variability in centrifugation protocol. Current PRP procedures start with the collection of whole blood in acid/citrate/dextrose, which are then centrifuged. The red blood cells are removed, and the PRP then undergoes a second centrifugation step to obtain a supernatant of platelet-poor plasma (PPP) and the pellet of platelets. Growth factor release of the PRP happens with platelet activation from thrombin, either bovine thrombin or autologous thrombin obtained by adding calcium gluconate to the PPP. Thrombin is combined to the PRP and allows handling as a gel [48].

PRF is considered a second-generation platelet concentrate, notably with a simplified preparation in comparison to PRP. Whole blood is collected without

anticoagulants and centrifuged to form a fibrin clot, which contains the platelets. As opposed to PRP where the activation of the platelets is due to thrombin, the PRF activation is a result of the centrifugation process itself. The PRF clot is homogenous and is interpreted to have the cytokines incorporated into the fibrin mesh, allowing for an increased lifespan of these intrinsic growth factors and cell signaling molecules [52]. The inflammatory markers present also indicate degranulation of the leucocytes, which may play a role in the reduction of infection [54].

3.3 Applications in Oral and Maxillofacial Surgery

Both PRP and PRF continue to be used and reviewed in the literature. The therapeutic effects are not validated with multi-center randomized trials, and there still exists discrepancies in overall benefits. In the literature, benefits have been documented when platelet concentrates are used in multiple maxillofacial applications. In post-extraction sites, including third molars, healing times have been improved, with reduction of complications including alveolar osteitis [55–61]. However there are studies that show no significant benefit using scintigraphic evaluation [62]. Many studies discuss platelet concentrates used in combination with bone grafting for both reconstruction and for site preparations for dental implants. Studies showed accelerated healing, particularly of the soft tissue [63]. Reviews of the literature in regard to sinus augmentation show increased bone density [64] but no significant improvement in bone formation or implant survivability [65, 66]. In the setting of poor wound healing, we see applications of platelet derivatives in the setting of medication-related osteonecrosis of the jaws (MRONJ) and other oral mucosal lesions, with cautious interpretation of results suggesting benefits of their use [67–70]. Successful treatment of alveolar cleft bone grafting has been shown by multiple teams [71–73].

In the temporomandibular joint (TMJ), platelet concentrates have been hypothesized to help, given that the cartilage is avascular and has difficulty with self-repair. Bone growth was significantly improved in osteoarthritis in the rabbit model, with improved, but not significant, regeneration of the cartilage [74]. Injections of platelet concentrates into the TMJ have been shown to be effective for treatment of temporomandibular osteoarthritis [75–77] and better than arthrocentesis alone [78]. However, it has been pointed out that growth factors associated with PRP, including VEGF, may be detrimental to cartilaginous healing [79].

3.4 Future Applications

The common complaint in the systematic reviews of PRP and PRF therapy continues to be a large discrepancy in preparation and use of platelet concentrates. Good evidence is available that there is a quantifiable increase in growth factors

when using platelet-rich products [80–83]. However, large multi-center trials need to be conducted to prove the efficacy of these treatments reliably and reproducibly.

4 Implantable Devices

4.1 Replacement of Teeth

Oral implants have become the sought-after method of treatment, which is scientifically accepted and well documented in the literature [84–86]. Oral implants were introduced some 30–40 years ago [87–89]. Since then, implants have revolutionized the concept of replacing missing teeth and improved the quality of life for patients [90, 91]. Today, there are over 1300 different implant systems worldwide. They vary in shape, dimension, bulk, surface material, topography, surface chemistry, wettability, and surface modification [92]. Titanium is the material most commonly used for oral endosseous implants, due to its mechanical strength, excellent biocompatibility, and osseointegration [93]. Some studies have reported regarding the clinical disadvantages of titanium, such as host sensitivity to titanium, electrical conductivity, corrosive properties, and esthetic concerns as a result of their dark-grayish coloring [94–96]. Furthermore, elevated titanium concentrations have been found in close proximity to oral implants [97] and in regional lymph nodes [98]. However, the clinical relevance of these facts is still unclear [99]. Ceramic materials have been suggested as a substitute to titanium for oral implants because of their esthetic benefits and excellent biocompatibility in vitro and in vivo [100–102], great tissue integration, low affinity to plaque, and favorable biomechanical properties [103]. These ceramic materials have already been investigated and clinically used since approximately 30–40 years ago. The first ceramic material utilized was aluminum oxide [104, 105], and later, the Cerasand ceramic and the ceramic anchor implant were introduced [106, 107]. The physical and mechanical properties of alumina ceramics are high hardness and modulus of elasticity, which make the material brittle. In combination with the relatively low bending strength and fracture toughness, alumina ceramics are vulnerable to fractures. Based on these drawbacks, there are no alumina implant systems remaining on the market [86, 108]. Currently, the material of choice for ceramic oral implants is zirconia (ZrO2), containing tetragonal polycrystalline yttria (Y2O3) (Y-TZP). In comparison to alumina, Y-TZP has a higher bending strength, a lower modulus of elasticity, and a higher fracture toughness [86, 109, 110]. Through in vitro and in vivo studies, zirconia has become an attractive alternative to titanium for the fabrication of oral implants [103]. However, animal studies have indicated a better bone-to-implant contact with titanium implants than with Y-TZP implants [101, 111]. In addition, early failures were significantly higher for zirconia implants than for titanium implants [103].

Surface topography is one of the important parameters for the achievement of osseointegration and can be classified into macro-, micro-, and nanoscale [112]. The three major modifications of macrotopography are screw threads (tapped or self-tapping), solid body press-fit designs, and sintered bead technologies. Recently, studies were mainly focused on micro- and nanogeometry. The osteoblast activity is significantly increased at 1–100 μm of the surface roughness compared to a smooth surface [113]. Increased surface roughness of dental implants can be achieved by machining, plasma spray coating, grit blasting, acid etching, sandblasting, anodizing, and applying a biomimetic coating, or other combinations of the several mentioned techniques [114–117] resulted in greater bone apposition [118] and reduced healing time [119].

4.2 Reconstruction of the Craniomaxillofacial Skeleton

Reconstruction of the craniomaxillofacial skeleton, resulting from resection of benign and malignant tumor, osteomyelitis, or osteoradionecrosis, still remains a challenge for the surgeon [120].

4.2.1 Natural Bone Grafts

Since the nineteenth century, autologous bone has been successfully used as bone substitute [121]. Different donor sites are described in the current literature. Intraoral donor sites include the symphysis of the mandible, mandibular ramus, and maxillary tuberosity [122]. The common extraoral donor sites for non-vascularized bone grafts are the iliac crest and rib. The non-vascularized iliac crest graft is a treatment possibility for reconstruction of moderate mandibular defects [123], whereas the costochondral graft from the rib is used predominantly for condylar reconstruction [124, 125]. During the past decade, a variety of donor sites for vascular bone flaps and soft tissue have been recommended. The osteocutaneous radial forearm free flap [126, 127], fibular free flap [127, 128], scapula free flap [128], and iliac crest free flap [129] are the most commonly utilized donor sites for vascularized reconstruction.

Allogenic bone refers to the bone that is harvested from one individual and transplanted into another individual, both of the same species. Due to the limitations of autologous bone grafting, allogenic grafts are considered an effective alternative. Allografts, to a limited extent, can be customized by being machined and shaped to fit the defect. It can be available in a variety of forms, including cortical and cancellous. The disadvantage, however, is that compared to autografts, they have a higher failure rate due to their immunogenicity [130, 131].

Xenograft bone has been taken from a donor of another species [122], usually of bovine origin. Mineral xenograft has been applied in oral and maxillofacial surgery for several years [132]. Demineralized bone, harvested from human donors, has

been frequently used in craniofacial reconstruction [133, 134]. The demineralization is achieved through the process of acidification, resulting in a matrix containing type I collagen and osteoinductive growth factors, predominantly BMP. Based on porosity, it can be easily formed and remodeled intraoperatively [135, 136].

4.2.2 Synthetic Bone Grafts

Craniofacial reconstruction using alloplastic implants has shown to be associated with low rates of infection and other types of morbidity [137]. Computer-aided designed and manufactured (CAD/CAM) titanium implants which are prefabricated are a reasonable option for secondary reconstruction [138]. The major disadvantages are the thermosensitivity and limited possibility of intraoperative customization [136]. Synthetically manufactured bioactive glass-ceramic is an option as a single CAD/CAM implant for craniofacial reconstruction with good clinical outcomes. As opposed to titanium implants, it allows intraoperative remodeling and adjustment without thermosensitivity [139]. Calcium phosphates belong to the group of bioactive synthetic materials. The most commonly used are hydroxyapatite, tricalcium phosphate, and biphasic calcium phosphate [140–142]. Calcium phosphates are osteoconductive, do not cause any foreign body response, and are nontoxic [136].

Hard tissue replacement (HTR)-sintered polymers consist of poly(methyl methacrylate (pMMA), poly(hydroxyethyl methacrylate) (pHEMA), and calcium hydroxide. The porosity of the plastic allows for the indwelling growth of blood vessels as well as connective tissue [136]. HTR implants can be used for the reconstruction of large defects of the cranio-orbital region when combined with simultaneous bone tumor resection [143]. The implants are fixated with titanium or resorbable plates and screws.

Polyetheretherketone (PEEK) is a synthetic material that has been used for a number of years in neurosurgery due to its excellent biocompatibility, good mechanical strength, and radiographic translucency. In recent years, studies of maxillofacial reconstructions have been reported using PEEK for the construction of patient-specific implants [144–146]. The major disadvantage of computer-designed PEEK is its high cost [147].

Porous polyethylene (PPE) or high-density polyethylene (HDPE) is a linear highly compressed (sintered) aliphatic hydrocarbon. It is a biocompatible, durable, and stable material. Furthermore, it shows rapid surrounding soft tissue ingrowth without capsule formation around it [137, 148, 149]. PPE has proven to be a reasonable alternative to PEEK as a material for craniofacial reconstructions. The use of this material seems to be safe and has minimal morbidity [149]. In summary, autografts are osteoconductive, osteoinductive, and osteogenic; however, they have limited availability and have donor-site morbidity. Allografts are osteoconductive and osteoinductive but are not osteogenic; they carry the same disadvantages as autografts with the addition of having disease transmission risk. Xenografts are osteoconductive, but not osteoinductive or osteogenic, and carry the potential for foreign body reaction. Alloplastic materials are osteoconductive but often costly [150].