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Antimicrobial surfaces for craniofacial implants: state of the art

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In an attempt to regain function and aesthetics in the craniofacial region, different biomaterials, including titanium, hydroxyapatite, biodegradable polymers and composites, have been widely used as a result of the loss of craniofacial bone. Although these materials presented favorable success rates, osseointegration and antibacterial properties are often hard to achieve. Although bone-implant interactions are highly dependent on the implant's surface characteristics, infections following traumatic craniofacial injuries are common. As such, poor osseointegration and infections are two of the many causes of implant failure. Further, as increasingly complex dental repairs are attempted, the likelihood of infection in these implants has also been on the rise. For these reasons, the treatment of craniofacial bone defects and dental repairs for long-term success remains a challenge. Various approaches to reduce the rate of infection and improve osseointegration have been investigated. Furthermore, recent and planned tissue engineering developments are aimed at improving the implants' physical and biological properties by improving their surfaces in order to develop craniofacial bone substitutes that will restore, maintain and improve tissue function. In this review, the commonly used biomaterials for craniofacial bone restoration and dental repair, as well as surface modification techniques, antibacterial surfaces and coatings are discussed.

Key words: Dental implants, Osseointegration, Antimicrobial agents, Surface-coated materials, Bone regeneration

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I. Introduction

The term 'cranio-facial implants' has been used to describe endosseous implants inserted in the mastoid, orbital and nasal regions; and although some authors exclude the upper and lower jaws, both are parts of the craniofacial skeleton[1]. Cranio-facial implants have been classified in two groups: intra-oral dental implants, which are well-developed and extensively studied; and extra-oral implants, which are not as developed or studied as the intra-oral ones. The development of extra-oral implants has been slower in terms of design and applications because this type of implants has limited demand compared to the intra-oral implants. Furthermore, the placement of extra-oral implants can only be done in an operating room, and requires trained oral and maxillofacial surgeons. Additionally, the fabrication of these prostheses has to be performed by trained prosthodontists resulting in extra-oral implants being more complex and costly than the intra-oral counterparts[2].

The loss of craniofacial tissues can result from neoplasm, trauma, tumor or cyst resection, infectious diseases, nonunion fractures, and congenital or developmental conditions (i.e., cleft palate defects); which results in serious functional, aesthetic and psychological sequelae. In these situations, the absence of hard and soft tissues can be disfiguring, and in many cases, it compromises basic functions such as mastication, speech, swallowing, leading to limited thermal and physical protection of important anatomical structures (i.e., brain, nerves, arteries, veins)[3-6]. In the United States, there is a clinical need for craniofacial bone regeneration, and more than 30,000 surgical procedures are performed each year to repair craniofacial bone defects[7]. Data also revealed that over 1 million skeletal-related craniofacial procedures were performed in 2002, including 16,338 craniotomies and 32,043 post-traumatic facial reconstructions[3]. The treatment

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of craniofacial bone defects remains challenging in terms of providing protection to the brain, preventing infection and maintaining adequate appearance. Consequently, the outcome of craniofacial bone reconstruction is thought to be dependent on surgical skills, the quality of adjacent soft tissues, the size and location of the defect and the choice of repair method[4,7,8].

The long-term success of dental, facial, orbital, or auricular prostheses beyond primary reconstruction is dependent on the maintenance of its anchorage function. Providing adequate retention and support of the implant has been a constant challenge; as the inherent mechanical retention within the defect or the use of adhesive systems has proven to be either problematic or unacceptable[3,4,7-10]. Additional hurdles in the treatment of craniofacial bone defects include the presence of bacteria from the oral and sinus cavities, the ability of the implant to withstand mechanical stresses from the masticatory function, and the challenge on finding a cost-effective solution[2-4,7,10].

II. Bone Response

In order to understand the causes of cranio-facial and dental implant failure it is first important to understand the process of implantation and the healing of the bone around the implant when the process is successful. Bone healing around an implant follows a similar process to fracture healing but is highly dependent on the surface characteristics of the implant. Blood at the implant surface supports the deposition of proteins, which is followed by coagulation, inflammation and tissue formation, all of which are regulated by the surface chemistry and topography of the implant[11]. Within seconds of blood contact with the implant, proteins adsorb to the implant surface which then allows for platelets to become activated and bind to the adsorbed protein. A clot then forms, which contains many signaling molecules which influence the migration of monocytes, neutrophils (both involved in inflammation), and mesenchymal cells (cells that can differentiate into osteoblasts) towards the implant surface[12]. When neutrophils and macrophages are activated they migrate to the implant site from nearby capillary beds release inflammatory mediators which are necessary for the initiation of bone formation. Members of the tissue growth factor β (TGF-β) superfamily are also expressed within 24 hours of implantation, including bone morphogenetic protiens (BMPs) and growth and differentiation factors (GDFs). These signaling molecules allow for the recruitment, migration, and differentiation of mesenchymal cells, which take part in the formation of woven bone[13]. Woven bone is then remodeled resulting in the formation of mature bone, the desired end result[13].

When proper bone healing around the implant does not occur, implant failure results. There are many causes of implant failure, but most can be broken up into two main categories: aseptic loosening and infection[14]. Aseptic loosening, not associated with infection, can result from the inability of the bone to integrate with the adjacent implant surface[15,16]. Inadequate bone integration with the implant can lead to implant migration which stimulates the foreign body reaction and can lead to infection and tissue necrosis. Modifying the surface roughness and chemistry of the implant can affect the ability of the implant to induce strong osseointegration[15]. Roughening treatments have been employed in attempts to increase cell attachment and cell proliferation[17]. Moreover, bioactive coatings have been added to implants to further improve cell attachment and differentiation while reducing the likelihood of loosening[15].

While prosthetic implant infection (PII) can arise perioperatively or postoperatively, the majority are due to the introduction of bacteria directly into the patient during or soon after the surgery (perioperatively) and occur within 3 months of implantation[18]. The bacteria can originate from skin flora present around the site of surgery, from the bacteria present in the mouth, or from the surgeon. Furthermore, the conditions of the surgical wound, such as clotted blood and compromised soft tissue, make the site ideal for bacterial colonization. In the cases of acute infection, local cellulitis is produced which leads to the death of leukocytes, an increase in bone pressure, a decrease in pH, and a decrease in oxygen tension. Blood circulation is thus compromised which ultimately leads to the necrosis of large segments of bone[19]. Chronic PII extending from the bone-implant interface into the surrounding native bone and marrow is termed osteomyelitis and can result in significant bone loss and implant damage in severe cases[20]. Postoperative PII is usually caused by a single bacterial species (monomicrobiotic), the most common of which is *Staphylococcus aureus*. Infections caused by these microorganisms are becoming more worrisome due to the increase in multiple-antibiotic-resistant strains, such as methicillin-resistant *S. aureus*, which is now the most commonly isolated nosoco-mial bacterial pathogen in most of the world. While the immature or compromised immune system of the host is the primary cause of initial infection, the development of the infection into a persistent and chronic one is generally caused by other species of

bacteria, such as *Enterococcus* spp., *Strepto-coccus* spp., *Pseudomonas aeruginosa*, *Enterobacter* spp., *Mycobacterium* spp., and *Candida* spp[19]. Bacteria present at the implant can also lead to biofilm formation which is of much concern due to the difficulty in eradicating them. Several strains of bacteria, especially those found in the oral cavity, are capable of forming biofilms. Biofilms form when they attach to the material surface and then begin to grow in multilayered cell cluster which are then surrounded by a slimy matrix produced by the bacterial cells[21]. Biofilms can be a thin single layer of cells, or they can be thick with complex architecture in which the microcolonies form distinct pillars or mushroom-shaped structures. Between these pillars runs an intricate channel network through which nutrients can be transported, even to the deepest areas of the biofilm[22]. One benefit for bacteria that exist in biofilms is that the extracellular matrix is able to seize and concentrate several environmental nutrients. Furthermore, the bacteria that grow in biofilms are more resistant to several removal tactics, such as elimination by antimicrobial or antifouling agents (mediated by low metabolic levels and downregulated rates of cell division), shear stress, host phagocytic clearance, and host oxygen radical and protease defense[23]. Biofilms are also able to slow the infiltration of some antimicrobial agents, and in many cases, inactivate them in the process. The biofilm can also prevent the host inflammatory molecules from entering the biofilm, thus leading to a resistance to the host response. The host response itself can lead to host cell lysis and subsequent damage to the host tissue, resulting in the release of host cell components which act as nutrients for the bacteria. Finally, the biofilm has the potential for dispersion by way of detachment. This means that the microcolonies that exist in the pillars can detach under the direction of mechanical fluid shear or through a genetically programmed response that mediates the detachment process. The detached microcolonies can then travel under the direction of the fluid flow and attach and promote biofilm formation to other areas in the host that were previously uninfected[19].

III. Current Clinical Solutions-Dental Implants

Titanium is the most commonly used material for bone-contacting dental implants due to its high biocompatibility and good mechanical properties. Titanium and its alloys spontaneously form a titanium oxide (TiO_2) layer on their surfaces which contribute to many of their excellent properties such as corrosion resistance. Furthermore, compared to other metals, titanium has a relatively low modulus, reducing the potential for stress shielding, as well as good fatigue strength[15,24,25]. It has been shown to produce very little fibrous tissue which allows for bone to easily grow on its surface[26]. Moreover, it has been shown to have a high capacity to join with bone. However, simple machined surfaces require several months of healing before bone integration occurs which means that there is a latency period of several months before the implant can undergo mechanical loading. To this end, several surface modification techniques have been employed to shorten the time between implantation and use of the site, summarized in Table 1[27].

Grit-blasting and acid etching among the most commonly employed surface modification techniques used in commercially available implants. Sand blasting increases the surface area of the implant compared to machined surfaces. This increase in surface area has been shown to improve cell attachment and proliferation which results in increased implant stability[15,24,28]. SLActive (Institut Staumann AG, Basel, Switzerland), for example, has been shown to increase wound-healing rate when compared to SLA (Institut Staumann AG) which may be attributed to its greater hydrophilic surface which results from its thicker oxide layer[29-31]. In these animal studies, a healing chamber model was used as opposed to appositional bone formation which is what is typically seen for screw root form implants. Electrochemical anodization is another chemical surface modification method that has been employed. It increases the surface microtexture and changes the surface chemistry of the implant resulting in a TiO_2 layer that is several orders of magnitude thicker than a passivated surfaces[32]. This surface modification, seen in the TiUnite implant, has been shown to increase the host/implant response at early implantation times relative to other surfaces[33-36].

The addition of a ceramic coating to the roughened surface has gained much popularity due to their increased osseoconductivity. Integra-CP (Bicon Dental Implants, Boston, MA, USA), for example, employs a plasma sprayed hydroxyapatite (HA) coating which results in an irregular surface. The process involves blasting the surface with HA particles at the implant surface at high temperatures, resulting in a cracked coating as the coating undergoes rapid cooling. While this coating has shown enhanced bone-to-implant contact magnitudes at early implant times *in vivo*, the technique has compromised bone-coating interface mechanical properties in addition to non-uniformity in degradation after long periods in function[37-43]. For these

Table 1. List of currently available dental implants in the US market detailing commercial name, type and advantages of surface treatment

Company	Implant	Surface treatment	Claims of surface effect
Astra	OsseoSpeed	Fluoride-modified nanostructure	Early bone formation and stronger bone-to-implant bonding
Bicon LLC	Integra-Ti	Grit-blasted with alumina and passivated in nitric acid solution	Enhanced early osseointegration
	Integra-CP	Integra-Ti plus plasma sprayed hydroxyapatite (PSHA) coating	Enhanced early osseointegration
Biohorizons	LaserLok	Cell-sized channels laser-machined onto implant surface	Attracts a true, physical connective tissue attachment
Biomet 3i	NanoTite	Discrete Crystalline Deposition (DCD; Solution-based form of self-assembly) of nano-scale calcium phosphate	Enhanced early osseointegration
	Osseotite	Dual-acid-etched (DAE)	Increasing platelet activation and red blood cell agglomeration
Dentsply Friadent	Ankylos	Microstructred surface by grit blasing and etching	Homogenous bond with surrounding bone; bacteria-proof connection between implant and surrounding tissue
Neoss	ProActive	Multistage blasting, etching, cleaning and chemical treatment	Rapid bone formation with greater strength at the implant interface
	Bimodal	Multistage blasting and cleaning	Optimized bone interlocking and stress distribution
Nobel Biocare	TiUnite	Ceramic coating through spark anodization	Increases predicability and speed of osseointegration
	NobelActive	Grooves in thread tips	Increases osseointegration
Straumann	SLA	Sand blasted and acid-etched	Optimal surface for cell adherence and proliferation
	SLActive	Sand blasted and acid-etched	Optimal surface for cell adherence and proliferation
Zimmer dental	MXT Microtextured Titanium	Grit-blasted surface with HA particles	Increased bone apposition for long-term success
	MP-1 HA Coating	Hydroxyapatite coating by MP-1 process	Achieves and maintains excellent bone-to-implant contact

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reasons, these types of coatings have fallen out of favor in dentistry. Alternatives have been recently employed in commercially available implants. This includes the discrete crystalline deposition of nano-sized calcium phosphate as seen in the NanoTite implant. In this surface modification, the titanium surface undergoes a dual acid-etched treatment followed by nano-HA deposition. A clincial pilot study showed higher bone implant contact (BIC) after two months[44]. The addition of a fluoride treatment to roughened titanium surfaces has also been employed as seen in Osseospeed. Fluoride treatment has been shown to enhance gene expression in cell arrays and enhance host-to-implant response at early implant times[45]. An *in vitro* study showed that after 14 days of culture with osteoblast cells, the cells grown on Osseospeed expressed increased levels of alkaline phosphatase activity and collagen I production compared to TiOblast and tissue culture plastic. Further, a higher number of calcium crystals were evident on the Osseospeed substrates[46]. An *in vivo* animal study conducted in canine mandibles, the Osseospeed implant was shown to have a higher BIC compared to the TiOblast implant[47]. While several advances in surface modification have been made in order to improve implant osseointegration, no treatments address the issue of infection to the best of our knowledge. While some claim to be bacteria-proof due to their tight interlocking, the implant itself does not prevent bacterial attachment which can lead to biofilm formation and finally implant failure.

IV. Current Clinical Solutions: Other Cranio-facial Implants

1. Metals

Fixation plates molded from various metal alloys have been used as materials for craniofacial implants, and have been quite popular owing to their relative ease of use and versatility[48]. As an example, titanium-based meshes have been widely used in adult cranioplasty, showing almost non-allergic reactions. However, the major drawbacks are the cost, the tendency to corrode with time, and the risk of migration[48,49]. Titanium and/or polymer/titanium meshes like M-TAM (Stryker, Kalamazoo, MI, USA) and TiMesh (BioMet, Warsaw, IN, USA) are examples of commercially used implants, and are very popular since they can be formed and shaped individually and easily cut with scissors by surgeons in the operating theatre. They are fixated with

titanium screws and are convenient for primary fractures where there is bone loss[49,50]. In particular, TiMesh is a monofilament, composite mesh combining polypropylene with a covalent bonded titanized surface. TiMesh titanized polymers were designed specifically to have the following properties: inertness, molecular permeability, pliability, transparency, mechanical integrity and biocompatibility. Studies have demonstrated that TiMesh conforms to the local anatomy and has a high degree of biocompatibility. This is because of the titanium surface as well as the reduced amount of material[51-53].

2. Ceramics

Calcium phosphates (CaP) are widely used in cranio-facial and orthopaedic applications due to their biochemical similarity to the mineral component of bone. HA is a biocompatible CaP compound, which promotes osteoconduction, i.e., bony ingrowth from adjacent surfaces as well as osteoinduction, i.e., bone formation with a high successs rate. On the other hand, it does not promote toxic or allergic reactions[48,49]. HA has been made available for clinical use as a bulk material, in granular form, in pastes, and also as a coating material for metallic implants in order to facilitate the growth of bone because of its excellent bioactivity. Fluoridated HA (FHA), a variation of HA has been shown to exhibit a better stability than HA in physiological environments; and released fluorine ions can affect bacterial metabolism as an enzyme inhibitor and act as an antibacterial agent. However, few reports quantitatively study the effect of FHA antibacterial activity[49,54]. A privately held biotechnology company, PolyPid Ltd. (PetachTikva, Israel) has developed BonyPid which is a fully biodegradable synthetic bone filler that consists of beta-tricalcium phosphate (β-TCP) particles, micro-coated with PolyPid, which is a controlled release formulation technology of antibiotics. Preliminary clinical data have clearly demonstrated BonyPid's safety and efficacy in early bone formation and anti-infective effects[55].

There are also a number of CaP injectable materials that are currently used and regulated in clinical applications. CaP cements combine a dry CaP powder and a liquid component (i.e., an inorganic or organic acid, or sodium phosphate solutions) in a setting reaction that occurs under physiologic pH and temperatures. The major purpose of the pastes has been to allow the surgeon to easily fill irregular defects and shape the material during surgery into reasonable aesthetic contours. However, further surgical experience has demonstrated that there are several problems associated with the use of these products, such as rate of degradation, and their mechanical profile, because they tend to become brittle over time and can revert to a crystal powder[48-50]. Examples of HA cements include BoneSource (Stryker), Norian SRS (DePuy Synthes, West Chester, PA, USA) and Mimix (Walter Lorenz Surgical, Jacksonville, FL, USA). In general, these cements can be easily handled and have good clinical performance, but one of the major drawbacks of BoneSource (Stryker) in particular, is that during the curing process the cement must not gain contact to any fluids (blood); conditions that are practically unachievable in craniofacial surgery[49,50,56-63]. However, case studies of the different products are documented for different uses[64-67]. One interesting commercially available material is Palacos (Zimmer, Warsaw, IN, USA), a bone cement with the addition of Gentamicin, which has demonstrated antibiotic release with a broad spectrum of kill. It also has a proven clinical history of low revision risk[68]. In general terms, while CaP cements have been successfully used for clinical applications such as vertebroplasty and cranial defect repair, they are brittle and contraindicated for use in areas of mobility, active infection, or in situations where they directly contact the sinuses or dura[50].

Bioactive glasses have been shown to form a surface apatite layer *in vivo* that enhances the formation and attachment of bone, minimizing the formation of a fibrous capsule around the implant[49]. NovaBone (NovaBone) is a bioglass composite which has been used as a bioactive dental and orthopedic filler. It has been shown to influence the formation of new bone, promote intensive bond between bone and implant, and induce accelerated bone formation. One of the major drawbacks is that substitution of the material does not occur. Also the main fields of application of NovaBone are dental surgery and reconstruction of the calvarium and the floor of the orbit because it is considered too fragile for load-bearing applications[49,50,69]. Bioverit (G+W Implantate, Łomianki, Poland), is another bioactive glass–ceramic used for bone substitutions in several fields of human surgery, as well as implant craniofacial reconstruction, showing good clinical results. These implants allow intraoperative remodeling, adjustment and, as opposed to titanium implants, do not show thermosensitivity[49,50,70]. Complications associated with the use of this type of implants include extrusion, which requires reoperation[49].

3. Polymers

Porous polyethylene (PPE) implants are produced from

high-density polyethylene microspheres, that form a porous matrix which is commonly used for facial augmentation and to restore continuity to craniofacial skeletal defects, and it is designed to allow for ingrowth of the host tissue including both osteogenic and angiogenic material. The major advantages of PPE are that it appears to have a low infection rate and that it can be cut and contoured easily[48,71]. Medpor (Stryker) is a commercial implant made of PPE, characterized for being inert, biocompatible and porous: It is mainly used for facial augmentation in post-traumatic or tumor resection defects of the calvarium, orbit, mandible and also aesthetic augmentation (e.g., chin). More than 400,000 procedures have been performed with Medpor, and there are over 350 published clinical reports in cranial, reconstructive, oculoplastic and cosmetic applications[49,50,72]. There are almost no reported cases of extrusion, migration, or capsule formation. Reported reoperation rates are about 10%, consisting of implant removal for infection (3%) or displeasing contour (2%), and implant revision/replacement for improvement of contour (6%)[49].

Methyl methacrylate (MMA) is an acrylic-based resin that is commonly employed together with titanium wire mesh to contour and fill large cranial defects, having acceptable low infection rates. Although MMA is resistant to absorption, it has several advantages such as its low cost, predictable resultant shape and suitability for complex defects. However, complications include exothermic reactions with the release of potential toxic monomers, causing local inflammation. In pediatric patients, some common complications are: infection, extrusion, migration, bone loss around the implant, undesirable thermal sensitivity. Another complication in growing children is that the implant can become isolated with time, forming a fibrotic tissue with no attachment to bone[48-50,71]. Commercially available MMAs include Clearshield (OsteoSymbionics, Cleveland, OH, USA) which has been proved in hard tissue replacement in the craniofacial reigion[73].

Resorbable polymeric systems such as poly-lactic acid and poly-lactide-go-glycolide (PLGA) are biologically compatible, but do not possess osteogenic, osteoconductive, or osteoinductive properties. However, properties such as their rate of degradation, pore size, porosity, interconnectivity, hydrophobicity/hydrophilicity, ability for cell attachment, morphology, and handling properties have made them attractive materials for investigation and implantation. Advantages of these devices over traditional titanium plates and screws include elimination of long-term palpable devices and continued skull growth in the pediatric population once they have degraded. Major disadvantages of these materials include screw breakage and inflammatory reactions due to their degradation products[49,50]. LactoSorb (Biomet Microfixation, Jacksonville, FL, USA) is a resorbable plating system of plates and screws composed of 82% poly L-lactic acid and 18% poly glycolic acid. Lactosorb systems have been used successfully in more than 50,000 craniomaxillofacial cases, showing reduced risk of inflammation as well as lower risk of implant migration, as it resorbs during the first 12 months, approximately[74].

4. Composites

PLGA microparticles incorporated within an injectable CaP formulation can, upon degradation of the PLGA, yield macroporosity for tissue ingrowth and, possibly through a lowered local pH upon degradation of the PLGA, can accelerate degradation of the CaP phase. The incorporation of other degradable particles such as poly(trimethyl carbonate) and gelatin microparticles has yielded similar favorable results within injectable formulations, and the potential for drug or growth factor release from these systems has been well demonstrated[50]. In this category, a commercially available implant BonAlive (BonAlive Biomaterials Ltd., Turku, Finland) is a 100% synthetic, osteoconductive, osteostimulative silica-based bone graft substitute that is used for bone cavity filling in orthopaedic and cranio-maxillofacial surgery including jaw surgery. It has been shown that BonAlive bonds firmly to bone and several clinical studies have shown bacterial growth inhibition[75].

V. Translational Studies with Antibacterial Surfaces

Several synthetic polymers and chitosan, have exhibited antibacterial properties and can be used as coatings on dental implants to prevent infection at the implant site. Martin et. al.[57], developed a poly (dimethylaminomethyl styrene) coating, deposited by chemical vapor deposition, that was effective in killing 99.9999% of *Escherichia coli* and *Bacillus subtilis* bacteria. While the coating was deposited on a nylon substrate, the authors suggest that the coating could be used for other biomedical implants, including dental and other craniofacial implants. Another polymer coating, a poly(L-lysine)-*grafted*-poly(ethylene glycol) copolymer was shown by Harris et al.[76], to reduce *S. aureus* adhesion as well as osteoblast adhesion. However, the addition of

an arginine-glycine-aspartate peptide showed improved osteoblast attachment without inhibiting its antibacterial activity. An antibacterial polymer, Poly(N,N-dimethyl-N-(ethoxycarbonylmethyl)-N-(2'-(methacryloyloxy)ethyl)-ammonium bromide), or (pCBMA-1 C2), was attached as a coating by a grafting technique known as surface-initiated atom transfer radical polymerization. The coating was shown to kill 99.9% *E. coli* bacteria followed by a release of the bacterial cells upon hydrolysis[77]. The coating shows promise, but bacteria more relevant to dental and craniofacial implants would need to be tested.

Polymers have also been combined with antibiotics to develop antimicrobial polymeric coatings. Al-Deyab, for example, soaked electrospun nylon-6/chitosan (nylon-6/Ch) nanofibers in an aqueous solution of glycidyltrimethylammonium chloride, an antibacterial agent, to make make nylon-6/N-[(2-hydroxy-3-trimethylammonium) propyl] chitosan chloride. The antibacterial efficacy of the fibers were tested against *E. coli, P. aeruginosa* and *S. aureus* and showed to negatively affect bacterial replication and induce cell damage. Significant zones of inhibition were also observed[78]. Grafted Allylamine, N-allylmethmylamine (AMA) and N,N-dimethylamine (DMAA) monomers with the addition of the antibiotic triclosan (TC) were tested for their antibacterial activity against *S. aureus* and *E. coli*. Bílek et al.[79], found that the grafted AMA and DMAA with TC showed antibacterial activity against both bacterial strains and that they actually exhibited greater antibacterial activity against the gram-positive *S. aureus*. Zhao et al.[80], developed a Poly(N-hydroxyethylacrylamide)/Salicylate hydrogel (polyHEAA/SA) coating that released antibacterial SA compounds resulting in a polymeric coating that resisted the attachment of *S. epidermis* and *E. coli* after 24 hours. The coating also inhibited bacterial growth which was determined by measuring the optical density of the bacteria.

Alternative antibacterial agents, such as zinc oxide (ZnO) and silver (Ag), have been combined with polymers as well. Liu and Kim[81], added ZnO and Ag to genipin-crosslinked chitosan/poly(ethylene glycol) (GC/PEG) hydrogel matrix. The nanocomposites showed enhanced antibacterial activity against gram-negative *E. coli* and *P. aeruginosa* as well as gram-positive *S. aureus* and *B. subtilis* over GC/PEG alone. Adding ZnO increased the zone of inhibition of the copolymer, which was further enhanced by the addition of Ag[81]. Antibacterial metals have also been deposited directly onto implant surfaces. In one study, zirconium oxid (ZrO_2), ZrO_2-copper (ZrO_2-Cu) and ZrO_2-Ag coating were deposited onto pure-Ti substrates using pulsed unbalanced magnetron sputtering using high-purity Zr, Ag and Cu targets. When tested against *S. aures* and *Actinobacillus actinomycetemcomitans*, ZrO_2 surfaces showed less bacterial attachment and proliferation than the ZnO_2-Cu surfaces, which in turn, showed less bacterial proliferation than ZrO_2 coatings[82]. Titanium oxide (TiO_2) and zinc-doped TiO_2 ($Ti(Zn)O_2$) and ZnO coatings deposited by cathodic arc deposition have also been developed. The ZnO coatings had the least bacterial attachment and the $Ti(Zn)O_2$ coating had less than the TiO_2 coating. However, when tested for osteoblast attachment, ZnO showed the least number of osteoblasts while TiO_2 showed the most.

VI. Antibacterial Surfaces

The presence of infection is an important parameter that must be considered for nearly any reconstructive technique. Infections following traumatic craniofacial injuries are common, and although success rate of dental implants are high, biomaterials for the restoration of oral function are prone to biofilm formation, and failure is commonly associated with bacterial infections. The consequences of implant associated infection are significant and usually require revision surgery, with removal of the implant, prolonged antibiotic treatment, impaired oral function, and in extreme cases even death. Furthermore, bacterial colonization of dental implants can lead to inflammatory reactions which prevent or result in loss of osseointegration. For those reasons, various approaches to reduce the rate of infection have been investigated. Therefore, antibiotic delivery and antibacterial surfaces may thus be important aspects of tissue engineering strategies in the craniofacial complex[18,50,83-86].

In this sense, the purpose of these bioactive surfaces would be to disrupt the metabolic machinery of the microbes or to prevent bacterial adhesion to the implant and, consequently, the development of biofilms. Different surface modification approaches and techniques have been developed for this purpose. Materials which promote the colonization of host tissue and suppress the colonization of bacterial species are often studied. These materials have many different mechanisms of action; some can interfere with bacterial adhesion by modifying surface energy, have surface immobilized molecules that are bactericidal, are photocatalytic, or more commonly, release metal ions or antibiotics[18,83].

Many drugs and coatings have been developed to create antibacterial surfaces that either kill bacteria or prevent their attachment to implant surfaces. A handful of polymers are

known to kill bacteria or prevent them from attaching and can therefore be used as coatings for antibacterial purposes[87]. There are also several low molecular weight molecules and inorganic ions that are known to also be antibacterial in solution and can either be released in a controlled manner or be grafted by covalent immobilization onto the implant surface[87]. The disadvantage to the controlled release method is that the duration of the antibacterial action is limited by loading and release kinetics[88]. Polymers can be coated onto medical implants by many methods including dip coating, spin coating, and layer-by-layer plasma polymerization which allows for a great variety of polymers to be applied onto material surfaces for the purposes of antibacterial action[87]. The majority of synthetic polymers, and the natural polymer chitosan, that have been reported to be antibacterial are cationic. The release of antibiotics from polymer coatings has also been extensively investigated. By releasing the drugs locally, as opposed to systemically, higher local doses can be administered without the risk of exceeding the systemic toxicity levels of the drug which could result in renal and liver complications[89]. When considering the release mechanism for these systems, it is important to consider the release kinetics of the drug; a fast release allows for a high dose but only for a short period of action whereas a slow release may not reach the required therapeutic levels and could also result in bacterial resistance[87]. According to Vasilev et al.[87] the ideal release coating should provide a fast initial release within the first 6 hours, that will protect the site while the immune system is weakened, followed by a slow release. The use of a polymer matrix that degrades in the body allows for a combination delivery by diffusion and polymer matrix erosion[90]. Some common antibiotics used in these polymeric coatings are gentamicin, norfloxacin, cefazolin, amikacin, and vancomycin[87]. Nitric oxide has also been used in release systems as an antibacterial agent and has been shown to reduce the adhesion of *P. aeruginosa, S. aureus*, and *S. epidermis*[87].

1. Silver nanoparticles

Due to the emergence of multiple drug-resistant bacterial strains, alternatives to traditional antimicrobials has been sought through inorganic agents[91]. Among these agents, silver ions and silver nanoparticles have been studied most extensively[91]. Silver has been used for centuries for the treatment of burns and chronic wounds[92]. However, with the advent of penicillin in the 1940s, the use of silver in bacterial infections was minimized. Yet, with the emergence of antibiotic-resistant strains of bacteria, interest has returned to the use of silver as metallic silver, silver ions, and silver nanoparticles[93]. Silver's antimicrobial properties are related to the amount of silver present and its rate of release. In its metallic state, silver is inert, but when it is exposed to moisture in the skin or the fluid in a wound, it becomes ionized and thus highly reactive. It binds to proteins in tissue and causes structural changes the cell wall of bacteria and their nuclear membrane leading to cell distortion and death[93]. It also binds to bacterial DNA and RNA, denaturing it and inhibiting bacterial replication[93]. Silver nanoparticles in particular have been receiving a lot of attention due to their enhanced antimicrobial properties especially in light of the growing antimicrobial resistance against metal ions[94]. This improved antibacterial activity is due in part to their large surface area to volume ratio[95]. They have been shown to have high antimicrobial and bactericidal activity on Gram-negative and Gram-positive bacteria, including multi-resistant strains such as methicillin resistant *S. aureus*[96]. Studies on both Gram-negative and Gram-positive bacteria have shown that silver nanoparticles show more efficient antibacterial properties (1.4-1.9×stronger) compared to silver ions[93].

The mechanism of action of silver is related with its interaction with thiol group compounds which are found in the respiratory enzymes of bacteria. Silver can also bind to the bacterial cell wall and cell membrane and inhibit the respiratory process. In order for DNA molecules to replicate themselves, they must be in a relaxed state. It has been suggested that when silver ions penetrate into the bacterial cell, the DNA molecule turns into a condensed form and loses its replication ability which ultimately leads to cell death[97]. Furthermore, proteins get inactivated when the silver ions attach to their thiol groups. Silver nanoparticles get attached to the bacterial membrane and can also penetrate inside the bacteria. The silver nanoparticles interact with the sulfur-containing proteins in the bacteria as well as with the phosphorus containing compounds, such as DNA[97]. When the silver nanoparticles enter the cell, they form a low molecular weight region in the cell which causes the DNA to condense so as to protect the DNA from the silver ions[98]. Furthermore, silver nanoparticles attack the respiratory chain and cell division which lead to bacterial death[99]. Silver nanoparticles also release silver ions which further increase their bactericidal activity[93]. Size and shape also seem to affect the antimicrobial activity of silver nanoparticles; silver nanoparticles with a smaller size have an increased surface

area to volume ratio and therefore are more effective in their actions against bacteria, and triangular nanoparticles were shown to inhibit bacterial growth at lower concentrations than spherical nanoparticles, and silver nanorods were shown to need the highest concentration[100]. Another advantage to silver is that there have been no regular reports of silver allergy, which can be of concern with other administered antibiotics[93]. Yet, while studies suggest that silver nanoparticles are nontoxic, some studies that have been conducted to this effect have shown that silver nanoparticles had negative effects on mitochondrial activity with increased concentrations[101]. Thus, for dental applications, caution should be taken to only use the maximal concentration necessary to prevent bacterial growth while maintaining host cell viability.

2. Anti-bioadhesion coatings

It has been shown that bioadhesion can be regulated by changing the surface hydrophilicity-hydrophobicity[18,85]. Strongly hydrophilic surfaces spontaneously form a monolayer of mobile water molecules which are not displaced by proteins and cells. Thus, the bioadhesion processes of both cells and bacteria are disrupted. However, in biomaterial applications which require cell attachment, such as osseointegration, these surfaces may not be useful because cellular adhesion is interrupted. Plasma deposition technique has been use for this purpose to coat materials used for fixed dental prostheses with hydrophilic molecules such as polyvinylpyrollidone[18].

Quaternary ammonium compounds (QACs) are widely used as antimicrobial agents to inhibit microbial growth. The antimicrobial activity provided by QACs results from both ionic and hydrophobic interactions between the QAC and components of the microbial cell wall that leads to cell death or malfunction of cellular processes[85].

Other examples are polymer-brush coatings which are currently some of the most promising nonadhesive coatings, since they reduce the initial adhesion of various bacterial strains and yeasts by several log-units, both in terms of adhesion numbers as well as in terms of adhesion forces. A polymer brush is formed when hydrophilic polymer chains are end-grafted to a surface in high density, forcing the polymer chains to stretch away from the surface into the adjacent medium. Compression of such a structure upon microbial approach gives rise to an osmotic pressure and decreased mobility (conformational entropy) of the polymer chains in the brush, which causes repulsion of approaching micro-organisms[85].

3. Other surface modifications

Covalent surface modification consists of immobilizing active antibiotics on metal surfaces. One example is use of aminopropylsilane to immobilize vancomycin on titanium surfaces. These surfaces have shown to have strong bactericidal activity and remain active over long periods of time (up to 1 month) *in vitro*. However, further testing is needed to prove the validity of this approach because permanent modification of the implant surface may lead to unfavorable tissue reactions[18]. The purpose of another generation of bioactive implants is the design of surfaces that are permanently rendered antimicrobial by covalent attachment of antibiotics or custom designed bactericidal peptides. As such, the active molecules are not allowed to elude off the surface of the implant, thus decreasing possible local and systemic toxicity and circumventing the problem of inconsistent elution characteristics while providing long-lasting protection[83].

Photocatalytic surfaces are thin films or coatings of TiO_2 that can be constructed on metal implants. They become bactericidal under near ultraviolet light and require up to 80 min of ultra violet exposure to eliminate 75-95% of bacteria. These surfaces can also be nitrogen-doped, which grant bactericidal activity under visible light and do not require long exposure times[18].

4. Antibiotic releasing coatings

Devices which rely on the release of antimicrobial agents enjoy only a finite duration of antimicrobial activity; and one of the major problems is the inability to discriminate between normal and pathogenic microflora of the mouth. There have been a variety of strategies to deliver antibiotics from implant materials. Some include coating biomedical alloys with degradable materials, such as poly-lactic acid, silica sol-gel, and chitosan. In theory, as the coating degrades, the infection is eradicated and the implant surface is left to achieve osseointegration. Additionally, the antimicrobial coatings can be effective against a wide spectrum of bacterial species and eliminate infection without the development of resistant strains[18,85].

Although antibiotics can and have been incorporated into many commercially available bone cements, poor release kinetics and the sensitivity of many antibiotics to the high curing temperatures associated with cements such as polymethyl methacrylate make incorporation into the bulk material an inefficient and in some cases ineffective strategy.

Many drug delivery systems for antibiotic and other bioactive factors utilize drug-loaded microspheres or microparticles. At small particle or sphere sizes, these systems are easily injectable, have well characterized and tunable release kinetics, and can be fabricated from biocompatible, biodegradable materials such as PLGA or gelatin[50].

Most coatings for biomaterial implants and devices are monofunctional, i.e., aimed solely at discouraging biofilm formation or enhancing tissue integration. New approaches include bifunctional coatings containing anti-adhesive functionalities, such as a polyethylene glycol polymer brush to discourage biofilm formation, while at the same time possessing functionalities like arginine-glycine-aspartic acid sequences to support tissue integration[85].

VII. Summary

Although current implant materials for the reconstruction of craniofacial bone defects have shown favorable results in most craniofacial and dental applications, the presence of complications related with infection and poor osseointegration still represent a challenge in the biomedical field. Different clinical circumstances may present different challenges; however, the multitude of dissimilar solutions for the repair of bone defects that have been proposed during the last few decades highlights the fact that an ideal solution has yet to be defined. There remains a need to develop strategies that will further reduce implant failure while simultaneously addressing different problems and causes of complications in a cost-effective manner.

Biomaterials for craniofacial bone repair and dental applications such as titanium, HA, bioactive glass, biocompatible and biodegradable polymers, and composites have been widely studied and used in clinical applications. Ongoing developments indicate that the tissue engineering field is moving towards the development of biomaterials with improved surfaces that will stimulate bone formation and avoid infections though the incorporation of surface modification techniques and antibacterial coatings and agents, as well as the incorporation of growth factors, stem cells and other pharmacological drugs. Scientists are paying far closer attention to the biological interface in terms of both the specific cellular and vascular responses necessary for stable osseointegration as well as the unique microbial strains in the oral space and the necessary steps to prevent biofilm formation to avoid infection related complications. Through the application of principles of engineering and biology, optimization and further investigation of surface manipulation and coating techniques is necessary in order to develop craniofacial bone substitutes that will restore, maintain and improve tissue function while combating infection.

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