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Review Article

THERAPEUTIC DENTAL IMPLANTS: GEARING TOWARDS CLINICAL REALITY

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ABSTRACT

The long-term success of an implant depends on the stability of bone support around an osseointegrated implant. The dental implant surfaces provide an ideal substrate for bacterial adhesion forming a biofilm. Biofilm performs vast functions ranging from physical defensive barrier against phagocytic predation to working as a selective permeable barrier. Once crestal bone loss starts, it can result in increased bacterial accumulation resulting in further peri-implant tissue destruction. These rapidly growing bacteria give rise to a chronic infection which is difficult to eradicate by conventional mechanical as well as antibiotic therapy. Biofilm matrix limits the diffusion of systemic antimicrobial agents that are capable of damaging the microbial complexes. Shortcomings of systemic antibiotics also include relatively low drug concentration at the target site and potential toxicity. Evidence based reviews show that surface modifications can significantly affect initial adhesion and biofilm formation on the implant surface. The various functional modifications on the implant surfaces which have been suggested include coatings on the titanium implant which are incorporated with disinfectants, antibiotics as well as antimicrobial peptides for which different methods of physical adsorption have been reported. The ultimate antimicrobial surface should be responsive to even the lowest bacterial load. Nano- related concepts are also an emerging area of research in controlled drug delivery through the use of nanostructures (nanotubes, nanospheres) as therapeutic surface modification of dental implants. Henceforth this review throws light on coated dental implants which exhibit therapeutic properties as a strategy to combat peri implant infections, thereby aid in bridging the gap between research and clinical implant dentistry.

KEYWORDS: *Dental implants, Biofilm, Antibiotics, Antimicrobial peptides (AMPs).*

INTRODUCTION

Peri implant infections are a major destructive complication in implant dentistry and are closely related to the surface characteristics of commercially available pure titanium and its alloys and the rate of biofilm formation on the implant surface. Peri implant infections are a collective term for inflammation which affect both the surrounding hard and soft tissues of an osseointegrated implant which is in function ***(Isidor F, 1996).*** The implant surface is susceptible to infection for the two main reasons, (1) formation of a surface biofilm and (2) compromised immune response at the implant/tissue interface ***(Zhao L et al, 2009).*** Titanium is the ideal material of choice for hard tissue fixation devices mainly due to its corrosion resistance and favorable biocompatibility. The biocompatibility of titanium implant can be attributed to the surface protein layer formed under physiological conditions. But this layer makes the surface suitable for bacterial colonization and biofilm formation leading to a compromised state ***(Hetrick EM et al, 2006).***

To overcome this limitation of biofilm formation on titanium surfaces researchers have developed anti-adhesive or bactericidal surface modifications. The most common strategy to overcome interaction between synthetic materials and microorganisms are to modify the implant surface with biofunctional molecules (functionalization of implant surface). The various functional modifications on the implant surfaces that has been researched include coatings on the titanium implant which are incorporated with disinfectants, antibiotics as well as antimicrobial peptides for which different methods of physical adsorption have been reported ***(Jasmin Grischke et al, 2016)***. Prophylactic coatings with the local application should possess sufficient release rate to prevent the bacterial adhesion or kill bacteria adhered to the implant surfaces and enhance implant success (***Antoci V Jr et al, 2008)***. The functionally modified surfaces may either exhibit (1) antimicrobial capacities which cause cell damage to adhering bacteria or (2) anti-adhesive properties that inhibit biofilm formation in the first place ***(Jasmin Grischke et al, 2016)***. Nano- related concepts are also an emerging area of research in controlled drug delivery through the use of nanostructures (nanotubes,

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nanospheres) as therapeutic surface modification of dental implants ***(Eriberto Bressan et al, 2013; Li, Tao, et al, 2017)***.

Henceforth this review throws light on coated dental implants which exhibit therapeutic properties as a strategy to combat peri implant infections, thereby aid in bridging the gap between research and clinical implant dentistry.

Importance of Antibacterial Coatings:

Biofilm is a microbial derived sessile colony characterized by cells that are irreversibly attached to the substrate or an interface to each other, embedded in a matrix of extracellular polymeric substances produced by the microorganisms and exhibiting an altered phenotype with respect to growth rate and gene transcription. ***(Donlan RM et al, 2002).*** The complex microbial communities are the major etiologic factors for caries, gingivitis, periodontitis and stomatitis. Also, in case of peri-implantitis it is a major cause of dental implant failure (**Paquette DW et al, 2006**). The composition of the biofilm and the rate at which biofilm formation occurs on the implant surface, along with the surface characteristics of the implant, abutment materials and the prosthetic components influence the rate of peri-implant tissue destruction.

Studies have demonstrated that both the quality and quantity of plaque adhesion on the implant surface are important in the long-term survival of dental implants (***Lindhe J et al, 1992***). A ten-year implant survival rate of 90-96% has been recorded (***Cecchinato D et al, 2014).***

The biofilm formed limits the diffusion of systemic antimicrobial agents that are capable of eliminating the microbial complexes. The shortcomings of systemic antibiotics also include relatively low drug concentration at the target site and potential toxicity. A recent systematic review concluded that within the limitations of the experimental conditions, surfaces smeared with organic or inorganic antimicrobial substances as well as AMP surfaces exhibit bactericidal activity. In addition, bioactive polymer coatings, nanoscale surfaces and UV-activatable surfaces have also shown to enhance the antimicrobial activity compared to uncoated titanium ***(Jasmin Grischke et al, 2016).***

Antimicrobial dental implant functionalization strategies:

Prevention of bacterial colonization on implant surfaces play a pivotal role in limiting the spread of infections. There are three major functionalization strategies for designing antibacterial coatings include: antibacterial agent release, contact-killing, and anti-adhesion/bacteria-repelling.

- ***Antibacterial agent release:*** These coatings exert their antibacterial activity by leaching loaded antibacterial agents over time leading to destruction of both adhered and adjacent planktonic bacteria. The incorporated antibacterial agents are released by diffusion of these agents into the aqueous medium, by erosion/degradation, or by hydrolysis of covalent bonds (***Campoccia, D. et al, 2013)***. However, their ultimate action can be considered as temporary only as these coatings have limited reservoirs of antibacterial agents.

- ***Contact killing:*** Contact-killing coatings have been developed to bypass the reservoir exhaustion of release-based materials (***Tiller, J.C. et al, 2001***). The antimicrobial agents are covalently anchored to the material surface by flexible, hydrophobic polymeric chains ***(Lewis, K et al, 2005)***. The main mechanisms of action are based on membrane interactions, such as physical lysing or charge disruption and hence the most effective compounds as contact-killing coatings are either cationic compounds (QACs, chitosan, AMPs, etc.) or enzymes ***(Green, J-B.D. et al, 2011).***

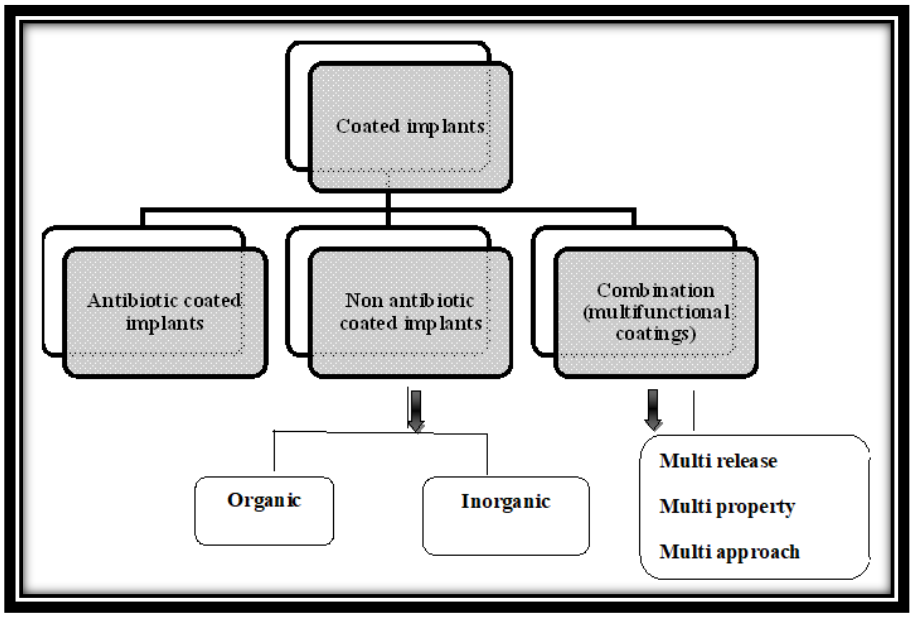

Fig. 1: Coated dental implants: an emerging therapeutic strategy

- ***Anti-adhesion/bacteria repelling:*** Anti-adhesion coatings aim to prevent the initial step of biofilm formation using non-cytotoxic mechanisms. Treating protein-surfaces and/or protein-bacteria interactions may be a good strategy with a therapeutic potential for preventing bacterial adhesion to a specific biomaterial ***(Campoccia D***

et al, 2013). Proteins such as albumin, fibronectin, fibrinogen, laminin, denatured collagens, and some plasma/tissue lipids are the first host substances that interact with the surface structure of the biomaterial ***(Wagner et al, 2011; Vadillo-Rodriguez et al, 2013)***. Friedman et al. using a rabbit model, demonstrated reduced bacterial adherence on pure titanium samples and decreased infection rates of implants coated with cross-linked albumin ***(Friedman, R.J et al, 1997)***. Surface molecules that can resist protein adsorption, such as PEG and zwitterion, have been demonstrated to have great anti-adhesion properties in vitro (***Hasan, J. et al, 2013).***

- ***Multifunctional and smart coating:*** A smart surface is a completely different methodology designed to be a self-responsive multitask micro- machine that releases antimicrobial (and other) substances after stimulation by microbiological (or other) signals. The response depends on the specific abilities of the coatings acquired during the manufacturing process ***(Jiri Gallo et al, 2014).***

Antibiotic coated implants:

The most effective strategy to battle periimplantitis would be the prevention of biofilm formation on the implant material. Antibiotic coated dental implant materials may either exhibit antibacterial capacities which cause cell damage to adhering bacteria or antiadhesive properties that inhibit initial bacterial adhesion ***(Zhao L et al, 2009)***.

Bioactive coatings release antibiotics, such as gentamycin (inhibit protein synthesis by binding to the bacterial 30s ribosome), vancomycin (disrupt cell wall peptidoglycan synthesis by binding to amino acids), and amoxicillin (inhibit cell wall synthesis by enzyme inhibition) but require a vehicle/vector which carries the agent to the desired site. Calcium phosphates, which are known to be biocompatible and osteoconductive, have been widely used as potential vectors. But antibiotics cannot be incorporated during its formation because of high processing temperature. Zhao et al in a review concluded that antibiotic-loaded hydroxyapatite (HA) coatings on titanium favors prevention of biofilm formation compared with standard HA coatings ***(Zhao L et al, 2009).*** Various methods for physical adsorption have been reported and they include: (a) Loading by dipping method which leads to burst release of antibiotics; (b) application of a lipid layer which acts to serve as a hydrophobic barrier and can retard the drug release; (c) biomimetic method by immersion into a supersaturated solution of calcium phosphate; (d) controlled release of antibiotics by biodegradable polymers and sol-gel coatings; and (e) electrospray deposition of amoxicillin combined with poly(lactic-co-glycolic acid) (PLGA) (***Varun Yarramaneni et al, 2016)***.

A biodegradable gentamicin-loaded Poly D, L, Lactic acid coating has been developed to prevent implant-related osteomyelitis in rats ***(Lucke M et al, 2003).***

Vancomycin covalently bonded to titanium using solid-state synthesis preserves the activity of the antibiotic. It is a preferred antibiotic for protection against both bacterial adhesion and biofilm formation by *S. epidermidis.* Titanium surface tethered with vancomycin is biocidal to the bacterial cell wall ***(Antoci V Jr et al, 2008).***

Cometa S in 2012 in a study stated that a possible solution to prevent the initial bacterial adhesion may be coating of the implant surface with a thin layer of antibiotic-loaded biocompatible polymer. Antibiotic-modified poly (ethylene-glycol diacrylate) hydrogel coatings on titanium substrates (vancomycin and ceftriaxone) were prepared by electrochemical polymerization and tested against methicillin resistant Staphylococcus aureus (ATCC 33591). The study reported that these coatings displayed an interesting antibacterial activity, but further studies on their cytotoxicity is required to prove their real clinical efficacy (*Cometa S et al, 2012).*

Hongbin Lv et al, 2014 observed that loading minocycline on the surface of implants based on layer by layer (LbL) selfassembly strategy could furnish implants with sustained antibacterial property. This can inhibit the immediate colonization of bacteria onto the surface of implants and reduce the occurrence of periimplantitis ***(Hongbin Lv et al, 2014).*** Yet another study by He S et al, 2014 used Ti substrate coated by the antibiotic cefotaxime sodium (CS) onto a polydopamine-coated Ti through catechol chemistry. The results of his study demonstrated that the antibiotic-grafted Ti substrate showed good biocompatibility and well-behaved hemocompatibility. In addition, the antibiotic-grafted Ti could effectively prevent adhesion and proliferation of *Escherichia coli* (Gram-negative) and *Streptococcus mutans* (Gram-positive) ***(He S et al, 2014).***

Fibers containing TCH at 5 wt.% demonstrated complete inhibition of Aa biofilm. Even though a marked reduction in CFU/mL was observed with an increase in TCH concentration, Pi proved to be the most resilient microorganism. SEM images revealed the absence of or a notable decrease in bacterial biofilm on the TCH-containing nanofibers. The results of the study suggest that tetracycline-containing fibers hold great potential as an antibacterial dental implant coating ***(RG Shahi et al, 2017).***

Nonantibiotic coated implants:

1. Organic antimicrobial agents:

The emerging risk of antibiotic resistance has provoked researchers to use non-antibiotic agents as antimicrobial agents. Certain of these substances has made its use applicable in daily life due to their broad antimicrobial activity. However, several reports have pointed out that the nonantibiotic organic antimicrobial agents may cause cell damage ***(Harris LG et al, 2006; 78:50–58; Schutze N et al, 2007).***

1.1. Chlorhexidine:

Regarding the risk of antibiotic resistance associated with the application of antibiotics-containing coatings, nonantibiotic organic antimicrobial agents such as chlorhexidine, chloroxylenol, and poly (hexamethylene biguanide) may be better alternatives ***(Morra M et al, 2004; Kim W-H et al, 2008).*** Their broad-spectrum antimicrobial action and lower risk of drug resistance has made its use applicable in daily life, especially chlorhexidine which is well known for its extensive application in the treatment of periodontal infection. ***(Heasman PA et al, 2001).***

Studies have shown that chlorhexidine can adsorb to the TiO2 layer on the titanium surface and desorb gradually over a period of several days ***[Kozlovsky A et al, 2006; Barbour ME et al, 2007).***

Natalie J et al in 2015 investigated the use of chlorhexidine (CHX) hexametaphosphate (HMP) nanoparticles

(NPs) with a total CHX concentration equivalent to 5 mM as a coating for dental implants. CHX HMP NP-coated surfaces exhibited antimicrobial activity against oral primary colonising bacterium *Streptococcus gordonii* within 8 h. The antimicrobial efficacy was greater in the presence of an acquired pellicle which is postulated to be due to retention of soluble CHX by the pellicle ***(Wood et al, 2015).***

1.2. Antimicrobial peptides:

Antimicrobial peptides (AMPs) are established antimicrobials due to their broad-spectrum activity against bacteria, fungi and virus, low host cytotoxicity, and low bacterial resistance ***(Chen, X et al, 2013).*** These AMPs which are derived from human proteins cause membrane lysis either by barrel stave, toroidal pore, or carpet mechanisms ***(Nguyen LT et al, 2011).*** GL13K is a small cationic AMP, i.e., derived from human salivary protein, parotid secretory protein (HPSP). Balhara et al in 2013 and Chen et al in 2014 found that GL13K has strong anti-inflammatory and antibacterial activities against both Gram-negative and biofilm-forming bacteria particularly effective against *Pseudomonas aerogenosa.* These AMPs cause membrane lysis by any of the proposed mechanisms of action.

GL13K peptide apart from bactericidal effect has additional resistance through hydrolytic and mechanical changes with no significant release of peptides from the titanium surface. It was found that GL13K is cytocompatible with osteoblasts and human gingival fibroblasts ***(Holmberg KV et al, 2013).*** Recombinant human beta defensin-2 (HBD-2) was used to study the influence on the proliferation and survival of cells in culture. They concluded that HBD-2 is not only biocompatible but also promotes proliferation of hMSCs, osteoblasts, and keratinocytes in culture ***(Warnke PH et al, 2013).***

Jue Shi et al in 2015 in their study used antimicrobial peptide coatings on smooth titanium surfaces which were assembled using a LBL technique. In this study, the broad-spectrum AMP, Tet213, was linked to collagen IV through sulfo-SMPB and has been renamed as AMPCol. This technique which allowed the controlled release of AMP decreased the growth of both a Gram-positive aerobe (*Staphylococcus aureus*) and a Gram-negative anaerobe (*Porphyromonas gingivalis*) up to one month. Early *S. aureus* biofilm formation was also inhibited by the coating ***(Shi, Jue & Liu, 2015).***

1.3. Essential oils:

Warnke et al in 2009 investigated the antimicrobial effectiveness of different essential oils on several pathogenic microorganisms with microbiological tests. The tested essential oils (lemongrass oil, tea tree oil) exhibited clear antimicrobial effects against staphylococci, streptococci and candida ***(P.H. Warnke et al, 2009).*** Functionalization of different dental implant material surfaces with essential oils resulted in immediate and ongoing antibacterial and antiplaque activities ***(Bazaka K et al, 2011).*** Yet another study by Afya Sahib et al in 2013 evaluated the effectiveness of essential oils (cinnamon oil and clove oil) on implant surfaces and they were shown to be effective in inhibiting biofilm formation. They were shown to be more effective against gram negative anaerobic bacteria than against facultative anaerobic gram-positive bacteria ***(Al-Radha et al, 2013).***

1.4. Bioactive Antibodies:

Antibodies or immunoglobulins have an intrinsic capacity of opsonization. They opsonize microbes and phagocyte them, thereby reducing their virulence. It is a natural immune function of the body which can be critically exploited at the implant and wound sites. These antibodies operate independently of antibiotic resistance mechanisms. The most significant antibody subtype is immunoglobulin G (IgG). The release of commercially pooled human polyclonal IgG from hydrophilic polyurethane (PU) hydrogel has shown validated results against the clinical strain of E. coli ***(Rojas IA et al, 2000).***

2. Inorganic antimicrobial agents:

2.1. Hydroxyapatite:

Inorganic antimicrobial agents are very attractive alternatives from the perspective of doping of biomaterials because they possess many advantages such as good antibacterial ability, excellent biocompatibility, and satisfactory stability. It has been observed that a thin layer of HA coatings on titanium (Ti) implant surface can be deposited by a mechanism known as "magnetron sputtering." Kulkarni et al, 2017 demonstrated that calcium phosphate coatings have excellent *in vitro* bioactivity. These coatings can enhance osseointegration and prevent infection in implants, thereby improving the success rates of implants ***(Kulkarni Aranya et al, 2017).*** These coatings have also been used as potential vectors along with antibiotics ***(Zhao L et al, 2009).***

2.2. Silver particles:

Silver (Ag) has also been used to coat Ti implants for antibacterial applications. It has a broad, long-lasting spectrum of activity against both Gram-positive and Gram-negative bacteria. Silver coating can remarkably prevent bacterial adhesion and growth without jeopardizing the activity of osteoblastic and epithelial cells ***(Ewald A et al, 2006; Chen W et al, 2006).*** The basic mechanism of action of Ag+ ions is that it causes DNA condensation on interaction with bacterial cell wall and disturb its permeability ***(Campoccia, D et al, 2013).***

Silver can be introduced by various techniques, such as magnetron sputtering, plasma immersion ion implantation (PIII), pulsed filtered cathodic vacuum arc deposition and physical vapour deposition (PVD) (***Chen W et al, 2006)***. Taking into consideration these advantages as a bactericide, silver has also been introduced into titanium to enhance the bactericidal ability. It is believed that anodization of Ag can yield extra antibacterial activity which is of special interest for dental implants ***(Zhao L et al, 2009; (Pokrowiecki R et al, 2017).***

2.3. Anodically oxidized/ ion implanted surfaces:

Certain elements such as fluorine (F), zinc, (Zn) calcium, (Ca), chlorine (Cl), iodine (I), copper (Cu), cerium (Ce) or selenium (Se) may be incorporated into titanium or hydroxyapatite coatings by anodic oxidation of their corresponding metal ions. The bactericidal activity depends on the slow release of ions from the implant surface into the surroundings. One mechanism of bacteriostasis is hydroxlyation into highly reactive components, such as HCl, HOCl, TiOH, hydrogen peroxide (H2O2) or superoxide (O2−). These reactive species evoke oxidation of the bacterial cell membranes, resulting in increased cell permeability and ultimately results in cell death. Also, an additional bactericidal mechanism of ion implant surface is mainly by inhibition of bacterial cell metabolism ***(Rodríguez-Valencia C et al, 2013; Jin G et al, 2014).***

Chemical modification of anodically oxidized titanium by incorporation of ions reduces growth of biofilm in models of *E. coli*, *P. gingivalis*, *S. mutans*, *S. aureus* and *A.*

actinomycetemcomitans ***(Lin DJ et al, 2013; Fang J et al, 2014; Cheng H et al, 2015)***. Ge X et al reported that bacterial counts on ion implanted surfaces were found to be reduced by 55–80% compared to pure titanium ***(Ge X et al, 2010).***

Anodically oxidized and ion-implanted surfaces reduce bacterial adhesion and may be beneficial in balancing the cytoactivity of osteoblast cells and bacteriostasis. When measured at 3- or 10-day intervals, Li J et al in a study concluded that ion-implanted surfaces exhibit enhanced dose-dependent *in vitro* antibacterial activity compared to uncoated titanium and TiO2, as well as enhanced adhesion, proliferation and differentiation of rat bone marrow stem cells and mouse fibroblasts ***(Li J et al, 2012; Zhang W et al, 2012).*** In vivo animal studies with ion implanted surfaces found reduced rates of infection and inflammation in tissues surrounding the implant, as well as an excellent osteoconductive response ***(Schröder K et al, 2010; Shirai T et al, 2011).***

2.4. Bioactive polymers:

Certain bioactive molecules such as chitosan ***(Singla AK et al, 2001)*** and hyaluronic acid ***(Chua PH et al, 2008)*** possess the ability to inhibit bacterial adhesion and/or kill them. Chitosan, with a chemical structure similar to hyaluronic acid, is obtained from deacetylation of chitin and is found in the exoskeletons of insects and marine invertebrates and the cell walls of certain fungi. Chitosan leads to differentiation of osteoprogenitor cells and improves the attachment, growth, viability, alkaline phosphatase (ALP) activity, and phenotypic expression of the osteoblast cells ***(Cai K et al, 2001; Bumgardner JD et al, 2003).***

Chitosan is noted for various biological properties including biocompatibility, biodegradability into harmless products and nontoxicity ***(Kim IY et al, 2008)***. Additionally, chitosan has a broad antibacterial spectrum of activity and hence, it has wide applications in bone substitutes, wound dressing, tissue engineering scaffolds for different tissues, and as potential carriers for various active agents. Chitosan has been bonded to titanium surfaces by a layer of certain linking molecules such as 3-aminopropyltriethoxysilane and triethoxsilylbutyraldehyde. ***(Martin HJ et al, 2007; Walters KB et al, 2008).***

F.Z.Bougueraa et al in 2014 concluded an improvement in the interaction of the implant with the biological environment and to better protect against all infections around the implants ***(F.Z.Bougueraa et al, 2014)***. Kalyoncuoglu et al in 2015 in a study proposed that the chitosan coating allowed the adhesion and proliferation of human gingival fibroblast cells and it showed a high level of cytocompatibility while preventing the growth of the P. gingivalis bacteria ***(Ulku Tugba Kalyoncuoglu et al, 2015).***

2.5. UV activable surfaces:

Ultraviolet A (UVA) light is electromagnetic radiation with a wavelength between 315 and 380 nm that interacts with organic molecules thereby causing chemical reactions and biological effects. The photo-functionalization of titanium dioxide (TiO2) following activation with UV light removes hydrocarbon contamination and results in a super-hydrophilic surface, which in turn decomposes adsorbed organic impurities by the process of oxidation. A secondary oxidation which is initiated by the reactive oxygen species (ROS) seems to be the necessary step to achieve antimicrobial activity as these active oxygen species can destroy the outer membrane of bacterial cells ***(Shibata Y et al, 2010)***. ROS are chemically reactive molecules containing oxygen, such as superoxide or hydrogen peroxide.

In an *in vitro* study under static and dynamic conditions, UVA illumination prior to bacterial colonization induced a reduction in adhesion rates and a significant decrease in the adhesion strength of *S. epidermidis* and *S. aureus,* without altering biocompatibility ***(Gallardo-Moreno et al, 2009)***. In a multispecies study authors found a positive effect on the attachment and biofilm formation of complex oral microbial communities to UV treated titanium ***(de Avila ED et al, 2015).***

2.6. Nitride coatings:

Titanium nitride (TiN) is a material used to improve the surface properties and esthetics of metal tools. It has been documented that TiN has excellent chemical stability, is biocompatible and is resistant to high temperatures and to corrosion and has low friction. These reduced surface interaction characteristics may be one reason for the antimicrobial effect of TiN, thus the overall antibacterial effect of nitride surfaces is a matter of discussion.

Studies on nitride surfaces are sparse and the results are controversial. Some authors found unaltered or increased bacterial adhesion on nitride titanium surfaces ***(Lai CH et al, 2011; Chang YC et al, 2013)***, but others found reduced biofilm formation ***(Lin N et al, 2012; Zhang X et al, 2012)***. Ji et al, 2015 found TiN to show antimicrobial effects against *S. mutans* but not against *P. gingivalis* ***(Ji MK et al, 2015).***

Nanostructured Surfaces and Coatings:

Nanoparticles are defined as clusters of atoms of size ranging from 1–100 nm, with a very large surface area to volume ratio ***(Taylor E et al, 2013)***. Several studies have demonstrated that nanoparticles in conjunction with other surface treatment could inhibit bacterial adhesion ***(Antoci, V et al, 2007; Mitik-Dineva et al, 2008; Wang, D.J et al, 2013).*** Yet another study used fabrication of polymers containing antibacterial nanoparticles and substances which inhibited both quiescent and sessile bacteria ***(Wang H et al, 2013)***. Synthetic polymers, natural polymers, and their derivatives (e.g., gelatin, chitosan) have potential to be used as implant surface scaffolds and delivery vehicles of antibacterial agents ***(Zan, X et al, 2010; Lischer S et al, 2011).***

Copper, zinc, magnesium and especially silver and gold NPs display antimicrobial activity7) and are therefore possible candidate molecules for antimicrobial implant surface modifications ***(Vishwakarma, V et al, 2009; Webster, T.J, 2012).*** Silver cations permanently disrupt bacterial cell wall, inactivate essential proteins, cause DNA condensation, and lead to reacting oxygen species generation (***Knetsch, M.L.W et al, 2011; Rizzello L et al, 2013)***. The antibacterial activity of the silver NPs is dependent on both size and shape. In vitro and in vivo experiments have shown long-lasting antibacterial protective effects of nanostructured titanium coating incorporated with silver NPs ***(Cheng, H et al, 2013; Kose N et al, 2013).*** Tantalum alloys are known to have excellent biocompatibility when used as a protective coating. It has been reported that Ag-doped TaN and Cu-doped TaN with nanoparticles can decrease the multiplication of *E. coli* bacteria. A twin-gun magnetron sputtering system is used for deposition of TaN-Ag coatings. TaN and TaN-Ag coated Ti possessed higher optical density value and showed better Human Gingival Fibroblasts (HGF) cell viability and proliferation than the

uncoated sample ***(Huang H-L et al, 2010).*** Initial clinical experiences with these "custom made" implants are promising ***(Hardes J et al, 2010; Hussmann, B et al, 2013)***.

Recent developments:

To tackle the problem of the dawning multidrug resistance, viable alternatives to biocidal antibacterial agents are being widely investigated.

Teixobactin: are likely to completely avoid the development of resistance. This was achieved by targeting less-mutable components of the bacteria (lipid precursors of cell wall components) rather than relatively mutable proteins ***(Ling, L.L. et al, 2015).***

Quorum sensing inhibitors: Bacteria secrete and detect signaling molecules (autoinducers), enabling cell to cell communication (quorum-sensing, QS) and the regulation of several bacterial processes, including gene expression, virulence factor production, and biofilm formation. Consequently, molecules that target and disrupt QS have garnered increasing interest as releasable antibacterial agents. Gram-positive bacteria typically use peptides for intercellular communication, while this role is fulfilled by acylhomoserine lactones (AHL) in Gram-negative bacteria ***(Sintim, H.O. et al, 2010).*** Various approaches are being investigated to inhibit this communication to control the diseases caused by bacteria. Evidence shows that these inhibitors act by interfering with the corresponding signal binding to the receptor (***Gholson J. Lyon et al, 2000)***, or by decreasing the receptor concentration Eg: Halogenated furanones ***(Manefield M et al, 2002).*** The other group of small chemicals is the enzyme inhibitors. For example, triclosan inhibits enoyl-ACP reductase whose product is the essential intermediate in AHL biosynthesis, and closantel is a potent inhibitor of histidine kinase sensor of the two-component system ***(Mounika Basavaraju et al, 2016)***. By inducing less evolutionary stress on bacteria than biocidal compounds, QS inhibitors are less likely to induce the development of resistance.

c-di-GMP: Another key target for bacterial signaling disruption is a small messenger molecule, bis-(30-50)-cyclic dimeric guanosine monophosphate (c-di-GMP), known as a central regulator of biofilm formation and dispersal in a wide variety of bacteria by controlling the switch between motile planktonic and sedentary, biofilm-forming phenotypes ***(Chua, S.L. et al, 2014)***. Tazin Fahmi et al suggested that due to its existence in diverse microorganisms, its involvement in crucial cellular activities, and its stimulating activity in host immune responses, c-di-AMP signaling pathway has become an attractive antimicrobial drug target ***(Fahmi T et al, 2017).*** Therefore, altering the intracellular c-di-GMP concentrations, either through c-di-GMP analogs or inhibitors, could emerge as a new pathway to reduce biofilm formation and biofilm-related infections.

Future perspectives:

Implant supported biosensors: The realization of a new biosensing platform technique may have a significant influence on current medical diagnosis and therapy, especially for chronic diseases. Yu-Jung Li and Chih-Cheng Lu in 2015 in their study proposed this new method of biological sensing to realize a non-invasive blood monitoring way in a painless manner without injections. ***(Yu-Jung Li et al, 2015)***. Such advances in medical science has dawned to a new era of diagnostic research in dentistry.

Digital drug delivery: An ultrasound (US)-responsive system was previously developed for an on-demand delivery of insulin, ciprofloxacin or other agents ***(Kwok CS et al, 2000; Kwok CS et al, 2015).*** In this system, a drug-containing polymeric monolith, poly (2-hydroxyethyl methacrylate) [pHEMA], was coated with a self-assembled multilayer (SAM) coating of long methylene chains. Conceptually, the resulting coating restricted the drug molecules to within the matrix in the absence of US and permitted the release of drugs with exposure to US. This system can be potentially used on or within long-term implants or biomaterials that might develop device-centered infections or biofilms after varying periods of implantation. Norris et al. demonstrated that this system can significantly reduce the accumulation of *Pseudomonas aeruginosa* biofilms in flow cell studies using a low intensity US source ***(Norris P et al, 2005).*** Exposure of this drug delivery system to US at periodic intervals could replace current antibiotic regimens of oral or systemic antibiotics for at least a two-week period ***(Schuck. EL et al, 2005)***. Thus, this on-demand system has the potential for delivering antibiotics locally at the site of infection.

CONCLUSION

The impact of biofilm associated infections and the unreliable efficacy of conventional peri-implantitis therapy have encouraged researchers to find new preventive strategies to combat implant-related infections. Numerous antimicrobial biomaterials have been reported in the scientific literature and this number is increasing rapidly. These "custom made" therapeutic implants have shown promising results in vitro and in animal studies. The application of coating technology to dental implants can be used to facilitate insertion, improve biocompatibility, extend lifetime, and reduce implant-related problems that can lead to failure and other serious complications for the recipient. The lack of *in vivo* human studies, have limited our discussions to only to theoretically transfer our findings in to clinical reality.

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