INTRODUCTION

Oral permucosal implants pose a very high risk of infection, as they breach the epithelial barrier and are thereby permanently exposed to the oral microflora. It has been reported that 90% of all implants show signs of inflammation and 50% of all implants show signs of irreversible tissue destruction. Nevertheless, the ten-year survival rates of endosseus implants are reported to be around 90–96%. The most frequent cause of failure of dental implants are peri-implant inflammatory diseases such as peri-implantitis. As peri-implantitis is generally caused by pathogenic biofilms, providing a critical step to establish biomedical device related infection, it seems promising to develop implant surfaces with antibacterial properties.

The development of a fully grown, multi-layered, adherent biofilm is initiated by primary attachment of single bacterial cells, followed by a multifactorial adhesion process. Adherent bacterial cells may switch to a more pathogenic, resident phenotype, accompanied by modification of their gene expression. These resident bacterial cells are encapsulated in a protective hydrated extracellular polymeric matrix and form tower- or mushroom-shaped microcolonies. Compared with their planktonic counterparts, sessile phenotypes show extraordinary resistance to antibiotics, disinfectants, phagocytosis and other components of the innate or acquired immune system. This factor contributes to high levels of biofilm resistance and makes most peri-implant infections difficult or impossible to eradicate.

Thus, the most effective strategy to combat peri-implantitis would be a prevention of biofilm formation on the implant material. Antimicrobial dental implant materials may either exhibit antibacterial capacities which cause cell damage to adhering bacteria or anti-adhesive properties that inhibit bacterial adhesion in the first place.

Titanium is currently the gold standard for dental implant materials. Most dental implants are fabricated from commercial pure titanium and its alloys. Although titanium meets the fundamental requirements for a successful implant biomaterial, it does not exhibit any obvious antiseptic qualities; thus, it is crucial to develop modified titanium surfaces with enhanced antimicrobial potential. Various approaches have been reported to convert the surfaces of biomedical devices into antimicrobial surfaces and lately several reviews have been published that describe some of these approaches. However, there has been no general review of this topic. The present systematic review therefore summarizes current strategies for the functionalization of titanium dental implant surfaces.

MATERIALS AND METHODS

Protocol development

The review employs the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement. A detailed protocol was designed according to the PICO system to answer the following research question: How do different surface functionalizations modify bacterial adherence to dental implants?

Search strategy

Electronic databases were searched up to and including June 2, 2015, in order to identify articles that included the following terms: (“dental implants” OR “dental implant”) AND (“surface modification” OR coating OR functionalization OR “chemical modification”) AND titanium AND (antimicrobial OR antibacterial OR “bacterial adhesion”) —review [(antiinfective OR

Keywords: Antimicrobial, Anti-adhesion, Antibacterial, Surface functionalization, Dental implant
anti-infective OR antimicrobial OR anti-microbial
OR “bacterial adhesion” OR “anti-bacterial” OR
antibacterial OR bactericidal] AND (“dental implant”
OR “dental implants”) —review. The search was applied
to MEDLINE via PubMed, SCOPUS and GOOGLE
SCHOLAR. Additionally, the references of relevant
articles were searched for any undetected studies.
Finally, citations in related previous reviews and
included studies were checked for relevant studies; no
additional manual search was performed.

**Study selection criteria**
Relevance was inferred from the titles and abstracts and
subsequently through full text analysis. The titles and
abstracts were screened by two independent reviewers
(J.G. and J.E.). Two reviewers assessed all potentially
relevant articles. Disagreements were double checked by
a third reviewer (M.S.) and discussed until a unanimous
decision was reached. The study selection criteria for the
present evaluation are presented below (Table 1).

**Risk of bias**
The risk of biases in the individual studies was
minimized by analyzing the study methodology. Risk
of biases in the present evaluation was decreased by
including published articles in Google Scholar.

**Data extraction**
An overview table was created to summarize the
relevant information. The table included the type of
functionalization, the tested bacterial strains, the
methodology of antimicrobial testing as well as the
methodology of any biocompatibility assays. The
articles were divided into 8 subgroups according to
their functionalization strategy (Table 2). Some surfaces
were assigned to more than one subgroup. Due to the
heterogeneity of the study methods and the outcome
variables, no meta-analysis was possible.

### Table 1  Inclusion and exclusion criteria

| Inclusion criteria                                                                 | Exclusion criteria                                                                 |
|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Relation to implant dentistry                                                    | Case report, Conference Paper, Patent, Citation, Review                          |
| Publication in English                                                            | Not related to implant dentistry or focus on the abutment material               |
| Focus on the antibacterial or anti-adhesive effect of the test surface           | No antimicrobial test                                                             |
| Controlled trials with titanium or hydroxyapatite as control                     | No surface modification or modification of the surface microtopography           |
|                                                                                  | No adequate control                                                              |

### Table 2  Evidence table summarizing the surface functionalization strategies reviewed in this article

| Functionalization strategy                                           | Reference                      |
|---------------------------------------------------------------------|--------------------------------|
| 1. Drug-loaded surface                                              | 21)–41)                        |
| 2. Silver-implanted surface                                         | 40)–95)                        |
| 3. Polymer-functionalized surface                                   | 29, 51), 78, 92, 96–107)       |
| 4. Anodized/ Oxidized/ ion-implanted surface                        | 6, 57, 63, 70, 79, 87–90, 100, 108–131) |
| 5. UV-activatable surface                                           | 114), 116), 132), 133)         |
| 6. Nanoscale surface                                                | 31, 34, 43, 52–56, 58–66, 73–78, 82, 84–86, 90, 95, 97, 128, 134–144) |
| 7. Nitride surface                                                  | 123, 124, 145–151)             |
| 8. AMP-surface                                                      | 37, 142, 152–159)              |

Some references may be mentioned in more than one subgroup, as different surfaces were tested in the same study or they were assigned to more than one subgroup.
RESULTS

The initial search yielded 2,990 potentially relevant publications. A total of 1,913 studies were identified by an electronic search in three databases and another 1,077 studies were found to be relevant after searching the references of review articles and the relevant publications. Screening the titles and abstracts led to the exclusion of 2,696 articles. One hundred fifty two articles were excluded after full text analysis, as they failed the study selection criteria. Data extraction was performed on 142 relevant studies as described above. A flowchart was created to demonstrate the process of inclusion and exclusion of potentially relevant articles (Fig. 1).

Drug-loaded surfaces

One approach to combat bacterial colonization of abiotic implant surfaces is to employ local drug delivery systems. The local delivery of drugs into the dental implant site is quite an effective method to decrease early bacterial adhesion and at the same time to bypass systemic toxicity and side effects caused by parenteral uptake. Because of these advantages, different antibacterials have been incorporated into titanium and tested for their antimicrobial effects. Potential disadvantages of this approach include the risk of bacterial resistance. Other drawbacks are the burst release kinetics (see below). Moreover, it is unclear whether drug metabolites may influence osseointegration.

The drugs investigated included conventional antibiotics such as amoxicillin, vancomycin, gentamicin, tetracycline, minocycline or cephalotin, which were incorporated in controlled release devices. A serious concern in the use of these antibiotics is the initial burst release, often followed by prolonged release at levels below the minimal inhibitory concentration (MIC), which in time is likely to evoke bacterial resistance. The development of safe surfaces exhibiting antimicrobial activity over a longer period would either require generation of slow release surfaces with reliable release above the minimal inhibiting concentration (MIC) or surfaces which only release drugs on contact with biofilms.

Unfortunately, the bactericidal effect of all antibiotic-loaded surfaces decreased within several days to less than the MIC. An interactive implant surface with pH-dependent or infection-dependent antibiotic release might avoid this shortcoming, but has not yet been introduced to dental implant materials research. Antibiotics are capable of reducing bacterial colonization with S. mutans, S. epidermidis and S. aureus, P. gingivalis, A. actinomycetemcomitans, P. intermedia, P. aeruginosa and E. coli on titanium surfaces. Chlorhexidine (CHX)-loaded titanium surfaces reduce colonization with streptococci and S. aureus in comparison to titanium control.

Furthermore, there have been in vitro studies on the antibacterial effect of dual drug-delivering systems, combining antibiotics with osteoconductive drugs; these have been found to reduce biofilm formation in comparison to titanium control. Interestingly, two studies investigated molecules as anti-biofilm coatings that were not initially intended to be antimicrobial substances. Yoshinari et al. (2001) found that bisphosphonate-loaded titanium modified with Ca-ion implantation inhibited adhesion of P. gingivalis without toxic effects on osteoblast cells in vitro. Kos et al. (2015), however, found both decreases and increases in S. mutans, S. aureus and P. aeruginosa on bisphosphonate-loaded hydroxyapatite (HA), depending on the growth conditions. It is currently unclear how bisphosphonates and bacterial cells interact.

Another drawback of active-release antibiotic surfaces is the risk of generating cell toxicity or possible impairment of osteogenic activity. The combination of gentamycin and bone-morphogenetic-protein-2 was tested for the dual function of antimicrobial activity and osteoblast function. The results showed enhanced alkaline phosphatase activity and calcium deposition by osteoblast cells. Antibiotic-releasing surfaces
were non-toxic to osteoblast cells and showed good cytocompatibility compared to uncoated titanium\(^{21,30,36}\). Load concentrations of 1.4 and 0.7% CHX resulted in harmful changes in eukaryotic cell morphology, including shrinkage, smaller and pyknotic cells, and loss of cytoplasmic processes, which suggests that there are cytotoxic effects. Conversely, assays with 0.35% CHX did not show such effects, but still demonstrated biofilm reduction after 6 and 48 h\(^{26}\). Drug-release surfaces generate dose-dependent cytotoxic side-effects, but controlled, sustained release, above the MIC, over a sufficient period of time, would minimize these local side-effects and simultaneously decrease the risk of bacterial resistance (Fig. 2).

**Silver-implanted surfaces**

Silver is an inorganic antimicrobial agent which has long been known for its antiseptic effects, although the use of silver decreased with the dissemination of antibiotics. The urgent need for effective strategies to fight the growing number of multi-resistant bacteria has recently revived interest in silver and numerous studies have reported the use of silver-implanted materials to reduce bacterial infections associated with dental implants. Inorganic antibiotic materials have several advantages compared to traditional organic agents; these include chemical stability, thermal resistance and protracted action\(^{30}\). In addition, silver has a wide spectrum of antibacterial susceptibility, a low propensity for bacterial resistance, and the ability to inhibit polymicrobial colonization\(^{42}\).

The main antibacterial effect of silver is mediated by the release of biocidal Ag\(^+\) ions, which interact with the bacterial cell wall and disturb its permeability,
inactivate essential proteins and cause DNA condensation\textsuperscript{10}. Silver exhibits a rather broad spectrum of antimicrobial activity and has not yet increased the risk of bacterial resistance. Pathogens found at infected oral implant sites, including \textit{S. mutans}\textsuperscript{80}, \textit{S. aureus}\textsuperscript{93,94}, \textit{S. oralis}\textsuperscript{93}, \textit{P. gingivalis} and \textit{A. actinomyctecomitans}\textsuperscript{54} were killed or significantly reduced upon contact with silver-implanted surfaces. All tested silver surfaces, such as hydroxyapatite (HA)-silver-surfaces\textsuperscript{42,44,46-51,91,161} or plasma sprayed silver-implanted HA\textsuperscript{45,93} shared good antimicrobial activity.

\textit{In vitro} investigations showed that silver ion surfaces, despite their powerful antibacterial efficacy, did not impair the growth of gingival fibroblast or embryonic cells\textsuperscript{42,52,57,58,84}. Silver-implanted surfaces exhibit non-specific antimicrobial activity without toxicity to mammalian cells at the given concentrations\textsuperscript{14,41,42}. Nonetheless, it is evident that Ag can enter human cells and induce a series of pro-inflammatory responses, and markedly increase the expression of TNF-\textit{\alpha}. Furthermore, accumulation of silver has been reported to have negative effects on several red blood cell parameters, brain tissues, liver cells and on general health. It has been reported that the toxicity of Ag ions affected basic metabolic cellular functions common to all specialized mammalian cells. Concentration- and time-dependent depletion of intracellular ATP content was attributed to the presence of Ag ions, which compromised the cell energy charge and could lead to cell death\textsuperscript{42}.

\textit{Polymeric coatings}

Planktonic bacterial cells recognize solid surfaces through mild deformations of their cell membranes. These activate the expression of microbial surface components that recognize adhesive matrix molecules (MSCRAMMs) and initiate the adhesion process as the bacterial cell transforms into its sessile phenotype. Thus, adhesion of polymeric surfaces may be reduced by electrostatic interactions, since polyanionic polymer surfaces can electrostatically repel bacterial cells with similarly charged glycocalices. Polymeric surfaces may be superhydrophobic, which induces a lotus-effect. This strategy counteracts “host adhesins” and consequently hinders the MSCRAMMs from binding to the implant surface. Some polymeric surfaces consist of hydrophilic, highly hydrated, non-charged surfaces to reduce any surface interactions.

Dextran and polyethylene glycol (PEG) surfaces have been shown to be effective in suppressing protein adhesion, platelet adhesion, bacterial adhesion and biofilm formation of oral relevant pathogens, such as \textit{S. aureus}, \textit{S. sanguinis}, \textit{L. salivarius} \textit{S. mutans} and \textit{S.gordonii}\textsuperscript{29,56,57,101,107}. Lignin, a complex, amorphous organic polymer found in plant tissues, exhibits antibacterial activity against \textit{S. aureus, P. aeruginosa} and \textit{C. famata}\textsuperscript{51}. Polypyrrole-coated titanium surfaces exhibit a three-fold greater repellent effect than a common TiAlV alloy against \textit{E.coli} and \textit{S. aureus}\textsuperscript{164}. A copolymer coating of 4-vinyl-N-hexylpyridinium bromide and dimethyl (2-methacryloyloxyethyl) phosphate (VP:DMMEP 30:70) reduces the bacterial load of \textit{S. aureus} and \textit{S. epidermidis} by up to 90% compared to titanium\textsuperscript{102}. Hyaluronic acid combined with chitosan forms polyelectrolyte multilayers (PEMs) with strong antimicrobial activity against \textit{S. aureus}\textsuperscript{99}. Plasma-polymerized hexamethyldisilazane reduces bacterial adhesion of \textit{E. coli}\textsuperscript{92}. In contrast, silicon-containing polymeric surfaces do not exhibit any bactericidal activity compared to control surfaces\textsuperscript{97}.

The ability of anti-adhesive polymeric surfaces to repel bacteria theoretically clears the way for uncompromised osseointegration; however, the adhesion of human osteoblastic cells may be equally reduced or weakened. For instance, PEG surfaces hinder not only non-specific protein adsorption and bacterial attachment but, to the same degree, the adhesion of mammalian cells. Recent studies have attempted to promote specific binding interactions between host tissues and implant materials by immobilizing bioactive proteins, such as cell adhesive proteins containing arginine-glycine-aspartic acid (RGD) sequences or bone morphogenetic proteins\textsuperscript{28,29,58,99,112,163}. Peptide-functionalized polymers exhibit a selective biointeraction pattern that may be useful in dental implantology, as they can enhance attachment of fibroblasts and osteoblasts while reducing non-specific protein adsorption, thus resulting in reduced bacterial adherence. Lignin, PEG, and silicon-doped surfaces exhibit improved osteoconductive characteristics, with high adhesion rates for epithelial and osteoblastic cells\textsuperscript{53,57,101}. However, polypyrrole surfaces reduce cell proliferation and adhesion of eukaryotic cells\textsuperscript{104}.

\textit{Anodically oxidized/ ion-implanted surfaces}

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 the corresponding ions. The bactericidal activity of these ions seems to depend on their gradual release from specimens into the surroundings. One mechanism of bacteriostasis is hydroxylation into highly reactive components, such as HCl, HOCI, TiOH, hydrogen peroxide (H\textsubscript{2}O\textsubscript{2}) or superoxide (O\textsuperscript{2}\textsuperscript{−}), as these evoke oxidation of the bacterial cell membranes, resulting in increased cell permeability and ultimately in cell death. Additionally, ion-implanted surfaces may act bactericidally, as the ions may inhibit bacterial metabolism\textsuperscript{108-111,113-118}.

Chemical modification of anodically oxidized titanium by incorporation of ions reduces growth of biofilm in one, two and three species models of \textit{E. coli}\textsuperscript{164}, \textit{P. gingivalis}\textsuperscript{131}, \textit{S. mutans}\textsuperscript{225}, \textit{S. aureus}\textsuperscript{165} and \textit{A. actinomyctecomitans}\textsuperscript{110,111,119}. Bacterial counts on ion-implanted surfaces were reduced by 55–80% compared to pure titanium\textsuperscript{112}. However, it is unclear how anodic oxidation without ion-implantation influences bacterial adhesion to titanium\textsuperscript{112,119,120,160}. Titanium samples treated with cold atmospheric plasma display strong antimicrobial activity against \textit{E. coli}\textsuperscript{169}. 

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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, ion-implanted surfaces exhibit enhanced dose-dependent in vitro antibacterial activity compared to uncoated titanium and TiO$_2$, as well as enhanced adhesion, proliferation and differentiation of rat bone marrow stem cells$^{121}$ and mouse fibroblasts$^{129}$. However, there are controversies concerning the effects of Zn on osseointegration and biocompatibility. On the one hand, Zn surfaces increase initial adhesion, spreading activity, alkaline phosphatase activity, collagen secretion and extracellular matrix mineralization of eukaryotic cells$^{6,108,129,164}$. On the other hand, they exhibit dose-dependent negative effects on cell proliferation, cell morphology, osteogenic gene expression and cell viability of eukaryotic cells$^{130}$. Zinc oxide appears to be cytotoxic to human cells, as it reduces the number of viable macrophages and increases production of pro-inflammatory cytokine by macrophages$^{109}$. Animal experiments with ion-implanted surfaces found reduced rates of infection and inflammation in tissues surrounding the implant, as well as an excellent osteoconductive response$^{100,117,122}$.

**UV-activatable surfaces**

Ultraviolet A (UVA) light is electromagnetic radiation with a wavelength between 315 and 380 nm that causes chemical reactions and biological effects by interacting with organic molecules. UV light-induced photo-functionalization of titanium dioxide (TiO$_2$) removes hydrocarbon contamination and results in a super-hydrophilic surface, which decomposes adsorbed organic impurities by oxidation. Secondary oxidation initiated by reactive oxygen species (ROS) seems to be the necessary step to achieve antimicrobial activity$^{116}$. ROS are chemically reactive molecules containing oxygen, such as superoxide or hydrogen peroxide. This photodecomposition of organic compounds is useful for killing bacteria, as it has been confirmed that these active oxygen species can destroy the outer membrane of bacterial cells.

After 120 min of UVA illumination, the survival rate of *A. actinomycetemcomitans* and *F. nucleatum* on a photocatalytic TiO$_2$ surface was reduced to less than 1% compared to a commercially pure titanium control surface$^{133}$. Petrini et al. (2006) found a transitory increase in hydrophilicity and significantly increased Zn binding capacity, which in turn led to a significant reduction in three oral streptococcal strains on TiO$_2$ surfaces illuminated with UV light$^{110}$. 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$^{132}$. In a multispecies study authors found a positive effect on the attachment and biofilm formation of complex oral microbial communities to UV treated titanium$^{165}$.

If the physicochemical properties of the surface of a biomaterial are modified by UV illumination, in order to diminish adhesion of microorganisms, this should not compromise bone-forming cell adhesion. Gallardo-Moreno et al. (2009) found that UV treatment of Ti$_6$Al$_4$V reduced bacterial adhesion without altering the biocompatibility of the alloy. They confirmed the excellent in vitro biocompatibility of a UVA-treated titanium alloy by culturing human Saos-2-cells, osteoblasts and mesenchymal stem cells on test surfaces$^{130}$. UV illumination of a TiO$_2$ surface reduced bacterial attachment and growth without compromising osteoblast cellular activity and initial cell adhesion in vitro$^{116}$. UVA light-induced photofunctionalization of TiO$_2$ surfaces have been investigated in vitro and in vivo rat models but have not been tested in humans due to the possible cell damage in host tissues. Its applicability is currently restricted to light-accessible dental implant surfaces$^{168,169}$.

**Nanoscale surfaces**

Nanoparticles are defined as clusters of atoms of size ranging from 1–100 nm, with a very large surface area to volume ratio. Copper, zinc, magnesium and especially silver and gold NPs display antimicrobial activity$^7$ and are therefore possible candidate molecules for antimicrobial implant surface modifications. Nanomaterials are used to create unique surfaces with altered physical and chemical characteristics. The natural surroundings of osteoblasts consist of structures with nano-scale topography. Nanoengineered surfaces aim to recapitulate the physiological environment of growing bone. There are comparatively very few structured animal and clinical studies that investigate the short and especially long-term effects of such surfaces, to evaluate whether the enhanced biological activities demonstrated in vitro actually translate to the complex in vivo environment$^{170}$.

Because ion release is the main action of metallic silver, silver NPs are used to enlarge the available silver specific surface. Hence, using silver NPs amplifies silver ion release and consequently the antimicrobial effect of a surface. The overall antimicrobial efficiency of nanomaterials is however controversial. Some authors did not find a convincing decrease or even an increase in bacterial colonization on nanomaterials in comparison to untreated titanium$^{56,134,136,137}$. Others found reductions in bacterial counts in vitro of up to 90% compared to commercially pure titanium on nano-Ti surfaces and of up to 100% for nano-AgHA when tested against *E. coli*, *S. epidermidis* and *S. aureus*$^{52,56,62,138}$. It has recently been shown that a titanium nanotube surface exhibited antimicrobial properties and down-regulated the glycosyltransferase genes of *S. mutans*$^{171}$. All studies that tested surfaces with a combination of nanostructures and organic or inorganic antimicrobial chemical compounds on the nano-level found reduced bacterial adhesion and viability$^{61,134,43,58,62,69,135,137}$. Surfaces containing Ag NPs show excellent biocidal activity towards *P. aeruginosa*, *S. oralis*, *S. mutans*, *P. gingivalis*, *S. aureus*.$^{145,146}$, *S.*
**pneumoniae** and *E. coli*\(^{43,59-62,108,143,144}\).

The evidence that nanoscale surfaces positively affect the cell response at the bone-implant interface and maintain cell proliferation capacity has encouraged the engineering of nanostructured dental implant surfaces\(^{135,172}\). Nanomaterials for bone applications increase osteoblast functions, namely viable cell adhesion, proliferation, differentiation and calcium deposition\(^{172}\). The reason for this is believed to be that hydroxyapatite nanofibers closely approximate the shape of HA crystals and collagen fibers in bone\(^{138}\).

Furthermore, the porous morphology of nanoscale surfaces helps the integrin receptor protein to anchor cells and thus makes them an excellent model for the signaling mechanism used by osteoblasts for adhesion and proliferation. Many classes of nanoparticles have been synthesized and widely applied; however, there is a serious lack of information concerning their effects on human health and the environment.

One major toxicological concern is that nanoparticles are easily taken up in the human body\(^{173}\). Translocation of NPs inside the human body is not fully understood and should be intensively investigated. For instance, there are concerns that silver NPs may act as a Trojan horse by entering human cells and releasing silver ions which then interfere with intracellular functions\(^{172}\). Size, surface charge and behavior of NPs seem to influence their ability to induce toxicological and perhaps reproductive toxicological effects\(^{173,174}\). AgNPs have been shown to cause cell death in *vitro*, including macrophage cells, liver cells, and neuronal cells. However, a study in Labrador dogs confirmed enhanced bone formation and found outstanding compatibility to both soft and hard tissue around AgNP dental implants. In this *in vivo* study, the plasma immersion ion-implantation technique seemed to reduce the mobility of AgNPs, resulting in favorable cytocompatibility\(^{177}\). Nonetheless, accurate and cost-effective measurement techniques for characterizing “nanotoxicity” are required, as the use of NPs will certainly increase.

**Nitride surfaces**

Titanium nitride (TiN) is a material used to improve the surface properties and esthetics of metal tools. It has been documented that TiN is of excellent chemical stability and is resistant to high temperatures and to corrosion. Moreover, its biocompatibility has been confirmed. Thanks to its characteristic golden color, it may help to camouflage the implant in areas with thin gingival tissues better than can be achieved with common titanium surfaces, which are grey\(^{151}\).

TiN is characterized as a surface with a very high chemical inertness, hardness, low friction coefficient and corrosion resistance. 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\(^{115,112,123,124,155}\) on nitride titanium surfaces, but others found reduced biofilm formation\(^{45-49,151,178}\). Ji *et al.* (2015) found TiN to show antimicrobial effects against *S. mutans* but not against *P. gingivalis*\(^{177}\).

The biocompatibility of nitride surfaces was consistently found to be good\(^{151,170}\).

**Antimicrobial peptide surfaces**

In the 1960s, Zeya and Spitznagel discovered that basic proteins and peptides in polymorphonuclear leukocytes display antimicrobial properties and this has led to a new area of research\(^{179}\). Antimicrobial peptides (AMP) have recently been used to improve implant performance, as they possess broad spectrum activity against bacteria, fungi and virus. Covalent anchoring of AMPs to implant surfaces is a feasible approach to create passive antimicrobial surfaces and has recently been shown to effectively inhibit bacterial adhesion and biofilm formation *in vitro*\(^{152,154}\). Unlike antibiotics, natural AMPs may spare the normal flora and kill only pathogenic bacteria.

*In vitro* antimicrobial studies have found that a GL13K peptide coating is bactericidal and inhibits biofilm growth for pathogens related to peri-implantitis, such as *P. gingivalis*, *S. gordii* and *P. aeruginosa* under static growth conditions\(^{142,155}\). Furthermore, AMP surfaces displayed antimicrobial activity under dynamic growth conditions against *S. gordii*\(^{156}\) and under static growth conditions against *Streptococcus mutans*, *Staphylococcus epidermidis* and *Escherichia coli*\(^{159}\). This passive antimicrobial coating resisted hydrolytic and mechanical challenges and exhibited no significant release of peptides from the modified titanium surface. A multifunctional streptococcal collagen-mimetic protein coating reduced the bacterial adherence of *S. aureus* and *S. epidermidis*\(^{159}\). Although AMPs show a low tendency to induce resistances, more and more naturally occurring human AMPs lose their antimicrobial effectiveness against various bacterial strains. As a result, costly design of synthetic peptides is necessary in order to fabricate bioactive coatings immobilized with active AMPs\(^{179}\).

AMPs show low host cytotoxicity, and a low tendency to induce bacterial resistance and therefore provide a promising alternative to conventional antibiotics\(^{142,179}\). The cytocompatibility of AMP surfaces has been investigated towards osteoblasts and human gingival fibroblasts\(^{87,153,156,157}\). Despite technical hurdles, such as cost, chemical and biological degradation, and unfavorable pharmacokinetics, several peptides have advanced to clinical trials, but not in the area of dental implants.

**DISCUSSION**

Biomaterial-associated infections are one of the most destructive complications in implant dentistry and are closely related to deficiencies in the surface characteristics of commercially pure titanium and its alloys. To overcome the limitations of titanium as the direct contact surface to the surrounding tissues,
researchers have developed anti-adhesive or bactericidal surface modifications.

The most common strategy to overcome insufficient interaction between synthetic materials and bacteria is to chemically modify the implant surface with biofunctional molecules. This functionalization of implant surfaces includes the covalent or non-covalent deposition of inorganic or organic chemical compounds; these are intended to reduce bacterial growth by suppressing non-specific interactions and by simultaneously improving the bone to implant contact. The candidate chemical compounds should have low susceptibility to hydrolysis and show chemical as well as thermal stability. The modified surfaces may either exhibit antimicrobial capacities which cause cell damage to adhering bacteria or anti-adhesive properties that inhibit biofilm formation in the first place. Some surface modifications show convincing results with respect to antimicrobial efficacy and biocompatibility, so that continuing research is justified.

The hunt for the perfect dental implant surface has many different aspects. The ideal surface should not only exhibit the most efficient antimicrobial properties but simultaneously show improved osseointegration and excellent biocompatibility. Unfortunately, antibacterial effects are sometimes accompanied by high cytotoxicity. Additionally, machining, thermal treatment, blasting, etching, coating or sterilization of a surface may leave traces of foreign material at the surface. Depending on the chosen type of surface treatment, trace compounds such as metals, metal ions, lubricants, detergents or other specific chemical compounds may alter the surface properties and provoke foreign body reactions of unknown type. These contaminants on the implant surface may affect the tissue response at the implant/body interface. Relatively little is known about these side effects, due to the lack of in vivo investigations. New surface modifications should be critically investigated, including their antimicrobial abilities, biocompatibility and aftereffects due to uncontrolled uptake and accumulation in the human body.

The susceptibility for peri-implantitis depends on the surface characteristics of an implant material. Studies on the surface topography already documented a higher bacterial adhesion rate to rough surfaces as niches and surface irregularities shelter attached bacterial cells from shear forces. Unfortunately, the effect of functionalized dental implant surfaces on peri-implantitis has not been documented so far.

Most of the included studies investigated the potential effect of bactericidal surfaces on eukaryotic cells. Some found good biocompatibility, sometimes even combined with enhanced adhesion, proliferation and differentiation of eukaryotic cells. However, the biocompatibility test methods varied strongly among the studies, which made it inappropriate to draw conclusions by comparing the results through a meta-analysis. Nevertheless, the studies identified in the present systematic review gave a good insight into the possibilities and limits of modern antimicrobial dental implant functionalization strategies.

Unfortunately, the antimicrobial effects of modification techniques tested in vitro do not reliably correlate with results found in in vivo studies. In vivo tests on this subject are sparse and have only been performed for ion-implanted, silicon, Ag and AgNP surfaces. To our knowledge, drug-loaded, nitrided, AMP, polymer surfaces (except for silicon) and UV-activated dental implant surfaces have not yet advanced to in vivo validation. This owes to the lack of sufficient in vitro and animal studies. In order to actually translate innovative surfaces into clinical set ups, candidate chemical compounds should be tested for low susceptibility to hydrolysis and show chemical, mechanical as well as thermal stability prior to animal testing. In order to proceed into human in vivo studies the biocompatibility of a surface needs to be successfully tested in animals.

A limitation of many included studies is the methodology of the antimicrobial tests. The majority of the included studies are monoculture-experiments performed in vitro and under static growth conditions. In fact, dental implants are in continuous contact with physiological fluids, including plasma in the human body and saliva in the oral cavity. This suggests that in vivo microbial adhesion and plaque formation on biomaterial surfaces is influenced by factors such as multi-species oral pathogens, “host adhesins” (e.g. fibrinogen, fibronectin, collagen, and plasma albumin), host cells (cells of the innate and adaptive immune system) and the pellicle, a rapidly created conditioning film which covers a newly implanted device. Another important limitation of in vitro studies is the protein concentration in artificial body fluids. This is because simply using a single host protein or a small selection of these does not reflect the highly complex oral conditions in vivo. Another shortcoming is the variability of the antibacterial test methods.

As we prepared the Review, we aimed to compare the efficiency of the different antimicrobial surfaces, in order to find out which surface was most promising to focus on for our future in vivo studies. Unfortunately, we found that the variations in the experimental set-ups made a comparison between the surfaces impossible and that the literature does not allow drawing conclusions. To the best of our knowledge we can only present the results given in the review, but we are not able to compare among the groups as the quality and quantity of the test methods varied a lot between the included studies.

Some studies assessed the antibacterial properties of a test surface only through the “spread plate method”. This test method is based on counting the number of viable bacterial cells in a sample by the visual appearance of a colony in a cell culture. The most crucial disadvantage of this system is the uncertainty whether the colony arose from only one bacterial cell or from a group of cells in first place. This may lead to the conclusion that the “spread plate method” is no more than a rough estimation of the actual antimicrobial
capacity of a tested surface. To overcome this disadvantage, many studies combined the "spread plate method" with other antibacterial assays, such as SEM evaluation, fluorescence microscopy, live/dead staining or gene expression assays and confirmed or strengthened their test results.

In order to validate the results and make them more comparable, it would be beneficial to find a consensus concerning the scientific approach, including the tested bacterial strains and the applied test systems. Future research on dental implant surfaces with reduced bacterial adhesion must employ validated experiments, preferably multicultural testing or co-culturing under dynamic growth conditions and subsequently backed up by validated in vivo studies.

CONCLUSION

Implant-related microbial infection is a serious threat. The impact of biomaterial-centered infections and the unreliable efficacy of conventional peri-implantitis therapy should encourage us 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. Unfortunately, most of the new biomaterials for dental implants have only been tested in vitro under static conditions. Bacterial adhesion may be strongly affected under dynamic conditions and results from static tests need to be validated under dynamic conditions or in vivo.

The review provides a general overview of the state-of-the-art-technology for dental implant functionalization strategies and summarizes recent advances in the development and fabrication of innovative implant surfaces. Within the limitations of the experimental conditions, it was concluded that surfaces doped 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 enhance antimicrobial activity compared to uncoated titanium.

Although these approaches are promising, it has not yet been conclusively demonstrated that any of the tested surfaces both reduces levels of bacteria and is biocompatible in man. Therefore, more studies —both in vitro and in vivo— should be conducted to further elucidate the effects of biocidal implant modifications on biofilm formation and peri-implant inflammatory disease. The hunt for the ideal surface is not over!

CLINICAL RELEVANCE

Due to the lack of in vivo human studies, we can only theoretically transfer our findings in to clinical reality. Drug-loaded and UV-activated surfaces may be bactericidal, thus restricted to a short period of action. Silver and NP-surfaces may be promising candidates, but are suspect to possible toxic effects. We assume polymer coatings to have a long lasting anti-adhesive effect, but their mechanical and chemical inertness is questionable.

A successful reduction of bacterial adhesion and pathogenic biofilm formation on antimicrobial dental implant surfaces may contribute to reduce severity and occurrence of dental implant related diseases and implant failure in future.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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