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FACULDADE DE MEDICINA DENTÁRIA
UNIVERSIDADE DO PORTO

"Innovative antibiofouling surface coatings for titanium dental implants"

"Revestimentos de superfície anti-bioincrustação inovadores para implantes dentários de titânio"

João Nuno Magalhães Esteves

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INDEX

1. FIGURE INDEX

2. TABLE INDEX

3. ABSTRACT

Introduction: Regarded as one of the best solutions to replace missing teeth in the oral cavity, dental implants have been the focus of plenty of studies and research in the past few years. However, the success rate of dental implants is still not as high as desired and one of the main reasons that cause their failure is bacterial infections. The focus of this review were antibacterial coatings that would reduce the occurrence of those infections and increase dental implant success rate.

Materials and Methods: The bibliographic research was conducted in the following electronic databases: PubMed/Medline, Scopus (Elsevier), Web of Science (Clarivate Analytics) and SciELO (Scientific Electronic Library Online). Articles published in the past 10 years and with full text in English, Spanish, or Portuguese were included.

Development: From improvements to already established coating surfaces such as silver by using silver nanoparticles instead of the bulk material, to new approaches such as antimicrobial peptides or biosurfactants, promising solutions to prevent biofilm adhesion to the surface of titanium implants are being reported in the past few years. In the present review, we summarize the diverse strategies proposed to enhance antibacterial properties of titanium dental implants.

Conclusion: Antibacterial coatings are a promising solution to control and prevent bacterial infections that compromise dental and orthopedic implant success. All referred coating surfaces show high antibacterial properties with effectiveness in biofilm control while maintaining implant biocompatibility. On the other hand, costs of fabrication and long-term antibacterial effect remain the major problems.

Keywords: “biofilm”; “dental implants”; “titanium implants”; “antibacterial”; “surface coating”; “antibiofouling”

4. RESUMO

Introdução: Considerado como uma das melhores soluções para substituir dentes ausentes na cavidade oral, os implantes dentários têm sido o foco de muitos estudos e investigações nos últimos anos. No entanto, a sua taxa de sucesso não é tão alta como seria desejado e uma das razões que leva ao fracasso dos implantes dentários são as infeções bacterianas. O foco desta revisão foram superfícies de revestimento com propriedades antibacterianas que diminuiriam a ocorrência dessas infeções e levariam ao aumento da taxa de sucesso dos implantes dentários.

Materiais e Métodos: A pesquisa teve como base as seguintes plataformas: PubMed/Medline, Scopus (Elsevier), Web of Science (Clarivate Analytics) e SciELO (Scientific Electronic Library Online). Os critérios de inclusão incluem artigos recentes (publicados nos últimos 10 anos) em português, inglês ou espanhol.

Desenvolvimento: Desde superfícies de revestimento já estabelecidas, como a prata, que foram melhoradas através do uso de nanopartículas, até novas abordagens como os péptidos antimicrobianos e os biossurfactantes, soluções promissoras para prevenir a formação de biofilme nas superfícies dos implantes de titânio foram reportadas nos últimos anos. Nesta revisão, foram resumidas as diversas estratégias propostas para melhorar as propriedades antibacterianas dos implantes dentários de titânio.

Conclusão: Superfícies de revestimento com propriedades antibacterianas são uma solução promissora para prevenir infeções bacterianas que comprometem o sucesso dos implantes dentários e ortopédicos. Todas as superfícies de contacto referenciadas nesta revisão mostram elevado sucesso antibacteriano e eficácia no controlo do biofilme, mantendo a biocompatibilidade do implante. Por outro lado, o custo de fabrico e a eficácia antibacteriana a longo prazo mantêm-se como os principais problemas destas superfícies de revestimento.

Palavras-chave: "biofilm", "dental implants", "titanium implants", "antibacterial", "surface coating", "antibiofouling".

5. INTRODUCTION

Dental implants are one of the most common procedures to replace missing teeth on the oral cavity with great success rate. However, they still fail a significant number of times due to infections such as peri-implantitis and peri-implant mucositis. [1]

Peri-implant mucositis is a biofilm-induced inflammation localized on the soft peri-implant mucosa, without any evidence of supporting bone loss. [8] If the inflammatory process progresses, it may cause gradual destruction of the bone surrounding the implant, a state designated as peri-implantitis. [8]

The ideal dental implant should have both great osseointegrative properties as well as protection from the bacteria that cause infections that lead to implant failure. [2, 3] Studies indicate that around 43% of dental implants eventually suffer from peri-implant mucositis and around 22% develop peri-implantitis. These type of infections when untreated, lead to implant loosening and require removal of the dental implant. [4]

Titanium and its alloys are present in about 95% of all commercialized implants nowadays. The decision to use titanium relies on its properties such as great resistance to corrosion, biocompatibility, high strength-to-weight ratio, good tolerance by the biological environment as well as on the presence of a reactive titanium oxide surface layer. [2, 3, 5-7]

The first development in dental implant modifications to improve their success rate was towards surface modifications. Changing the surface's physic and chemical characteristics such as roughness, surface free energy and wettability was the focus of several studies and helped to improve osseointegration.[5] Increasing the surface's roughness allowed to get bigger implant surface area which lead to an improvement in cell migration and attachment, thus enhancing the osseointegration process. [7] Also, a faster proliferation of osteoblasts onto the implant surface will discourage bacterial adhesion and, therefore, reduced infection risk. [8]

After achieving satisfying results regarding implant osseointegration, the next step was to control and prevent the accumulation of bacteria around the implant. Bacterial adhesion occurs immediately after implantation which leads to biofilm formation. Biofilm would then cause inflammation of the tissues around the implant and eventual development of peri-implant infections. Biofilm is also resistant to many antibacterial agents, making it difficult to treat after established.[9] To prevent bacterial infections, surface coatings with antibacterial properties were hypothesized to be a reliable solution for this problem.

From nanoparticles such as silver or gold to antibiotic loading, many coatings were developed, tested, and studied. Throughout this research, a variety of coating materials and techniques will be discussed, trying to access which innovative solutions shows the most promising results regarding a viable antibiofouling surface coating.

6. MATERIALS AND METHODS

The bibliographic research was conducted in the following electronic databases: PubMed/Medline, Scopus (Elsevier), Web of Science (Clarivate Analytics) and SciELO (Scientific Electronic Library Online).

Inclusion criteria included the most recent articles published (last 10 years) related to titanium surfaces and titanium surface coatings, written in Portuguese, English or Spanish.

The exclusion criteria included thesis, letters and articles not referring innovative titanium surfaces or surface coatings.

7. DEVELOPMENT

Success of oral rehabilitation using dental implants depends on numerous factors with implant-related infections being responsible for a big part of their failure.(10)

In the oral cavity, there are more than 700 species of bacteria (11, 12) with *Actinobacteria*, *Bacteroidetes*, *Firmicutes* and *Proteobacteria* being the most relevant for oral health.(12) Regarding dental biofilm, which may variate between individuals and even among different sites of the oral cavity, a core microbiome was proposed and it included the following species: *Streptococcus*, *Veillonella*, *Granulicatella*, *Rothia*, *Actinomyces*, *Prevotella*, *Capnocytophaga*, *Porphyromonas*, and *Fusobacterium*. (11) After the establishment of the biofilm, bacteria from the red complex, namely *Tannerella forsythia*, *Tannerella denticola*, and *Porphyromonas gingivalis* trigger the inflammatory process that leads to prei-implant mucositis.(13)

The process of biofilm formation starts with salivary glycoproteins developing a conditioning film, also known as pellicle, on the teeth surface which allows the initial bacterial adherence.(11) After that, weak long-distance forces between charged molecules of the pellicle and the pioneer bacterial species will grant initial adhesion. These forces grow stronger via receptor-pairs between adhesins in the bacteria surface and glycoprotein receptors in the acquired pellicle.(11) After the initial adhesion, the biofilm development continues with cell aggregation until a stable microcolony is achieved. At last, due to multiple factors such as lack of nutrient or fluid dynamics, the biofilm can disperse from the surface of the implant and migrate. (14)

Medical devices, namely dental titanium implants, show a process of biofilm formation quite similar to natural teeth. Titanium surface, when in mouth is immediately coated by plasma and saliva proteins. This will lead to the formation of a protein layer which allows the initial colonizers, like various species of *Streptococcus,* to bind to it. Co-aggregation follows and interactions by different species induce biofilm accumulation. Finishing this process, the extracellular matrix starts embedding the microbial communities and the biofilm is established.(15)

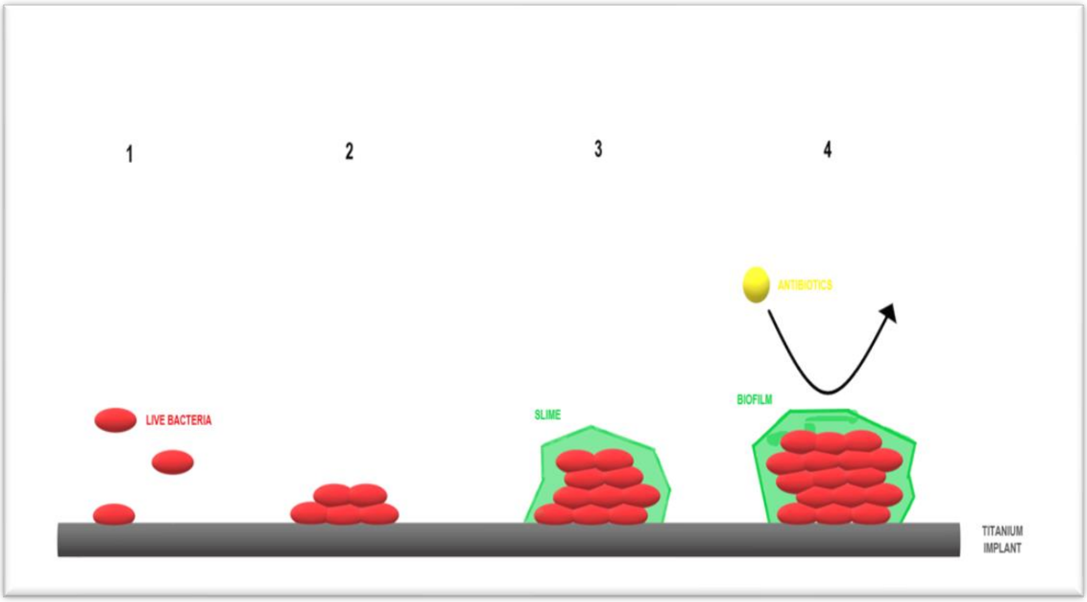

Figure 1- Steps of biofilm formation, from bacterial adhesion (1 and 2) to biofilm maturation (3) and established biofilm (4).

On itself, titanium implants are prone to bacterial adhesion.(16) Once a bacterial infection was able to develop into a mature biofilm on the implant surface there was no efficient treatment to guarantee its destruction and to prevent the recurrence of the infection.(8, 10)

The need of improvements in surface properties regarding antibacterial effect compelled the appliance of surface coating materials such as silver, copper, zinc, chlorhexidine, and some antibiotics, as they presented to be a promising solution due to the creation of an additional layer on the surface of the implant with antibacterial properties that would fight bacterial invasion. (2, 10)

Nonetheless, the methods required to modify and incorporate coatings in the implant surface were complex and expensive. An even bigger problem was that while trying to achieve maximum antibacterial properties, we could be losing biocompatibility and osseointegrative properties. Balance will always be key to determine the potential of a coating.(17) An ideal implant should have both osseointegrative and antibacterial properties. (2)

There are numerous coatings developed through the years with promising results enhancing antibacterial properties, achieved by either physical or chemical modification or even a combination of both and we will discuss the most relevant ones.

7.1 Bacteriostatic Materials

Various molecules show bacteriostatic properties, which means, they are able to repel the bacteria from the surface of the implant, without killing it. (10)

Polymers such as polycations to biosurfactants, some materials have been studied and applied to titanium surfaces and were able to provide bacteriostatic properties to titanium surfaces. Moreover, scientists were able to combine bactericidal and bacteriostatic materials granting both bactericidal and bacteriostatic properties to titanium surfaces.(10)

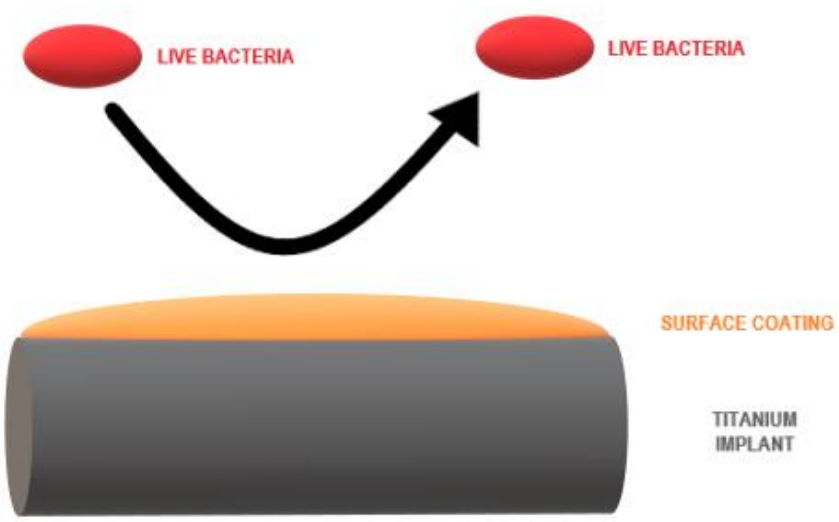

Figure 2- Behavior of bacteriostatic coating surfaces against bacteria.

7.1.1 Polymer Coatings

Polyethylene glycol (PEG) is one of the most widely used polymers to provide antifouling properties to material surfaces, namely titanium surfaces.(8, 18) Thanks to its hydrophilic and flexible chains it possesses great bacteriostatic properties. However, the very efficient antibacterial repelling properties also inhibit eukaryotic cell (e.g., osteoblasts) attachment thus compromising osseointegration. Therefore, they require the addition of cell adhesive sequences such as RGD peptide to preserve its biocompatibility.(8)

Aiming to prevent the adhesion of bacteria to the surface of medical implants, polymer coatings with hydrophobic polycations such as N,N-dodecyl,methyl-PEI, as described by Schaer et *al.* (19), were studied and have shown promising results. Membrane proteins, teichoic acids (Gram-positive bacteria) and negatively charges phospholipids (Gram-negative bacteria) grant a negative surface charge to microbial cells. Polycations are attracted to the negativity present in microbial cells' surface and based on their amphiphilic properties they can disrupt their membrane and enable cell lysis leading to cell death, adding bactericidal potential to the polymer coating.

Unfortunately, fabrication of the coating structure is a costly and challenging process and there is a risk of polymer degradation with time which could compromise the long-term stability and effect of the coating surface. Also, some polymer coatings are not yet available to uses in titanium dental implants since the process of screwing the implants to the bone would compromise the structure of the coating, making it and unviable option.(10) Nonetheless, when a stable structure of polymers and cell adhesive sequences is achieved, both antibiofouling and osseintegrative results are very promising. (8)

7.1.2 Biosurfactants

Biosurfactants are the most recent addition to the list of possible coatings with antibacterial properties for dental implants. Tambone et *al*.(20) published the only article available in Pubmed regarding titanium dental implants using rhamnolipids, a microbial surfactant mainly produced by *Pseudomonas aeruginosa.*

Rhamnolipids can preserve the biocompatibility of the titanium surface due to their low cytotoxicity, while interfering with the microbial adhesion process due to their amphiphilic structure. They also can modify permanently cell membranes which could lead to cell lysis.(20)

The coated titanium disk with 4mg/ml of rhamnolipid solution was tested against *Staphylococcus aureus* and *Staphylococcus epidermidis* for 72 hours. After 24 hours, the *S. aureus* inhibition was higher than 90% and *S. epidermidis* inhibition ranged from 62 to 78% depending on titanium surface morphology. After 72 hours the reduction of *S. aureus* was about 7% and 10,3% for *S. epidermidis*. No cytotoxicity was verified in any coated surface.(20)

Rhamnolipids proved to be another promising strategy for reducing both bacterial adhesion and biofilm reduction on titanium surfaces.

7.2 Bactericidal Materials

There are numerous ways to kill bacteria. Damage to the membrane or cell wall of bacteria, penetration of the cell wall, DNA damage that prevents bacteria replication, generation of reactive oxygen species (ROS), blocking of ATP synthase and preventing cell respiration are some of the mechanisms known to kill bacteria. (10, 21) Some materials imbued in surface coatings can, through some of the mechanisms mentioned, grant bactericidal properties to titanium dental implants, preventing biofilm formation.

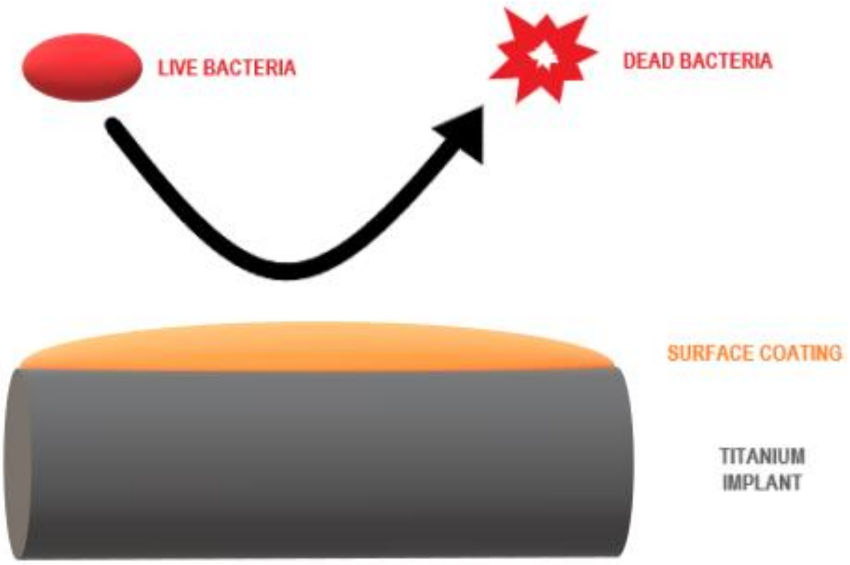

Figure 3- Behavior of bactericidal coating surfaces against bacteria.

7.2.1 Antimicrobial Peptides (AMP)

Peptides are a potential solution against biofilm colonization in titanium dental implants due to their bactericidal properties. Geng et *al.* (22) studied engineered chimeric peptides with antimicrobial activity and concluded that, despite the need of further studies, these peptides had promising results regarding antimicrobial activity. Zhou et *al*. (23) studied a cationic antimicrobial peptide, GL13K and through X-ray photoelectron spectroscopy and ultrasonication proved that this AMP improved both antibacterial and cytocompatibility properties of titanium implants, inhibiting biofilm growth and preventing peri-implantitis.

AMPs can be a good alternative to commonly used antibacterial materials such as silver, due to their flexibility when combining antibacterial and osseointegrative properties. Despite having a broad spectrum of action against bacteria, they appear to have lower propensity to develop antibacterial resistance and non-toxicity.[8, 18]

In spite of promising results, bioactive coatings with AMPs require complex designs of synthetic peptides that are quite costly to fabricate, which may compromise their broad use in titanium dental implants.[10]

7.2.2 Ion-implanted Surfaces

Ions from elements such as fluorine (F), copper (Cu), zinc (Zn), chlorine (Cl), iodine (I), selenium (Se) or cerium (Ce) can be incorporated into coatings in titanium implants.(10) Zhou et *al.*[24] studied the potential of doped fluorine in Ti02/calcium-phosphate coatings (TiCP). With 3 different amounts of fluorine in the coating, designated TiCP-F1 (least amount of fluorine), TiCP-F6 and TiCP-F9 (most amount of fluorine), they concluded that the TiCP-F1 coating had higher osteogenic properties than pristine (uncoated) Ti but lacked antibacterial properties whilst with increased amount of fluorine in the TiCP-F6 and TiCP-F9 coatings exhibited significantly improved osteogenic and antibacterial properties.

One common coating applied to titanium surfaces is calcium-phosphate (CaP) due to its bioactive and osteoconductive properties.[2] Aranya et *al.* [2] modified the CaP surface by doping it with fluoride and zinc ions, both alone and combined. Fluoride is known for its bactericidal effect while Zinc is more associated with osseotingration promotion, despite also showing antibacterial properties.[2]

They studied the effectiveness of this coating against *Porphyromonas gingivalis*, a bacteria highly associated with peri-implant infections. FZn-CaP coating had great results regarding inhibition of bacterial adhesion with ~88% reduction when compared to uncoated control disks, in the first 72 hours. F-Cap and Z-Cap coatings had each ~89% reduction of bacterial adhesion. After 7 days, the biofilm reduction was significantly lower for both coatings. Zinc and Fluoride doped into CaP coating is a great option for dental implants since it enhances titanium surfaces with both bactericidal and bioactive properties. [2]

Shen et *al.* [25] studied and verified that incorporating Zn ions in titanium dental implants surface coatings reduced the growth of *P. gingivalis*, while Lin et *al.*[26] used Bismuth (Bi) to chemically modify Ti implants and was able to reduce *Strep. Mutans* colonization.

A variety of tested ions also proved to be a promising solution to grant antibacterial properties to the surface of titanium dental implants although they still lack long-term effect.

7.2.3 Photoactivatable Bioactive Titanium

Titania or titanium dioxide (TiO2) is a nanocomposite coating with antimicrobial properties once it is photo-activated.[10] Under strong UV light, reactive oxygen species (ROS) are generated which allows TiO2 to kill a wide range of microorganisms such as bacteria while maintaining biocompatibility. [10, 27]

TiO2 properties like its' low-cost, stability, reactivity, durability, biocompatibility, and corrosion resistance make it a great option for commercial antimicrobial coatings. Thus, it is also possible to incorporate inorganic metals such as copper (Cu) or Silver (Ag) or even non-metals like fluorine (F) or calcium (Ca), particles previously mentioned, to enhance even further the antibacterial properties demonstrated by TiO2 coatings.[28]

7.2.4 Nanomaterials

Nanoparticles (NPs) are small particles with diameters between 1 to 100 nm, from metals such as silver, gold, and other nanomaterials like magnesium, zinc, or copper who display antimicrobial activity. Their antibacterial properties lead to research towards their incorporation in coatings for titanium implants.[10, 29]

The biocidal mechanisms shown by these NPs, mainly the metallic ones, are diverse which prevents bacteria to develop resistances against them. [21] Silver ions are released for a long period of time, expanding its antibacterial effect. [30, 31]

Massa et *al*. [32] incorporated silver nanoparticles in a nanoporous silica coating through a sol-gel technique and observed a significant increase in both bactericidal and bacteriostatic properties of the titanium implant.

Silver nanoparticles (AgNPs) have shown a strong and wide antibacterial spectrum. Their exact mechanism against bacteria is still up for discussion, but the most accepted one so far is that AgNPs produce reactive oxygen species that inhibit the growth of bacteria, killing them in the process. For this reason, silver (Ag) is one of the most used coating agents for titanium dental implants and other titanium medical devices. [11] However, some reports state that high concentrations of silver could be cytotoxic towards eukaryotic cells (e.g, fibroblasts, osteoblasts), which would reduce the osseointegrative properties of the implant.[8] Further studies are required to fully understand silver nanoparticles behavior when coated in titanium implants.

7.2.5 Antibiotic Coatings

Antibiotic treatment is strongly connected with dental implant placement since they are often prescribed as prophylactic treatment for this procedure.[33] Despite having numerous different protocols with different antibiotics, different concentrations, and different periods of time for its' administration, the available bibliography supports the benefits of prophylactic antibiotic administration against implant failure due to immediate bacterial colonization. [34]

Although the success rate of implant placement is higher when prophylactic antibiotic is administrated to the patient, it only affects the early colonization of bacteria to the implant surface, not preventing the biofilm establishment in the following days or weeks. Not to mention, the actual amount of antibiotic that reaches the site of the implant is lower when compared to local delivery of the same antibiotic. [33, 35]

A surface coating with controlled antibiotic delivery system would be a great long-term solution to control and prevent biofilm formation. Specific agents released over time that target early colonizers without compromising the mechanical, physical and chemical properties of the dental implant and showing non-cytotoxic effects to host tissues and cells would drastically decrease the occurrence of peri-implant infections. (15)

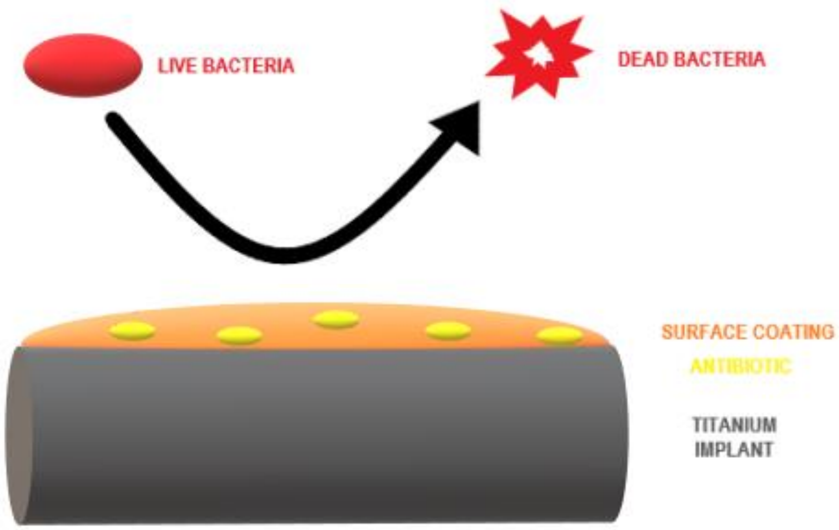

Figure 4- Antibiotics loaded in coating surface achieve bactericidal effect on titanium implants.

Nichol et *al.* (35) developed a single-layered sol-gel coating loaded with gentamicin in a titanium surface and tested it against *Staphylococcus* strains. Gentamicin is active against both Gram-negative and Gram-positive bacteria, being considered a broad-spectrum antibiotic.

Within 1 hour, the Minimum Inhibition Concentration (MIC) was achieved and after 24 hours, all marked *Staphylococcus* variants were eliminated. 48 hours later 99% of the gentamicin present in the coating was eluted.

These results were satisfactory to the author but do not represent the ideal coating for dental implants since the antibiotic release was too fast for long-term prevention.(35)

Zhang et *al.* (33) prepared titanium implants coated with vancomycin through electrospinning technique. Vancomycin was chosen due to its broad antimicrobial spectrum that covers both methicillin-resistant *S. epidermidis* as well as methicillin-resistant *S. aureus*.

The prepared coating showed an initial burst of vancomycin release on the first day (about 50,3%) followed by a slower and steadier release over the following 27 days (32,4%) making it a total release of approximately 528,2 μg of antibiotic from around 627,6 μg loaded in the coating (82,7%). No cytotoxicity to the cells was detected and the antibacterial effect of Vancomycin was validated both *in vitro* and *in vivo* showing promising results towards prevention of early implant-associated infections, but still lacking long-term effects. [33]

Lv et *al*. [36] also proposed an antibiotic loaded coating to inhibit biofilm formation. They studied titanium substrates coated with chitosan/alginate layer loaded with minocycline through a layer-by-layer self-assembly. Minocycline is a broad-spectrum tetracycline antibiotic with clinical use together with mechanical treatment of periodontal and peri-implantitis lesion.

Their approach is extremely promising since the multilayered coating allows higher quantities of loaded antibiotic and a more controlled and over-time release of the substance.

The results obtained showed an initial burst of minocycline release in the first 24 hours which could fight the immediate colonization of bacteria. The antibiotic release stabilized through the first 7 days and after that, the average concentration of minocycline in the fourteenth day was ~25,13 4.1 μg /ml. No bacterial cells with intact shape could be found in the titanium surface after 7 days.

In a recent review by Souza et *al*.[15] all available references about antibiotic coated titanium surfaces was analyzed, compiled, and, applying PRISMA guidelines, 33 articles were selected to study.

Out of those 33 articles, 11 studied the use of gentamicin, 11 used vancomycin, being the 2 most tested antibiotics. Other antibiotics had 3 or less studies. *Staphylococcus aureus* was the infection model of choice for 31 of the 33 studies.[15]

Comparing the results obtained among all 33 articles, there was a big disparity from authors studying the same antibiotic. For example, gentamicin-loaded coatings bacterial reduction varied from ~5% up to ~99,9%. Vancomycin-loaded coatings bacterial reduction ranged from ~45,3% up to ~99,2%. In 3 of the 33 studies, there was no reduction at all or even higher bacterial load in the tested group.(15)

Bearing in mind the widespread, and even contradictory range of results obtained, as well as the scarce amount of data available, especially regarding human clinical data, there is not currently a consensual opinion regarding the best therapeutic approach for antibiotic loaded coatings to prevent peri-implant infections.(15) There are also concerns towards toxicity and possible development of bacterial resistance, risks that should be avoided.(8)

The fact that both gentamicin and vancomycin are not the gold standard for treatment of oral infection, since they act mostly on aerobic gram-negative bacilli, (15) lead to the necessity to develop studies with antibiotics such as amoxicillin and metronidazole that would be more relevant for dental implants and treatment of the gram negative anaerobic bacteria preset in peri-implantitis.

Another important aspect to consider is that most of these studies were not conducted in the oral cavity or mimicking its' environmental conditions so any conclusion regarding their behavior in dental titanium implants needs further studies.(15)

Table 1- Summary of results obtained in with different antibiotics.

Antibiotic	Model	Efficiency	Reference
Gentamycin	*Staphylococcus* variants	~99% (24h)	(35)
	S. aureus	From ~5% to ~99%	(15)
Vancomycin	*S. epidermidis* and *S. aureus*	Significant reduction	(33)
	S. aureus	From ~45,3% to ~99,2%	(15)
Minocycline	*S. aureus*	~99% (7 days) and ~80% (14 days)	(36)
	S. aureus	Non-Reported	(15)

7.2.6 Chlorhexidine Coatings

Chlorhexidine has been used together with mechanical debridement to improve effectiveness of treatment against peri-implantitis.[10]

Lauritano et *al*.[37] studied the effectiveness of a silicone coating containing chlorhexidine against bacteria inside and outside the implant-abutment junction (IAJ). They achieved the coated surface by immersion of the abutment in the polysiloxane solution for 10 minutes followed by centrifugation and heat treatment.

After 24-hour incubation following contact with a microbial pool of *Staphilococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans*, the results showed no living bacteria in the internal part of coated implants.[37]

Considering the different approach of coating the inside of the implant, preventing bacterial growth in the IAJ, chlorhexidine also had promising results against the bacteria responsible for peri-implant infections, in the short therm.[37]

Table 2- Summary of reviewed antibiofouling coatings.

Coating surface	Mechanism of action	Major Upside(s)	Major Downside(s)
Polymer Coatings	Bacteriostatic (mainly)/ Bactericidal	Great antibiofouling and osseointegrative properties when paired with cell-adhesive sequences. Great bacteriostatic results *in vitro*.	Risk of polymer degradation. Require pairing with cell adhesive sequences.
Antimicrobial Peptides (AMP)	Bactericidal	Broad spectrum; Low citotoxicity; Low propensivity to develop antibiotic resistance.	Complex structure. High cost of fabrication.
Ion-implanted Surfaces	Bactericidal	Flexibility; Can be paired with other coatings to promote both osseointegrative and antibiofouling properties.	Difficulty to achieve long-term antibacterial effect
Photoactivatable Bioactive Titanium	Bactericidal	Cheap; Stability; Biocompatibility;	Inability to photoactivate once the implantation occurs.
Nanomaterials	Bactericidal (mainly)/ Bacteriostatic	Longer antibacterial Effect.	Efficiency is controversial. Some studies report cytotoxicity.
Antibiotic Coatings	Bactericidal	Cheap. Good efficiency against targeted bacteria.	Development of bacterial resistance. Difficulty to achieve long-term release. Toxicity.
Chlorohexidine Coatings	Bactericidal	Great results *in vitro* regarding biofilm reduction	Absorption by the titanium surface
Biosurfactants	Bacteriostatic	Some bactericidal effect, increasing effectiveness.	Scarce studies.

8. CONCLUSION

Materials such as silver have been used over the past few years as a coating material to reduce bacterial infections, but its use has been decreasing over time.[10] Concerns about toxicity to the patients led to the switch to other solutions like titanium dental implants with modified surfaces to improve osseointegrative properties along with systemic administration of antibiotics.[10].

There is a wide range of options and techniques to achieve antibacterial effect on coating surface. Most of the mentioned coating possibilities only have *in vitro* studies and the few using *in vivo* models are not enough to establish conclusions. We are taking the first steps towards better solutions for dental implants, but the ideal one with promotion of cell adhesion, good biocompatibility, and antibacterial effect over a long period of time for a reasonable price is still a few years away. More *in vivo* studies using relevant animal models and studies over longer periods of time are required for better understanding on what is viable and what is not.

Another important concern is the lack of data of the longevity regarding the bioactive surfaces long after the implantation occurs. Most mentioned solutions show very good results but only until 24/48 hours after implantation. Some techniques address this question, such as antibiotic loaded coatings using the layer-by-layer, but it is still not enough and further improvements are required for it to be a fitting solution.

It is important to highlight the question of cost-benefit of surface coatings. There is a lot of effort being put in the discovery and applicability of established and new antibacterial materials, but the coating methods are complex and expensive. With such scarce *in vivo* studies with the correct models of study as of today, it is difficult to predict when we will have an effective antibiofouling coating surface without drastically increasing the cost of the titanium dental implant.

In addition to the mentioned problems so far, there is also the question that many of the materials presented in this review were studied as orthopedic solutions and not always focused on the dental aspect of titanium implants. Despite similar in most aspects, there are still quite a few and relevant differences regarding orthopedic and dental implants. The oral cavity and oral microbiota are unique and distinct from the rest of the body, so many of the results obtained require further investigation mimicking the environmental conditions of the oral cavity before they become possible solutions for dental implants.

There is no question that antibacterial coatings are indeed a promising solution to control and prevent bacterial infections that compromise dental and orthopedic implant success once more studies and developments are conducted.

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