UNIVERSIDADE
FERNANDO
PESSOA

BIOFUNCIONALIZAÇÃO DO IMPLANTE PARA PREVENIR A PERI-IMPLANTITE

[Biofunctionalization of the implant to prevent peri-implantitis]

Dissertação de Mestrado Integrado em Medicina Dentária

Laetitia Harmouche

Orientador:

Dr. Pedro Jorge Gonçalves Pereira

Abril 2024

UNIVERSIDADE
FERNANDO
PESSOA

BIOFUNCIONALIZAÇÃO DO IMPLANTE PARA PREVENIR A PERI-IMPLANTITE

[Biofunctionalization of the implant to prevent peri-implantitis]

Dissertação de Mestrado Integrado em Medicina Dentária

Laetitia Harmouche

Orientador:
Dr. Pedro Jorge Gonçalves Pereira

Abril 2024

Laetitia Harmouche

Biofunctionalization of the implant to prevent peri-implantitis

Trabalho apresentado à Universidade Fernando
Pessoa como parte dos requisitos para obtenção do
grau de Mestre em Medicina Dentária

RESUMO

Os implantes de titânio são utilizados para substituir dentes em falta, sendo o titânio o padrão de ouro devido à sua capacidade de osseointegração. O sucesso dos implantes depende principalmente da osseointegração, mas também da prevenção de complicações biológicas tardias, conhecidas como "peri-implantite", uma das causas mais comuns de perda de implantes devido à colonização bacteriana.

Recentemente, o desenvolvimento de superfícies bioactivas de implantes provou ser eficaz na melhoria da osteointegração. Além disso, foi relatado que a biofuncionalização possui atividade antibacteriana. O que leva à seguinte questão, à qual esta revisão pretende responder: A biofuncionalização de implantes dentários previne o desenvolvimento de peri-implantite?

Para realizar esta revisão integrativa, foram pesquisadas as seguintes bases de dados: PubMed, Medline, Scopus, Cochrane Central Register of Controlled Trials, e Science Direct.

22 artigos preencheram os critérios de inclusão: 1 ensaio clínico aleatório, 12 estudos *in vitro* e 10 artigos que combinavam estudos experimentais *in vitro* e *in vivo*.

Todos os estudos relataram a redução do acúmulo de biofilme e a regulação positiva da resposta celular.

No que diz respeito às superfícies bioactivas investigadas, os iões metálicos e as nanopartículas foram as superfícies bioactivas mais frequentemente utilizadas. De acordo com os resultados desta revisão integrativa, as superfícies bioactivas têm um efeito positivo na prevenção da peri-implantite. É necessário uma investigação mais aprofundada neste campo para avaliar o seu efeito sustentável para combater o processo crónico da peri-implantite.

Palavras-chave: Antibacteriano; Revestimento bioativo; Biofuncionalização; Peri-implantite; Tratamento de superfície; Implantes de titânio.

ABSTRACT

Titanium implants are used to replace missing teeth, with titanium representing the gold standard due to its ability to provide osseointegration. The success of implants depends on osseointegration primarily, but also on the prevention of late biological complications, known as “peri-implantitis”, one of the most common causes of implant loss due to bacterial colonization.

Recently, the development of bioactive surfaces of implants proved effective in enhancing osseointegration. Furthermore, biofunctionalization was reported to possess antibacterial activity. Which leads to the following question to which this review aims answering: Does biofunctionalization of dental implants prevent the development of peri-implantitis?

To conduct this integrative review, the following databases have been searched: PubMed, Medline, Scopus, Cochrane Central Register of Controlled Trials, and Science Direct.

22 articles met the inclusion criteria: 1 randomized clinical trial, 12 *in vitro* studies, and 10 articles combining *in vitro* and *in vivo* experimental studies.

All studies reported reduction of biofilm accumulation and upregulation of cellular response.

Regarding the bioactive surfaces investigated, metallic ions and nanoparticles were the most frequently used bioactive surfaces. According to the results of this integrative review, bioactive surfaces have a positive effect on the prevention of peri-implantitis. Further and more in-depth research in this field is required to evaluate its sustainable effect to match the chronic process of peri-implantitis.

Keywords: Antibacterial, Bioactive coating; Biofunctionalization; Peri-implantitis; Surface treatment; Titanium implants.

AGRADECIMENTOS

This work is dedicated to my husband and pillar, David, without whom this whole adventure would not have been possible. I will be forever grateful to his constant love and support.

To my family as well, Nicolas, Grace, Céline and Muriel, who have never failed to encourage me, and bear with me the obstacles of this rollercoaster.

To my "meninas d'uva", my beautiful warriors, who rendered this Porto stay an experience of a lifetime.

To the teachers of UFP, who took the time to teach and exchange with us, while also trusting us.

TABLE OF CONTENTS

I-INTRODUCTION

Titanium dental implants are being widely used to replace missing teeth, and their number is continuously increasing following the introduction of osseointegration principles and the improvement of surgical protocols.

Implants present high survival rates up to 97.1% at 10 years (Roccuzzo et al., 2014), 82.4% at 10–16 years (Simonis et al., 2010) and 73.4% at 20 years (Deporter et al., 2014). However, biological and mechanical complications are present during implant function. Biological complications affecting these medical devices are categorized as peri-implant mucositis and peri-implantitis. Peri-implant mucositis is considered the precursory step of the infection process characterized by a biofilm-induced inflammation of the peri-implant mucosa, in the absence of continuous marginal peri-implant bone loss, and is considered a reversible event (Heitz-Mayfield et al., 2018). Peri-implantitis is characterized by inflammation in the peri-implant mucosa and progressive loss of supportive bone. Peri-implantitis is considered irreversible and potentially leading to implant loss (Schwarz et al., 2018). Indeed, a cause-effect relationship has been established between bacterial plaque accumulation and development of peri-implant inflammation (Salvi et al., 2017).

Titanium (Ti) is still the gold-standard biomaterial for oral implantology, due to its mechanical and biological properties (high corrosion resistance, biocompatibility, and lightweight properties) (Kasemo, 1983). However, its antimicrobial properties are insufficient to avoid bacterial colonisation. Consequently, microbial infection remains the major cause of implant loss. Peri-implantitis, while being modulated and mediated by the host, is always biofilm-induced (Berglundh et al., 2018). The surface topography of implants (on a micro- and nanoscale) plays a crucial role in osseointegration and it is known that cell response can be modulated by the implant surface texture. The most common surface roughness treatments to achieve osseointegration are sandblasting, acid etching, anodizing, and titanium plasma spraying (Jemat et al., 2015). However, these surface modifications (with increased surface energy and hydrophilicity), aiming at enhancing osseointegration, could potentially amplify the risks of implant surface contamination, hence leading to a possible development of peri-implantitis.

Recently, new strategies have been proposed to help the titanium surface meet both functional and biological goals, among which “biofunctionalization” promises great potential. The bio-functionalization of a certain material consists of a modification of the physicochemical properties of its surface, so that it allows improvement in the biological response, and modulation of the interaction with its environment. Currently, most research is focused on antibacterial and antiadhesive surfaces: the aim being able to reduce bacterial adhesion on implant surfaces while also having active antimicrobial activity (Asensio et al., 2019).

Bioactive agents that impede bacterial infection can be classified based on their mechanism of action, including as mentioned the passive coatings that prevent bacteria from adhering to the implant surface, and active coating releasing antibacterial agents. Passive systems are using mostly polymeric coatings that reduce cell and protein adhesion. They don't involve the use of drugs, and are easy to handle, which makes them an appealing choice. However, because of their anti-adherent property, the osseointegration process is hampered because it equally interferes with osteoblasts’ attachment to the implant. In order to counteract this adverse impact, antifouling coatings are functionalized with cellular adhesive peptides, which promote the connection between the implant and the cell, hence promoting osteogenesis while preventing bacterial fixation. Regarding active coatings, antibacterial agents (metallic ions, antibiotics, or disinfectants) can be covalently anchored to the coating (antimicrobial peptides) or physically embedded in a polymeric matrix (such as antifouling polymers) (de Avila et al., 2020).

To summarise, the incorporation of antibacterial agents to prevent the biofilm formation, compromises the viability of osteoblasts, generators of new tissue, while physico-chemical surface alterations promote both the fixation of bacteria and osteoblasts. Therefore, research has aimed at developing surfaces that combine antibacterial agents (preventing infections) along with osteconductive/osteoinductive substances (promoting the differentiation of native cells). These systems would allow both antimicrobial action and peri-implant tissue integration.

Overall, bioactive agents can be classified into 4 categories so far (Asensio et al., 2019):
- Metal ions and nanoparticles

- Bactericidal peptides
- Antibiotics
- Anti-adhesive coatings

Metal ions and nano particles

Ions and nanoparticles of metallic elements have an antimicrobial capacity. Silver is the most commonly used antibacterial agent, followed by zinc and copper. Antimicrobial properties have also been reported for cerium and tantalum (Jin et al., 2014; Qin et al., 2015).

Regarding the incorporation of nanoparticles of silver for instance, plasma immersion ion implantation (PII) technique has allowed strong fixation of metal elements avoiding hazardous consequences.

Also, other dental implants coatings have consisted of TNTs (TiO2 nanotubes developed with an anodization process) combined with reservoirs of nanoparticles (Cheng et al., 2014).

Polydopamine (PDA) coatings, consisting of soaking in a dopamine solution then self-polymerization, are also an attractive system due to the simplicity of the process, and the biocompatibility of the coating (Zhang et al., 2018).

Bactericidal peptides

Bactericidal peptides have demonstrated an antimicrobial activity of broad spectrum, with short times of action and low risks of developing resistant strains. Adhesion molecules and cytokines, two groups of the aforementioned agents, are contributing factors to osteogenesis. For example, fibronectin and vitronectin, both ECMs adhesion proteins have proved to speed up the adhesion of osteogenic cells to the implant surface. Another group of bioactive proteins are growth factors, such as cytokines. Bone Morphological Protein (BMP), and a recombinant of this protein BMP-2, for instance have been incorporated to titanium implants to improve bone healing. Other peptides with an interesting application in oral implantology are the double peptide RDG (Arg-Asp-Gly), RGD (Arg-Gly-Asp), and P15 which is a synthetic peptide with 15 amino acids (Geng et al., 2018).

Antibiotics, Disinfectants and Drugs

Implants can also be loaded with antibiotics which allows to selectively target bacteria. In their study, Shahi et al. tested a novel bioactive tetracycline-containing electrospun polymer fibers as a potential antibacterial dental implant coating (Shahi et al. 2017), and obtained a total eradication of the biofilm containing peri-implantitis associated pathogens. This system has also been found to exhibit osteogenic ability besides its bactericidal activity (Bottino et al., 2017).

Recently also, biofunctionalization of titanium surfaces with flavonoids, such as taxifolin and quercetin, have proven to induce osteogenesis and prevent peri-implantitis (Córdoba et al., 2015).

Gentamycin has also been employed and loaded with RGD peptides, obtaining a bioactive nanorough surface of the implant. This coating inhibited the growth of *Staphylococcys aureus* while promoting the osteoblast adhesion and differentiation (Aggarwal et al., 2022). In another study, gentamycin was incorporated with Ag nanoparticles allowing a strong antibacterial activity with a bone formation capacity (Zhou et al., 2017).

As previously mentioned before for metal ions, dopamine coatings can also be used to covalently bind antibiotics. For instance, the fixation of bacitracin has been reported in polydopamine-modified titanium surfaces, and has shown significant inhibition of against *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA). Also, it resulted in a diminution of pro-inflammatory cytokines accompanying the inhibitory effect of macrophage spreading (Nie et al., 2016).

Other studies have resorted to the combination of polymers like chitosan and hyaluronic acid with vancomycin-encapsulated TNTs. The degradation of hyaluronic acid by bacterial hyaluronidase allowed the slow release of the bactericidal peptide (Boot et al., 2021). The results showed significant antibacterial potential allowing inhibition of *S. aureus* and increased formation of new bone tissue.

Furthermore, chlorhexidine has been used as an antibacterial agent, with a controlled release from a mesoporous silica-containing macroporous titanium dental implant. This system effectively prevented microbial biofilm formation, and showed ostegenic properties as well (De Cremer et al., 2017).

Finally, some studies functionalized titanium implants with alendronate, an agent typically used to treat and prevent osteoporosis, and known for its capacity to promote bone growth. The combination of alendronate in a self-assembly monolayer technique, resulted in a coating that exhibited excellent osteogenic differentiation of human mesenchymal stem cells (hMSC) (Rojo et al., 2016).

Anti-Adhesive Coatings

The use of anti-adhesive polymers that inhibit the attachment of bacteria is another method that have been also used. The downside of these coatings is their unspecific suppression of both osteoblasts and bacteria fixation. That is why they are functionalized with peptides or other bioactive compounds, aiming to enhance the adhesion of cells. Chitosan and carboxymethyl chitosan are the most extensive antimicrobial polymers employed. Also, several studies have incorporated different osteogenic agents, such as hydroxyapatite, bone morphogenetic protein-2 (BMP-2) protein, ALP, silica–chitosan hybrid materials, and chitosan-58S bioactive glass nanocomposite. These coatings have been proven to be efficient in inhibition of bacterial adhesion combined with an improved osteointegration (Asensio et al., 2019). Bioactive surfaces seem to achieve faster and better osseointegration, hence allowing to reduce healing times for prosthetic loading (López-Valverde et al., 2020).

Also, the physicochemical enhancements of biofunctionalization represent a promising approach towards bacterial reduction and maximisation of tissue integration (de Avila et al., 2020).

Given the fact that implants do not possess the ability to shed-off microorganisms by epithelial desquamation, especially in the peri-implant sulcus compartment, and that peri-implantitis is initiated by the adherence of microorganisms, bioactive surfaces represent a very promising approach to prevent the development of peri-implantitis. A special emphasis on the prevention rather than the treatment of peri-implantitis is established since this condition is considered the most challenging biological complication, leading to possible implant loss, and which treatment requires complicated resources in dentistry. Prevention of the disease is therefore a high priority in everyday clinical practice to minimize the occurrence and the severity of the problem (Jepsen et al., 2016).

Studies regarding the use of biofunctionalized dental implants in the prevention of periimplantitis are scarce, and no clinical review has been realized regarding this topic. Therefore, the aim of this review is to address both the role of microbial colonization and peri-implant tissue integration around bioactive implant surfaces. This leads to the question: Are biofunctionalized dental implants effective in the prevention of peri-implantitis?

II-MATERIALS AND METHODS

Research strategy

To conduct this integrative review, the following databases have been searched: PubMed, Medline, Scopus, Cochrane Central Register of Controlled Trials, and Science Direct. The search's algorithm through which the databases were explored consisted of the following Boolean operators: "dental implant" AND "peri-implantitis" AND ("antibacterial" OR "antimicrobial") AND ("bioactive" OR "coating" OR "surface" OR "biofunctionalization" OR "nanoparticles" OR "ions" OR “peptides” OR “antibiotics")

Eligibility criteria

The inclusion and extrusion criteria were the following *(Table 1)*

Intrusion Criteria	Extrusion Criteria

▪ Articles written in English without date restriction ▪ Articles reporting effects of biofunctionalization of titanium surfaces on cell adhesion and/or bacterial contamination ▪ Studies carried *in vivo* and/or *in vitro*	▪ Studies of implants in medical areas other than dentistry. ▪ Studies on implants undergoing peri-implantitis ▪ Studies reporting effects on only osseointegration ▪ Studies reporting on biofunctionalization of surfaces other than titanium ▪ Papers not published in peer-reviewed journals. ▪ Repeated articles in the baseline research

Table 1. Inclusion and Exclusion Criteria

Study selection and data extraction

Two researchers, (LH) and (JP), independently reviewed the titles and abstracts of relevant studies. They eliminated studies that failed to meet the eligibility criteria. Any disagreements between them were resolved through discussion.. Data from selected articles were analyzed and organized according to the authors' names, year of publication, journal, study design, surface features, and surface modification techniques.

Search outcomes and evaluation

Primary outcome measures of interest were reduction of microbial charge or antibacterial activity and tissue adherence around implants (adherence of cells).

III-RESULTS

Study selection

The PRISMA flow chart details the review and the selection process (Fig. 1). By February 2024, a total of 92 papers had been gathered and evaluated by the reviewers. From these, 43 were considered relevant. After complete evaluation of the remaining articles, 23 fulfilled the inclusion criteria and were included in this integrative review: 12 studies were carried *in vitro*, 9 were both *in vitro* and *in vivo* experiments, one was a clinical trial carried on humans, and one tested titanium biofunctionalization in vitro, in vivo and on humans. (Fig.1).

Table 1 provides a general description of the details of each study.

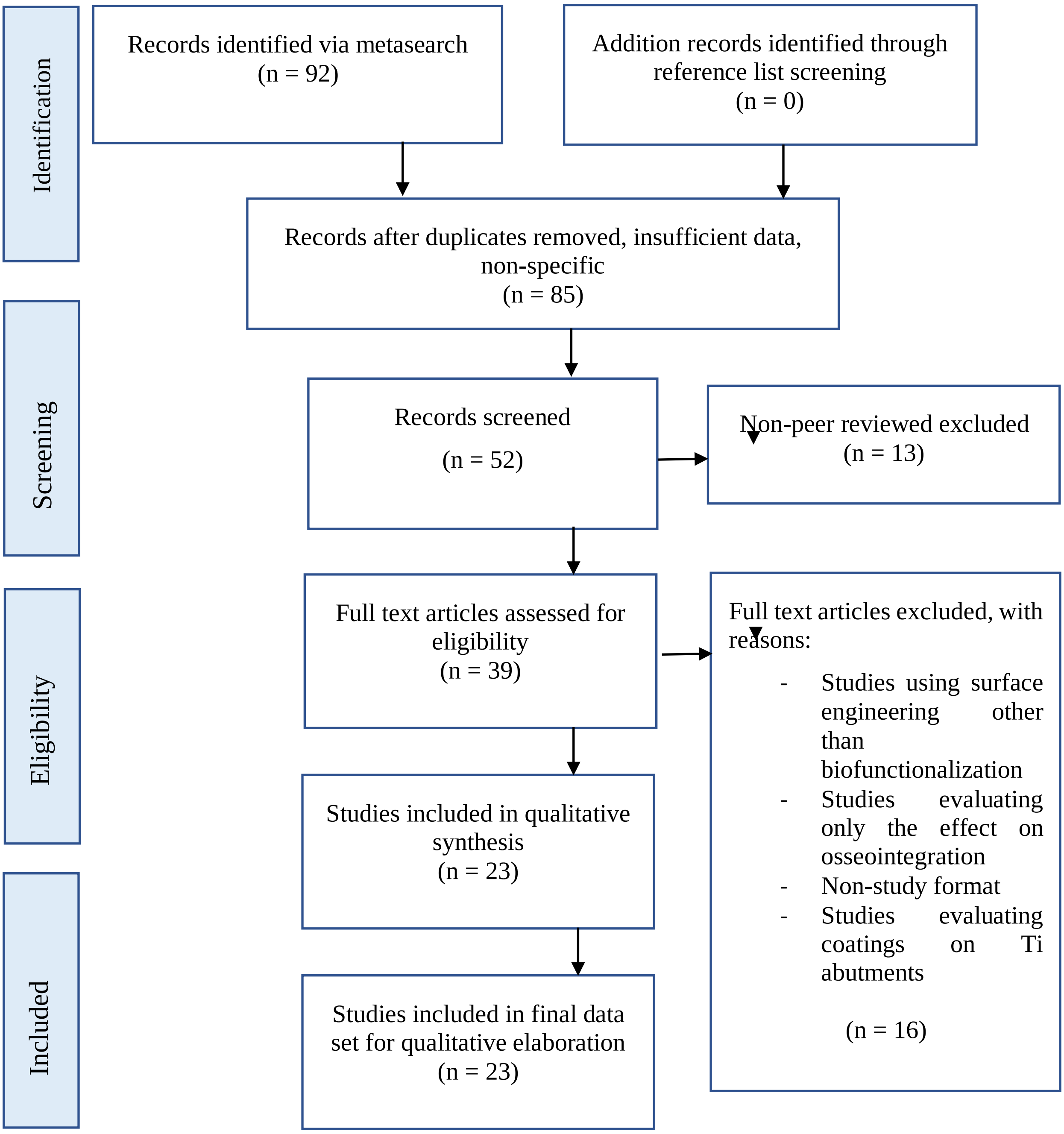


Fig. 1. Flowchart results

Study characteristics (Table 1)

Design of the studies

All the studies included were published between 2015 and 2023. The majority, twelve, were *in vitro* studies (Abdulkareem et al., 2015; Alécio et al., 2019; Choi et al., 2019; Dabbah et al., 2022; El-Telbany and El-Sharaki, 2022; Li et al., 2023a; Mendhi et al., 2021; Pierre et al., 2022; Souza et al., 2020; Wang et al., 2022; Wisdom et al., 2020; Xu et al., 2020); 9 carried out *in vitro* experiments before testing also on animals (Chan et al., 2018a; Cho et al., 2019; Lee et al., 2019; Li and Wang, 2020; Li et al., 2019a; Ma et al., 2023a; Shi et al., 2015; Wen et al., 2023; Zhang et al., 2019). One study was a randomized clinical trial with a parallel design (Carinci et al., 2019) and one carried out experiments *in vitro*, *in vivo* and on humans (Wu et al., 2021). The mean follow-up period ranged from 24h (for *in vitro* studies) to 6 months.

Sample characteristics

The majority of the studies evaluated biofunctionalization on titanium disks. Some studies evaluated mini screw-shaped titanium implants with bioactive surfaces (Chan et al., 2018a; Li and Wang, 2020; Wen et al., 2023; Wu et al., 2021) and 5 studies evaluated standard oral titanium implants (Alécio et al., 2019; Carinci et al., 2019; Cho et al., 2019; Lee et al., 2019; Zhang et al., 2019).

Furthermore, most studies tested bioactive coatings on machined titanium, while some also tested these coatings on modified titanium surfaces such as SLA (sandblasted and acid-etched) surfaces. Some studies compared SLA surfaces to the bioactive surface (Cho et al., 2019; Dabbah et al., 2022; Lee et al., 2019), while others regarded the SLA titanium surface as the standard test surface and applied the bioactive coatings on the SLA modified surface (Li et al., 2019b; Ma et al., 2023a; Zhang et al., 2019).

To evaluate the action of biofunctionalized titanium in the prevention of peri-implantitis, the majority of studies resorted to incubation of samples in peri-implantitis related pathogens. Hence the antimicrobial action of the coatings was tested against *Porphyromonas gingivalis* in 10 studies (Choi et al., 2019; Dabbah et al., 2022; Li and

Wang, 2020; Li et al., 2023b; Ma et al., 2023a; Pierre et al., 2022; Shi et al., 2015; Wen et al., 2023; Wu et al., 2021; Zhang et al., 2019); against *Fusobacterium nucleatum* (Dabbah et al., 2022; Li et al., 2023b, 2019b; Pierre et al., 2022; Zhang et al., 2019); against *Streptococcus gordonii* (Pierre et al., 2022; Xu et al., 2020); against *Aggregatibacter actinomycetemcomitans* (Pierre et al., 2022; Wang et al., 2022; Wen et al., 2023); against *Streptococcus aureus* (Shi et al., 2015; Wu et al., 2021) ; *Streptococcus sanguinis* (Dabbah et al., 2022; Li et al., 2019b), *Actinomyces naeslundii* (Dabbah et al., 2022; Pierre et al., 2022); and *Streptococcus mutans* (Choi et al., 2019; Ma et al., 2023a; Wang et al., 2022; Wisdom et al., 2020). Incubation with human saliva from volunteers or artifical saliva have also been tested in 3 studies (Abdulkareem et al., 2015; Mendhi et al., 2021; Souza et al., 2020).

One *in vivo* study created a peri-implantitis, ligature-induced, experimental model (Wu et al., 2021), and 2 *in vivo* studies realized subcutaneous implantation (Li et al., 2019a; Ma et al., 2023a).

Regarding the experimental sites *in vivo*, most of the studies chose as implantation site the mandibula (Lee et al., 2019; Wen et al., 2023; Wu et al., 2021; Zhang et al., 2019), some also implanted in the femur (Chan et al., 2018a; Li and Wang, 2020), and in the tibia (Cho et al., 2019).

The parameters/outcomes taken into account to evaluate the effectiveness of titanium's biofunctionalization in the prevention of peri-implantitis were:

-antibacterial activity properties, surface contamination and biofilm formation

-tissue adherence and cellular response

Treatment modalities

Several types of biofunctionalization have been used by the authors.

Nanomaterials have been evaluated by Li et al. 2020 (Graphene Oxide), and Wu et al. 2021 (Porous N-halamine polymer) (Li and Wang, 2020; Wu et al., 2021).

The majority of the studies assessed metallic ions and nanoparticles: Silver was studied by (Choi et al., 2019; El-Telbany and El-Sharaki, 2022; Wang et al., 2022). Copper was evaluated in 5 studies ((Dabbah et al., 2022; Li et al., 2023b; Ma et al., 2023a; Mendhi et al., 2021; Pierre et al., 2022). Zinc was studied by (Abdulkareem et al., 2015; Dabbah et al., 2022; Wen et al., 2023). And Zhang et al. evaluated Tantalum, while Xue Li et al., Ceria (Li et al., 2019b; Zhang et al., 2019).

Peptides were also used to create bioactive surfaces by Cho et al. 2019 (VnP-16 and Scrambled peptide SP), Wisdom et al. 2020 (Fluorescein 5(6)-isothiocyanate bifunctional peptides), and Shi et al. 2015 (CS-(HA-AMPCol) (Cho et al., 2019; Shi et al., 2015; Wisdom et al., 2020).

Only one study evaluated the biofunctionalization with antibiotics, they incorporated doxycycline in the implants' surface (Alécio et al., 2019).

Furthermore, 2 studies used antiseptics: Carinci et al. 2019 (chlorhexidine), and Xu et al. 2020 (Totarol) (Carinci et al., 2019; Xu et al., 2020).

Finally, anti-adhesive coatings have also been tested: Lee et al. 2019 (hydroxyapatite), Chan et al. 2018 (Bioactive glass fiber reinforced composite), and Souza et al. 2020 (Superhydrophobic coating with Ar, O2, and hexamethyldisiloxane gases) (Chan et al., 2018a; Lee et al., 2019; Souza et al., 2020).

Study outcomes

Cellular adhesion and Osteogenic property

Ten studies reported a significant difference on overall cellular responses around bioactive titanium coatings. Attachment, spreading, migration and viability of osteoblasts were upregulated in the following studies: (Chan et al., 2018a; Cho et al., 2019; Dabbah et al., 2022; Lee et al., 2019; Li and Wang, 2020; Li et al., 2023b; Ma et al., 2023a; Wen et al., 2023; Wu et al., 2021; Zhang et al., 2019).

On the contrary, some studies found no significant difference regarding cellular behaviour. Wu et al. found no difference in growth and proliferation of MC3T3-E1 preosteoblasts (Wu et al., 2021). There were also no activation of fibroblasts and protein adsorption on the biofunctionalized coating in the study of Xue Li et al. 2019 (Li et al., 2019b). Finally, Souza et al. found the same density of fibroblasts on both titanium surfaces and biofunctionalized titanium surfaces. There was no difference regarding the growth and proliferation of fibroblasts (Souza et al., 2020). However, in spite of the lack of significant effect, it was proven in these study that these coatings did not present any cytotoxic aspect.

Antibacterial activity and Microbiological changes

Eighteen studies examined the impact of titanium's biofunctionalization on peri-implantitis related microorganisms. All of them revealed a positive and significant antibacterial activity of bioactive coatings.

For instance, an increased reduction regarding red, orange and purple complex bacteria including *Aa*, *Pg*, *Fn,* but also primary colonizer such as *S. gordonii*, was obtained with biofunctionalization. Furthermore, biofilm thickness was also reduced in the studies of Abdulkareem et al. 2015, Souza et al. 2020 and Mendhi et al. 2021(Abdulkareem et al., 2015; Mendhi et al., 2021; Souza et al., 2020).

Interestingly, there was also a shift of microbiological profile of biofilms formed, reducing pathogens associated with the peri-implant disease (Souza et al., 2020). Choi et al. demonstrated that the lag phase (of the bacteria's growth curve) for *Streptococcus mutans* and *Porphyromonas gingivalis* changed to exponential phase after 9 and 15 h, respectively, when both bacteria were cultured with uncoated titanium, comparing to microbial colonies cultured with surface-modified titanium (Choi et al., 2019).

Wu et al., with their porous N-halamine polymeric coating on the titanium surface (Ti-PAA-NCl), found that after consumption, their coating regained its antibacterial ability by rechlorination (Wu et al., 2021).

Determining factors inherent to the biofunctionalization methods

Besides the differences in the type of biofunctionalization studied, the protocol of application of these coatings differed between the studies. Thus, there is a variance affecting the antibacterial property, stability of non-cytotoxity and behavior of surrounding cells, that is the method of incorporation of the bioactive substances.
For instance, Li et al. used the hydrothermal method to incorporate copper ions while Pierre et al. resorted to electrodeposition followed by ionic exchange for the anchoring of copper (Li et al., 2023b; Pierre et al., 2022). Ma et al. employed plasma immersion ion implantation and deposition (PIII &D) to produce Mg/Cu- PIII Ti surfaces (Ma et al., 2023b), and Mendhi et al. used simple dip coating technique to incorporate the copper (Mendhi et al., 2021).

Regarding silver embedding, Choi et al. immersed the PDA-coated titanium in silver nitrate solutions, in contrast to Wang et al., where the authors charged a mesoporous bioactive glass film system with different concentrations of silver (Choi et al., 2019; Wang et al., 2022).

Zinc was also incorporated with different techniques in each study: electrohydrodynamic deposition (Abdulkareem et al., 2015), sonochemical method (Dabbah et al., 2022), and TiO2 nanotubes (TNTs) used as carriers to load bioactive substances (Wen et al., 2023).

Another example can be shown with the studies of Wisdom et al. and Shi et al., where Wisdom et al. accomplished titanium implant disc functionalization with bifunctional peptides by incubation, while Shi et al. used the layer-by-layer technique for the antimicrobial peptide assembly (Shi et al., 2015; Wisdom et al., 2020).

Polymeric coatings were used in the study of Wu et al. to incorporate nanoparticles, on the other hand they were used by Alécio et al. to load them with doxycycline (Alécio et al., 2019; Wu et al., 2021).

Disinfectants like totarol were applied with the spin coating process (Xu et al., 2020), whereas for chlorhexidine implantation centrifugation on a sintered glass filter and subsequent heating were used in the study of Carinci et al. (Carinci et al., 2019).

Different protocols were also used to create anti-adhesive coatings: Souza et al. created their superhydrophobic coating by the glow discharge plasma using Ar, O2, and hexamethyldisiloxane gases (Souza et al., 2020). On the other hand, Chan et al. used polymerization of a novel bioactive glass fiber reinforced composite (GFRC) (Chan et al., 2018b).

Finally, the technique of ultrasonic atomization spraying technique was used to create the SLA/Graphene Oxide surface (Li and Wang, 2020), and sputtering was employed for the deposition of tantalum in the study of Zhang et al. (Zhang et al., 2019).

Table 1 : Characteristics of the included studies

Study Journal Region	Type of study M&M	**Bioactive surface** *Surface treatment & Type of biofunctionalization*	Cell adhesion activity	Antibacterial activity	Follow-up	Findings
Abdulkareem et al. 2015 *J Dent.* Iraq	*In vitro study* Smooth machined Ti discs (5 mm x2 mm). Using human saliva as an inoculum, biofilms were grown on coated discs for 96 h with artificial saliva and peri-implant sulcular fluid.	Metal oxide nanoparticles of zinc oxide (nZnO), hydroxyapatite (nHA) and a combination of 50% nZnO+ 50% nHA) were coated using electrohydrodynamic deposition. *Metal nanoparticles*		Viability assays and biofilm thickness measurements were used to assess antimicrobial activity.	96h	Following 96 h, reduced numbers of facultatively anaerobic and *Streptococcus spp.* on all nano-coated surfaces were demonstrated. The proportion of non-viable microorganisms was shown to be higher on nZnO and composite (nZnO+nHA) coated surfaces at 96 h compared with nHA coated and uncoated titanium. Biofilm thickness comparison also demonstrated that nZnO and composite coatings to be the most effective The findings support the use of coating Ti dental implant surfaces with nZnO to provide an antimicrobial function. The use of metal oxide nanoparticles to coat implants could provide osteoconductive and antimicrobial functionalities to prevent failure.
Alécio et al. 2019 *J Oral Implantol* USA	*In vitro study* Nine dental implants with titanium nanotube surface (DINS) at different pHs to examine drug loading.	Polylactic-co-glycolic acid (PLGA) coating loaded with doxycycline *Antibiotics*	Cytotoxicity of the DINS was evaluated by an assay using 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT).	High-performance liquid chromatography (HPLC) was used to measure the amounts of released doxycycline in a 30-day period.	30 days	The results showed that the experimental DINS coated with doxycycline and PLGA showed a mean drug release during the experimental period for the groups pH 7.4 (8.39 g/mL), pH 6.4 (8.63 g/mL); and, pH 5.4 (15.18 l/mL). Doxycycline release from DINS was faster at pH 5.4 than those at pHs 6.4 and 7.4 (p= 0.0031 and 0.0034 respectively). This new surface treatment of dental implants with titanium nanotubes and subsequent drug loading demonstrated biocompatibility and sustained doxycycline

					release over a 30-day period.
Chan et al. 2018 *Dent Materials* Taiwan	*In-vitro and in-vivo animal experimental study* *In vitro:* Control: Ti6Al4V disks (10x2mm) Test: Bioactive GFRC disks *In vivo:* Animals: New Zealand white rabbit model. Implantation site: Femur Control: screw-shaped implants (3.5 mm x 6mm) manufactured using a computer numerical control (CNC) milling machine without any additional surface modifications. Test: GFRC implants	Novel bioactive glass fiber reinforced composite (GFRC) *Anti-adhesive coatings*	Compare three new bioactive glass fiber reinforced composite (GFRC) implants to metal (Ti6Al4V) implants in terms of osseointegration and biocompatibility. *In vitro* biological performance was assessed using MG-63 human osteoblast-like cell morphology, cell proliferation assays and the alkaline phosphatase (ALP) activity testing. *In vivo* osseointegration performance was examined using micro-CT, histology and histomorphometrical analysis Surface morphology, surface roughness and water droplet contact angle, were also assessed.		MG-63 (human osteoblast-like cell morphology) grew well with a different morphology when cultured on any of the GFRC substrates as opposed to cells grown on Ti6Al4V substrate. GFRC implants appear to improve osteogenesis and osseointegration and may replace Ti6Al4V or other metal-based implants.

Cho et al. 2019 *Materials* Switzerland	*In vitro and in vivo animal experimental study* *In vitro:* Control: Ti disks of commercially pure grade 4 prepared with polishing sandpaper. Test: Discs with SLA surface. One group of the SLA discs was left untreated, another was treated with a scrambled peptide (SP; 10.5 μg/cm^2), and the other was treated with VnP-16 (10.5 μg/cm^2). *In vivo:* Animals: New Zealand white rabbit model. Implantation site: Tibia Control: 4 implants without any surface modification (turned surface) Test: 4 implants with SLA surface (Deep Implant System, Seongnam, Korea). 4 implants treated with SP. 4 implants treated with VnP-16 (1.0 mg/cm2).	A human vitronectin-derived peptide, VnP-16 and Scrambled peptide SP *Bactericidal Bioactive Peptides*	Analyze the *in vivo* early bone reaction to the VnP-16-treated SLA titanium surface. Additionally, in vitro experiments with osteoblast- like cells were carried out. Cellular responses, such as attachment, spreading, migration, and viability of human osteoblast-like HOS and MG63 cells were evaluated *in vitro* on the titanium discs.		2 weeks	When applied to the SLA surface, VnP-16 strengthens the osteogenic potential of a titanium dental implant. VnP-16 was non-cytotoxic and promoted attachment and spreading of the human osteoblast-like cells. VnP-16 would further reinforce the osteogenic potential of the SLA surface. These results support that VnP-16 is functionally active in promoting osteoblastic responses (attachment and migration). The VnP-16-treated SLA implants showed no antigenic activities at the interfaces between the bones and the implants and indicated excellent bone-to-implant contact ratios, the means of which were significantly higher than those in the SP-treated implants.

Choi et al. 2019 *Appl Biomater Funct Mater* Korea	*In vitro study* Group control: Pure Ti plates (10 × 10 × 1.5 mm) Group tests: PDA-coated Ti with silver nitrate concentrations of 5 g/L (Ag5) and 50 g/L (Ag50).	Silver-loaded polydopamine coating *Metal ions*		Microbial growth inhibition and microbial growth curve analyses for bacterial solutions of *Streptococcus mutans* and *Porphyromonas gingivalis* incubated with the specimens were evaluated by counting the numbers of colonies on agar solid medium and by measuring absorbance using enzyme-linked immunosorbent assay reader.		The numbers of microbial colonies for both bacteria cultured with surface-modified titanium were significantly lower than those cultured with uncoated titanium. When *Streptococcus mutans* and *Porphyromonas gingivalis* were cultured with surface-modified titanium, the lag phase of the growth curves for both bacteria was continually maintained, whereas the lag phase for *Streptococcus mutans* and *Porphyromonas gingivalis* changed to exponential phase after 9 and 15 h, respectively, when both bacteria were cultured with uncoated titanium. The growth curve of bacteria can generally be divided into four phases: the lag phase, the exponential phase, the stationary phase, and the death phase. The lag phase is the period when bacteria adapt to a new environment. The Ti specimens coated with PDA and silver inhibited the metabolism of *S. mutans* and *P. gingivalis* by retarding the progress to the exponential phase from the lag phase. In conclusion, the coating of polydopamine and silver on the surface of titanium effectively retards the microbial growth, which can cause the formation of biofilm and pathogenesis of peri-implantitis.
Carinci et al. 2019 *Int J Mol Sci.* Italy	Randomized Clinical trial A total of 15 healthy patients (60 implants) All patients' candidates were scheduled to receive bilateral fixed prosthesis supported by implant fixture.	CHX (chlorhexidine gluconate at 1%) internal coating *Antiseptic*		The aim is to investigate the bacterial quality of the antibacterial coating of the internal chamber of the implant at six months. Three real-time PCR runs were performed for each sample. The first reaction quantified the total amount of bacteria. The	6 months	The mean of total bacteria loading (TBL) detected in each PCR reaction was lower in treated implants compared to untreated implants ($p < 0.01$). The polymeric chlorhexidine coating of the internal chamber of the implant showed the ability to control the bacterial loading at the level of the peri-implant tissue, with a continuous release of CHX. The investigation demonstrated that the coating is able to

	PIXIT implant (Edierre srl, Genova Italy) with a coating of alcoholic solution containing polysiloxane oligomers and chlorhexidine gluconate at 1%. The coating of the internal chamber of the implants was produced by filling with the PIXIT solution. The coating of abutment, healing cups, and screws was obtained by immersion in PIXIT solution.			second reaction detected and quantified the three red complex bacteria, i.e., *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, in a multiplex PCR. The third reaction detected and quantified two members of the orange complex *Fusobacterium nucleatum* and *Campylobacter rectus* and a member of purple complex *Aggregatibacter actinomycetemcomitans*.		influence also the quality of the microbiota, in particular on the species involved in the pathogenesis of peri-implantitis. Similar results were obtained when amounts of a single bacterial specie was investigated: *Corinebacterium rectus* (p = 0.006) and *Fusobacterium nucleatum* (Z =p = 0.001)
Dabbah et al. 2022 *Materials (Basel)* Israel	*In vitro study* Group 1: Ti (Ti 6AI-4V) discs (5 mm x 1 mm) machined Group 2: sandblasted discs Group 3: sandblasted + acid-etched (SLA) disks Group 4: machined surface discs coated with ZnCuO nanoparticles Group 5: Hydroxyapatite discs.	ZnCuO nanoparticle coating *Metal nanoparticles*	Osteoblast-like and macrophage-like cells grown on the various discs for 48 h were examined for proliferation using an XTT assay, and for activity using ALP and TNF-α assays.	Multispecies biofilm composed of *Streptococcus sanguinis*, *Actinomyces naeslundii*, *Porphyromonas gingivalis*, and *Fusobacterium nucleatum* were inoculated on disc samples. Bacterial species were quantified with qPCR, and their viability was examined via confocal microscopy.	Biofilms grown for 14 days 48h for osteoblasts	The Confocal Laser Scanning Microscopy (CSLM) revealed more dead bacteria in biofilms grown on titanium than on hydroxyapatite, and less on sandblasted than on machined and ZnCuO-coated surfaces, with the latter showing a significant decrease in all four biofilm species. The osteoblast-like cells showed increased proliferation on all of the titanium surfaces, with higher activity on the ZnCuO-coated and sandblasted discs. The macrophage-like cells showed higher proliferation on the hydroxyapatite and sandblasted discs, and lower activity on the SLA and ZnCuO-coated discs. The ZnCuO-coated titanium has anti-biofilm characteristics with desired effects on host cells, thus representing a promising candidate in the complex battle against peri-implantitis.

El-Telbany et al. 2022 *J Oral Biol Craniofac Res* Egypt	*In vitro study* Ti Disks 3 *pseudomonas aeruginosa* isolates were obtained from 30 samples from patients with peri-implantitis, with gingival inflammations around implant. Susceptibility of isolated *p. aeruginosa* to 16 antibiotics was evaluated using the VITEK 2 system	Silver nanoparticles *Metal nanoparticles*		Estimation of the biological potential of AgNPs against pseudomonas strains was carried out by disk diffusion method. Antibiofilm activity of AgNPs was determined by microtiter plate assay.		Current study showed that the AgNPs can increasingly inhibit the growth of *p. aeruginosa* involved in dental plaque biofilms This finding suggests the potential application of AgNPs to prevent the pathogenesis of infections caused by multi-drug resistance (MDR) *p. aeruginosa*.
Lee et al. 2019 *J Periodontal Implant Sci* Korea	*In vitro and in vivo animal experimental study* Animals: Beagle dogs Implantation site: Mandibula 3 groups of implants (3.5x8mm) with different surfaces: -6 implants with hydrophobic SLA surface implant (IS-III Active®, Neobiotech, Seoul, Korea; self-tapping, surface roughness [Ra]=approximately 3.5 µm; contact angle=109.2°) -6 implants with hydrophilic SLA surface implant with HA nanocoating (IS-III Bioactive®, Neobiotech; self-tapping, Ra=approximately 3.5 µm; contact angle=approximately 4°)	Hydroxyapatite nanocoating *Anti-adhesive coatings*	Mineralized BIC (mBIC), osteoid-to-implant contact (OIC), total BIC (tBIC), mineralized bone area fraction occupied (mBAFO), osteoid area fraction occupied (OAFO), and total bone area fraction occupied (tBAFO) were measured in the threads at the region of interest (ROI)		2, 4, 12 weeks	Implant surface wettability facilitates bone healing dynamics. There is an upregulation of osteoblastic activity in the remodeling phase, which might last for a long period on HA-coated implant surfaces, compared with hydrophobic surfaces.

	-6 implants with hydrophilic SLA surface implant stored in sodium chloride solution (bone level SLActive®, Straumann, Basel, Switzerland; non-self-tapping, Ra=approximately 1.8 µm; contact angle=0°					
Li et al. 2020 *Int J Nanomedicine* China	*In vitro and in vivo experimental study* Control group: SLA surface on pure titanium substrates (10x10x1 mm) of grade IV. Test group: nano-GO deposited on the SLA surface via an ultrasonic atomization spraying technique to create the SLA/GO group. *In vivo:* Animals: SD rats Implantation site: Femur Microimplants (2.2x3.5 mm) with SLA or SLA/GO surfaces.	Bioactive Graphene Oxide (GO) coating *Nanoparticles*	Make a bioactive Graphene Oxide (GO)-modified titanium implant surface with osteoinductive potential, and look into the underlying biological processes. Their effects on rat bone marrow mesenchymal stem cells (BMSCs) responsive behaviors were assessed *in vitro*, and the underlying biological mechanisms were further systematically investigated. Moreover, the osteogenesis performance *in vivo* was also evaluated.		2, 4 and 6 weeks	GO-modified titanium implant compared to SLA: -Improve hydrophilicity and protein adsorption capabilities -Better cell adhesion and spreading -Enhanced osteogenic differentiation and cell proliferation of BMSCs. -FAK/P38 signaling pathways seem involved, accompanied by an upregulated expression of vinculin -Accelerated osseointegration and osteogenesis when inserted into rat femurs. Rapid bone-implant integration may be possible by using GO modification on titanium implant surfaces. It exerts a positive influence on the bone regeneration and bone-implant integration.
Li et al. 2023 *Front Bioeng Biotechnol* China	*In vitro* Grade 1 pure Ti plates (1×1×0.1 cm^3 and 2×2×0.1 cm^3)	Antibacterial copper coating *Metal ions*	Cell adhesion and morphology observation with immunofluorescence microscopy. The cell proliferation activity of the BMMSCs seeded on each	*Fusobacterium nucleatum* Gram-negative bacteria) and *Porphyromonas gingivalis* (Pg, Gram-positive bacteria) were utilized to test the antimicrobial activity of each sample against	14 days	Bone marrow mesenchymal stem cells (BMMSCs) on the coating displayed enhanced cellular mineral deposition ability, higher alkaline phosphatase activity, and upregulated expression of osteogenic-related markers (OCN, OPN,

	BMMSCs derived from Wistar rats were isolated and cultured according to previously published procedures (Wu et al, 2022).		sample was tested by MTT metabolic assay. The potential activity of osteogenic differentiation of BMMSCs (bone marrow mesenchymal stem cells) seeded on implant surface, mineral deposition assay, alkaline phosphate (ALP) activity, and real-time quantitative polymerase chain reaction (RT-qPCR) assays were performed.	oral pathogens. SEM were used to evaluate anti-oral pathogens ability of the prepared Cu- TiO2 coating. For fluorescence staining, the viability of bacteria (Fn and Pg) on samples was investigated using a LIVE/DEAD BaclightTM Bacterial Viability Kit. The samples were also examined with a confocal laser scanning microscope.		and BMP-2) without the addition of osteoinductive chemical factors, which improved osseointegration. This coating also reduced the viability of oral pathogens (*Fusobacterium nucleatum* and *Porphyromonas gingivalis*). These findings suggest that biofunctionalization of the implant coating by surface modification methods and the incorporation of antibacterial copper (Cu) offer superior osteogenesis capability and effective antibacterial activity. The surface of Ti after PEO (plasma electrolytic oxidation) treatment presented a rough and porous topography—with numerous micron- sized holes distributed uniformly. The surface of Cu-TiO2 became more hydrophilic than that of TiO2 after the hydrothermal treatment. Thus, the coating provides cytocompatibility, osteoinduction, and antibacterial properties.
Ma et al. 2023 *Colloids Surf B Biointerfaces* China	*In vitro* and *in vivo experimental study* *In vitro* Commercial disks of pure SLA Ti (10 mm × 10 mm × 1 mm) and (16 mm × 16 mm × 1 mm) In vivo Animals: Sprague-Dawley rats Implantation site: subcutaneous pocket.	Plasma immersion coimplantation of Mg and Cu ions *Metal ions*	Surface roughness, corrosion resistance and surface wettability have been tested. Also, protein absorption ability and hemo/cytocompatibility were assessed.	The activity against periimplantitis-causing bacteria, namely *Streptococcus mutans* and *Porphyromonas gingivalis* was assessed. Reactive oxygen species release (ROS) was also evaluated.	24h in vitro 4 weeks in vivo	The best-performing sample Mg/Cu-Ti promoted cell proliferation and initial cell adhesion while exhibiting high hydrophilicity, excellent activity against the tested pathogens, and good bio-/hemocompatibility. Additionally, higher levels of cellular ROS generation in *S. mutans* and *P. gingivalis* could provide insight into the antibacterial mechanisms involved in Mg/Cu-Ti. In conclusion, Mg/Cu coimplantation renders the Ti surface highly bacteriostatic and biocompatible, promising a wide range of use of biofunctionalized Ti-based dental implants.
Mendhi et al. 2021	*In vitro*	Polydopamine copper coating		The effectiveness of coated surfaces on biofilms were	24h and	PDAM@Cu coating with NO (Nitric Oxide) generating property was found to

Mater Sci Eng C Mater Biol Appl. Australia	Coated squares of commercial titanium (Ti) (1 cm × 1 cm)	(PDAM@Cu) *Metal ions*		assessed using four different methods: crystal violet assay, scanning electron microscopy imaging, metabolic assay, and live/dead staining. ROS was used to detect NO (nitric oxide) generation from interaction of the Cu from the coating with blood. Biofilms were prepared with three different mixtures, one of which was saliva only, the second had an addition of sheep's blood, and the third was prepared with NO donors S-nitrosoglutathione (GSNO) and L-glutathione (GSH).	48h	reduce *in vitro* salivary biofilm formation, metabolic activity, viability, thickness, and attachment. This dual copper coating has a dual functionality of significant dispersal and reduction of biofilms. Indeed, Nitric Oxide (NO) generation, which can be modulated via polydopamine coatings, causes biofilm dispersal. The copper present in the coating allows killing of previously dispersed bacteria from the biofilm. In conclusion, PDAM@Cu coatings with NO generating surfaces have a dual anti-biofilm function, with a synergistic effect on biofilm dispersal from regulated NO generation and bactericidal effects from Cu ions from the coatings. This approach can be translated into the prevention of peri-implantitis. PS: In the the group with saliva alone, which had no potential of NO release, there was no significant difference between the uncoated and PDAM@Cu coated samples. The reason for this could be that the antimicrobial action of copper alone is not sufficient for a complex multispecies biofilm.
Pierre et al. 2023 *J Funct Biomater* France	*In vitro* Ti disks (diameter 6mm) of commercially pure grade 4 titanium. The machined samples were sandblasted with alumina particles and acid-etched. + Artificial jawbone (to test the	Copper-Doped Calcium Phosphate Coatings *Metal ions*		Colony-forming units (CFUs) were determined for Gram positive (*Streptococcus gordonii Actinomyces naeslundii Parvimonas micra*) and Gram negative bacteria (*Fusobacterium nucleatum Aggregatibacter actinomycetemcomitans Prevotella intermedia Porphyromonas gingivalis*),	1 and 2 weeks	Copper-doped CaP coatings have shown an antibiofilm effect against the bacterial strains encountered in peri-implantitis for primary to secondary colonizers without a noticeable dose effect, indicating that the lower copper incorporation rate (11%) in the CaP coating is sufficient to impair the implant colonization without being cytotoxic. This study demonstrates that combining the electrodeposition and ionic exchange

	mechanical stability of the coating after electrodeposition)			evaluating also the macroscopic and microscopic morphologies.		processes appears as a promising route to producing antibacterial CaP-coated titanium dental implants with tunable thickness and copper doping.
Shi et al. 2015 *Sci Rep* China	*In vitro* and *in vivo experimental study* Titanium plates (10 × 10 × 1 mm) *In vivo* Animals: Inbred male BALB/c mice Mice were intraperitoneally injected with AMPCol (2.5 mg/kg/day) or AMP (2.5 mg/kg/day) for 4 weeks (7 days/week).	Solutions of chitosan (CS) (5 mg/ml) in 0.2% acetic acid, hyaluronic acid (HA) (0.5 mg/ml) in distilled water, and AMPCol solution (1 mg/ml) were used sequentially for this LBL technique. *Peptides*	*In vivo* immunotoxicity assay Cell cytotoxicity (erythrocyte hemolysis and serum immunoglobulin levels) was evaluated	Two different types of bacteria were cultured to determine antimicrobial activity. *S. aureus*, a Gram-positive aerobe, and *P. gingivalis*, a Gram-negative anaerobe	1 month	This coating with controlled release of AMP (antimicrobial peptides) decreased the growth of both Gram-positive aerobe *Staphylococcus aureus* and Gram-negative anaerobe *Porphyromonas gingivalis* up to one month. Early *S. aureus* biofilm formation was inhibited by the thicker multilayer coatings, specifically CS-(HA-AMPCol)7 and CS-(HA-AMPCol)10. The excellent long-term sustained antimicrobial activity of this multilayer coating is a potential method for preventing peri-implantitis through coating on the neck of implants before surgery.
Souza et al. 2020 *ACS Appl. Mater Interfaces* Brazil	*In vitro* study Commercially pure Ti discs (8 mm / 10 mm / 15 mm in diameter)	Superhydrophobic coating on Ti created by the glow discharge plasma using Ar, O2, and hexamethyldisiloxane gases *Antiadhesive coating*	To study if this coating affects fibroblast growth and proliferation. Cell morphology was assessed by SEM. The electrochemical stability of the coating was also studied.	To study the polymicrobial adhesion and biofilm formation on this coating. Fresh stimulated human saliva from 5 volunteers was used as a microbial inoculum to mimic the human oral microbiome. Fungal adhesion on the superhydrophobic surface was tested using *Candida albicans*, the main oral fungal opportunistic pathogen that is frequently associated with oral bacteria on implanted materials.	4 days	The newly developed coating presented an increased surface roughness and, consequently, superhydrophobicity (contact angle over 150°) and enhanced corrosion resistance ($p < 0.05$) of the Ti surface. Furthermore, proteomic analysis showed a unique pattern of protein adsorption on the superhydrophobic coating without completely changing the biologic processes mediated by proteins. Superhydrophobic treatment did not present a cytotoxic effect on fibroblasts or reduction of proliferation; however, it significantly reduced (≈8-fold change) polymicrobial adhesion (bacterial and

				In addition, because extracellular polymers synthesized by *Streptococcus* species in biofilms can improve microbial adhesion, the evaluation of whether bacteria were able to produce these polymers to overcome the anti-biofilm property of the super-hydrophobic coating, was tested.		fungal) and biofilm formation *in vitro*. Interestingly, superhydrophobic coating shifted the microbiological profile of biofilms formed *in situ* in the oral cavity, reducing by up to ≈7 fold pathogens associated with the peri-implant disease. Hence it changed the pathogenic potential of biofilms formed in the oral cavity. In conclusion, this new superhydrophobic coating developed by a one-step glow discharge plasma technique is a promising biocompatible strategy to drastically reduce microbial adhesion and biofilm formation on Ti-based biomedical implants. Superhydrophobic coating also improved the corrosion resistance of Ti.
Wang et al. 2022 *Int J Mol Sci* Taiwan	*In vitro study* Ti implant discs MBG-Ag-coated Ti (diameter 15mm)	80SiO2-15CaO-5P2O5 Mesoporous Bioactive Glass film system containing 1, 5, and 10 mol% of silver *Metal ions*	Wettability and adhesion strength of the films were evaluated using contact angle measurements and adhesion strength tests.	The antibacterial ability of the coating was evaluated studying the early colonizing bacteria *Aggregatibacter actinomycetemcomitans* and *Streptococcus mutans*, with different Ag compositions.	24h	From the contact angle measurement results, it was found that MBG–Ag–coated Ti could convert the hydrophobic properties of the surface of the filmless titanium implant into a hydrophilic surface. The adhesion strength test results revealed that the adhesion strength decreased with increasing silver content. The *in vitro* bioactivity test showed MBG-Ag-coated Ti to have good mineralization ability and biocompatibility. After the disk diffusion test, it was found that MBG-Ag-coated Ti exhibited significant antibacterial activity against both *Aggregatibacter actinomycetemcomitans* and *Streptococcus mutans*. These results suggest new strategies for the surface functionalization of titanium implants with silver-containing mesoporous bioactive glass. Such implant functionalization may be promising for the prevention and treatment of early implant

						failure and peri-implantitis, considering the potential of MBG–Ag for the controlled release of bioactive and antibacterial agents. Next-generation implants made of SLA Ti infiltrated with mesoporous SiO2 did not seem to compromise the osseointegration process.
Wen et al. 2023 *ACS Appl Mater Interfaces* China	*In vitro* and *In vivo experimental study* *In vitro* Ti disks (10 mm × 10 mm × 1 mm) *In vivo* Animals: Sprague-Dawley rats Implantation site: immediate bilateral implantation after tooth extraction. Oral implants (1.6 mm × 3.5 mm) 4 groups for the *in vitro* and *in vivo* experiments: -Pure titanium (Ti) -Mesoporous TiO2 coating-titanium (MTC-Ti) -ZnO nanoparticle-loaded-titanium (nZnO-Ti) -ZnO nanoparticle-loaded mesoporous TiO2 coating-titanium (nZnO/MTC-Ti). The samples of the 4 types of oral implants were contaminated with *Porphyromonas gingivalis* at a density of 104/ml prior to	ZnO nanoparticle-loaded mesoporous TiO2 coatings *Metal ions*	Cell adhesion assay and cell proliferation measurements using a fluorescence microscope were evaluated. PCR analysis of the relative mRNA expression of osteogenic genes, and immunofluorescence analysis of Osteocalcin and Osteopontin were carried out.	*Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans* were used to estimate the bacteriostatic activity of the various samples against oral pathogens.	24h in vitro 8 weeks in vivo	The increased extracellular Zn2+ further promoted a favorable intracellular zinc ion microenvironment through the modulation of zinc transporters (ZIP1 and ZnT1). As a consequence, the adhesion, proliferation, and osteogenic activity of bone mesenchymal stem cells (BMSCs) were improved. Additionally, nZnO/MTC-Ti inhibited the proliferation of oral pathogens (Pg and Aa) by inducing bacterial ROS production. For *in vivo* experiments, the nZnO/MTC-Ti implants were found to possess a higher capability for enhancing bone regeneration, antibiosis, and osseointegration. These findings suggested the remarkable performance of nZnO/MTC-Ti implants in accelerating osseointegration and inhibiting bacterial infection, indicating a huge potential for solving immediate/early loading risks and peri-implantitis of dental implants.

	implantation.					
Wisdom et al. 2020 *ACS Biomater Sci Eng* USA	*In vitro study* Ti grade IV disks (10 x 0.5mm)	FITC-labeled bifunctional peptides (Fluorescein 5(6)-isothiocyanate) TiBP-AMPA and TiBP-GL13K (titanium binding peptides (TiBP) *Peptides*		Following incubation with *Streptococcus mutans*, the disks were imaged with a fluorescent microscope to visualize FTIC-labeled bifunctional peptides on the disc surface after bacterial challenge. The dead bacteria were stained with propidium iodide and imaged using a fluorescent microscope. The aim was to evaluate antimicrobial activity, extent of film coverage and binding, binding under competition from an interloper contaminant, and mechanical durability within clinically relevant parameters needed by dentists to treat peri-implant disease.	24h	These bifunctional peptides achieved : -nearly 100% surface coverage within minutes -nearly 100% binding to a titanium surface even in the presence of contaminating serum protein -durability to brushing with a commercially available electric toothbrush -retention of antimicrobial activity on the implant surface following bacterial challenge. The bifunctional peptide film can be applied applied in 2 min and can be repeated at follow up appointments to both new implants and/or repeatedly applied to previously placed implants to control bacterial colonization, mimicking the re-treatment of implants affected by peri-implant disease in a dental office. The peptide films have been shown capable of rebinding ability through up to five cycles of bacterial fouling, cleaning and reapplication. These results suggest that the TiBP-AMPA peptide has strong potential as a treatment for peri-implant disease due to its ability mitigate bacterial biofilm formation.
Wu et al. 2021 *Nat Commun.* China	*In vitro and in vivo experimental study* Ti disks (9.5x0.3mm) Animals: New Zealand white rabbits Implantation site: Mandible	Porous N-halamine polymeric coating on the titanium surface (Ti-PAA-NCl),	The newly formed bone surrounding implants was evaluated via Van Gieson's staining after implantation for 4 weeks Biocompatibility assessments consisted of studying the proliferations of preosteoblasts on	*Antibacterial activity assessments :* The antibacterial effect of Ti-PAA-NCl was evaluated with aerobe *S. aureus*, and anaerobe *P. gingivalis*. *Long-lasting and renewable*	4, 8, 12 weeks	N-halamine polymeric coating (functionalized by N-Cl) on titanium surface has long-lasting renewable antibacterial efficacy with good stability and biocompatibility. This coating is a powerful bactericidal against both main pathogenic bacteria of peri-implant infection and complex bacteria from peri-implantitis patients. Its antibacterial

Group test: 2 mini-implants with Ti-OH into the edentulous area of the left mandible Group control: 2 mini-implants with Ti-PAA-NCl surfaces into the edentulous area of the right mandible. The rabbit model of ligature-induced peri-implantitis was built after 4 weeks of osseointegration: *After gingiva above implants was cut, non-absorbable silk ligatures were tied firmly around the neck of implants, pressed into gingival groove along the apical direction and left an end in the oral cavity to induce bacterial accumulation. Oral cleaning was stopped, and ligatures were replaced every 2 weeks and finally removed after 8 weeks. Then, implants underwent a re-osseointegration progress to detect the long-lasting antibacterial effect against peri- implantitis.* Assessment of long-lasting and renewable *in vivo* antibacterial effect against human bacterial colonies : 8 volunteers for 4 weeks and 3 volunteers for 12 weeks. For each volunteer, 2 titanium disks (3x0.2 mm) with Ti-PAA-NCl surfaces were	*Nanoparticles*	Ti-OH and Ti-PAA-NCl. Fluorescent staining was carried out to detect cell adhesion on coatings. The osteogenic abilities of the preosteoblasts on coatings were evaluated by ALP activity and calcium content as well as expression levels of osteogenic proteins and genes. To analyse the osseointegration effect, the rabbits were sacrificed after implantation for 4 weeks, and the mandibles were retrieved. After the successful induction of peri-implantitis (confirmed by micro CT), ligatures were removed for re-osseointegration for 4 weeks, the bone height and BV/TV surrounding Ti-PAA- NCl implants have almost risen to the original level of osseointegration, while those surrounding Ti-OH implants remain at a relatively low level, although with slight improvement. In addition to radiographic analysis, biomechanical evaluation was also conducted to quantitatively detect the bonding force between implant and bone.	*antibacterial effect assessments :* The long-lasting antibacterial abilities were evaluated using *P. gingivalis* through two methods. After Ti-OH and Ti-PAA-NCl samples were incubated with Pg for different durations (0, 2, 4, 6, 8, 10 and 12 weeks), adhered bacteria were detached by ultrasonification. The cyclic antibacterial effect of Ti-OH and Ti-PAA-NCl samples was tested by immersion of Pg for 24h before proceeding to ultrasonication. After disinfecting with 75% ethanol for 24 h, samples were resubjected to antibacterial test until the 27th cycle. After storing in PBS for 12 weeks or the 27th cycle of antibacterial test, samples were regenerated in 10% NaOCl. Bacteria were collected from peri-implant pockets of patients with peri-implantitis. To evaluate the long-lasting antibacterial and anti-biofilm effect, for each volunteer, one Ti-OH disk and one Ti-PAA-NCl disk were taken out after 4 or 12 weeks, and stained with LIVE/DEAD BacLight Bacterial Viability Kit, followed by confocal observation of 2D and 3D morphologies. To estimate the renewable	efficacy can persist for a long term (12~16 weeks) *in vitro*, in animal model, and even in human oral cavity. Additionally, after consumption, it can regain its antibacterial ability by facile rechlorination, highlighting a valuable concept of renewable antibacterial coating in dental implant. These findings indicate an appealing application prospect for prevention and treatment of peri-implant infection.

	bonded on the middle-third of buccal surfaces of upper and lower first molars, respectively, on one side (right or left) based on randomization, while 2 titanium disks (3x0.2 mm) with Ti-OH surfaces were bonded on the same sites of the opposite side as the control group. Volunteers continued their daily lives as usual, such as eating, tooth brushing etc…			antibacterial effect, at both 4-week and 12-week, the remaining disks (one Ti-OH disk and one Ti-PAA-NCl disk) in the mouth were irrigated with NaOCl solution (5%) for 15 min and pure water for another 5 min with rubber dam technique, and were taken out after 48 h to do the same detections.		
Xu et al. 2020 *Mater Sci Eng C Mater Biol Appl* Germany	*In vitro study* Ti disks grade IV (1 cm x 1cm x 1mm) Bacterial suspension *S. gordonii* strain DL1 Ti disks coated with 20 mg/ml ethyl acetate dissolved totarol were incubated with *S. gordonii* in the stirring system. Samples were harvested after 4 h, 8 h, and 24 h of incubation (each group, n = 6) Dynamic biofilm formation model system to simulate the oral clinical situation.	Totarol antibacterial coating *Antiseptic*		To analyze the antibacterial effect of totarol coatings of different concentrations towards the oral primary colonizer *S. gordonii* and isolates of mixed oral bacteria. The stability and antibacterial efficiency of totarol coating was evaluated through SEM. Minimal inhibitory concentration (MIC) of totarol towards *S. gordonii* MIC of totarol towards S. gordonii was 16 μg/ml.	4 d, 8 d, 12 d, 16 d, and 24 d	The results indicated that totarol coatings on both silicon wafer and Ti surfaces caused efficient contact killing and an inhibition effect towards *S. gordonii* and mixed oral bacterial film growth after 4 h, 8 h, 24 h, and 48 h incubation. After longtime salivary incubation of 12 d, the bactericidal effect started to weaken, but the anti-adhesion and inhibition effect to biofilm development still exist after 24 d of salivary incubation. *P. gingivalis*, one of the main potential pathogens involved in peri-implantitis, colonizes subsequently to the pioneer colonizer S. gordonii, which itself specifically binds to salivary pellicle. This colonization plays an essential role in developing a pathogenic plaque. According to these results, towards S. gordonii, totarol shows significant bactericidal effects. This effect might interfere with the colonization of *P. gingivalis* on *S. gordonii* films, and thus inhibit the pathogenic plaque formation by disturbing its primary stage. Totarol coating appeared bactericidal and

						with an anti-adhesion function for at least 2 weeks, which could postpone and inhibit the bacterial colonization and biofilm growing process and subsequently offer a better condition for soft tissue attachment on the implant surface.
Xue Li et al. 2019 *Acta Biomater.* China	*In vitro and In vivo experimental study* Ti disks grade IV (10x2mm) Four different surfaces of Ti were fabricated: -Control group: pure Ti disks without coating ("Ti control") -Nanorod CeO2 group: Ti surface modified by nanorod CeO2 ("rod-CeO2@Ti") -Nanocube CeO2 group: Ti surface modified by nanocube CeO2 ("cube-CeO2@Ti") -Nano-octahedra CeO2 group: Ti surface modified by nano-octahedra CeO2 (denoted "octa-CeO2@Ti") Subcutaneous implantation models were created in 4-week-old male Wistar rats (Center area of the back)	Ceria coating *Metal ions*	Evaluation the different CeO2-modified surfaces on cell inflammatory response *in vitro* and *in vivo:* - Human gingival fibroblasts were used to assess the cytocompatibility of CeO2-modified Ti substrates at 24, 48 and 72 h. -Protein adsorption -Expression of inflammatory factors in acute and chronic cell models in vitro -Inhibition of LPS-induced NF-kB activation in macrophages -Histomorphometric and immunofluorescence (IF) analyses *in vivo*	Investigation and comparaison of the inhibition efficacy of different shapes of CeO2-modified surfaces against biofilms of peri-implantitis-related pathogens: *Streptococcus sanguinis, Porphyromonas gingivalis* and *Fusobacterium nucleatum.* -Early attachment of *S. sanguinis* and *F. nucleatum* on Ti disks - Formation of single-species biofilm on Ti disks - Live/dead fluorescent staining -CFU counts of periodontal biofilm on Ti	3 and 6 weeks	The results showed that nanorod CeO2-modified Ti had more bacteria attachment of *Streptococcus sanguinis* in the early stage, compared with other CeO2-modified Ti ($p < 0.05$). They all exhibited similarly substantial CFU reductions against peri-implantitis-related biofilms. Nanocube and nano-octahedron CeO2-modified Ti exerted much better anti- inflammatory effects and ROS-scavenging ability than nanorod CeO2 *in vitro* ($p < 0.05$). *In vivo*, the mean mRNA expression of TNF-a, IL-6 and IL-1b in the tissues around Ti was decreased by the three shapes of nano-CeO2; nano-octahedron CeO2 showed the strongest anti-inflammatory effect among all groups ($p < 0.05$). In conclusion, all three types of CeO2-modified Ti exerted equally strong antibacterial properties; nano-octahedron CeO2-modified Ti had the best anti-inflammatory effect. Therefore, CeO2-modified Ti surfaces are highly promising for enhancing antimicrobial functions for dental implants. Novel nano-octahedron CeO2 coating on Ti had great therapeutic potential for alleviating and eliminating peri-implantitis.
Zhang et al. 2019	*In vitro and in vivo animal experimental study*	Tantalum	Examination of the *in vivo* biocompatibility and	Examination of the antibacterial activity of titanium (Ti) implants	60 days	Ta-modified surfaces demonstrated excellent antimicrobial activity against

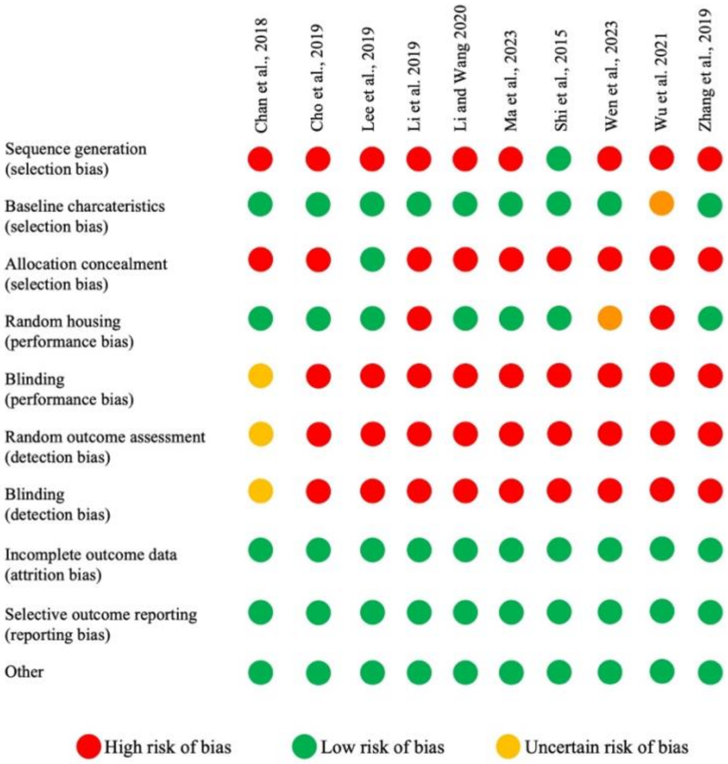
Int J Nanomedicine China	Animals: Beagle dogs Implantation site: Mandibula Commercial pure Ti discs (15 mm x 1 mm) and Ti implants (3.3 mm x 10 mm) of grade IV with SLA (sand-blasted, large-gritted, acid- etched) surfaces were prepared. Ta was implanted onto the SLA Ti disk by magnetron-sputtering technique.	*Metal ions*	osseointegration activity with MicroCT analysis, histological analysis, and immunohistochemical analysis of osteogenic proteins, including COL1 and OCN.	modified with Tantalum (Ta) against peri- implantitis-related microbes and possible molecular mechanisms : *Fusobacterium nucleatum* and *Porphyromonas gingivalis*.	of bacterial incubation	*Porphyromonas gingivalis* and *Fusobacterium nucleatum.* The incorporation of Ta and the Ti base may result in the formation of micro galvanic, which could consume protons and reduce ATP synthesis while increasing ROS (reactive oxygen species). Bacterial virulence factors linked to cellular attachment, invasion, and viability had their gene expression downregulated. Ta modification significantly aided implant osseointegration by increasing the expression of proteins. *In vivo* biological studies showed that Ta modification significantly promoted the osseointegration of implants by stimulating the expression of bone-forming proteins.

Quality assessment of the included studies

To assess the quality of the evidence provided in the studies selected for this integrative review, both authors (LH and JP) have independently used the criteria made available by the Cochrane Collaboration's tool, ROB 2.0, "Risk of bias in randomized trials" ("RoB 2: A revised Cochrane risk-of-bias tool for randomized trials | Cochrane Bias," n.d.), for the randomized clinical study included (Carinci et al., 2019). In this study, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment and selective reporting, were at low risk of bias.

For animal studies, the criteria made available by SYRCLE (Systematic Review Centre for Laboratory Animal Experimentation) were followed (Hooijmans et al., 2014). SYRCLE presents an ROB tool but for animal intervention studies, and it contains 10 entries related to selection bias, performance bias, and detection bias among others. For each domain, low, high or uncertain (i.e., when insufficient information exists) risk of bias was assigned (Fig 1). Among the *in vivo* studies, no article met the random sequence generation domain, and neither the blinding of researchers.

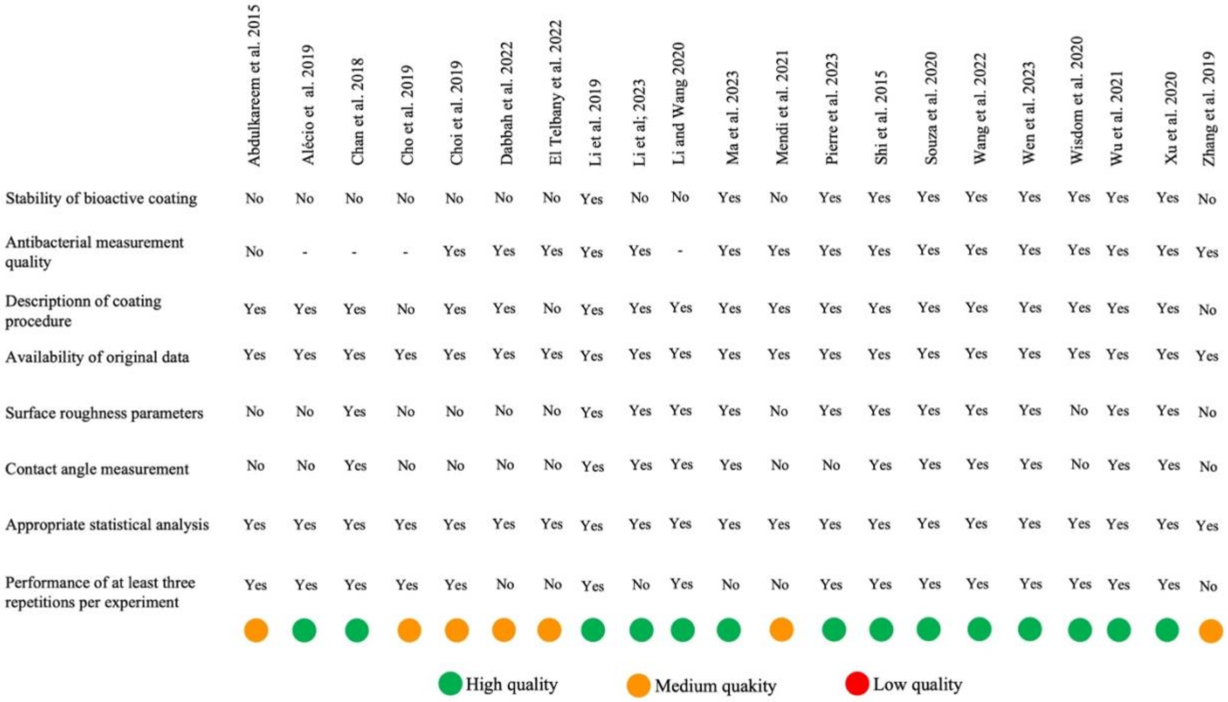
For *in vitro* studies, to our knowledge, there is no standard assessment tool to evaluate their risk of biases. Thus, the criteria used by Wehner et al. were adapted (Tran et al., 2021; Wehner et al., 2020). The evaluation was based on the reporting of criteria such as: stability of the bioactive coating, description of the coating procedure, and surface roughness parameters. The 8 entries of this tool are also shown in figure 2. The articles were then rated as of low, medium or high quality. Six articles were considered to be of medium quality, mainly for not reporting the wettability and surface's characteristics of the coating (Fig 2).



	Chan et al., 2018	Cho et al., 2019	Lee et al., 2019	Li et al. 2019	Li and Wang 2020	Ma et al., 2023	Shi et al., 2015	Wen et al., 2023	Wu et al. 2021	Zhang et al., 2019
Sequence generation (selection bias)	🔴	🔴	🔴	🔴	🔴	🔴	🟢	🔴	🔴	🔴
Baseline charcateristics (selection bias)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟠	🟢
Allocation concealment (selection bias)	🔴	🔴	🟢	🔴	🔴	🔴	🔴	🔴	🔴	🔴
Random housing (performance bias)	🟢	🟢	🟢	🔴	🟢	🟢	🟢	🟠	🔴	🟢
Blinding (performance bias)	🟡	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴
Random outcome assessment (detection bias)	🟡	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴
Blinding (detection bias)	🟡	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴
Incomplete outcome data (attrition bias)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Selective outcome reporting (reporting bias)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Other	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢

🔴 High risk of bias 🟢 Low risk of bias 🟡 Uncertain risk of bias

Figure 1: SYRCLE risk of bias assessment tool for in vivo studies



	Abdulkareem et al. 2015	Alécio et al. 2019	Chan et al. 2018	Cho et al. 2019	Choi et al. 2019	Dabbah et al. 2022	El Telbany et al. 2022	Li et al. 2019	Li et al; 2023	Li and Wang 2020	Ma et al. 2023	Mendi et al. 2021	Pierre et al. 2023	Shi et al. 2015	Souza et al. 2020	Wang et al. 2022	Wen et al. 2023	Wisdom et al. 2020	Wu et al. 2021	Xu et al. 2020	Zhang et al. 2019
Stability of bioactive coating	No	No	No	No	No	No	No	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Antibacterial measurement quality	No	-	-	-	Yes	Yes	Yes	Yes	Yes	-	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Descriptionn of coating procedure	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Availability of original data	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Surface roughness parameters	No	No	Yes	No	No	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Contact angle measurement	No	No	Yes	No	No	No	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Appropriate statistical analysis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Performance of at least three repetitions per experiment	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
	🟠	🟢	🟢	🟠	🟠	🟠	🟠	🟢	🟢	🟢	🟢	🟠	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟠

🟢 High quality 🟠 Medium quakity 🔴 Low quality

Figure 2: Risk of bias assessment tool for in vitro studies

IV-DISCUSSION

Peri-implantitis is defined by an inflammation of the peri-implant tissues due to biofilm accumulation accompanied by bone loss around the implant. In spite of the well-established etiology, there is still no consensus about the best clinical protocol to control microbial accumulation on dental implant surfaces and treat peri-implant disease. Indeed, therapy for peri-implantitis is often complex, including nonsurgical and surgical phases, necessitating sometimes the removal of the implant. Which is why the focus has shifted towards the prevention of this disease, hence looking into enhancing bone contact to implant, improving the adherence of the peri-implant soft tissue attachment, as well as improving anti-bacterial properties of the surface implant.

Titanium is still regarded as the biomaterial of choice in oral implantology with its adequate mechanical and biological properties, however its antimicrobial activity is insufficient to avoid bacterial colonization. Consequently, microbial infection remains the major cause of implant loss (de Avila et al., 2020).

Several implant surface modifications have been already tested, since it has been demonstrated that implant surface and wettability can change the behavior of surrounding cells (Albrektsson and Wennerberg, 2019). Microscopic roughness for instance, can adsorb more proteins, consequently facilitating adhesion of osteoblasts. At the microscopic level, two surface modifications are most common: the sandblasted large-grit acid-etched (SLA) Ti surface, and the anodically oxidized Ti surface.

Recently, some researches have shown that surface treatment at the nano-level increases the surface’s hydrophilicity, hence promoting osseointegration (Kligman et al., 2021).
Finally, recent research has also shown that functionalizing titanium surfaces in a biomimetic manner, at both the micro- and nanoscales, combines positive effects (Yeo, 2019).

Biofunctionalization or bioactive surfaces of the dental implant, have been evaluated with regards to osseointegration. In the systematic review of Lopez-Valverde et al., 30 studies were included, and all animal studies reported better bone-to-implant contact surface for bioactive surfaces as compared to control implants with a statistical significance (López-Valverde et al., 2020). Subsequently, the role played by these bioactive substances on the prevention of peri-implantitis was tested in several trials. The aim of this review was to gather information about the effect of biofunctionalization on the adherence of peri-implant cells and on peri-implantitis-related bacteria. No systematic review could be made with the large discrepancy present between the studies. To our knowledge, this is the first integrative review treating this topic.

In the majority of the studies included in this review, the authors have tested peri-implantitis related pathogens. Gram-negative periodontal pathogens (*Porphyromonas gingivalis, Prevotella intermedia/ Prevotella nigrescens,* and *Actinobacillus actinomycetemcomitans*) are generally the main bacteria behind peri-implant inflammation (Lafaurie et al., 2017). Hence, authors researched antimicrobial properties against Gram-negative pathogens mainly, with *Porphyromonas gingivalis* being the most frequently investigated. Furthermore, *Staphylococcus aureus* has been associated with bleeding upon probing and suppuration in peri-implant diseases, likely due to its relatively high level of adhesiveness to titanium surfaces (Renvert et al., 2008). *S. aureus* is also a multi-drug resistant bacteria such as methicillin-resistant (MRSA), explaining why Wu et al. and Shi et al. investigated the effect of bioactive coatings on this microorganism (Shi et al., 2015; Wu et al., 2021).

Numerous types of bioactive substances were evaluated in the gathered studies. Metal ions and nanoparticles were the most widely investigated, such as Silver, Copper, Zinc, Tantalum and Cerium.

Silver ions and nanoparticles have shown a strong antibacterial spectrum, with several hypotheses explaining their strong activity (Wang et al., 2022): silver ions enter bacterial cells and interfere with the ATP synthesis reaction of the bacterial cell membrane, inhibiting bacterial growth. Nano-silver particles directly cause the destruction of the bacteria's outer membrane. They also produce reactive oxygen species (ROS) which are bactericidal (Esteves et al., 2022). El telbany et al. showed in their study that AgNPs could increasingly inhibit the growth of *P. aeruginosa* involved in dental plaque biofilms. Choi et al. used a silver-loaded polydomamine coating which inhibited the metabolism of

S. mutans and *P. gingivalis,* which retarded the microbial growth. Wang et al. tested Mesoporous Bioactive Glass film system containing 1, 5, and 10 mol% of silver. Their coating (MBG–Ag) could convert the hydrophobic properties of the surface of titanium implant into a hydrophilic surface. It also exhibited significant antibacterial activity against both *Aggregatibacter actinomycetemcomitans* and *Streptococcus mutans*. The thickness of the coating was controlled to be less than than 20 µm, which could avoid cracks and peeling due to too thick film (Wang et al., 2022). Indeed, while the upside of metal ions and nanoparticles are their long antimicrobial effect and flexibility (ability to be paired with other coatings to promote both osseointegration and anti-fouling properties), the major downside is their potential cytotoxicity (Esteves et al., 2022). For example, in the trials using Copper or Zinc, although the results were efficient in preventing peri-implantitis, previous tests had to be made to insure no cytotoxic effect of the bioactive substances on bone marrow mesenchymal stem cells and gingival fibroblasts (Mendhi et al., 2021). Wu et al. 2014 established that the concentrations of copper ranging from 1 nM to 1 µM showed no significant cytotoxic effect. Furthermore, excessive ZnONPs might impair cellular behaviors, including proliferation and osteogenic differentiation, which is why, according to their previous studies, Wen et al. used 1.0 wt %. of zinc oxide (Wen et al., 2023).

Two studies evaluated the use of antimicrobial peptides (AMP). AMP are short cationids, interesting for their broad spectrum, low cytotoxicity, low propensity to develop antibiotic resistance, and their possession of both antibacterial and osseointegration properties. Cho et al. demonstrated in their study that the peptide VnP-16 promoted osteoblastic responses (Cho et al., 2019). In the study of Wisdom et al., a bifunctional peptide film showed ability to mitigate bacterial biofilm formation. Interestingly, it could be applied in two minutes and be repeatedly applied to previously placed implants to control bacterial colonization, mimicking the re-treatment of implants affected by peri-implant disease in a dental office (Wisdom et al. 2020). Up to this point, the major inconvenient of AMP is their complex structure, which leads to a high cost of fabrication, a debatable stability and lifespan (Asensio et al., 2019).

Biofunctionalization with antibiotics was tested in one study: Alécio et al. tested the controlled release of doxycycline by a Polylactic-co-glycolic acid (PLGA) coating. In their experiment, they measured the mean drug release over a 30-days period, with regards to the environmental pH. The results showed that the doxycycline released with Ti nanotubes was at a higher concentration at a lower pH, which could have been due to the faster dissolution of the PLGA coated layer in an acidic environment. The latter simulates the presence of an infection. However, additional studies are needed in order to adopt a stable drug release at neutral pH environment while warranting a constant drug release in an acidic pH environment (Alécio et al., 2019). Also, no infection model with oral pathogens was tested with this coating in their study.

Carinci et al. studied a polymeric coating trapping chlorhexidine in the internal chamber of the implant, which showed the ability to control the bacterial loading at the level of the peri-implant tissue. Moreover, the investigation demonstrated that the coating is able to influence also the quality of the microbiota, in particular on the species involved in the pathogenesis of peri-implantitis (Carinci et al., 2019). Another disinfectant, totarol, a natural antibacterial agent was the subject of another study. The authors found that totarol coating was bactericidal and with an anti-adhesion function for at least 2 weeks, which could postpone and inhibit the bacterial colonization and biofilm growing process and subsequently offer a better condition for soft tissue attachment on the implant surface. The coating was tested against *S. gordonii*, a pioneer colonizer to which subsequently *P. gingivalis* attaches (Xu et al., 2020).

Anti-adhesive coatings were investigated as well. Souza et al. tested a superhydrophobic coating, which shifted the microbiological profile of biofilms formed *in situ* in the oral cavity, reducing by up to ≈7-fold pathogens associated with the peri-implant disease. Although a high hydrophobicity can negatively affect fibroblast adhesion force, this was counteracted by high surface roughness, which favors cell adhesion. This superhydrophobic coating appeared to be biocompatible, allowing adequate colonization and proliferation of fibroblasts (Souza et al., 2020).

With regards to the manufacturing processes of these coatings, a large discrepancy between studies was encountered. As previously mentioned, several surface engineering methods were used, such as dip coating, hydrothermal methods, plasma immersion, electrodeposition, TiO2 nanotubes, ultrasonic atomization, polymeric coatings, and layer by layer technique. The best strategy regarding surface modification would be combining the contact-killing effect by incorporating an antimicrobial molecule, with a sustained release of the immobilized bactericidal substance, to prevent the pathogen from reaching the surface (Oirschot et al., 2022).

Dipping or soaking a functionalized implant into an anti-bacterial substance solution is the simplest method, however it lacks solid binding. Traditional TiO2 nanotubes (TNTs) have been used as carriers to load bioactive substances, however the downside of this technique is the poor control of initial drug release along with the short duration of actuation. Compared with TNTs, mesoporous structures can more effectively control the release of loading components through the loading amount, release rates, and duration time. The latter was used by Wang et al., where the authors charged a mesoporous bioactive glass film system with different concentrations of silver (Wang et al., 2022).

It is worth noting too that some techniques may alter the surface's hardness, such as the plasma immersion ion implantation and deposition (PIII &D), however these alterations have been found insignificant (Ma et al., 2023b).

Loaded composite coatings were employed as well; they seem to be good candidates for long-term safe and consistent antibacterial ion release, together with very low cytotoxicity threat (Wen et al., 2023). Finally, the layer-by-layer assembly technique (LBL) seems quite attractive due to its versality and prolonged delivery rate. In fact, it is possible to change the number of layers to control the desired film thickness. Hence, following degradation of each layer, the antimicrobial agent can be released continuously at a sustained level over time (Shi et al., 2015).

There were very few researches that used human trials, the majority were *in vitro* and *in vivo* studies, which is due in part to the potential cytotoxicity of bioactive substances. Their optimal concentration is still being investigated which renders their clinical translation limited. Consequently, there is a need in extensive investigation in more accurate peri-implantitis models, simulating the onset and development of human peri-implantitis (Chen et al., 2021).

In the systematic review of López-Valverde et al. the authors concluded that due to the high risk of bias in the majority of the studies, it is challenging to draw conclusions on such bioactive modifications of dental implants in terms of osseointegration (López-Valverde et al., 2020).

Reducing the possibility of bias in the research is important in order to establish the impact of bioactive and biofunctionalized surfaces on the surrounding peri-implant tissues and microorganisms and to provide scientific data that might assist clinical dentistry practice. Also, a common assessment and evaluation should be set in order to reduce results' heterogeneity.

On another note, very few studies evaluated screw thread designed implants, with the majority having tested biofunctionalization on titanium disks. This is a variable that influences the healing process of bone. The implants' macro-design affects the biological and mechanical micro-environment, leading to a differential peri-implant tissue healing response (Vandamme et al., 2021).

Furthermore, besides biofunctionalization of implants' surface to avoid subgingival biofilms, it is also necessary to prevent bacterial colonization at the coronal margin, thus strengthening the peri-implant epithelial sealing. Biofunctionalization titanium abutments would allow the formation of a denser epithelial barrier at the tissue-abutment interface, to fulfill more efficiently its role of protective barrier against bacterial penetration, and subsequently protecting hard tissue from resorption. The antibacterial surface engineering of implants abutments has started to be investigated with yet future studies needed (de Avila et al., 2020).

On another note, using bioactive coatings to prevent peri-implantitis is the first line of action regarding this disease. In the future, this strategy would be proposed to further address the peri-implantitis' treatment. Indeed, while the prevention's strategy is mainly based on antimicrobial coatings to have an effect on microbial adhesion, the proposed mechanism to treat peri-implant diseases would rely on the synergy of an antimicrobial agent, together with an osteoclastogenesis inhibitor (for example an antagonist of RANK, that would bind to RANK-L receptor to inhibit osteoclasts), to succeed in interrupting the bone resorption (de Avila et al., 2020). Future coatings would have to be suitable for debridement protocols and resistant to mechanical treatments.

Biofunctionalization represents also an interesting technology for patients with systemic diseases such as diabetes, cancer, bone metabolic illnesses…It has been shown that titanium implants incorporated with strontium (SLA-Sr) produced better implant osseointegration compared to SLA in diabetic rats (Xu et al., 2020). Peri-implantitis being also host-mediated, incorporating antibacterial and immunomodulatory bioactive agents into titanium surfaces would warrant successful dental implant therapy for those patients.

Future perspectives regarding surface engineering include the use of other surface modifications that are not bioactive. For instance, the use of antisense oligonucleotides (ASOs) seems promising. ASOs are short fragments of a nucleic acid that can be used to interfere biological processes of bacteria, which is helpful against bacterial infections (Esteves et al., 2022).

V- CONCLUSION

The different techniques to biofunctionalize the implant that were assessed in this review seem promising in terms of osseointegration potential and anti-microbial properties. By combining micro and nanoscale modification and functionalization with protein, peptides, and bioactive compounds, titanium implant surface wettability and bioactivity have been improved. Such morphological and chemical alteration of titanium surfaces speeds up the osseointegration process, which is the primary concern regarding implantology, followed by successful control of bacterial accumulation, main etiologic factor of peri-implantitis. Incorporating bioactive molecules into nanostructured surfaces seem to be a promising way to prevent early and late implant failures due to biofilms accumulation.

In accordance with the articles reviewed in this review, the anti-peri-implantitis functionality of bioactive surfaces is effective and promising. Biofunctionalization showed ability to control bacterial loading.

However, the effectiveness and success of such techniques still needs to be validated through long term clinical trials, to ensure their long-term durability and capacity to prevent chronic peri-implantitis diseases.

REFERENCES

Abdulkareem, E.H., Memarzadeh, K., Allaker, R.P., Huang, J., Pratten, J., Spratt, D., 2015. Anti-biofilm activity of zinc oxide and hydroxyapatite nanoparticles as dental implant coating materials. J. Dent. 43, 1462–1469. https://doi.org/10.1016/j.jdent.2015.10.010

Aggarwal, D., Kumar, V., Sharma, S., 2022. Drug-loaded biomaterials for orthopedic applications: A review. J. Control. Release Off. J. Control. Release Soc. 344, 113–133. https://doi.org/10.1016/j.jconrel.2022.02.029

Albrektsson, T., Wennerberg, A., 2019. On osseointegration in relation to implant surfaces. Clin. Implant Dent. Relat. Res. 21 Suppl 1, 4–7. https://doi.org/10.1111/cid.12742

Alécio, A.B.W., Ferreira, C.F., Babu, J., Shokuhfar, T., Jo, S., Magini, R., Garcia-Godoy, F., 2019. Doxycycline Release of Dental Implants With Nanotube Surface, Coated With Poly Lactic-Co-Glycolic Acid for Extended pH-controlled Drug Delivery. J. Oral Implantol. 45, 267–273. https://doi.org/10.1563/aaid-joi-D-18-00069

Asensio, G., Vázquez-Lasa, B., Rojo, L., 2019. Achievements in the Topographic Design of Commercial Titanium Dental Implants: Towards Anti-Peri-Implantitis Surfaces. J. Clin. Med. 8, 1982. https://doi.org/10.3390/jcm8111982

Berglundh, T., Armitage, G., Araujo, M.G., Avila-Ortiz, G., Blanco, J., Camargo, P.M., Chen, S., Cochran, D., Derks, J., Figuero, E., Hämmerle, C.H.F., Heitz-Mayfield, L.J.A., Huynh-Ba, G., Iacono, V., Koo, K.-T., Lambert, F., McCauley, L., Quirynen, M., Renvert, S., Salvi, G.E., Schwarz, F., Tarnow, D., Tomasi, C., Wang, H.-L., Zitzmann, N., 2018. Peri-implant diseases and conditions: Consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J. Clin. Periodontol. 45 Suppl 20, S286–S291. https://doi.org/10.1111/jcpe.12957

Boot, W., Schmid, T., D'Este, M., Guillaume, O., Foster, A., Decosterd, L., Richards, R.G., Eglin, D., Zeiter, S., Moriarty, T.F., 2021. A Hyaluronic Acid Hydrogel Loaded with Gentamicin and Vancomycin Successfully Eradicates Chronic Methicillin-Resistant Staphylococcus aureus Orthopedic Infection in a Sheep Model. Antimicrob. Agents Chemother. 65, e01840-20. https://doi.org/10.1128/AAC.01840-20

Bottino, M.C., Münchow, E.A., Albuquerque, M.T.P., Kamocki, K., Shahi, R., Gregory, R.L., Chu, T.-M.G., Pankajakshan, D., 2017. Tetracycline-incorporated polymer nanofibers as a potential dental implant surface modifier. J. Biomed. Mater. Res. B Appl. Biomater. 105, 2085–2092. https://doi.org/10.1002/jbm.b.33743

Carinci, F., Lauritano, D., Bignozzi, C.A., Pazzi, D., Candotto, V., Santos de Oliveira, P., Scarano, A., 2019. A New Strategy Against Peri-Implantitis: Antibacterial Internal Coating. Int. J. Mol. Sci. 20, 3897. https://doi.org/10.3390/ijms20163897

Chan, Y.-H., Lew, W.-Z., Lu, E., Loretz, T., Lu, L., Lin, C.-T., Feng, S.-W., 2018a. An evaluation of the biocompatibility and osseointegration of novel glass fiber reinforced composite implants: In vitro and in vivo studies. Dent. Mater. Off. Publ. Acad. Dent. Mater. 34, 470–485. https://doi.org/10.1016/j.dental.2017.12.001

Chan, Y.-H., Lew, W.-Z., Lu, E., Loretz, T., Lu, L., Lin, C.-T., Feng, S.-W., 2018b. An evaluation of the biocompatibility and osseointegration of novel glass fiber reinforced composite implants: In vitro and in vivo studies. Dent. Mater. 34, 470–485. https://doi.org/10.1016/j.dental.2017.12.001

Chen, Z., Wang, Z., Qiu, W., Fang, F., 2021. Overview of Antibacterial Strategies of Dental Implant Materials for the Prevention of Peri-Implantitis. Bioconjug. Chem. 32, 627–638. https://doi.org/10.1021/acs.bioconjchem.1c00129

Cheng, H., Li, Y., Huo, K., Gao, B., Xiong, W., 2014. Long-lasting in vivo and in vitro antibacterial ability of nanostructured titania coating incorporated with silver nanoparticles. J. Biomed. Mater. Res. A 102, 3488–3499. https://doi.org/10.1002/jbm.a.35019

Cho, C.-B., Jung, S.Y., Park, C.Y., Kang, H.K., Yeo, I.-S.L., Min, B.-M., 2019. A Vitronectin-Derived Bioactive Peptide Improves Bone Healing Capacity of SLA Titanium Surfaces. Mater. Basel Switz. 12, 3400. https://doi.org/10.3390/ma12203400

Choi, S.-H., Jang, Y.-S., Jang, J.-H., Bae, T.-S., Lee, S.-J., Lee, M.-H., 2019. Enhanced antibacterial activity of titanium by surface modification with polydopamine and silver for dental implant application. J. Appl. Biomater. Funct. Mater. 17, 2280800019847067. https://doi.org/10.1177/2280800019847067

Córdoba, A., Satué, M., Gómez-Florit, M., Hierro-Oliva, M., Petzold, C., Lyngstadaas, S.P., González-Martín, M.L., Monjo, M., Ramis, J.M., 2015. Flavonoid-modified surfaces: multifunctional bioactive biomaterials with osteopromotive, anti-inflammatory, and anti-fibrotic potential. Adv. Healthc. Mater. 4, 540–549. https://doi.org/10.1002/adhm.201400587

Dabbah, K., Perelshtein, I., Gedanken, A., Houri-Haddad, Y., Feuerstein, O., 2022. Effects of a ZnCuO-Nanocoated Ti-6Al-4V Surface on Bacterial and Host Cells. Materials 15, 2514. https://doi.org/10.3390/ma15072514

de Avila, E.D., van Oirschot, B.A., van den Beucken, J.J.J.P., 2020. Biomaterial-based possibilities for managing peri-implantitis. J. Periodontal Res. 55, 165–173. https://doi.org/10.1111/jre.12707

De Cremer, K., Braem, A., Gerits, E., De Brucker, K., Vandamme, K., Martens, J.A., Michiels, J., Vleugels, J., Cammue, B.P., Thevissen, K., 2017. Controlled release of chlorhexidine from a mesoporous silica-containing macroporous titanium dental implant prevents microbial biofilm formation. Eur. Cell. Mater. 33, 13–27. https://doi.org/10.22203/eCM.v033a02

Deporter, D., Pharoah, M., Yeh, S., Todescan, R., Atenafu, E.G., 2014. Performance of titanium alloy sintered porous-surfaced (SPS) implants supporting mandibular overdentures during a 20-year prospective study. Clin. Oral Implants Res. 25, e189-195. https://doi.org/10.1111/clr.12043

El-Telbany, M., El-Sharaki, A., 2022. Antibacterial and anti-biofilm activity of silver nanoparticles on multi-drug resistance pseudomonas aeruginosa isolated from dental-implant. J. Oral Biol. Craniofacial Res. 12, 199–203. https://doi.org/10.1016/j.jobcr.2021.12.002

Esteves, G.M., Esteves, J., Resende, M., Mendes, L., Azevedo, A.S., 2022. Antimicrobial and Antibiofilm Coating of Dental Implants—Past and New Perspectives. Antibiotics 11, 235. https://doi.org/10.3390/antibiotics11020235

Geng, H., Yuan, Y., Adayi, A., Zhang, Xu, Song, X., Gong, L., Zhang, Xi, Gao, P., 2018. Engineered chimeric peptides with antimicrobial and titanium-binding functions to inhibit biofilm formation on Ti implants. Mater. Sci. Eng. C Mater. Biol. Appl. 82, 141–154. https://doi.org/10.1016/j.msec.2017.08.062

Heitz-Mayfield, L.J., Aaboe, M., Araujo, M., Carrión, J.B., Cavalcanti, R., Cionca, N., Cochran, D., Darby, I., Funakoshi, E., Gierthmuehlen, P.C., Hashim, D., Jahangiri, L., Kwon, Y., Lambert, F., Layton, D.M., Lorenzana, E.R., McKenna, G., Mombelli, A., Müller, F., Roccuzzo, M., Salvi, G.E., Schimmel, M., Srinivasan, M., Tomasi, C., Yeo, A., 2018. Group 4 ITI Consensus Report: Risks and biologic complications associated with implant dentistry. Clin. Oral Implants Res. 29 Suppl 16, 351–358. https://doi.org/10.1111/clr.13307

Hooijmans, C.R., Rovers, M.M., de Vries, R.B.M., Leenaars, M., Ritskes-Hoitinga, M., Langendam, M.W., 2014. SYRCLE’s risk of bias tool for animal studies. BMC Med. Res. Methodol. 14, 43. https://doi.org/10.1186/1471-2288-14-43

Jemat, A., Ghazali, M.J., Razali, M., Otsuka, Y., 2015. Surface Modifications and Their Effects on Titanium Dental Implants. BioMed Res. Int. 2015, 791725. https://doi.org/10.1155/2015/791725

Jepsen, K., Jepsen, S., Laine, M.L., Anssari Moin, D., Pilloni, A., Zeza, B., Sanz, M., Ortiz-Vigon, A., Roos-Jansåker, A.M., Renvert, S., 2016. Reconstruction of Peri-implant Osseous Defects: A Multicenter Randomized Trial. J. Dent. Res. 95, 58–66. https://doi.org/10.1177/0022034515610056

Jin, G., Qin, H., Cao, H., Qian, S., Zhao, Y., Peng, X., Zhang, X., Liu, X., Chu, P.K., 2014. Synergistic effects of dual Zn/Ag ion implantation in osteogenic activity and antibacterial ability of titanium. Biomaterials 35, 7699–7713. https://doi.org/10.1016/j.biomaterials.2014.05.074

Kasemo, B., 1983. Biocompatibility of titanium implants: surface science aspects. J. Prosthet. Dent. 49, 832–837. https://doi.org/10.1016/0022-3913(83)90359-1

Kligman, S., Ren, Z., Chung, C.-H., Perillo, M.A., Chang, Y.-C., Koo, H., Zheng, Z., Li, C., 2021. The Impact of Dental Implant Surface Modifications on Osseointegration and Biofilm Formation. J. Clin. Med. 10, 1641. https://doi.org/10.3390/jcm10081641

Lafaurie, G.I., Sabogal, M.A., Castillo, D.M., Rincón, M.V., Gómez, L.A., Lesmes, Y.A., Chambrone, L., 2017. Microbiome and Microbial Biofilm Profiles of Peri-Implantitis: A Systematic Review. J. Periodontol. 88, 1066–1089. https://doi.org/10.1902/jop.2017.170123

Lee, J., Yoo, J.M., Amara, H.B., Lee, Y.-M., Lim, Y.-J., Kim, H., Koo, K.-T., 2019. Bone healing dynamics associated with 3 implants with different surfaces: histologic and histomorphometric analyses in dogs. J. Periodontal Implant Sci. 49, 25–38. https://doi.org/10.5051/jpis.2019.49.1.25

Li, Q., Wang, Z., 2020. Involvement of FAK/P38 Signaling Pathways in Mediating the Enhanced Osteogenesis Induced by Nano-Graphene Oxide Modification on Titanium Implant Surface. Int. J. Nanomedicine 15, 4659–4676. https://doi.org/10.2147/IJN.S245608

Li, R., Li, S., Zhang, Y., Jin, D., Lin, Z., Tao, X., Chen, T., Zheng, L., Zhang, Z., Wu, Q., 2023a. Titanium surfaces with biomimetic topography and copper incorporation to modulate behaviors of stem cells and oral bacteria. Front. Bioeng. Biotechnol. 11, 1223339. https://doi.org/10.3389/fbioe.2023.1223339

Li, R., Li, S., Zhang, Y., Jin, D., Lin, Z., Tao, X., Chen, T., Zheng, L., Zhang, Z., Wu, Q., 2023b. Titanium surfaces with biomimetic topography and copper incorporation to modulate behaviors of stem cells and oral bacteria. Front. Bioeng. Biotechnol. 11, 1223339. https://doi.org/10.3389/fbioe.2023.1223339

Li, X., Qi, M., Sun, X., Weir, M.D., Tay, F.R., Oates, T.W., Dong, B., Zhou, Y., Wang, L., Xu, H.H.K., 2019a. Surface treatments on titanium implants via nanostructured ceria for antibacterial and anti-inflammatory capabilities. Acta Biomater. 94, 627–643. https://doi.org/10.1016/j.actbio.2019.06.023

Li, X., Qi, M., Sun, X., Weir, M.D., Tay, F.R., Oates, T.W., Dong, B., Zhou, Y., Wang, L., Xu, H.H.K., 2019b. Surface treatments on titanium implants via nanostructured ceria for antibacterial and anti-inflammatory capabilities. Acta Biomater. 94, 627–643. https://doi.org/10.1016/j.actbio.2019.06.023

López-Valverde, N., Flores-Fraile, J., Ramírez, J.M., Sousa, B.M. de, Herrero-Hernández, S., López-Valverde, A., 2020. Bioactive Surfaces vs. Conventional Surfaces in Titanium Dental Implants: A Comparative Systematic Review. J. Clin. Med. 9, 2047. https://doi.org/10.3390/jcm9072047

Ma, M., Zhao, M., Deng, H., Liu, Z., Wang, L., Ge, L., 2023a. Facile and versatile strategy for fabrication of highly bacteriostatic and biocompatible SLA-Ti surfaces with the regulation of Mg/Cu coimplantation ratio for dental implant applications. Colloids Surf. B Biointerfaces 223, 113180. https://doi.org/10.1016/j.colsurfb.2023.113180

Ma, M., Zhao, M., Deng, H., Liu, Z., Wang, L., Ge, L., 2023b. Facile and versatile strategy for fabrication of highly bacteriostatic and biocompatible SLA-Ti surfaces with the regulation of Mg/Cu coimplantation ratio for dental implant applications. Colloids Surf. B Biointerfaces 223, 113180. https://doi.org/10.1016/j.colsurfb.2023.113180

Mendhi, J., Ramachandra, S.S., Prasadam, I., Ivanovski, S., Yang, Y., Xiao, Y., 2021. Endogenous nitric oxide-generating surfaces via polydopamine-copper coatings for preventing biofilm dispersal and promoting microbial killing. Mater. Sci. Eng. C 128, 112297. https://doi.org/10.1016/j.msec.2021.112297

Nie, B., Ao, H., Zhou, J., Tang, T., Yue, B., 2016. Biofunctionalization of titanium with bacitracin immobilization shows potential for anti-bacteria, osteogenesis and reduction of macrophage inflammation. Colloids Surf. B Biointerfaces 145, 728–739. https://doi.org/10.1016/j.colsurfb.2016.05.089

Oirschot, B.A.J.A. van, Zhang, Y., Alghamdi, H.S., Cordeiro, J.M., Nagay, B.E., Barao, V.A.R., Avila, E.D. de, Beucken, J.J.J.P. van den, 2022. Surface Engineering for Dental Implantology: Favoring Tissue Responses Along the Implant. Tissue Eng. Part A. https://doi.org/10.1089/ten.tea.2021.0230

Pierre, C., Bertrand, G., Pavy, I., Benhamou, O., Rey, C., Roques, C., Combes, C., 2022. Antibacterial Electrodeposited Copper-Doped Calcium Phosphate Coatings for Dental Implants. J. Funct. Biomater. 14, 20. https://doi.org/10.3390/jfb14010020

Qin, H., Cao, H., Zhao, Y., Jin, G., Cheng, M., Wang, J., Jiang, Y., An, Z., Zhang, X., Liu, X., 2015. Antimicrobial and osteogenic properties of silver-ion-implanted stainless steel.

ACS Appl. Mater. Interfaces 7, 10785–10794. https://doi.org/10.1021/acsami.5b01310
Renvert, S., Lessem, J., Dahlén, G., Renvert, H., Lindahl, C., 2008. Mechanical and Repeated Antimicrobial Therapy Using a Local Drug Delivery System in the Treatment of Peri-Implantitis: A Randomized Clinical Trial. J. Periodontol. 79, 836–844. https://doi.org/10.1902/jop.2008.070347

RoB 2: A revised Cochrane risk-of-bias tool for randomized trials | Cochrane Bias [WWW Document], n.d. URL https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials (accessed 4.9.24).

Roccuzzo, M., Bonino, L., Dalmasso, P., Aglietta, M., 2014. Long-term results of a three arms prospective cohort study on implants in periodontally compromised patients: 10-year data around sandblasted and acid-etched (SLA) surface. Clin. Oral Implants Res. 25, 1105–1112. https://doi.org/10.1111/clr.12227

Rojo, L., Gharibi, B., McLister, R., Meenan, B.J., Deb, S., 2016. Self-assembled monolayers of alendronate on Ti6Al4V alloy surfaces enhance osteogenesis in mesenchymal stem cells. Sci. Rep. 6, 30548. https://doi.org/10.1038/srep30548

Salvi, G.E., Cosgarea, R., Sculean, A., 2017. Prevalence and Mechanisms of Peri-implant Diseases. J. Dent. Res. 96, 31–37. https://doi.org/10.1177/0022034516667484
Schwarz, F., Derks, J., Monje, A., Wang, H.-L., 2018. Peri-implantitis. J. Periodontol. 89 Suppl 1, S267–S290. https://doi.org/10.1002/JPER.16-0350

Shi, J., Liu, Y., Wang, Y., Zhang, J., Zhao, S., Yang, G., 2015. Biological and immunotoxicity evaluation of antimicrobial peptide-loaded coatings using a layer-by-layer process on titanium. Sci. Rep. 5, 16336. https://doi.org/10.1038/srep16336

Simonis, P., Dufour, T., Tenenbaum, H., 2010. Long-term implant survival and success: a 10-16-year follow-up of non-submerged dental implants. Clin. Oral Implants Res. 21, 772–777. https://doi.org/10.1111/j.1600-0501.2010.01912.x

Souza, J.G.S., Bertolini, M., Costa, R.C., Cordeiro, J.M., Nagay, B.E., de Almeida, A.B., Retamal-Valdes, B., Nociti, F.H., Feres, M., Rangel, E.C., Barão, V.A.R., 2020. Targeting Pathogenic Biofilms: Newly Developed Superhydrophobic Coating Favors a Host-Compatible Microbial Profile on the Titanium Surface. ACS Appl. Mater. Interfaces 12, 10118–10129. https://doi.org/10.1021/acsami.9b22741

Tran, L., Tam, D.N.H., Elshafay, A., Dang, T., Hirayama, K., Huy, N.T., 2021. Quality assessment tools used in systematic reviews of in vitro studies: A systematic review. BMC Med. Res. Methodol. 21, 101. https://doi.org/10.1186/s12874-021-01295-w

Vandamme, K., Thevissen, K., Mesquita, M.F., Coropciuc, R.-G., Agbaje, J., Thevissen, P., da Silva, W.J., Vleugels, J., De Cremer, K., Gerits, E., Martens, J.A., Michiels, J., Cammue, B.P.A., Braem, A., 2021. Implant functionalization with mesoporous silica: A promising antibacterial strategy, but does such an implant osseointegrate? Clin. Exp. Dent. Res. 7, 502–511. https://doi.org/10.1002/cre2.389

Wang, Y.-C., Lin, S.-H., Chien, C.-S., Kung, J.-C., Shih, C.-J., 2022. In Vitro Bioactivity and Antibacterial Effects of a Silver-Containing Mesoporous Bioactive Glass Film on the Surface of Titanium Implants. Int. J. Mol. Sci. 23, 9291. https://doi.org/10.3390/ijms23169291

Wehner, C., Lettner, S., Moritz, A., Andrukhov, O., Rausch-Fan, X., 2020. Effect of bisphosphonate treatment of titanium surfaces on alkaline phosphatase activity in osteoblasts: a systematic review and meta-analysis. BMC Oral Health 20, 125. https://doi.org/10.1186/s12903-020-01089-4

Wen, Z., Shi, X., Li, X., Liu, W., Liu, Y., Zhang, R., Yu, Y., Su, J., 2023. Mesoporous TiO2 Coatings Regulate ZnO Nanoparticle Loading and Zn2+ Release on Titanium Dental Implants for Sustained Osteogenic and Antibacterial Activity. ACS Appl. Mater. Interfaces 15, 15235–15249. https://doi.org/10.1021/acsami.3c00812

Wisdom, E.C., Zhou, Y., Chen, C., Tamerler, C., Snead, M.L., 2020. Mitigation of peri-implantitis by rational design of bifunctional peptides with antimicrobial properties. ACS Biomater. Sci. Eng. 6, 2682–2695. https://doi.org/10.1021/acsbiomaterials.9b01213

Wu, S., Xu, J., Zou, L., Luo, S., Yao, R., Zheng, B., Liang, G., Wu, D., Li, Y., 2021. Long-lasting renewable antibacterial porous polymeric coatings enable titanium biomaterials to prevent and treat peri-implant infection. Nat. Commun. 12, 3303. https://doi.org/10.1038/s41467-021-23069-0

Xu, Z., Krajewski, S., Weindl, T., Loeffler, R., Li, P., Han, X., Geis-Gerstorfer, J., Wendel, H.-P., Scheideler, L., Rupp, F., 2020. Application of totarol as natural antibacterial coating on dental implants for prevention of peri-implantitis. Mater. Sci. Eng. C 110, 110701. https://doi.org/10.1016/j.msec.2020.110701

Yeo, I.-S.L., 2019. Modifications of Dental Implant Surfaces at the Micro- and Nano-Level for Enhanced Osseointegration. Mater. Basel Switz. 13, 89. https://doi.org/10.3390/ma13010089

Zhang, W., Wang, S., Ge, S., Chen, J., Ji, P., 2018. The relationship between substrate morphology and biological performances of nano-silver-loaded dopamine coatings on titanium surfaces. R. Soc. Open Sci. 5, 172310. https://doi.org/10.1098/rsos.172310

Zhang, X.-M., Li, Y., Gu, Y.-X., Zhang, C.-N., Lai, H.-C., Shi, J.-Y., 2019. Ta-Coated Titanium Surface With Superior Bacteriostasis And Osseointegration. Int. J. Nanomedicine 14, 8693–8706. https://doi.org/10.2147/IJN.S218640

Zhou, W., Jia, Z., Xiong, P., Yan, J., Li, Y., Li, M., Cheng, Y., Zheng, Y., 2017. Bioinspired and Biomimetic AgNPs/Gentamicin-Embedded Silk Fibroin Coatings for Robust Antibacterial and Osteogenetic Applications. ACS Appl. Mater. Interfaces 9, 25830–25846. https://doi.org/10.1021/acsami.7b06757