

Overview of Nanoparticle Coating of Dental Implants for Enhanced Osseointegration and Antimicrobial Purposes

Feridoun Parnia¹, Javad Yazdani¹, Vahid Javaherzadeh², Solmaz Maleki Dizaj^{3,4}

¹ Faculty of Dentistry, Tabriz University of Medical Sciences, Tabriz, Iran. ² Science and Research Branch, Islamic Azad University, Tabriz, Iran. ³ Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran. ⁴ Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran.

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ABSTRACT - PURPOSE: Nanomaterials are suitable candidates for coating of titanium based (Ti-based) dental implants due to their unique properties. The objective of this article is to summarize the application of nanoparticles as Ti-based implant coating materials in order to control and improve the implant success rate with focus on enhanced osseointegration and antimicrobial purposes. **METHOD:** This review was conducted using electronic databases and MeSH keywords to detect associated scientific literature published in English. **RESULTS:** The reviewed articles exhibited that a significant progress in research has occurred in the case of nanomaterial-based coatings for dental implants. Coating of Ti surfaces with nanoparticles can improve soft tissue integration and osteogenesis that leads to improved fixation of implants. Furthermore, osteoconductive nanoparticles induce a chemical bond with bone to attain good biological fixation for implants. Surface modification of implants using antibacterial properties can also decrease the potential for infection, and certainly, present improve clinical outcomes. **CONCLUSIONS:** Considering the reported success, more clinically and in vivo information on the nanoparticle-based implant coatings will add to the successful application of the device in the clinic.

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INTRODUCTION

Titanium based (Ti-based) materials have been used for dental implants due to their good biocompatibility, commendable mechanical strength and great corrosion resistance (1). Since the earliest reports in 1960s, dental implants have been successfully used for the replacement of dental elements in the treatment of total or partial edentulism with the success rates above 90% (2). However, success rates have been reported to be rather low when treatment failures are calculated based on patients who lost implants, and not based on implants lost by the population in general (2, 3, 4).

Frequent failures in dental implants therapy are related to lack of stability or misfit at the implant-abutment interface (5). Indeed, micro-gap on the interface of two-piece implants with variable fluid flow at this interface (6, 7) leads to the occurrence of bacterial infiltration and inflammatory cells that result in bone loss around this area (8). Some failures

are due to the infection and inflammation that contribute to healing and soft tissue integration (9). The biological fixation of dental implants is named osseointegration and occurs due to the intimacy of bone growth onto implant surfaces after its surgical insertion into the jaw bones. Such a fixation is considered to be a requirement for implant-supported prostheses and their long-term success (10). The properties of bone surroundings extensively influence implant osseointegration and then, affect the shape and contour of the overlying soft tissues and therefore, the esthetic outcome (11). To achieve successful functional and esthetic treatment results, careful consideration of biologic principles of peri-implant soft and hard tissues, as

Corresponding Authors: Javad Yazdani, Faculty of Dentistry, Tabriz University of Medical Sciences, Golgasht Street, Daneshgah Ave., Tabriz, Iran. E-mail: yazdani@tbzmed.ac.ir or Ja_yazdani@yahoo.com Solmaz Maleki Dizaj, Faculty of Pharmacy, Tabriz University of Medical Sciences, Golgasht Street, Daneshgah Ave., Tabriz, Iran. E-mail: Maleki.s@tbzmed.ac.ir.

well as suitable selection of implant type and location are necessary (12). Early bacterial colonization can occur within minutes after implantation by microorganisms associated with periodontitis (12, 13). Microorganisms may grow into this fixture–abutment interface (FAI) micro-gap, which results in a bacterial reservoir, and lead to inflammation of soft tissue facing the fixture–abutment junction (13, 14, 15). Such complication leads to studies on reduction of bacterial penetration by increasing the accuracy and stability of the jointed pieces through fabricating very high precision mechanical parts. Internal conical joints have superior mechanical stability of the I-A interface and have revealed no crest bone loss (5, 16). This has been explained by the stress distribution of the implant's long axis through function. The greater stability of the soft tissues provided by the tapered abutment design and its reduced diameter compared with the platform, as well as lack of abutment micro-mobility by the self-locking feature reduces bacterial leakage at the interface or even prevents it (5, 17). However, *in vitro* bacterial studies at the I-A interface of the implants have attempted to evaluate the actual benefit of mechanical locking of these joints; however, variable results have been obtained in this regard.

Avoidance of implant failures is one of the main reasons for surface modification of Ti-based implant. Due to the interaction of the implant surface with bone and gingival and also, partial exposition of implant to the oral cavity that includes bacteria, fabricating a coating material with both antimicrobial activity and biocompatibility is important and leads to enhancing the probability of implant success (18).

Nanoparticles are ultrafine particles with nano-range dimensions in diameter, and are made from basically any type of biocompatible substance. They can advantageously enhance properties of the material, as compared to its similar bulk material (19, 20, 21). Nanoparticles have been applied to enhance bone incorporation of dental implants (22, 23, 24, 25, 26) that aims to offer practically ideal oral health (27). Nanoparticles have also been used as particle coatings to the dental implant surface to improve soft tissue integration and increase dental implants success. Coating of dental implants by osteoconductive nanomaterials could induce a chemical bond with bone and attain good biological fixation. Bone generation and regenerative potential of these materials can also provide a good condition

to bone formation. It is revealed that coating of bio-inert nanomaterials (e.g., zirconium and aluminium) over Ti implant surfaces may change the physical properties and also, increase the osteogenic potential of implants (28). It has been also reported that some materials (such as titanium nanotubes) are able to increase the density of osteoblast cells on the implant that may lead to better implant stability. Testing the cell–substrate interface is vital for designing a successful implant because of the interaction that occurs between the cells and the biomaterial surface after the implantation (29).

Due to the importance of bacterial attachment to success of a Ti-based implant, surface modification of titanium by coating or adding antibacterial properties of metal nanoparticles can decrease the number of bacteria and can definitely present more beneficial clinical treatments. Indeed, antimicrobial possessing nanoparticles present a way to impart antimicrobial properties to implant surfaces. The small size of these nano-coatings offers the chance to leave the majority of the Ti-based surfaces uncoated and thus, the surface is available for osteoblast colonization and following osseointegration (30).

The objective of this review article is to summarize the application of nanoparticles as Ti-based dental coating materials in order to control and improve the implant success. The search strategy was based on electronic databases. Data regarding nanoparticles, dental failures, dental implants and coating materials, as well as their combinations were collected and subjected to descriptive data analysis. The literature search in electronic databases according to MeSH keywords and their combination “nanoparticles as dental implants coating materials” provided 543 titles. Data screening led to 38 titles, among which 17 papers were relevant to this review. Nanoparticles with antimicrobial activity were the most studied agent for dental implant failures. TiO₂ nanoparticles with ability to increase the density of osteoblast cells, induce osseointegration, and improve antimicrobial effect and bone forming ability are important coatings that can improve osseointegration. Calcium derivative (as nanostructures) and nanocrystalline diamond with bone connection ability can also lead to implant stability and improved osseointegration. The novelty of the work is separation of nanomaterials, as dental coating materials, based on their properties including antimicrobial activity or osseointegration properties or both of them. This paper provides comprehensive

information to readers with respect to recognized nanomaterials (and their properties) associated with dental implants. Searching strategies (inclusion and exclusion criteria) for the review are shown in Figure 1 and Table 1.

NANOPARTICLE COATINGS WITH ANTIMICROBIAL ACTIVITY

Implant surfaces should preferably be designed to support the attachment of target tissue cells as well as to prevent bacterial adhesion. One main strategy to decrease bacterial infiltration is to respectively increase and decrease the antibacterial ability and compatibility of implant surfaces for bacteria in order to limit biofilm formation (31). Zhao et al reviewed the *in vitro* and *in vivo* investigations for antibacterial coatings on Ti-based implants. They concluded that progress is made regarding antibacterial coatings of implants. However, no wide clinical utilization of antibacterial coatings of implants has been reported. Particularly, *in vivo* information about antibacterial coatings is still scarce (32).

Nanotechnology has enabled addition of metals into their nanosize, leading to extreme changes in chemical, physical and optical properties of metals. The metallic nanoparticles are the most promising agents as they show ideal properties such as enhanced antibacterial activity (33). Metallic nanoparticles as dental implant coatings have been reported to be efficient agents to improve the success of implants. It has been also reported that using antimicrobial medicines as nanoparticles-coated Ti can show sustained release pattern and improved antimicrobial efficiency. Some examples of research works on nanoparticles with antimicrobial activity as dental coating materials are described in this section.

Silver nanoparticles

Silver (Ag) has been used since time immemorial in the form of metallic silver, silver nitrate, and silver sulfadiazine for treatment of several bacterial infections (33). Silver ion (Ag⁺) is a strong antibacterial agent with reasonable stability and broad spectrum antimicrobial effects on both gram-positive and gram-negative bacteria. A comparative study of nano-silver, silver nitrate and silver chloride showed that silver nanoparticles showed higher

antibacterial potency than free silver ions (33). According to studies, antibacterial activity of Ag nanoparticles results from damaging of the bacterial cell membrane (34). Some studies also suppose that Ag ions interact with disulfide or sulfhydryl groups of enzymes, resulting in disruption of metabolic processes and finally, the cell death. It has also been known that induction of gaps in the bacterial membrane and then, fragment of the cell is the reason for antibacterial activity of Ag nanoparticles (19). Nontoxicity of Ag⁺ to human cells and its antimicrobial activity have also attracted growing attention. According to studies (both *in vitro* and *in vivo*), silver-containing materials could inhibit bacterial attachment onto the dental implants. Excellent biocompatibility of silver containing implants without genotoxicity or cytotoxicity was demonstrated. Silver containing implants also indicated no local or systemic side-effects (1).

Elemental Ag has been applied as an antimicrobial agent in many fields of medicine, and Ag nanoparticles embedded in various film coatings have been applied to Ti implant surfaces to present antimicrobial activity. Ag nanoparticles are known as biocompatible coatings due to typically low doses required in dental implants. Therefore, by incorporating an appropriate amount of Ag, not only the antibacterial ability of the implant is enhanced, but also the surface remains biocompatible (30). There are different techniques to prepare silver-containing coatings like plasma ion implantation. Micro arc oxidation (MAO) is a type of ion implantation that can provide a porous bio-functional TiO₂ coating with good adhesion to the surface of titanium implants (1). Zhang et al coated TiO₂ implants by silver nanoparticle using MAO method. Their results showed enhanced antimicrobial effect resulted from interaction between the silver nanocrystals and the bacterial membrane. Their cell culture tests also indicated that the Ag-containing coatings possessed superior biocompatibility and noncytotoxicity. The authors proposed that, due to antibacterial ability, biocompatibility and noncytotoxicity of Ag nanoparticles, their applied ion implantation method may act as a promising approach for the production of a long-term antibacterial (1).

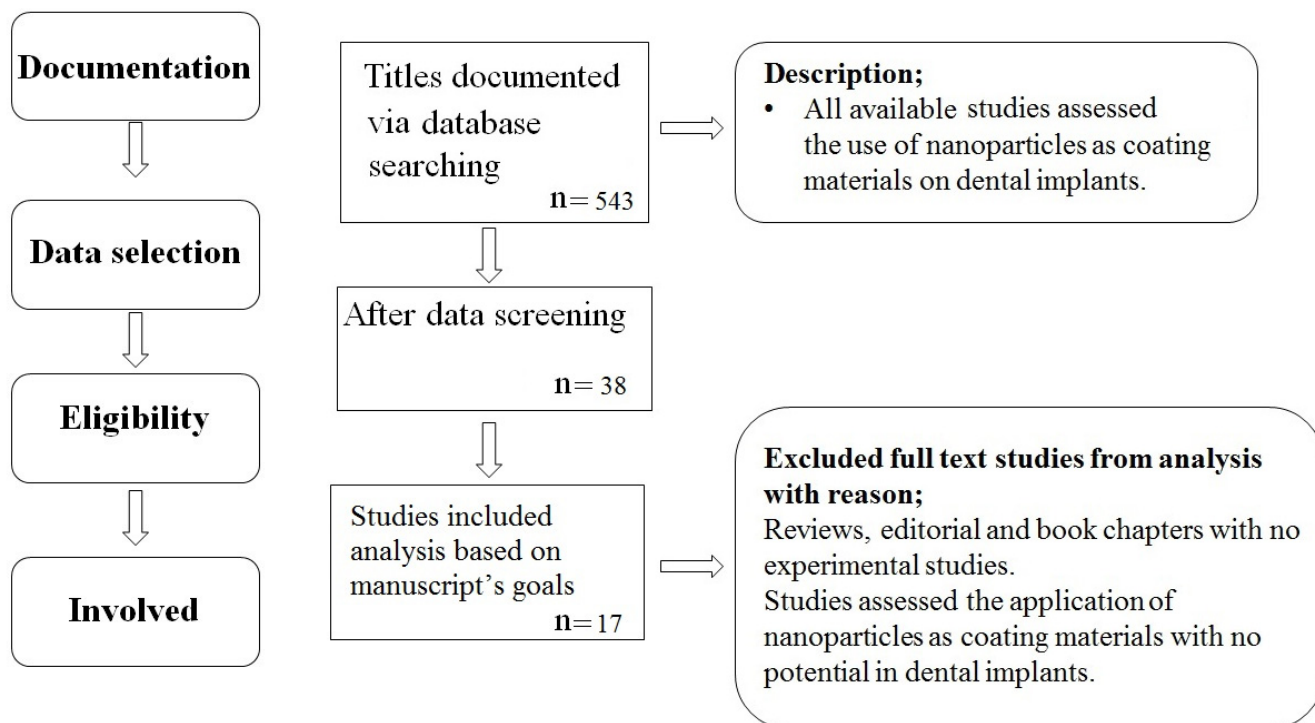


Figure 1. The searching strategies for the review

Table 1. Searching strategies for the review

MeSH keywords and their combination	Number of full-text articles in PubMed central	Number of MeSH
Nanoparticles	52291	5
Dental failures	5269	1
Dental implants	9168	2
Coating materials	48434	1
Nanoparticles as coating materials	12035	-
Nanoparticles as dental coating materials	915	-
Nanoparticles as dental implants coating materials	543	-
Nanoparticles as dental Ti- based implants coating materials	239	-
After data screening	38	-
Studies including analysis based on manuscript's goals	17	-

Zinc oxide (ZnO) nanoparticles

The compatibility of Zinc oxide (ZnO) nanoparticles with human skin has turned them into a suitable agent for addition to textiles and surfaces that come in contact with the human body, like sunscreens. ZnO nanoparticles have been reported to show antibacterial activity against both gram-positive and gram-negative bacteria, as well as against the spores

which are resistant to high temperature and high pressure (34, 35). The proposed mechanisms for ZnO nanoparticles are the generation of hydrogen peroxide as well as the accumulation of the particles on the bacteria surface due to the electrostatic forces. In addition, ROS generation on the surface of the particles, zinc ion release, membrane dysfunction,

and nanoparticles internalization could also be taken into account as the possible reasons of the antimicrobial activity of these nanoparticles. Memarzadeh et al tested a system containing mixtures of ZnO nanoparticles and nano-hydroxyapatite as a coating material to reduce bacterial adhesion and support osteoblast growth. They found that ZnO can be considered as an optimal coating for implants in terms of both antimicrobial activity and biocompatibility. They used an electrohydrodynamic atomisation (EHDA) to deposit mixtures of ZnO nanoparticles and nano-hydroxyapatite onto the surface of glass substrates. Their results indicated that ZnO nanoparticles and 75/25% ratio of ZnO/nano-hydroxyapatite coated substrates showed considerable antimicrobial activity. In addition, their results showed minimal toxicity for UMR-106 cells exposed to ZnO nanoparticles and no release of TNF- α and IL-6 cytokines for MG-63 cells cultured on ZnO substrates. According to proliferation and differentiation studies, the substrate exclusively coated with ZnO nanoparticles showed more efficiency than that with composite surface coatings. Other biologic assessments also revealed that all the tested cell types maintained their normal morphology when adhered onto the surface of the nano ZnO-coated substrates (36).

Copper oxide nanoparticle

Cu nanoparticles, owing to their unique biological, chemical and physical properties and antimicrobial effects, as well as their low cost of preparation, are of great interest to scientists. Antibacterial and antifungal activities of these nanoparticles on several microorganisms have been reported by investigators. The results of researches indicated the high potential of Cu nanoparticles as antimicrobial agents. However, rapid oxidation of Cu nanoparticles on exposure to the air limits their application. Copper oxide (CuO) nanoparticles are proper alternatives that have been reported as potential agents in controlling bio-film formation within the oral cavity (37). Researchers believe that crossing of CuO nanoparticles through the bacterial cell membrane and then, damaging the vital enzymes of bacteria are the critical factors that lead to cell death. It is also reported that, CuO nanoparticles restrict bacterial growth via passing through nano-metric pores existing on cellular membranes of most bacteria. The result of researches also has shown that these nanoparticles are not cytotoxic on HeLa cell line.

According to literature, bactericidal activity of CuO nanoparticles depends on their size, stability, and concentration added to the growth medium (34).

Anu et al coated dental implants using CuO nanoparticles by a standard slurry dipping method and chemical synthesis. Their obtained results showed that CuO nanoparticles can be efficient as dental coating to suppress dental infections. They calculated the diffusing ability of the antibacterial drugs from the CuO nanoparticles coated titanium dental implants to retard the growth of test bacteria seeded on plate using the zone of inhibition. The results of zone of inhibition measured (in millimeters) revealed the antibacterial activity of copper oxide nanoparticles coated titanium dental implants for all the test organisms. The results showed no inhibitory zones for uncoated materials, while the CuO nanoparticles coated titanium dental implants showed significant inhibitory zones. They also discussed the antimicrobial and anti-inflammatory effects of Ti due to the formation of peroxides at the Ti surface as well as spontaneous surface oxidation in air, leading to the biocompatibility of Ti. They supposed that the proliferation, adhesion and spread of cells are significantly influenced by the formation of oxidation layer on Ti (37).

Quercitrin-nanocoated implants

It has reported in the literature that many of implant failures are because of infection and inflammation together with poor healing and soft tissue integration (38, 39). Quercitrin is a natural flavonoid with the ability to improve soft tissue integration and therefore, can increase dental implants success. Gomez-Florit et al tested the anti-inflammatory properties and potential of quercitrin-nanocoated titanium surfaces to improve soft tissue regeneration using human gingival fibroblasts. In order to evaluate the anti-inflammatory properties, they also mimicked an inflammatory situation using interleukin-1- β . Their obtained results showed that quercitrin-nanocoated surfaces increased human gingival fibroblasts attachment. The anti-inflammatory results showed increased collagen mRNA levels, decreased matrix metalloproteinase-1/tissue inhibitor of metalloproteinase-1 mRNA ratio and decreased pro-inflammatory prostaglandin E₂ release under basal and inflammatory conditions (40).

Chlorhexidine (CHX) nanoparticles

Chlorhexidine (CHX) is a broad antimicrobial and antifungal spectrum belonging to a group of medicines called antiseptic antibacterial agents. It is used for a varied range of applications in medicine and dentistry, more important as a pre-surgical topical cleansing agent. In a research work by Barbour et al, CHX adsorbs to TiO₂ surfaces to investigate whether functionalization of TiO₂ surfaces with CHX reduces subsequent colonization of the surface by *Streptococcus gordonii*. Their results showed that the CHX coated surface can reduce growth of *Streptococcus gordonii*, but the CHX is rapidly depleted, leading to a short-term antimicrobial effect. Natalie et al investigated the use

of CHX hexametaphosphate (HMP) nanoparticles as a porous aggregating coating on titanium dental implants. The prepared CHX–HMP nanoparticles-coated Ti showed sustained release of CHX and improved antimicrobial efficiency. According to their microbiological results, colony-forming units (CFUs) in the wells containing the CHX–HMP nanoparticles-coated Ti decreased as a function of time, whereas CFUs in the uncoated Ti remained constant. Also, their results revealed existence of more live bacteria on uncoated Ti than on nanoparticle-coated Ti after 24 and 48 h (30).

The reviewed research works on nanoparticles as coating material for dental implants with antimicrobial activity are summarized in Table 2.

Table 2. Research works on nanoparticles with antimicrobial activity as dental coating materials

Type of material	Advantages as dental implant coating	Main finding(s) as dental implant coating in research works	Reference(s)
Ag nanoparticles	Antimicrobial activity, biocompatible coatings due to typically low required doses in dental implants	Enhanced antimicrobial effect, superior biocompatibility and noncytotoxicity	(1)
ZnO nanoparticles	Compatibility with textiles and surfaces that come in contact with the human body, antimicrobial activity	Enhanced antimicrobial effect and good biocompatibility	(36)
CuO nanoparticle	Potential to control the formation of bio films within the oral cavity, as a function of their biocidal, anti-adhesive, and delivery capabilities	Enhanced antimicrobial effects (significant inhibitory zones)	(37)
Quercitrin-	Ability to improve soft tissue integration and therefore, to increase dental implants success, anti-inflammatory properties	Increased collagen mRNA levels, decreased matrix metalloproteinase-1/tissue inhibitor of metalloproteinase-1 mRNA ratio and decreased pro-inflammatory prostaglandin E ₂ release under basal and inflammatory conditions	(40)
Chlorhexidine (CHX)	Antimicrobial efficiency, reduced subsequent colonization of the bacteria	Sustained release of CHX and improved antimicrobial efficiency	(30)

NANOPARTICLE COATINGS WITH OSTEOINTEGRATIVE ACTIVITY

Al₂O₃ nanoparticles

It is reported that Al₂O₃ nanoparticles have sufficient stability, high hardness and ability to improve osseointegration properties, therefore, are one of main candidates as dental implant coatings (41).

Rsul et al studied a nano-biocomposite coating of a dental implant including Al₂O₃ and metallic AgNO₃ on the bond strength at bone – implant interface and tissue reaction with the purpose to improve osseointegration to avoid implants failures due to infection. They coated Ti dental implants with a nano-biocomposite of Al₂O₃ and AgNO₃ using electrophoretic deposition method (EFD). They implanted the screw type of dental implants

[uncoated and coated with nano (Al_2O_3 and AgNO_3)] in tibias of white male New Zealand rabbits. According to their results, the coated screws showed that bone trabeculae occupied a base of implant bed with osteoblast and osteocyte at 2 weeks. At 4 weeks, they observed a progress in the healing process around the dental implant including new bone with haversian canals, osteoblast and osteocyte. They suggested that such a nano-biocomposite coating of a dental implant with alumina and silver nitrate can lead to formation of a multifunctional implant surface (42).

Some dental composite materials are based on polymers such as poly methyl methacrylate (PMMA) that has disadvantages such as low flexural strength properties and impact strength. Safarabadi et al tested the influences of additive Al_2O_3 and hydroxyapatite nanoparticles on the mechanical and strength properties of PMMA. Their results showed that the mechanical properties of hybrid nanocomposites (Al_2O_3 and hydroxyapatite) meaningfully improved in comparison with the pure samples (41).

Calcium derivatives nanoparticles

Calcium derivatives like hydroxyapatite, calcium carbonate and calcium phosphate are the most important natural constituents of bone and teeth. The primary tissues of bone, osseous tissue, mostly contain calcium derivatives. Thus, calcium derivatives have been reported to show great potentials for bone and teeth related applications owing to their ideal biocompatibility with the natural bone and teeth structures (23, 24). Furthermore, hydroxyapatite or calcium carbonate may act as calcium and phosphate sources to retain these ions in supersaturation state in the enamel minerals and also, may support remineralization process of the outer enamel caries lesion.

Dental materials containing hydroxyapatite coatings have attracted great attention due to the enhanced integration of osseous tissues to coat implant surfaces. Hydroxyapatite coated implants seem to be greater in sites which are compromised in either quantity or quality of bone, comparing with healing around commercially pure or titanium alloy implant surfaces. Hydroxyapatite nano-coated dental implants can induce a chemical bond with bone and result in biological fixation (43). Jimbo et al prepared a nanoscale hydroxyapatite-coated implant surface to study hasten osseointegration and improve its quality comparing with non-coated implants. They

inserted the prepared implants into rabbit femurs and pre-operatively characterized the implants related to morphology and topography. According to their results, while both the implants (coated and uncoated) showed similar bone-to-implant contact, the tissue quality was significantly enhanced around the nano hydroxyapatite-coated implants (43). Zablotsky et al reviewed hydroxyapatite coatings in implant dentistry (44), and Wennerberg et al examined the in vivo stability of hydroxyapatite nanoparticles coated on titanium implant surfaces (45).

Schouten et al prepared calcium phosphate nanoparticle-coated implants using electrospraying and tested their mechanical properties and potential beneficial effects on the in vivo osteogenic response compared to grit-blasted, acid-etched (GAE) implant surfaces as controls. The results of their study showed a comparable extent for electrosprayed calcium phosphate nanoparticle coatings and GAE implants, both with respect to implant fixation and bone healing response. Such a result showed that calcium phosphate nanoparticles can act as a proper candidate to alternate with conventional coatings (46).

Calcium carbonate has been known as a biocompatible and osteoconductive material. A direct contact has been reported between the bone and calcium carbonate without interposition of soft tissue at the interface. The bone forming response of CaCO_3 has been tested by Ohgushi et al who reported it to be comparable to that of the well-known bioactive hydroxyapatite. They also introduced a method to determine the interaction between osteogenic cells and porous CaCO_3 , without influences from the preexisting host bone. Nanoparticles with osteointegrative activity that have been used as coating for dental implants are summarized in Table 3.

NANOPARTICLE COATINGS WITH OSTEOINTEGRATIVE AND ANTIMICROBIAL ACTIVITIES

TiO₂ nanoparticles

TiO₂ nanoparticles have been coated on the surface of dental implants. Some benefits are expected to obtain from coating with TiO₂ nanoparticles. High flexural strength, biocompatibility, bone generative and regenerative potential of these nanomaterials, as well as their osteogenic potential have converted TiO₂ nanoparticles to bioinert dental materials (32, 47).

Table 3. Nanoparticle coatings with osteointegrative activity

	Advantages as dental implant coating	Main finding(s) as dental implant coating in research works	Reference(s)
Al₂O₃ nanoparticles	Osseointegration, good mechanical and strength properties	Progress in the healing process around dental implant including new bone with haversian canals, osteoblast and osteocyte	(42)
		Improved mechanical properties of dental implants	(41)
Hydroxyapatite	Enhanced integration of osseous tissues to coated implant surfaces, inducing a chemical bond with bone, resulting in biological fixation	Significantly enhanced tissue quality around the nano hydroxyapatite-coated implants	(43)
Calcium phosphate	Potential beneficial effects on the in vivo osteogenic response	A comparable extent for calcium phosphate nanoparticle coatings and GAE implants, both with respect to implant fixation and bone healing response	(46)

TiO₂ nanoparticles are also able to increase the density of osteoblast cells on the implant and therefore, lead to better implant stability (1). Kim et al conducted an experiment for implant fixture surface modification. They prepared a sol containing TiO₂ nanoparticles and coated it as a thin film on the implant surface using sol-gel method. They concluded that the fixture treated with TiO₂ nanoparticles leads to nontoxic and effective surface appearance and can induce initial bone formation after the implantation. The authors suggested that, to increase the uniformity of the coated TiO₂ nanoparticles on the surface of the fixture and to enhance the adhesion of nanoparticles, anodic oxidation technique can be used as a complementary method together with the sol-gel method (48). In another published work, Shokuhfar et al studied the interaction of MC3T3 osteoblast cells on commercially pure and alloy (Ti₆Al₄V) Ti surfaces treated with amorphous and crystalline titanium dioxide nanotubes. Their results indicated that TiO₂ crystalline nanotubes could increase the density of osteoblast cells comparing with the surfaces without nanotubes. They also suggested that the chemistry of the substrate affects the cell density rather than the morphology of the cells. Their tests about the biophysical cell-substrate interaction revealed that the cells migrated inside the crystalline nanotubes that can be related to the super hydrophilic properties of the crystalline TiO₂ nanotubes (29).

Another merit attributed to coating of implants with TiO₂ nanoparticles could be their antimicrobial behavior. It has been reported in the literature that coating of TiO₂ nanoparticles on Ti implants can increase the antimicrobial efficacy of the implants, as compared to other osteogenic materials like ZrO₂ and Al₂O₃ nanoparticles. Singaravel et al assessed the anticandidal effect of titanium, zirconium and aluminium nanoparticles coated TiO₂ plates against *C. albicans* at 24 and 72 hours, as well as one week time intervals. According to their results, the TiO₂ nanoparticles coated titanium plates showed significant anticandidal effect compared to ZrO₂ and Al₂O₃ nanoparticles at the tested time intervals (28).

Development of drug-eluting implants may provide subsequent drug therapy regimens to prevent infection or inflammation of implantation. Furthermore, drug release directly rather than systemically from the implant surface can reduce unnecessary side effects. By production of drug-eluting implants, no additional coating process is required. TiO₂ nanotubes have been reported as suitable materials for the development of drug-eluting implants. Furthermore, TiO₂ nanotubes have shown an increased osseointegration comparing with conventional TiO₂ surfaces. Shokuhfar et al provided drug-eluting materials by encapsulating an anti-inflammatory drug (sodium naproxen) inside biocompatible TiO₂ nanotubes. They suggested that these nanotubes can be used as stand-alone drug

carriers or as surface modification of orthopedic and/or dental implants (49).

Lin et al reported the preparation of titania nanotubes with various diameters (80, 120, 160, and 200 nm) and 200 nm length via electrochemical anodization method and the nanotubes were loaded with gentamicin using a lyophilization method and vacuum drying. Their results showed significant antibacterial activity for gentamicin-loaded titania nanotubes compared to titania or titania nanotubes without gentamicin. Their obtained results also exhibited that the gentamicin-loaded titania nanotubes with 160 nm and 200 nm diameters had stronger antibacterial effect because of the extended drug release time in such nanotubes with larger diameters. They also tested the osteogenic differentiation ability of the prepared gentamicin-loaded nanotubes using human marrow derived mesenchymal stem cells; their results revealed significantly promoted cell attachment, proliferation, spreading, and osteogenic differentiation when compared to titania. Then results also showed the efficiency of titania nanotubes loaded with antibiotics for local delivery to a specific site and presenting a promising strategy to prevent implant-associated infections (50).

Nano-crystalline diamond

Due to its excellent properties including good hardness, chemical inertness, high thermal conductivity and high optical transparency, diamond has been reported to be one of the most desired materials in the past years. Nanocrystalline diamond, diamond coatings with nanosized crystallites, has shown a great potential for different applications in biomedicine and biotechnology. Combination of the surface smoothness with high corrosion resistance and biotolerance results in excellent nature for nanocrystalline diamond. These nanostructures can act as a coating material for dental implants. Such a coating may be a selective protective barrier between the implant and the human environment, preventing the release of metallic ions into the body. Also, Nanocrystalline diamond has been reported to show the highest resistance to bacterial colonization comparing to medical steel and titanium. Therefore, this property is very important in the case of implant rejection because of infection. In addition, it is shown that diamond particles present antioxidant and anticarcinogenic properties at small sizes and molecular levels (51). Amaral et al tested the

cytotoxicity and biocompatibility of nanocrystalline diamond films by seeding human gingival fibroblasts on their surface for 14 days. They also investigated biocompatibility on samples seeded with human bone marrow-derived osteoblasts during 21 days. Their results proved that nanocrystalline diamond is noncytotoxic in the preliminary human gingival fibroblast cell cultures. These nanostructure coatings also induced human osteoblast proliferation and the stimulation of differentiation markers comparing with standard polystyrene tissue culture plates (52).

Despite good description about promising biomaterial characteristics of diamond-coatings in the literature, there is little information about implant osseointegration of this surface modification compared to the currently used sandblasted acid-etched Ti-Al6-V4 implants. Metzler et al investigated the osseointegration of diamond-coated Ti-Al₆-V₄ dental implants after healing periods of 2 and 5 months in the frontal skull of eight adult domestic pigs. Their histomorphometry analyses showed the bone-to-implant contact and an adequate interface between the bone and the diamond surface (53).

It is reported that irradiation leads to reduced bone healing, which causes increased failure rates of the osteosynthesis procedures. To improve osseointegration, Kloss et al tested the irradiation effect on immobilized bone protein-2 (BMP-2) on nanocrystalline diamond-coated implant surfaces of a pig's mandible for 4 weeks. Their results showed that immobilized BMP-2 resulted in an initial increased bone contact and consequently, an osteoinductive effect in irradiated bone (51). Nanoparticle coatings with osteointegrative and antibacterial activities are summarized in Table 4.

SUMMARY

Dental implant has demonstrated clinical success over recent years despite its major problem due to implant fixation that leads to bacterial infection and rejection of the implant. Recently, nanomaterial-coatings have been reported to have beneficial properties to improve implant fixation and increase the success rate. Nanoparticles are used as particle coatings on the implant surface that may increase the functionality and improve the stability and fixation of the implant.

Table 4. Nanoparticle coating with osteointegrative and antibacterial activities

Type of material	Advantages as dental implant coating	Main finding(s) as dental implant coating in research works	Reference(s)
TiO₂ nanoparticles	Nontoxicity, ability to increase the density of osteoblast cells on the implant, enhanced osseointegration, anticandidal effect, bone formatin ability	Nontoxic surface coating with ability to induce initial bone formation	(36)
		Significant anticandidal effect compared to ZrO ₂ and Al ₂ O ₃ nanoparticles at the tested time intervals	(33)
		Ability to apply as stand-alone drug carriers or as surface modification of orthopedic and/or dental implants	(32)
		Cells migration on the Ti-based implants due to super hydrophilic properties of crystalline TiO ₂ nanotubes	(37)
Nano-crystalline diamond	Act as a selective protective barrier between the implant and the human environment to prevent the release of metallic ions into the body, highest resistance to bacterial colonization comparing to medical steel and titanium, antioxidant and anticarcinogenic properties at the small sizes and molecular levels, bone-to-implant contact	Significant antibacterial activity compared to titania or titania nanotubes without gentamicin Stronger antibacterial effect for nanotubes with 160 nm diameter compared to larger diameters (because of the extended drug release time) A promising strategy to prevent implant-associated infection	
		Nontoxic in the preliminary human gingival fibroblast cell cultures, induced human osteoblast proliferation and stimulation of differentiation markers comparing with standard polystyrene tissue culture plates	(49)
		Bone-to-implant contact and an adequate interface between the bone and the diamond surface	(50)
		Initial increased bone contact, osteoinductive effect on bone	(48)

Nanoparticles have been known as one of the most effective antibacterial agents, and can be used as effective growth inhibitors of various microorganisms. Surface modification of titanium using antibacterial properties of metal nanoparticles can decrease the number of bacteria and certainly, present more beneficial clinical treatments. Ti surfaces are also coated with nanoparticles to improve soft tissue integration and osteogenesis that leads to good fixation of implants. Furthermore, the surfaces of implants improve to control the doping and distribution process. In addition, osteoconductive nanomaterials could induce a chemical bond with bone to attain good biological fixation for implants. It has been revealed that coating of bio-inert nanomaterials over Ti implant surfaces may change the physical properties and also, increase the osteogenic potential of implants. It

has been also reported that some crystalline nanomaterials have ability to increase the density of osteoblast cells on the implant that may lead to better implant stability. The reviewed articles exhibited that a good progress in research has occurred in the case of nanomaterial-based coatings for dental implants. However, clinical and *in vivo* information about these nano-size coatings and their beneficial applications is still rare. The long-term antibacterial as well as physical and clinical effects of nanoparticles on dental and medical biomaterials should be investigated in future studies.

DECLARATION OF INTEREST

The authors report no declarations of interest in this study.

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