REVIEW PAPER

Effects of doping metal nanoparticles in hydroxyapatite in Improving the physical and chemical properties of dental implants

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ABSTRACT

There are strong proofs for the therapeutic benefits of dental implants utility in regards to the replacement of dental elements throughout the treatment of complete or partial edentulism. Many materials were used for the manufacturing of dental implants throughout the history of this field. Hydroxyapatite is one of the popular structures due to being highly biocompatible, however, its poor stability fences its application. Therefore, the approach of doping with other structures, such as metal nanoparticles, can be proposed to circumvent this obstacle. Various metal nanoparticles are exerted in the role of dopants, which include manganese, silver, magnesium, cobalt, zinc, silicon, strontium, lithium,cerium, yttrium, neodymium, hafnium, erbium, and cadmium. According to available evidences, the doping of metal nanoparticles with hydroxyapatite can improve the obtained mechanical stability, biocompatibility, osteoinductivity, osteoinductivity, the integrity of bone tissues, antibacterial properties, and other features, which is effective in increasing their potential applications. Apart from the offered benefits, the process of doping metal nanoparticles in dental implants is still in its infancy and struggles with several challenges.

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INTRODUCTION

The application of dental implants proved to be beneficial for the replacement of dental elements in the treatment of complete or partial edentulism. The advancements in implant design and operation technology resulted in extending the conditions of implant surgery, while in addition, the 10-year survival rate of an implant-supported denture has surpassed 95%. In comparison to fixed or removable dentures, implant-supported dentures are commonly utilized in patients with dentition defects or loss due to their superior chewing efficiency and the lack of causing any damages to the neighboring teeth [1-3]. There is a long and complicated history behind the usage of dental implants, which were developed and fabricated as artificial tooth roots to ease the replacement of natural ones. These products are designed to provide a stable anchorage for permanent or removable dental prostheses in order to improve the living quality of dental degenerations patients, as well as those that struggle with partial or complete edentulous [4-6]. Dentures, fixed prostheses, and orthodontic appliances are generally supported by dental implants, which are surgically implanted into the alveolar bone. However, even the achievement of great success and survival rates of dental implants has not surpassed

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the numerous challenges that cause the reported implant failures. Implant-, clinician-, and patient-related factors, as well as infection and non-ideal local microenvironment such osteoporosis, and foreign body reactions that can accelerate the rate of alveolar bone loss, are the factors that contribute to the failure of dental implants [7-11]. Implant surface engineering is important for optimizing implant-related osseointegration, which is attained by improving a number of physiological processes throughout the peri-implant alveolar bone that involve attachment, proliferation, differentiation, matrix synthesis, and calcification of osteoblasts. The surface design of an implant can create a secure area to avoid a large portion of oral microorganisms and even provide sterilizing effects. Furthermore, producing an optimized implant surface proved to be more significant among the varying designs of an optimal osseointegration process. The survival rate of an implant can be affected by several features throughout the design of endosseous implants, which includes body shape, size, chemical surface composition, and topographical features. In addition, the applied materials proved to be stronger and more fatigue resistant. Nanostructured implants are considered as a rapidly evolving therapeutic approach in the fields of medical research and dental implants. Surface nano-features, involving coating, patterning, functionalization, and molecular grafting at nanoscale, can compromise medical obstacles through the facilitation of producing more promising biomaterials, arrangement of enhanced implant design, and preparation of surface engineering methods including coating, patterning, functionalization, and molecular grafting [12-15]. Among the promising options that were discovered for dental implant coatings, one can point out carbon, bone stimulating substances, bisphosphonates, bioactive glass, bioactive ceramics, titanium/titanium nitride, fluoride, and, calcium phosphate and hydroxyapatite (HA or HAP). In this regard, hydroxyapatite is widely employed in dental implants due to its amazing biocompatibility. Although the more innovative bioglass products exhibited promising results, yet the HA coatings are still recognized as the most biocompatible coatings even though they contain poor strength and mechanical qualities in general [16, 17]. Various studies were conducted on the addition of varying materials for improving the properties of HA [18, 19]. Also, the exertion of varying types of nanomaterials (metals, metal oxides, ceramics, polymers and hydrides) were attempted for dental implants due to their distinct features, the effects of elemental compounds, surface morphology, and potent applications. For example, the structural modification of an implant micro-nano surface can increase the obtained hydrophilicity and conductivity of implant-bone, while reducing the rate of stress conduction [20-22]. Up to this date, several researchers focused on promoting implant surface engineering concepts based on metal nanoparticles. Huang et al. applied titanium-based materials for dental implants since they are capable of exhibiting mazing biological compatibility, remarkable mechanical strength, and high corrosion resistance[23]. Also, Salaie et al. reported the application of Ag NP-coated titanium dental implants with hydroxyapatite (HA). According to their results, the coated implants with Ag + nHA were capable of maintaining a higher degree of biocompatibility in comparison to the coated samples with solitary Ag + mHA, or Ag NPs [24]. Therefore, we attempted to review the applications and characteristics of hydroxyapatite dental implants that were doped with metal nanoparticles.

THE MOST COMMON MATERIALS EXERTED IN THE MANUFACTURE OF DENTAL IMPLANTS: CHALLENGES

The success of a dental implant is determined through the existing relationship among the implant's design, chemical composition, and its intended usage, as well as the surgeon's capabilities and patients' ability to return to their normal lifestyle after surgery.Fig. 1 represents some of the most important features of a good dental implant. A consistent amount of materials were exerted to produce implants for replacing the lost or damaged teeth over the years. The quality of implants were improved in tandem with rapid technological advancements that were achieved primarily through the performance of extensive studies in the field of materials science. Metals were the most commonly applied materials in implant manufacturing at first, which was followed by the exertion of polymers and more recently, ceramics and composites. In general, the main materials that have been used in the production of dental implants since the beginning of its history up to the present include: Titanium ,Titanium Alloy, Stainless Steel, Cobalt Chromium Alloy, Gold Alloys, Tantalum,

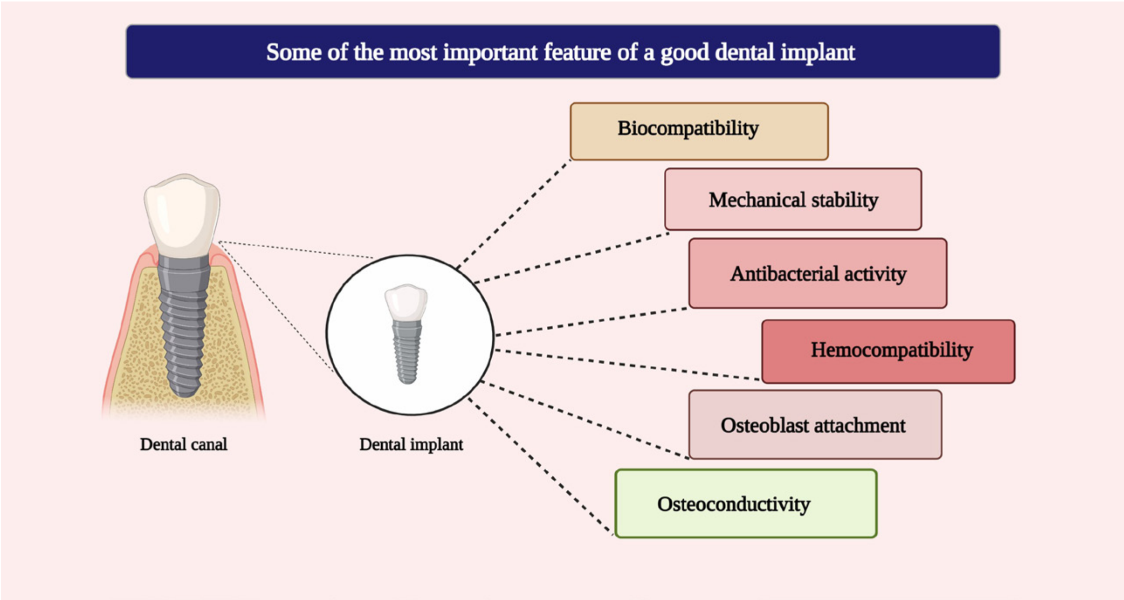

Fig. 1. The most important features of a good dental implant include biocompatibility, mechaniacal stability, antibacterial activity, hemocompatibility, osteoblast attachment, osteoconductivity

Ceramics, Alumina, Hydroxyapatite, Beta-Tricalcium, Phosphate, Carbon, Carbon-Silicon, Bioglass, Polymers, Folymethylmethacrylate , Polytetrafluoroethylene, Polyethylene, Polysulfone, and Polyurethane. Despite the extending popularity of dental implants, there are still hurdles that need to be resolved, which are based on implant body materials [25-29]. Some of the existing challenges in this field are provided in the following:

- Mismatches of the implants modulus with human jaw bone. Elastic modulus mismatch is a common difficulty in implantology, which is not exclusive to dental implants. According to Hooke's law, if the implant and bone contain a parallel amount of modulus, they will consequently face the same percentage of deformation under stress. The durability of the coupling of prosthesis and bone is much higher and can also improve the stability and osseointegration of prosthesis [30, 31].

- The limitations of metal materials lead to the production of unstable implants structures that consequently result in their irreversibility. Considering the fact that the threaded components are relatively long and thin, the exceedingly difficult force conditions in the mouth cavity, particularly cyclic occlusal force and non-axial stress, would gradually cause fatigue. For example, snaps are a common inducement on the cross-core screws that link abutments and implant bodies and it is quiet difficult to detach an snapped screw [32, 33].

- Being exposed to a diverse external oral environment for a long duration can stimulate the bacterial infection of tissues that surround implants and lead to the annihilation of their biological connectivity. Considering the tendency of bacterial plaques for amassing at the neck of dental implants, the produced substances on the germ's surface, metabolite, and toxin cause the annihilation of biological barriers and the osseointegration interface that is constructed by the soft tissues around the implant; this procedure was observed throughout numerous clinical cases. Destruction can inspire inflammation in the tissues around the implant and result in the inducement of osseointegration failure, which is another common cause of implant failure [34-37].

HYDROXYAPATITE: A MATERIAL WITH EXCELLENT PROPERTIES FOR DENTAL IMPLANTS

Surface modification of orthopedic and dental implants proved to be an efficient method for accelerating the process of bone healing during the early stages of implantation. Due to its outstanding biocompatibility and osteoconductive behavior, covering implants with a layer of hydroxyapatite stands as one of the most commonly utilized methods among the available several options. The crystalline structure and composition of HA can provide an space for a variety of ionic substitutions with specific utilities such as antibacterial capabilities or osteoinduction. Hydroxyapatite of biologic (coral, bovine, or marine algae-derived) or synthetic origin is currently exerted in the forms of granules, blocks, and scaffolds for bone repair and regeneration, either alone or in composites with polymers or other ceramics, or applied in the form of coatings on orthopedic or dental implants. The promising outcomes of hydroxyapatite coatings relies on the improved integration of osseous tissues to coated implant surfaces. This material was designed as a bone replacement product due to containing a parallel construction to that of bone minerals[16, 38-40]. They can be applied in bone repair, replacement, and augmentation, as well as scaffolds in tissue engineering for bone regeneration. It can act as a bone substitute material due to containing a comparable composition to that of bone mineral. HA is also utilized as abrasive to roughen metal implant surfaces and as a source material for bioactive coatings to be deposited on orthopedic and dental implants. Additionally, other products can be manufactured by the usage of these materials such as transfection agents, medication carriers, and percutaneous devices. Substituted apatites were exerted for the production of HA-based biomaterials with improved characteristics. Bioactive surfaces, such as HA coatings, are utilized to improve the attachment of bones to the dental implants and orthopedic prostheses. Several studies evaluated the usage of a variety of implant materials with and without HA coatings for bearing implant applications throughout the last few years. Interface shear bond properties of HA-coated implants proved to be superior than non-coated implants. The samples with a coating of HA obtained the maximum adhesion strength at a shorter postoperative period, while conferring faster tissue adaption to implant surfaces. HA coatings generate an osteophilic, conductive surface with the ability to improve the strength of bone's attachment to the implant, while promoting the bones adaption to the surface of HA-coated implants as well [41-47]. In a related study, Jung et al. evaluated the surface properties and bond strength of HA coated titanium implants through a new approach. Upon the exertion of SHS blasting approach, a homogeneous HA coating layer was generated on the titanium implants without deforming the surface microtexture of RBM titanium. In comparison to the RBM implants, these HA-coated implants contained a higher roughness, crystallinity, and wettability[48]. The modification of titanium surface by HA coating for dental implants was studied by Hung and colleagues. The goal of this research was to distinguish the process parameters of plasma-sprayed HA coating on titanium surfaces in order to achieve the desirable combination of biocompatibility and mechanical qualities for dental implants[49].

Hydroxyapatite Limitations: *Effects of doping metal nanoparticles on overcoming challenges*

Despite the excellent quality of HA as an implant coating material, its medical implementation is limited due to containing adverse mechanical properties such as brittleness, poor fracture toughness, and low tensile strength. Furthermore, HA-coated implants require a longer remodeling time, contain a slower osseointegration rate, and lack any antibacterial actions or characteristics. Unfortunately, the accommodation of weak mechanical qualities has obstructed its application. Furthermore, bacteria can easily adhere and multiply on the surface of HA as a result of its remarkable biocompatibility. Bacterial infection is a major complication of implant surgery that can lead to sepsis, implant translocation, and other serious complications, as well as putting clinical applications at risk. Thereby, it is necessary to produce a composite material with multiple components to provide antibacterial activity and biocompatible qualities. The majority of current research focused on the addition of various components into HA coatings to increase its mechanical characteristics[50-53]. HA can be utilized directly in bone tissue engineering or face the doping of a variety of metallic or nonmetallic dopants to customize its properties for the upcoming applications. The performed substitution can improve the properties of modified HA based on the properties of the dopant. Metal nanoparticles, such as zinc, silver, cobalt, lithium, manganese, silicon, magnesium, strontium, neodymium, yttrium, cerium, hafnium, cadmium and, erbium are among the list of viable dopants, which can cause distinct beneficial effects on HA and consequently enhance its quality and application fields (Table 1). This structural composition can also improve antibacterial activity, bone-implant biocompatibility, coating stability, and biocompatibility with primary human

Table 1. Doped metal nanoparticles in HA and their effect on improving the physical and chemical properties of dental implants

Type of nanoparticle	The effect of nanoparticles on implants	Reference
Silver-doped HA	-Effective antibacterial ability	[56]
Titanium dioxide and HA nanocoatings	-Antibacterial activity -Biological Stability	[57]
Titanium Dioxide-coated HA	-Improving the hydrophobic properties of HA -The regeneration of bone defects	[58]
Titanium isopropoxide (TiO_2) and HA	Improved mechanical property and osteoinductivity	[59]
Silver and HA	-Antimicrobial activity -Enhanced the biocompatibility -Improved The stability	[24]
Silver–HA/Titania nanocomposite	-Antimicrobial activity against Staphylococcus aureus and Escherichia coli	[60]
Cerium-doped HA	-Antibacterial activity -Contribute to the integrity of the bone tissue	[60]
HA-Alumina-Zirconia Composite	-Improved mechanical properties -Improved phase purity	[61]
Copper oxide/HA Composites	-Improved antibacterial properties -Improved bioactivity and cell compatibility	[54]
Zinc oxide and HA	-Provide osteoconductive -Antimicrobial functionalities -Prevent failure	[62]
Cu-HA/f-MWCNT nanocomposite	-Enhanced antibacterial activity -Corrosion resistance property	[63]
Iron doping HA	-Improved mechanical strength ,biocompatibility and Hemocompatibility	[64]
Iron-doped/substituted calcium hydroxyapatite	-Improved bone regeneration and remodeling	[65]
Silver and zinc oxide doping HA	-Improved antibacterial activity -acceptable biocompatibility	[66]
zinc oxide doping hydroxyapatite	-Improved antibacterial and anti-biofilm activities	[67]
Hydroxyapatite Coating on Zinc Oxide	-Improved mechanical properties -Improved biocompatibility -Improved osteoblast attachment	[68]
HA doped with magnesium and zinc	-Enhanced mechanical properties -Improved biological properties	[69]

osteoblasts, enhancing osteoblast cell adherence to the implant surface, boosting bone cell proliferation, and subsequent calcium deposition to form a fresh bone. Relevant data suggested that the bacterial adhesion to implants can be affected by modifying the surface nanotopography. The usage of osteoconductive nanoparticles for coating dental implants can facilitate the formation of a chemical contact with the bone and achieve effective biological fixation. Furthermore, the capability of these materials in producing bones along with their regenerative potential can help to improve the conditions (Fig. 2) [1, 24, 54, 55].

PROSPECTS AND CHALLENGES

The application of nanosystems is a rapidly growing field throughout dentistry and the oral health industry. As it is predictable, future will be indulged with an exceeding rate of novel products that would be certified and offered in the market. The unique traits of nanoparticles include adjustable construction and smart features that involve bio-adhesive behavior and stimuli-responsive capability. The exertion of internal or exterior functionalization, tweaking of the core formulation, or the coupling of nanostructures with specific molecules can be all considered as an approach to impose chemical or physical qualities on the entire system [70-73]. However next to the mentioned benefits, there are various hurdles that must be overcome in order to provide the possibility of translating these products to the clinic and facilitate the subsequent commercialization. For this purpose, the first step requires the conduction of further research into the potential harmful effects of nanoparticles to improve their biocompatibility [74-76]. As a result, numerous preclinical studies must be performed to investigate the immune system interactions and unanticipated toxicities. Secondly, enhancing the precision of functional nanoparticles-based formulations is of paramount importance. Therefore, it is necessary to preserve the pharmacological activity of nanoparticles upon their binding to the target. The significance of nano structure designs and production processes in this framework is undeniable, due to the lack of understanding the various biological mechanisms that are related to nanoparticle and can effect the

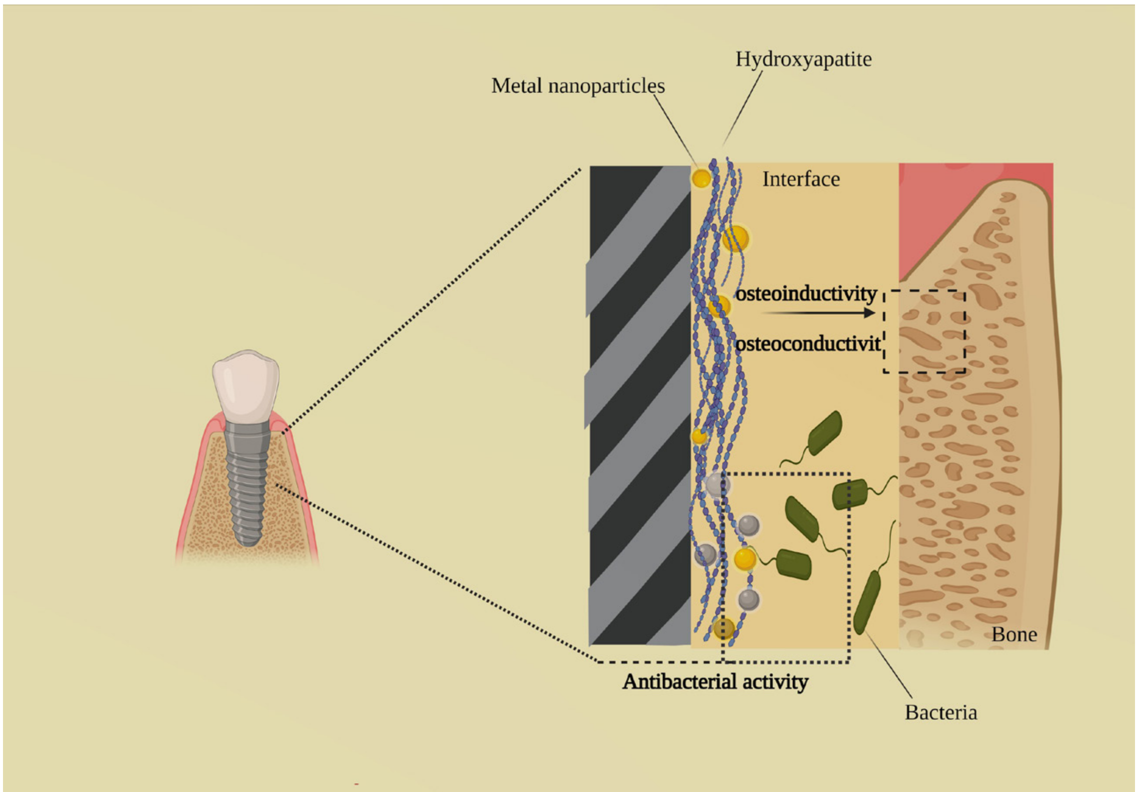

Fig. 2. Some effects of doping metal nanoparticles on improving the properties of hydroxyapatite to overcome challenges

human body, which highlights the necessity of clinical efficacy trials. Also, there are other critical factors that are efficient in causing a difference among dental implementations and other diseases, which include being capable of providing scale up manufacturing, control over crucial design features, and ultimate cost. One of the most important characteristics of dental and orthopedic implants is the ability to exhibit osseointegration with the host bone tissue for achieving the privilege of a long-term mechanical performance. Commercial implants were produced with topographic and/or physicochemical surface modification in order to confer the capacity for triggering a biological response and accelerating the bone regeneration procedure. Surface modifications, in particular, affect the primary interfacial reactions that befall among the implant and blood, connective tissue, and surrounding cells. The device's first point of contact after implantation occurs with the produced blood caused by bone damage, leading to the formation of a fibronectin-rich blood clot, which serves as a framework for the cells of the new tissue. In the following, the accumulated osteogenic cells in the blood clot release a mineralized collagenous interfacial matrix on the implant surface for initiating the development of a new bone[77-80]. Finally, bone remodeling occurs at distinct places, which results in the formation of a bone-implant interface that is consisted of a newly formed bone. In this regard, hydrophilic surfaces were discovered with the ability to stimulate the up-regulation of angiogenesis-associated genes even during the early phases of bone healing, as well as capable of producing a more resistant blood clot that is difficult to disintegrate. Meanwhile, essential parameters, which include free surface energy and surface wettability that are associated with protein adsorption or blood clothing, are determined through the chemical composition of the implant along with the appearance of grafted bioactive molecules and coatings. In this method, a hydrophilic surface can encourage the formation of a strong blood clot anchorage and ensure the attachment of generated interfacial bone to the implant surface for facilitating rapid osteointegration. Although an antibacterial coating can help in limiting microorganisms, however, it can also impact the function of autologous bone cells around the implant and result in reducing the strength of joint surface [81-84]. In addition, silver is a dangerous material for mammalian cells, including wound healing fibroblasts, since the fatal dosage of AgNO3 is reported to be 50 mg L1. The in vitro application of Ag NPs also proved to be hazardous for cells (EC50 26.7 mg L1). As a result, next to enhancing the antibacterial qualities, the addition of Ag NPs to a dental implant can also compromise its biocompatibility with human tissues. The factor of being biocompatible with osteoblasts, which are crucial for the implant's osseointegration into the surrounding bone, stands as a major distress. To reduce the risk of post-operative infection and also promote osseointegration, an implant should be incorporated with Ag NPs in order to become antimicrobial for many days after the surgery. Nevertheless, the specific volume of Ag NPs that would be biocompatible with osteoblasts remain to be unknown, while designing carriers/scaffolds is also a costly process. Next to the problematic procedure of acquiring regulatory permission for commercialization, to commercialize an implant, it is critical to become ascertain of the affordability and simple repeatability of the product's industrial scaling up in order to prove the economical viability of the manufacturing process [85-90].

CONCLUSION

The advent of metal nanoparticle-based dental implants has revolutionized the application of implants in a variety of fields. The doping of these nanoparticles into specific structures, such as hydroxyapatite, can be very effective in improving their physical stability and antimicrobial activity, while facilitating a better regeneration and tissue repair, etc as well. Hopefully, the results of using structures that are composed of doped metal nanoparticles in hydroxyapatite will succeed in opening a promising window for the wider applications of implants.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest

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