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# Ceria nanoparticles – A versatile material for conducive osseointegration of dental implants

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## Abstract

Osseointegration is the direct structural and functional connection between living bone and the surface of a load-bearing artificial implant. It plays a vital role in the excellent clinical outcome of dental implants on a long term basis. Nanoparticles with their size of 100nm are increasingly used as surface modification on the implants due to their beneficial effects. Nanostructured implant surfaces have been studied in order to shorten the time for osseointegration. Usually the properties of nanoparticles are different from those of larger particles of the same substance. Numerous dental biomaterials such as ceramics, polymers and composites have been used for various purposes in the form of their pertaining nanoconstituent. Cerium, an element of the lanthanide series has been utilized extensively for various biomedical purposes as well as in dentistry as a cardinal entity in ceramics, dental adhesives and lately on implants, owing to their potential biocompatibility. Ceria nanoparticles have additional antioxidant, anti-inflammatory and antibacterial activity which are of significance in preventing implant failures. Surface modifications of ceria by various methods have proven their efficacy as a multifaceted dental implant material fulfilling the required necessitating properties for the successful outcome of the dental implants. The structure, composition and hydrophilicity of implant surfaces play a major role in adhesion of bone and in the prevention of bacterial accumulation. Therefore, ceria nanoparticles are promising in alleviating peri-implantitis and can be accepted widely in future endeavours to achieve successful osseointegration of the dental implants.

**Keywords:** Osseointegration, implants, ceria nanoparticles, antioxidant, anti-inflammatory, antibacterial.

## Introduction

Currently, lost teeth are being replaced extensively with titanium dental implants which have empowered to be the most popular method in prosthetics. Proteins and platelets from blood are in connection with the implant surface after implantation. The primary bone formation around the implants is greatly influenced by their chemical composition as well as the micro/nano-scale attributes of the implant surfaces. [1] Most of the time, dental implants encounter severe postsurgical complications remarkably infections, leading to implant failure. Peri-implantitis caused by microbes, for instance, bacteria which ultimately become attached and adhere to the implant surfaces. There are three pivotal factors of importance for the success of dental implants clinically which comprise osseointegration, prevention of inflammation and bacterial adherence to the implant surface. [2]

The process of osseointegration has been enhanced by the high surface energy and low water contact angle values offered by the titanium implants which reveal a high affinity and wettability of blood [3] which has been the key focus of the technological advancements in implant dentistry. The average bone healing time is approximately 3 months in the mandible and 6 months in the maxilla which essentially resulted in nanostructured implant surfaces, which have been studied to shorten the time for osseointegration. [4] Implant surface modification at the micro- and nano-scale level have shown an enhancement of the titanium integration to the bone tissue. In recent times, implant surfaces can be improved by mimicking the morphological aspects and make-up of natural tissues, with extent ranging from 1 to 100 nm, which encompass the nano-scale. [5]

**Nanoscale Modification And Implants**

Nano particle is presumably defined as a particle of matter which is between 1 and 100 nanometres (nm) in their diameter. One nanometer is one-billionth or $10^{-9}$ of a metre. The properties of nanoparticles are often different from those of larger particles of the same substance. They have three major physical properties: (1) highly mobile in the Free State (2) have enormous specific surface areas; and (3) quantum effects. [6]As the material size approaches the nanoscale dimensions, a greater number of these nanoscale materials exhibit an increase in surface area. Quantum effects refer to the optical, electric and magnetic properties that are altered when the material approaches the smaller end of the nanoscale. [7]

The combination of micro with nanoscale modification and functionalization with protein, peptides, and bioactive compounds results in an improvement in wettability and bioactivity of titanium implant surfaces. Such morphological changes and chemical modification on the titanium surfaces induce the migration and differentiation of osteogenic cells. This along with an enhancement of the mineral matrix formation result in rapid osseointegration. A mixture of grit blasting, acid etching and surface conditioning techniques results in high hydrophilicity which along with the nanostructured morphological aspects of the titanium surface are responsible for shortening the first phase of osseointegration which is also a key factor to mimic the natural structure of bone and soft tissues enhancing bone healing. [8]

Thus grit-blasting with biphasic calcium phosphate (BCP) ceramic particles have shown a high average surface roughness as well as a particle-free surface after acid etching of titanium implants. [9] Anodization is a method commonly used to obtain nanoscale oxides on metals including titanium. Nanoscale properties could be controlled by adjusting the anodization condition such as voltage, time, and shaking. [10] Titanium nanotubes are fabricated using electrochemical anodization in which an array of $TiO_2$ nanotubes are hexagonally close packed onto Ti surfaces with diameters of 100-300nm and lengths of 0.5-1000 µm. Kang et al had found that $TiO_2$ nanotube arrays were arranged more uniformly on electro-polished than machined titanium surfaces. It has also been shown that enhanced bioactivity to the implant surfaces resulted when loaded with a variety of therapeutics, including growth factors (GFs), antibiotics, anti-cancer drugs, etc. These can be released locally at the site of trauma upon implantation. [11] In addition, TiO2 nanotubes present on Ti enhanced the alkaline phosphatase (ALP) activity by the osteoblastic cells. Nanotubes with a diameter of 100 nm upregulated level of ALP activity when compared with surfaces of 30-70nm diameter. These surfaces may demonstrate enhanced bone tissue integrative properties as ALP is a marker of osteogenic differentiation. [9] Hence, additional research must be conducted so as to overcome some drawbacks connected with such structures as in, like toxicity of coatings or stability of titania nanolayers in the in vivo conditions. Tantalum and niobium metals were also used as base material for implants due to their inherent corrosion stability, but tantalum is considered moderately toxic as its processing leads to high concentrations of fumes or dust released into the air.[12] Hence, the dose-dependent cytotoxicity of metal particles and nanoparticles limits their applications which led to use of other biomaterials.

Various other dental biomaterials used are ceramics, polymers and composites with each having its own merits and demerits. Conclusively, drawbacks of ceramics include low ductility, inherent brittleness and that of polymers include inferior mechanical properties and immunologic reactions. In addition, zirconia which became popular after titanium had its own failure modes such as mechanical failure due to functional loading and areas of stress concentration can be a primary trigger for implant failure. [13] Nanoceramics and nanocomposites as a propitious implant biomaterial are still under research which paved the way for nanoceria which emerged as a promising modification strategy to facilitate osseointegration.

**Cerium**

Cerium (Ce) is known to be a rare earth element (atomic number 58) and is a member of the lanthanide series of the periodic table. It is the most abundant rare earth metal and is unique due to the fact that it is present in two oxidation states i.e. +3 and +4. [14] Cerium by itself does not have much of biological significance in mammalian physiology, but soluble Ce3+ salts (nitrate, acetate, chloride, etc.) have been primarily used by humans for varied biomedical purposes due to their bacteriostatic, bactericidal, antiemetic, immunomodulating and antitumor activity. [15] Cerium oxide or cerium dioxide, also called ceria being a lanthanum metal oxide has numerous commercial applications including glass and glass polishing, phosphors, ceramics, catalysts, metallurgy, ultraviolet absorbers and even in gas sensors. [16] Ceria has favorable applications in biology, such as biological detection of nucleic acids, disease diagnosis and treatment, drug carriers and biological scaffolds [2] as well as in biomedical applications due to their ability to exhibit protection against radiation, cellular damage mediated by toxicants and during pathological conditions such as brain or cardiac ischemia, neurological disorders or neurodegeneration of retina. [17] In dentistry, $CeO_2$ was primarily used for dental ceramics as this compound simulates the natural fluorescence found in human dental enamel. [18] Cerium has a high atomic number of 58 which suggests that it can cause attenuation of the dental X-ray beam. Recently, $CeO_2$ was investigated for the first time as a promising filler to improve the radiopacity of dental adhesives which could be used as a reliable strategy to assist the clinicians in the diagnosis of recurrent caries. This contribution has been of importance due to the fact of misinterpretation of radiolucency of dental adhesives below the resin composites for recurrent caries, as the adhesive systems mimic the radiolucent appearance of carious lesions. [19] In addition, this ceria has been an evolutionary rise as a nanotherapeutic material due to their free radical scavenging properties and reported biocompatibility. Ceria nanoparticles (CNPs) or nanoceria as they have known to be, possess a larger surface area associated with an increased number of $Ce^{3+}$ ions and oxygen vacancies, which also showed enhanced antioxidant properties in living systems. CNPS are widely applied in chemical mechanical polishing as well as in the development of corrosion protection coatings for metals and alloys. [20] [Figure 1]

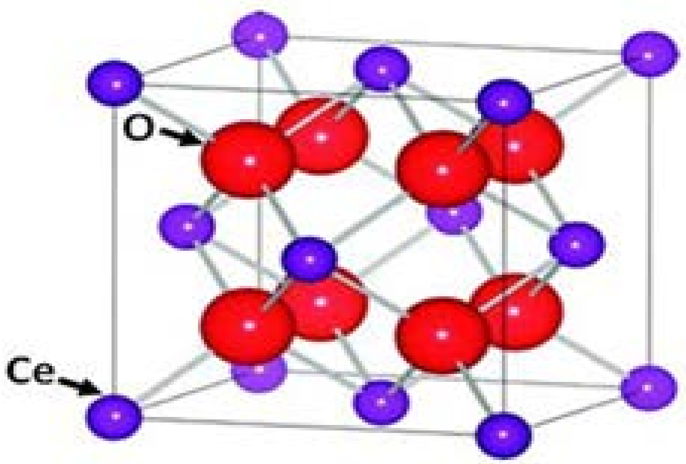


Figure 1: Structure of ceria with oxygen vacancies

Synthesis of nanoceria can be prepared by three means i.e. chemical method, green synthesis and synthesis from nutrients. Chemical methods comprise of co-precipitation, chemical precipitation, microwave, and also by means of apoferritin, where in this protein acts as a biotemplate for the oxidation of trivalent cerium ions. Green method involves the synthesis of nanoceria using various sources such as Gloriosa superba L.leaf extract, fungal culture infiltrate of Curvularia lunata, Acalypha indica & aloe vera plant extract and Hibiscus sabdariffa's flower aqueous extract. The method of synthesis from nutrients include the aid of ovalbumin and lysozyme, the two proteins of egg white which act as stabilizing agent for the synthesis of nanoceria. [21]

**Antioxidant Activity**

Reactive Oxygen Species (ROS) are constantly generated during normal cellular metabolism and they contribute to the emergence of numerous diseases including osteoporosis. As one of the main ROS, $H_2O_2$ possesses the ability to cross the biological membranes and thereby produce a wide range of injury. It has also been reported that $H_2O_2$ decreased the bone formation of the osteoblastic cells by inhibition of proliferation and/or differentiation of the osteoblastic progenitors as well as the bio-mineralization process. In this context, therapeutic strategies aimed at attenuating $H_2O_2$ induced damage on osteoblastic cells which might be reasonable choices for bone regeneration of osteoporotic patients. [20] Antioxidant enzymes such as superoxide dismutase SOD and catalase CAT can fortify the cells from oxidative stress by utilizing intracellular antioxidative defense system. Among the two enzymes, SOD plays an important role in inhibiting superoxide radical and $H_2O_2$ induced oxidative stress and thereby maintain the cellular membrane integrity. Enzymes such as catalase, glutathione peroxidases and peroxiredoxins reduce $H_2O_2$ levels in cells. Catalase (CAT) acts to disproportionate $H_2O_2$ into $O_2$ and $H_2O$, being the most efficient among all. [22] [Figure 2]

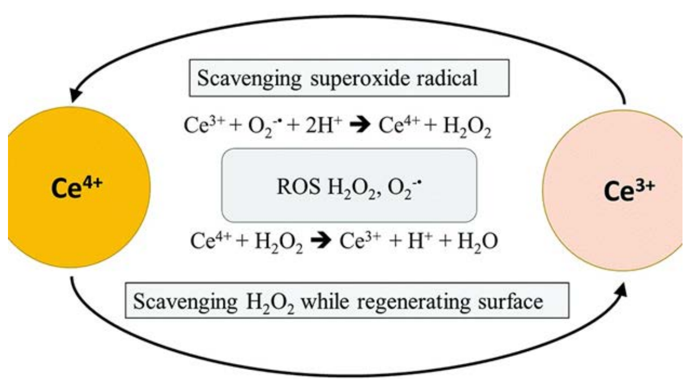


Figure 2: Scavenging activity of cerium oxide nanoparticles

CNPs have showed antioxidant enzyme-mimetic activity and the capacity to scavenge both reactive oxygen species (ROS) and reactive nitrogen species (RNS) in cell and animal models. Various studies state that CNPs with high amounts of Ce3+ (40% to 60%) [23] on the surface perform better as SOD-mimetic while CNPs with high amounts of Ce4+ (70% to 80%) [24] on the surface perform better as CAT-mimetic. As previously mentioned, $H_2O_2$ functions as a member of ROS due to the ability to generate the destructive species through the Fenton reaction. [2]It is worth noting that $H_2O_2$ is one of the end products when CNPs are used as a SOD enzyme-mimetic. The CAT enzyme could turn $H_2O_2$ into $O_2$ and $H_2O$, decreasing the risk of invasion of $H_2O_2$.Therefore SOD activity needs to be combined with CAT activity to protect against oxidation. [2] Thus the antioxidant activity produced by the CNPs enable the prevention of perimplantitis when used in the form of surface modification over the implant surface.

Recent work has also demonstrated that the addition of CNPs in bioactive glass scaffolds increased the proliferation and collagen production of human mesenchymal stem cells (hMSCs) by acting as free radical scavenger. [20]

**Antibacterial Activity**

Subgingival plaque being an initiating factor in the pathogenesis of peri-implantitis is a biofilm composed of a complex unmineralized microbial community that adheres to the tooth/implant surface and cannot be washed away by water. [25]The bacterial colonizers are grouped into three during biofilm formation such as initial, middle and late colonizers. S.sanguinis is the earliest colonizing bacteria in the formation of plaque. F.nucleatum adheres in the middle of the plaque development and tends to connect between early and late colonization of bacteria. Various studies have asserted that F. nucleatum could cause specific co-aggregation between the bacillus and peri-implant pathogens. [26] P. gingivalis is the most important dominant strain in the pathological or active part of peri-implantitis and is responsible for the late colonization of the biofilm. Therefore S. sanguinis, F. nucleatum and P. gingivalis were selected as representative strains for peri-implantitis-associated biofilm experiments in vitro. [2]

Current studies have suggested that the bacterial attachment to mucosal surfaces is the preliminary event in the development of most infectious diseases. Saliva-derived protein adsorption is a prerequisite for bacterial attachment which is present on the material's surface. [26] Thus the repellency of salivary protein pellicle from the surface of dental implant is of importance for inhibiting the occurrence and progression of peri-implantitis. Surface nanotextures possessed a high surface density of nano-irregularities, which represented a strong limitation for bacteria adhesion as they strongly restricted the availability of berth points. [27] Hence, the nanoceria coated surface had restricted free-area which would prevent the adhesion of Gram-positive bacteria. This adhesion-inhibition mechanism could not prevent gram negative bacteria, yet it should be noted that S. sanguinis was regarded as the earliest colonizing bacteria in the formation of dental plaque. Thus it is important to prevent the adherence of S. sanguinis more than F. nucleatum. Furthermore, presence of nano-CeO2 caused biofilms to consist of mostly dead P. gingivalis bacteria in comparison to titanium which showed live bacteria on its surface. [2] Various studies have also asserted that nanoceria had manifested antimicrobial activity against Pseudomonas aeruginosa; and at lower temperature antibacterial activity was seen against E.coli, B. subtilis, Shewanellaneidensis and Pseudokirchneriella supcapitata. [21]

**Anti-Inflammatory Activity**

Peri-implant tissues have more tendency to cause inflammatory disease than tissues of periodontium due to their reduced vascularization and parallel orientation of the collagen fibers. The bacteria known to cause peri-implantitis instigate tissue destruction by releasing toxic products, and indirectly by activating the host defense systems resulting in inflammation. [27]

Chemokines essentially IL-6 were produced by lymphocytes, epithelial cells, monocytes as well as fibroblasts in response to bacterial LPS; and they could stimulate the formation of osteoclasts and bone resorption. Additionally, there was a higher expression of IL-6 in diseased gingival tissues than the healthy tissues. TNF-α plays a prominent role in the pathogenesis of peri-implantitis and is involved at an early stage in the inflammatory cascade to promote the release of other inflammatory mediators in order to increase the inflammation. [28] IL-1b is noticed in inflamed gingival tissues disrupting the activities of connective tissue cells and exerting a catabolic effect on bone. These pro-inflammatory mediators that cause local and systemic inflammation may result in damage to the injured tissues, thus accelerating the eventual failure of dental implants. $CeO_2$ exerted its anti-inflammatory effect mainly by its capability of switching between Ce3+ to Ce4+ valence states. [22] Since CeO2 has both CAT and SOD activities, it resulted in predominant antioxidant activity which is a prime factor responsible for the anti-inflammatory mediation.

To further confirm the anti-inflammatory mechanism of nano-CeO2, the NF-kB signal pathway was evaluated by the NF–kB/p65 subunit translocation experiment. P. gingivalis-LPS could activate the NF-kB signal pathway that leads to high expressions of inflammatory factors such as TNF-a, IL-6 and IL-1b. [29] The nano-CeO can decrease the expression of TNF-a, IL-6 and IL-1b in macrophages, inhibit the NF–kB/p65 subunit translocation from cytosol to nucleus and thus exert a remarkable anti-inflammatory effect by deactivating the overt NF-kB signal pathway. [2]

**Surface Modification of Ceria**

According to a study by KaI Li et al, nanostructured $CeO_2$ coating was prepared via plasma spraying technique and this coating exhibited no toxicity to MC3T3-E1 cells and promoted cell adhesion compared to the Ti–6Al–4V control. [20]The MC3T3-E1 is an osteoblastic cell line established from a C57BL/6 mouse calvaria, which is known to have the capacity to differentiate into osteoblasts and osteocytes and has also demonstrated the formation of calcified bone. Importantly, the $CeO_2$ coating preserved the cells' antioxidant defense system by maintaining SOD activity and suppressing intracellular ROS generation and lipid peroxidation in the MC3T3-E1 cells exposed to $H_2O_2$ and therefore protected cells from oxidant-mediated damage. [20] The use of the $CeO_2$ coating is its ability to act as antioxidant and promote bone regeneration under oxidative stress.

Li et al. incorporated nano-CeO2 onto Ti alloy surface by magnetron sputtering. [30]Increasing the Ce4+/Ce3+ ratio in nano-CeO2 was effective in modulating the osteogenic capability of stem cells and the polarization of macrophages, resulting in favorable new bone formation and osseointegration. [30]Recently, endeavors to augment the catalytic activity of CeO2 were realized through the synthesis of nano-CeO2 with controlled shapes. Shape manifestation in nano-CeO2 is closely correlated with the amount and mobility of oxygen vacancies coupled with Ce3+ ions on each crystalline plane. Therefore, shape controlled synthesis of nano-CeO2 enclosed by particular crystalline planes appears to be an effective approach for enhancement of intrinsic catalysis. [31]

Study by Xue Li et al, synthesized nano-$CeO_2$ with three different shapes (nanorod, nanocube and nano-octahedron) using hydrothermal methods by changing the reaction conditions. [2]This study successfully synthesized different shapes of nano-$CeO_2$ (rod-$CeO_2$, cube-$CeO_2$ and octa-$CeO_2$) and developed novel $CeO_2$-modified surfaces with substantially enhanced anti-inflammatory and antibacterial activities. The octa-$CeO_2$, due to its smallest size and the unique octahedral structure exposing more crystalline planes exhibited the highest $Ce^{3+}$ value and the strongest ROS-scavenging capacity. The excellent bactericidal performance of nano-$CeO_2$ was demonstrated in the formation of bio-films wherein octa-$CeO_2$ had the strongest inhibition against early adhesion of bacteria and it also had the best anti-inflammatory effect among the three shapes due to its potential scavenging property. [2]

**Conclusion**

In this burgeoning era of dentistry, implants play a pivotal role in almost all facets of dental treatment. Osseointegration has known to be the principal aspect contributing to the favourable outcome of these implants. Many studies have attempted to enhance the osseointegration of implants by various surface modifications. The topography of the surface of dental implants is critical for adhesion as well as for differentiation of osteoblasts in the primary phase of osseointegration and long term bone remodeling. Nanotechnology, yet another booming scope of dentistry has aided in the manipulation of implant surfaces to mimic the surface topography formed by extracellular matrix components of natural tissue. Nano-roughness, chemical composition, and hydrophilicity of implant surfaces are prime determinants with regard to the adhesion of osteogenic cells, prevention of bacterial accumulation during the healing process as well as for the maintenance of the soft and bone tissues surrounding the implant. Though bioactive CaP nanocrystals have proved to stimulate bone apposition and healing previously, the incorporation of ceria nanoparticles had auxiliary antibacterial, anti-inflammatory and antioxidant activity on implants. Thus these innovative modalities of development in the surface modification of titanium implant surfaces not only offer mechanical merits, but have a valuable therapeutic potential as well.

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