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Review Article

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Osteoconductive Metallic Implants Using Hydroxyapatite Nanoparticles

T P Gamagedara[1,2,3]* and R M G Rajapakse[1,2]

[1]*Post Graduate Institute of Science, University of Peradeniya, Peradeniya, Sri Lanka*

[2]*Deparment of Chemistry, Faculty of Science, University of Peradeniya, Peradeniya, Sri Lanka*

[3]*Department of Basic Science, Faculty of Allied Health Sciences, University of Peradeniya, Peradeniya, Sri Lanka*

***Corresponding author**

T P Gamagedara, Dept of Basic Science, Faculty of Allied Health Sciences, University of Peradeniya, Augusta Hill, Peradeniya, Sri Lanka, E-mail: piumnilg@ahs.pdn.ac.lk

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Abstract

Bone is a dynamic and highly vascularized connective tissue that has a unique capability of spontaneous regeneration and to remodel its micro- and macro-structure. The nano-hydroxyapatite has a nano-crystalline feature similar to the bone, thus being used as a bone substitute material. In the case of severe defects, bone would not heal by itself and grafting is required to restore function without damaging living tissues. Most commonly used prostheses material in orthopedics is 316L stainless steel (SS). Due to some problems in SS, various surface modification techniques have been developed to improve the corrosion resistance and biocompatibility of the metals.HA coatings have been extensively studied for the bioactive surface treatment of bio inert metals and ceramics due to its similarity with bone material. This article gives an overview of using hydroxyapatite in preparing osteoconductive metallic implants.

Introduction

Hydroxyapatite ($Ca_{10}(PO_4)6(OH)_2$) (HA) is the main inorganic component of natural bone, constituting about 70% of the mass of the bone matrix. Nature has built extremely hard and tough bone using soft and brittle ingredients. Here, the polymer, collagen acts as a structural framework in which plate-like tiny crystals of HA are embedded to strengthen the bone [1]. HA provides rigidity to the bone and collagen provides flexibility and tensile strength. In the case of severe defects and loss of volume, bone would not heal by itself and grafting is required to restore function without damaging living tissues. The biocompatibility and bone-bonding ability has been troubling researches for years [2-7]. HA coatings have been extensively studied for the bioactive surface treatment of bio inert metals and ceramics because of the attractive biocompatibility [8-13].

316L SS is one of the important materials both in orthopedics and dentistry for use in bone screw/plate, intra-medullary rod, fixation wire, hip joint, and knee joint. However, the biocompatibility and bone-bonding ability has been troubling researches for years [2-7]. HA coatings have been extensively studied for the bioactive surface treatment of bio inert metals and ceramics because of the attractive biocompatibility [8-13].

Various surface modification techniques have been developed in recent times to improve the corrosion resistance and biocompatibility of the metals. One of the most effective methods is to deposit a protective bioactive ceramic coating layer on the metal surface. HA has been coated on metallic dental and orthopedic implants by high-temperature plasma thermal spray since the 1980s [14].

Bone and HA Nanoparticles

HA Nanoparticles

The main composition of the biological bone is nano-grained hydroxyapatite with the grain size of about 5 to 50 nm.Nanostructured hydroxyapatite is defined as the HA material with the grain size of less than 100 nm. The nanostructured materials exhibit some unique properties that normal microstructure materials do not have, such as high hardness and low wear rate for engineering materials. For HA, the nanomaterial will have extremely high surface area. Since the atoms in the surface layer has un-saturated atomic bonds, nano-HA exhibits high bioactivity, which accelerates the early stage bone growth and tissue healing [15,16]. The smaller the grain size, the higher the surface atoms, resulting in quicker bone growth and faster dissolution rate [17].

It has also been proven that the nano-HA, compared to conventional micro HA, promotes osteoblast adhesion, differentiation and proliferation, osteointegration, and deposition of calcium-containing minerals on its surface, leading to enhance formation of new bone tissue within a short period [18].

Role of the Bone

Bone is a dynamic and highly vascularized connective tissue that has a unique capability of spontaneous regeneration and to remodel its micro- and macro-structure. This is accomplished through a delicate balance between an osteogenic (bone forming) and osteoclastic (bone removing) process. Bone can adapt to a new mechanical

environment by changing the equilibrium between osteogenesis and osteoclasis [19]. It is a highly specialized form of connective tissue pertaining to the formation of the skeleton of the body. It ensures that the skeleton has adequate load-bearing capacity, and acts as a protective casing for the delicate internal organs of the body and an anchoring point for most skeletal muscles and ligaments [20]. In addition, bone serves as a reservoir for minerals, particularly, calcium and phosphorous, so that it is involved in homeostasis by regulating the concentration of key electrolytes in the blood [21].

The nano-HA has a nano-crystalline feature similar to the bone, thus being used as a bone substitute material [22]. Synthetic nano-HA has been used in medical applications since 1970s. The major products are coatings on metallic dental, hip, and spine implants for the acceleration of early stage healing and decreasing the pain. Other products such as nano-HA powders or porous blocks are used as bone fillers [17].

Bone Grafting

Clinical Need for Bone Engineering

Many circumstances call for bone grafting owing to bone defects either from traumatic or from non-traumatic destruction such as tumors, infections, biochemical disorders, abnormal skeletal developments, etc. [21,23].

Majority of fractures will heal well without the need for major intervention due to the high regeneration capacity of the bone, particularly in younger people. Nature provides different types of mechanisms to repair fractures in order to be able to cope with different mechanical environments of a fracture [24]. There are four prerequisites for bone healing described by the diamond concept, those are, cells with osteogenic potential, an osteoconductive matrix, an osteoinductive stimulus and a mechanically stable environment [25]. But the fractures of bones due to various trauma or natural aging are a typical type of a tissue failure. An operative treatment frequently requires implantation of a temporary or a permanent prosthesis, which still is a challenge for orthopedic surgeons, especially in cases of large bone defects as observed after bone tumor resections and severe nonunion fractures [26,27].

Bone Grafting

The need for a bone graft depends on the type and the degree of complication of the bone defect. For example, if the defect is minor, bone has its own capacity to self-regenerate within few weeks. Therefore, surgery is not required. In the case of severe defects, bone would not heal by itself and grafting is required. The graft materials not only replace missing bones but also help body to regenerate its own lost bone. There are multiple methodologies available for the treatment of bone defects, which include autografting, allografting, xenografting, and alloplastic or synthetic bone grafting.The key role of bone grafts is to provide an ideal framework for the host bone to regenerate newbone tissue, soft tissue, and vascular and other metabolic components. In this regard, selection of a bone grafts is of great importance as the clinical success rate depends in part, on the characteristics of those grafts [28-30].

Osteoinduction by Calcium Phosphate Biomaterials

In the past two decades, a large number of publications have illustrated osteo induction by diverse calcium phosphate biomaterials, such as synthetic hydroxyapatite ceramic in dogs, coral derived hydroxyapatite ceramic in dogs, monkeys and baboons, α-tricalciumphosphate, β-tricalcium phosphate, biphasic calcium phosphate, α-pyrophosphate and β-pyrophosphate ceramics. In addition, calcium phosphate cements and coatings were shown to be osteoinductive in various animal models. Besides calcium phosphate-containing biomaterials, osteoinduction was also observed in alumina ceramic, titanium and glass ceramics. The last group of materials was shown to be able to precipitate a calcium phosphate layer on their surface in a calcium- and phosphate-rich environment, and the in vivo ectopic bone formation was preceded by the process of calcification [23,31-37].

Although the exact processes involved in the mechanism of osteoinduction by biomaterials are still largely unknown, work by many groups has shown that biomaterials need to meet very specific requirements in terms of (a) macrostructure, (b) microstructure and (c) chemical composition in order to be osteoinductive.

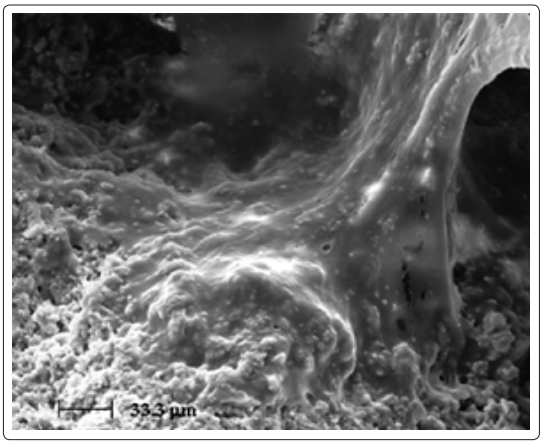

Figure 1: Structural and functional connection between bone cells and the surface of an artificial implant (38)

Biomedical Prosthetic Devices

Biomedical prosthetic devices are used in the human body to fulfill the functions that are no longer performed by the original human parts. Prostheses are made of biocompatible materials, which can be metallic, ceramic, polymeric or composites [39]. Fig. 2 and 3, 4 show some images of biomedical prosthetic devices.

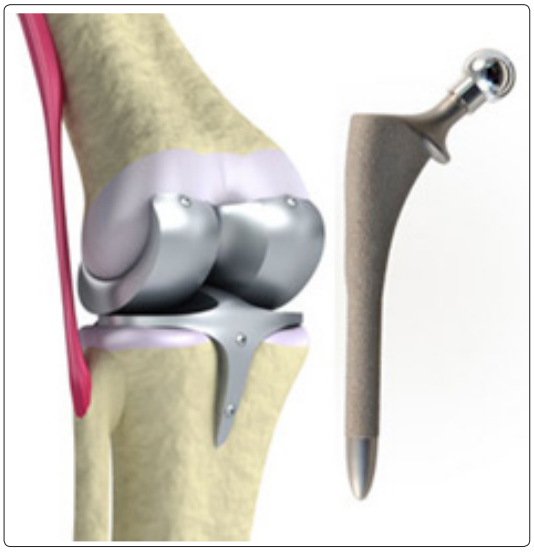

Figure 2: Illustrations of some knee prostheses

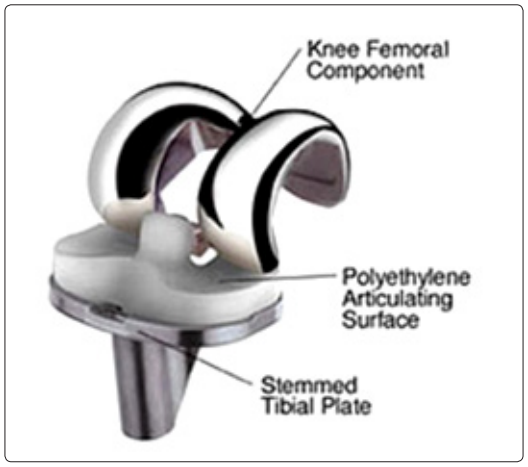

Figure 3: Illustrations of some knee prostheses

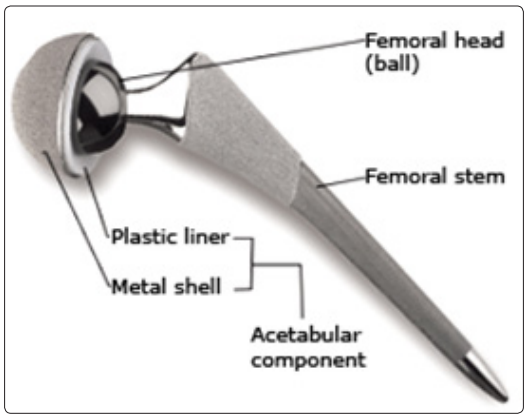

Figure 4: An illustration of a hip prosthesis

Metals have been used in clinical orthopedics since the early 1900s. 316L stainless steel, Co-Cr alloys, Ti_6Al_4V, Au-Ag-Cu-Pd alloys, Amalgam, Ni-Ti alloys, titanium (Ti) are some of the metallic biomaterials in use. Pure Ti and its alloys were proposed as implant materials, and have been successfully used in reconstructive surgery and prosthetic treatment because of their biocompatibility and osseo integration [40,41]. Among the various metallic materials that are used for orthopedic devices, 316L SS is one of the most commonly used because of its low cost and acceptable biocompatibility and it has been frequently used for temporary implants in orthopedic surgery. Although stainless steels are biologically tolerated, no chemical bonds are formed between the steel and the bone tissue. However, under some conditions this alloy suffers localized corrosion and releases significant quantities of iron to its neighboring tissue inducing fibrosis around the implant [3]. In addition, as it is a foreign material, the metallic implants get encapsulated by fibrous tissues [41]. The only means of bio-fixation is mechanical interlock where hard tissues can grow into the implant and anchor it in place. If the implant does not integrate well with the surrounding bone or is not held rigidly with a fastening device, the implant will be subjected to micro-movement and the surrounding bone will remodel. This may lead to implant loosening over a period of time. The long-term success of joint replacement largely depends on the stable fixation of the implant to bone. Current methods rely on mechanical fixation either with or without the use of acrylic bone-cement [42, 43].

The elastic moduli of those biometals are 5-10 times greater than that of the natural bone, which gives complications of mechanical compatibility [21]. According to Wolff's law, if a stiffer implant material is placed into bone, the bone will be subjected to reduced mechanical stress that gradually leads to bone resorption. This phenomenon is known as stress-shielding. It has been recognized that matching the stiffness of the implant with that of host tissue limits the stress-shielding effect. Owing to insufficient interfacial bonding between metal implant and host tissue, there is limited osteointegration [44].

Surface Modification Techniques of Metallic Implants

Bioactive Ceramic Layers

Various ceramic coatings have been identified to induce bioactivity on the metallic prosthesis, such as titanium dioxide, calcium phosphate and silica based glasses. HA coatings deposited on stainless steels improve osseointegration, due to their capacity to form chemical bonds (bioactive fixation) with the bone tissue and due to the osteoconductive and Osseo integrative nature of HA, it has become a popular coating material for orthopedic implants for over two decades. HA coated metallic prostheses that combine the osteoconductivity of HA and the high strength of metallic alloys have been increasingly favored by surgeons for younger patients seeking joint replacement [3,13,42-46].

Many attempts have been made in the coating of metallic prosthesis with bioactive ceramic layer by using different coating techniques such as plasma spray, electrophoresis, electrochemical deposition, chemical vapor deposition, blast coating, ion beam sputtering etc. In high-temperature plasma thermal spray process, HA powders are fed into a plasma flame (temperature 5,000 to 15,000°C) where the powders are quickly melted and quenched on the metallic implant substrate toform a thick film coating. As the temperature is high, the coating contains melt and crystallized HA, unmelted HA, amorphous phase, and some decomposed phases such as C_4P, α-TCP, β-TCP, and CaO. Clinically, plasma thermal sprayed HA coating has been successfully used in dental implants and femoral stems for hip replacement, but the HA coating on cups has a high failure rate. However, the plasma thermal sprayed HA has the disadvantage of low bond strength at coating/implant interface, and the strength decreases over time in simulated body fluid (SBF) as well as the higher coating thickness (>100μm) associated with the plasma spraying technique poses a major problem as it can cause failure due to fatigue under tensile loading [13,17,42].

Nano-scaled coatings are being used to produce orthopedic implants with better hard- and soft-tissue attachment, higher biocompatibility and enhanced bioactivity for bone-regenerative purposes. The biological mechanisms that rule these enhanced characteristics are not fully defined. However, several performance guidelines of the biomimetic nanoapatites can be addressed, as listed below [47,48].

a) In vivo dissolution of the biomimetic nanoapatite, leading to the saturation of surrounding fluids and thus accelerating the precipitation of truly biological apatites onto the coated implant.
b) Adsorption of large amounts of protein from the neighboring environment due to the surface charge of the nanoapatite, thus triggering cell.
c) The microstructure of the substrate/apatite coating increases the surface roughness, which is beneficial for osteoinduction as compared to smooth surfaces.

d) The apatite could be the source for Ca^{2+} and PO_4^{3-} ions that may signal cells toward the differentiation pathway and trigger bone formation.

e) Since the biomimetic nanoapatite is similar in structure and properties to natural biological apatites, it could constitute an excellent substrate for new biological phase nucleation.

Preparation of Osteoconductive Metallic Implants

It is very important to provide a nanostructured coating surface, because in addition to materials chemistry, Nano topography can be recognized by cell receptors as such influenced biological response. To prepare osteoconductive metallic implants, many attempts have been made by using different coating techniques such as plasma spray, electrophoresis, electrochemical deposition, blast coating, ion beam sputtering etc.

Surface topography has long been established to affect the behavior of cells of all lineages. An in vivo study showed that increased bone growth occurred on electrophoretic deposition coated screws where there was increased roughness and porosity in comparison with the smooth bio mimetically coated implants. Roughening the implant surface has been recognized as the way to improve implant fixation. Texturing and patterning are the two major types. *Texturing* thesurface of the implant enhances the interaction betweenthe biomaterial and growing bone and overcomes the problem of coating delamination. Larger the nanometer scale roughness, the lower the contact angle and higher the surface energy of the nano-porous surface, leading to enhanced osteoblast-material interactions. Nanostructured surfaces (mesoporous nanoscaffolds, nanoflowers, nanoneedles, nanorods and octahedral bipyramids) showed enhanced protein adsorption behavior when compared with polished surfaces. Moreover, *patterning* surfaces provide optimum cell growth and functionality. These surfaces further control cell proliferation and differentiation in building complex tissues that are otherwise not possible with a uniform surface. There is now increasing evidence that surface topography both on the micro- and nanoscale are important in determining the cell response to biomaterials [51,52].

It was shown in a study that HA-coated specimens are highly porous and they can only provide a small increase in the corrosion resistance of the system through the partial blockage of the pores in the coating due to the precipitation of salts. In a previous study, it was found that a continuous and porous TiO_2 coating on the 316L SS impedes strongly the ion release, thus avoiding bio-toxicity. The porous TiO2 coating acts as a viable alternative for improved corrosion resistance and it also enhances the biocompatibility of the implant. However, bone does not bond directly to these materials, therefore, in order to enhance the bone-bonding ability, titanium and its alloys are often coated with HA by various methods. Hence the combination of nano-TiO_2 and nano-HA coating on 316L SS may be used as an alternative in orthopedic appliances, providing a competitive and low cost alternative related to highly expensive conventional Co-Cr and Ti alloys [3,41,53].

In an *in vitro* study, human monocyte-derived macrophages and human osteoblast-like (HOB) cell models have been used to study the biocompatibility of nano-HA coatings where nano-HA was observed to support the attachment and the spread of HOB cells. In another study using porous nano-HA scaffolds, periosteal-derived osteoblast (POB) was isolated from the periosteum of four-month human embryos aborting and seeded on porous nano-HA scaffolds where POB could fully attach to and extend on HA scaffolds, and form extracellular matrix. In a comparison study between nanosize HA filler and microsize HA filler using a rat calvarial defect model, histological analysis and mechanical evaluation showed a more advanced bone formation and a more rapid increase in stiffness in the defects with the nanosize HA augmented poly (propylene glycolcofumaric acid), suggesting an improved biological response to the nano-HA particles [16,54].

Since the biological apatite of bone mineral is a nanoapatite, the synthesized nano-HA is expected to be recognized as a part of the body. Therefore, rather than being phagocytized, the synthesized nano-HA could be directly involved in the natural bone remodeling process [17].

Conclusion

HA coated metallic prostheses combine osteoconductivity of HA and high strength of metals or metallic alloys. It is increasingly favored by surgeons for younger patients seeking joint replacements.

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