Surface modifications of titanium based dental implant to accelerate osseointegration process

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ABSTRACT
Dental implants is a prosthesis that is invasively implanted in the patient's to replace missing teeth. Osseointegra-gration is the process where structural and functional relationships take place between bone and embedded dental implant surfaces. Unfortunately, titanium based dental implants show lack of osseointegration. Therefore, dental implant modifications could be one way to overcome this limitation. This article intensively reviews several surface modification methods to accelerate the osseointegration process on titanium dental implants. A literature review presented in this article. It is concluded that implant surface modification with other materials could accelerate the osseointegration process. Otherwise**,** modification of surface implants such as physical, chemical and biological mo-dification are discussed.
Keywords: implant surface modification, dental titanium, osseointegration

INTRODUCTION

Dental implants are one of denture abutments which are inserted into maxillary or mandible that interfaces with the alveolar bone for replacing missing teeth.[1,2] Dental implants are implanted to jaws in order to increase retention and support to the denture. Dental implant placement can restore the function of mastication, esthetic, and articulation.[1,3] Clinically, the success of dental implants can be seen in several indicators such as patient satisfaction, aesthetics, stability of dental implant, absence of soft tissue infection around the implants, retention of dental implants, and minimal bone loss radiographically.[3] Materials for dental implant can be divided into four groups: metal, ceramics, polymers, and hybrids.[4] Until now, widely used material for dental implants is titanium (Ti) because it has low density, high strength, non-toxic, and resistant to corrosion. Despite these advantages, one of the disadvantages of titanium is the lack of osseointegration between the implant and bone.[3]

Osseointegration is the structural and functional relationship between bone and dental implants surface.[5] This osseointegration is the key to the stability of dental implants and considered a pre-requisite for the success of a dental implant.[3,5] Osseointegration in dental implants is considered to develop if there is no progressive movement between dental implants and bone in direct contact.[6] The osseointegration process can be influenced by two factors, the bone-dental implant interface environment and the design of the dental implant itself. The material, surface, and topology of the implant can affect the osseointegration process.[4] Dental implants made of titanium produce poor osseointegration so that modifications of implant surface are required.[3]

Implant surface modification is a technique used on the surface of dental implants to increase surface roughness, physically mimic bone structure, and improve implant biocompatibility. Modification of dental implants surface plays an important role because that is one of important factors affecting the osseointegration process. Methods of implant surface modification can be divided into three categories; physical, chemical, and biological, which have their own advantages and limitations.[4] Based on this, the authors are interested to investigate more thoroughly about the various surface modifications to accelerate the osseointegration process in titanium dental implants.

LITERATURE REVIEW

Dental implants are prosthetic devices surgically implanted into the alveolar bone in either the maxilla or mandible to replace missing teeth. Dental implants can also be defined as substances placed in bone to provide retention and support for fixed or removable dental prostheses.[2,7]

The materials used for implants have undergone significant developments. Being able to withstand mastication loads, biocompatible, resistance to fracture, and non-corrosion are properties that must be possessed by an ideal implant material. Materials with mechanical properties similar to bone can increase the amount and rate of bone growth. Based on the nature of the materials used for fabrication, dental implants can be divided into three groups: metals, ceramics, and polymers.[4,8]

Metal has been used for many years and remains the most frequently used material in orthopedic surgery due to its biomechanical properties.[4]

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Titanium (Ti) is the most commonly used metal for implants worldwide and material of choice for implants because it has a good potential to fuse with bone. It has high durability, resistance to corrosion, and low modulus of elasticity. Ti6Al4V (Titanium; 6% aluminum; 4% vanadium) is titanium alloy with good mechanical properties compared to other titanium alloy. Aluminum in Ti6Al4V can increase the strength and density of metals while vanadium can prevent corrosion of aluminum. The disadvantage of titanium is it can cause allergic reactions. Allergy to titanium material can cause facial eczema, dermatitis, rash, and hyperplastic gingiva.[4,8]

Osseointegration is a structural and functional relationship between bone and implant surface without involving connective tissue. Osseointegration consists of two Latin words; *os*, which means bone and *integration*, which means to unite as a whole. The American Academy of Implant Dentistry (AAID) defines osseointegration as the strong, direct and lasting biological attachment of an implant to bone without the intervention of connective tissue.[7,9,10]

Osseointegration is a dynamic process involving a cascade of responses and the nature of the implant surface plays a major role in the success of the process. A cascade of cellular and extracellular biological events is involved in the healing of the bone around the implant. When the implant is inserted, an inflammatory response causes the release of several proteins such as cytokines and growth factors to form a blood clot. Proteins and lipids from the blood clot are then absorbed by the surface of the implant and then coat the surface of the implant. This pro-tein coat acts as a marker for cell proliferation and migration. Adhesion strength and protein type are influenced by properties of the implantsurface such as topographic features, surface roughness, and hydrophilicity. Blood platelets then form a fibrin matrix that acts as an intermediary or *bridge* for cell adhesion and migration.[4]

Macrophages and neutrophils will then adhere to the implant via the fibrin matrix 2-3 days after implant placement. Macrophages and neutrophils then remove pathogens and necrotic tissue and provide room for new blood vessels by breaking down the clot. Angiogenesis then occurs in the gap between implant and the bone four days after the implant placement. Mesenchymal stem cells (MSCs) will then gather around the blood vessels. Affected by cytokines and growth factors, MSCs differentiates and transforms into osteoblasts which can produce extracellular matrix and form immature woven bone. Implant surface and cell communication can direct MSCs to differentiate into fibroblasts which can stimulate the formation of a fibrobrous membrane on the surface of dental implants and interfere with the bone formation process.[4]

Woven bone formation will occur for 1-2 weeks after the implant is implanted and this phase is called the osteoconductive phase. Woven bone is a primitive type of bone tissue that is characterized by random collagen fibrils, low mineral density, and irregular shaped osteocytes.[4,10] There are two types of osteogenesis that occur based on where the MSCs is attached, distance osteogenesis and contact osteogenesis. Distance osteogenesis is the formation of bone that starts from the bone following migration to the implant surface through the fibrin matrix. Contact osteogenesis is bone formation initiated directly at the implant surface. These two processes of osteogenesis occur interactively, in which bone undergoing distance osteogenesis transmit signals to induce contact osteogeesis.[4] Distance and contact osteogenesis can provide secondary stability of implant (Fig.1).[4,10]

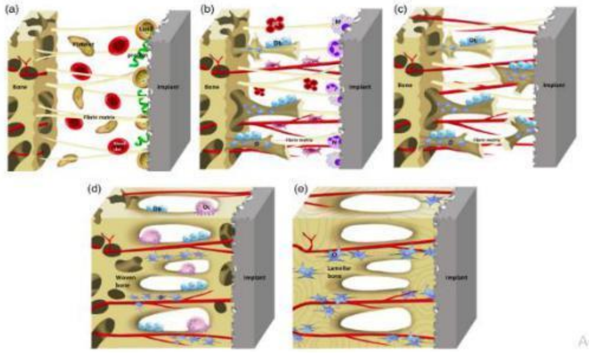

Figure 1 Osseointegration process in implants; **a** absorption of proteins and lipids from blood clots, **b** angiogenesis and woven bone formation, **c** distant osteogenesis and contact osteogenesis, **d** woven bone fills the gap between bone and implant and bone remodeling occurs, **e** woven bone turns into lamellar bone (Sources: Liu Y, Rath B, Tingart M, Eschweiler J. Role of implants surface modification in osseointegration).

The gap between the bone and the implant will then be filled with woven bone within two weeks and then the final process of osseointegration, i.e. apposition and bone remodeling, occurs. At this stage, the osteoclasts and osteoblasts work in harmony and the woven bone will gradually become parallel fiber bone and then turn into lamellar bone.[4] Parallel fiber bone is an intermediate stage between woven bone and lamellar bone while lamellar bone is the most complex type of bone with the highest strength.[10] At this stage the osteoclasts absorb the newly formed bone to overcome the microcrack and optimize the bone surface for lamellar bone formation. Osteoclasts form a sealing zone and create various microtopography and nanotopography containing biochemical information that will direct osteoblasts to areas that require new bone formation. This process then occurs continuously for a year or more.[4]

DISCUSSION

The nature of the implant surface has an important role in the osseointegration process therefore modifications of the implant surface are needed to improve the properties of the implant surface and assist the osseointegration process. Surface modification is a technique used on the surface of dental implants to increase the surface roughness of the implant, mimic the original bone structure, and improve implant biocompatibility[4] and accelerate the osseointegration process so that patient treatment time can be shortened. Modification of the implant surface produces changes in the morphology of the implant surface without affecting the physical properties of the implant material.[11] Surface modification can be divided into three methods, i.e. physical, chemical, and biological methods.[4]

Surface modification with physical methods

Surface modification with physical methods changes the topography and morphology of the implant surface using dry transformation technology to create a favorable environment for the osseointegration process. Surface modification using physical methods are grit blasting, plasma spraying, physical vapor deposition (PVD), and additive manufacturing (AM).[4]

Grit blasting is a surface modification method to increase the surface roughness of implants by firing abrasive particles at the implant surface.[2,4] There are several types of particles that can be used for grit blasting, they are titanium, calcium phosphate, and aluminium. Aluminium is the most commonly used particle. This is a simple method and does not cost much.[2,4]

The rough surface resulting from grit blasting will aid cell adhesion to the implant surface. Implant surface roughness is affected by size, shape, and properties of particles used. Aluminium particles in grit blasting can form an isotropic surface. Grit blasting can be combined with acid-etching to accelerate the process of osteogenesis. The disadvantage of this method is that the surface roughness formed can increase the adhesion of bacteria.[2,4]

The AM is a technology capable of making complex 3-D structures at the micro or nanometer scale. This method can form a layer-by-layer structure that is difficult to obtain through traditional processes. The layer-by-layer manufacturing process in AM can be carried out using lasers and electron beams.[4,10] The advantages of this method are that it can be used on all types of materials available in powder form, can produce complex shapes with details, and has high flexibility. This surface modification method can contribute to MSCs adhesion, alkaline phosphatase secretion, and collagen deposition.[4] This method can make implants based on computerized tomography (CT) of the patient thus produce suitable junction between implant and the bone contour of the patient.[13]

Plasma spraying is a thermal spraying technique in which the material is sprayed to coat the entire implant surface when the material is in a molten or semi-melted state. The material in powder form is put into the plasma and then melted at approximately 1000°C. The melted material spreads over the implant surface and subsequently solidifies and forms a deposit or lamellae layer.[4,14] An appropriate temperature is required for the material to reach a liquid state and not return to a solid state before reaching the implant surface. Temperatures that are too high can cause the material to evaporate before it reaches the implant surface.[14] This surface modification method is a safe and inexpensive method and the chemical composition present during the surface modification process does not persist on the implant surface. This surface modification method can improve biocompatibility, resistance to heat, corrosion, and damage, and osseointegration process.[4,14]

The PVD is a surface modification method that produces a vaporous material to cover the implant surface. This surface modification method converts the viscous material into a vapor then deposited on the implant surface in a viscous form. Sputtering deposition is the most commonly used technique for dental implants. Ion dispersion during the sputtering process removes substrate ions on the implant surface to create a space for the material for implant surface coating. The coating material will adhere firmly to the implant surface. This surface modification method can increase the resistance to corrosion and damage as well as increase the biocompatibility and hardness of the implant surface. Research shows that PVD can provide antibacterial properties and can increase angiogenenesis at the implant surface.[4,15]

Surface modification with chemical methods

The purpose of implant surface modification using chemical methods is to form a chemical junction between the implant surface coating material and bone. Chemical modifications can alter the implant surface through various chemical reactions

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such as carbonization, oxidation, or nitriding.[4]

Anodic oxidation (anodization) is an accelerated electrochemical process in which an oxide film is applied to the surface of the anode implant while the implant is immersed in a liquid electrolyte. This surface modification method is used to enhance anodization by accelerated electrochemical process in which an oxide film is applied to the surface of the anode implant while the implant is immersed in a liquid electrolyte. This surface modification method is used to improve the anti-corrosion properties of implants. Anodization can increase the bioactivity, osseointegration, surface roughness, and hydrophilicity of implants. Micro and submicro surface roughness formed by anodization can increase the adhesion of osteoblasts to the implant surface.[4,16]

Sol-gel is a low-temperature method that forms oxides or solids by heat treatment. In this method, organic or inorganic compounds undergo hydrolysis polymerization and turn into a colloidal solution (sol) which will then gradually turn into a two-phase system that resembles a gel. The implant furthermore dipped in the solution and removed at a predetermined time. The remaining liquid afterward removed through a drying process resulting in shrinkage of the structure. Heat treatment subsequently carried out to improve the mechanical properties and polycondensation. This method is fulfilled at low temperatures hence, the chemical composition of the coating material can be adjusjusted. When combined with other coating materials, sol-gel may form a bioactive layer that can respond to bone structure.[4,11]

Acid etch; this surface modification method uses a strong acid to change the surface of the implant. The acids used can be nitric acid (HNO_3), hydrofluoric acid (HF), and sulfuric acid (H_2SO_4).[17] The reduced surface of the implant in this method can be affected by the acid concentration, type of acid, etching time, and temperature.[2,17] Sulfuric acid is an acid that has been shown to be effective in increasing implant surface roughness.[17] Acid etching can remove the passivation layer and expose the underlying implant surface. Acid etching can produce a rough implant surface, increase the migration and retention of osteogenic cells, increase bone adhesion and formation, and promote osseointegration. This method can reduce the risk of contamination in the blasting method.[2,11,17] The disadvantage of this method is that chemical changes can occur on the surface of the implant treated with this method.[11]

Alkaline treatment is a surface modification method that involves immersing the implant in a high-alkaline solution and then heat treatment. Alkaline treatment can form nano holes and increase apatite nucleation on the implant surface.[10,18] This combined with acid etching can increase surface porosity and develop bioactivity without disturbing the shaft structure and mechanical properties of the implant material.[2,18]

Chemical vapor deposition (CVD) is a surface modification in which a gaseous compound undergoes a chemical reaction on a heated surface and furthermore creates a solid film on the implant surface. Just like PVD, deposition and condensation procedures of materials are also involved. The thing that distinguishes between PVD and CVD is the coating of deposits on the surface of the implant, CVD coats the surface of the implant through chemical bonds while PVD coats the surface of the implant using physical force. This method can enhance the potential for osseointegration and make homogeneous structure.[4]

Surface modification with biological methods

This method uses cell implants and biological coatings that can elevate the attachment, differentiation, and proliferation of osteoblasts. It is an additional method to improve osseointegration. Cells implanted onto the implant surface could be bone marrow-derived stem cells (BMSCs), mesenchymal adipose stem cells (AMSCs), mesenchymal stem cells (MSCs), and embryonic stem cells. The proteins implanted could be vascular endothelial growth factor (VEGF) and extracellular matrix protein (EMP). Implantation of cells may promote osteogenic adhesion, growth, and differentiation and advance bone formation. The disadvantage is cells and proteins embedded into the implant can penetrate the surrounding tissue or space, causing side effects and formation of fibrous membrane.[4]

Platelet rich plasma; biologically, plasma is the non-cellular part of the blood. The PRP is a platelet-rich blood plasma that can promote healing and early bone apposition. The application of PRP with zoledronic acid to the implant surface can provide good functional and aesthetic results. Studies have shown that implant surfaces modified using PRP with zoledronic acid can amplify the number of filopodia in osteoblasts attached to the implant surface, indicating the potential of PRP to improve early bone apposition and stability of dental implants, especially in patients undergoing bisphosphonate treatment.[19]

Extracellular matrix (ECM); during the osseointegration process, fibroblasts secrete ECM mole-

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cules such as collagen, vitronectin, and fibronectin that guide osteoprogenitor cells to surfaces that require new bone growth. ECM cell interactions can activate signals to promote bone healing. The implant surface coated with ECM molecules such as collagen sulfate or hyaluronan collagen might boost bone formation and maturation accordingly the application of ECM on the implant surface is considered to provide good results for the osseointegration process.[19]

Arginylglycylaspartic acid (RGD) is a specific amino acid which plays an important role in migration and adhesion of osteogenic cells. The RGD could initiate cell interactions resulting in cell attachment such as osteoblast adhesion.[19] Research has shown that RGD-coated implants might elevate bone-to-implant contact for three months post-implantation. However, there are studies showing that within two weeks post-implantation, there is no bone-to-implant contact and new bone filling on implant surface.[19]

The P15 peptide is an artificial amino acid which mimic cell-binding properties of human collagen. The application of P15 peptide on the implant surface can increase the attachment of osteoblasts and mesenchymal cells and increase the discharge and differentiation of osteogenic cells, accelerating the osseointegration process. When combined with competence-stimulating peptide (CSP), this peptide can have an impact on osteogenic activity and suppress biofilm formation.[19]

Strontium-incorporated protein can significantly improve bone-to-implant contact, bone formation, and mechanical properties of implants when applied to the implant surface. More specifically, this method may increase the initial adhesion, proliferation, and osteogenic differentiation of bone marrow stromal cells, increase the release of osteogenic genes such as bone morphogenetic protein 2 (BMP-2), and increase ability of new bone formation. There are several techniques to coat the implant surface with strontium-incorporated protein but it does not have a major effect on the contact between the bone and the implant surface.[19]

Growth factors; platelets and macrophages present in the early phase of osseointegration release several growth factors such as transforming growth factor β (TGFβ), and fibroblast growth factor (FGF) to facilitate the next phase of osseointegration. The application of these growth factors to the implant surface can accelerate the osseointegration process. Bone morphogenic proteins (BMP) such as BMP-2, BMP-4, and BMP-7 which are part of TGFβ for stimulating bone formation. When applied on the implant surface, BMP can enhance bone regeneration and provide better bone-to-implant contact and new bone formation.[19]

The FGF, especially FGF-2, can directly amplify the proliferation of osteoblasts. Cell dispersion and differentiation as well as osseointegration might enhance if FGF 2 nanoparticles are applied to the implant surface.[19]

It is concluded that titanium is the material of choice for dental implants because titanium has a good potential to integrate with bone. It is the most commonly used material because it has high durability, resistance to corrosion, and low modulus of elasticity. Ti6Al4V alloy is titanium with good mechanical properties compared to other titanium alloy.

Properties of the implant surface have an important role in the osseointegration process hence, modifications to the implant surface required to improve the properties of the implant surface and assist the osseointegration process. Surface modification is a technique used on the surface of dental implants to increase the surface roughness of the implant, mimic the original bone structure, and improve implant biocompatibility.

Surface modification can be divided into three methods, i.e. physical, chemical, and biological methods. Physical methods include grit blasting, plasma spraying, PVD, and AM. Chemical methods include anodization, sol-gel, acid etching, alkali application and CVD. Surface modification with biological method use cell implants and biological coatings which might increase the attachment, differentiation, and proliferation of osteoblasts.

The main disadvantage of the current implant surface treatment is the lack of clinical data which necessitates more clinical and laboratory studies. The future of dental implants will depend on more efficient, sophisticated and well-designed standardized clinical and laboratory research methodologies for developing and attaining implant surface treatment standards.

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