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Review Article

Osseointegration and Foreign Body Reaction of Dental Implants

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Abstract

The concept of titanium dental implant osseointegration is associated with mechanical stability and the formation of mineralized bone tissue at the organism-implant interface. However, a conceptual divergence exists explaining why only titanium implants have osseointegration. It is possible to explain the differences between the interaction mechanisms of cells and proteins with titanium, zirconia, stainless steel, or other material implants. Due to this lack of explanation, some researchers proposed that titanium implants have a foreign body reaction and zirconia implants have osseointegration. This work presents the differences between the organism's responses to titanium and zirconia.

Introduction

Considering the basic concepts of materials biocompatibility, it is possible to explain the divergences in understanding the osseointegration of titanium and zirconia. There are divergences in the concepts of biocompatibility, inflammatory processes, osseointegration, foreign body reaction, and the mechanisms of protein interaction with the surfaces of titanium and zirconia implants. The biocompatibility of materials is limited and must be evaluated by possible applications. For example, one material (CoCrMo alloy and stainless steel) is biocompatible enough for hip prosthesis application but unsuitable for dental prostheses. The interactions of proteins and cells with biomaterials can induce different inflammatory processes, the formation of fibrous tissue, osseointegration, and foreign body reactions. The interaction between proteins and the surfaces of stainless steel, CoCrMo, titanium, and zirconia implants differ and define the material biocompatibility and applications.

In medicine, three requirements are analyzed to state that an implant is osseointegrated: in the visual analysis of the radiograph, there must be no space between the implant and the bone, the implant must present mechanical stability, and the patient must not feel pain [1]. Based on this medical concept, some researchers [2] cite that zirconia dental implants, cemented orthopedic prostheses, stainless steel prostheses, and Co-Cr-Mo alloys have osseointegration. There are differences of opinion regarding the statement that zirconia dental implants osseointegrate and that titanium implants induce foreign body reactions. In dentistry, a bond between bone cells and the implant surface through proteins characterizes the osseointegration of titanium dental implants. Only titanium implants surface with microroughness have osseointegration. Smooth Ti implants or other materials do not have osseointegration. Proteins are attached to the surface of titanium implants through chemical, physical, and mechanical bonds. These proteins interact with bone cells and transmit signals for bone tissue formation in the region surrounding the implant. In this case, there is no fibrous connective tissue interface formation. The bond between the proteins and the titanium implant has mechanical strength capable of maintaining mechanical stability and supporting functional loads during chewing.

Some authors [3,4] presented the hypothesis that inflammatory cells are associated with the presence of the biomaterial (graft or implant). They do not consider the influence of the injury caused during the surgery. From the second hypothesis, it is assumed that, since inflammatory cells are present at the site, foreign body reactions are associated with the implants. Titanium dental implants do not induce foreign body reactions.

Cells' Interactions with Biomaterial Surface and Reactions

The human body reacts differently when organ transplants, tissue grafts, and biomaterial insertions are performed. Surgery to perform organ transplants involves complex surgical intervention and the use of medications to inhibit the immune system and reduce the possibility of infection and rejection. These body reactions are caused by the transplanted organs having leukocyte antigens or Major Histocompatibility Complex (MHC). The human body's immune system recognizes the antigens on the surface of the cells of the transplanted organ. Rejection will occur when the immune system recognizes that the antigens of the transplant are aggressive [4]. Synthetic biomaterials (metallic alloys, polymers, or ceramics) for specific applications do not have antigens and are not recognized as harmful by the body. Complications with synthetic biomaterials and reactions to natural autogenous grafts are lower than with homologous grafts, isografts, and xenografts.

Cell interactions with synthetic implants vary by chemical composition, physical properties, surface morphology, and mechanical loading conditions. The human body does not reject Co-Cr, Co-Cr-Mo, polymer, and zirconia implants because they do not have antigens on their surface. These implants do not have osseointegration and form fibrous connective tissue at the interface with the body. Only medical devices with a titanium oxide layer osseointegrate. Unalloyed titanium (ASTM F67) and Ti-6Al-4V (ASTM F136) implants with surface treatment osseointegrate. The osseointegration depends on the surface roughness, surgical technique for inserting the implant, insertion torque, and prosthesis loading conditions after healing tissue. Titanium implants with polished surfaces form fibrous connective tissue at the interface with the body.

Cells' response to biomaterial depends on the signals from proteins attached to the surface. Adhesion receptors on the cell membrane interact with proteins adsorbed on the biomaterial's surface. Pro-adhesive proteins, including fibronectin, vitronectin, and fibrinogen, are recognized by cellular integrins and platelets. Plasma proteins play a significant role in recruiting cells from the biomaterial's surface. Fibronectin is a glycoprotein from the extracellular matrix that binds to the

biomaterial surface. Fibronectin is recognized by receptors located on the membrane of osteoblasts. Osteoblasts recognize fibronectin as signal-transmitting elements of material characteristics. The osteoblasts adhere to fibronectin adsorbed on the surface of the biomaterial. Fibronectin contains an RGD tripeptide that transmits signals to cells to form tissues. With the information received by the receptors on the membrane, the osteoblast response results in the spreading or incorporation of cells onto the titanium surfaces. Some components of the extracellular matrix or related peptides (RGD) on the implant surface activate the osseointegration process. They serve as a signal and transmit instructions to the cells to attach on the surface, spreading, differentiating, and inducing bone tissue formation. In addition to fibronectin, bone sialoprotein is another essential protein involved in osseointegration. Sialoprotein is found in mineralized tissues, including bone, dentin, and cementum.

Fibronectin contains a terminal cell adhesion sequence (RGD) and two glutamic acid domains. It nucleates hydroxyapatite formation, stimulates bone remodeling, and mediates the adhesion of fibroblasts, osteoblasts, and osteoclasts. The adhesion sites between the cells and the substrate are called focal contacts or adhesion plates, with the joining distance between them being around 10-15 nm. The external faces of the focal contacts present specific receptor proteins such as integrins. On the internal side, proteins such as talins, paxillins, vinculins, and tensins are known to mediate interactions between actin filaments and integrins. The formation of focal contacts generally occurs in cells with low motility and can be produced in vitro through extracellular matrix proteins such as fibronectins or vitronectins.

Figure 1 shows a representative drawing of proteins, neutrophils, and monocytes interacting with the implant surface. After recognition of the biomaterial, the proteins transmit signals to the cells to form hard tissue (osseointegration), fibrous tissue (fibrointegration), or induce a foreign body reaction. The selective protein adsorption on the biomaterial surface determines its biocompatibility [4,5]. The proteins in contact with the biomaterial recognize its characteristics that determine the organism's reaction and the type of tissue that will be formed at the interface. Proteins identify the biomaterial's chemical composition, physical properties (rigidity, density), electrical charges, and residual stress. After initial recognition, the proteins transmit signals to the immune system. The first and foremost proteins interacting with the biomaterial are from blood plasma, the complement system, growth and coagulation factors, and those from the extracellular matrix. Mast cells act as sentinels and transmit signals about the presence or absence of the antigen in the biomaterial. Signals are transduced, and information is transmitted to cellular receptors. In this phase, the development of modulation of responses related to inflammatory phenotypes determined by M1 (pro-inflammatory) and M2 (anti-inflammatory) macrophages occurs. Next, tissue reconstitution begins (tissue regeneration or healing process), and different types of tissues can form at the interface (osseointegration, fibrointegration, or foreign body response).

Inflammatory and Immunological Response Due to Materials

The surgical procedure to place the implant damages tissues. The most common lesions are blood vessels at the level of capillaries and tissues originating from connective tissue (dense connective tissue and bone tissue), which are highly vascularized. The natural inflammatory response begins (acute inflammation) for tissue reconstruction (repair and regeneration) due to tissue damage. Tissue reconstruction involves the participation of different types of cells (Figure 1), mainly mast cells, neutrophils, and macrophages [6]. The inflammatory process caused by damage from the surgical wound differs from the presence of biomaterials. The body's reactions vary with the intensity of the damage caused by the preparation of the surgical socket and the type of implant inserted. Among the proteins that participate in this process, the most common are: Blood plasma (albumin, types of globulins, LTF, SERPINC1, TF, KNG1, HBB, LYZ, GC, HPR, OMR1, OMR2, CLEC3B, A2M, PONT1, GSN, PTH1R, APO A1, APO C1, APO E, PLG, CP, Apo, Hp, Hpx), Growth factors (fibrinogen, factor Ia, F12, PROC, APOH SERPINF1, SP TFG-α, TFG-β1, TFG-β2, TFG-β4 and TFG-β7, and complement system (C3, C4A, C6 and C8B).

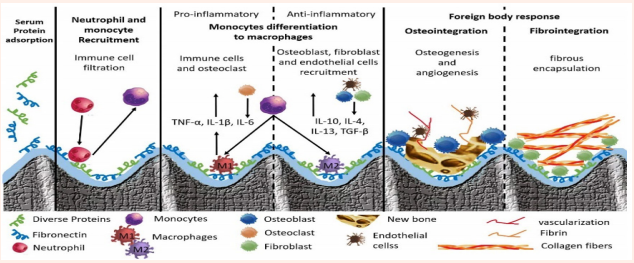

Figure 1: Representation of the interaction between the organism and the biomaterial. From left to right side: protein adsorption, neutrophil and monocyte recruitment, pro-inflamatory and anti-inflamatory system, osteointegration or fibrointegration body reaction.

For inserted devices to be recognized as "foreign bodies and not belonging to the organism," a specific immune response is necessary after T lymphocytes recognize the device's antigens on the device's surface. Since synthetic biomaterials do not have antigens, the immune system does not activate a response-specific immune system, and B lymphocytes do not create antibodies to combat the biomaterial.

Osseointegration

To explain the mechanisms involved in osseointegration or the formation of fibrous connective tissue (fibrointegration) at the interface with dental and orthopedic implants, the interactions of proteins with the devices' surface and bone cells must be analyzed. Different definitions of osseointegration are used in medicine and dentistry. In dentistry, osseointegration is the contact between bone cells and the implant surface through a nanometric layer of proteins and glycoproteins (Figure 2). The concept of osseointegration of dental implants is associated with implant retention by approximating bone cells to the implant surface (ISO 164430) [7]. Osseointegration is a phenomenon in which the bone is connected to the implant surface through proteins without the interposition of connective tissue. The mechanical resistance to removal of an osseointegrated implant is higher than that of an implant encapsulated by fibrous connective tissue. Figure 2 represents the possible interaction processes between titanium, the organism, and the interface types.

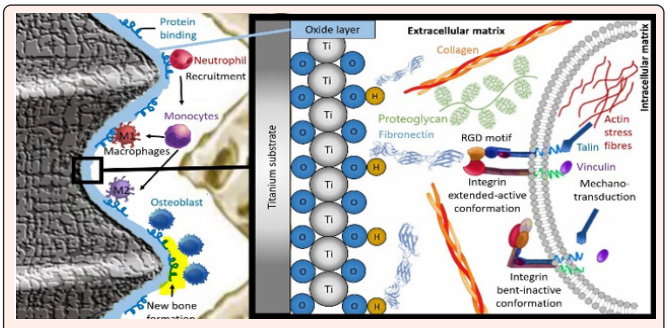

Figure 2: Representative interaction among proteins and the titanium oxide layer.

The surface of the titanium implant is coated with a nanometric layer of titanium oxide TiO_2. Titanium oxide has a property that breaks the chemical bonds of the body's water, forming OH^- and H^+ ions. From this moment on, the implant is coated with electrical charges that interact with the proteins of the extracellular matrix. Other biomaterials do not induce the formation of OH^- and H^+ ions. For this reason, the

reactions of CoCrMo alloy, zirconia, or stainless-steel implants are different from those of titanium. The interactions of extracellular matrix proteins with the implant surface and cells define whether there will be osseointegration or the formation of different fibrous tissue [8]. The tissue formed depends on the implant's chemical composition, the properties of the implant surface, stiffness, roughness, wettability, and surface energy. For osseointegration to occur, osteoclasts must remove the layer of bone tissue damaged during the preparation of the surgical socket.

Some implants made with the same material may react differently with the body. The morphology of the implant surface influences the specific reactions of the organism. Titanium implants with a rough surface osseointegrate, whereas those with a smooth surface do not osseointegrate and form fibrous tissue [9]. When implants are made of other metal alloys, polymers, or ceramics, proteins adsorbed on the surface transmit signals to cellular receptors to form dense connective tissue at the implant-tissue interface.

Conclusion

Based on the concepts presented, it can be concluded that:

a. Biomaterials do not have unlimited biocompatibility, and each material has biocompatibility for a given application.
b. The body can reject the organ implants because they have antigens on their surface.
c. Synthetic biomaterials (implants) do not have antigens and are not rejected.
d. Only medical devices with a titanium oxide layer have osseointegration, and other biomaterials induce the formation of fibrous tissue (fibrointegration) at the implant-body interface or foreign body reaction.

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