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Protein interactions with osseointegrable titanium implants

Marvin do Nascimento[1], Thays Obando Brito[1], Andreza Menezes Lima[1], Carlos Nelson Elias[1]*

[1] Department of Materials Sciences, Military Institute of Engineering, Rio de Janeiro, RJ, Brazil.

Aim: this review aims to present the mechanisms of protein interactions with titanium dental implant surfaces. **Methods:** the analyses were based on searches of scientific articles available in English and Portuguese in PubMed (MEDLINE), Bireme (LILACS), Scielo, Web of Science and Google Scholar. **Results:** titanium dental implant treatments success rates (95-98%) are mainly due to the biocompatibility of titanium oxide on the implant surface, surgical techniques adopted, good implants manufacturing processes and biomechanical knowledge of the systems. Studies in past decades has empirically developed implant surfaces with significant changes in morphologies, roughness, wettability, surface energy, chemical composition, and chemical groups density or deposited molecules. These changes promoted better protein adsorption, osteoblast adhesion, and changes in the mechanisms involved in osseointegration. Thus, the time to put the implant in function has been reduced and the success rates have increased. In the osseointegration process, at the nanoscale, there is no contact between the bone and the implant surface, but there is the formation of a protein anchorage between the periosteum and the implant with an interface formed by proteins. In all the reactions between the body and the implant surface, the activities of fibronectin and integrin are essential, since they are responsible for transmitting information to the cell for its differentiation, adhesion and mobility. **Conclusion:** thus, the analyses of protein-implant interactions are indispensable for a better understanding of the performance of osseointegrated dental implants.

Keywords: Osseointegration. Bone-implant inteface. Dental implants. Proteins.

Corresponding author:
Carlos Nelson Elias
Military Institute of Engineering
Pr Gen Tibúruco, 80
Rio de Janeiro, RJ 22290-270
elias@ime.eb.br

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Introduction

In the past, materials used as biomaterials were selected based on their performance in other than medical-dental applications[1]. The material selection for dental implants was made considering mainly mechanical and corrosion resistance (first generation biomaterials). No consideration was given to the immune response or hypersensitivity reactions that could occur a few years after implantation due to ion release and the proteins interactions with the implant surfaces[2]. In many applications the implantations' results were disastrous and even led to irreversible damage of the patient's organs with the need for amputation[3].

The knowledge about the interactions between organisms and biomaterials developed, paradigms were changed and the molecular and biomechanical aspects associated with the cells interactions with surfaces began to be considered (second generation biomaterials). Biomaterials are no longer just organs or functions replacements, but devices that interact with cells[4].

The new biomaterials allow adhesion of specific proteins in order to stimulate cell differentiation to obtain the expected physiological response[5]. In some situations, adhesion of cells or proteins to the biomaterial is not desired, as in the case of coronary stents. In others, implants are encapsulated by fibrous tissues, orthopedic devices[3]. The trend is to select the biomaterial for individualized and personalized application, which may be suitable for one recipient organism and inappropriate for another[6].

Thus, to reach this level, researchers need to know the interactions of the biomaterial with the body. There is a need to understand how the mechanical or biochemical bonding of the implant to the tissues occurs. Current data show that the bonding of osseointegrable dental implants to bone occurs through layers of proteins and glycoproteins forming a bone-implant interface[7].

However, knowledge about the regulatory mechanisms, or formation, of this bone-implant interface is still incomplete[8]. Information related to this topic is scattered and often researchers from complementary fields do not exchange information. The hypothesis is that there is probably an interaction between cell membrane proteins (integrins) with the titanium oxide layer mediated by other proteins (fibronectin). Given this deficiency, the aim of this review is to present the mechanisms of protein interactions with titanium dental implant surfaces.

Methodology

This study is a literature review that aims to present the interactions of proteins with the surface of titanium osseointegrable dental implants. Articles published in Portuguese and English during the last fifteen years were searched. The following databases were used as search tools: PubMed (MEDLINE), Bireme (LILACS), Scielo, Web of Science and Google Academic. The keywords were: "biomaterials", "dental implants", "dental implant surfaces", "osseointegrable implants", "bone matrix", "bone proteins", "osteogenesis", "osseointegration", "osseointegration AND dental implants", "integrin", "integrin AND osseointegration", "fibronectin", "fibronectin AND osseointegration". Manual

searches were also performed in the references of the researched articles and books. The main inclusion criterion for the articles was that they addressed the interaction process between proteins and biomaterials.

Results

Biological Response and Osseointegrated Implant Integration

Brånemark's osseointegration concept appeared in 1960 with the perspective that the bone maintained full contact with the implant, so that it was firmly anchored to the titanium implant surface on a microscale. As time went by, new researches emerged and new paradigms began to be considered, such as biocompatibility. Thus, the biocompatibility conception emerged as a primordial property for the establishment of an excellent interaction between bone tissue and the biomaterial[9].

Osseointegration process on nanoscale allows for the anchoring of proteins between the endosseous implant and the bone tissue. This is so that it can support the functional loads of mastication. This process can be divided into three phases: osteoconduction, bone formation, and bone remodeling[4]. Osteoconduction is a process defined by the migration of cells from the bone extracellular matrix to the osseointegrable implant surface. This event occurs at the level of migration, attachment activity, proliferation, differentiation, and bone proteins expression such as osteocalcin, osteopontin, and fibronectin[10].

However, osteoconduction is already part of the natural bone remodeling process, so the difference is that in implant installation, there is the presence of a blood clot in contact with the implant surface in peri-implant repair. Thus, it can be seen that angiogenesis precedes osteogenesis in both bone regeneration and remodeling[11].

As bone tissue cells begin to migrate to the implant and approach the surface, these cells start to differentiate. The osseintegration process is initiated by adsorption of the blood plasma proteins, but the phenomena involved are slow and it takes several days for the osteogenic deposition to reach the implant surface[11-13]. When the biocompatibility principle is not fully favorable, the fibrointegration process occurs. Cell proliferation, tissue regeneration, and the normal bone tissue reconstitution do not occur. The tissue around the implant is replaced by scar tissue, forming a fibrous connective tissue capsule[1].

Thus, after the implant is inserted into the gnatic bones, a cascade of biological responses will sustain the bone integration process. Immune and inflammatory responses associated with the complement system are mediated in the osteoconduction space[4]. Therefore, seconds after implant insertion, a temporary matrix of fibrin and plasma proteins (2-5nm) is formed[2]. Based on this process and on the biocompatibility response of the dental implant with the surrounding tissues, the integration process will be determined.

Bone Extracellular Matrix Proteins

The osseointegration concept used to be associated with the cell's adhesion to the implant surface. Today, this concept involves the bone cells contact with the implant

surface via a protein interface[14]. Osseointegration is not characterized by bone matrix contact with the implant surface. The process begins with the deposition of extracellular matrix proteins on the implant surface. After adsorption, protein adhesion to the implant surface occurs, followed by protein interaction with undifferentiated cells via specific receptors[15].

In protein-cell interaction, signal-transduction mechanisms are mediated by proteins in the cytoplasm, leading to cell differentiation, attachment and propagation on the implant surface[16]. Protein's adsorption on planar surfaces occurs almost instantaneously after implantation, forming a 2-5nm layer through molecular-scale interactions with the substrate[17].

The bone extracellular matrix provides a suitable environment for the growth and differentiation of various body cell types, and has various proportions of proteins that participate in the osseointegration process[18].

Among the matrix extracellular constituents, the various macromolecules such as glycoproteins, proteoglycans, glycosaminoglycans and other proteins are essential in the biomaterial recognition mechanisms and interactions. Glycoproteins are proteins that have oligosaccharide chains attached to polypeptide side chains. Glycoproteins interact between the extracellular matrix components, help in the structure formation, promote adhesion and cell signaling[19].

The main matrix extracellular proteins are fibronectin, vitronectin, laminin, osteonectin, entactin, tenascin, osteopontin, thrombospondin, collagen, entactin and chondronectin. The top five are adhesive proteins and have a particular function of interest in the implants osseointegration. They can bind to cell surface proteins (integrins), collagen fibers, and other proteoglycans[19,20].

Fibronectin and vitronectin are extracellular adhesion proteins, they induce the actin microfilaments reorganization inside the cells and transmit messages for cell adhesion and dissemination to occur, which in turn affects cell morphology and migration. They favor cell adhesion, proliferation, and differentiation by interacting with specific integrins. These interactions are essential in the mechanisms surrounding implant osseointegration[15-20].

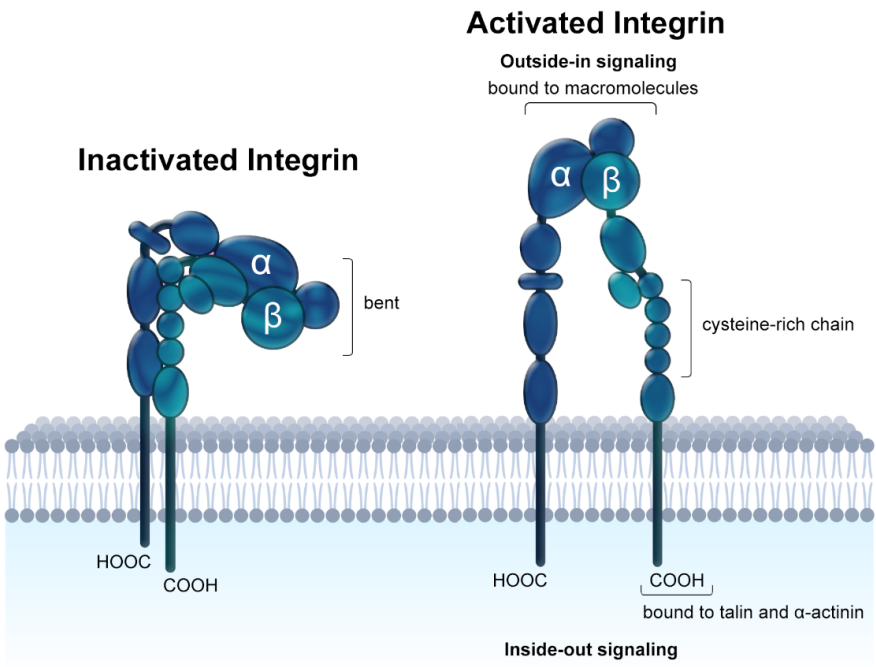
The Role of Integrin in the Osseointegration Process

Integrin is a transmembrane protein that belongs to the extracellular matrix that binds to the intracellular cytoskeleton. Each integrin types has a specificity, but most of them bind to the actin filaments through an adaptor protein (talin) or to the intermediate filaments[21]. In the extracellular space, integrins bind to collagen fibers, fibronectin, and laminin. However, there are other cells that possess integrins, such as the white blood cells, which bind to other cells that help search for infections. In the blood, the binding with fibrinogen assists in clot formation[22].

The integrin structure is composed of two heterodimeric α and β chains. The α part contains about 1008-1152 amino acids, with a cytoplasmic region of 22-32 amino acids and a transmembrane part of 20-29 amino acids. The β part consists of 770 amino acids with a cytoplasmic region of 20-50 amino acids and a transmembrane

part of 26-29 amino acids. The α- and β-parts contain disulfide bridges for protection against proteolysis (they do not covalently bind) and bind to the sequence-specific arginine-glycine-aspartic acid (RGD) amino acid sequence found in matrix proteins such as fibronectin and vitronectin[21,22].

When integrin is in the inactive state, it is in the folded form described as jackknife-like, it does not bind and does not signal. However, when activated, it opens and extends away from the cell surface. The signaling depends on the ligand and the integrin. The ligand affects integrin binding and integrin clustering and works in both directions. When a ligand adheres to a target, it sends signals for the cell to undergo changes, such as controlling its growth and shape[23,24]. Figure 1 shows schematically the integrin binding to its intracellular receptor.



Legend: Representation of the integrin. On the left side the inactivated integrin, while on the right side the activated protein. Adapted from BioRender (2022).
Figure 1. Integrin Structure Schematic

Integrin performs bidirectional signaling: inside-out and outside-in. The first is configured with the cellular processes/mechanisms that promote the change in affinity for ligands. While the second initiates a signals cascade to modulate cell behavior. Thus, integrins provide anchoring and signaling in the development, organization, maintenance, and repair of various tissues. They act in the processes of survival, migration, and cell cycle progression, as well as in the expression of differentiated phenotypes. In other words, they act as regulators of cellular response to implanted devices and biomaterial biological interaction[25].

Bone tissue cells, especially, osteoblasts, express a range of integrins, usually the integrin subunits α1, α2, α3, α4, α5, α6, αv, β1, β3 and β5. This expression is not constant, i.e., it varies with the stage of osteoblast development[26,27]. Cell behavior changes following integrin-signaled cell adhesion. This signaling can be from the outside in (signal transduction from the matrix to the cell) and from the inside out (cell binding to the matrix). Depending on the type of signaling, the cell moves, grows, proliferates, and undergoes differentiation[25]. Specifically, in the presence of titanium alloys, osteoblasts express the integrin subunits α2, α3, α4, α6, αv, β1, and β3[27].

β1 integrin (ITGB1) is a cell surface receptor that in humans is encoded by the ITGB1 gene. This integrin associates with α1 integrin and α2 integrin to form integrin complexes that function as collagen receptors. It also forms dimers with α3 integrin to form integrin receptors for netrin 1 and reelin. These and other β1 integrin complexes are historically known as very late activation antigens[28].

Integrin receptors exist as heterodimers and more than 20 different heterodimeric integrin receptors have been described. All integrins, α and β forms, have large extracellular and short intracellular domains[26]. The cytoplasmic domain of β1 integrin binds to the actin cytoskeleton. β1 integrin is the most abundantly expressed β-integrin and associates with at least 10 different α integrin subunits[27].

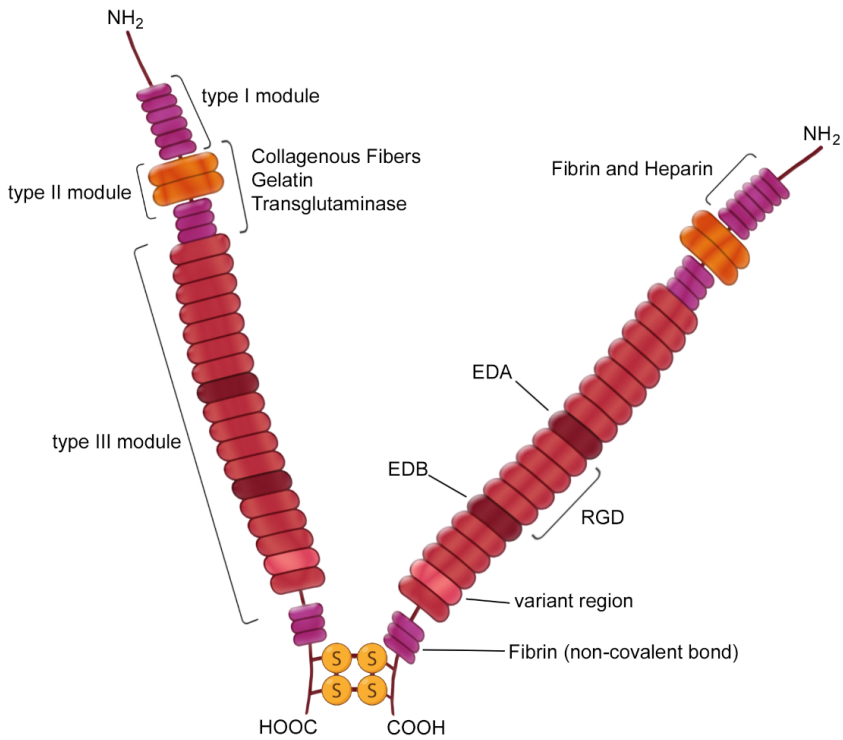
Integrin family members are membrane receptors involved in cell adhesion and recognition in a variety of processes, including embryogenesis, hemostasis, tissue repair, immune response, and metastatic spread of tumor cells[25,26]. Integrins bind the actin cytoskeleton to the extracellular matrix and transmit bidirectional signals between the extracellular matrix and the cytoplasmic domains. The β-integrins are primarily responsible for directing integrin dimers to the appropriate subcellular sites, which in adhesive cells are mainly focal adhesions. β1 integrin mutants lose the ability to target to focal adhesion sites[28].

Three isoforms of β1 integrin have been identified, named β1B, β1C and β1D. β1B integrin is transcribed when the proximal 26 amino acids of the cytoplasmic domain in exon 6 are retained and then succeeded by a 12 amino acid stretch from an adjacent intronic region. The β1B integrin isoform acts as a dominant negative in that it inhibits cell adhesion[26,28]. The second β1 integrin isoform, called β1C, is described as having 48 additional amino acids attached to the 26 amino acids in the cytoplasmic domain. This isoform integrin function is inhibitory on DNA synthesis in Phase G1 of the cell cycle. The third isoform, called β1D, is a striated muscle-specific isoform, which replaces the canonical β1A isoform in cardiac and skeletal muscle cells. This isoform is produced from splicing into a new additional exon between exons 6 and 7. The cytoplasmic domain of β1D integrin replaces the 21 distal amino acids (present in β1A integrin) with an alternative stretch of 24 amino acids (13 unique)[25-28].

The β1D integrin is developmentally regulated during myofibrillogenesis, appearing immediately after myoblast fusion in the C2C12 cell with increasing levels throughout myofibrillar differentiation[26]. The β1D integrin is located specifically in costomeres and intercalary disks of cardiac muscle, myotendinous junctions and neuromuscular junctions of skeletal muscle, and appears to function in general like other integrins, such as the β1D integrin cluster on the surface of skeletal muscle[28].

The Role of Fibronectin in the Osseointegration Process

Fibronectin (FN) is one of the most widely studied glycoproteins. It belongs to a family of 20 high molecular weight glycoproteins (440-500kDa) with about 5% carbohydrates. FN is an elongated (2 similar polypeptide subunits) dimeric glycoprotein (Figure 2) found in all vertebrates in soluble (blood plasma and other fluids) and insoluble (associated with the matrix extracellular meshwork) forms[29].



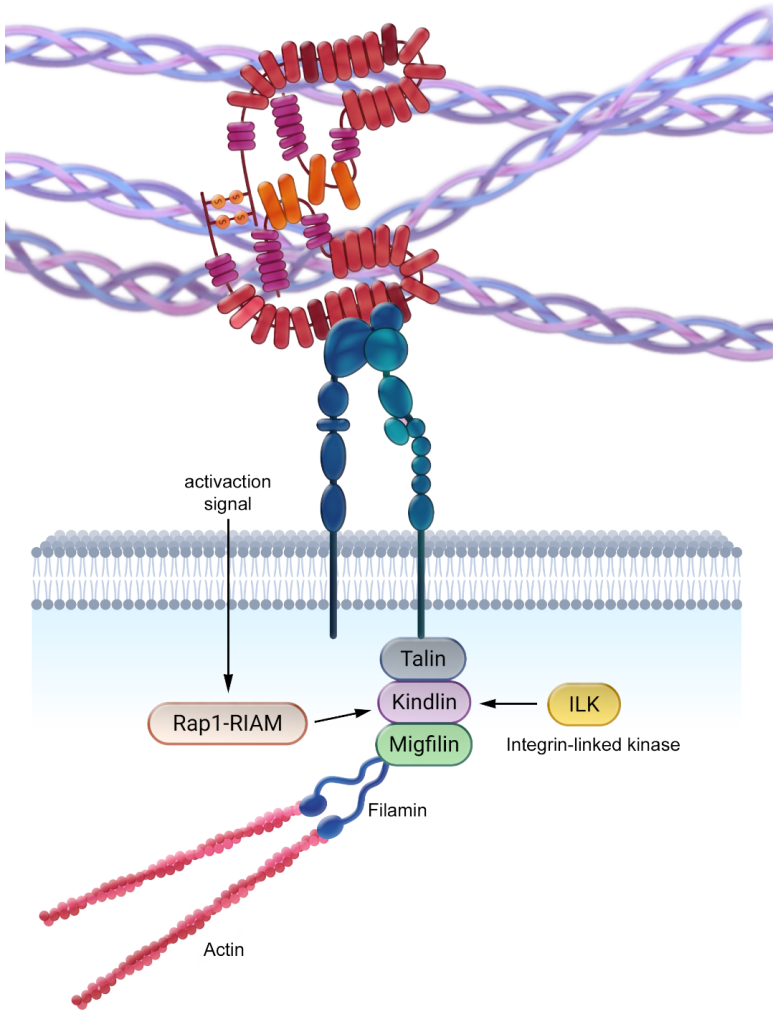
Legend: Representation of fibronectin showing its three modules (type I, II and III). Highlighting its specific domains and ligands. Adapted from BioRender (2022).
Figure 2. Fibronectin Structure Schematic

Each fibronectin subunit has an amino-terminal portion and a carboxy-terminal portion. Disulfide bridges connect one subunit to the other in the region near the each carboxyterminal portion. They have folds that lead to structural remodeling and various conformations according to the medium[30]. The subunits have a modular architecture formed by the repetition of 3 structures types (type I, II, and III) separated by short stretches of flexible polypeptide chains. Each subunit has 40-90 amino acids forming the various α and β domains. In the subunits there are regions of adhesion with non-epithelial cells, with other fibronectin molecules and with extracellular matrix components[31].

In the type III structure, with about 90 amino acid residues, is located the RGD sequence, which is specific for adhesion to the cell surface. The RGD region

of FN is recognized by and binds to eukaryotic cells via cell membrane protein receptors called integrins. It can bind to other molecules such as collagen fibers, fibrin, and heparin. FN, being an adhesive protein, mediates the cells adhesion to biomaterials[30].

Integrin has low-affinity binding domains for divalent cations, which in turn form a ternary complex with the divalent ion bound to the receptor. At contacts between RGD and integrin, the divalent ion is displaced. Figure 3 shows a schematic diagram depicting the connection between the cell interior and the matrix extracellular via the integrin. Integrin binds directly to an extracellular protein such as FN, its intracellular tail binds to an adaptor protein such as talin, which in turn binds to actin filaments[31,32].



Legend: representation of fibronectin binding to integrin and one of its receptors in the cytoplasm (collagen fibers). Adapted from BioRender (2022).
Figure 3. Fibronectin Interactions Schematic

When cells come into contact with the protein layer adsorbed on the biomaterial surface, they attach themselves through physicochemical interactions such as ionic and van der Walls forces. This is followed by cell-binding recognition on these proteins that is mediated by integrins[32]. Upon making bonds with their specific intracellular receptors, the integrins rapidly make contact with the actin filaments network of the cytoskeleton and assemble to form focal adhesions. Actins filaments are discrete complexes that contain structural and signaling molecules and function as structural links between the cytoskeleton and the plasma membrane to mediate cell adhesion and migration[33]. In conjunction with growth factor receptors, focal adhesions activate signaling pathways, which regulate transcription factor activity and direct cell proliferation and other functions[34].

On the cell membrane and in the cytoplasm, there are specific receptors for the different proteins. The main receptors in cells to bind most extracellular matrix proteins are integrins. Integrin is a heterodimer formed by non-covalently linked α and β chains consisting of several domains with flexible portions between them. It has a small intracellular tail (C-terminal) and a large extracellular domain (N-terminal). The extracellular portion recognizes and binds to the RGD amino acid sequence in the ligands, while the intracellular portion binds to a complex of cytoskeleton-associated adaptor proteins[32].

The integrins are activated as a result of the conformational changes. These, in turn, enable them to interact with their potential ligands. The basis for this phenomenon is the regulation of structural changes at one end that are related to structural changes at the other end. In their inactive state, the intracellular portions of the chains adhere to each other, making it difficult to expose and bind to talin, the main receptor protein in the cytoplasm. When the extracellular portion unfolds, the contact is broken, the intracellular portions separate, and the talin-binding site on the β-chain is exposed[33,34].

Similarly, internal conformational changes can trigger activation of the extracellular integrin portion. Talin competes with the α-chain for its binding site on the β-chain. When talin binds to the β-chain, it undoes the bond between the intracellular tails, separating them, which causes the extracellular portion of the integrin to acquire its active conformation[35]. The binding of integrins to their ligands is also influenced by the concentration in the extracellular medium of divalent cations, such as Ca^{+2} and Mg^{+2}, which can act in different ways such as promoting binding to the ligand, inhibiting binding to the ligand, and altering the specificity and binding to the ligand[36].

Integrin-mediated cell adhesions are multiprotein complexes that bind the extracellular matrix to the cytoskeleton. The adhesions can involve about 200 components, which are associated with distinct functions, including actin regulators, adaptor proteins that directly or indirectly bind actin to integrins, and a variety of signaling molecules, such as kinases, phosphatases, and G proteins and their regulators. Integrin-mediated cell-extracellular matrix adhesion complexes include focal complex, focal adhesion, and fibrillar adhesion[37].

Discussion

The osseointegration concept proposes the idea of bone regeneration, where the tissues are anchored by proteins on the implant surface[38]. Davies[13] (2007) considers it important to understand the cellular mechanisms involved in bone regeneration and remodeling during the planning and selection of the surgical technique for installing osseointegrable implants.

According to Mendes and Davies[4] (2016), there is no direct bone connection with the implant surface, as was previously believed. After implant installation, an adsorption of blood plasma proteins occurs followed by differentiation and production of the bone matrix at the interface with the implant surface. In this process, integrin, a plasma membrane glycoprotein, acts to control cell response and biological interaction with implants[25].

In this sense, the initial phase of protein adsorption and desorption will be described by the Vroman effect. In which proteins with high mobility and concentration, such as albumin (40mg/ml, molecular weight 67kDa and diffusion coefficient $6.1x10^{-7}cm^2/s$), are the first to be adsorbed after implant insertion and over time are replaced by other proteins such as fibrinogen (3mg/ml, molecular weight 340kDa and diffusion coefficient $2.0x10^{-7}cm^2/s$). The whole anchoring process is influenced by the implant surface characteristics[1].

Kumar et al.[39] (2004) states that still in the initial phase of osseointegration, thrombin and fibrinogen adhere to the implant surface, subsequently, neutrophils populate the implant receptor site before monocytes and macrophages infiltrate the area. And only five days after implantation, newly formed bone tissue is already present. In about eight to twelve weeks, osseointegration occurs.

Furthermore, according to Nascimento[38] (2022) protein adsorption on the implant surface creates a cell-implant layer, characterizing a sequence of protein anchors around of the dental implant, providing an osteoconductive space that will subsidize the osteoconductive ligament to form the peri-implant ligament.

These proteins facilitate and regulate cellular events for tissue regeneration, so the properties of the biomaterial surface, especially the roughness, influence the amount and properties of the proteins[1].

Kastantin et al.[40] (2014) highlights that the biomaterial physicochemical properties, such as *pH*, temperature, surrounding solvent system, ionic strengths, different protein concentrations or even the size and structure of these proteins affect the adsorption behavior of proteins. This adsorption occurs in monolayer and not by stacking, within a few seconds from the biomaterial implantation. Cells have no direct contact with the biomaterial surface, which characterizes the implant body response by the nature of protein adsorption[39,40].

The biomaterial surfaces properties influence the binding interface of biomolecules. Morphology, chemical composition, wettability, homogeneity, and energy are the main surfaces properties. However, when several proteins simultaneously come into contact with the surface, there is a competition between them. The proteins properties

that influence these interactions, among them molecular weight, electrical charge, size, structure stability, and unfolding ability, are important parameters.

Due to the hydrophilicity, the electrical charges of the amino acids are on the outside of the protein. Proteins with a higher number of charges tend to have a greater influence on adsorption. The unfolding ability also influences the protein adsorption. Proteins that unfold easily are those that expose the greatest number of contact sites[25].

According to Elias et al.[3] (2011) the chemical composition of the surface of titanium implants practically selects the type of anchoring protein. Titanium oxide allows osteoblasts to adhere via proteins. Adhesion of osteoblasts on stainless steel and zirconium surface is negligible.

Thus, surfaces with higher roughness have more contact area than the ones with lower roughness, or smooth surfaces, referring to the machining processes. In this sense, focusing on better osseointegration performance, several researchers, in an attempt to improve the osseointegrable implants performance, have made use of mimicking techniques, coating the surface with RGD[41]. The results showed that recognition of the RGD tripeptide alone is not sufficient to transmit messages for cells to form tissue. The cells behavior depends on the simultaneous association of receptors, integrins and co-receptors present on the membrane and in the cells cytoplasm. For the cell to have a specific response, it must decipher the complete message, such as fibronectin, and not just a part of the message containing one of the amino acids of the RGD sequence.

Based on these results, implant surface treatments were developed with surface properties that favor the unfolding and elongation of FN to increase their binding and attachment to the implant surface. It can be observed that cell spreading and its incorporation into the surface are rapid on fibronectin-coated surfaces at *pH*[4,5]. In this condition, fibronectin exposes all its parts, in particular the RGD region, which is recognized by intracellular receptors. The result is spreading or adhesion of cells on the surface[3].

Schierano et al.[42] (2021) point out that cell attachment is enhanced by additional synthesis and deposition of proteins that promote stronger binding. The adsorbed protein layer mediates subsequent interactions with cells in neighboring tissues, promoting cellular functions pertinent to new tissue formation, leading to implant integration and stabilization. The chemical and physical characteristics of the material surface influence the amount, distribution, density, conformation, and orientation of the adsorbed proteins. Although all the underlying aspects and mechanisms of protein interactions with the surface are not well understood, it is known that the chemical composition of the biomaterial surface is a determining factor. In addition to composition, surface topography also plays an important role in osseointegration. For example, morphologies with nanometric features enhance cellular functions compared to microstructured surfaces.

Although there are several papers that have analyzed the biomaterial-tissue interface, knowledge gaps still exist to explain how the biomaterial surface properties and the adsorbed protein layer affect cell behavior[42].

The unfolded FN acts as a binding site for many proteins and growth factors, including BMP-2 and, favors the differentiation of mesenchymal stem cells. Work has shown that the number of osteoblasts in the bone surrounding implants with a surface containing FN is higher than that observed in implants without FN. The number of osteoblasts is higher 7 days after surgery.

This result confirms the ability of FN to facilitate early adhesion and differentiation of osteoblasts. In FN-treated implants, the number of inflammatory cells was similar to that observed in control sites at 7 days and decreased over time. In addition, FN reduces inflammation, with a decrease in IL-1β expression observed. Few research papers have analyzed the pro-inflammatory or anti-inflammatory properties of FN.

The reported results are contradictory, mainly regarding the experimental protocol used. The heparin/fibronectin complex immobilized early on the titanium surface decreases the number of macrophages and their response to TNFα, a known pro-inflammatory molecule. Furthermore, a decrease in IL-1β release was also observed in the heparin/fibronectin treated implants. A similar anti-inflammatory effect was reported in the case of monocyte-derived macrophages seeded on FN-coated poly (L-lactic acid) films, where a significant decrease in the release of IL-6 (inflammatory cytokines) and an increase in IL-10 (anti-inflammatory protein) were observed. Differently, FN-treated expanded polytetrafluoroethylene induced an extensive inflammatory process when inserted into rat adipose tissue. In this case, foreign body giant cells typical of chronic inflammation were also observed.

Following this line, a main limitation of this results was the absence of articles that evaluate the biochemical mechanisms of integrin-fibronectin-implant interactions. Another factor is that most articles do not explicitly suggest the participation of other proteins in this process, and when they do, the mechanisms are not clear and/or explained. Another variance is the type of biomaterial; in most of the results it is not identified if it is commercially pure titanium (and its grade) or if it is a titanium alloy. Thus, it is difficult to determine which factors are more significant in the protein-implant interaction or even how or what explains this interface in the osteoconduction space.

Conclusion

In the present work the concepts and processes involved in osseointegration of titanium implants were presented. These concepts are essential to understand the influence of the titanium implants surface properties and to analyze the biological mechanisms response between proteins of the bone tissue extracellular matrix and biomaterials. In the osseointegration process, fibronectin and integrin are one of the main proteins that participate in the anchoring process between the bone tissue (periosteum) and the implant. Integrin acts as a transmembrane mediator with the protein ligaments between the two interfaces. Cell-protein-implant interactions are indispensable for understanding cellular responses to implanted devices and involving osseointegration. While fibronectin is an adhesive protein that can mediate adhesion with implants, this is through integrins. In this way fibronectin is able

to bind to other molecules such as collagen fibers. Therefore, the comprehension is that the proteins interaction mechanism with dental implants is important for a better understanding of the osseointegration process, and thus, a better planning of titanium osseointegrable implants.

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Conflict of interest

The authors have no connections or conflicts of interest with companies that contributed to this article.

Data availability

The datasets related to this article cannot be shared at this time because they are part of ongoing research.

Authors contribution

Marvin do Nascimento: reviewed the literature and developed the topics worked on in the manuscript as well as the figures, reviewed and approved the final version. Thays Obando Brito: acted in the search for the review of the findings, reviewed and approved the final version of the manuscript. Andreza Menezes Lima: assisted in the search for the review of findings, and reviewed and approved the final version of the manuscript. Carlos Nelson Elias: guided the structuring of the content, helped in the development of the manuscript, and reviewed and approved the final version of the manuscript.

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