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Review

Performance evaluation in titanium implant surface: A literature review

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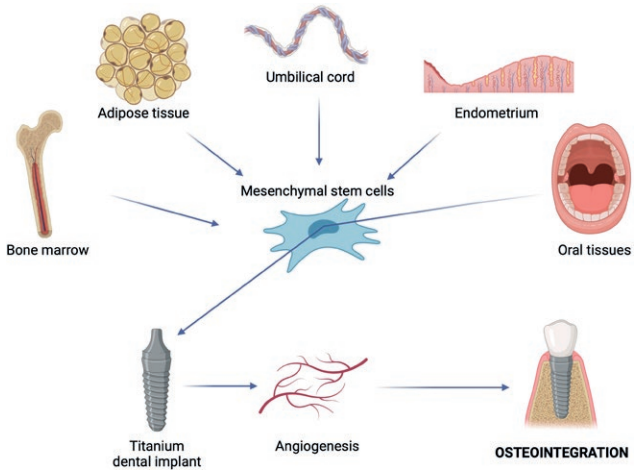
Abstract. The development of biomaterials is a constantly evolving. In the last decades, several biomaterials have been developed in various applications which have led to important advances in the processing of materials in medical fields such as orthopedics, dentistry, as well as in tissue engineering. Titanium is one of the most widely used biomaterials for dental implants due to its good mechanical properties and its excellent biocompatibility. The surface of titanium implants can be treated with various methods that improve the implant osteointegration. A better implant integration is possible also due to the interaction between titanium and oral cavity mesenchymal stem cells (oral MSCs) allowing an increase of osteogenic differentiation and release of matrix components. Furthermore, the interaction between titanium with certain surface treatments and oral MSCs leads to an increase in vascularization, fundamental for osseointegration. This review aims to analyze titanium as a dental implant biomaterial in the wound healing and osteointegration processes.

Keywords: dental implant, osteointegration, vascularization, oral stem cells, titanium implants.



1. INTRODUCTION

The term "biomaterial" refers to natural or synthetic materials that are placed in contact with living tissues and / or biological fluids (1). The development of biomaterials is a constantly evolving scientific field that began thousands of years ago since prehistoric times through the experimentation of natural remedies for the treatment of diseases and the preservation of health. These remedies were essentially based on the understanding of the beneficial properties of the available materials and studies of procedures to transform them into tools for medical applications. The gradual evolution of materials has produced biomaterials with more efficient performance and superior versatility and reproducibility (2). In the last decades, several biomaterials have been developed in various applications which have led to important advances in the processing of materials in medical fields such as orthopedics, dentistry, as well as in tissue engineering (3). Directly associated with the term biomaterial is the definition of 'biocompatibility' since to define a material as biomaterial it must be biocompatible. "Biocompatibility" is now only loosely defined as "the ability of a material to function with adequate host response in a specific application". Biocompatible biomaterials should be chemically inert, hypoallergenic, non-carcinogenic, without negative influences on the biological system (4). In particular, since the biocompatibility of dental materials is of fundamental clinical interest, it has acquired growing interest in research in recent years (1). Research on the development of different types of materials for dental applications is continuously improving for oral health preservation (5). Biomaterials can be classified according to their chemical structure, distinguishing in metals, ceramics, polymers, and composites, or according to their degree of interaction with the surrounding biological environment: inert, bioactive, bioabsorbable. Another type of classification is based on the origin depending on whether it is of synthetic or natural production (6). One of the most widely used biomaterials in implants is titanium, which was first introduced as a dental implant by Brånemark in the late 1970s (7). Titanium and Ti alloys have biocompatibility and good mechanical properties. However, osseointegration of the Ti implant surface with new bone is slow. Since the osseointegration process depends not only on the implant material, but also on other characteristics such as the implant surface, different implant surface modification techniques are tested to accelerate the osseointegration (8). Furthermore, the interaction of titanium with mesenchymal stem cells (MSCs) also affects the process of osseointegration (9). Bone degradation and formation is enabled by the differentiation of MSCs into specialized cells such as osteoclasts and osteoblasts. The extracellular matrix (ECM), containing proteins such as collagen (especially type I), fibronectin, laminin and proteoglycans, interacts with resident cells influencing their behavior. The ECM, by modulating growth factors, could support the self-renewal capacity and differentiation of MSCs. The interaction between cells and the ECM is critical for maintaining tissue homeostasis (10). Furthermore certain titanium implants in contact with the MSCs determine the process of osseointegration through the induction of angiogenesis (11). An important role in osseointegration seems to be played by the interaction between the titanium of the implant and the extracellular vesicles (EVs). EVs are cell derivatives delimited by a membrane that contain materials of different nature (proteins, nucleic acids, lipids) and are involved in intercellular communication. EVs include exosomes, microvesicles/microparticles induced by activation or apoptosis, and apoptotic bodies. Current research interest in the field mainly focuses on two main types of EVs: exosomes and microvesicles (12). Exosomes could promote angiogenesis and upregulate the expression of genes related to osteogenic differentiation through miRNAs (13). The present review analyzes the titanium surface modifications in dental implant material and its interaction with MSCs and EVs for the induction of angiogenesis and osseointegration processes.

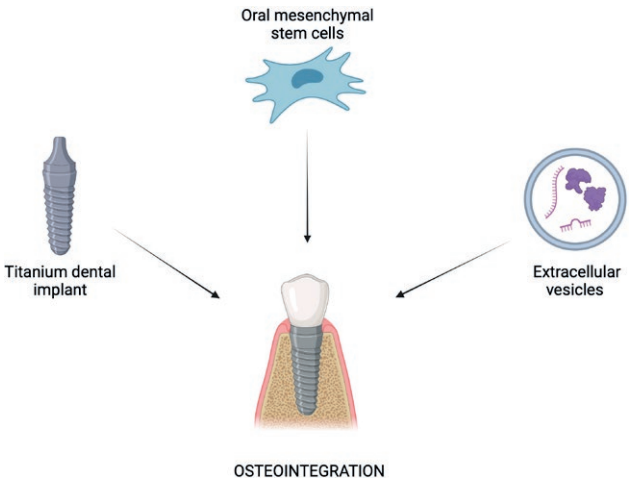


Figure 1. Interaction between titanium dental implant, mesenchymal stem cells (MSCs) and extracellular vesicles (EVs) that leads to osteointegration. (Created with BioRender.com).

2. TITANIUM IN DENTAL IMPLANTS

Titanium is considered one of the best biological metal material (14). The wide use of titanium is mainly due to its good mechanical properties, high corrosion resistance and its excellent biocompatibility. Titanium is used for many dental applications, as well as for various dental instruments such as orthodontic wires, endodontic files, dental implants and cast restorations (15). The surface characteristics of titanium implants appear to be particularly relevant for the establishment of the osseointegration process and bone remodeling at the boneimplant surface level (16). The surface structure of titanium dental implants can in fact modulate the activity of MSCs leading to upregulation of genes related to the formation of osteoblasts and the release of components of the ECM, that is the first step that leads to the early stage of bone formation (17). The surface topography of the titanium implant regulates the cellular response and therefore represents one of the main factors influencing the success of a dental implant (18, 19). There are different treatments that generate different titanium implant surfaces leading to more or less rapid bone-titanium integration. Sandblasted/etched surfaces performed more efficiently than sandblasted surfaces; furthermore, Sandblasted/etched surface results showed them to be more biocompatible, better tolerated, and appropriate for allowing hPDLSC growth and proliferation. The bone-titanium integration is rapid (20). Similarly, the double acid etched titanium surface is more biocompatible resulting in greater cell growth and adhesion, also increasing osteogenic and angiogenic processes compared to the machined titanium surface (21). [102]

3. HUMAN PERIODONTAL LIGAMENT STEM CELLS (HPDLSCS) IN TITANIUM DENTAL IMPLANTS

The biological biomaterials are those that lead to natural tissue restoration. This goal is more easily achievable when the properties of a good biomaterial are combined with those of the stem cells abilities. Regenerative medicine is based on the use of stem cells, including adult MSCs, that can be used in cellular therapy to replace damaged cells or to regenerate tissues (22). MSCs are stromal cells characterized by: the ability to self-renew and multilinear differentiation. MSCs can be isolated from a variety of tissues, including the umbilical cord, bone marrow, adipose tissue, and also from menstrual blood and endometrium (23). Alternative sources of adult MSC have been identified that are readily available in tissues of the oral cavity (dental pulp, apical papilla, dental follicle, gingiva and periodontal ligament) (24, 25). In general, MSCs possess immunomodulatory properties since they are able to influence the immune response by interacting with components of the immune system and exhibiting antiinflammatory effects (26). In particular, human periodontal ligament stem cells (hPDLSC) have demonstrated not only the ability to differentiate into mesengen lineages, but also the ability to interact with immune cells (27), avoiding the improper activation of T lymphocytes. This demonstrates immunomodulatory properties of hPDLSC especially during the healing processes (28).

In several studies it has been demonstrated that biomaterials, including titanium, in association with hPDLSCs, determine a better yield of implant osteointegration thanks to the increase in osteogenic differentiation associated with a major release of matrix components such as fibronectin and collagen. Some titanium treatments in association with hPDLSCs culture show promising results. Li et al. have demonstrated that stimulation with Enamel matrix derivative promotes not only the proliferation of hPDLSCs cultured on the Ti surface but also their differentiation towards the osteogenic lineage, probably following the activation of the Protein kinase B/ mammalian target of rapamycin (Akt/mTOR) pathway (29). Chemically modified implants create a microenvironment that can improve osseointegration. A roughened and chemically modified implant surface increases the proliferation of hPDLSCs and increases osteoblastic differentiation. Furthermore, by regulating

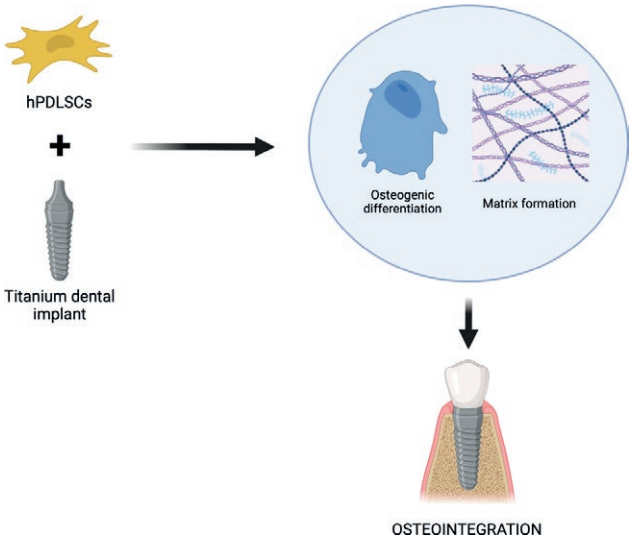


Figure 2. Interaction between titanium dental implant and human periodontal ligament stem cells (hPDLSCs) that leads to osteointegration trough osteogenic differentiation and matrix release. (Created with BioRender.com).

the RANKL-RANK-OPG axis, it interferes with osteoclastogenesis leading to its decrease (30). Titanium Carbide MXene promotes the osteogenic differentiation of hPDLSCs, probably through modulation of the Hypoxia-inducible factor 1-alpha/ wint (HIF-1α/WNT) signaling pathway related to metabolic reprogramming. This improves tissue regeneration and osseointegration (31).

4. VASCULARIZATION PROCESS IN TITANIUM DENTAL IMPLANTS

The term angiogenesis defines the process by which new capillary blood vessels are formed from existing ones. This process is governed by a balance of positive and negative angiogenic factors within the vascular microenvironment and is the result of the functional activity of these factors together with ECM proteins, adhesion receptors and proteolytic enzymes (32). Angiogenesis is a fundamental process during embryonic development and remains a physiological process even during adult life, in which it intervenes in processes such as the formation of the corpus luteum. On the other hand, angiogenesis is also the protagonist of pathological conditions, such as chronic inflammation and tumors, in which it can contribute to the progression of the disease (33). In vasculogenesis there is the differentiation of endothelial progenitor cells which are subsequently incorporated into the vessels (34). Angiogenesis is induced by various cytokines produced mainly by macrophages and platelets during the inflammatory phase, since the macrophage produces tumor necrosis factor alpha (TNFα) influencing the angiogenic process (35). Angiogenesis is a physiological process necessary for the growth and development of bodily structures in the human body as well as in tissue repair and regeneration (36). Vascular endothelial growth factor (VEGF), a member of the PDGF family of growth factors, is the key molecule of the vascularization process having a powerful angiogenic activity with a mitogenic and anti-apoptotic effect on endothelial cells. This increases vascular permeability as well as cell migration (37). Angiogenesis in regenerative dental practices is critical for the growth of new bone in bone regeneration of osseointegration after the installation of the dental implant, since a blood supply is required in order to provide nourishment, oxygen (38).

For the engraftment of titanium implants, the vascularization process is fundamental since the bone formation depends on it, which then closes the bone-implant interface. This process becomes even more important especially in the presence of large bone

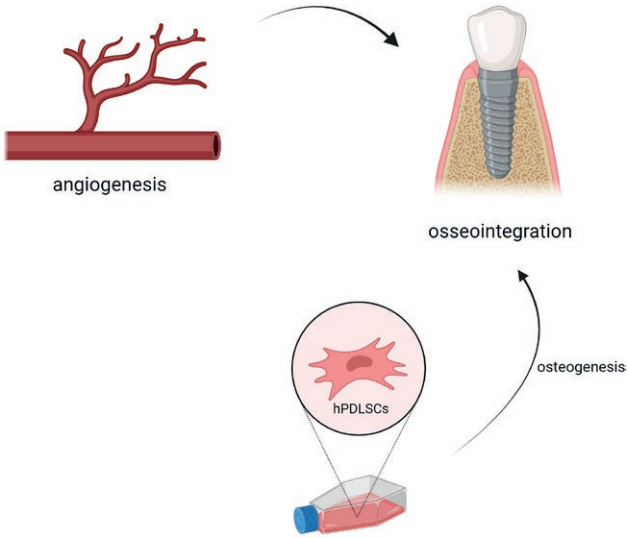


Figure 3. Vascularization in dental implant.

defects, in which early vascularization is a prerequisite, since a long distance must be bridged for the transport of nutrients, growth factors and for gas exchange (39). Increased levels of VEGF and its receptor could lead to faster bone-titanium integration. Furthermore, the expression of VEGF and consequently the vascularization process and therefore of osseointegration is increased in titanium implants with certain surface treatments compared to others. The hPDLSCs cultered on Sandblasted/etched surfaces have showed an higher VEGF expression respect to the cells seeded on sandblasted surfaces (20). Human PDLSC cultured on double acid etched titanium surface showed higher expression of VEGF compared to hPDLSC cultured on machined titanium surface (21).

5. DENTAL IMPLANTS: WOUND HEALING AND OSTEOINTEGRATION

The positioning of the dental implant gives rise to a series of biological reactions that allow bone remodeling. The first phase is bone turnover at the implant interface. The endpoint is represented by the integration of the implant with the absence of chronic inflammation and lack of mobility. This is followed by confirmation with radiographic evaluation of the reformed bone at the implant interface. Wound healing around the dental implant involves three stages of repair: initial formation of a blood clot, cellular activation, and finally by a cellular response (40). Adhesion to the implant surface leads to the activation of platelets, producing factors such

as PDGF, TGF-Beta, PDEGF, IGF-1, induce the recruitment and differentiation of mesenchymal cells towards the bone tissue, accelerate the healing process (41). When titanium surfaces are modified with a controlled etching process, they alter platelet adhesion leading to the formation of thrombin-antithrombin complexes (42). In general, smoother machined surfaces demonstrated greater platelet adhesion but reduced activation; rougher surfaces determine reduced platelet adhesion but the relative degranulation is almost 100% (43). Platelets are followed by macrophages migration, which not only remove debris but also appear to mediate the formation of new bone on the implant surface and wound healing (44) (45, 46). The early macrophage population expresses growth factors such as fibroblast growth factor (FGF-1, FGF-2, FGF-4), transforming growth factors, epithelial growth factor, and bone morphogenetic proteins (BMPs) (47, 48). These factors influence processes such as cell recruitment, migration, proliferation and formation of an extracellular matrix on the implant surface, crucial for wound healing and angiogenesis since macrophages mediate the release of bFGF, TNF-α and VEGF (49). Another fundamental process for osseointegration is the formation of a mineralized matrix mediated by multipotent MSCs that differentiate into osteoblasts. The differentiation of osteoblasts is mediated by central binding factor alpha (Cbfa1) or RUNX-2, which is a transcription factor belonging to Runt that regulates the transcription of genes coding for bone sialoprotein (BSP), the osteocalcin and type I collagen (50, 51). Human MSCs cultured on titanium surfaces with a nanoetched topography show elevated expression of RUNX-2 and type I collagen with increased expression of alkaline phosphatase, required for biomineralization on the implant surface (52). Tissue regeneration and interaction with biomaterials is also mediated by the production of EVs, through which cells communicate and exchange functional material. EVs interact with matrix proteins such as fibronectin and type I collagen (53). Furthermore, EVs can induce and influence MSC differentiation in a certain direction, including the osteoblastic one in the process of osteogenesis (54). It has been demonstrated that the EVs produced by MSCs during the administration of dental implants, thanks to their immunomodulatory action, contribute to an increase in bone tissue density near the device and determine an almost complete fusion of the screw device with the bone tissue (55). Exosomes at the level of titanium disc implants significantly promote osteogenic differentiation and mineralization probably through microRNAs that influence mTOR, AMP-activated protein kinase (AMPK), Wnt pathways in the osteoimmune regulation mechanism of implant osseointegration (56). EVs derived from MSCs have been shown to contain microRNAs that can induce bone remodeling and mineralization such as miR-10b-5p, miR-21, miR-31-3p, miR31-5p, mRi-199a- 3p, miR-223-3p (57).

CONCLUSIONS

In summary, significant advances have concerned dental implant procedures and surface modification techniques for titanium dental implants. We provide a summary of titanium as a biomaterial in dental implants with related surface modifications, interaction with MSCs and EVs, in vascularization and wound healing processes on the base of osseointegration. However, further studies, especially in osseointegration from a molecular point of view, are necessary.

LIST OF ABBREVIATIONS

MSC: mesenchymal stem cell
Ti: titanium
ECM: extracellular matrix
EVs: extracellular vesicles
miRNA: micro RNA
hPDLSC: Human Periodontal Ligament Stem Cells
AKT/mTOR: activation of the Protein kinase B/ mammalian target of rapamycin
RANKL: Receptor activator of nuclear factor kappa-B ligand
RANK: Receptor activator of nuclear factor κ B
OPG: Osteoprotegerin
HIF-1α: Hypoxia-inducible factor 1-alpha
WNT: Wint
TNF-α: tumor necrosis factor alpha
VEGF: Vascular endothelial growth factor
PDGF: Platelet-derived growth factor
TGF-Beta: Tumor growth factor beta
IGF-1: Insuline-like growth factor
FGF-1; FGF-2; FGF-4: (fibroblast growth factor 1; 2; 4)
BMPs: bone morphogenetic proteins
bFGF: basic fibroblast growth factor
Cbfa1: central binding factor alpha
RUNX2: Runt-related transcription factor 2
BSP: bone sialoprotein
AMPK: AMP-activated protein kinase

AUTHOR CONTRIBUTIONS

Conceptualization: Y.D.R.,. and G.D.M.; writing—original draft preparation: Y.D.R. and G.D.M.; writing—

review and editing: G.D.M., Y.D.R., F.D., J.P., and A.M.; visualization: G.D.M., F.D., J.P., A.M, O.T. and Y.D.R.; supervision: G.D.M., J.P., and O.T. and A.P.; project administration: G.D.M., J.P., F.D., and O.T.

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