Review Article

Osseointegration—the biological reality of successful dental implant therapy: a narrative review

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Objective: This article aims to provide an overview of factors affecting dental implant osseointegration.

Background: Osseointegration has proven to be a biologically sound foundation for contemporary dental implant therapy. Its success is dependent on principle-driven clinical procedures. Important observations have been made at cellular and macroscopic levels regarding osseointegration at the earliest stages of bone healing to the later stages of bone formation and remodeling. The formation of bone at the titanium dental implant surface is dependent on osteoprogenitor cell recruitment, proliferation and differentiation under complex control. In addition, macrophages play a determinant role in the process of osteoinduction that supports osseointegration. The role of signaling pathways and transcription factors in modulation of cell behavior and fate is critical. The current relatively high success of dental implant therapy is due, in part, to the effects of enhanced surface topography on implant-adherent cell functions. Other immune cells also appear to be influenced by surface topography and impact the process of osseointegration. Immunomodulation plays a key role in determining the bone forming process at endosseous dental implants and underscores the important relationship between the technical aspects of dental implant therapy and the local and systemic biological factors acting upon the population of implant-adherent and adjacent cells. Given the growing knowledge base regarding the complex molecular and cellular basis of osseointegration, it is also possible to reconsider dental implant failure in that context.

Methods: The relevant literature was identified and consulted through PubMed/Medline.

Conclusions: The success of osseointegration is determined by an array of clinical and molecular factors all of which have to be considered in contemporary dental implant therapy.

Keywords: Osseointegration; immunomodulation; surface topography; osteoprogenitors; macrophages

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Introduction

The modern era of dental implant therapy, however, has a foundation established in the search for a solution to complete edentulism. The technical challenges were focused on how to retain and stabilize complete dentures and as such earliest studies involved the use of subperiosteal implants and transmandibular implants as ways to stabilize and retain dentures (1). Unfortunately, these clinical approaches

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Table 1 Interrelated factors affecting osseointegration*

Implant material biocompatibility
Topographical features of the implant surface
Bone health (non-infected) and bone quality/quantity
Surgical technique
Undisturbed healing phase
Prosthesis effects (loading, hygiene, esthetics).

*, adapted from reference (10).

met with varied success at best and were associated with chronic inflammation and infection leading to bone loss, implant loss and dissatisfaction. In the late 1950s through the early 1980s, another concept emerged and that was the use of metallic root form implants anchored in bone to support a fixed prostheses. The pioneering efforts of Dr. P.I. Branemark were based on fundamental studies of vascularization in bone marrow that used metallic chambers to view this process. These chambers were found to be essentially irreversibly fixed to bone. Dr. Branemark quietly developed and documented commercially pure Titanium 'fixtures' and their placement into the parasymphyseal mandible to support fixed dentures. Early publications established the potential of this approach based on clinical cohort studies displaying remarkable 10-year 'fixture' and prosthesis survival (2).

The term osseointegration was subsequently defined by Branemark as ""a direct structural and functional connection between ordered, living bone, and the surface of a load carrying implant" (3). This general understanding of the direct interface was appreciated by information obtained from histological observations. The development of ground section histology (4) and advances in Transmission Electron Microscopy (5) permitted the identification of bone opposing the titanium implant surface. In a similar manner, Dr. Schroeder observed the growth of bone into a titanium plasma sprayed implant surface in the absence of 'formation of a soft tissue bed' noting that the implant was anchored to bone (6). Prior to the established definition of osseointegration, he suggested that bone was "ankylotically" related to the implant surface. Albrektsson and co-workers optimistically concluded in 1981 that "the technique of osseointegration is a reliable type of cement-free bone anchorage for permanent prosthetic tissue substitutes" (7). Thus, osseointegration had been established as a reproducible biologic outcome associated with the fixation of a metallic root-form or screw-shaped implant in alveolar bone. This article aims to provide an overview of factors affecting dental implant osseointegration. We present the following article in accordance with the Narrative Review reporting checklist (available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-77/rc).

Methods

The relevant literature was identified and consulted through PubMed/Medline.

The foundation for clinical dental implant success

As indicated above, a central factor in the acceptance of osseointegration as a clinically successful therapy or tooth replacement was the early studies in Sweden that produced relatively large cohort studies [e.g., 1,000 subjects (8)] that demonstrated high success with limited biological or clinical morbidity. Such early study outcomes were predicated on strict clinical protocols that underscored key biological principles for attaining osseointegration. The key clinical guidelines included (I) step-wise drilling to limit thermal stress to cells and tissues, (II) achieving primary implant stability, and (III) isolation from the oral environment by adhering to submerged (undisturbed) implant placement for 3–6 months (9). The clinical challenge to reproducibly achieving osseointegration was defined as multifactorial (*Table 1*).

Each of the enumerated clinical factors were, presumably, thought to influence the biological process of bone formation at the titanium dental implant surface. With the evolution of dental implant therapy, the warnings implicit to this list of factors affecting osseointegration remain with us in clinical management of our implant patients. The one exception is the undisturbed (submucosal or two-stage) healing phase; one-stage implant placement under conditions where other factors are not limiting has been proven to provide equal osseointegration success as submucosal or two-stage healing. A two-stage approach may be advantageous when there is sub-optimal primary stability or where excessive forces may be transmitted through the exposed healing abutments (11). How each of these clinical factors affects the biological processes involved in osseointegration was not well characterized or possibly mis-characterized when clinical success was realized. Over the past three to four decades the explosion of cell and molecular biological knowledge has enabled important new insights into the biological processes that direct the formation of the bone-

Table 2 Implant surface factors affecting cell and tissue responses at the interface

Bulk chemical composition (e.g., titanium, zirconia, hydroxyapatite)
Surface energy (wettability)
Surface topography (microscale, nanoscale)
Surface modification (protein, ion, drug)

to-implant interface essential to osseointegration success.

Osseointegration observed

As stated above, osseointegration was defined histologically and largely at the light microscopic level to represent the direct contact of formed bone with the implant surface. How this direct bone-to-implant interface forms remains incompletely defined. The concept that the implant surface directly promoted bone formation is valid; both animal and cell culture studies demonstrate that bone and bone-derived cells form bone or bone-like tissue on experimental implant surfaces. With the emergence of osteoblast cell culture studies, the effect of the implant surface bulk chemical composition, surface energy, sterilization effects, were quickly investigated (*Table 2*). Together, these studied demonstrated that changes in the surface character of the implant could influence cell behavior (12-14). It was further observed that the process of cellular attachment by integrin receptors and signaling through focal contacts was influenced by the nature of the implant surface (14). Implied was that the implant surface itself could be modified to enhance the formation at the bone to implant surface.

In the 1960's and 1970's when early development of osseointegration was ongoing, scientific knowledge of mesenchymal stem cells (MSCs), immunology, genetics, and genomics was in its infancy or not existent. New basic knowledge emerged and has been applied to the study of osseointegration. Central to this has been the understanding of the MSC's role in bone formation (15). Applied to osseointegration, the MSC's function in formation of the bone-to-implant interface has been widely explored. These osteoprogenitor cells are found in multiple tissues including bone and bone marrow. Upon injury, the MSC is recruited to the site of injury (here the implant/wound interface) and contributes to bone regeneration (16). At bone fracture sites, MSCs are recruited quickly to the site and begin proliferation at about 3 days following injury (17). This is promoted by inflammatory responses to injury and the release of growth factors, cytokines and chemokines (considered below).

Important observations have been made regarding osseointegration at the earliest stages of wound healing. The formation of the fibrin blood clot creates a scaffold upon which early cellular events occur. The platelets integral to the fibrin clot are rich sources of growth factors and contribute to osseointegration. Structurally, the fibrin scaffold is necessary for cellular movement from adjacent sites onto the implant surface. This process underscores the concept "contact osteogenesis" as described by Davies (18) where new bone formation occurs on the implant surface and not only toward the surface from adjacent sites of neo-osteogenesis.

The population of the implant surface with osteoprogenitors is followed by their proliferation and subsequent differentiation to osteoblastic cells that form a mineralizing matrix (*Figure 1*). Osteoblastic differentiation is now well defined (19) and multiple studies have demonstrated that implant adherent osteoprogenitors readily form bone (20,21). This process recapitulates in many ways the process of woven bone formation that begins with the recruitment of MSs and the signaling of osteoinduction. Multiple signals are involved in osteoinduction, however, two molecular 'switches' are now defined to be essential for the osteoblast formation. They are transcription factors that regulate osteoblast-specific gene expression and are known as Runx2 and Osterix (SP7). If either of these genes are deleted, osteoblast formation and bone formation is not observed in development (22,23). Thus, the activity of these osteoinductive factors drive bone formation and their expression is observed in implant adherent cells. Other major mediators of osteogenesis include bone morphogenetic protein (BMP) signaling pathway, Wingless-related integration site (Wnt) signaling pathway, and parathyroid hormone (PTH) signaling pathway among others. In addition, adhesive extracellular matrix proteins elaborated at the implant surface also influence osteogenesis (24). All appear to be active in the process of osseointegration.

In osteoprogenitor cells on the implant surface, the activity of Runx2 and Osterix is increased in the early phases of osseointegration and direct bone formation at the implant surface (25,26). The early increase in Runx2 and Osterix was affirmed in studies of experimental implants retrieved from humans (27). BMPs are primary inducers of osteoblastic differentiation and they are expressed in implant

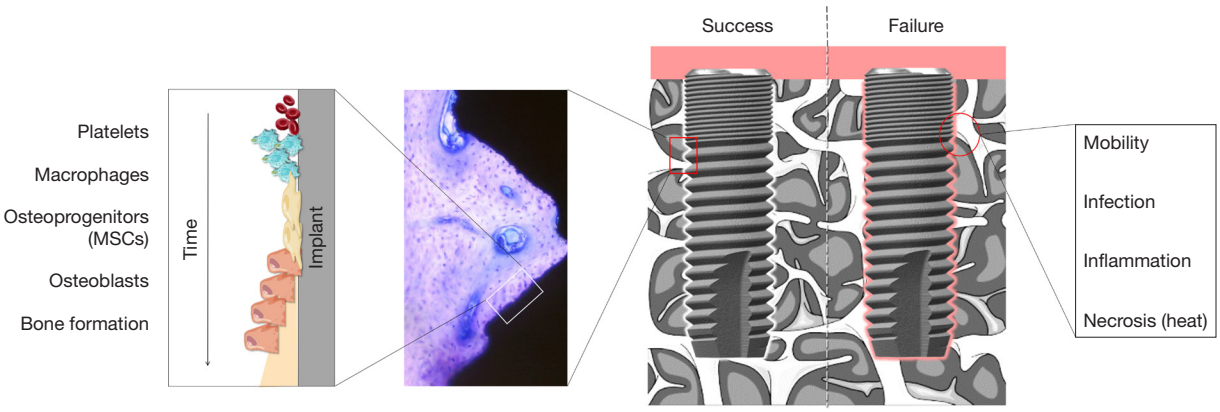

Figure 1 Osseointegration success and failure: the successful formation of bone at the implant surface is dependent on the cellular interactions at the interface. The initial interactions involving platelets and immune cells (e.g., macrophages) contribute to the subsequent recruitment of osteoprogenitor cells. The differentiation of implant adherent and adjacent osteoprogenitor cells to osteoblasts is an essential step in assuring robust bone formation at the implant surface. Failure to achieve osseointegration may be the result of several factors including the absence of primary stability (mobility) that alters the environment for osteoblast differentiation, inflammation or necrosis that all lead to the impairment of de novo bone formation at the implant. Healing does occur, but without effective osteogenesis. More rarely, frank infection can cause implant failure by promoting inflammation. MSC, mesenchymal stem cell.

adherent cells; enhanced surface topography is associated with increased BMP expression and related osteoinduction. BMP expression by implant adherent cells has been further demonstrated using experimentally retrieved implants from humans (28). There are several Wnt ligands that are active in the process of osseointegration and they ultimately activate another transcription factor, β-catenin. Enhanced micron/nanoscale surface topography increases the expression of Wnt proteins that signal the activation of β-catenin to promote osteoblast differentiation and bone formation among implant adherent osteoprogenitor cells. For example, Wnt3A appears to activate local cells contributing to osseointegration (29) and Wnt5a and Wnt11 also play contributing roles (30). Eventually, bone formation ceases in a controlled process. One protein produced by osteocytes that inhibits osteogenesis is Sclerostin. Sclerostin is expressed by implant adherent cells and is increased in the absence of primary stability (31). Antibodies to Sclerostin are used therapeutically to block its damping effect on osteogenesis thereby enhancing bone formation. This has been explored at endosseous implants with positive results (32). Cell directed osteogenesis as the foundation of osseointegration implies that that disruption of the local, systemic or clinical (technical) factor which interferes with osteoprogenitor cell function can interfere with osseointegration. Conversely, it is possible to direct osteoprogenitors to enhance bone formation with the goal of improving osseointegration.

Osseointegration improved

Current titanium dental implants currently possess enhanced surface topography of one-type or another. Implants with surfaces of S(a) values approximating 1.5–2.0 mm may offer increased bone-to-implant contact compared with machined implant surfaces. These surfaces are created in different ways commonly grit-blasting, acid etching or anodizing. Further modification has been achieved by the superimposition of nanoscale features onto the moderately rough surface or by alteration of the surface energy to further accelerate or increased the experimentally defined bone-to-implant contact (33-35). The possible role of surface topography in promoting more rapid and extensive bone formation at the topographically modified implant surface has been revealed in cell culture studies where molecular markers of osteoinduction and osteogenesis have repeatedly been shown to be increased at topographically enhanced titanium implant surfaces (36). The superimposition of nanoscale features on micron-rough titanium topography increases the expression of bone forming proteins beyond that observed on micron scale surfaces, suggesting that nanofeatures provide adherent

osteoprogenitor cells additional cues for differentiation and subsequent bone formation (37,38). At least one human study has demonstrated that alteration of micron scale surface topography using nanofeatures increases osteoinductive gene expression during the early phases of healing (27). In a detailed investigation of adherent cell activity as a function of implant surface topography, gene expression data demonstrated that enhanced surface topography (and hydrophilicity) was associated with increase expression of genes associated with the TGFβ-BMP signaling cascade, and BMP2 protein demonstrated a large topography associated increased expression (39). Many studies have shown that surface topography is an important factor in the clinical control of osseointegration that works through the regulation of osteoinduction and subsequent bone formation.

These studies indicate that surface topography alters adherent cellular responses leading to greater bone formation. Bone accrual at the implant surface is the result of bone formation and bone resorption that occurs throughout the lifetime of the implant in function. Enhanced implant surface topography can also influence bone remodeling and osteoclast activity. This was indicated by cell culture studies of bone marrow-derived monocyte differentiation on implant surfaces cultured with osteoprogenitor cells. The rough surface provided local cues to adherent osteoprogenitors to direct osteoclast production (40,41). There are multimodal effects of enhanced surface topography that positively affect the accrual of bone at the titanium dental implant surface.

Osseointegration re-defined

Several observations made regarding the population of the implant surface by cells *in vivo* raised the important question of what different cells that adhere to the implant surface contribute to the process of osseointegration. In fact, the population of cells adherent to the implant surface was observed by retrieval analysis of implants in a rat model of osseointegration to change quickly over the first days and weeks of healing (42). This suggested that other cells beside osteoprogenitor or osteoblastic cells contribute to the process of osseointegration.

Recent studies have highlighted the concept of immunomodulation in the process of osseointegration. Immunomodulation refers to the modification of a biological response by cells of the immune system. In the case of osseointegration, it may be interpreted as the modification of osteoprogenitor, osteoblast and osteoclastic cells by cells of the immune system. A highly orchestrated series of cellular events must occur following tissue injury (implant surgery) to assure successful regeneration or osseointegration.

Current investigations have begun to explore how cells that populate the implant surface early and potentially prior to osteoprogenitor cells may influence osseointegration. Primary among these inflammatory cells is the macrophage. When macrophages are depleted from mice, early osseointegration is impaired, indicating that these cells do play a role in bone regeneration at dental implants (43). Macrophages polarize into so-called M1 (pro-inflammatory) and M2 (pro-regenerative) phenotypes and help direct these functions (44). Multiple investigations have demonstrated that shifting the population of macrophages to an M2 phenotype promotes the resolution of inflammation and regeneration. Endosseous implants with enhanced surface topography promote the M2 phenotype and associated enhanced osseointegration (45), while surfaces that promoted M1 phenotype impair bone regeneration. Multiple studies have now shown that macrophages play a determinant role in the process of osteoinduction that supports osseointegration. For example, in a comprehensive analysis of gene expression at titanium implant in the rat tibia, enhanced surface topography was associated with expression of osteogenesis associated gene expression that was temporally related to expression of genes associated with inflammatory/immune responses and particularly macrophages (46). In an earlier study, the expression of both osteoblast and osteoclast gene markers illustrated the aforementioned complex regulation of bone accrual at the titanium implant surface. The study did not characterize downregulated gene expression which may have included inflammation-related transcripts (47). A recent *in vivo* study illustrated that macrophages play a role in MSC and T-cell recruitment to titanium implant/bone interfaces (48).

Other immune cells also appear to be influenced by surface topography and impact the process of osseointegration. T lymphocytes (Th1, Th2, Treg, and Th17 cells), B lymphocytes, dendritic cells, and macrophages are each implicated in the control of bone metabolism, often involving osteoclast formation and bone resorption. However, these cells can also be involved in regulation of osteogenesis and the implant surface appears to mediate their various functions. For example, at 10 days in the rabbit tibia model, titanium implants demonstrated a consistent upregulation of a CD4-lymphocyte reaction

at the implant interface (49). T lymphocyte production of IL-17 has been shown to increase cultured osteoprogenitor cells' osteoblastic gene expression (50). Both B- and T- cells are involved in the process of bone remodeling and T-cells are enriched resources of both OPG and RANKL that regulate osteoclastogenesis and subsequent bone resorption to affect bone mass (51). The absence of T and B cells in a mouse fracture model negatively impacted bone repair in a mouse fracture model and demonstrated the relative absence of osteoblasts at the site where bone formation would otherwise occur (52).

Neutrophils are among the first extravasated cells at wound sites, including at the dental implant surface. They are actively recruited to sites of acute inflammation where the phagocytize microbe and particles. Recent studies have investigated the effects of neutrophil interactions with various dental implant surface topographies and reveal that neutrophils are responsive to surface topography and can be activated to release inflammatory cytokines. When adherent to rougher surface topography, neutrophil inflammatory cytokine expression is reduced, suggesting a favorable bone healing response (53). The contribution of cells other than osteoprogenitors to the process of interfacial bone formation highlights the importance of more broad consideration factors influencing dental implant success.

Multiple investigators have demonstrated that the culture of MSCs on titanium surfaces with enhanced surface topography reduces pro-inflammatory gene expression and increases anti-inflammatory gene expression (54). Human studies that use an implant retrieval method to question the functionality and types of cells acting in the process of osseointegration have also highlighted the importance of immunomodulation in osseointegration (40,55). Such studies have shown that genes encoding inflammatory cytokines and chemokines are expressed by implant adherent cells and that enhanced surface topography (or hydrophilicity) can suppress or reduce the pro-inflammatory cytokine/chemokine expression associated with greater bone-to-implant contact.

Osseointegration disturbed

Given the growing knowledge base regarding the complex molecular and cellular basis of osseointegration, it is possible to reconsider dental implant failure in that context. In fact, many of the aforementioned studies have shown that the use of BMPs, PTH, Wnts, inhibitors of osteoclastogenesis, or anti-inflammatory strategies all can enhance bone formation in animal models of disease including diabetes, osteoporosis and of aging. For example, PTH administration increased bone formation at titanium implants in an osteoporotic rabbit model (56) and increased early bone formation at implants in an aging rat model (57). The treatment of titanium implant surfaces with IL-4, a cytokine the promoted M2 (pro-regenerative) macrophage polarization and reduce pro-inflammatory cytokine production by adherent cells (58). Blocking the inhibitory action of sclerostin by linking sclerostin-neutralizing antibodies to titanium implant surfaces promoted greater osseointegration (32). These few examples demonstrate that the cellular and molecular events that control osseointegration are targetable factors that may be translated for clinical improvement of osseointegration (59).

Improving osseointegration at first glance may not seem terribly important given that there are many reports of high dental implant success and survival. However, the process of osseointegration is known to be disturbed by systemic (and local) factors. Several reviews have recently summarized some of the more common systemic factors that negatively influence dental implant success (60,61). In addition, the medications taken to address common chronic systemic conditions also reduce dental implant success at the level of bone accrual (62). Included were selective serotonin reuptake inhibitors, proton pump inhibitors, and bisphosphonates. These drugs have specific targets but also have indirect effects and potential off-target effects that can negatively influence osseointegration (63). Addressing osseointegration at its cellular/molecular level may provide solutions to these known clinical challenges.

Conclusions

Osseointegration has proven to be a biologically sound foundation for contemporary dental implant therapy. Its success is dependent on principle-driven clinical procedures. The formation of bone at the titanium dental implant surface is dependent on osteoprogenitor cell recruitment, proliferation and differentiation under complex control. The current relatively high success of dental implant therapy is due, in part, to the effects of enhanced surface topography on implant-adherent cell functions. Immunomodulation plays a key role in determining the bone forming process at endosseous dental implants and underscores the important relationship between the technical aspects of dental implant therapy and the local and systemic biological factors acting upon the

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