Foreign Body Reaction to Biomaterials: On Mechanisms for Buildup and Breakdown of Osseointegration

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ABSTRACT

Background: The last few decades have seen a progressive shift in paradigm, replacing the notion of body implants as inert biomaterials for that of immune-modulating interactions with the host.

Purpose: This text represents an attempt at understanding the current knowledge on the healing mechanisms controlling implant–host interactions, thus interpreting osseointegration and the peri-implant bone loss phenomena also from an immunological point of view.

Materials and Methods: A narrative review approach was taken in the development of this article.

Results: Osseointegration, actually representing a foreign body reaction (FBR) to biomaterials, is an immune-modulated, multifactorial, and complex healing process where a number of cells and mediators are involved. The *buildup* of osseointegration seems to be an immunologically and inflammatory-driven process, with the ultimate end to shield off the foreign material placed in the body, triggered by surface protein adsorption, complement activation, and buildup of a fibrin matrix, followed by recruitment of granulocytes, mesenchymal stem cells, and monocytes/macrophages, with the latter largely controlling the longer term response, further fusing into foreign body giant cells (FBGC), while bone cells make and remodel hydroxyl apatite. The above sequence results in the FBR that we call osseointegration and use for clinical purposes. However, the long-term clinical function is dependent on a foreign body equilibrium, that if disturbed may lead to impaired clinical function of the implant, through a *breakdown* process where macrophages are again activated and may further fuse into FBGCs, now seen in much greater numbers, resulting in the start of bone resorption – due to cells such as osteoclasts with different origins and possibly even macrophages degrading more bone than what is formed via osteoblastic activity – and rupture of mucosal seals, through complex mechanisms in need of further understanding. Infection may follow as a secondary event, further complicating the clinical scenario. Implant failure may ensue.

Conclusions: Dentistry is still to embrace the concept of the biomaterials' healing- and immune-modulating effect when in contact with body tissues. The presented knowledge has the potential to open the door for a different interpretation of past, current, and future observations in dental implant science. From a clinical standpoint, it seems recommendable to react as rapidly as possible when facing peri-implant bone loss, trying to reestablish a foreign body equilibrium if with some bone resorption.

KEY WORDS: biomaterials, foreign body reaction, immune system, implant, inflammation, osseointegration, titanium

INTRODUCTION

The *Williams Dictionary of Biomaterials* defines *foreign body response* as the "overall response of a host to the presence of a foreign body."[1]

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In dentistry, there has been the perception of titanium dental implants as "inert" materials. *Inert* is something that chemically has little or no ability to react (dictionary.com). Therefore, titanium dental implants would, by this definition, behave as inert when placed in living tissues (bone and gingiva), hence becoming integrated through an uneventful wound healing process.

From an immunological and healing point of view, this is very unlikely. Basic knowledge in medicine leads to assume that anything foreign to the body will immediately be signaled by the immune system and a cascade of reactions ensues in parallel to a modulated inflammation, as part of tissue repair.

Here lies the dilemma: if titanium dental implants are considered chemically and biologically inert, then the osseointegration process is perceived as a purely wound healing phenomenon; if, on the other hand, as the authors believe, any material penetrating the body tissues renders activation of the immune system, to whichever extent, then osseointegration must also be perceived as an immune-modulated inflammatory process, where the immune system is locally either up- or down-regulated, largely influencing the whole healing process.

In fact, clinicians and material scientists soon realized that inertness was not synonymous with biocompatibility, which led to the Consensus Conference of the European Society for Biomaterials in 1986, where there was an attempt to clarify the interaction of biomaterials with living tissues.[2]

In a recent publication from the field of bone replacement materials, it is stated that the paradigm for the development of such materials has been shifted from inert to immunomodulatory.[3] The authors of the current review believe that this shift in paradigm will also occur for dental implants.

At this point, a question arises: which cascade(s) of events allow for a material to be "accepted" by the body tissues, without a reaction perceived as the body "refusing" this material?

Recent work from Albrektsson and colleagues[4] has introduced the concept of foreign body equilibrium (FBE), applied to the osseointegration of titanium dental implants. This meaning that an immune-mediated foreign body reaction (FBR) balance is achieved when integration in the bone occurs. The loss or failure to establish this balance may lead, and potentially be the main cause, of peri-implant bone loss.

Although, to date, no study has been conducted in dentistry addressing the FBR to titanium dental implants alone – despite its widespread use in the world – a study by Donath and colleagues published in 1992 explored the FBR to different materials used in dentistry, from both a soft and a hard tissue perspective.[5] In this publication, it was already stated that the success of osseointegration of dental implants could be explained by the particular characteristics of an FBR to the biomaterials used.

Bone loss around dental implants is an increasing problem and solutions lack in predictability. The authors believe that, despite continued efforts, a full understanding of the molecular and cellular reactions, which affect and control the relationship between bone and titanium dental implants, is still needed. Accepting that bone loss should be perceived as an immune-modulated foreign body type of reaction seems paramount. It is hypothesized that immune reactions may be the key to prevent the loss of FBE or provide predictable solutions if this has occurred.

This review article aims at understanding the current knowledge on FBR to implanted biomaterials, as a starting point to describe osseointegration of titanium dental implants and the bone loss phenomena from an immunological point of view.

MATERIALS AND METHODS

A Narrative Review Approach Was Taken

For this task, a search was performed using the PubMed specialized search engine and Google generic search engine, as well as textbooks on biomaterials and immunology.

Key words used for this search included "foreign body reaction," "implant," "titanium implant," "titanium dental implant," and "biomaterial foreign body reaction." The articles were selected by relevance of contribution to the understanding of the FBR to biomaterials, including reviews and both in vitro and in vivo studies that addressed soft and hard tissues and their relation to biomaterials.

Current Understanding of FBR

If largely ignored in oral implant science, the potential benefits and risks with an FBR have been discussed in many publications on implants placed in other sites than oral ones. FBRs to titanium and other materials have

been studied in orthopedics and material sciences for several years, in an attempt to understand how the immune system responds to biomaterials regarding their application in terms of safety, biocompatibility, and long-term continued function.[6]

A continued function is of major importance, as it relates to long-term clinical success. The coupled inflammatory/immune processes regulating the FBR are present for the in vivo lifetime of the medical device.[6] It is, therefore, considered fundamental that all the parts in this process and their roles are understood, such as the cells and mediators involved, the genetic variations, as well as the phenotypical changes that may occur to some of these cells and their different pathways of activation, as shown by some studies.[7,8]

This knowledge could hypothetically lead to the development of medical devices that have the potential to guide the tissue response to a more favorable outcome, making clinical treatments more predictable and long-lasting.

The role of different cells and mediators has been identified, although in need of further studies, making this a very interesting and tremendously important field to explore, as it seems to lead and contribute to the understanding of the reparative processes of the human body in response to implanted foreign objects.

Immunological studies were performed in the late 1980s, following the observation of poor results with a number of materials, some assumingly inert when in contact with living tissues. The conclusion was that a host response was unavoidable, as the adsorption of proteins by the material surface occurs as soon as the biomaterial gets in contact with any living tissue, altering the conformation of these molecules, which will then act as antigens, triggering an immune and inflammatory response ending up in the form of an FBR.[2]

No triggering factor has been clearly identified in this early phase, but there is very convincing suggestion that the complement system might play a pivotal role.[4]

In vitro experiments with titanium, aluminium, and silicon in blood plasma have shown, with time, increasing surface binding of complement factor 3b (C3b) and its degradation products.[9] Many inflammatory and immune cells are known to express receptors to C3b/inactivated C3b (iC3b), hence mounting to the notion that in the early phase of inflammation, it is likely that implant surfaces become recognized by the immune system through the complement system.

Another in vitro study, on the role of complement in the important interaction between the immune system and bone, has suggested that complement can directly induce osteoclastogenesis, while also participating in enhancing the inflammatory response of osteoblasts when in a pro-inflammatory environment, such as during bone healing or in inflammatory bone disorders.[10] This may be of special interest when considering that complement is closely connected to both B- and T-lymphocyte regulation[11,12] and that, for instance, B-lymphocytes seem to be an important source of osteoprotegerin, a suppressor of osteoclastogenesis.[3] The question regarding osseointegration is whether the immune activation persists over a longer period of time, or if this is overshadowed and overridden by the progressing innate (genetically programmed) wound healing and remodeling processes.

Monocyte/macrophages (and their fusion into foreign body giant cells [FBGCs]/multinucleated giant cells) seem to play a central role in the bone loss pathway during FBR.[6,8,13–19] Interestingly, macrophages may have a direct osteolytic role, as suggested in some studies,[14,19] whereas bone degrading cells, osteoclasts, may possibly also originate from fusing macrophages (Figure 1),[20] a process dependent on receptor activator of nuclear factor kappa-B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF).

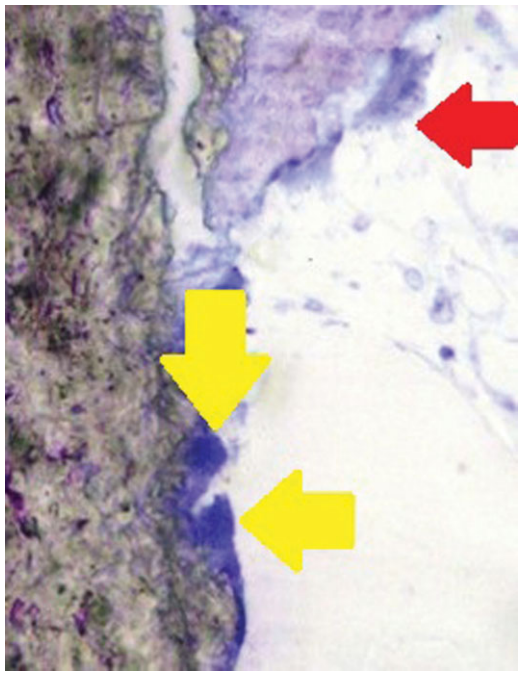

Figure 1 *Yellow arrows* indicate foreign body giant cells on the implant surface; *red arrow* indicates osteoclasts-degrading bone.

The current view is that different types of macrophages can be identified, depending on the specific activation pathway. Anti-inflammatory M2-macrophages have various functions, including maintenance of tolerance, and are involved in tissue repair and wound healing,[21] rather than the purely phagocytic role displayed by pro-inflammatory M1-macrophages. One should, therefore, move away from the classic view on macrophages, for which the name "phagocytes" was even proposed by Metchnikoff, in one of the first attempts to characterize these cells[22]: macrophages should, indeed, be seen as the effector cells of the immune system, when an immune reaction to implants is considered.[3]

Also of interest is a recent publication where an interleukin (IL)-1 receptor antagonist (IL-1ra) was used in an in vivo ligament healing model. IL-1ra is a decoy molecule that binds to IL-1 receptor but triggers no response in the cell; instead, it avoids IL-1 from binding to its receptor, thus inhibiting the IL-1 characteristic pro-inflammatory signaling, which in this experiment changed the healing process direction, not only by reducing pro-inflammatory cytokines and increasing anti-inflammatory ones (IL-10) but also by increasing the number of M2-macrophages,[23] showing the versatility of these cells to change according to the environment.

These facts put macrophages in the center of the FBR process and elicit a possible role in the equilibrium concept.

In many studies of implant-associated hypersensitivity responses, a delayed-type hypersensitivity (DTH, or type IV) has been reported as the principal immunologic concern associated with metallic biomaterials, although more rarely in the case of allegedly chemically inert metallic biomaterials (oxides) such as titania, zirconia, tantalum, and niobium oxides. DTH is suggested to be mediated by degradation products forming haptenic complexes, leading to specific responses such as dermatitis, urticaria, or vasculitis. In addition to direct immune system responses, leading to unforeseen symptoms, DTH responses may be accompanied by effects such as metabolic changes, alterations in host/parasite interactions, formation of lymphocyte toxins, and initiation and promotion of chemical carcinogenesis.[24] One question that may arise from the above is "Does the immune system react preferentially on the presence of particulate material, or are the DTH reaction pathways valid also for macroscopic implants?" Yet another interesting issue is the tentative coupling between immune responses, DTH, and FBR. A specific immune-mediated inflammatory FBR to biomaterials has indeed been suggested by some authors (through T-lymphocytes, type IV reaction),[25] although other authors have explored this and found no such link.[26]

Therefore, at present, it is assumed that the FBR is a nonspecific immune-mediated reaction, possibly starting with the innate complement system[4] and where monocyte/macrophage lineages play a major role, either through innate and/or adaptive immunity.[21]

At the molecular and biochemical levels, several mediators have been identified to control FBR, such as cytokines, that can be pro-inflammatory (IL-1, IL-6, IL-8, prostaglandin E2 (PGE2), RANKL, M-SCF, tumor necrosis factor (TNF)-alpha)[7] or anti-inflammatory (IL-10 and IL-13).[27,28]

The importance of cytokines is starting to become clear. IL-4, for instance, was found to promote the formation of FBGCs in vitro (resulting from the fusion of macrophages, usually to deal with larger size foreign entities) and to participate in the development of FBR to implants in vivo.[13] Other such example has been cited above, when referring to the macrophages role in FBR, where IL-1ra changed the course of an immune reaction.[22] In order to further understand the importance of IL-1, a study reported that in dental peri-implant bone loss, IL-1α is the most prevalent cytokine found in the population of cells identified in the bone defect.[29]

Another aspect of the equation that is still to unveil is cell-to-cell communication. *In vitro* models have limitations in representing the *in vivo* complexity of inflammatory signaling, but one in vitro study has managed to establish that a co-culture of fibroblasts and macrophages leads to a more pronounced FBR when compared with single cultures of the same cells.[30] Further understanding of how this communication takes place could be important for future FBR modulating strategies.

Materials and Bone Loss

Several materials have been used in studies – and some are in clinical use – which induce different degrees of FBR, such as polyethylene,[19,31–35] polylactic acid,[36–41] and beeswax,[42] to mention but a few. Polyethylene and polylactic acid have extensively been used as comparative materials to titanium. Polyethylene, especially, has demonstrated a predictable ability to induce a pronounced inflammatory FBR, leading to bone loss.

These studies support the view that a material implanted in the body will induce a tissue response in the form of an FBR.

In soft tissue models, after weeks to months of implant insertion, the end point result is a fibrous encapsulation (fibrosis) of the nonself object, the biomaterial. The tissue organization and cellular composition of this fibrosis are radically different from that of a healthy soft tissue, characterized by a surface sheath with parallel collagen-dominated fibers of several hundred micrometers thickness, with scarce vascularization and innervation, a low cell density, most often populated by fibroblasts and monocytes/macrophages, and in a later stage FBGCs.[6] An analogous "shielding off" by bone tissue, creating a foreign body response to dental implants, is supported by a lot of evidence listed under this heading.

According to Donath and colleagues, titanium implants under load are seldom totally covered by mineralized bone,[5] and hence macrophages and FBGCs, characteristic of a typical FBR, can be observed at the implant-bone interface. From a cell biology point of view, these cells, as well as for instance, osteocytes, are continuously under influence of growth signals (or they would atrophy) and are biosynthetically active, otherwise cell function and survival simply would not be possible.[43] Thus, different stimuli – most probably local, although a systemic etiology cannot be discarded – may hypothetically trigger activation, or even a change in phenotype, resulting in different possible outcomes that include the setting off of bone degradation, through some of the mechanisms discussed in this text. Hence, the concept that osseointegration is most probably a dynamic phenomenon, as opposed to a static event.

FBR has been related to titanium as a material, in the form of titanium particles, leading to increased bone loss when mixed with polyethylene, compared with polyethylene particles alone.[32]

The described FBR to titanium is in all probability not limited to this specific biomaterial. Other implant materials such as titanium alloys, tantalum, or zirconia frequently used in oral implantology, with the addition of stainless steels and chrome cobalt molybdenum alloys used in orthopaedic surgery, are hypothetically also representatives of foreign bodies. Lamentably, specific knowledge still lacks on what mechanisms in the immune system act in embedding certain other materials in soft tissue instead of allowing their integration with the bone. One may speculate that one such material, copper, emits toxic ions that prevent bone formation as a shielding off mechanism, but much more research is needed in this field. In addition, even if a specific material is embedded in bone, we lack evidence of "the ideal" bone to metal percentage for clinical function. In the infancy of osseointegration, it was believed that the more bone, the better the clinical function, but this assumption has never been fully clinically verified. However, the fact that certain moderately rough implant surfaces have resulted in a stronger bone reaction than seen to smoother or rougher implants is interesting, not the least as there is a coupling between improved clinical function of moderately rough surfaces at least in compromised cases.[44,45]

It can be argued, when trying to apply the FBR concept to the peri-implant bone loss seen in dentistry, that in orthopedics and in vivo experimental models, there is a closed environment – referred to as *aseptic loosening* in the literature[46–48] – that is not open to a cavity where microorganisms proliferate, as is the case of the oral cavity. However, it is quite possible that even bone loss around oral implants may start primarily by an *aseptic loosening* rather than an infectious process.

Such hypothesis of an aseptic loosening mechanism behind marginal bone loss around oral implants does not contradict the possibility of a bacteria-derived marginal bone resorption in individual cases. For instance, it is known that hip implants suffer from infection in 1 to 2% of the cases.[49] Nevertheless, the majority of these infections is of an early nature and depends on intraoperative contamination,[49] a condition that is greater for orthopedic implants than for oral ones, presumably related to the much greater surgical trauma inevitable when placing a hip implant in comparison with an oral implant. Of particular interest are late infections that are hematogenously acquired; in hip replacements, those are rare and in the range of a few tenths of a percent of operated cases.[49,50] One can, therefore, certainly not exclude the possibility of bacteria-derived infections around oral implants too, but the aseptic mechanisms behind marginal bone resorption have been more or less ignored in the dental implant literature so far.

A publication reporting on dental implants has made an attempt at describing the molecular and cellular environment of a clinical peri-implant bone loss,[29] but without stating that it represented an FBR, even though it described such characteristics, with macrophages, fibroblasts and FBGCs, among which several mediators

known to participate in FBR were present. This might add some light into this novel approach of understanding dental implant osseointegration and the mechanisms behind peri-implant bone loss.

A special attention should be paid to how the interplay between the web of inflammatory reactions and the immune system with monocyte/macrophage, osteoblast, and fibroblast cell lineages may in concert induce and control osteoclastogenesis[51] and if other cell lineages such as certain B-lymphocyte[3] phenotypes could also play a role, when in presence of a foreign biomaterial.

Research teams studying the FBR to biomaterials consistently report on new pathways in which inflammatory and immune mediators participate in the process and an increased understanding of cellular specific roles starts to unfold. This highlights the importance given by the scientific community to these phenomena.

Hence, further studies are needed to increase the knowledge of an FBR equilibrium to titanium dental implants.

Clinical Implications

When an oral implant is placed in the bone, it may become bone anchored, provided there is appropriate control of a number of implant-, patient-, and clinician-related factors.[52] Implant factors include biocompatibility, design, and surface features; a typical provocation would be to use either an unsuitable material such as copper (which emits toxic copper ions resulting in a prolonged inflammatory reaction),[53] an unsuitable design such as a blade implant (that reacts adversely to attempts of loading), or pretreatment of the surface to prevent proper protein adhesion.[54] The result after such provocations will be a soft tissue rejection of the implant. The same may follow if implants are placed in infected bone sites or with the use of too traumatic surgery or prosthodontics.[52]

However, with proper control of implant-, patient-, and clinician-related factors, different blood proteins may be adsorbed to the surface of the implant. This may activate the coagulation and complement systems, triggering off both a fibrinolytic and an immune response at an early phase of wound healing. The recruitment of neutrophils at an initial phase and monocytes at a subsequent stage ensues, the latter then differentiating into macrophages, which in turn will control the immune response. The subsequent reaction will be bone formation from bone cells balance that shields off the foreign body implant from surrounding tissues. These series of events may result in an FBR equilibrium,[4] but are in need of further research for precise understanding of the different inherent mechanisms.

Hence, implant placement would trigger the following *buildup* events (Figure 2), in its path to osseointegration:

- Titanium implant surface causes adsorption of body fluid proteins;
- Coagulation and complement systems activation by adsorbed and non-adsorbed proteins triggers an innate immune response;
- Macrophages differentiate from recruited monocytes and control the immune response; bone cells (osteoblasts, osteocytes, and osteoclasts) originate from Mesenchimal stem cells (MSC) and in the right balance lead to bone formation (extracellular matrix formation, angiogenesis, and hydroxyl apatite precipitation);
- Newly formed bone shields off the foreign body implant from surrounding tissues;
- FBR equilibrium is achieved and an up-/down-regulation balance of specific immune responses occurs (immunological equilibrium); and
- Implant in clinical function.

When the process of *breakdown* of osseointegration starts (Figure 3), one would basically be facing a serious disturbance to the FBE. As described above, this process seems to be dominated by an immunologically derived series of events that, with time, result in bone resorption and breakage of the soft tissue seals (in a process still to be clarified), characteristic of the balanced FBE:

- Events, such as overloading, cement remnants or systemic disturbances affecting the immune system, cause the disruption of the immunological equilibrium;
- Reactivation of inflammation and complement system mediators;
- Macrophages are reactivated or recruited, some fusing into increasing numbers of FBGCs, while at the same time osteoclastogenesis is induced;
- Breakdown of FBR equilibrium leads to bone resorption and rupture of mucosal coronal seal;
- Possible secondary bacterial invasion; and
- Implant failure.

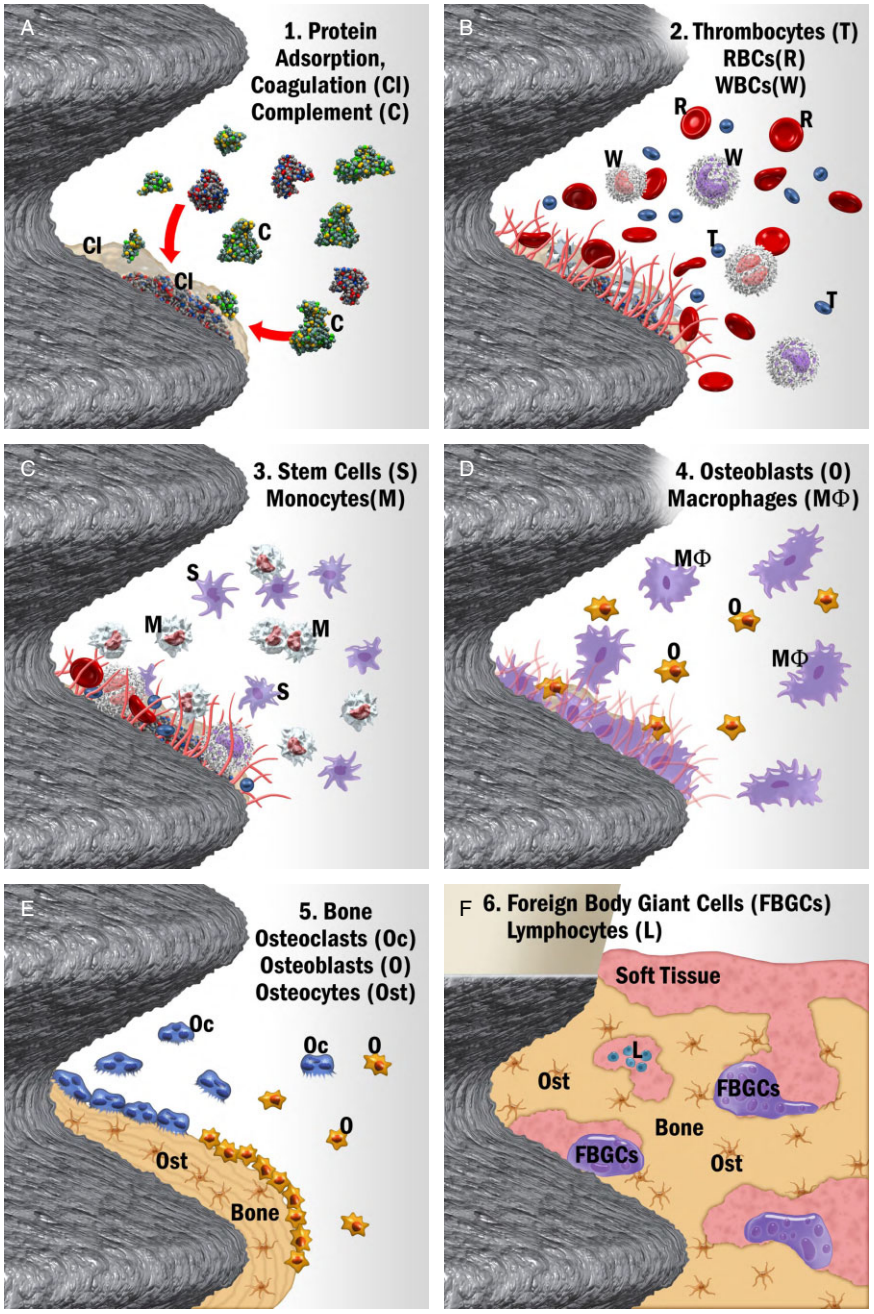

Figure 2 *A–F*, Osseointegration *buildup*, with the parallel and interacting healing, bone forming, and immunological pathways, leading to the foreign body reaction in equilibrium. RBC = red blood cell; WBC = white blood cell.

The hypothesized disturbance of balance as a start of bone resorption may sound strange as very similar mechanisms are involved in bone formation. Again, this is in need of more research but it may be noted that cells of opposing function such as osteoblasts that build bone and osteoclasts that resorb bone actually function in a delicate balance and seem to be in need of one another for function. When the outer environment is suitable for bone formation, this will not take place without the presence of osteoclasts and alternatively, when bone resorption occurs, osteoblasts are needed as these cells have a coupled function.[55–57]

Infection may follow marginal bone loss and further complicate the scenario – an increase in inflammatory and immunological signals in reaction to bacterial lipopolysaccharide (LPS) were hypothesized in one study,[58] although it is not clear whether infection would actually trigger the *breakdown* cascade or merely be acting as a secondary event as suggested in another study.[28] When reaching this later stage of developments, clinical treat-

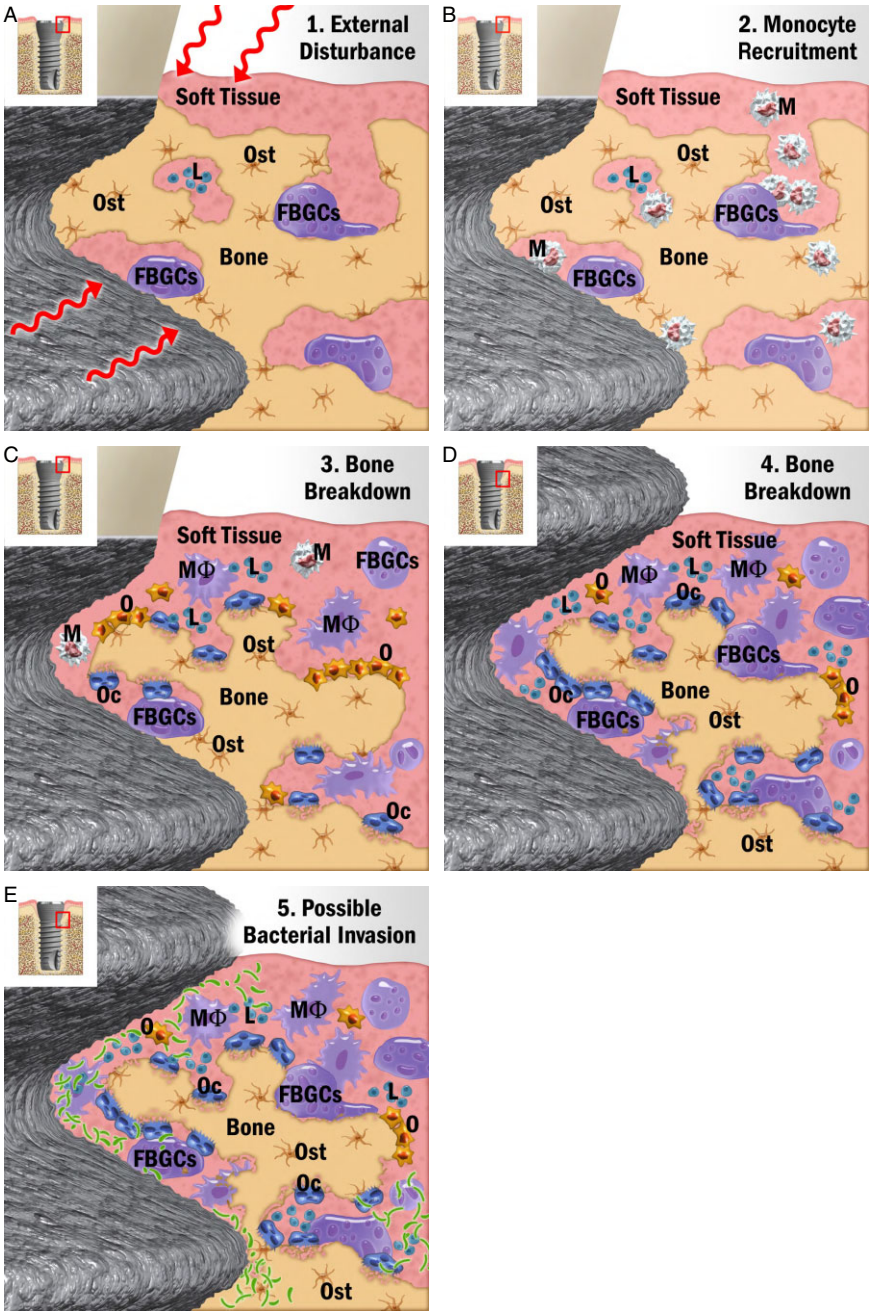

Figure 3 *A–E,* Osseointegration *breakdown*, with the loss of the foreign body reaction balance and consequent peri-implant bone loss. FBGC = foreign body giant cell; L = lymphocyte; MΦ = machropage; O = osteoblast; Oc = osteoclast; Ost = osteocyte; Green bodies = bacteria.

ment to save the implant is much more difficult than in earlier parts of the process, because of the limited efficacy of the treatment modalities made available so far. This fact may serve as motivation for clinicians to be most alert and never forget their lifetime commitment for patient recalls, encompassing early detection of clinical problems that may threaten the equilibrium of osseointegration.

For instance, in a case where the patient for whatever reason has lost a number of teeth close to an implant, one may suspect the problem of too rapidly increasing implant loads and then take adequate and rapid clinical actions to avoid losing the implant (Figures 4 and 5). This is another topic where there is a lack of precise information, the relationship between factors such as overloading and loss of marginal bone. Prosthodontists have claimed that their primary action when marginal bone loss is observed is to change the occlusal pattern, which allegedly leads to a steady

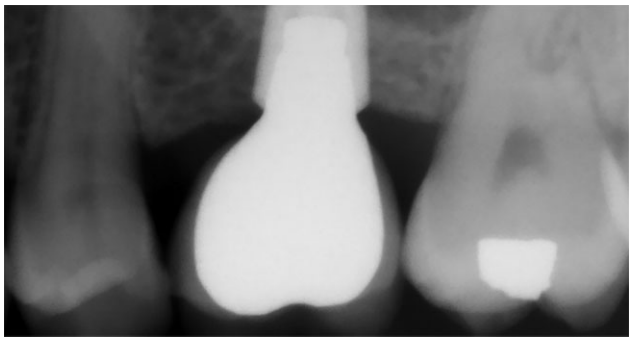

Figure 4 The figure demonstrates a low-risk single-unit implant, with adjacent healthy teeth.

state situation with respect to further bone loss, but lamentably no particular references were found on such hypothesis. There is some animal data indicative of a connection between loading and marginal bone loss,[59,60] but a recent literature review reported on conflicting data.[61] The lack of precise knowledge of a potential connection between loading and marginal bone loss is further supported by reports from orthopedic surgeons who have claimed that bone loss around hip and knee implants is due to stress shielding, that is, underloading.[62,63]

In another case, where the clinician may suspect cement remnants in the soft tissues, remove those as rapidly as possible as the implant may reach a second state of equilibrium, if with some marginal bone loss.

More difficult to perceive, yet equally important, are host individual factors of genetic and acquired nature, for their potential to modulate the immune and healing responses in ways that are still to be clarified in their entirety. Rheumatoid arthritis is of particular interest. It has been reported for rheumatoid patients that the production of RANKL by synovial fibroblasts and T-lymphocytes, in turn involved in the differentiation of osteoclasts, may result in bone resorption.[64] This finding supports the notion that other stimuli than bacteria may trigger an immune response leading to bone loss. Interestingly, another study, comparing genetic markers of peri-implant healthy and bone loss sites of different individuals, has incidentally observed that differences were only found in a patient diagnosed with rheumatoid arthritis, who presented with augmented genetic markers.[65] Both these cases serve as an alert to the possible risks of treating patients with conditions affecting the immune system, a link still vastly unexplored.

Clinicians are, therefore, recommended scheduled revisits of patients to encompass early detection of threatened osseointegration. The more rapidly the clinician can react, the better is the prospect of saving the implant. In case a secondary infection has developed, it may be at least difficult and sometimes impossible to turn the negative series of events for implant rescue. However, there is clear evidence of the possibility of rapid action; despite the start of marginal bone resorption, an FBE may be reestablished.[66]

CONCLUSIONS

The precise relationship between a foreign body material such as a titanium dental implant and the hard and soft tissues of the body is complex and many details are in need of further research.

It seems clear that an FBR involves a large array of phenomena and is a complex process. It also seems clear

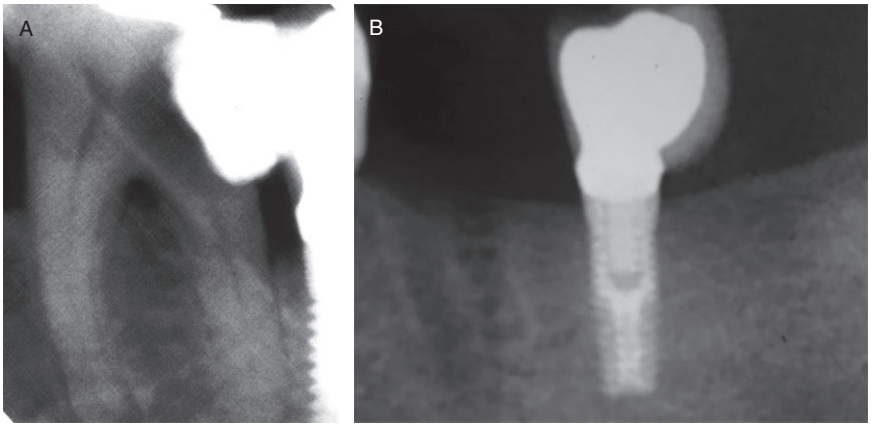

Figure 5 The extraction of a hopeless carious lower first molar (A) leaves a lower second molar single implant at high risk of overloading (B), resulting in a probable disturbance to the FBE, increasing the risk of marginal bone loss.

that all materials getting in contact with living tissues will be recognized as foreign bodies and trigger a response from the immune system.

In the specific case of osseointegrated titanium dental implants, several events follow the surgical implantation. There is no doubt that the immune response is an important part of the governing of inflammatory events after placement of an implant, but the inevitable traumatic nature of the procedure leads to a concomitant wound healing process of the offended tissues. These processes combine with individual, genetically derived patient characteristics to result in a clinical outcome that may end as successful biomaterial osseointegration, through an FBE.

Further studies are needed to clarify the precise regulation and the individual input of the inflammatory immune and healing processes in the *buildup* and *breakdown* of osseointegration. One resulting hypothesis is that the primary etiology for crestal bone loss around osseointegrated implants is a change in the inflammatory balance of the FBE. This inflammatory response may be elicited by sudden changes to the loading situation or through foreign body disturbances in the form of accidental tissue spread of cement particles, to mention but a few clinically relevant implant equilibrium disturbing events. Microbial colonization (infection), although classically considered as the triggering factor for peri-implant bone loss in dentistry, could possibly be a later event and hence be seen as a further clinical complication.

The desired FBE of an oral implant is continually threatened by altered clinical conditions. A combination of implant adverse inflammatory and immunologically derived reactions may threaten implant longevity and, in this context, it may be considered surprising that the great majority of placed oral implants, after all, function very well for decades after placement.

The above described biological scenario, where living tissues face the presence of biomaterials within an immunologically active environment, allows for a better understanding of osseointegration dynamics and could lead to the development of new inflammatory modulation strategies, with the ultimate goal of improving clinical success and decreasing the number of treatment complications in implant dentistry.

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