An Imbalance of the Immune System Instead of a Disease Behind Marginal Bone Loss Around Oral Implants: Position Paper

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Purpose: The purpose of this paper is to present evidence that supports the notion that the primary reason behind marginal bone loss and implant failure is immune-based and that bacterial actions in the great majority of problematic cases are of a secondary nature. ***Materials and Methods:*** The paper is written as a narrative review. ***Results:*** Evidence is presented that commercially pure titanium is not biologically inert, but instead activates the innate immune system of the body. For its function, the clinical implant is dependent on an immune/inflammatory defense against bacteria. Biologic models such as ligature studies have incorrectly assumed that the primary response causing marginal bone loss is due to bacterial action. In reality, bacterial actions are secondary to an imbalance of the innate immune system caused by the combination of titanium implants and ligatures, ie, nonself. This immunologic imbalance may lead to marginal bone resorption even in the absence of bacteria. ***Conclusion:*** Marginal bone loss and imminent oral implant failure cannot be properly analyzed without a clear understanding of immunologically caused tissue responses. *Int J Oral Maxillofac Implants 2020;35:495–502. doi: 10.11607/jomi.8218*

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Peri-implant disease is described as a common problem in dentistry today, and no definitive protocol exists for its treatment. Historically, the proposed treatment protocols have been based on the assumption that marginal bone loss (MBL) is driven by the presence of bacteria adjacent to the oral implants. Initially, there were four cornerstones of the bacterial theory behind MBL: *(1)* that implants are the same as teeth, *(2)* that implants display a disease called peri-implantitis that is an identical ailment to periodontitis around teeth, *(3)* that the only reason for MBL is bacteria, and *(4)* that ligature studies in animals may be used as experimental replica studies verifying primary bacterial attacks. Lamentably, none of these cornerstones has survived the scrutiny of time. Taking all evidence together, we can come to no other conclusion than that seeing MBL generally as a primary disease is not correct; instead, it represents a condition.[1] This is why we have decided to add quotation marks to the term "peri-implantitis" in this paper.

Are Oral Implants and Teeth the Same?

One issue seen as essential for the bacterial theory behind MBL is the assumption that teeth and oral implants are similar, as also stated in a recent publication.[2] When this theory of similarity was formulated, it seemed correct, not the least dependent on reports from the original team of osseointegration[3–5]; commercially pure (c.p.) titanium was regarded as bioinert, and the incorporation of this material was frequently compared with a simple wound healing phenomenon. Donath et al[6,7] was the first to present an alternative explanation; titanium was seen as a foreign body, and osseointegration was but a foreign body reaction. Bone tissue demarcated the c.p. titanium implant to separate it from the tissues, a unique phenomenon providing possibilities to load the implant over a long time.

Today, we have clear evidence that Donath was correct. Trindade[8] was the first investigator to demonstrate that c.p. titanium evokes the immune system. Osseointegration is the body's way to separate titanium from adjacent tissues.[9] This is, of course, different from a

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tooth, which is part of the body and not at all similar to a foreign material such as an oral implant. In addition, there are very clear differences in interfacial arrangements between implants and teeth. The former are, if successful, anchored in a relatively sparsely vascularized bone tissue, whereas the latter depend on anchorage via a richly vascularized periodontal ligament.[10] Therefore, we can state today that one of the cornerstones of the bacterial theory, that implants and teeth are the same, has not been verified by recent research.[11–13]

Is "Peri-implantitis" an Identical Ailment to Periodontitis?

Since implants and teeth were assumed to be identical, it was natural to believe that what was assumed to be a disease around implants mimicked the known disease around teeth. This way of thinking was reinforced by the fact that patients who had lost their teeth due to periodontitis generally were found with an increased level of peri-implantitis around their implants.[10] The general thinking was that bacteria on teeth would jump to the implants and infect the latter. This type of reasoning was common until it was demonstrated to be incorrect.[14]

Studies have demonstrated several differences between implant MBL and loss of bone around teeth. Some authors reported that lesions were twice as large around "peri-implantitis" compared with periodontitis and that there were cellular differences as well.[15] Others found different mRNA transcription/gene expression when they compared "peri-implantitis" with periodontitis.[16] The fact that many studies have found that patients with previous periodontitis have more problems with MBL around oral implants than normal patients is presumably explained genetically; periodontitis is a well-described hereditary disease in all probability characterized by numerous different genes compared with the healthy patient. It is possible that one or two of these genes may cause problems with MBL around implants without the two ailments, periodontitis and "peri-implantitis," being similar tissue reactions. This genetic reasoning is supported by the finding of a patient cluster effect with respect to implant failure; less than 5% of the patients lost 56% of the implants in a study of more than 10,000 implants.[17]

Are Bacteria the Only Causative Agent for MBL?

Originally, it was claimed that only bacterial actions caused MBL around oral implants.[18,19]

However, it has been clearly demonstrated today that bacteria are not necessary for MBL. Orthopedic implants are usually placed in aseptic environments and may, nevertheless, lose bone in a mode similar to that of oral implants.[1] The imbalanced immune system is sufficient to cause MBL in cases referred to by orthopedic surgeons as "aseptic loosening."[20–22] The immune system establishes MBL by controlling the balance between the osteoblast and the osteoclast. The osteoblast and the osteoclast are not only bone cells but a functioning part of the immune system as well.[23–25] Disturbance of the balance between these two cells may cause MBL with or without the presence of bacteria. From the growing field of osteoimmunology, we know that chronic inflammation is a well-established cause of such disturbance.[26] On the systemic level, even a mild inflammation has been shown to increase the risk for nontraumatic bone fractures in otherwise healthy patients.[27] On the local level, focal bone resorption may result from a multitude of inflammatory triggers, such as autoimmune disease, the presence of hostile foreign materials, or infection, as long as the inflammation occurs in the near-vicinity of the bone.[26]

Do Animal Ligature Studies Present Support for the Bacterial Theory?

Reinedahl and coworkers[28] (2018) reported 133 ligature studies that commonly used additional ligatures placed during the course of the investigation. Reinedahl et al[28] (2018) noted that none of the studies actually proved that the bacterial reactions were necessary to achieve MBL; other potentially causative stimuli could be the repeated trauma at exchange of the ligatures or possible immune reactions. Having said this, other researchers have been convinced that ligature studies present similar bone defects as seen in patients with advanced "peri-implantitis."[29,30] Rarely, researchers have pointed out a difference between ligature-induced bone resorption and clinical MBL in "peri-implantitis": that the ligature may act as a foreign body.[31]

To test whether the action of ligatures in inducing MBL must be related to bacteria, two different research projects decided to place ligatures in sites where bacteria usually are absent, namely, the long bones of animals.[32,33] Reinedahl et al[32] used a careful aseptic technique to place implants and ligatures in the femur and proximal tibia of rabbits. Silk and cotton ligatures were found to result in MBL despite no presence of bacteria. In contrast to the bony encapsulation of the c.p. titanium, both types of ligatures induced a foreign body reaction of the soft tissue encapsulation type with large numbers of immune cells viable in close contact with the ligatures. No plaque was seen on the implants with or without ligatures. The authors pointed to the necessity of validation of the infectious model of explaining MBL due to ligatures.[32] Dahlin et al[33] reported identical findings when using a similar model in the rat tibia, where implants with ligatures were placed in a nonplaque environment. Polymerase chain reaction (PCR) analyses and histologic evaluations suggested that the MBL was driven by a provoked foreign body reaction.

Further Critique on the Primary Bacterial Theory and the Relation of Perioindices and Plaque to MBL

Inherit in the incorrect assumption that implants and teeth are the same, it was seen as natural to transfer probing tests from teeth to implants without any preceding controlled studies. However, since there are, in reality, substantial differences between peri-implant and periodontal tissues, probing may be criticized for automatic usage around oral implants.[34] Frequently used, if surrogate, markers involve pocket probing depth (PPD), bleeding on probing (BOP), and clinical attachment level (CAL). The relevance and safety of these markers can be critically discussed.[34,35] We have been unable to find any validation of using periodontal indices in implant sites. Many papers have demonstrated clinical success despite PPD values of more than 4 to 6 mm as well as BOP positive scores, which is why the value of the indices has been doubted.[36–39] Göthberg[38] described increasing PPDs and BOP despite MBL being steady over time. It is not at all surprising that several studies have failed in reporting periodontal indices to be reliable tools for implant examination.[40–42] It has been demonstrated that peri-implant probing causes significantly more discomfort and pain compared with periodontal probing.[43] Another issue of potentially great importance is whether actual probing of implants may be related to increased inflammation and even MBL.[34] It would seem important to investigate in a controlled manner whether frequent probing around oral implants is a harmless procedure or not. Further critical comments on the probing of implants compared with teeth are found in the paper by Coli et al.[35]

Presence of plaque has been associated with an ongoing bacterial attack on the implants. However, plaque may just as well be a normal finding on exposed implant surfaces due to MBL for whatever reason than serving as a cause of further bone breakdown. Menini et al[44] demonstrated that plaque gave rise to inflammation but was unrelated to MBL in a clinical material followed up to 14 years. In a micro-RNA study in seven patients, Menini et al[45] described that some specific micro-RNA signatures appeared to be preventing MBL despite the presence of plaque accumulation.

Greatly varying figures of alleged disease have been described, presumably since there are numerous definitions of how to define "peri-implantitis."[46] Implants are, by definition, characterized by a chronic state of inflammation as pointed out already by Donath et al.[7] Therefore, it seems dubious to see soft tissue inflammation as a prestage of a disease, which has been suggested.[47] Instead, the inflammatory response acts in cooperation with the inevitable immune response to defend the implant tissues against infection.[48] The repeatedly investigated bacterial seal may, in fact, be a cellular rather than anatomical phenomenon.

Current Knowledge About the Immune System and Oral Implants

Before pathology is discussed, the normal situation with immunologic reactions to oral implants must be briefly presented. As late as the last few years, we have received final proof that c.p. titanium implants indeed result in an immune reaction.[49–51] The immune reaction is mild compared with materials such as copper and polyether ether ketone (PEEK). That titanium is immunogenic and displays significantly stronger immune signals than seen in sham situations may be seen as evidence in support of the visionary Karl Donath, who realized that osseointegration was but a foreign body reaction more than 30 years ago.[6] With respect to c.p. titanium implants, Donath et al[7] described two possible immune reactions: either demarcation with bone (osseointegration) or rejection of the foreign element. In the case of bone demarcation, this is a defense reaction to separate the foreign material from the bone tissues. In parallel to eliciting clear immune signals, the incorporation of titanium implants during the first month is almost solely characterized by interfacial bone formation, whereas bone resorption is downturned.[49,50] The immune reaction around oral implants is generally in good balance and may function over a very long time (Fig 1). Ten-year clinical data have demonstrated failure rates of between 1% and 4% only of clinically documented implants.[52] Results over 25 years have been described, with survival rates around 90%.[53] In case reports, osseointegrated oral implants have functioned for 50 years or more.[54]

What Happens with Allegedly Sick Implants with Increasing Follow-up Time?

One important study analyzed what happened afterward to allegedly sick implants. Fransson et al[18] reported that using one particular definition, 12.4% of old Brånemark implants were diagnosed with progressive bone loss, what some investigators have called "disease," at a median time of approximately 11 years. Patients with allegedly sick implants were recalled on an average 9 years afterward. Jemt and coworkers[55] reported that 91.4% of the assumed sick implants had lost no significant further bone. No fewer than 95.3% of the "sick" implants were still functioning adequately carrying loads. The number of failed "sick" implants (Figs 2a and 2b) was similar to failed implants at approximately 20 years of follow-up, which had not been declared "sick" previously.

Actual Reasons for MBL Around Oral Implants

The low figures of long-term problems with implants diagnosed with "disease"[55] are quite remarkable. All the presented evidence so far seriously questions whether we actually have a primary disease around oral implants.

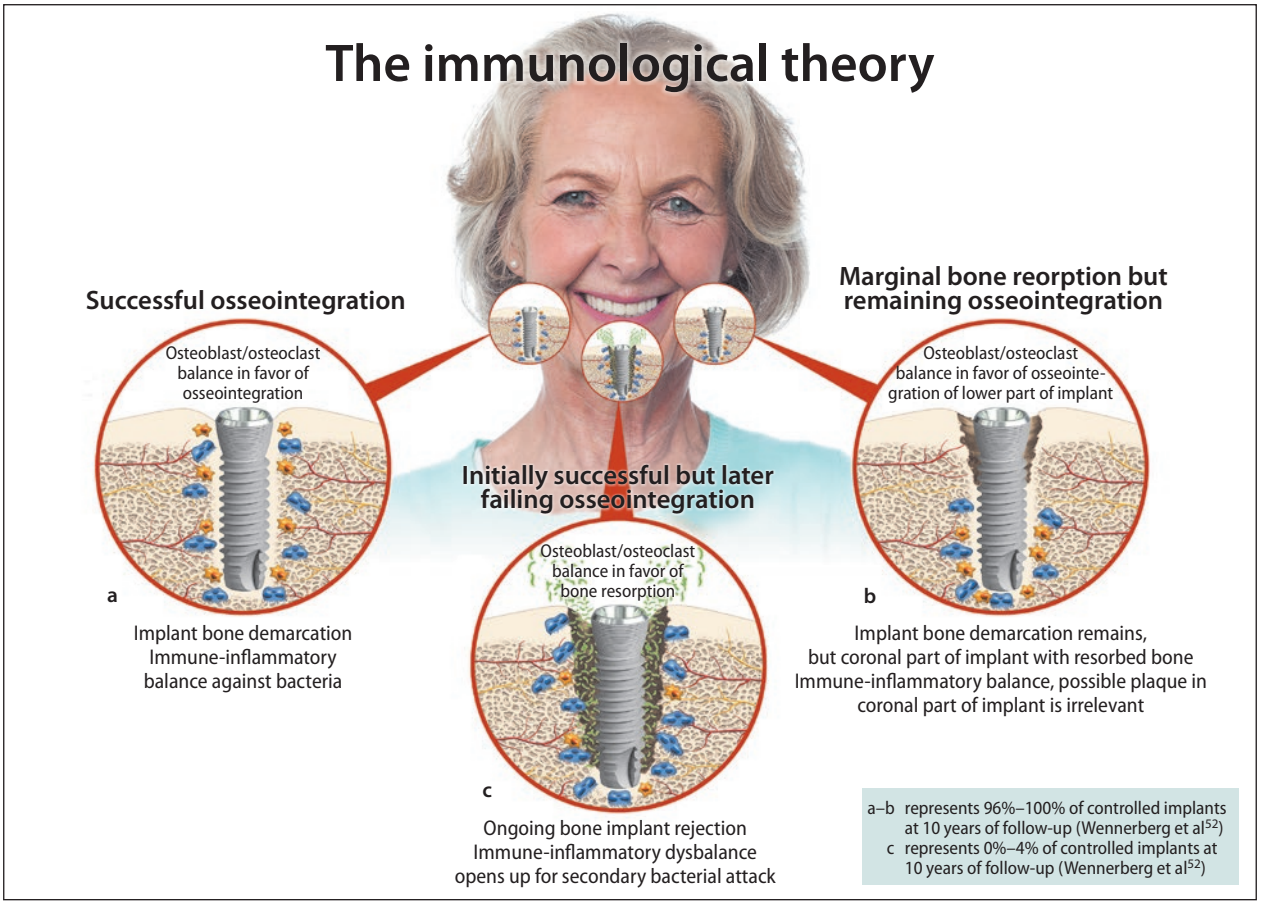
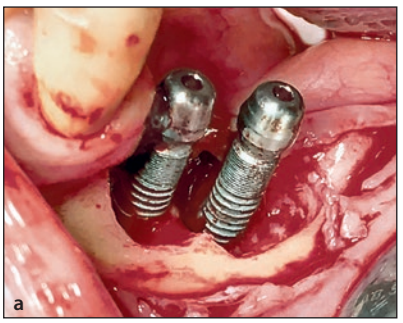


Fig 1 Most implants either display no MBL or display some MBL that does not progress *(a,b)*. In rare cases, the MBL continues due to local imbalance of the immune system, which further results in a gradual lowering of the bacterial defense and implant failure *(c)*.



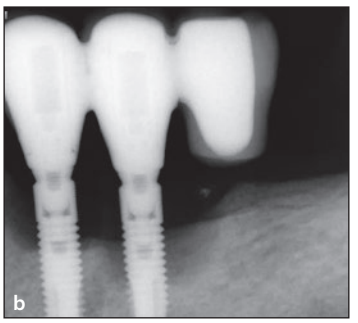


Fig 2a Two implants prior to removal due to progressive marginal bone loss after 10 years of function in a male patient 89 years of age with a history of caries and bruxism. The usual initial reaction in such cases is a continued imbalance of the immune system that leads to lowering of the bacterial defense and an aseptic as well as a septic attack on the marginal bone.

Fig 2b Radiograph of the same patient displaying implant-threatening bone loss evident from radiographs aquired after 9 years of loading.

However, oral implants, like orthopedic implants, may lose bone, and the question is why. We have identified two types of MBL: one is dependent on a complication to treatment that may temporarily further activate the immune system; the other is more serious and related to a continued imbalance of the immune system.

MBL Due to Complication to Treatment

This reason for MBL is dependent on poor implants, poor clinical handling, and "poor" patients. Poor implant systems were summarized by Qian et al.[10] These oral implant systems were initially osseointegrated, but gradually lost their osseointegrated state for reasons not known, with one exception. These types of oral implants commonly gave rise to quite-acceptable 5-year survival rates, but displayed ongoing MBL in comparison to other implants.[56] There is certainly no logical reason why they continuously lost marginal bone, but "disease" seems a poor response. In one case, it proved possible to pinpoint the reason for MBL with a particular implant design. In case the implant was malaligned, clinicians were recommended to grind it down in situ

followed by direct loading. This clinical handling, never tested in studies before it was introduced, resulted in dreadful results, with one-third of the implants either failed or suffering from 3 mm of MBL at 18 months of follow-up.[57] However, the same implant, if placed conservatively, displayed a quite good short-term clinical outcome with very little MBL.[57] Excellent 8.5-year clinical outcomes have later been demonstrated with such conservatively treated implants.[58] The incriminating factors were the clinical recommendations rather than the implant design in these cases.

Complications to treatment may follow poor clinical handling as indicated above, which is another cause for MBL that is most difficult to explain with the disease theory. Ross Bryant[59] analyzed MBL in relation to the individual oral surgeon and was able to show that each surgeon had his own (only males worked as surgeons at the University of Toronto at the time) continued MBL curve despite all using the same implant system and treating similar types of patients. The diagrammatic description of each surgeon displayed differences in MBL not only in the first year after treatment but later as well. A similar investigation of the first restorative dentist displayed similarly interesting results over follow-up times of up to 17 years.[59] The restorative dentists differed with respect to observed MBL in a similar manner as had been observed due to the individual surgeon.

Patients who smoke, take certain medications, have been irradiated for tumors, or are bruxers likewise lose more bone than do "normal" individuals.[10,54,60,61] Another interesting observation was made by Ross Bryant[59]: patients who had been edentulous for a long time lost much less bone than their peers who had been edentulous only for approximately 2 years. Many of the reasons for MBL described here may indeed provoke an immunologic/inflammatory response that takes care of the problem, and no further MBL is seen as described by Jemt et al.[55]

MBL Due to a Continued Imbalance of the Immune System

There is a risk that implants with what is initially relatively harmless MBL due to complications to treatment may go over to a more harmful and vicious stage (Fig 3). There is, at present, no solid evidence why this transfer occurs, but it may be related to the sum of the trauma put upon the implant.[54] In such desperate clinical cases, conditions may become unfavorable, and a rapid and continued increase in the immunologic response to oral implants will follow. As previously mentioned, the immune system may decide the only way to tissue recovery is implant rejection. This serious tissue reaction is fortunately limited to 0% to 4% of all placed implants at 10 years of follow-up,[52,62] provided properly trained clinicians are using documented oral implant systems. Thus, osseointegration of the implant ceases gradually, and it will be rejected from the body. Incriminating factors behind this overreaction of the immune system depend on a sum of the trauma put on the implant. Numerous such traumatic factors exist,[54] and it is important to remember that they may act together. The mechanisms behind the bone loss are osteoblasts/osteoclasts, which, like macrophages, represent immunocompetent cells. To understand MBL around oral implants, it is important to realize that the basic mechanism is an imbalance of the immune system. No bacteria are needed for the initial MBL, which may occur as aseptic loosening around orthopedic or oral implants. However, once the immune system displays continued imbalance, its function to serve as defense against surrounding bacteria automatically goes down,[48] and we may now see a secondary bacterial action. Bacteria are everywhere in the oral cavity, including a dormant presence within the bone itself.[63–66] Therefore, when the immune system ceases to defend the osseointegrated state of the implant, we may see secondary bacteria-driven bone resorption as well.[67–70] In fact, we see a similar secondary bacterial response in ligature studies in the oral cavity of experimental animals, where large amounts of bacteria have been observed.[71] However, again, the primary response is in reality imbalance of the immune system that removes the defense against bacteria.[32,48] Furthermore, local mechanical overload is known to evoke an inflammatory response: similarly too-low load induction of bone resorption via the canonical Wnt-osteoblast/osteoclast axis. Mechanical load shielding may thus be an important causative here.[72]

Fig 3 Implant in a bruxing patient that has lost so much bone that rescue actions in the form of removing all possible trauma seem to be needed.

In a situation where it seems like a dangerous MBL is starting due to a continued imbalance of the immune system, we recommend clinicians to be most active. In many cases, additional help to the immune defense may be given by the

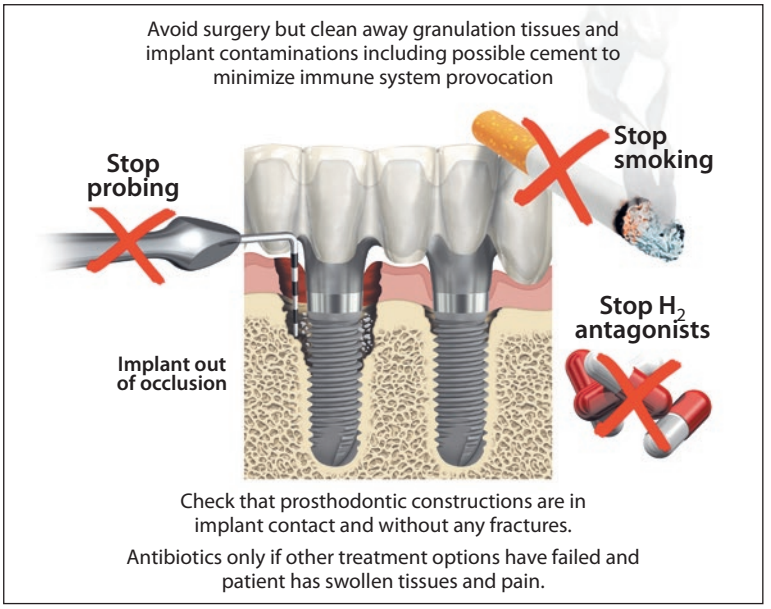


Fig 4 Our suggestion on how to handle a situation with dangerously progressive bone resorption is based on the combined factor theory,[54,77] ie, to minimize all potentially vicious factors that together may disturb osseointegration.

clinician, such as removing accidental cement from the interface. If done in time, this simple procedure leads to instant cessation of further MBL. No disease was cured, since there was no disease in the first place, only a combined elevation of the immune response from the implant and the cement acting together. Another clinical action that stops ongoing MBL is discovering that the patient has been given H_2 antagonists, which after discussion with the physician who prescribed them, may be changed to an alternative drug with immediate response in the form of cessation of further MBL. In cases with ongoing MBL without obvious reasons, it seems to be a good policy to remove as much trauma as possible around the implant. One action can be to motivate patients to stop smoking, and another is to put implant crowns out of occlusion. The same load level that can be carried without a problem by an ordinarily functioning implant may represent a threat to an implant with ongoing MBL. We would fear probing trauma in these delicate cases more than in normal situations without ongoing MBL. Proper clinical actions may prevent the implant from further MBL and possibly avoid a shift in the immune response from bone demarcation to rejection (Fig 4).

However, even if bacterial reactions as a rule are secondary, we cannot totally rule out that a primary bacterial attack may, in fact, exist. Cases of sepsis have been described to result in primarily caused orthopedic failures, and primary bacterial attack is possible at the time of oral implant insertion before the inflammatory/immune defense has properly developed.[48] At this critical time for the implant, we are helped by prophylactic antibiotics given before surgery.[73] Such cases of primary bacterial attack are quite rare, but they may exist in clinical situations with impaired immunologic response for one reason or another. To learn more about oral implants and problems with them, we need to focus "our attention on elements that, therefore, influence the immune response or the consequence of a patient's immune response."[74]

Concluding Remarks

In this paper, we have presented evidence that teeth and implants have very little in common and that building a theory about MBL on what happens to teeth is an incorrect approach. Fortunately, the most common reasons for MBL impose no threat to implant survival, but it may leave 1 to 3 mm of the implant with resorbed bone and esthetic problems. Since such implants commonly see secondary plaque formation, cleaning them mechanically to achieve re-osseointegration has been difficult or even impossible. Having said this, re-osseointegration of oral implants has proved possible with a newly developed electrolytic cleaning technique.[75,76]

We recognize that problems with dangerous bone resorption are not very common in published long-term studies.[52] However, many clinicians are poorly trained and may in addition use undocumented implant systems with an unknown rate of complications, indicative of the possibility of a more substantial problem than reported in the published figures. Treatment of implants with dangerous MBL is difficult, but ought to be centered on removal of all sorts of adverse influence around the implants to as much as possible prevent combined attack on osseointegration.[77] Secondary bacterial attacks characterized by swollen tissues and patient pain ought to be treated with antibiotics at the level of our present knowledge. However, we need clinical studies to find out whether it would be possible to treat the basis of the problem: the immune system, rather than the symptoms caused by MBL. In other words, great focus has to be put on "the study of the immunomodulatory capacity of the device and the osteoimmunobiology of the host."[78]

CONCLUSIONS

1. Many oral implants see no marginal bone resorption at all.
2. MBL around oral implants, even if occurring after the first year of function, is not at all synonymous with disease.

3. The great majority of oral implants with MBL will survive for decades.
4. The oral implant is a foreign body that is protected by inflammatory and immune cells against infection.
5. In rare cases, continued massive immune imbalance may result in MBL that may be reinforced by a lowering of the inflammatory/immune defense against bacteria, which may end in a gradual rejection of the implant due to a combination of immunologically and bacterially driven bone resorption.
6. Cases with massive detrimental overreaction of the immune system represent only approximately 1% to 2% of all placed implants at 10 years of follow-up, provided properly trained clinicians are using adequately documented oral implant systems.

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