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REVIEW

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Implications of considering peri-implant bone loss a disease, a narrative review

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Abstract

Background: Peri-implantitis has been suggested to cause significant increasing proportions of implant failure with increasing time.

Purpose: To assess whether implant failure rates in long term studies are matching the supposed high prevalence of peri-implantitis.

Material and Methods: This paper is written as a narrative review of the long-term clinical investigations available in the literature.

Results: Some implant systems have seen unacceptable marginal bone loss figures with time coupled to increased implant failure rates, resulting in the withdrawal of these systems. The reasons for such mishap are generally unknown, with the exception of one system failure that was found to be due to improper clinical handling. Modern, moderately rough implant systems have functioned excellently over 10–15 years of follow up with minor problems with marginal bone loss and implant failure rates within a few per cent. Machined implants have functioned adequately over 20–30 years of follow up. Implant failures occur predominantly during the first few years after implant placement. No significant increase of implant failures has been observed thereafter over 20–30 years of follow up.

Over the years of our new millennium, scientific and technical advances have allowed the discovery of numerous molecular pathways and cellular interactions between the skeletal and immune system promoting the development of the interdisciplinary field called osteoimmunology. Nowadays, this knowledge has not only allowed the emergence of new etiologic paradigms for bone disease but also a new dynamic approach on the concept of osseointegration and MBL around oral implants, re-evaluating our older disease oriented outlook. This facilitates at the same time the emergence of translational applications with immunological perspectives, scientific approaches based on omics sciences, and the beginning of an era of personalized dental implant therapy to improve the prognosis of oral implant treatment.

Conclusions: Oral implant systems have been found to function with very good clinical outcome over follow-up times of 20–30 years. Registered implant failures have occurred predominantly during the first few years after implantation, and there has been no significant increase in late failures due to peri-implantitis.

KEYWORDS
bone resorption, dental implants, immuno-modulation, peri-implantitis

What is known

- In the past, peri-implantitis has been suggested to affect up to 43% of machined oral implants and up to 77% of the patients.
- Moderately rough implant surfaces have been hypothesized to run a higher risk than machined implants to develop peri-implantitis.
- The general belief is that peri-implantitis is a common disorder around oral implants.

What this study adds

- Only 1–2 % of moderately rough implants present with peri-implantitis at 10 years of follow up. Peri-implantitis has been assumed to cause a steadily growing failure rate of implants. In reality, failures of implants occur predominantly in the first few years after implant placement and are unrelated to any disease. At a follow up of 20–30 years, machined implants have not displayed any increasing percentages of late failures due to the disease.
- Peri-implantitis as a common disorder around oral implants is critically discussed.

1 | INTRODUCTION

In the year of 2022, we see two paradigms of oral implants being challenged. One of those challenges is related to the very nature of osseointegration itself that will be discussed in another paper by the same authors,[1] whereas the other challenge is about the assumed implant disease, peri-implantitis, that will be discussed here. We intend to scrutinize whether implant bone loss justifies the use of a term such as "disease." An assumed integral part of the alleged disease is that the bone loss would result in great figures of implant failures with increasing time. One aim of this paper is, therefore, to analyze what happens over time and summarize long-term (10 years or more) reports on oral implant survival. The hypothesis is that, in reality, no increased implant failure rate can be observed with time.

Another aim of the present paper is to perform clinical observations with relevance to the immune system, an important mission since a new science of osteoimmunology may have a greater clinical impact than previously believed. Osteoimmunology from a basic science point of view will constitute an important part of our other paper.[1] A discussion about immune-centered therapeutic approaches and omics sciences will be presented as well as some concluding remarks.

2 | IS PERI-IMPLANT BONE LOSS A "DISEASE"?

The use of dental implants as a routine restorative treatment since the early 1980s has certainly prevented the sacrifice of many teeth that would otherwise be used as retainers for conventional, fixed partial dentures. Furthermore, implants have been used for the provision of fixed restorations and/or well-retained overdentures in partially and totally edentulous patients with clear improvements in patient's life quality. The success of rehabilitations with dental implants relies on osseointegration. As a consequence, the stability of marginal bone level has been considered a critical factor for the long-term treatment outcomes. Any marginal bone loss (MBL) occurring after an initial phase of remodeling (usually 1 year of function) has, therefore, been considered a potential threat to the longevity of implant rehabilitations. However, in the past, the key focus was that progressive bone level changes should not exceed 0.2 mm/year after the implants first year in situ.[2] In contrast, MBL surged to the status of disease "per se" when associated with bleeding on probing (BOP) of the peri-implant soft tissues.[3–5] The definition of such an alleged disease, peri-implantitis, has varied during the last 20 years, including or not the deepening of peri-implant pockets, but mainly depending on the amount of marginal bone loss that should be considered pathologic, once the remodeling phase is considered finished.[6] Currently, one commonly used definition of disease is set at 3 mm of MBL in association with BOP.[7] Such a definition implies that a diagnosis of peri-implantitis is established whenever the peri-implant mucosa bleeds on probing and an MBL of 3 or more mm is detected radiographically at a dental implant site, independently on how long the implant has been functional in the oral cavity and independently of whether the bone loss is progressive or not. Such a diagnosis may lead to treatment intervention. Another commonly used definition of peri-implantitis has an even lower threshold; any MBL after the implant's first year in

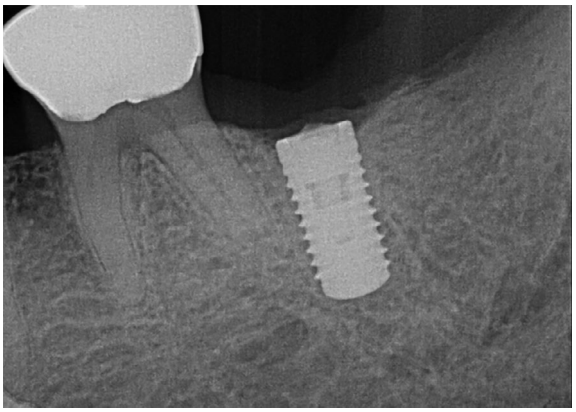

FIGURE 1 Abutment screw fracture with some marginal bone loss. Fracture of implants or implant components is one reason for loss of marginal bone. Courtesy of Dr Jacob Zellner, Texas, USA.

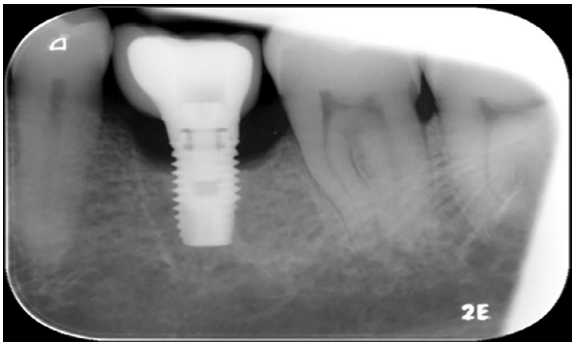

FIGURE 2 A clinical case 2 years after implant placement with MBL that was found dependent on the accidental presence of a ligature, of iatrogenic nature or patient caused(dental floss), around the implant. The ligature was removed and further MBL ceased immediately. Ligatures are known to cause significantly disturbed immune reactions that precede possible bacterial attacks. Had the ligature remained in situ in this case, it is likely that it would, with time, have caused a shift in the immune reaction from shield off to implant rejection in the same manner known for accidental cement remnants in the implant interface. Courtesy of Dr Örnhall Britse, Gothenburg, Sweden.

situ coupled to bleeding upon probing.[8] The weakness of both these definitions is obvious; MBL is known to depend on a series of combined factors including patient genetics and patient smoking or consumption of certain pharmaceuticals, clinical handling, Fracture of implant or abutment screws (Figure 1) overloading, accidental presence of cement or other foreign materials (Figure 2), the time the patient has been edentulous prior to implant treatment and, if limited to local reactions, microbes.[9,10] None of these factors are relevant for the diagnosis of a disease, but they may combine and result in MBL around the implant.

As pointed out by Temple et al,[11] "disease is *a state* that places individuals at *increased risk* of *adverse consequences*. Treatment is given to those with a disease to prevent or ameliorate adverse consequences. The key element in this definition is risk: deviations from normal that are not associated with risk should not be considered synonymous with disease."

It is interesting to note that there are increasing concerns about the effect of overdiagnosis.[12] Brodersen et al[13] discussed this issue in general medicine. "Overdiagnosis" means making people patients unnecessarily, by identifying problems that were never going to cause harm or by medicalizing ordinary life experiences through expanded definitions of diseases. Accordingly,"overdiagnosis has two major causes: overdetection and overdefinition of disease and, ultimately, causes more harm than benefit."

With the aim of preventing disease and premature death, more and more healthy individuals are redefined as sick individuals and prescribed lifelong pharmaceutical solutions to reduce their alleged risks[14,15] suggesting that the definition of common conditions have broadened to the point that the entire older adult population is suffering of at least one chronic disease. By setting treatment threshold low, people with mild problems or modest risks are exposed to the harms and costs of treatment with little or no benefit[16] and in some cases, hundreds of people at low risk of future illness need to take medications, in order for one of them to benefit by having a bad event prevented.[17] It has been pointed out that mass intervention on a fragile basis may lead to mass harm and that turning risk factors (surrogate end-points) into diseases also needs careful reflection.[18] In light of these observations, the question whether the issue of peri-implantitis falls in the frame of overdiagnosis appears to be compelling and has been raised previously.[19] Is a 2 mm (or more) MBL and BOP (peri-implantitis) *a state of disease* that places dental implants (and individuals) at *increased risk* of *adverse consequences* (loss of the implants, poor general health)? Or is the actual definition of peri-implantitis making dental implants and patients unnecessarily "sick", thus exposing patients to harms and costs of treatments with little or no benefit?

In reality, it would appear that peri-implantitis exists only when the immune system has set for implant rejection and therefore the defense against bacteria goes down. In such a case MBL occurs as a combined effect of bacterial attacks from biofilms, from freely circulating microbes and from bacteria harbored in the bone tissue itself.[20,21] In contrast, as long as the immune system is in balance, its bacterial defense will prevent any dangerous MBL.[22]

3 | MISMATCH BETWEEN HIGH PREVALENCE OF PERI-IMPLANT DISEASES AND HIGH LONG-TERM CUMULATIVE SURVIVAL RATE (CSR) OF DENTAL IMPLANTS

A high prevalence of disease has been claimed by those who, as of yet, have not reflected on the fundamental role of the immune system for maintenance of the bacterial defense as well as for substantial loss of MBL when implants are in the rejection phase. For those who believe in the concepts of disease coupled to any MBL around the implant, it seems natural to expect a strong increase in implant failure rates with increasing time of follow-up. The prevalence of disease then becomes totally dependent on the MBL threshold defined based on empirical presuppositions. For example, within the same sample

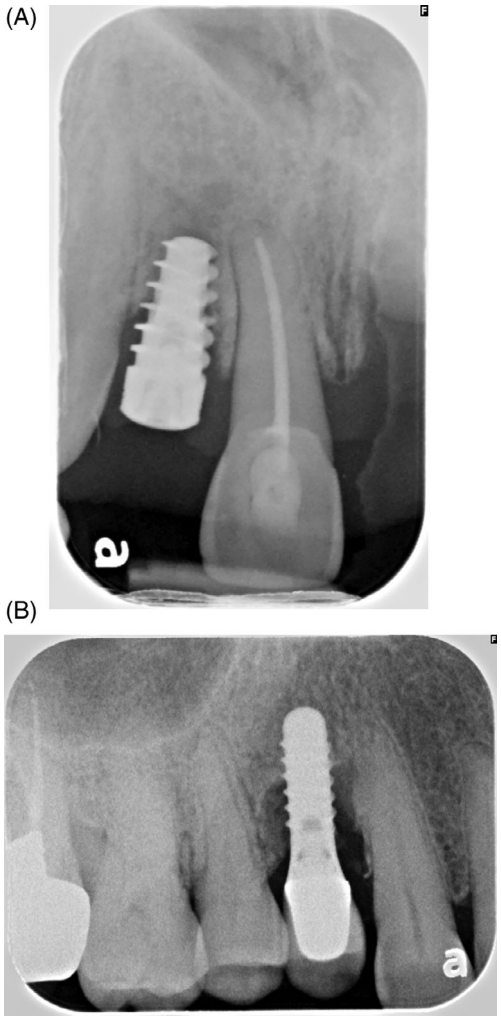

FIGURE 3 Marginal bone loss of a magnitude that may threaten the survival of the implant. Such cases occur, but have not been demonstrated to cause any significant increase of implant failure rates over long time. The great majority of implant failures occur during the first 1–2 years after implant placement. Courtesy of Dr. Kaleb Esplin. Texas, USA.

population of 164 adults attending a Scandinavia University clinic,[23] the prevalence of peri-implantitis ranged from 11 to 47% depending on MBL thresholds. Election of 2 mm versus 3 mm of MBL from the expected platform level as assessed cross-sectionally without longitudinal bone loss rate led to a nearly 3-fold increased prevalence estimate in the same subjects. Nonetheless, it is unclear if any of these cross-sectionally elected thresholds have any impact on the long term prognosis of the implant or rate of bone loss progression. In other words, the prevalence of peri-implant bone loss does not necessarily reflect the prevalence of peri-implantitis when long-term implant success rates are considered. Therefore, it appears relevant to analyze long term clinical results with different implant systems and scrutinize their failure rates over long times of follow up. (Figure 3a,b). A PubMed search using keywords such as "15-year", "16-year" (etc up to "35-year"), "follow-up", "outcome(s)", "long-term", "dental implants" provided the bulk of the relevant articles discussed in this paper. A further search in the reference list of the identified articles confirmed/completed the relevant list.

4 | IMPLANT SYSTEMS WITH SUBSTANTIAL MBL AND/OR HIGH FAILURE RATES

Some implant systems have indeed displayed very high levels of Marginal Bone Loss which in many cases have resulted in withdrawal of specific implant systems. Examples of such implant systems are the threaded hollow cylinder Core Vent, where one paper reported drastic MBL within 5 years of follow up,[24] the cylindrical IMZ implant that never displayed any steady state bone levels,[25,26] HA-coated cylinders with unacceptable MBL[27] and Direct implants that displayed either implant failure or more than 3 mm of MBL at 18 months of follow up.[28] Other implant systems which lack reports of steady state bone levels include hollow cylinder implants without threads. Sintered porous-coated surfaces demonstrated a CSR of only 73.4% at 20 years of follow up.[29] It is difficult to state why implant-threatening MBL has been observed for some implant designs, but there is no evidence that failure or high MBL levels had to do with any disease in these cases. With the Direct implant, there is clear evidence that problems had nothing to do with the implant design, but instead with inappropriate handling recommendations to grind the implants down in situ to fit to supra constructions followed by direct loading of them. If the same implant system was placed and handled conservatively, it performed well with minor MBL and high CSRs over short and long-term follow ups.[28,30]

Other assumed reasons for the noticed MBL may be related to the use of cylindrical designs without threads in combinations with plasma sprayed surfaces. Theoretically, cylindrical non-threaded implants may display undue micro movements, causing implant failure with increasing time. One indication that the non- threaded cylindrical design per se and not the HA material itself may cause vulnerable MBL is found with reports of HA-coated *threaded* implants in 24 patients that were found with quite acceptable results up to 20 years of follow up with a CSR of 91.8% at 16.9 years and 80% at 19.6 years with the drop in implant survival at the latter time coinciding with a tumor resection.[31] This study further concluded that implant failure is more common before loading, therefore consistent with previous reports.[32–34]

5 | MODERATELY ROUGH IMPLANT SURFACES OVER 10 YEARS OF FOLLOW UP

Ten-year or longer follow-up documentation is available for four different types of newer, moderately rough implant surfaces, namely Tioblast, SLA, TiUnite and Osseospeed implants. The SLA and TIUnite designs share low failure rates and minor MBL (when followed up for 10 years or more). The failure rates are in the range of 1.46%–3.3% for about 1000 documented TiUNite implants and for about 800 documented SLA implants and about 5% for Tioblast surfaces. Implant-threatening MBL was observed in 1–2% of these moderately rough surfaces.[35]

Three ten-year follow- up retrospective studies of 42, 36 and 13 single Osseospeed implants reported, respectively, 95,4, 100 and 100% survival rates and minor MBL.[36] Two failures occurred at an early time period. A 10 year outcome of 105 mandibular Osseospeed implants

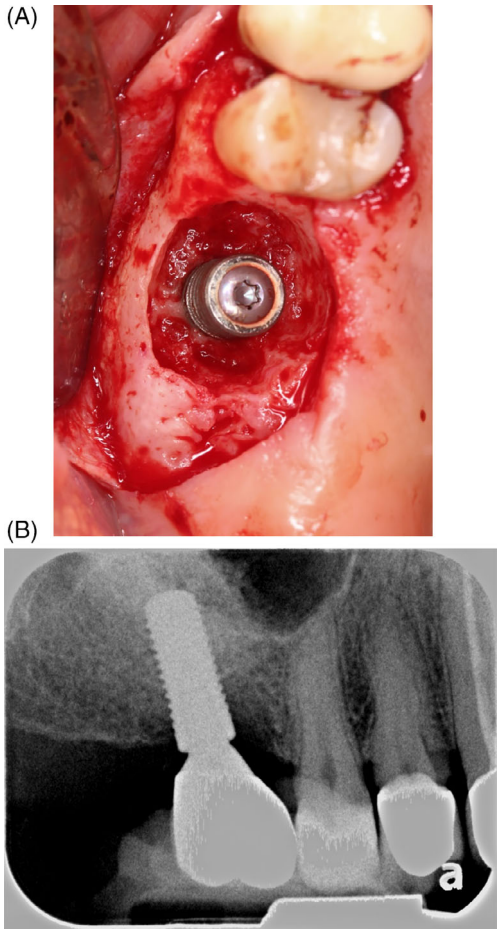

FIGURE 4 A clinical case with marginal bone loss. The implant was placed in an angle giving the restoration a mesial cantilever, but it is unknown whether this was the reason for the loss of bone. Courtesy of Dr Antonella Botto DDS, Texas, USA

showed a survival rate of 100% with an average MBL of 0.49 mm (SD 1.08) and 397 Osseospeed implants showed a survival of 92.7%.[37,38] The estimated average failure rate of these 593 Osseospeed implants was about 4%. (Figure 4).

Some of the included papers quoted by Wennerberg et al[35] had moderately rough implants followed up for 10–15 years without finding any major differences from what was reported at 10 years of follow up. Moderately rough surfaces were originally described by Albrektsson & Wennerberg[39] and were defined by referring to an Sa value between 1. 0 and 2.0 μm. Turned implants described elsewhere in this paper had Sa between 0.5 and 1.o μm, whereas <0.5 μm surfaces were called smooth. Today the great majority of used oral implants are of a moderately rough surface.

6 | 15 YEARS OF MORE OF FOLLOW UP OF IMPLANT SURFACES

6.1 | Turned-surfaced implants

Looking at these reports, the CSR of single implants with turned surface appears to range from 91.5% to 100% between 15 and 25 years of follow-up.[40–47] Similar CSR figures for implants placed in edentulous jaws to support fixed prosthesis have been presented, these figures ranging from 89.8% to 100% for follow-up periods between 15 and 30 years.[33,34,47–52]A CSR range from 93% to 95.5% for implants placed in edentulous jaws to support overdentures and followed-up for periods between 10 and 20 years have been reported.[32,53] For implants placed in partially edentulous jaws to support fixed prosthesis, reports of CSR above 90% at 20-year follow-up[54,55] and CSR of 88.3% at 25-year follow-up[56] are available in the literature. Irrespective of the treatment indications, it is evident that implants with machined surfaces have CSRs of over 90% in studies with an average follow-up time of over 20 years. Frisch et al[57] reported of no failures for machined implants at a follow-up ranging from 23 to 28 years. A CSR of 97.7% in a follow-up study up to 32 years[58] and a CSR of 87.9% for an investigation up to 36-years have been reported.[59] Most interestingly, many of these studies also detected that the majority of failures occurred during the first years of function[33,44,46,50,51,54,59,60] therefore ruling out peri-implantitis as a major cause of implant failures. Several of these investigations also reported that soft tissue conditions suggesting presence of inflammation (i.e. presence of BOP, mucosal problems, persistent fistula) did not affect/correlate to bone level changes,[40,42,43,45] and that only 2.5%–5% of implants showed progressive bone loss.[43,49,53] A great variation in MBL could be detected between studies, with Örtorp & Jemt[34] and Jemt & Johansson[33] reporting of only 1.3% implants showing >3.1-mm accumulated bone loss after 15 years, Simion et al recording a peri-implantitis prevalence of 1.8% at 13 to 32 years of follow-up,[58] Chrcanovic et al reporting of 11.7% of the implants showing at least 3 mm of MBL at the last follow-up,[59] Ekelund et al finding that up to 24% of the implants showed more than two exposed threads after 20–23 years of function[49] and Thöne-Muhling et al detecting MBL of >3 mm in almost 20% of the functional implants after 20 years.[55]

The implant failure figures must be analyzed against known early failure rates of the same implant surface. Jemt and co-workers[61] reported this early (within the first two years) failure rate to be about 11% for maxillary and 4.5% for mandibular implants. It seems evident that most failures of turned implants occur at an early instead of a late follow up time. This is an important observation, since turned implants are the clearly most documented ones in long term studies, representing about 75% of all long term reports.[61]

6.2 | TPS-surfaced implants

In regards to TPS implants from the late 1980s, CSRs ranging from 82.9% to 89.8% between 10 and 25 years of follow-up have been reported[57,62–67] One of these studies showed that loss of implants without signs of infection was more frequent than loss of implants with signs of peri-implantitis,[64] while another investigation found that 46.7% of all removed implants failed within the first 12 months of insertion.[66] Peri-implantitis detection on the remaining implants ranged between 9.7% and 27.9%.[66,67] A 92.5% CSR after 20 years of function was reported for turned-surfaced and TPS-surfaced implants used to retain mandibular overdentures. Minor MBL was detected during the first 10 years and no further loss thereafter. Three out of

eight lost implants were lost within the first year after placement. An observed high plaque index and deteriorated oral hygiene observed due to increasing frailty of the patients did not result in excessive peri-implant bone loss or unfavorable peri-implant parameters.[68]

6.3 | Ti blasted-surfaced implants

CSR ranging from 86.8% to 100% as well as minimal MBL for follow-ups between 14 and 20 years have been reported for implants with blasted surfaces (Astra)[41,69,70] In a 20-year follow-up of a randomized controlled clinical trial a mean MBL difference of 0.4 mm between turned and blasted implant surfaces was detected. Of the implants lost to the 20-year recall, no implants were reported to have failed because of peri-implantitis, although 17 had fractured and 1 disintegrated during the study period.[69]

6.4 | Other long term followed up implants

Implants with a sandblasted surface (ANKYLOS) were found having a CSR of 93.3% after an average of 17 years (up to 20 years) with most of the failures occurring during the first year after placement due to failed osseointegration. In total, 2.6% of implants failed because of peri-implantitis throughout the study period. Bone loss of 1 mm or less was detected for 85.7% of the implants.[71] A CSR of 91.6% over a median follow-up time of 16 years (range 11–20) was reported for sandblasted and acid-etched implants (Frialit).[72] Again, 50% of the implant failures (14 out of 29) were due to failed initial osseointegration. The median MBL was 1.25 mm and 20% of the implants had a MBL of 2 mm or more. Anitua et al[73] reported of a 93.3% CSR and of a mean MBL of <1 mm after a mean follow-up time of 15 years for short implants with acid-etched surfaces (unidentified implant manufacturer) used to restore partially edentulous areas. After a minimum follow-up time of 17 years and up to 19 years, implants with acid-etched surfaces (TSA Defcon) used in partially and in totally edentulous cases showed a CSR of 92.9% and a 4.1% failure rate due to peri-implantitis that was diagnosed in 10.6% of all of the implants initially placed.[74] A 1.2% early implant loss and a 5.4% late implant loss, for a CSR of 93.4% at 9–15 years of follow-up for implants with either machined, anodized or sandblasted surfaces (Astra, Nobel Biocare, Straumann) was reported by Adler et al.[75] Interestingly, implant losses were associated with complications during implant surgery (narrow bone volume, rotation instability of implant, or cervical gaps between implant and bone). Peri-implantitis (defined as 2 mm MBL and BOP) was detected in 21% of the patients (no data at implant level were presented).[75]

7 | COMMENTS ON LONG TERM FOLLOWED UP IMPLANT SYSTEMS

It should be noted that the majority of the long-term studies appears to concentrate on the CSRs and on the maintenance of the function of the implant-retained restorations. Patient-centered outcomes such as patient's satisfaction and comfort and ideal aesthetics were rarely, if ever reported. Similarly, the long-term investigations including BOP assessments are scarce, probably due to the fact that MBL has historically been seen as the most indicative surrogate endpoint and a threat to the implant survival. However, it could be assumed that most of the patients with functional restorations for 10–30 years were probably satisfied. Another aspect to be considered is that the long-term data presented represent the overall implant failure rate with a >10-year follow-up and therefore do not link the cumulative implant failure to the prevalence of peri-implantitis. In addition to the diagnosis of peri-implantitis, there are other factors contributing to the prognosis of the implants, as noted in several of the cited investigations in which most of the failures occurred before implant loading and within the first two years of function.

Within their limitations, the long-term investigations show that 1) during the years, there is a cumulative, if slight, increase of MBL in cases with hexed (flat-to-flat) connections, but not in cases with conical solutions, 2) the CSR is above 90% for dental implants in range of function 15–30 years, 3) the majority of failures occurs during the first years of function, unrelated to what is defined as peri-implantitis, 4) progressive MBL occur in a few per cent of the implants, 5) turned implant-surfaces have a higher risk of failures compared to moderately rough surfacers.[35]

Taken together, these long-term data indicate the poor correlation between detection of MBL and future implant failures and, therefore, the poor correlation of traditionally defined peri-implantitis and an increased risk of adverse consequences for patients such as loss of implants and related restorations.(Figure 5a-d). One could therefore ask the question about how long should one wait for an implant to fail because of the presence of BOP and the occurrence of some bone loss during the years. An alleged disease that after 15–30 years have not yet caused the "terminal" event (or very few events) should be considered a disease? Or should be rather considered "normality"?

From this point of view, the long-term follow-up data suggest that peri-implantitis, as currently defined and as a severe threat to implant longevity, is overestimated due to the phenomena of over-detection and overdefinition. This generates the need of possibly unnecessary intervention and/or diversion of resources. As noticed by Moynihan,[14] there is a tendency in focusing reviews on interventions rather than on assessing the evidence used to make decision about disease definition or diagnosis. "as a result, the claims about the nature and extent of medical conditions are rarely exposed to the same scrutiny as the studies of treatment for them."

Studies with follow-ups between 15 and 30 years have clearly demonstrated an implant CSR between 85% and 100% with a majority of failure occurring in the first 2 years after implant placement indicating a very minor effect of MBL on long term implant survival that is the true endpoint of the treatment (maintenance of the implant and its associated restoration). Long-term studies also demonstrated that, in general, there is a cumulative increase in MBL whereas the risk of implant failures decreases with time. Nevertheless, implant failures and overt inflammatory events do occur, more often in patients with multiple implants

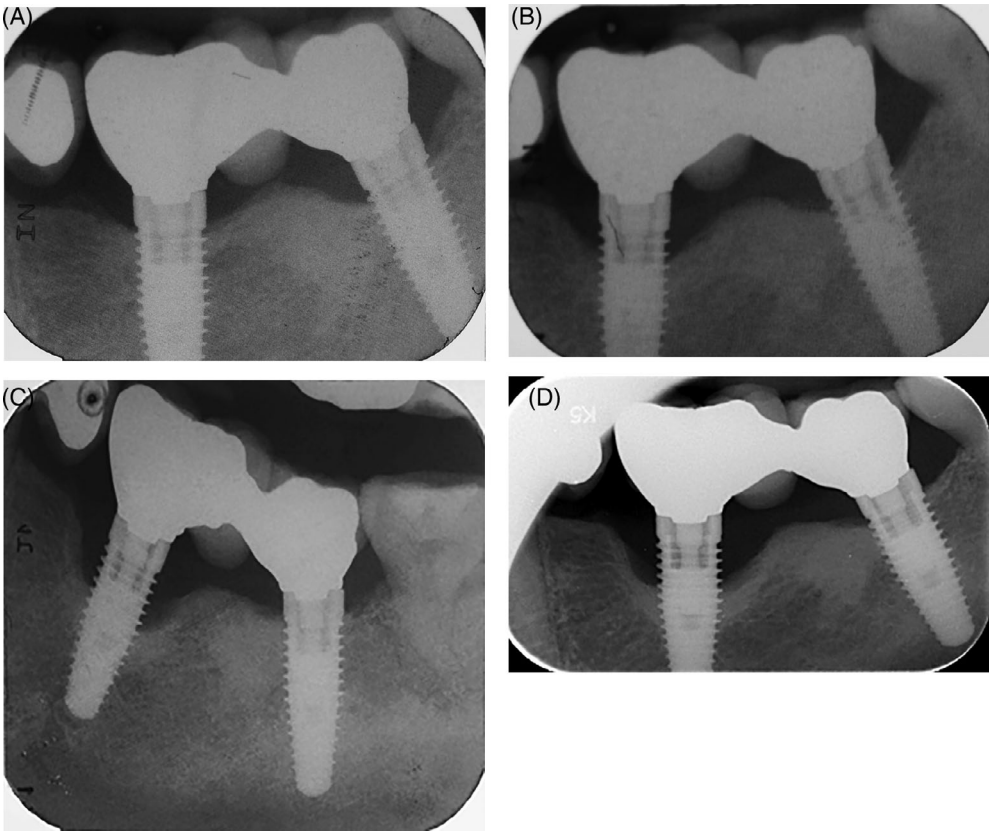

FIGURE 5 Initially progressive Marginal bone loss which ended in a foreign body equilibrium. (a) Perfectly stable bone level after 4 years of function. (b). Three years later, bone loss was observed and considered dependent on a loose distal prosthetic screw and fractured mesial prosthetic screw. Patient chews only on the contralateral side of the jaw. (c) 10 years of function. Further bone loss assumed to be dependent on renewed loosening of distal prosthetic screw and fracture of mesial prosthetic screw 35. (patient is still only chewing on the left side). (d) 13 years of follow up. Bone level is now stable. Chewing ability in the right side has been re-established. Note the thickening of the marginal bone around the re-established "foreign body equilibrium."

compared to patients with single implant restorations,[47,76] often in clusters, suggesting that patient immunological mechanisms may be behind such an event. In a study of 10.096 consecutively placed implants it was reported that 2.5% of patients had 50% of all failures, a substantial cluster effect.[77] These findings taken together have failed in verifying any long-term implant threatening disease and they open up for alternative explanations of implant function. The inevitable immune reaction to implants[78] represents an alternative mode of interpreting short- and long-term reactions,

8 | IMMUNE-CENTERED THERAPEUTIC APPROACHES FOR CLINICAL IMPROVEMENT, OMICS SCIENCES AND PERSONALIZED DENTAL IMPLANT THERAPY FOR CLINICAL IMPROVEMENT

Growing evidence supports the critical role of the immune system in the modulation of peri-implant healing after dental implant placement. Specifically, we now know that the complex harmony of this triad of elements, i.e. bone cells, immune cells and implants finally determines the fate of the foreign body equilibrium.[1,22,78] Hence, to improve osseointegration and prevent bone loss around implants, a better understanding of the osteoimmunology of the peri- implant environment would lead to the development of new therapeutic approaches.[79] Thereby, these scientific advances and knowledge are allowing us to focus on the basis of the problem: the immune system, rather than the symptoms caused by MBL.[22] Therefore, the focus is now to apply strategies that incorporate, modulate and even encourage an immune response rather than attempting to suppress it. In this sense, it is important to introduce the framework of osteoimmunology into the concept of immunomodulation for a new approach with oral implants.[78,80] (Figure 6).

8.1 | Strategies focused on osteoimmunomodulatory capacity of the device

Due to the specialized nature of immunobiology within the bone environment, the convergence of osteoimmunology and immunomodulation seems to be necessary, and the modulation of bone immune response should be categorized as osteoimmunomodulation.[80] In this sense, scientific efforts have focused on achieving immunomodulatory effects on osseointegration through the influence of M2 macrophage polarization in the osteogenic environment.[81]

Currently, different immunomodulation strategies have been proposed for clinical improvement, among which we can highlight the modification of implant surfaces properties to improve osseointegration, by switching the phenotype of peri-implant macrophages. On the other hand, reducing an eventual secretion of pro-inflammatory cytokines through ionic-treated implant surfaces with LiCl or Mg and modulation of macrophage phenotype using polarizing cytokines such as IL-4 represents another possibility.[78] After implantation, the first immune component contacting the implant is the macrophage. Micro- nano-topography

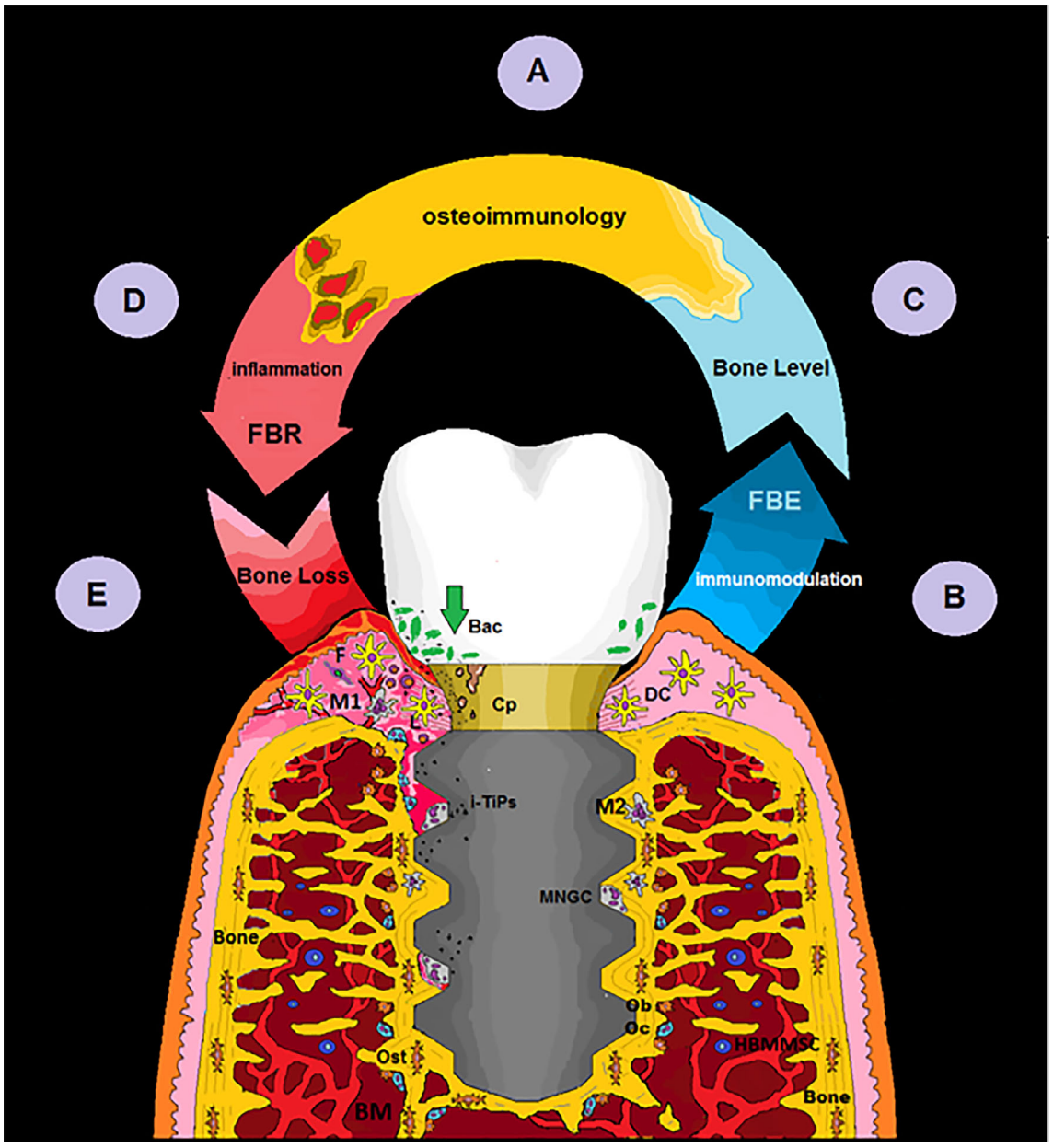

FIGURE 6 (A) In the complex peri-implant osteoimmunology lies the biological mechanism behind osseointegration. (B) In turn, osseointegration is achieved after the generation of the FBE as a result of the immunomodulation capacity of the implant on the host. (C) Bone level can be maintained unchanged for years. (D) However, dental implants can display cumulative levels of ions, nano and microparticles at the implant–tissue interface activating an immune-inflammatory response capable of triggering a FBR. (E) FBE susceptibility to implant close conditions could be represented by a transient imbalance in the local immune/inflammatory state, where MBL represents a clinical condition due to the special transmucosal arrangement. In some cases, if the inflammation is not resolved or reactive due to the stress signals and the immunogenicity of the elements present, persisting inflammation could impede tissue repair and favor bacterial overgrowth. Bac = bacteria; Cp = cement particle; i-TiPs = Implant-derived Titanium particles; DC = dendritic cell; F = fibroblast; HBMMSC = human mesenchymal stem cells derived from bone marrow; L = lymphocyte; M1 = macrophage; M2 = Macrophage; MNGCs = multinucleated giant cells; Ob = osteoblast; Oc = osteoclast; Ost = osteocyte.

could induce a stronger cytoskeleton tension which would make macrophages to polarize to the M2 type, forming an anti-inflammatory osteoimmune microenvironment that promotes the proliferation and differentiation of osteoblasts. Recently, it has further been demonstrated in osteoblast-like cell experiments that auto phagocytosis plays an important role in this process, which could explain the mechanism of implant osseointegration in the osteoimmune micro environment.[82] Along the same line, electrical and electromagnetic treatments could have a revival when we have acquired a greater understanding of the relation between such externally applied signals and cellular function.[83]

8.2 | Strategies focused on the peri-implant osteoimmunology of the host

It has recently been proposed that mechanical stimulation could promote the conversion of myeloid-derived monocytes into an activated status, suggesting that occlusal force might determine the immune microenvironment of the alveolar bone.[84] In addition, a recent study demonstrated that there is a synergy between cellular mechanotransduction and biochemical signals in the regulation of macrophages which would be related to CD11b and Piezo1 crosstalk.[85] In this context it has been proposed that shockwave-induced immunomodulation has potential as a non-invasive physical therapy to regulate macrophage functions linked with wound healing[86] and osseointegration.[78,79,87] This could be a biological mechanism behind the re-fixation of orthopedic implants.[88,89]

Mesenchymal stem cells (MSCs) represent one of the most promising tools in regenerative medicine thanks to their immunomodulatory properties.[90] For this reason, the use of modified MSCs on joint replacements has been suggested to facilitate bone healing in inflammatory scenarios.[91] On the other hand, to stimulate new bone formation and modulate the immune response induced by ROS production, various natural anti-oxidants have been included in different biomaterials/scaffolds and, so far, have resulted in positive outcomes.[92]

Yet another approach to positively modulate the immune/inflammatory response in bone may be via localized pharmacological interventions. For instance, it was observed after 2 weeks of implantation in rat tibia that the early bone fixation, measured as pull out force, of Pamidronate-coated Ti-screws was improved by 28%.[93] In another example, a randomized clinical dental experiment with Zoledronate(Zol) coated Ti-implants showed after the early healing period less MBL than the reference without Zol,[94] a positive difference that remained observable after a five year follow up.[95] The total amount of locally administered bisphosphonate(BP) in the above experiments was approximately 300–500 ng per implant. Other osteoporosis and other drugs than BPs can, of course be used locally and, thereby, avoid systemic drug effects. For good and for bad, the BPs possess high affinity to bone mineral and remain, therefore, locally for a long time to likely be cyclically re-used during the bone remodeling process.

8.3 | Omics sciences and personalized dental implant therapy

In recent years there has been a notable scientific trend in the use of omics sciences and technologies to gain new insights into how different molecules interact and crosstalk at the biomaterial interface. In this line, advanced omics technologies may confer novel approaches for further understanding of cell-to-cell communication and genes profiling during inflammo-immuno-angio-neuro-osteogenesis process and osseointegration, with the aim of evolving new modalities and strategies in implant therapy.[96]

Furthermore, through molecular approaches and genetic data, we will be able to reveal the molecular basis of osseointegration to ultimately pave the way for personalized implant therapy. In this regards, it has been hypothesized that residual ridge resorption (RRR) may have a genetic association resulting from genome sequence variation between individuals in terms of single nucleotide polymorphisms (SNPn). The presence of SNPn may lead to genetic diagnostic tests, which should identify patients at risk of alveolar bone resorption.[96] Herein is the importance of breakthrough technologies and the development of now conceptual fields such as implantomics which would allow us to individualize the treatment with dental implants to different osetoimmune peri-implant scenarios.[96]

9 | CONCLUDING REMARKS

Our findings in this analysis of implants in the clinical reality have come to the conclusion that the mere observation of some loss of marginal bone is unrelated to any known disease. There seems to be no increase of failures of oral implants with increasing time at least up to 20–30 years of follow up. This observation further supports our critical attitude to the concept of an implant disease. We hypothesize that a more realistic analysis of oral implant function is dependent on the inevitable immune/inflammatory reactions to any foreign material such as an implant. This hypothesis will be discussed in a second paper by the same authors.[1]

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Tomas Albrektsson; concept/design, author contribution, data analyses/interpretation; Pentti Tengvall; critical revision of article, drafting article; Luis Amengual; author contribution, critical revision of article; Pierlugi Coli; author contribution, concept/design, data analysis/interpretation, drafting article; Georgios Kotsakis; data analysis/interpretation, drafting article; David L Cochran; data analysis/interpretation, drafting article.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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