Review Article

Dental implant risk factors for peri-implant disease: a narrative review

Michael Alterman[1,2], Ole T. Jensen[3], Paul L. Glick*, Dor Mazor[1], Nardy Casap[1,2]

[1]Faculty of Dental Medicine, Hebrew University of Jerusalem, Jerusalem, Israel; [2]Department of Oral and Maxillofacial Surgery, Hadassah Medical Center, Jerusalem, Israel; [3]Department of Oral Maxillofacial Surgery, University of Utah, School of Dentistry, Salt Lake City, UT, USA

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Correspondence to: Michael Alterman, DMD. Senior lecturer, Faculty of Dental Medicine, Hebrew University of Jerusalem, Jerusalem, Israel; Attending physician, Department of Oral and Maxillofacial Surgery, Hadassah Medical Center, Jerusalem, Israel. Email: michael.alterman@gmail.com.

Background and Objective: Dental implants have become a leading method to rehabilitate areas of missing teeth. Their success and survival rates, as well as their supporting tissues health, are influenced by various intrinsic and exogenous factors. Each year the total number of implants in function rises with more patients becoming at risk for peri-implantitis (PI). Various treatment modalities have been suggested for PI, varying from minimally invasive methods to extensive regenerative surgeries. In advanced stages of PI, implant removal and reimplantation may be required. There is little long-term data regarding the effectiveness of treatment as counter measure to assure the long-term effectiveness of dental implant therapy. It remains the responsibility of the individual clinician to understand the risk factors involved in development of PI and incorporate mitigation strategies as part of overall patient treatment. The aim of the manuscript is to review the scientific literature regarding risk factors for peri-implant disease (PID).

Methods: A comprehensive review of the English literature (published between 2005 and May 2021) was conducted in MEDLINE, PubMed, Cochrane and Google Scholar databases on intra-oral and extra-oral risk factors.

Key Content and Findings: Implant supported rehabilitation is a most predictable method to replace missing teeth. Both intrinsic and extrinsic factors may danger the long term success of dental implants, and should be addressed properly before, during, and after implants installation and restoration.

Conclusions: PI is a major challenge for implant long-term success and longevity. Hence, it is important to understand the risk factors associated with this entity and strive to eliminate them as much as possible on the one hand and be familiar with the methods to treat and control them on the other hand. Our narrative review presents putative risk factors associated with the formation of PI. Among these are history of periodontitis, tissue phenotype, diabetes mellitus (DM), osteoporosis, bruxism, bone turnover impairment pharmaceuticals, smoking, alcohol consumption, implant structural aspects, surgical installation errors including implant mal-positioning or inadequate spacing, prosthetic restorative risk factors and oral hygiene maintenance, frequency, and plaque control.

Keywords: Peri-implantitis (PI); peri-implant disease (PID); periodontal disease (PD); implant bone loss; implant failure

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* Retired, Denver Co., USA

Introduction

Dental implant therapy has provided long-term successful treatment in a wide variety of prosthetic tooth replacement scenarios. However, failure of treatment often occurs and is related to the structural elements of the prosthesis, particularly the dental implant. This failure is biological rather than mechanical and is due to plaque induced inflammatory alteration of the epithelial, connective tissue, and hard tissue attachment milieu of the implant device—this peri-implant disease (PID) process commonly termed, peri-implantitis (PI). The etiology of PI is multifactorial. A number of these factors are systemic in nature, but there are also several local biological factors to consider as well as various prosthetics elements of treatment and the ever-present variable of patient behavior including substance habituation, all of which add risk to treatment.

The directive of this review to identify those risk factors associated with development and progression of PI so as to develop appropriate measures to mitigate there effect and provide optimal long-term success of therapy.

The consensus report of workgroup 4 of the 2017 world workshop on the classification of periodontal and PIDs and conditions defined PI as "*a plaque-associated condition occurring in tissues around dental implants, characterized by inflammation in the peri-implant mucosa and subsequent progressive loss of supporting bone*" (1). This definition specifies the presence of plaque as a necessary condition and a major contributing agent for the formation of PI. In addition, it ties together the inflammatory condition and the bone resorption process of PI. Nevertheless, PI is known to be of multifactorial origin (2-4), with many other factors and conditions that have been described as possible contributors to the formation and progression of PI which may be considered as "risk factors" for this disease (5-8). In addition to PI per definition, there are other PID designations, such as peri-implant mucositis (PM) and peri-implant bone resorption (PIBR) (9-11), which are also caused by multifactorial processes.

Risk factors for PID may include genetic factors, acquired factors and environmental factors. While some of these factors are intrinsic in nature and may be difficult to diagnose and manage, others are matters of patient history or examination that may be diagnosed and sometimes mitigated prior, during or after the implant therapy.

The aim of this manuscript is to review significant risk factors for PID. These are categorized into four broad categories including: (I) intra-oral biological risk factors; (II) systemic risk factors; (III) patient behavioral risk factors; and (IV) surgical/prosthetic treatment related risk factors. We present the following article in accordance with the Narrative Review reporting checklist (available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-100/rc).

Methods

Literature search strategy

This review was identified by MEDLINE, PubMed, and Cochrane databases, using combination of the following term: "Peri-implantitis", "Peri-implant disease", "Periodontal disease", "Dental implant bone loss" and "Risk factors". A comprehensive review of specific factors that may predispose to PI was undertaken. The review utilized PubMed and Google Scholar databases from the time period of 2005–2021 with the last database accessed July 2021 relative to specific subjects requiring additional clarification. The search was conducted by two authors (PLG and MA) utilizing the MESH (Medical Research Heading) terms and keywords alone in combination with the Boolean operators "and" or "or". A comprehensive review of specific factors that may predispose to PI was undertaken.

The search strategy was limited to human studies as published in the English language. Specific focus was on the most recent pertinent articles. The bibliography of such articles was used to access the source material. Additional articles not specifically identified in review articles were identified by the search term "peri-implantitis" in combination with the following single terms: cement, restorative, implant, oral hygiene, reimplantation, maintenance therapy, smoking, attached gingiva, recession, and early bone loss—as well as specific medical conditions and drugs thought to be associated with PI. The source material was likewise used to identify additional articles. Pertinent articles were then assessed and reviewed by three authors (PLG, MA, OTJ) to reach a consensus for inclusion (*Table 1*).

Discussion

Intra-oral risk factors

Periodontitis versus PI

Chronic periodontal disease (PD) and PI are both initiated by dental plaque developing at their respective gingival

Table 1 The search strategy summary

Items	Specification
Date of search	February 2021–May 2022
Databases and other sources searched	MEDLINE, PubMed, Cochrane and Google Scholar databases
Search terms used	"Peri-implantitis", "Peri-implant disease", "Periodontal disease", "Dental implant bone loss" and "Risk factors"
Timeframe	2005–2021
Inclusion and exclusion criteria	Human studies
	Published in the English language
	Articles identified by the term "peri-implantitis" in combination with the following single terms: cement, restorative, implant, oral hygiene, reimplantation, maintenance therapy, smoking, attached gingiva, recession, and early bone loss—as well as specific medical conditions and drugs thought to be associated with peri-implantitis
Selection process	PLG, MA, OTJ

interfaces and subgingival root or implant surfaces. Both result in inflammatory lesions within the gingival connective tissues and initiate loss of supporting bone. However, differences in periodontal connective tissue attachment is a distinct factor in both the initiation and progression of the disease process (12,13).

Attachment of teeth versus implants

Natural teeth exhibit a connective tissue attachment apical to termination of a firm epithelial attachment. Attached to the root cementum is an organized gingival fiber complex extending both to the gingival crest as well as vertically to the sub-epithelial tissues. Additional trans-septal fibers extend between the root cementum of adjacent teeth. The structural organization of the epithelial and connective tissue components is important in supporting the dental papillae as well as providing a defense mechanism against plaque-induced inflammatory lesions, with the breakdown of the connective tissue attachment being necessary for the progression of the inflammatory lesion to progress to bone (12,14-16). In contrast, the peri-implant gingival attachment is less firmly bound to the implant surface than the junctional epithelium around teeth (17,18). The connective tissue adjacent to the implant surface exhibits thin collagen fibers in a *parallel organization* relative to the implant surface, with a high concentration of fibroblasts. Fewer fibroblasts and collagen are present in the supra-crestal connective tissue, and with fewer vascular structures observed compared to teeth (19). These histological observations suggest that the composition of peri-implant tissues resembles that of scar tissue (20).

Periodontal versus peri-implant inflammatory lesions

PI lesions also exhibit different histopathological characteristics than periodontal lesions. The apical extent of the inflammatory cell infiltrate (ICT) is often apical to the termination of the epithelial attachment in direct proximity to the implant surface. Although plasma cells and lymphocytes are found in both lesions, neutrophils and macrophages are present in greater proportions with dental implants.

Experimentally induced disease

Experimentally induced PD sites exhibit a remission or "self-limiting" response following ligature removal. Whereas, peri-implant sites continue to exhibit signs of acute inflammation and presence of osteoclast response on the crestal bone (21).

Attachment mechanism

One may suggest therefore, that the epithelial and connective tissue components of teeth not only provide structural integrity of the gingival complex but respond in a highly adaptive way to limit bacterial mediated inflammation. This dissimilarity of protective attachment for an implant leads to loss of attachment integrity with much less of a bacterial insult advancing down the implant surface more easily causing PID.

Microbiome

The microbiomes of PD & PI are generally similar with no recognizable differences other than changes in quantitative composition to suggest a specific pathogenic etiology

responsible for the onset and progression of PI (22-24). Therefore, one may expect patients exhibiting active PD to exhibit a higher incidence of PI once treated with adjacent oral penetrating titanium implants.

Implant treatment with periodontitis history

In a 5-year retrospective study, Lee compared the outcome of implant therapy in a group of periodontally healthy patients (PHPs) to a group of periodontally compromised patients (PCP) defined as having at least one periodontal pocket greater than 6 mm following periodontal therapy (25). All patients were placed on a regular hygiene maintenance schedule. The study evaluated the occurrence of bone loss greater than 2 mm from restoration to study completion. The PHP group exhibited 14.3% and 20% occurrence of bone loss on the implant and patient-level respectively whereas the PHP group exhibited much less at 6.6% and 13% bone loss respectively.

10-year study of periodontitis and PI

Derks reported on a 10-year retrospective study involving 1,778 implants from 988 patients. At the termination of the study, patients were evaluated for the presence of PD and assessment of bone loss. PD was determined by the presence of two or more teeth exhibiting bleeding on probing (BOP), attachment loss equal to or greater than 2 mm, as well as pocket depth of equal to or greater than 6 mm. PI was based upon bone loss from baseline. At the end of the study, 45% of patients exhibited some form of PI and 14.5% of the patients exhibited a more severe form defined as ≥2 mm bone loss. The OR for the development of PI in the patients exhibiting PD was 4.1 compared to the PHP group (26).

PD and development of PID

Dreyer in a recent systematic review assessed the relationship between the concurrent presence of PD and PI. This review which included 11 studies concluded that there is a "strong tendency" relating the presence of PD and PI. However, it was also noted that there was high heterogeneity between studies which may result from differing definitions of PI and PD, as well as differing duration of the studies, differing levels of patient oral hygiene effectiveness, and/or frequency of hygiene maintenance (27).

Prior history of periodontitis and PI

The effects of PD on the development of PI are not limited to patients with an active PD process. Shou demonstrated that those patients with a prior history of PD were more susceptible to the development of PI. However, the overall implant survival rate was not affected (28). A subsequent systematic review by Lin further supports that a history of PD remains a risk factor for the development of PI even for patients under regular supportive maintenance especially in those having a rough surface implant placed (29).

Aggressive PD

In addition to the concept that patients with current chronic PD have a propensity towards the development of PI, it has also been reported that patients treated for aggressive periodontal (AGP) disease continue to have a high risk for development of PI, as well as implant loss. In one 10-year prospective study, PHP subjects exhibited significantly greater implant survival than the AGP group. The AGP group additionally exhibited 2.0 mm of bone loss during the first year with an additional 1.3 mm at the end of the study, which was significantly greater than the PHP group. During the study, patients received hygiene maintenance every 3 months and showed low, similar plaque and gingival index scores between the groups. At the conclusion of the study overall survival rate of PHP was 100% versus 83% in the AGP group (30).

Monje *et al.*, in a systematic review, demonstrated that prior history of AGP disease is associated with an increased risk ratio (4.0) of disease development compared to PHPs or patients with a history of chronic non-aggressive disease. It was also suggested in their review that this increased risk may result from factors other than plaque pathogenicity. Indicating that increased risk may be influenced by innate genetic or epigenetic factors including adaptive immune response. Oral hygiene efforts and the level of tobacco consumption were also considered important. This systematic review also demonstrated that long-term maintenance care is essential to maintain implant health for high-risk patients, with a minimum recall period of 5–6 months proposed (31).

Keratinized tissue (KT)

Adequate width of attached gingival tissue has been proposed as necessary to maintain gingival health and prevent gingival recession and marginal bone loss around teeth. Minimal width attached gingival tissue has been defined as 2 mm of KT with 1mm to be considered "attached" (32). Periodontal and peri-implant tissues both serve to resist marginal tissue trauma in addition to

resisting plaque-mediated inflammatory lesions within their respective connective tissues (16,33,34). One may further suggest that peri-implant tissues are more susceptible to inflammation and infection due to structural differences within the connective tissue as well as a physically weaker epithelial attachment to the implant surface compared to that of natural teeth (16,33-35).

Several studies have suggested that an adequate band of KT (≥2 mm) is necessary to prevent tissue loss and associated bone loss (2,36-39). Conversely, other studies suggest KT is not necessary when "adequate" oral hygiene is maintained (40-42). Lim further explored these findings by following 113 patients with 232 implants over 5 years with all patients maintained by a strict hygiene maintenance schedule. But this study failed to demonstrate a minimal value of KT that related to increasing probing depth, BOP, or marginal bone loss (42).

A possible explanation for these divergent findings may be related to differences in the populations studied and other factors including smoking habits, frequency, and ability to perform adequate oral hygiene as well as deficiencies in implant placement, prosthetic restoration, and limited duration of the observation period.

Hygiene maintenance and KT

Patients who received hygiene visits less than twice a year were shown to be at risk for PI when associated with inadequate KT. These patients exhibited increased probing depth, plaque index, and marginal bone loss when compared to a control group. Additionally, these patients reported an increase in discomfort with brushing contributing to inadequate oral hygiene. These findings are in accord with that of Wennström and Derks's findings, that lack of adequate KT does not in itself predisposes to PI with adequate oral hygiene (42,43).

Gingival recession and KT

Roccuzzo *et al.*, in a 10-year prospective study, demonstrated that patients complying with regular hygiene maintenance, yet with inadequate KT exhibited greater tissue recession compared to patients with KT of ≥2 mm (2.08 *vs.* 0.16 mm respectively). Those patients with inadequate KT required a larger percentage of soft tissue grafting procedures to control discomfort and improve oral hygiene. It was concluded that gingival recession is prevalent in patients with inadequate KT even in patients receiving regular maintenance therapy and maintaining adequate oral hygiene. The grafting procedure was demonstrated to reduce discomfort, improve plaque control as well as prevent further recession (44).

Tissue phenotype and KT

A further contributing factor relative to the development of PI is the additive effect of thin tissue phenotype (TNP) when associated with inadequate KT. This prospective study evaluated patients extended over a mean period of 7 years. The patients maintained a strict oral hygiene maintenance program and were classified as non-smokers. When assessing the occurrence of PI relative to the width of KT, patients with inadequate KT (2 mm or less) exhibited a 24% incidence compared to 17% of those with adequate KT. Patients with TNP exhibited a 27% occurrence of PI compared to the group exhibiting thicker KT of 11.3%. The prevalence ratio of 3.18 between TNP and inadequate KT indicates that "*thin tissue phenotype and inadequate keratinized tissue are highly associated*" and when both factors are present the incidence of PI may be increased (45).

Facial implant malposition

Monje *et al.* further suggested that the factors of inadequate KT, TNP, and facial implant malposition when present are highly associated with PI with facial implant positioning beyond the buccal line being the greater influencing factor (46).

Soft tissue grafting

Based on these conflicting reports and the lack of long-term prospective studies it remains the responsibility of the treating dentist to assess all risk factors involved relative to the soft tissue characteristics at the implant site, with specific attention given to patients' history of hygiene maintenance and make the appropriate recommendation to allow for successful long-term treatment. In those cases where deformities in soft tissue profile or aesthetic concerns are present, soft tissue grafting procedures should be completed before or at the same time as implant placement, however, soft tissue grafting is effective in minimizing further recession when performed after initial implant placement (44).

Vertical thickness of connective tissue

The vertical thickness of the connective tissue in the area of implant placement has also been implicated as an intrinsic biological factor (*ampieizza biologica*) in the development of early post-surgical bone loss. Puisys *et al.* compared sites of less than 1.5 mm thickness, to sites augmented with

allograft to greater than 1.5 mm. In those sites of less than 1.5 mm, 0.86 mm of bone was lost in the first two months, increasing to 1.86 mm following 1 year of observation. This was significantly greater than for the augmented tissue sites which exhibited 0.2 and 0.38 mm bone loss during the same timeframes (47).

Vertical bone loss and biological width

In a canine study designed to demonstrate development of "biological width", it was demonstrated that when initial vertical tissue was less than 2 mm bone resorption resulted. In this study shortly following abutment placement biological width was established resulting in an increase of vertical tissue thickness to 3.65 mm which approximates a normal value of 4 mm in this animal model. Interestingly, the study also demonstrated that the epithelial tissue component had a consistent dimension of 2.0 to 2.1 mm for both test and control animals. The increase in biological width therefore came in the connective tissue component which increased from 1.3 to 1.8 mm in the test group (48). These dimensions are greater than those reported for human teeth which were 1.7 mm for the epithelial component and 1.1 mm for the connective tissue interface (49).

Clinical findings implant abutments and biological width

Windael *et al.*, in a 10-year study of full-arch mandibular prostheses, demonstrated that those implants with restorative abutments under ≤1.5 mm in height exhibited greater bone loss in comparison to abutments ≥3 mm in height (50). These findings are in accord with a prior study of Vervaeke who evaluated bone stability of implants supporting mandibular over-dentures. In this study, when using 1 mm of bone level change as a successful outcome 100% of those with abutment height of ≥4 mm were successful. Whereas the corresponding values for success of when abutment heights of 3, 2, or ≤2 mm were used led to success rates of 79%, 44%, and 31% respectively.

In this well-maintained group of patients, it was also demonstrated that bone loss did not correlate to plaque scores or BOP but rather to the establishment of adequate biologic width (51).

This concept should lead the clinician to consider soft tissue grafting and sometimes bone reduction as required to establish adequate soft tissue height and restorative space for adequate height abutments suggested to be 3 to 4 mm.

Early post-surgical bone loss

Early peri-operative bone loss is predictive statistically for subsequent PID. This "risk factor" or "risk predictor" for PI becomes evident in the post-surgery healing period where it has been shown that greater than 0.4 mm of bone loss from the time of implant placement to post-restoration is highly correlated with bone loss of greater than 2 mm at 18 months follow-up. Abutment connection is a consideration as well as it is well known that there is a greater bone loss when using an external versus internal connection (52).

Ten-year study early bone loss and PI

Early bone loss correlation to PI has been substantiated in a 10-year prospective study involving 1,482 implants. This study, demonstrated bone loss of 0.5 to 1 mm following the first year of implant function demonstrated a significantly greater risk in developing PI, being 11.8% on the implant level and 18.7% on the patient level as compared to those patients exhibiting under 0.5 mm bone loss following the 1-year follow-up time. It was further shown that those patients exhibiting 0.5 mm or more of bone loss at one year, and with a history of both smoking and prior PD have a further increased risk of developing PI (53).

Oral hygiene compliance

Oral hygiene compliance should be considered a necessary part of dental implant therapy, particularly in patients presenting with one or several implant risk factors. However, there is only limited data that describes long-term patient compliance. One particular study of eight years demonstrated patient compliance at only 30% following three years. This decreased and stabilized to 12% during the duration of the 8-years (54).

A further study involving 1,853 patients from four independent offices over a period of up to 10 years demonstrated that 30%, 34%, and 36% of the patients were considered as either non-compliant, partially compliant, or compliant to hygiene maintenance respectively (55). A systematic review relative to compliance towards regular maintenance failed to establish any valid statistical consensus, other than stating compliance "is unsatisfactory". Of the 11 studies reviewed the percent of full compliance ranged from 10% to 80%, 12% to 45%, and 18% to 38%, following 5-, 10-, and 15-year follow-ups respectively. The largest decrease in the rate of compliance was after the first three to four years. In attempting to analyze patient factors associated with compliance it was suggested that those patients with a history of PDs exhibited increased compliance. Whereas patients with smoking habits were

associated with a lower level of compliance. Eight studies provided patients with questionnaires regarding the reasons for lack of compliance. The most commonly associated reason was inadequate information or motivation provided to the patient. Other factors included bad experiences and dissatisfaction with general dentist experiences, as well as the distance to the practice. Economic concerns were not cited as a major factor (56). Those factors that preclude patients from continuing regular hygiene need to be further explored and addressed. While implant procedures can be provided that have the potential for long-term success, once a patient ceases in maintaining periodic hygiene maintenance implant success cannot be assured. The dental profession lacks the ability to address disparate patient attitudes, habits, or psychological traits which potentially hinder outcome and contribute to PID.

Systemic risk factors

Diabetes mellitus (DM)

DM is a chronic metabolic disorder that is clinically defined by hyperglycemia (57,58). DM has been shown to increase the frequency of PD and tooth loss (59,60), to delay wound healing including interfering with bone healing via osteocalcin-induced glucose metabolism and impairing the immune-microbiome response to infection (61,62).

Oates *et al.* (63,64) checked the effect of DM type II on the osseointegration process. In two consecutive reports Oates showed that patients with poorly controlled DM (HbA1C >10%) have lower implant stability at the first two to six weeks. Overall, the final implant stability of DM patients reached the same stability as healthy patients, but it took two times the duration compared to healthy patients. One year after implant installation DM patients had a similar implant stability to the healthy patients.

Ferreira *et al.* (65) showed that patients that had a high glycemic index result at the time of implant installation showed a 26% incidence of PI compared to a 6% incidence of PI in patients that had normal glycemic index at the time of implant installation.

Daubert *et al.* (66) also showed that patients diagnosed with diabetes at the time of implant placement had a three-fold higher rate of PI 11 years after implant installation compared to healthy patients.

Aguilar-Salvatierra *et al.* (67) showed that HbA1C rates have a direct influence on the level of PI. They showed that with HbA1c >10% had higher levels of PI compared with patients with HbA1c between 8–10%, which in turn had greater PI levels compared with HbA1c below 8%.

Gómez-Moreno *et al.* (68) showed a trend of positive correlation between higher HbA1C levels and PIBR, with higher bone resorption in the diabetic population compared with healthy patients after three years, although these results where no significant.

No significant differences were found in the literature review between diabetic and healthy patients in regard to long-term implant survival.

Osteoporosis

Patients with osteoporosis and other osteopenia metabolic conditions are widely treated with anti-resorptive medications (ARM). These usually include IV Bisphosphonates, oral bisphosphonates, RANKL inhibitors and antiangiogenic medications, although the use of the latter is relatively preserved for other resorptive conditions (69,70).

Wang *et al.* (71) and Goss *et al.* (72) showed higher rates of implant loss following long-term (more than 4 years) of bisphosphonate therapy. Griffiths *et al.* (73) demonstrated, in a randomized, blinded, controlled study, a decreasing trend in peri-implant bone mineral density in patients treated with alendronate after the osseointegration of implants. Hence, it may be suggested that long-term bisphosphonate therapy may increase the risk of PI.

In addition to its potential effect on PI, it is mandatory to address the ARM treatment regimen both prior and post dental implant therapy, since it may have other influences on the peri-implant environment.

In 2011, the American Dental Association (ADA) council on Scientific Affair advised cessation of the use of ARM, in order to reduce the risk for medication related osteonecrosis of the jaws (MRONJ). This "drug holiday" was offered in cases of patients treated for more than four cumulative years, starting three months prior to surgical procedures involving the jaw bones and continuing for three more months after the surgical procedure (74). The 2014 AAOMS (American Association of Oral and Maxillofacial Surgeons) (69) position paper revised these recommendations and adopted the Damm and Jones (75) suggested protocol of medication therapy cessation for two months prior to surgery within the bone of the jaws.

Nevertheless, these recommendations did not address the effect of the ARM after installation and consolidation of bone around dental implants. Although ARM therapy in itself is not a risk factor for PI, the presence of PI, or any other infective process that involves dental implants, may

become a cause of MRONJ in the peri-implant region (76). Non-vital bone from MRONJ may be proximal to implant osseointegration adding risk for PI. In settings where ARM therapy is used in cases of implant supported overdentures, it is mandatory to avoid excess prosthesis pressure being transferred to supporting soft tissues which may cause bone exposure leading to peri-implant osseous necrosis that becomes secondarily infected and progressing to PI (77).

Bruxism

Many have discussed the possible effect of bruxism on dental implants (78,79). The majority describe the mechanical effect of bruxism and occlusal overload on the implant and rehabilitation structure and function. However, most authors find bruxism unlikely to be a risk factor for biological complications around dental implants, especially after the consolidation of implants.

Nevertheless, it has been shown that when pathologic overload (>12 kg/mm^2) is applied on dental implants prior to osseointegration, it may result in peri-implant bone loss (80). Hence, bruxism must be taken into consideration when planning an immediate loading procedure because trauma induced early bone loss in itself is a risk factor-predictor for PI.

Medications

Kumar (81) reviewed the effect of several medications on the development of PID. Of the medications he reviewed, two common and popular medications were found to potentially play a role in the development of PID. The two drugs were nonsteroidal anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors (SSRI).

NSAIDs inhibit the cyclo-oxygenase (COX-1 and -2) pathways of arachidonic acid metabolism. COX-2 plays a central role in mesenchymal cell differentiation and endochondral ossification. In a retrospective study, Winnett *et al.* (82) showed that there were reduced bone-to-implant contact, bone area, and bone density around implants in patients that were treated with NSAIDs in the perioperative period. In contrast, Jeffcoat *et al.* (83) showed an opposite result, with bone sparing activity of flurbiprofen, a phenyl-alkanoic acid derivative of NSAIDs.

SSRIs are a widely used anti-depression medications. Osteocytes, osteoblasts, and osteoclasts all have serotonin receptors, and may be affected by the use of SSRI. This influence of SSRI on bone metabolism may increase osteoclast differentiation and inhibit osteoblast proliferation. Wu *et al.* (84) showed higher implant failure rates in patients using SSRI. He assumed that this was due to a decreased bone remodeling potential in SSRI patients in response to mechanical loading.

Patient habituation risk factors

Smoking

Smoking has been acknowledged by many as one of the major risk factors for PI (85-88). Vervaeke *et al.* (89) showed that smokers are at 2.5 times higher risk of experiencing implant failure and more prone to show peri-implant bone loss, especially in the maxilla. They also showed that smoking at the time of implant placement was seen as the "decisive factor" due to its immediate and direct effect on the initial processes of bone and soft-tissue healing. Hinode *et al.* (90) and Vandeweghe *et al.* (91) also showed that smokers have a 5 times higher rate of implant failure in the maxilla compared with non-smokers, but with no such difference in the mandible.

Windael *et al.* (92) evaluated the long-term effect of smoking on 10 years' survival and success of dental implants. They showed that the maxilla was more prone to implant failures in smokers but mentioned that while most implant failures in non-smokers are early, before implant rehabilitation, the failure in the smoker population was significantly later.

The long-term implant failure rate in smokers was 2.7 times higher compared with non-smokers. Beside implant failure, smokers had significantly higher PI in comparison to non-smokers. Again, maxillary implants were more prone to PI than mandibular implants.

The authors explained the reason for this finding descriptively. They surmised that the maxilla is more susceptible to the detrimental effect of smoking for three reasons including: more intense and direct contact between the palatal maxilla and tobacco smoke, the relatively less cortical phenotype of maxillary bone, and the often-jeopardized bone quality of the maxilla. Additionally, they mentioned the protective role of the tongue to explain the lower bone loss and lower implant failure rates in the mandible.

Peri-implant sulcular fluid (PISF) and tobacco

Abduljabbar *et al.* (93) and Akram *et al.* (94) have shown that the PISF of cigarette smokers (CS) contained a significantly higher levels of proinflammatory cytokines compared with non-smokers.

ArRejaie *et al.* (95) compared the proinflammatory

cytokine levels and peri-implant parameters among CS, individuals vaping electronic cigarettes (ECS), and non-smokers. He found that both CS and ECS had a significant higher levels of matrix metalloproteinase (MMP)-9 and interleukin (IL)-1β in the PISF. These are known to correlate with PI, and indeed, the results showed a positive correlation between the higher proinflammatory cytokine levels in the CS and the ECS groups and elevated levels of marginal bone loss (in the CS group) and peri-implant probing depth >4 mm (CS and ECS groups) that were significantly higher compared with non-smokers.

Another interesting finding was significantly higher levels of BOP in the non-smoking groups compared to the CS and ECS groups. The authors explained this finding by the fact that nicotine exerts vasoconstriction on gingival blood vessels, which in turn reduces gingival bleeding in smokers compared with individuals who do not smoke (96,97).

Alcohol consumption

Alcohol consumption has been linked to bone loss around dental implants and has been related to the development of PI (98). It was shown that patients that consume more than 10 grams of alcohol a day had a significantly more marginal bone loss around dental implants compared to patients that consume less alcohol or do not consume alcohol at all.

Carr *et al.* (99) showed that 38% of heavy alcohol users present with PI, compared with 20% of the non-alcohol users. Paradoxically, mild, and moderate alcohol consumption may reduce the presentation of PI to 11% and 6% respectively. This may be explained by an alcohol related decrease of local and systemic inflammatory markers, that may result in greater overall peri-implant health in the surrounding hard and soft tissues (100,101). Another hypothesis mentioned is that mild to moderate consumption of alcohol may increase bone mineral density compared with no alcohol consumption owing to osteoblast differentiation. In contrast, heavy consumption may promote high levels of acetaldehyde production, inhibit osteoblast activity, and stimulate osteoclast activity (102). Likewise, chronic alcohol use is often associated with the concomitant use of tobacco.

Surgical and prosthetic related risk factors

Implant installation, positioning and spacing

Ng *et al.* (103) reported that horizontal proximity of implants to adjacent teeth in cases of <1 mm might be considered as a risk factor for PI by increasing the prevalence of inflammation and risk of bone resorption in the interproximal bone area of the adjacent tooth. According to Ng, bone loss caused by implant proximity can result from the lack of access for oral hygiene, as well as from the lack of proper contour of the prosthetic restoration. The implant horizontal position may also compromise proper contour of the prosthetic restoration, interproximal contacts, and thus inhibit the development of protective soft tissue.

Emergence angle

Katafuchi *et al.* (104) showed that an evaluation of implants placed at bone level with an emergence angle of greater than 30 degrees exhibited an incidence of PI on the implant level of 31.3% *vs.* 15.2% compared with emergence profiles of less than 30 degrees.

When the contour of the restoration was classified as being convex rather than concave and with an emergence profile of greater than or equal to 30% the incidence of PI increased to 37.8%.

Tooth-implant distance

Esposito *et al.* (105) reported a strong correlation between the horizontal tooth-implant distance and bone level at neighboring teeth, especially for the lateral upper incisor facing a fixture in the canine or central incisor region.

Adjacent PD to implants

As a site-specific factor, the presence of PD adjacent to a single implant is also a factor in the development of PI and early implant failure. This presumably is the result of the transfer of periodontal pathogens directly to the implant site (24,106).

Reduced inter-implant distance

Scarano *et al.* (107) reported a negative effect of reduced inter-implant distance on the mid-proximal crestal bone levels, caused by adjacent implant overlap, resulting in an increased crestal bone loss. This condition of localized bone resorption may lead to compromised oral health, causing deep soft tissue pockets. Further, PI may often develop and increase the crestal bone loss due to immune response factors. It can also cause an apical position of the papilla, or even lead to absence of the papilla between the two implants.

Schuldt Filho *et al.* (108) showed that implants with less than 3 mm inter-implant distance were three times more likely to develop PI, with 48.48% of the cases with <3 mm

inter-implant distance (n=33) presenting with PI. The small distance was explained by the surgeon's technique and lack of experience of implant installation.

Angulated implants

A review on angulated implants and their prognosis was conducted by Monje *et al.* (109) to analyze the implant marginal bone loss, and the incidence of bio-mechanical complications for patients being rehabilitated by tilted and straight implants. This meta-analysis included two retrospective studies and six prospective studies on tilted implants.

It was suggested that tilted implants receive higher compressive stress around the neck with five times higher vertical load, which result in higher marginal bone loss compared to straight implants. In addition, it was shown that tilted implants are also subjected to higher bending forces, possibly increasing marginal bone stress and bone loss.

In contrast, animal studies have shown that tilted implants are also subjected to higher horizontal compressive tensile stresses, which are associated with more dynamic remodeling of the surrounding cortical bone and trabecular bone (110,111).

Having theorized all these hypotheses for tilted implants the meta-analysis did not show an increased marginal bone loss around tilted implants. This finding was once again attributed to biomechanics—the use of long implants with better stress distribution and to prosthetic implant splinting.

Interproximal contact between teeth and implants

Varthis *et al.* reported that 52.8% of implants placed adjacent to natural teeth exhibit interproximal contact loss (ICL) of 0.07 mm or greater at 3 to 11 months post restorations, with 76% of ICL present on the mesial surface. This was further confirmed by Latimer who reported incidence rates of ICL to be 54% on the implant level with mesial involvement being 68%. This was associated with a prevalence rate of PI of 23.4% in the ICL group compared to patients with closed contacts being 13.9%. Patients in the ICL group likewise presented with an increase in plaque index and gingival index scores compared to the closed implant group (112).

Implant rough surface

Implant surface topography has been shown to have a significant effect on implant success survival rates (113). Many types of implant surface modifications have been described mostly aiming to enlarge the implant surface area to improve the mechanical and biological implant characteristics, to increase the potential bone-implant contact area, and to improve primary implant stability (114,115).

In a systematic review and meta-analysis, Doornewaard *et al.* (116) evaluated the long-term effect of different degrees of implant surface roughness on crestal bone loss around implants. They showed that peri-implant bone loss around minimally rough implant systems was statistically less significant in comparison to the moderately rough and rough implant systems.

The implant collar design and surface characteristic also have been evaluated in regard to its effect on bone loss around dental implants.

Collar design and degree of roughness

Stein *et al.* (117) evaluated the effects of implant geometry and collar macrostructure and microstructure on bone loss around implants. They concluded that Implants with straight wall collars had less bone loss at the 5-year interval than implants with stepped collars. In addition, they showed that bone loss around roughened collars was significantly lower compared to machined collars.

Weiner *et al.* (118) also showed that roughened collar implants have significantly less radiographic crestal bone loss compared to machined collar implants. Furthermore, they showed that within the roughened collar implants, roughened collars with microgrooves have significantly less bone loss compared to random-patterned roughened collars.

Titanium particle debris

Titanium particles have been shown to scatter into the adjacent hard and soft tissue of oral implants provoking a foreign body reaction (119). Particle release varies with implant surface treatment and precision fit of the abutment/implant interface where micromovement may occur to release wear matter into the peri-implant environment. It has been shown in soft tissue biopsies around failing implants that aggregates of titanium particles can be found which are surrounded by severe inflammatory processes (120,121).

Eger *et al.* (122) showed that such particles may be also be released from ultrasonic scaling around dental implants, and in turn induces a marked inflammatory response in macrophages, with increased expression of pro-inflammatory cytokines, mainly IL-1β, IL-6, and tumor

necrosis factor-alpha (TNF-α). They also showed that these titanium particles activate osteoclasts *in vitro* and trigger inflammatory bone resorption *in vivo*.

Prosthetic risk factors

Crown contour

In a cross-sectional study, Yi *et al.* (123) describes the influence of several prosthetic features and PID. They showed that the risk of PID was significantly raised with over-contoured restorations showing significantly higher bone loss in cases of prosthetic emergence angle larger than 30°. In addition, convex shape restorations had a significantly higher bone loss compared with concaved and straight shaped restorations.

Splinting

Another study suggests that splinting adjacent implants could be a significant risk indicator leading to a 4.66-fold increase in prevalence of PID when implants are splinted to both mesial and distal adjacent implants compared to independently rehabilitated implants. However, this finding is in contrast to other publications that do not show differences in bone loss patterns between splinted and non-splinted implants (124,125), the disparity explained by the authors due to the difficulty of maintaining oral hygiene around splinted implants when insufficient access is present.

Cement versus screw retained

Shi *et al.* (126) compared cemented and screw-fixed restorations in regard to PID. They did not observe a significant difference between the groups in bone loss rates with 6.38% bone loss in the screw-fixed group and 6.1% in the cemented group. Significantly higher rates of PM were observed in the screw fixed group (42.1%) compared to the cemented group (32.2%). Both groups maintained high implant survival rates of 100% and 98.8% respectively. It was suggested that the specific glass-ionomer cement used in the study might have helped to reduce the incidence of PID.

Excess cement

In a case-control study, Wilson *et al.* (127) compared 39 patients with 42 implants supporting cemented restorations affected by PI and 12 patients with 20 implants supporting cemented restorations unaffected by PI. Using a dental endoscope, they explored the subgingival environment. Subgingival cement excess though inert was observed in 80% of the PI affected implants, compared to 45% of the unaffected implants. One month after cement removal 75% of the implants showed healthy peri-implant tissues, whereas 25% demonstrated ongoing inflammatory disease.

The cement elimination can be accomplished with a non-surgical approach, using a dental endoscope, or with an open flap surgical approach which was necessary in three cases. In this study, patients displayed the development of PI as early as four months and as late as nine years post-restoration. Some patients displayed no reaction to residual cement.

PI incidence in cement and screw-retained restorations

A further study by Kotsakis *et al.* (128) evaluated the association between cemented and screw-retained restoration and the development of PI. The overall rate of PI was 11.9% for a mean follow-up timeframe of 5.5 years when either zinc-phosphate or non-eugenol zinc oxide were used for cementation. This study failed to reveal a difference in the development of PI between these groups of patients. It was suggested that with meticulous cementation techniques and astute detection of and removal of cement, adverse effects may be minimized.

"Deep" sub-gingival restorative margins may be a factor resulting in complete cement removal (128). Removal of cement in areas with subgingival cement margins might be problematic and therefore, in such cases, there is indication for the use of custom abutments that raise the position of the crown/abutment margin coronally to facilitate cement detection and removal.

Cement excess and PID

Linkevicius *et al.* (129) analyzed 77 patients with 129 implants supporting cemented restorations exhibiting technical or biologic complications. Thirty-five of the patients had a history of periodontitis and 42 were from PHPs. Cement excess was found in 11 of the 32 implants presented with technical complications and in 62 of the 97 implants presented with biologic complications. PI was present in 85% of the implants that had cement excesses. Furthermore, PI was observed in 100% of the implants with cement excess in patients having a history of periodontitis, compared to 9% in the periodontally healthy group. It was concluded that excess cement had a significant contribution to the development of PI if there was a history of periodontitis which acts as a predisposing factor. In addition, it was suggested that the pressure developed during the cementation process can push cement into sub-

gingival tissues toward the crestal bone since there is a lack of an organized gingival fiber network around implants as opposed to natural teeth.

Partially edentulous versus fully edentulous

In a systematic review, de Waal *et al.* (130) compared between fully and partially edentulous patients later rehabilitated with dental implants. He showed that fully edentulous patients had higher plaque accumulation around dental implants. They hypothesized that these patients were probably less committed to oral hygiene maintenance. Another explanation was that plaque accumulated more around implants supporting removable dentures than around fixed crowns due to decreased natural cleansing of the tongue, lips, cheek, and saliva.

Overdenture implants and PM

This may also explain the finding that implants that are used as support for overdentures show PM in approximately 52% and 57% at 5 and 10 years respectively (131).

Cantilever restoration

Prosthetic design using a cantilever may result in excessive nonaxial forces that may be transmitted to the crestal bone around the cantilevered implant (132). Mumcu *et al.* (133) showed that marginal bone loss was increased around implants that were restored with a cantilever. But other studies have not supported these findings, and showed that distal implants that support cantilevered full-arch restorations did not present higher levels of PI (134,135).

Re-implantation after implant failure

Although implant placement has been demonstrated as being an effective and predictable method for the replacement of missing or non-restorable teeth, implant failures necessitating removal do occur. In these instances, appropriate bone regenerative procedures can be considered to enable subsequent implant placement. In a large retrospective study of 5,532 implants placed an overall survival rate of 94.4% was reported. Of the 5.6% of implants that failed and were subsequently replaced, the implant survival rate was 77.4%. A further group of patients had a second failure and proceeded with second reimplantation which was reported to have a success rate of 72.7% being significantly lower than the first reimplantation. Patients who proceeded with the third reimplantation had a success rate of 50% (n=2). In evaluating the timing of implant failure subsequent to reimplantation, for a first reimplantation, 90% were classified as early failures whereas those implants that failed after the second reimplantation were 100% early failures. The majority of failed implants presented with clinical mobility (63–67%) as the initial clinical finding associated with postoperative pain (136). Reimplantation in failed sites was therefore a "risk factor" for failure of osseointegration, PID and subsequent implant failure.

Summary

PID (PI) is defined as an inflammatory process that leads variably to attachment loss, and when present not infrequently, to implant removal. This process is multifactorial and clearly determined by risk factors elucidated in this narrative review.

A listing of risk factors for PID is warranted in a summary not the least of which is the implant itself—a foreign body element, though biocompatible, sterilized and prophylaxed with systemic antibiotics nevertheless frequently becomes contaminated with oral biofilm. The implant is not a biological entity like a tooth. The implant/abutment assembly commonly self-circulates bacteria at the bone level abutment/implant interface from micromovement and also potential sheds titanium wear debris into the peri-implant milieu. So the implant itself is the unspoken risk factor *a priori*.

From whatever the initial cause of PID might be there were many statistically important risk factors identified. One important risk factor is early loss of bone in which the implant is exposed a half to one millimeter during the first year. This in itself is a significant risk factor-predictor for PI in the future.

A history of periodontitis, tobacco smoking, alcohol abuse and oral hygiene noncompliance are also highly contributory to development of PI.

Still, it cannot be said with certainty that in any one instance what the causative agents are for loss of bone as dental implants persist without bone loss despite the presence of antecedent risk factors in a high proportion of implants placed—perhaps as high as 80% of the time, over a ten-year span of health.

Still, one must take pause at the foreboding evidence from clinical report. From 1980 to 1990, there were 30 reports describing peri-implant infection including bone loss. In the year 2000, there were 118 articles published using the term "peri-implantitis." In 2021, the number rose to more than 3,800 articles published in that single year

on the subject of PI. Many of these present-day articles are advisory in their conclusions suggesting strategies to mitigate risk factors prior to surgical placement. But resolution of all risk factors prior to treatment is not possible and include underlying medical conditions or drug therapy. Habitual or behavioral conditions such as the use of alcohol, tobacco or bruxism can however be addressed prior to surgery with medical colleague referrals as needed.

Patients with chronic PD, particularly if aggressive, should initiate treatment to lessen the impact of this risk factor.

Mucogingival or bone augmentation procedures done in advance can aid in successful outcome. And patient oral hygiene compliance through education and careful follow-up is an important risk factor to address for both able bodied as well as patients unable to care adequately for themselves.

Surgical or prosthetic error is an important risk factor. If the dental restoration does not allow for cleanability the risk for PID increases as was shown in one study where inadequate hygiene access was found in more than half of PI cases.

As was stated in the introduction, the morbidity data set of this disease process has become inordinately large as 150 million implants are placed annually with at least 20% of this number likely to be diagnosed with significant bone loss from PID over time. This truly alarming figure suggests an urgent need for technological innovation to combat biofilm for both endosseous and prosthetic elements. Until that time careful evaluation of the following risk factors found to have positive correlation with PID is warranted including: history of periodontitis or PI, exposed implant surface of 0.5 to 1 mm after one year, excessive smoking, excessive alcohol ingestion, TNP especially if combined with absence of KT, bruxism, diabetes with high A1C, osteoporosis and associated medicinal therapy, errors in surgical installation, errors in prosthetic management, oral hygiene non-compliance, and inadequate oral hygiene follow-up care.

Despite these well-known risk factors, the multifactorial complexity of causation remains nondefinitive, circumstantial and descriptive and therefore lacks scientific specificity and does not account for genetic and epigenetic proclivity for PI. Nevertheless, the practitioner is charged with using present implant technology, flawed and inadequate as it may be, to make an informed effort to mitigate implant placement risks and improve the prospect for long term health of dental implant restorations.

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