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CLINICAL PERIODONTICS (P STATHOPOULOU, SECTION EDITOR)

Risk Factors for Peri-implantitis

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Abstract

Purpose of Review This manuscript reviews the literature concerning risk factors associated with the development and/or progression peri-implantitis, focusing on studies published within the last 3 years (2017–2020). For the purpose of this review, all factors that can potentially contribute to the development of peri-implantitis will be considered "risk factors."

Recent Findings Recent studies have focused on evaluating various risk factors associated with the development of peri-implantitis. Research shows that peri-implantitis lesions are associated with complex microbial biofilms consisting of not only periodontal pathogens, but also certain unique bacteria and other microorganisms such as viruses, yeasts, and parasites. Recent evidence reinforces the role of previously well-established risk factors in the pathogenesis of peri-implantitis such as smoking, diabetes, lack of oral hygiene and maintenance, history of periodontitis, and poor peri-implant soft tissue quality. Bone quality, obesity, metabolic syndrome, implant surface characteristics, and placement depth have also been reported to be predisposing factors for the development of peri-implantitis. Few studies suggest that factors like certain medications, age, gender, vitamin D, and autoimmune diseases also play a role, but are currently not well-understood. The role of genetics is still unclear, but studies show that certain polymorphisms may be associated with peri-implantitis. Prosthetic risk factors such as improper restorative design, occlusal overload, microgap, and residual cement are significant as well. A recently emerging risk factor for peri-implantitis is the presence of peri-implant tissue-bound titanium particles.

Summary Several risk factors have been associated with peri-implantitis in the literature published over the past 3 years. While some risk factors such as smoking, diabetes, history of periodontitis, and some restorative factors are well-recognized, there is still a need for well-designed randomized controlled trials and longitudinal studies in order to establish the association of some other more recently emerging risk factors for peri-implantitis.

Keywords Peri-implantitis · Risk factors · Dental implants

Introduction

Dental implant therapy has evolved significantly over the past few decades and is a common treatment option for the replacement of missing teeth. However, peri-implant diseases pose a significant problem affecting dental implants. Prevalence rates of peri-implantitis reported in the literature are variable. A recent systematic review reported a prevalence of 9.25% at the implant level and 19.83% at the subject level, after heterogeneity between studies was incorporated into the analysis [1•].

The newest classification of peri-implant diseases and conditions was recently developed by the 2017 AAP/EFP World Workshop [2••]. Peri-implant mucositis and peri-implantitis are considered plaque-associated conditions. Peri-implant mucositis precedes peri-implantitis and is characterized by bleeding on probing and visual signs of inflammation [2••]. Peri-implantitis is characterized by signs of peri-implant mucosal inflammation and progressive bone loss around dental implants [2••]. The pathogenesis of peri-implant diseases can be associated with a number of factors. The purpose of this manuscript is to review current human clinical research and review

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articles (primarily systematic reviews) published within the last 3 years (between 2017 and 2020) on risk factors associated with the development of peri-implantitis. "Risk factors" are considered those factors that have a direct causal relationship with a disease as proven by longitudinal studies and "risk indicators" are considered those established via cross-sectional, observational, or retrospective studies [3]. However, for the purpose of this review, all factors that can potentially contribute to the development of peri-implantitis will be considered "risk factors."

Review Search Strategy

MEDLINE through the Ovid interface and Embase was searched in February 2020. The searches included MeSH and Emtree terms along with keywords including but not limited to peri-implantitis, risk factors, and factors known to contribute to the development of peri-implantitis such as smoking, plaque, occlusion, and genetic predisposition to disease. Searches were limited to articles published between 2017 and February 2020. The full texts of the searches are included in Tables 1 and 2. A total of 1225 citations were retrieved from the searches and downloaded into RefWorks; 363 duplicates were removed, leaving 862 citations for review. Manual search within the reference list eliminated articles that were animal or in vitro studies and also certain review articles with general information. Finally, a list of 151 journal articles were included in this review.

Microbial Biofilm

The primary etiologic factor for peri-implantitis is microbial plaque or biofilm in a state of dysbiosis, and this is superimposed by other risk factors. Biofilms associated with peri-implantitis have been shown to consist of periodontal pathogens [4], but tend to be more complex in nature. Some recent human clinical studies using traditional techniques have reported the association of specific pathogens associated with peri-implantitis lesions, consisting of predominantly bacteria and also certain yeasts, viruses, and parasites. Other studies have used more sophisticated open-ended techniques to study microbiomes associated with peri-implantitis.

Specific Pathogen Studies

Recent case-control studies found that the periodontal pathogens *Porphyromonas gingivalis* (Pg), *Prevotella intermedia* (Pi), *Tannerella forsythia* (Tf), *Fusobacterium nucleatum* (Fn) [5] and also *Parvimonas micra* [6] in the peri-implant pocket were positively associated with peri-implantitis. Other data demonstrated the correlation of bacterial species *Porphyromonas* spp., *Fusobacterium* spp., and Tf to the peri-implant pocket depth [7]. *Treponema denticola* (Td) and Pi were found to be more prevalent in peri-implantitis lesion patients undergoing supportive therapy [8]. Certain unique bacterial species have also been reported to be associated with peri-implantitis. *Enterococcus faecalis* was suggested to be a "keystone" player in peri-implantitis bone loss [9]. Cement-retained restorations of implants were associated with peri-implantitis and the presence of gram-negative enteric rods/*Pseudomonas* [10]. A study that examined methanogens did not find any specific associations between methanogens and peri-implantitis sites [11].

An observational study-based review concluded that the presence of herpesviruses in subgingival biofilms, including cytomegalovirus (CMV) and Epstein-Barr viruses (EBV), are indicative of peri-implant diseases [12]. EBV has been found to be associated with specific periodontopathogens in peri-implantitis lesions [13, 14]. Herpes simplex virus type I (HSV-1) was not found to be a similar indicator of peri-implantitis [15]. Light microscopic examination of peri-implantitis plaque samples demonstrated the presence of two parasites *Entamoeba gingivalis* and *Trichomonas tenax* that were not detected in clinically healthy implant sites [16]. A review of seven studies concluded that there is no direct evidence to support an association of yeasts with peri-implantitis [17]. However, studies on subgingival biofilms reported associations of *Candida albicans* with peri-implantitis [18], more specifically in diabetic patients [19•].

Microbiome Studies

Open-ended techniques now available such as 16s rRNA amplification and sequencing enable researchers to explore the entire microbiome and provide a holistic view of microbial associations with peri-implant diseases. A systematic review of 26 observational studies of entire microbiomes reported that peri-implantitis is a heterogeneous mixed infection that largely consists of periodontopathic microorganisms, uncultivable asaccharolytic anaerobic gram-positive rods, and uncultivable gram-negative rods. Rarely, opportunistic microorganisms such as enteric rods and *Staphylococcus aureus* are also detected [20].

A wide variation of operational taxonomic unit (OTU) composition between subjects has been reported in periodontal and peri-implant microbiota [21]. Consistently, increasing dysbiosis and changes in the microbiome has been observed in increased peri-implant pocket depths [22]. Peri-implantitis has been shown to have a higher relative abundance of phylum Bacteroidetes and species *Fusobacterium nucleatum*, besides an association with red complex bacteria (Pg and Tf) [23]. Peri-implantitis-associated microbiome analysis in patients with a history of periodontal disease showed that genera *Prevotella* and *Porphyromonas* in addition to *Synergistetes*

Table 1 Ovid MEDLINE® ALL 1946–February 12, 2020

No.	Searches	Results
1	Peri-implantitis.mp. or Peri-Implantitis/	2458
2	Risk factors.mp. or Risk Factors/	1,007,619
3	1 and 2	275
4	Dental Plaque/ or dental plaque.mp.	21,742
5	Biofilm.mp. or exp. Biofilms/	47,338
6	Exp Microbiology/ or microbiology.mp.	858,091
7	Smoking.mp. or Smoking/	277,850
8	Periodontitis.mp. or Periodontitis	39,430
9	Diabetes.mp. or Diabetes Complications/ or Diabetes Mellitus/	604,592
10	Exp Osteoporosis/ or osteoporosis.mp.	85,163
11	Keratinized tissue.mp.	738
12	(Coated Materials, Biocompatible/ and Surface Properties/ and Dental Implants/) or (implant surface or implant coating).mp.	3493
13	Periodontal maintenance.mp.	407
14	Excess cement.mp.	117
15	Exp Dental Restoration, Permanent/ or Dental Restoration, Temporary/ or dental restoration.mp.	32,470
16	Dental prosthesis.mp. or exp. Dental Prosthesis/	106,903
17	Exp Bruxism/ or bruxism.mp.	3736
18	Occlusion.mp. or exp. Dental Occlusion/	178,739
19	Malocclusion.mp. or exp. Malocclusion/	35,881
20	Genetic Predisposition to Disease/ or genetic*.mp.	3,877,459
21	Bisphosphonate*.mp. or exp. Diphosphonates/	31,715
22	Exp Autoimmune diseases/ or autoimmune disease*.mp.	496,863
23	Dental Implants/ OR Dental Prosthesis Design/	5036
24	Dental implant design.mp.	43
25	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	5,997,024
26	3 and 25	252
27	1 and 25	2076
28	3 or 27	2099
29	Limit 28 to yr = "2017-Current"	746
30	Limit 26 to yr = "2017-Current"	99
31	29 or 30	746

were more prevalent, compared to patients with a history of periodontal health, where the genera *Actinobacillus* and *Streptococcus* were more prevalent [24]. A case-control study within the Uygur population reported that genera *Moraxella*, *Micrococcus*, and *Acinetobacter* were dominantly associated with peri-implantitis [25].

History of Periodontitis

There is abundant evidence including from systematic reviews that implants placed in patients with a history of periodontitis (HOP) are at a higher risk for developing peri-implantitis [3, 26, 27] and biologic complications, resulting in lower survival and success rates [28]. Recent data from cross-sectional studies consisting of 183 to 200 patients with 412 to 916 implants showed that patients with a HOP have a 2.2- to 2.5-fold higher risk of developing peri-implantitis [29, 30]. Another cross-sectional study of 206 implants in 115 patients reported that a HOP increased the risk of developing peri-implantitis and influenced the compliance risk profile of patients on peri-implant maintenance [31].

Retrospective studies have reported that HOP was a significant risk factor for peri-implantitis [32–34], and implant loss was more frequent in subjects ($n = 376$ patients, 1095 implants) with a HOP [35]. A multicenter retrospective study reported that short implants in patients with a HOP developed more peri-implantitis-related failures [36]. Prospective studies that followed up patients up to 5 years were in agreement that a HOP was a significant factor related to the development of peri-implantitis, compared to patients with a healthy periodontium [37–39].

Table 2 Embase February 14, 2020

No.	Searches	Results
13	(#10 OR #11) AND [2017–2020/py AND [English]/lim	503
12	#10 OR #11	1330
11	#1 AND #9	1330
10	#3 AND #9	230
9	#4 OR #5 OR #8	7,042,382
8	#6 OR #7	5,152,685
7	Bruxism:ti,ab,kw OR occlusion:ti,ab,kw OR malocclusion:ti,ab,kw OR genetic*:ti,ab,kw OR heredit*:ti,ab,kw OR bisphosphonate*:ti,ab,kw OR 'dental prosthesis design':ti,ab,kw OR 'dental implant design':ti,ab,kw	1,603,529
6	'bruxism'/exp. OR 'occlusion'/exp. OR 'malocclusion'/exp. OR 'genetics'/exp. OR 'heredity'/exp. OR 'bisphosphonic acid derivative'/exp. OR 'autoimmune disease'/exp. OR 'prosthesis design'/exp	4,645,931
5	'diabetes mellitus'/exp. OR diabetes:ti,ab,kw OR 'osteoporosis'/exp. OR osteoporosis:ti,ab,kw OR 'keratinization'/exp. OR 'kerantinized tissue':ti,ab,kw OR 'implant surface':ti,ab,kw OR 'implat coat*': ti,ab,kw OR 'periodontal maintenance': ti,ab,kw OR 'excess cement':ti,ab,kw OR 'dental restoration'/exp. OR 'dental restoration':ti,ab,kw OR 'dental prosthesis and implant equipment'/exp. OR 'dental implant':ti,ab,kw OR 'tooth implant':ti,ab,kw	1,337,917
4	'tooth plaque'/exp. OR 'tooth plaque':ti,ab,kw OR 'dental plaque':ti,ab,kw OR 'biofilm'/exp. OR biofilm*:ti,ab,kw OR 'microbiology'/exp. OR microbiology:ti,ab,kw OR 'smoking'/exp. OR smoking:ti,ab,kw OR 'periodotitis'/exp. OR periodontitis:ti,ab,kw	1,108,947
3	#1 AND #2	266
2	'risk factor'/exp. OR 'risk factor*':ti,ab,kw	1,313,174
1	'periimplantitis'/exp. OR periimplantitis:ti,ab,kw OR 'peri-implantitis':ti,ab,kw	1730

Implants placed in patients with current periodontal disease on adjoining natural teeth [40, 41] as well as the presence of deeper pockets and attachment loss around existing natural teeth [42–44] had a significantly higher risk of peri-implantitis. A study reported a much higher susceptibility to peri-implantitis specifically in patients with generalized aggressive periodontitis, when compared to generalized chronic periodontitis [45]. In a case report, three patients with a history of Ehlers-Danlos syndrome-associated severe periodontal disease who received dental implants experienced severe peri-implant bone loss [46].

Putative periodontal pathogens have been found to prevail in the microbiome of peri-implantitis sites in patients with a HOP [24], which is the likely explanation for the correlation between periodontitis and peri-implantitis. An interesting and plausible observation made in patients with a HOP is that implants with smoother surfaces seem to be less prone to peri-implantitis than rougher surfaces which exhibited higher levels of bone loss [47, 48].

Maintenance and Oral Hygiene

Lack of regular follow-up maintenance and good oral hygiene following implant are well-established risk factors for the development of peri-implantitis. A retrospective analysis of 200 patients who received implant-supported prostheses concluded that the lack of supportive maintenance care following implant therapy was a risk indicator for peri-implantitis [49]. A higher incidence of peri-implantitis and increase in bacterial load was associated with absence of regular maintenance in a 5-year follow-up study of 80 patients [50]. Regular maintenance was reported by a systematic review of 9 clinical controlled trials to be preventative for peri-implantitis [51]. A cross-sectional study concluded that peri-implant maintenance therapy for ≥ 2 years is a crucial factor in prevention of peri-implantitis [31]. Standardized recall regimens have been proven to play an important role in decreasing peri-implantitis [52–54], while in the absence of regular maintenance, one in five patients developed peri-implantitis 5 years post-loading [55]. Consistent with the lack of regular recalls, peri-implantitis was reported to be correlated with the presence of plaque [56–59], bleeding [57, 59, 60], poor oral hygiene, and compliance [61–66].

Smoking

Cigarette smoking apart from being considered an important risk factor for periodontitis has also been related to peri-implant bone loss and implant failure [67]. In a 3-year open cohort study of 22,009 patients, prevalence of peri-implantitis was recorded as 13.9%, with smoking being reported as a risk indicator with an odds ratio of 1.84 (OR = 1.84, 95% CI 1.32–2.57) [68]. Similar outcomes were also reported in a 9- to 15-year retrospective study of 1095 implants placed in private practice, where smoking was recorded as a risk indicator for peri-implantitis; however, as noted by the authors, more specific information regarding smoking habits were lacking and the numbers of cigarettes smoked per day could have

modified the results [35]. In another cohort study of 4591 implants placed in private practice with 5–10-year follow-up, heavy smoking (> 15 cigarettes a day) was associated with increased peri-implant crestal bone loss (CBL), which was more rapid after 4 years in function [69••]. The effects of smoking on CBL were even more significant in implants placed in staged maxillary sinus augmentation (OR 6.563) after 5 years in function [38] as well as in short implants where smoking had a significant negative influence on implant success both at patient and implant levels [36]. In a cohort of 147 patients with 490 dental implants, smoking increased the probability of peri-implantitis by 3 times [42]. Finally, a systematic review of 57 studies noted a 2-fold higher risk for smokers to develop peri-implantitis (OR 1.7), compared to non-smokers, which was similar to the effect of diabetes [26]. However, a recent review from the 2017 world workshop on the classification of periodontal and peri-implant diseases and conditions reported that the evidence reviewed was conflicting and inconclusive to support the role of smoking as a risk factor for peri-implantitis. The authors questioned the data from these studies due to potential confounding factors such as the history of periodontitis, differences in categorization methods for smokers vs. non-smokers, and reliance on potentially inaccurate self-reported information [3].

Smoking is related to an increased prevalence of periodontal pathogens such as *P. gingivalis*, *P. micra*, and *F. nucleatum* in the submucosal peri-implant area even in clinically healthy implants, with these bacteria having been linked with a greater risk for developing peri-implantitis [70]. Similarly, in another study where peri-implant biofilm was collected around clinically healthy implants from non-smokers (NSMK) and smokers (SMK), the SMK microbiome showed an abundance of periodontal pathogens whereas the NSMK microbiome revealed presence of bacteria usually related to periodontal health. The authors concluded that smoking negatively affected peri-implant microbiome, leading to a disease-associated state, even in clinically healthy subjects [71].

Smoking status seems also to be associated with peri-implantitis through maintenance therapy compliance. A cross-sectional study of 115 patients noted that compliance was associated with 86% lower chance for peri-implantitis, while smokers were more likely non-compliers, resulting in a greater prevalence of the disease. The authors commented that this might be explained by patients' poor belief that their actions/habits impact their health or maybe shame toward not fulfilling recommendations for smoking cessation [31]. Another study using a predictive model for peri-implantitis also noted that patients who smoke were more prone to developing peri-implantitis, with a higher risk being observed when smoking was combined with irregular maintenance care [49]. Apart from cigarette smoking, waterpipe smoking (WS) has also been linked with greater peri-implant inflammation and bone loss [72] as well as increased levels of pro-inflammatory cytokines IL-6, IL-1β, and tumor necrosis factor alpha (TNF-α) [73] and MMP-8/MMP-9 [74] in the peri-implant sulcular fluid, when compared to non-smokers.

Diabetes Mellitus

Diabetes has been known to negatively affect osseointegration and implant survival. A systematic review of 57 studies reported that patients with diabetes mellitus were 2 times more likely to have peri-implantitis compared to those without (OR 2.5, 95% CI 1.4–4.5); however, the majority of the data came from cross-sectional studies, thus providing a medium level of evidence [26]. Similarly, a systematic review reported that the risk of peri-implantitis was about 50% higher in diabetes than in non-diabetes, independently of smoking, concluding also that the higher the glycemic level (i.e., poor glycemic control) the greater the prevalence of peri-implantitis [75]. The effects of various levels of glycemic control on peri-implant health were also assessed in a study where peri-implant plaque index (PI), bleeding on probing (BOP), probing depth (PD), and CBL were significantly higher in diabetic vs. non-diabetic patients. This was also observed in poorly controlled diabetics (HbA1c 8.1–10% and HBA1c > 10%) vs. well-controlled diabetics (HbA1c 6.1–8%). Also, the levels of advanced glycation end products (AGEs) in peri-implant sulcular fluid (PISF) were significantly increased in patients with higher levels of HBA1c as well as positively correlated with PD and CBL, suggesting that PISF AGEs could be considered as a potential marker of inflammation in peri-implantitis diabetic patients [76]. In a similar study, peri-implant PI, BOP, PD, CBL, and levels of PISF AGEs were significantly higher in patients with prediabetes and type 2 DM compared to non-diabetic individuals, with PISF AGEs also being positively correlated with PD, again suggesting that they may play an important role in peri-implant inflammation [77]. Moreover, subgingival levels of *Candida* species and most predominantly *C. albicans* [19•] as well as salivary levels of IL-1β and IL-6 [78] seem to also be upregulated in peri-implantitis patients with diabetes vs. those without, possibly suggesting a different immunological and microbiological profile for this group of patients.

In summary, diabetes may be associated with a greater risk for peri-implantitis, with the level of glycemic control also being an important factor to be considered regarding the prevalence and severity of peri-implant disease. Although the majority of evidence points to a positive correlation of diabetes and peri-implantitis, a recent review of systematic reviews concluded that the rate of implant failure may not be higher in diabetic patients compared to non-diabetic subjects, although greater marginal bone loss was noted in diabetics [79]. Additionally, a recent review from the 2017 world

workshop on the classification of periodontal and peri-implant diseases and conditions reported that the evidence reviewed was inconclusive to support the role of diabetes as a risk factor for peri-implantitis, due to failure of several studies to report an association and due to potential flaws in the design of studies reviewed.

Metabolic Syndrome and Obesity

Metabolic syndrome (MetS) is a combination of conditions including increased plasma glucose, hypertension, hypertriglyceridemia, low HDL cholesterol, and visceral obesity. Since evidence suggests that individuals with MetS are more likely to present with periodontitis due to an upregulated systemic inflammatory status, such an association has also been assessed between MetS and peri-implantitis. Two recent studies reported that patients affected by MetS showed greater prevalence of peri-implantitis, when compared to non-MetS patients with an odds ratio of 15.26 and 7.44 respectively [80, 81]. In a 5-year study comparing peri-implant parameters of obese vs. non-obese individuals, the obese group recorded significantly higher BOP, PD, and marginal bone loss (MBL), with the authors concluding that obese patients are at an increased risk for peri-implant diseases [82]. The severity of obesity may also affect markers of peri-implant disease as peri-implant PI, BOP, PD, and MBL were significantly higher in patients with severe obesity (BMI ≥ 35 kg/m^2), when compared with less obese patients [83].

Medications

Certain medications have recently been associated with peri-implantitis. Medications such as selective serotonin reuptake inhibitors (SSRIs), bisphosphonates (BPs), and proton pump inhibitors (PPIs) have a negative impact on bone formation and affect overall bone metabolism, thus potentially impacting dental implant osseointegration. Patients on SSRIs for depression have been reported to have more implant failures, peri-implantitis being one of the causes [84, 85]. In a recent study of 5456 patients who received dental implants, SSRI use was a significant factor associated with implant failure with a 60% increased risk, after adjusting for other factors [86]. BP therapy and osteoporosis have been reported by retrospective studies to impact bone levels around implants [33, 69••, 85]. A recent systematic review reported that low-dose BP intake does not compromise implant therapy, but that there is a lack of information on the effect of high-dose BP and other antiresorptive drugs like denosumab [87]. PPIs used for the treatment of Crohn's disease were also associated with greater loss of bone around implants [88].

Genetic Polymorphisms

Past studies suggest that certain genetic polymorphisms could be associated with peri-implantitis and implant failure [89]; however, the diagnostic value of these genetic patterns in identifying individuals at higher risk for peri-implantitis is limited at this time [85, 90].

Recent studies have explored genetic polymorphisms that could potentially play a role in the pathogenesis of peri-implantitis. A study in a Serbian population reported that smokers with TNF-α polymorphisms, specifically TNF-α-308 GA/AA genotypes, may be at a higher risk for peri-implantitis [91]. The same study indicated that cluster of differentiation gene polymorphism, specifically CD14-159 CT/TT genotypes, decreased the risk of peri-implantitis. A significant association of CD14-159, TNF-α-308, and IL6-174 genotypes and clinical parameters was also reported [91]. Fc gamma receptor gene polymorphisms FCGRIIa (rs1801274), FCGRIIIa (rs396991), and FCGRIIIb (rs1050501) reportedly exhibited a significant association with chronic periodontitis and peri-implantitis [92]. Interleukin-1 gene polymorphisms IL-1A-889C/T or IL-1B+3954C/T were also recently found to have an association with the risk of peri-implantitis and periodontal status [93].

Other Systemic Factors

The role of other systemic factors in peri-implantitis has recently been investigated, with limited evidence to support these associations. Vitamin D is reported to have an effect peri-implant bone health [94]. Autoimmune diseases were recently reported to be associated with implant bone levels [69••]. For implants placed in patients following jaw reconstruction followed by 12–24 months of radiotherapy, success and survival were negatively impacted [95]. Age and male gender may also play a role in peri-implant disease development and implant failure [33, 56].

Bone Quality

Bone quality is related to the jaw or specific location of implant placement and a history of previous surgery such as bone augmentation procedures. A systematic review reported that more implant failures were observed in poorer bone quality and when there was a lack of bone volume [96]. From a consensus report, prevalence of peri-implantitis was low in bone augmented sites [97]. A recent systematic review concurred that lateral ridge augmentation can be beneficial to maintain peri-implant health [98]. A retrospective study concluded that implants placed in augmented bone had a favorable 5-year result overall, with short dental implants

exhibiting lesser marginal bone loss than standard diameter implants [99]. In contrast, a retrospective study of 540 implants placed in 304 patients reported that a vertical bone loss pattern (beyond physiologic remodeling) was associated with implants placed in augmented bone, with a higher odds ratio for wider diameter implants [100]. However, it is noteworthy that this study reported several limitations in its design such as not being able to account for timing and level of implant placement, maintenance intervals for patients, and type of restoration (cement vs. screw-retained) [100]. Late implant failures with marginal loss were also reported to be related to the presence of high radiodensity and cancellous bone consolidation [101]. A recent interesting observation made was that patients who received implants more than 12 months after orthognathic surgery had lower rates of peri-implantitis compared to those who received implants 4 to 12 months after [102], suggesting that a longer healing period may be beneficial.

Jaw location is often related to bone quality. Several studies since 2017 have concluded that placing implants in the maxillary bone is a significant factor associated with increased bone loss, peri-implantitis, and implant failure [33, 45, 58, 62, 64, 66]. In a large retrospective cohort study of 4591 maxillary and mandibular implants, over time, greater mean crestal bone loss was observed for anterior implants compared to posterior implants and also when there was presence of a bone defect [69••]. Active peri-implantitis was associated with implants with exceptional vertical bone defect configurations, in a retrospective study with an average observation period of ~ 19 years [103].

Peri-implant Soft Tissue

The role of peri-implant soft tissue has emerged as a significant factor in implant therapy due to its potential ability to improve implant esthetics, health, and long-term stability. Thus, multiple studies have assessed whether peri-implant tissue health is associated with the presence of peri-implant keratinized tissue (pKT) and the thickness of the peri-implant buccal mucosa. In a retrospective multicenter study of 543 subjects with 1613 implants, peri-mucositis and peri-implantitis were positively associated with pKT width < 2 mm [66]. Similarly, a cross-sectional study of 237 subjects with 831 implants reported a 35% prevalence of peri-implantitis, with patients presenting with < 1 mm of pKT having higher odds ratios for the presence of the disease [57]. The presence of pKT may be of greater importance in maintenance patients with erratic compliance as noted in a cohort of 37 erratic compliers with 66 implants, the presence of < 2 mm of pKT was associated with peri-implant disease [104]. However, in a 5-year retrospective study of peri-implant health in compliant patients, pKT was not correlated with either peri-mucositis or peri-implantitis [105].

In terms of buccal mucosa thickness (BMT), a thin BMT was associated with greater recession but not with peri-implant bone loss after 1 year of function [106]. On the contrary, in a cross-sectional study of 87 patients with 229 implants, thin BMT was associated with BOP, recession, and CBL, and the authors concluded that thin BMT may be a risk indicator for peri-implantitis [107]. BMT is also reported as a factor influencing peri-implant marginal bone loss in a 5-year study [39]. Surgical interventions aiming at peri-implant soft tissue augmentation could also potentially improve long-term peri-implant health. A recent meta-analysis reported that gain of pKT with autogenous grafts resulted in greater improvement in bleeding indexes and marginal bone levels, as well as gain in BMT resulted in less marginal bone loss over time [108].

Implant Placement Depth

The depth of implant placement can affect the stability of the crestal bone. Subcrestal implant placement has been shown to have a positive effect on crestal bone levels [109]. Subcrestal placement of 1–1.9 mm is recommended to avoid exposing the platform of platform-switched implants over time. However, according to a retrospective analysis, implant placement at a depth of 6 mm or more in relation to the CEJ of existing teeth is associated with an increased risk of peri-implant disease [40]. While subcrestal placement of the implant is an important consideration, it is also important to consider the distance of the implant platform to the CEJ of the adjacent teeth, particularly in periodontally compromised patients.

Implant Surface

Many different types of implant surfaces currently exist. A roughened implant surface increases its surface area, thereby allowing for higher bone to implant contact. Minimally roughened surfaces are preferred over moderately rough or rough surfaces, especially in patients with a history of periodontal disease [47, 67]. However, implant surface roughness is also a factor associated with peri-implantitis [47, 110]. A retrospective study evaluating 4591 dental implants reported that among the other risk factors, implant diameter and design are also risk factors for peri-implantitis [69••]. Another retrospective study looked at machined surfaced implants over a period of 13–32 years. Mean marginal bone loss was 1.9 ± 0.9 mm, with a survival rate of 97.7% and success rate of 92.7%, indicating good reliability of machined surface implants [111]. Hybrid implants which have a machined collar

and a rough periapical surface could possibly reduce the risk of peri-implantitis [112]. Two retrospective studies have also shown that anodized implant surfaces are more prone to peri-implantitis than non-anodized surfaces [48, 113]. Due to the multifactorial nature of peri-implantitis, a systematic review and meta-analysis evaluating the long-term effects of surface roughness and patient factors on crestal bone loss reported that there was limited evidence indicating that the surface roughness causes crestal bone loss [114, 115]. However overall, a history of periodontitis and smoking are considered greater risk factors than implant surface characteristics in peri-implantitis [29, 67, 114].

Titanium Particles

In orthopedics, metal particle release has been extensively researched and is considered a factor for implant failure. Recent studies have suggested that there are increased levels of dissolved titanium particles around dental implants in patients with peri-implantitis [116–120]. Implants and implant restorations are exposed to saliva intraorally which can dissolve the titanium oxide layer and initiate corrosion [121]. Mechanical factors, the presence of fluorides, and the microgap at the implant-abutment connection can also influence the release of titanium particles and ions from implants and their restorations [121]. A systematic review evaluated studies on the basis of anatomical location and suspected titanium particle release. A higher number of titanium particles were found in peri-implantitis sites than healthy implants [120]. In a clinical study, titanium particles were found in over 90% of 10 peri-implant tissue sample biopsies, with increased inflammatory markers. An over-expression of the receptor activator of nuclear factor kappa-B ligand (RANKL), transforming growth factor-ß1 (TGF-ß1), and interleukin 33 (IL-33) was observed. While a larger sample size was needed to confirm these findings, there was evidence to suggest that the presence of titanium particles may be associated with bone loss [119]. In another study, submucosal plaque samples were collected from 15 implants that were 10 years in function to investigate whether the presence of titanium particles caused a change in the oral microbiome and was associated with bone loss. Titanium particles were found to be a principle component of the oral microbiome in patients with peri-implantitis [122]. Similar in vitro findings confirmed that the presence of titanium particles changed the microbial composition, which may potentially lead to peri-implantitis [123]. However, a recent critical review reported that titanium particles are present in healthy, diseased peri-implant sites as well as in the gingiva of patients without any implants. It was suggested that while there is a correlation between the presence of titanium particles and peri-implant disease, there is insufficient evidence to prove that the presence of the particles is a causative factor [124].

Implant Prosthetic/Restorative Factors

Restorative Design

In addition to biologic, implant-related and systemic considerations, the restorative design and management of the peri-implant tissues while fabricating the restoration can significantly influence the presence of peri-implantitis [125, 126]. Ill-fitting fixed restorations are associated with an increase in peri-implantitis [32]. Also, having two or more implants and splinted prosthesis was found to be associated with increased levels of peri-implantitis [57, 127, 128]. This is likely due to the compromised accessibilty to oral hygiene procedures when multiple implants are present.

Implant-abutment design is also critical in determining the peri-implant health. A multilevel cross-sectional study evaluated 490 implants for peri-implant mucositis and peri-implantitis based on implant and prosthetic-related factors. Poisson's regression model indicated that platform switching reduced peri-implantitis (PR = 1.96) and implants in function for longer than 5 years increased this probability (PR = 2.11) [42]. Over-contouring restorations also increase the risk for peri-implantitis [129]. Increase in the marginal bone loss was noted when the emergence angle was greater than 30° and when restorations had a convex emergence profile. Also, implants located in the middle that were splinted to implants anterior and posterior to it had a higher risk for peri-implantitis [129]. Platform switching along with using a custom abutment with an extra-oral cementation of the prosthesis to the abutment are conducive to peri-implant health [42, 130, 131]. With regard to the type of prosthesis (single crown, fixed, or removable implant prosthesis), removable implant prostheses were associated with a greater incidence of implant complications than single implant crowns [132]. For edentulous areas spanning three teeth, an implant-supported fixed dental prosthesis on two implants is considered the most favorable for soft tissue health [133]. PD and BOP values observed on single implants that received a veneered zirconia restoration cemented to non-original titanium bases found a significant increase in BOP and PD after 1 year [134].

Implant-Abutment Connection

The microgap at the implant-abutment connection (IAC) is prone to plaque accumulation and bacterial microleakage which is a risk factor for peri-implantitis [135]. A review article examining the relationship of the IAC and bacterial leakage reported an association between the two [136].

Implants that have a conical connection or a mixed connection system had reduced bacterial microleakage and also better load distribution. A randomized clinical trial compared screwed vs. cemented abutment implant connections in a total of 20 implants (10 in each group) by obtaining a sample of the peri-implant flora 360 days after placement of the restoration and analyzing it with PCR. The bacterial colonization for the screwed abutment implant connection was over the pathogenic threshold for 5 bacteria vs. 1 for the cemented group. They concluded that implants with a screw-retained connection had a higher risk of peri-implantitis than its cement-retained counterpart [137].

Residual Cement

The presence of residual cement being a risk factor for peri-implantitis is well documented previously and in the recent literature since it may lead to an increase in peri-implant probing depths, inflammation, bone loss, and suppuration [10, 29, 32, 138, 139]. A cross-sectional study looking at the differences in peri-implant health between screw- and cement-retained restorations found a significantly higher number of gram-negative bacteria around cement-retained restorations [10]. The emergence profile of a restoration plays a role in the amount of residual cement present. Concave emergence profiles have significantly more residual cement around them compared to convex profiles [140]. Interdental areas are also more prone to cement remnants than other surfaces. Zinc oxide eugenol cements are preferable over resin cements, particularly in patients with a history of periodontitis [141, 142]. Placing the abutment margin equigingival to allow for easy removal of the cement following a strict cementation protocol and early post-cementation follow-ups are some ways to reduce the chances of leaving behind excess cement [138, 143]. An equigingival margin placement also allows accessibility for better plaque control [139].

Occlusal Overload and Immediate Loading

While a direct cause and effect relationship is yet to be determined, the presence of crestal bone loss in the absence of any clinical signs of inflammation may be attributed to occlusal overload [144, 145]. A proposed mechanism is that occlusal overload can influence the bone remodeling around an implant by changing the way the cells respond to the overload and thus result in the loss of osseointegration [146]. Marginal bone levels and marginal bone loss were measured on 154 implants, 1.6–6.8 years after placement in an exploratory study. Overall, the rate of marginal bone loss reduced with increasing time. Implants that showed greater bone loss levels preloading had worse actual bone levels post-loading [147]. In addition, molar sites are more prone to bone loss than premolar sites [148]. A retrospective study that evaluated the outcomes of 28 full-arch prostheses in which 11 were immediately loaded and 17 delayed loaded reported a higher marginal bone loss in the immediately loaded group [149]. While clinical signs of occlusal overload in the presence of plaque and inflammation could be a risk factor for peri-implantitis, a recent review from the 2017 world workshop on the classification of periodontal and peri-implant diseases and conditions concluded that there is no conclusive evidence that occlusal overload is a predictor for the onset of peri-implantitis [3].

Years in Function

The amount of time restorations that have been in function is also an important consideration. A retrospective cohort study evaluated implants that had been in function for up to 10 years. The cumulative incidence of peri-implantitis was 24.4% and a peak in peri-implantitis was seen after the seventh year. After 10 years in function, the rate of peri-implantitis was 12.9%. The study concluded that peri-implantitis begins to appear after the fifth year in function and is most frequently seen between the seventh and eighth years in function [150]. Another ten-year retrospective study that looked at 384 implants (full-arch rehabilitations) with a mean follow-up time of 8 years found a significantly higher proportion of implants without peri-implantitis in the mandible (89.76%) than in the maxilla (81.71%) at 10 years [151].

Conclusions

The following are some conclusions from this review of clinical research and review articles published from 2017 to 2020:

1. Microbiomes associated with peri-implantitis lesions consist of peridontopathogenic bacteria, but they tend to be more complex in nature and also can contain certain unique microorganisms.
2. Recent literature further reinforces the influence of previously well-established risk factors on peri-implantitis such as smoking, diabetes mellitus, lack of oral hygiene and maintenance, history of periodontitis, and poor-quality peri-implant soft tissue.
3. Recent evidence suggests that certain factors like medications, age, gender, vitamin D, and autoimmune diseases also play a role, but require further investigations to confirm their roles.
4. The influence of genetic factors on peri-implantitis is unclear, but recent evidence suggests that certain polymorphisms may predispose patients to peri-implantitis.
5. Titanium particles released into the peri-implant tissue are a recently emerging risk factor that could increase inflammatory markers and potentially contribute to the development of peri-implantitis.

6. Prosthetic risk factors such as improper restorative design, occlusal overload, microgap, and especially the presence of residual cement, as known previously, remain significant factors that can increase the risk for peri-implantitis.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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