Host response and peri-implantitis

Abstract: Considering the absence of predictable and effective therapeutic interventions for the treatment of peri-implantitis, scientific evidence concerning the host response profile around dental implants could be important for providing in the future a wider preventive and/or therapeutic window for this peri-implant lesion, indicating biomarkers that provide quantifiable measure of response to peri-implant therapy. Moreover, a better knowledge of pattern of host osteo-immunoinflammatory modulation in the presence of peri-implantitis could either benefit the early diagnostic of the disease or to cooperate to prognostic information related to the status of the peri-implant breakdown. Finally, new evidences concerning the host profile of modulators of inflammation and of osseous tissue metabolism around dental implants could explain the individual susceptibility for developing peri-implant lesions, identifying individuals or sites with increased risk for peri-implantitis. The focus of this chapter was, based on a systematically searched and critically reviewed literature, summarizing the existing knowledge in the scientific research concerning the host osteo-immunoinflammatory response to the microbiological challenge related to periimplantitis.

Keywords: Peri-Implantitis; Dental Implants; Mucositis.

Introduction

Although dental implants present predictable outcomes and characterize a procedure often performed in daily clinical practice for oral rehabilitation, the development and progression of peri-implantitis has expressively impaired implant survival and success. In this context, Derks and Tomasi reported in a meta-analyses study that weighted implant-based prevalence for peri-implantitis were 22% (95%CI: 14–30), whereas another meta-analysis recognized that weighted implant and patient-based peri-implantitis prevalences achieved 9.25% (95%CI: 7.57–10.93) and 19.83% (95%CI: 15.38–24.27), respectively. In addition, recently, a multi-level cross-sectional investigation pointed-out that 9.2%of implants (95%CI: 4.7–13.7) and 19.1% of patients (95%CI: 12.6–25.5) presented peri-implantitis. It is well recognized that peri-implantitis is an inflammatory disease that promotes soft tissue inflammation and also progressive bone loss beyond biological osseous remodeling. Importantly, it has been evidenced that the presence of periodontopathogens is necessary but not sufficient for peri-implantitis initiation and previous data noticeably
showed that osteo-immunoinflammatory mediators produced by the host response exert an essential impact on peri-implant tissue breakdown.\textsuperscript{8,9,10,11,12,13,14}

Considering the absence of predictable and effective therapeutic interventions for the treatment of peri-implantitis,\textsuperscript{15,16} scientific evidence concerning the host response profile around dental implants could be important for providing in the future a wider preventive and/or therapeutic window for this peri-implant lesion, indicating biomarkers that provide quantifiable measure of response to peri-implant therapy. Moreover, a better knowledge of pattern of host osteo-immunoinflammatory modulation in the presence of peri-implantitis could either benefit the early diagnostic of the disease or to cooperate to prognostic information related to the status of the peri-implant breakdown. Finally, new evidences concerning the host profile of modulators of inflammation and of osseous tissue metabolism around dental implants could explain the individual susceptibility for developing peri-implant lesions, identifying individuals or sites with increased risk for peri-implantitis.

The focus of this chapter was, based on a systematically searched and critically reviewed literature, summarizing the existing knowledge in the scientific research concerning the host osteo-immunoinflammatory response to the microbiological challenge related to peri-implantitis.

**Host response in patients with peri-implantitis**

**Host response to the bacterial challenge in peri-implant lesions**

The understanding that microorganisms exert essential influence on the establishment of peri-implantitis is well recognized and the cause-related effect between biofilm deposition and peri-implant lesions development has been supported by experimental and clinical studies.\textsuperscript{17,18,19,20} Peri-implant tissue collapse involves a intricate and organized microbiota, narrowly approximating that observed in chronic periodontitis.\textsuperscript{21,22} However, as described by Berglundh et al.,\textsuperscript{23} based on data from experimental investigations,\textsuperscript{24,25} in peri-implantitis the inflammatory connective tissue infiltrated surrounding implants prolonged to the alveolar bone crest and was related to elevated density of osteoclastogenic cells when compared to natural teeth.

Noteworthy, the individual host response to the microbiological challenge has a deep impact on the establishment and development of peri-implant lesions. Based in this concept, mainly the peri-implant sulcus fluid and saliva has been investigated for diverse molecules associated with inflammatory pattern, bone turnover and proteinases.\textsuperscript{14,26,27,28,29,30}

**Modulation of host osteo-immunoinflammatory mediators in peri-implantitis**

**Pro- and anti-inflammatory mediators**

Interleukin-1 (IL-1) is a chief pro-inflammatory cytokine produced essentially by macrophages but also by neutrophilic granulocytes and other cells.\textsuperscript{26,27} Tumor necrosis factor (TNF)-α is another pro-inflammatory marker that promote stimulation of several events, including alveolar bone loss.\textsuperscript{31} The destructive role of these mediators is well known in the presence of periodontitis\textsuperscript{26,31} and studies also demonstrate augmented production of IL-1 and TNF-α, in the manifestation of peri-implantitis.\textsuperscript{32,33,34,35,36} In this context, a meta-analysis showed that both TNF-α and IL-1β in crevicular fluid of peri-implant pockets might be utilized to determine the early diagnosis of peri-implantitis.\textsuperscript{36} Most investigations described up-regulation of IL-1β in mucositis and peri-implantitis.\textsuperscript{37,38} Additional evidences confirmed that the levels of IL-1 was positively correlated to failing dental implants at the patient and site level, showing a precise profile of host response in patients with peri-implant collapse.\textsuperscript{39} Moreover, IL-1β was reported as a promising candidate in differentiating peri-implantitis from healthy implants.\textsuperscript{40} Other cross-sectional data demonstrated that IL-1β and IL-8 were significantly up-regulated in the peri-implant crevicular fluid from subjects with peri-implantitis.\textsuperscript{41}

In line, Schminke et al.,\textsuperscript{42} that studied the gene and protein expression profiles of peri-implantitis osseous tissue when compared to healthy bone
tissue, reported up-regulation of the inflammatory marker IL-8 in inflamed tissues, whereas the anti-inflammatory molecule PPARγ was reduced in peri-implantitis. Concentrations of the anti-inflammatory cytokine IL-10 have also been mentioned to decline in peri-implantitis. Of interest, Ata-Ali et al. demonstrated augmented levels of IL-1β/IL-10 ratio in patients with peri-implant disease when compared to the healthy peri-implant sites.

IL-17, whose immune response is mediated by T helper 17 (Th17) cells, is another pro-inflammatory molecule that intercedes numerous biological inflammatory actions including neutrophil and macrophage recruitment and stimulation of other pro-inflammatory mechanisms. In this context, IL-23 exert a crucial role in intensifying Th17 responses. Conversely, Treg cells, characterized by the elevated expression of suppressive cytokines as transforming growth factor (TGF)-β, exert regulatory functions. Interestingly, a recent study investigating the IL-17, IL-23, and TGF-β gene expression levels in healthy and diseased peri-implant tissues showed a predominant Th17 response and a diminution of Treg response in the presence of peri-implantitis when compared to peri-implant healthy condition, especially caused by the up-regulation of IL-23 and down-regulation of TGF-β observed in peri-implantitis tissues.

Matrix metalloproteinases

Modifications in the individual pattern of the host response in peri-implant crevicular fluid may also impact the levels of matrix metalloproteinases (MMPs), such as MMP-1, MMP-7 and MMP-8, MMPs, especially MMP-8 that is recognized to be the main MMP in periodontitis, exert a vital action in numerous tissues damaging inflammatory processes by destroying extracellular matrix and basement membrane components. MMP-8, or collagenase-2, was described as an early sign of peri-implant breakdown and related to the development of experimental mucositis around implants in response to plaque deposition. Thierbach et al. and Ramseier et al. also supported that MMP-8 levels are up-regulated in dental implants diagnosed with peri-implantitis. Other cross-sectional findings revealed that augmented MMP-8 concentrations in peri-implant crevicular fluid may indicate the active phase of the inflammatory peri-implant disease and that MMP-8 is the main collagenase in active peri-implantitis. In line, Irshad et al. also sustained that up-regulation of inflammatory mediators, including MMP-1, in fibroblasts from peri-implantitis sites in response to P. gingivalis may exert a relevant impact in the pathogenesis of peri-implantitis.

A relevant aspect to be highlighted concerning the impact of MMPs in the peri-implant tissues is that the activities of these enzymes are blocked by tissue inhibitors of matrix metalloproteinases.
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Interestingly, evidence indicated that fibroblasts from peri-implantitis granulation tissue showed up-regulation of mRNA MMP-1 and reduced gene expression for TIMP-1 when compared to cells collected from chronic periodontitis granulation tissue. Additional evidence suggested that reduced MMP-1/TIMP-1 levels could be an indicator of loss of clinical attachment around dental implants, although complementary research should be directed to examine MMP-1 bound to TIMP-1 as a prognostic marker for the peri-implant diseases.

Bone resorption/remodeling mediators

Importantly, in the presence of lesions around dental implants, the up-regulation of pro-inflammatory markers and metalloproteinases in the peri-implant tissues can also induce the chemotaxis of active osteoclasts, modifying the patter of expression of bone resorption/remodeling mediators around the implants. In this context, earlier data from a cross-sectional study showed increased amount of C-telopeptide pyridinoline crosslinks of type I collagen (ICTP) in the peri-implant fluid of implants with peri-implantitis, suggesting that augmented type I collagen breakdown and bone resorption in these sites, although Tümer et al. have not confirmed significant ICTP level changes in the peri-implant sulcular fluid of dental implants with or without peri-implant bone destruction.

In their study, Arikan et al. also demonstrated that significantly lower OPG and increased soluble RANKL concentrations in the peri-implantitis sites than the healthy control sites. In addition, the authors reported that RANKL/OPG ratio was increased in peri-implantitis compared with the clinically healthy implants, supporting the negative impact of peri-implantitis on alveolar bone resorption. In line, Rakic et al. demonstrated that not only concentrations of RANK, sRANKL and OPG were significantly augmented in patients with peri-implantitis compared with those with healthy peri-implant tissues, but also sclerostin levels, a marker recognized to leads to decreased bone formation. According to these findings, RANKL, OPG, and sclerostin may be suggested as prognostic biomarkers in peri-implantitis.

Remarkably, Che et al. revealed that osteopontin (OPN) may exert a crucial role for IL-1β production and apoptosis in peri-implantitis, as evidenced by the investigation of patient’s peri-implant crevicular fluid and cell-culture experiments, reducing inflammation by down-regulation of pro-inflammatory cytokines in peri-implantitis. In fact, OPN is an osteo-immunoinflammatory marker related to both bone development and mineralization and also in infective inflammation as an immune modulator by regulating cytokine production. However, the role of osteo-immunoinflammatory mediators, as OPN, in peri-implantitis is not well understood and additional investigations would be important to improve this knowledge.

In their study, Schminke et al. investigating the molecular configuration of healthy and peri-implantitis bone tissues with the help of a microarray, as well as qPCR and Western blotting, demonstrated that BMPs such as BMP-7 were down-regulated in inflamed bone tissues when compared to peri-implant healthy tissues. According to the authors, the osteogenic transcription factor RUNX2 was reduced, in agreement with the collapse course of the bone during peri-implantitis.

Additionally, representative bone matrix biomarkers, as SPP1, BGLAP, and COL9A1, were decreased in the peri-implantitis bone tissues, while enhanced expression of fibrocyte markers were detected. Accordantly, earlier evidences have already showed that fibroblasts contribute to the pathogenesis of peri-implantitis up-regulating both vascularity and matrix degradation. Further, marginal bone breakdown in initial experimental diseases may encourage an imbalanced host response, which is also suggested to promote the stimulation of fibroblasts.

Other molecules recently mentioned in the literature by interfering in the pathogenesis of peri-implantitis are semaphorins, a class of cell surface proteins related to inflammatory pathways also involved in the regulatory mechanisms of bone metabolism. According to Bastos et al., that investigated the gene expression of semaphorins 3A, 3B, 4A, and 4D in peri-implant tissue biopsy from healthy and diseased dental implants, it was identified that peri-implantitis sites presented
augmented mRNA levels of Sem3A and Sem4D and reduced expression of Sem4A when compared to peri-implant healthy tissues. Considering that is the first investigation evaluating the role of semaphorins in peri-implant lesions, further data are required to clarify the involvement of these molecules in the peri-implantitis.

Oxidative stress biomarkers

Besides the peri-implant breakdown be attributed to the modulation of numerous cyto/chemokines in favour of a pro-inflammatory host response profile, it could be also related to oxidative stress mechanisms and excessive production of reactive oxygen species which also exert a vital impact in the host response. In this context, Sánchez-Siles et al. investigated, in a transversal study, salivary concentration of oxidative stress molecules in individuals with peri-implantitis. The outcomes from this study revealed that patients with implants (four to five) diagnosed with peri-implantitis do not display high salivary malondialdehyde (MDA), a key lipid peroxidation by-product, and myeloperoxidase (MPO), the only peroxidase that catalyzes the alteration of hydrogen peroxide and chloride to hypochlorous acid concentrations. It suggests that peri-implantitis does not promote quantifiable oxidative impairment in saliva. However, additional prospective studies in patients with a greater number of dental implants with peri-implantitis could be important to clarify the real impact of peri-implantitis in the levels of oxidative stress molecules in saliva.

The role of host genetic susceptibility for peri-implantitis

It is noteworthy, studies have elucidated whether the host genetic susceptibility regulates the vulnerability for biological complication of dental implants. Some investigations suggest that IL-1 genotype may be associated with augmented predisposition to peri-implant tissue breakdown. Although, in a systematic review, Dereka et al. have concluded that there is no clear connection between biological complications, such as early dental implant loss, and precise genetic polymorphisms of IL-1, IL-2, IL-6, TGF-β or TNF-α, the authors revealed that a propensity may be highlighted demonstrating a possible association between IL-1 genotype and peri-implantitis. In agreement with these data, Shimpuku et al. suggested that a specific genetic polymorphism (IL-1B-511 2/2 genotype) of the IL-1 gene was related to early marginal peri-implant bone loss.

Remarkable, a polymorphism in the MMP-1 promotor (G-1607GG), recognized to lead augmented transcriptional activity, was reported to be related to dental implant failure. Other researchers demonstrated that TNFα -308 A/G and CD14-159 C/T polymorphisms are related to peri-implantitis and could contribute as markers related to peri-implantitis. In line, recently, Petkovic-Curcin et al. also suggested that the occurrence of TNFα-308 GA/AA genotypes could augment the risk for peri-implantitis lesions, whereas, conversely to Rakic et al. findings, CD14-159 polymorphic CT/TT genotypes have reduced the risk.

Supplementary data in greater samples and in different population are required to support these findings.

Altered peri-implant host response in patients at risk conditions

It is important to highlight that a noticeable number of patients submitted to dental implants therapy are individuals at risk conditions to develop worsened host osteo-immunoinflammatory response to the pathogens related to peri-implantitis, such as smoking and diabetic patients. Thus, in these patient profiles, a bacterial challenge in combination with an exacerbated or altered host reaction may more easily or pronouncedly contribute to the advance of peri-implant tissue destruction.

Although clinical trials reporting dental implant success in type 2 diabetic individuals with well-controlled glycaemia and unknown or compromised glycaemic status have demonstrated varying failure rates without a defined relation to glycaemic control, it has been established that poor glycaemic status is the most relevant factor affecting the rates of implant complications (including peri-implant bone loss) in diabetics.
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It is well known that diabetic patients have an augmented risk of developing periodontitis, and that the poor glycaemic status may negatively modulate immunoinflammatory mediators in the gingival crevicular fluid, leading to periodontal attachment and tooth loss over time. Moreover, diabetes has also been suggested as a biological factor related to peri-implant diseases and, in addition, data have indicated that the poor glycaemic control may promote an overproduction of the proinflammatory biomarkers, in the presence of peri-implantitis.

According to Al-Sowygh et al., that evaluated the concentrations of advanced glycation end products (AGEs) in peri-implant crevicular fluid of type 2 diabetes mellitus patients with different glycemc control, higher AGES levels were also detected in patients with elevated glycemic status, suggesting that AGES may be considered as probable biomarker of inflammation in diabetic subjects with peri-implantitis, which could modify bone physiology, troubling remodeling and promoting bone loss. Moreover, another recent study evidenced that the levels of AGES in peri-implant sulcular fluid were also increased in patients presenting prediabetes. In line, Venza et al. verified that type 2 diabetic patients with poorly controlled glycaemic status showed overexpression of TNF-α and IL-8 in sites with peri-implantitis when compared to patients with normoglycaemic and well-controlled diabetes. Altogether, these data indicate that the balance between immunoinflammatory mediators in the peri-implant fluid of patients with diabetes would be shifted towards a state of hyperinflammatory characteristics, especially when glycaemic control is poor, which could create an at-risk-for-harm environment for a peri-implant tissue breakdown over time.

It is relevant to note that TNF-α acts synergistically with IL-1β to start essential mediators of inflammatory cascade (Duaarte et al. 2009), and these molecules are considered the two most relevant in osteoclast formation and bone resorption. In line, it was previously reported significantly augmented bone loss prevalence in peri-implantitis sites from poorly controlled than well-controlled diabetics or healthy patients (60.2% vs 46.3% vs 45.5%).

Noteworthy, Ghiraldini et al., that evaluated the influence of glycaemic in the local release of bone-related factors during the peri-implant bone healing, displayed that key osteogenic and/or bone mineralization molecules were decreased in poorly controlled diabetic individuals, supporting that diabetics with inadequate glycaemic status have a different local profile of bone markers, which could impair the host reaction during the peri-implant healing course.

Tobacco smoking is another relevant condition that has been described as highly related to altered peri-implant host response in favor of peri-implantitis establishment, increasing the prevalence of diseases around dental implants and harmfully inducing the peri-implant bone breakdown. In this context, innumerable studies describe that smoking negatively alters the profile of individual host response and stimulates down-regulation of local osteo-immuno-inflammatory molecules around implants even in non-manifesting inflammation sites, contributing to an augmented predisposition to peri-implant disturbing.

Accordantly, a recent investigation of Akram et al. supported that higher probing depth and increased crestal bone loss were detected among cigarette-smokers and smokeless-tobacco users when compared to those never exposed to tobacco smoking and, according to the authors, the up-regulation of local pro-inflammatory biomarkers, such as IL-1β and MMP-9, may justify the superior susceptibility of cigarette-smokers and smokeless-tobacco users to peri-implant breakdown. Of interest, waterpipe (narghile) smoking also promotes negative impact on host response and contributes to peri-implantitis establishment. According to these last authors, waterpipe-smokers presented significantly higher local levels of pro-inflammatory IL-1β, IL-6 and TNF-α in the peri-implant fluid when compared to never-smokers in sites with peri-implantitis.

Remarkably, Negri et al. also pointed-out that smoking habit may modify the local mediators’ profile around implants, promoting decreases in TNF-α, IL-4, IL-8 and OPG levels and an augmented ICTP and TH1/TH2 ratio in peri-implant crevicular fluid, which appear modulate the bone-related
molecules towards osteoclastogenesis situation and create an immunosuppressive scenario even in non-manifesting inflammation sites. Anyway, additional investigations should confirm the impact of smoking in the pathway of interactions among the global net of pro- and anti-inflammatory mediators and bone-related markers on molecular and cellular levels during peri-implantitis.

Although the impact of obesity on host osteo-immunoinflammatory response is yet scarce in the literature, interestingly, Vohra et al.,\textsuperscript{100} based in a cross-sectional retrospective study, demonstrated that peri-implant clinical and radiographic conditions are worse in patients with severe obesity, and suggested that this finding may be related to systemic low-grade inflammatory marker (C-reactive protein) that was increased in these patients.

Overall, additional studies are required to provide a better elucidation of the pattern of host response related to peri-implantitis in individuals at most vulnerable conditions, which could make easier to predict which patient is at risk for peri-implant complications during maintenance of dental implants.

**Impact of degradation products released from dental implants in peri-implant host immunoinflammatory response**

Metal wear particles, as titanium and iron elements, from dental implant surfaces have been observed both in soft and hard peri-implant tissues,\textsuperscript{101,102} and although their impact in the pathogenesis of peri-implantitis and in the host osteo-immunoinflammatory response is still indefinite, some studies have related the presence of these particles to inflammatory processes\textsuperscript{103,104}. Tribocorrosion product release from dental implants may be promoted in diverse ways such as by the detachment from the implant surface during its insertion; wear promoted by micro-movements between contacting surfaces at implant/prosthetic connections; by the corrosive impact of therapeutic formulations as fluorides or bleaching substances; and during peri-implantitis therapies such as polishing of the implant surface or implantoplasity.\textsuperscript{105,106,107,108}

Irshad et al.,\textsuperscript{53} in an in vitro investigation, showed that peri-implant granulation tissue fibroblasts challenged with titanium dioxide (TiO$_2$) particles in association with viable *Porphyromonas gingivalis* infection augmented the pro-inflammatory response, up-regulating the gene expression and production of TNF-\(\alpha\). In line, recently, Pettersson et al.\textsuperscript{109} demonstrated in vitro that Ti ions form particles in cell culture and that the activation and secretion of IL-1\(\beta\) was associated to particles and not to the soluble ions.

Other evidences demonstrated showed that soluble ions, more than particles, are responsible for the pro-inflammatory response stimulated in monocytes/macrophages\textsuperscript{110} and by the increasing in the ratio of RANKL/OPG, inducing to the alveolar bone resorption\textsuperscript{111}. In line, Taira et al.\textsuperscript{112} revealed that macrophages cultivated in a medium containing 1 ppm titanium produced 170\% more TNF-\(\alpha\) than cells cultivated free of titanium.

Noteworthy, according to Pettersson et al.\textsuperscript{109} in vitro and in vivo findings, leaked Ti ions from a dental implant could be converted into particles in the surrounding tissue and be phagocytized by macrophages, producing a pro-inflammatory peri-implant response which may be significantly potentialized by the presence of bacteria. Despite the current evidence concerning such issues, further investigations are essential to clarify the mechanisms involved in the pathogenesis of peri-implantitis related to the metal particles and wear debris from dental implants.

**Final considerations**

In a different way to what has been extensively studied and intensely exposed concerning the treatment of periodontitis, until now no predictable and effective therapeutic intervention has been defined for the treatment of peri-implantitis.\textsuperscript{15,16} Thus, primary prevention of peri-implantitis becomes extremely relevant.

As observed in this review, based on the presented literature, innumerable immunoinflammatory mediators and bone-related molecules could be considered as potential biomarkers to be used in combination with clinical evaluation for monitoring peri-implant health and disease. A probable approach would be to monitor host-derived biomarkers related
Host response and peri-implantitis to inflammation, as IL-1β, enzymes that degrade extracellular matrix, as MMP-8, simultaneously with bone loss mediators, as RANKL, OPG and sclerostin, whose levels are recognized to be modified in patients with peri-implant diseases and proposed as prognostic biomarkers in peri-implantitis. The idea of prevention supported by premature detection and systematic maintenance therapy may have a crucial impact on decreasing the occurrence of peri-implant lesions.

Nevertheless, it should be kept in mind that additional data from longitudinal and interventional studies could offer more consistent information on the probable impact of certain immunoinflammatory mediators and bone-related molecules in the pathogenesis of peri-implant diseases. Importantly, individual genetic data might potentially contribute as valuable information during the clinical practice to establish therapeutic planning and prognosis, considering that preventive and management method could be positively coordinated depending on observed genotype. Thus, supplementary evidence concerning the molecular pathophysiology of peri-implant infections may, in the future, benefit the treatment of dental implants presenting peri-implantitis in a long-term basis and cooperate in the development of preventive approaches to avoid peri-implant tissue breakdown establishment.

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