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REVIEW ARTICLE

Peri-implantitis and systemic inflammation: A critical update

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Abstract Peri-implantitis is an inflammatory condition induced by bacterial biofilm that affects the soft and hard tissues surrounding dental implants, compromising the success of implant therapy. Recent studies have highlighted the potential links between peri-implant health and systemic inflammation, including uncontrolled diabetes mellitus, psychological stress, cardiovascular disease, obesity, and infectious diseases such as COVID-19. As an inflammatory disease, peri-implantitis may trigger systemic inflammation by elevating circulating levels of pro-inflammatory cytokines, which could have unknown impacts on overall health. While the relationship between periodontal health and systemic conditions is better understood, the association between peri-implant disease and

Abbreviations: BoP, bleeding on probing; CRP, C-reactive protein; COVID-19, coronavirus disease 2019; CVDs, cardiovascular diseases; DM, diabetes mellitus; GCF, gingival crevicular fluid; IL, interleukin; MBL, marginal bone loss; MMs, monocytes/macrophages; OR, odds ratio; PD, pocket depth; PI, plaque index; PMNs, polymorphonuclear neutrophils; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TNF-α, tumor necrosis factor alpha; WBCs, white blood cells

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Systemic disease

systemic inflammation remains unclear. Therefore, this comprehensive review aims to summarize the most recent evidence on the relationship between peri-implantitis and systemic inflammation, focusing on biological complications, microbiology, and biomarkers. This review aims to enhance our understanding of the links between peri-implantitis and systemic inflammation and promote further research in this field by discussing the latest insights and clinical implications.

Contents

1. Background

Dental implants have become a pivotal part of the dental practice for replacing missing or failing dentition, as they offer excellent long-term results (French et al., 2015). However, clinicians are becoming more aware of epidemiological studies reporting on peri-implant inflammatory diseases, specifically peri-implantitis (Afrashtehfar et al., 2022a). The prevalence of peri-implantitis has been reported to be as high as 56%, and the reported prevalence widely ranges from 12% and 43% (Zitzmann and Berglundh, 2008; Romandini et al., 2021). This difference in reported prevalence is due to the lack of strict diagnostic criteria and case definitions of the disease (Afrashtehfar and Esfandiari, 2017; Berglundh et al., 2018a).

Peri-implantitis occurs in the hard and soft tissues surrounding dental implants, similar to periodontitis around natural teeth. It typically results in adverse biological effects, such as bleeding on probing (BoP), suppuration, progressive bone loss (MBL) beyond physiological remodeling, and eventually, a catastrophic complication electing implant removal (i.e., explantation) (Salvi et al., 2022; Roccuzzo et al., 2023). A large body of evidence supports that peri-implant inflammatory diseases are biofilm-initiated infectious diseases and that biofilm control is essential for the health of surrounding tissues (Salvi et al., 2012; Berglundh et al., 2018b). Although the initiation of the disease is biofilm-induced, other systemic factors should always be taken into consideration during the treatment planning process and the maintenance of peri-implant health. Owing to the microbiological biofilm characterization that initiates the disease, the hypotheses that the periodontal pocket can lead to systemic circulation if breached, this could also stand true in regard to the peri-implant sulcus in disease, as it has been established that this soft tissue-implant interface is weaker than its counterpart around natural dentition (Berglundh et al., 2011; Ivanovski and Lee, 2018). This infiltration through the sulcular epithelium results in an inflammatory response with the recruitment of polymorphonuclear neutrophils (PMNs) and monocytes/macrophages (MMs), which could be drastic in terms of the production of proinflammatory cytokines and elicit systemic inflammation (Berglundh et al., 2011; Berglundh et al., 2018a). Efforts have been made to investigate the differences in biomarkers between periodontitis and peri-implantitis sites in the same individual; interestingly, the diseased sites in the same individual, whether being an implant or tooth site, presented with elevated levels of similar cytokines (Jansson et al., 2021).

Although some risk factors/indicators, such as smoking, history of periodontitis, and diabetes mellitus (DM), have been investigated regarding peri-implantitis, evidence is still scarce for systemic inflammation and peri-implant inflammatory diseases. Thus, this study aimed to review the available evidence that investigates peri-implant diseases and systemic inflammation.

2. Inflammatory systemic conditions

2.1. Diabetes

Uncontrolled DM is known to result in subclinical chronic inflammation, thus resulting in multiple inflammation-mediated conditions, including but not limited to neuropathy, nephropathy, and retinopathy. One such complication is periodontal disease, which has been called "the sixth complication of diabetes" (Loe, 1993). Due to some similarities between the periodontal and peri-implant tissues, their relationship with peri-implant diseases, namely, peri-implant mucositis and peri-implantitis, has been explored in the literature. It has been found that glycemic control could influence peri-implantitis but not peri-implant mucositis (Monje et al., 2017).

In contrast, another clinical study examined the survival of dental implants in patients with poor glycemic control (HbA1c of 8% and above) at the time of implant placement. They found that at 2 years, there was a 96.2% survival rate. It was also noted that the only biological complication that occurred was peri-implant mucositis (29.4% of implants), and no peri-implantitis was reported (Eskow and Oates, 2017). Interestingly, a clinical study that assessed the performance of hydrophilic implants placed in canine and molar sites in patients with type II DM (DM-II) showed that poor glycemic control at 1 year (having elevated levels of HbA1c [7.5 or more]) did not negatively impact the survival of that specific implant surface (Latimer et al., 2022). Nevertheless, these findings must be interpreted with caution. The follow-up period was short, and only one implant surface was used in the population of such a cohort study. Other studies have reported that patients with uncontrolled DM could have a higher risk of developing peri-implantitis compared to normoglycemic patients (Tawil et al., 2008). Hence, this relationship must be further investigated to establish direct causality.

When comparing these findings to the relationship between periodontitis and uncontrolled DM/poor glycemic control, solid evidence supports the relationship between the two conditions. However, the relationship with peri-implant diseases needs to be further understood. The bidirectional nature of the relationship between periodontitis and DM has been established (Lalla and Papapanou, 2011). Some studies have shown that patients with hyperglycemia could have an odds ratio (OR) of 2.5 for presenting periodontal disease (Katz, 2001). This mechanism is explained by the presence of a hyperinflammatory state, which could exacerbate insulin resistance, thus impairing glycemic control and the reparative capacity of the body.

2.2. Hyperlipidemia

A pilot study that compared the lipid profile in patients with healthy peri-implant tissues versus patients with peri-implantitis found that patients with peri-implantitis were more prone to have higher levels of leukocytes (i.e., white blood cells [WBCs]), which could potentially result in more systemic inflammation (Blanco et al., 2021). Another finding of that study was that total cholesterol was also increased when compared to individuals with healthy implants. The downregulation of interleukin 10 (IL-10) was also of interest. Animal and human studies have shown that IL-10 carries anti-inflammatory properties, and its reduction could mean a heightened state of inflammation (Blanco et al., 2021). Interestingly, statin medications used for treating hyperlipidemia have shown promising results in promoting dental implant osseointegration in animal studies. However, these findings have yet to be confirmed in humans (Tahamtan et al., 2020), and further clinical studies are required to define their role in modern dental implant practice.

In contrast, studies from the periodontal literature have explored the effect of hyperlipidemia on periodontal health and found that patients with hyperlipidemia present with higher levels of periodontal indices (BoP, pocket depth [PD], and plaque index [PI]), which could also be associated with an increase in IL-1 production (Fentoğlu et al., 2009).

2.3. Obesity

Obesity is a chronic condition associated with multiple systemic conditions, including but not limited to DM-II, hypertension, cardiovascular diseases (CVDs), and some types of cancer (Endalifer and Diress, 2020). As this inflammatory condition could result in oral manifestations, the association between obesity and peri-implant health has been an area of interest in research. A cross-sectional study showed that peri-implant BoP and MBL were increased in obese patients compared to nonobese individuals (Abduljabbar et al., 2016). These findings were further analyzed within the same study, and they found that the levels of pro-inflammatory cytokines (IL-1 and IL-6) were higher in the saliva of obese patients than in that of nonobese patients (Abduljabbar et al., 2016). This could further explain the presence of more obvious signs of clinical inflammation in that group.

Other studies have also evaluated the serum C-reactive protein (CRP) levels, which are indicative of the inflammatory status, and found that elevated CRP levels were associated with peri-implant BoP in obese patients compared to nonobese controls (Vohra et al., 2018). These findings correlate with what has been reported in the literature regarding the relationship between obesity and periodontitis. Obesity could impact periodontal health and the progression of periodontal disease. This mechanism could be explained by the insulin resistance that develops in obese patients and the production of pro-inflammatory cytokines by the adipose tissue, resulting in a hyperinflammatory state and increased tissue breakdown (Makki et al., 2013).

2.4. Depression and anxiety

The increased levels of psychological stress, depression, and poor coping mechanisms for these conditions have been linked to systemic diseases and inflammation, with evidence confirming increases in the levels of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and IL-6, in depressed patients (Dowlati et al., 2010). Evidence for the association between peri-implant diseases and the heightened levels of circulating inflammatory cytokines is scarce. Some studies have reported an increase in triglyceride and uric acid levels in sites presenting with peri-implantitis when compared to healthy

counterpart sites (Ustaoglu and Erdal, 2020). These findings are associated with increased inflammation and, possibly, increased breakdown of tissues. Remarkably, some groups have also evaluated the effect of selective serotonin reuptake inhibitor (SSRI) and serotonin and norepinephrine reuptake inhibitor (SNRI) medications, which are used for managing such conditions, on periodontal and peri-implant health and showed that this type of medication could have a deleterious effect on implant survival and peri-implant bone level (Wu et al., 2014). A retrospective study conducted in a university setting showed that patients on antidepressants were 4.3 times more likely to have implant failure than patients who did not take this type of medication (Hakam et al., 2021). This combined effect of the condition and the medications used to treat it should be considered when planning surgical implant therapy to replace oral, dental, and facial structures.

More recent evidence shows an association between depression and periodontal disease, and stress and depression have even been considered risk indicators for periodontal disease. However, causality needs to be established to determine its value in the initiation and progression of periodontal disease (Genco and Borgnakke, 2013).

2.5. Cardiovascular diseases

There is emerging evidence that supports the notion that CVDs have an impact on periodontal and peri-implant health and vice versa. The biological plausibility of this relationship could be explained by the migration of bacteria into the bloodstream through the ulcerated epithelium of the periodontal and peri-implant sulci, subsequently leading to atherogenesis, which has been confirmed in animal studies (Kebschull et al., 2010). A retrospective study reported that patients with a history of cardiovascular diseases have an odds ratio of 8.7 for peri-implantitis after adjusting for other confounding factors, such as age, smoking, and sex (Renvert et al., 2014).

Van Dyke et al. assessed the relationship between periodontal inflammation and major cardiovascular events and suggested that periodontal inflammation leads to increased arterial inflammation, subsequently causing atherosclerotic diseases (Van Dyke et al., 2021). These findings were also investigated in longitudinal human studies, which showed that a decrease in the progression of atherosclerosis was associated with an improvement in periodontal health (Desvarieux et al., 2013; Hajishengallis, 2015). Further evidence from a systematic review on the association between cardiovascular diseases and periodontitis and peri-implantitis (Froum et al., 2020) indicated that the literature supporting the hypothesis that CVDs cause peri-implantitis or vice versa is weak, and more studies are needed to further understand this mechanism.

2.6. Coronavirus disease 2019

Ever since the start of the coronavirus disease 2019 (COVID-19) pandemic originated by the severe acute respiratory syndrome coronavirus 2 and coronavirus disease 2019 (SARS-CoV-2), many oral lesions have been reported in patients infected with the virus. However, many of those lesions were incidental findings by healthcare professionals. A differentiation between lesions that were caused by the viral infection, a secondary manifestation of the systemic condition, or an outcome of treatment is yet to be known (Bhujel et al., 2021).

When it comes to periodontal health specifically, it has been found that the SaRS-CoV-2 virus can be detected in the subgingival environment of periodontitis patients (Natto et al., 2022). However, a low sensitivity was reported by this method as compared to nasopharyngeal swabs; this presentation would likely be similar in the peri-implant sulcus. The implication of this finding yet to be fully explored, as it could have a role in systemic inflammation. Interestingly, a case control study reported that patients with untreated periodontal disease could have an increased odd ratio (3.9) of developing life-threatening symptoms due to the infection when compared with treated periodontitis patients (Said et al., 2022). These findings need to be researched further in order to establish a relationship between the two diseases. Studies have reported that both peri-implantitis and COVID-19 cause an upregulation of IL-6 and these findings need to be further investigated to establish a relationship between the two conditions (Han et al., 2020; Rutkowski et al., 2020). Other factors to consider are the stress related to the pandemic that may impact periodontal and peri-implant health and the lack of regular maintenance appointments of the implant patient (Kadkhodazadeh et al., 2020).

3. Other factors

3.1. Biomaterials

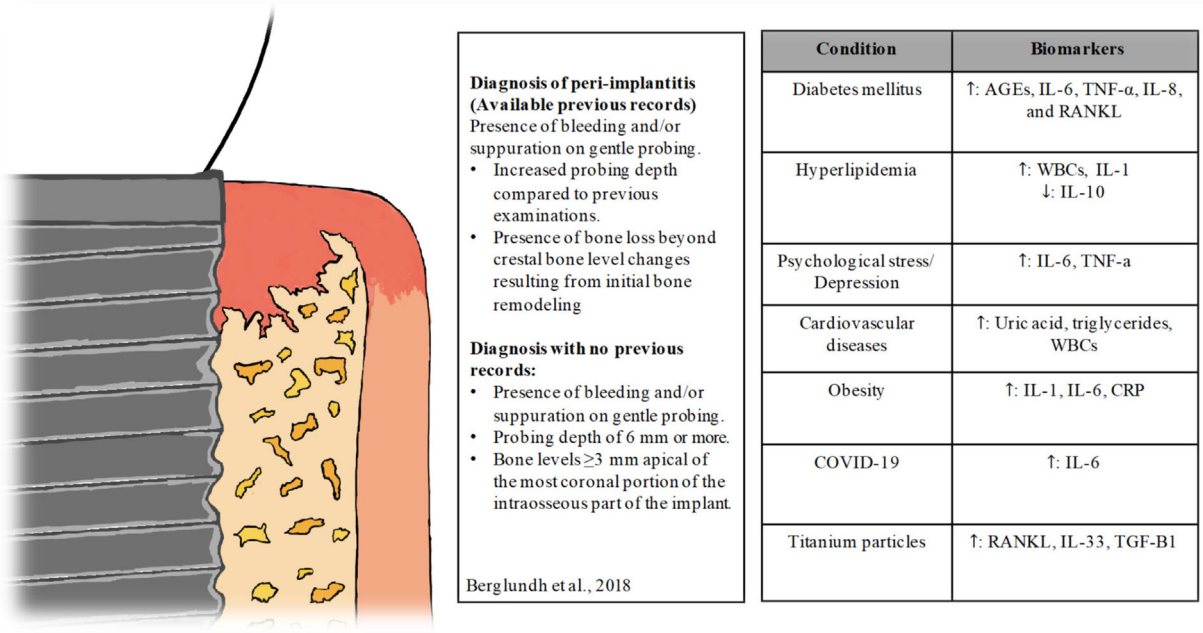
3.1.1. Titanium particles

Although titanium is considered a biocompatible material that promotes osseointegration (Adell et al., 1981), recent findings show that titanium particles could elicit an inflammatory response in the surrounding soft tissue and bone, contributing to peri-implantitis. This was investigated by Berryman et al., where they found that 90% of tissue specimens from areas adjacent to peri-implantitis lesions present with titanium particles. The inflammatory reaction was further looked into, and the areas with titanium particles presented with upregulation of RANKL, IL-33, and TGF-B1, which could have a role in the progression of inflammation and breakdown (Berryman et al., 2020). These findings are of utmost importance as healthy implants could present with titanium corrosion. In contrast, compromised implants are frequently decontaminated with physical or chemical methods that have been shown to produce surface alterations and disseminate titanium particles into the surrounding tissues (Kotsakis et al., 2021; Romanos et al., 2021).

Consequently, these findings should be interpreted with caution, as the current level of evidence cannot support or refute the fact that titanium particles play a role in the progression of peri-implantitis. Zirconia implants have been recommended as a solution to overcome the titanium particles' potential risk; however, there is a need for long-term studies (Cionca et al., 2017; Afrashtehfar and Del Fabbro, 2020).

4. Future diagnostics implications

Although clinical parameters such as probing depths, radiographic interpretation, bleeding on probing, and suppuration are widely accepted for diagnosing peri-implant conditions



Condition	Biomarkers
Diabetes mellitus	↑: AGEs, IL-6, TNF-α, IL-8, and RANKL
Hyperlipidemia	↑: WBCs, IL-1 ↓: IL-10
Psychological stress/ Depression	↑: IL-6, TNF-a
Cardiovascular diseases	↑: Uric acid, triglycerides, WBCs
Obesity	↑: IL-1, IL-6, CRP
COVID-19	↑: IL-6
Titanium particles	↑: RANKL, IL-33, TGF-B1

Fig. 1 Biomarkers found in both peri-implantitis lesions and systemic/localized inflammatory conditions. AGEs: Advanced glycation end products, TNF-a: Tumor necrosis factor-alpha, IL: Interleukin, WBCs: White blood cells, RANKL: Receptor activator of nuclear factor κ B, CRP: C-reactive protein, TGF-*B*: Transforming growth factor- Beta, ↑: Upregulation, ↓: Downregulation.

(Berglundh et al., 2018b; Monje et al., 2021), future research should investigate reproducible minimally invasive methods in diagnosing these conditions, and predicting their development (De Ry et al., 2021).

Biomarkers are becoming more critical as they can be utilized in many aspects of the treatment process (Fig. 1). This can be achieved by measuring cytokine levels (salivary, gingival crevicular fluid [GCF], and peri-implant crevicular fluid). Multiple studies have reported the presence of IL-1, IL-6, CRP, TNF-α, and other pro-inflammatory cytokines in salivary samples. The presence of IL-6 in peri-implantitis patients has been investigated, and the level increased when compared to healthy implants was reported (Liskmann et al., 2006). These techniques could also have a high value for prognostication purposes (Rakic et al., 2021; Afrashtehfar et al., 2022b, Touyz and Afrashtehfar, 2017). For instance, some of the measured markers could estimate disease outcomes and a possible response to treatment and guide clinicians during the treatment process. Furthermore, studies that assess inflammatory biomarkers around dental implants reported that there is an increase in the levels of IL-6, TNF-a, IL-8, AGE, and RANKL in peri-implantitis lesion when compared to healthy counterparts (Lv et al., 2022).

5. Future treatment implications

The resolution of peri-implantitis or peri-implant mucositis will result in an implant in a state of health, thus, potentially less systemic involvement and inflammation. In the meantime, the effectiveness of implant maintenance protocols has shown to be as essential as periodontal maintenance for the prevention and early detection of disease, even after surgical treatment of peri-implantitis, as some studies have shown that non-compliance to supportive therapy after surgical treatment could result in recurrence of the disease, and eventual loss of the implant (Costa et al., 2012; Roccuzzo et al., 2021).

An ample number of publications for peri-implantitis management use closed or surgical approaches with the adjunct use of laser treatment, host modulation, probiotics, resective approaches, or regenerative therapy (Bassetti et al., 2014; Nevins et al., 2014; Tada et al., 2018; Laleman et al., 2020; Monje et al., 2020;, Roccuzzo et al., 2020; Roccuzzo et al., 2022). Nonetheless, clinicians must be cautious when choosing a treatment modality, as most studies show promising results but lack long-term follow-up (Bassetti et al., 2014; Froum et al., 2016; Cosgarea et al., 2022). Therefore, more well-designed trials with longer follow-ups are needed to determine the feasibility and safety of the treatment approaches.

6. Final remarks

Based on the available evidence, it is clear that peri-implant inflammatory diseases are primarily caused by biofilm formation. Thus, removing biofilms is essential for maintaining the health of the surrounding tissues (Salvi et al., 2012; Berglundh et al., 2018a). However, it is important to consider other systemic factors during the treatment planning and maintenance of peri-implant health. While it is challenging to establish direct causality for peri-implantitis due to the difficulty of isolating confounding factors, current research suggests a correlation between inflammatory peri-implant diseases and systemic inflammation.

It is worth noting that emerging evidence supports the association between systemic inflammation and peri-implant diseases. However, further research is needed to fully comprehend the connection between these conditions and peri-implant infection. Future studies should determine the

extent of the relationship between systemic inflammation and peri-implantitis, focusing on the underlying mechanisms.

In summary, it is essential to recognize the role of biofilms in peri-implant diseases and consider systemic factors during the treatment planning and maintenance of peri-implant health. The current evidence suggests a correlation between inflammatory peri-implant diseases and systemic inflammation, but further investigation is needed to establish a causal relationship (Fig. 1). As research in this field continues to evolve, a better understanding of the pathophysiology of peri-implant diseases and their systemic implications will lead to improved treatment outcomes and better patient care.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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