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CLINICAL FEATURE  
REVIEW



## Chronic periodontitis, inflammatory cytokines, and interrelationship with other chronic diseases

Elsa Maria Cardoso <sup>a,b,c</sup>, Cátia Reis<sup>d</sup> and Maria Cristina Manzaneres-Céspedes <sup>e</sup>

<sup>a</sup>CICS-UBI, Health Sciences Research Centre, Faculty of Health Sciences, University of Beira Interior, Covilhã, Portugal; <sup>b</sup>Faculty of Health Sciences (FCS-UBI), University of Beira Interior, Covilhã, Portugal; <sup>c</sup>Instituto Politécnico da Guarda, Guarda, Portugal; <sup>d</sup>Instituto de Investigação e Formação Avançada em Ciências e Tecnologias da Saúde, CESPU, Gandra PRD, Portugal; <sup>e</sup>Human Anatomy and Embryology Unit, Departament de Patologia i Terapèutica Experimental, Health University of Barcelona Campus (HUBc), University of Barcelona, Barcelona, Spain

### ABSTRACT

Periodontal diseases, such as chronic periodontitis, share common inflammatory risk factors with other systemic and chronic inflammatory disorders. Mucosal tissues, such as oral epithelia, are exposed to environmental stressors, such as tobacco and oral bacteria, that might be involved in promoting a systemic inflammatory state. Conversely, chronic disorders can also affect oral health. This review will summarize recent evidence for the interrelationship between chronic periodontitis and other prevalent chronic diseases such as cardiovascular diseases, diabetes, cancer and chronic respiratory diseases. The association with pregnancy is also included due to possible obstetric complications. We will focus on inflammatory cytokines such as TNF-alpha, IL-1, and IL-6, because they have been shown to be increased in patients with chronic periodontitis, in patients with chronic systemic diseases, and in patients with both chronic periodontitis and other chronic diseases. Therefore, an imbalance towards a proinflammatory immune response could underline a bidirectional link between chronic periodontitis and other chronic diseases. Finally, we highlight that a close coordination between dental and other health professionals could promote oral health and prevent or ameliorate other chronic diseases.

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### Introduction

Periodontal disease contributes significantly to the global burden of oral diseases and shares common risk factors with several chronic diseases. Recently, the World Health Organization (WHO) highlighted the importance of strengthening the control of periodontal disease worldwide [1,2]. According to the WHO, chronic noncommunicable diseases, including cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes, remain the leading causes, about 70% of death globally [3]. In addition, periodontal disease is one of the most important oral diseases contributing to the global burden of chronic diseases and therefore represents a major public health problem [4]. In the present review, we will first summarize the current classification of periodontal diseases, and lately, we will focus the discussion on chronic periodontitis and cytokines in the context of common systemic chronic inflammatory diseases.

### Classification of periodontal diseases

Periodontal disease is a broad term for the spectrum of inflammatory diseases affecting the periodontium which comprises a set of structures that support the teeth: gingiva, cementum, periodontal ligament, and alveolar bone. In the 1999

classification system for periodontal diseases and conditions, over 40 different gingival diseases were listed, that were either dental-plaque induced or not associated with dental plaque [5]. In addition, other major categories of destructive periodontal diseases were listed and periodontitis can also be a manifestation of systemic diseases. An abbreviated version of the 1999 classification of periodontal diseases and conditions is shown in Table 1. Chronic periodontitis refers to the progression of the disease over time without treatment while aggressive periodontitis shows rapid attachment loss and bone destruction, and possible familial aggregation of disease. According to that consensus, both are subcategorized in local or generalized forms, depending on the percentage of tooth affected sites (above or below 30%) and regarding the severity of attachment loss (slight: 1 or 2 mm, moderate: 3 or 4 mm; severe  $\geq 5$  mm) [5,6]. The distinction between chronic and aggressive periodontitis is also based on several clinical features, namely age of onset, rates of progression, patterns of destruction, signs of inflammation, and relative amounts of plaque, and calculus [7]. However, the features of chronic periodontitis have been partially updated in 2014 by the American Academy of Periodontology (AAP) who have also announced that an update would commence in 2017 [8]. This AAP task force report addressed three specific areas of concern with the current classification: attachment level, chronic

**Table 1.** Abbreviated version of classification of periodontal diseases and conditions [5,6].

I.	Gingival diseases
II.	Chronic periodontitis
III.	Aggressive periodontitis
IV.	Periodontitis as a manifestation of systemic diseases
V.	Necrotizing periodontal diseases
VI.	Abscesses of the periodontium
VII.	Combined periodontic-endodontic lesions
VIII.	Development or acquired deformities and conditions

**Table 2.** Guidelines for determining severity of periodontitis [8].

	Slight (mild)	Moderate	Severe (advanced)
Probing depths	>3 and <5 mm	≥5 and <7 mm	≥7 mm
Bleeding on probing	Yes	Yes	Yes
Radiographic bone loss	Up to 15% of root length or ≥2 and ≤3 mm	16–30% or >3 and ≤5 mm	>30% or >5 mm
Clinical attachment loss	1–2 mm	3–4 mm	≥5 mm

versus aggressive periodontitis, and localized versus generalized periodontitis [8]. Accordingly, diagnosis of periodontitis is based on multiple clinical and radiographic parameters (Table 2), all of which may not be required. In general, patients would have periodontitis when one or more sites had inflammation (bleeding on probing, BOP), radiographic bone loss, and increased probing depth (>3 mm) or clinical attachment loss (CAL ≥1 mm) [8].

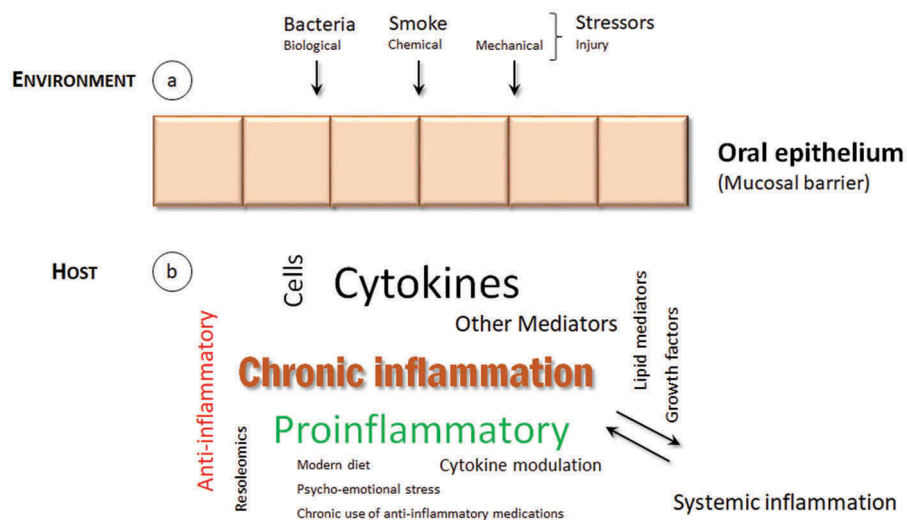
Patients with gingival recession or on periodontal maintenance therapy could present attachment loss, probing depth ≤3 mm, but with no signs of inflammation (no bleeding on probing). These patients should be diagnosed with a healthy but reduced periodontium [8]. However, if inflammation (bleeding on probing) is present, the diagnosis should be a reduced periodontium with inflammation, i.e. gingivitis. However, in patients with probing depth >3 mm and with

inflammation, the diagnosis should be periodontitis with severity according to guidelines shown in Table 2 [8]. This report recognized some features already published in 1999 consensus report that would help to differentiate chronic versus aggressive periodontitis. However, the clinician should base diagnostic decisions based on the patient history, clinical and radiographic signs (see ref 8). Regarding generalized chronic periodontic, AAP task force preferred the percentage of 30% affected teeth, instead of affected sites as an extent descriptor [8]. Nevertheless, as mentioned above, a comprehensive update is planned for the current year (2017).

### Chronic inflammation and cytokines in chronic periodontitis

Chronic inflammation is a complex biological process that occurs in response to infection and/or other triggers and leads to tissue injury [9]. Chronic periodontitis is a periodontal disease characterized by both dysbiosis of oral microbiota and proinflammatory events involving both cells and mediators from innate and adaptive immunity [10]. These events lead to chronic inflammation of periodontal soft and hard tissues sharing many features with other chronic inflammatory diseases [11,12]. Chronic inflammation is driven by various mediators, of which an important part is attributed to the interactions within cytokine networks. While proinflammatory cytokines, including IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$ , IL-6, and IL-17 contribute to acute and chronic inflammation and tissue injury, a second group with antagonist effects is formed by cytokines such as IL-10 [13].

Chronic periodontitis is characterized by deregulated inflammatory interactions, involving both innate and adaptive responses, that lead to a chronic inflammation in periodontal tissues [14]. As other mucosal surfaces, the periodontal epithelium is located at the interface between outside body environment and inside underlying connective tissue (Figure 1). From outside, it is firmly established that the principal trigger of

**Figure 1.** A conceptual framework for chronic inflammation in periodontal tissues.

Environmental stressors, (a), and host responses, (b), contribute to periodontal chronic inflammation. Several cellular and molecular factors are responsible for an imbalance towards a proinflammatory rather than anti-inflammatory immune response, that culminates into tissue injury. A bidirectional link with other systemic inflammatory diseases may operate and need to be further investigated.

chronic periodontitis is the presence of dysbiotic microbial communities with potential for destructive inflammation. However, in addition to periodontal microbiome influence, smoke is also an important factor underlying the development of periodontitis [15]. Other environmental stressors, either chemical or mechanical, that cause or promote oral inflammation, could have a role in the development of chronic periodontitis. This is still an unexplored research area and future investigation is needed to identify other relevant etiological factors. In the inside of the epithelial barrier, host genetic factors may predispose to or protect from disease. Finally, systemic health status and environmental factors that modify the host response have also been implicated in chronic periodontitis [15]. Overall, both environmental and host proinflammatory events favor a chronic state of inflammation in the periodontal tissues, that lead to injury and ultimately to bone resorption and tooth loss.

Extensive and detailed reviews on molecular and cellular aspects of cytokines in periodontitis have been published [13,14,16]. Cytokines might be divided into proinflammatory or anti-inflammatory groups and imbalances between their relative concentrations might lead to tissue destruction in chronic periodontitis [13,14]. Other mediators such as lipid mediators, growth factors, or chemokines have also an important role in the perpetuation of inflammation [17,18].

Thus, chronic periodontitis is characterized by a persistent inflammation of the periodontal tissues and is now considered a chronic noncommunicable disease that shares epidemiological associations and underlying inflammatory mechanisms with other systemic chronic inflammatory diseases [18–20]. Several potential therapies, ranging from diet to cytokines, capable of suppressing inflammation warrant to for further investigations (Figure 1) [17,21,22]. Cytokine-based treatment strategies have potential to improve both chronic periodontitis and systemic health [23–26]. However, given the complexity of cytokine networks, we believe that it is fundamental to investigate further their role in the chronic periodontitis disease process. The understanding of the equilibrium between inflammatory (proinflammatory) and suppressor (anti-inflammatory) responses, integrated with both internal and external environmental factors, could bring improved therapeutic interventions to modulate host responses in chronic periodontitis and other chronic inflammatory diseases.

### **Chronic periodontitis and systemic diseases**

The evolution of healthcare in the last century has led to improvement in the treatment of several diseases, leading to an increased quality and life expectancy of patients. Dental care and oral health is also a key factor involved in the improvement of patients' health. Indeed, in the recent Tokyo Declaration on dental care and oral health for healthy longevity [27], it was recognized that maintenance of oral and dental health through life is a fundamental factor for improved quality of life, helping to protect against noncommunicable diseases and contributing toward preventing the aggravation of such diseases. Dental associations and other health professionals around the world are encouraged to facilitate and enhance

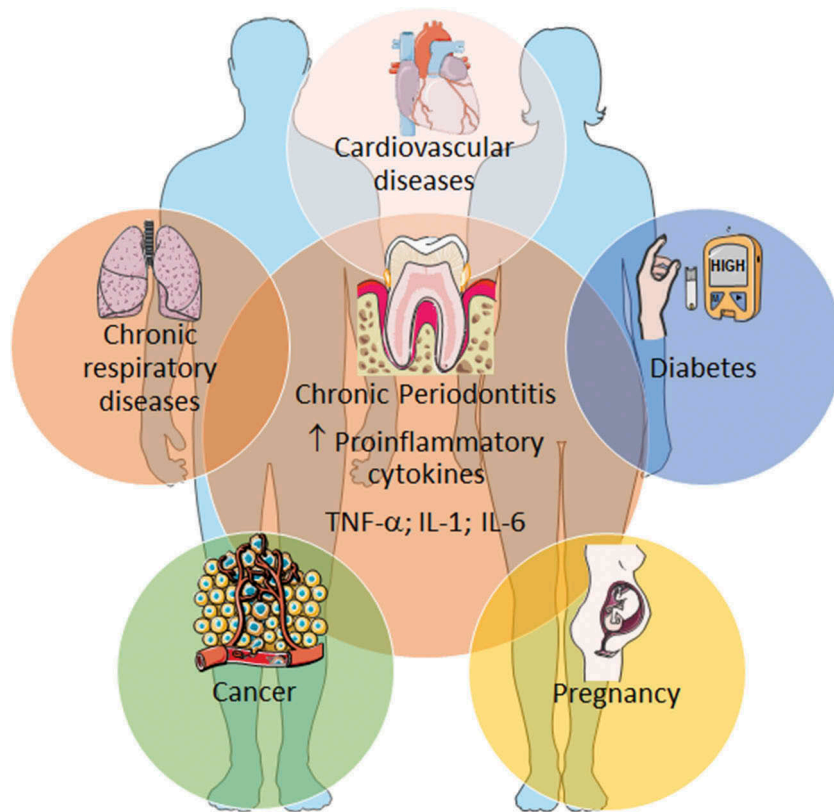
coordination of activities to increase global awareness of and contribute to the implementation of WHO's Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020 [27]. Periodontal and systemic diseases share many features of inflammaging and seem to be intertwined diseases [28,29].

Hence, the association between chronic periodontitis and systemic illnesses may be bidirectional. One mechanism that has been proposed for chronic periodontitis as a risk factor for other systemic diseases, comprises systemic dissemination of oral bacteria and inflammatory mediators, that are capable of initiation and maintaining mechanisms associated with the development of chronic systemic diseases [15]. Although several systemic diseases (e.g. rheumatoid arthritis, renal diseases, neurodegenerative diseases) show associations with chronic periodontitis, in this review we will focus on the most prevalent noncommunicable diseases (cardiovascular, diabetes, cancer, and respiratory disease) and on pregnancy complications. Moreover, we will also give emphases to the proinflammatory common systemic mediators such as TNF- $\alpha$ , IL-1 and/or IL-6. Interestingly, we have shown that these cytokines were increased in gingival crevicular fluid in patients with chronic periodontitis who did not have chronic systemic diseases (Figure 2, chronic periodontitis at the center) [30].

### **Chronic periodontitis and cardiovascular disease**

In a recent report of the Joint EFP/AAP workshop on periodontitis and systemic diseases, it was concluded that there is a consistent and strong epidemiologic evidence that periodontitis imparts increased risk for future cardiovascular disease [31]. It was also concluded that although *in vitro*, animal and clinical studies do support interaction and biological mechanisms, still, well-design intervention trials to investigate the impact of periodontal treatment on prevention of atherosclerotic cardiovascular disease, are a needed.

Vascular diseases are nowadays recognized to have a strong local and systemic inflammatory pathogenic contribution. In atherosclerosis, along with the accumulation of cholesterol debris on the artery wall, it is well established that immune reactions and the participation cells and mediators such as cytokines are implicated in the immunopathogenesis of vascular diseases [32]. Among several factors, inflammatory cytokines such as TNF- $\alpha$ , IL-1, and IL-6, have been shown to be secreted by infiltrating leukocytes or by foam cells [33]. Parallely, several investigations have demonstrated the importance of chronic infections in the atherosclerotic process, namely by inducing a systemic inflammatory state and of autoimmunity [33–36]. Some microbes can cause persistent infection in the vessel wall and promote a proinflammatory environment. Alternatively, the infection may also induce autoimmunity against vascular cells and lead to atherosclerotic process [37]. In this context, chronic periodontitis and its chronic inflammatory nature are associated with an increased risk for cardiovascular disease [38]. Bacteremia and an inflammatory systemic state associated with chronic periodontitis are important factors in the initiation of the endothelial lesion as well as in the potentiation of the vascular wall inflammatory



**Figure 2.** Chronic periodontitis and some common systemic diseases.

Chronic periodontitis shares several associations with numerous chronic inflammatory diseases. Proinflammatory cytokines are, among other factors, important immune-related mediators involved in the disease pathogenesis. Only the most common noncommunicable diseases and pregnancy complications were exemplified, although others (rheumatoid arthritis, neurodegenerative disorders, etc.) exhibit also associations with chronic periodontitis. Illustration adapted medical elements from Servier Medical Art <http://smart.servier.com/>, with permission to reproduce under the Creative Commons Attribution 3.0 Unported License <https://creativecommons.org/licenses/by/3.0/>

process [39–41]. The inflammatory process is also modulated by proinflammatory cytokines such as TNF- $\alpha$ , IL-1, and IL-6 both in chronic periodontitis and in cardiovascular diseases (Figure 2) [42]. Finally, some studies demonstrate a decrease on systemic inflammatory biomarkers following periodontal treatment and consequent possible benefit in the reduction of cardiovascular risk [43–46]. However, while there is evidence suggesting that periodontal therapy reduces systemic inflammation and improves endothelial function, evidence on its effects on cardiovascular events in long term is still limited [43] and further studies are needed. Accordingly, a recent publication of American Heart Association (AHA) stated that although periodontal interventions result in a reduction in systemic inflammation and endothelial dysfunction in short-term studies, there is no evidence that they prevent atherosclerotic vascular disease or modify its outcomes [47].

### **Chronic periodontitis and diabetes**

Association between chronic periodontitis and diabetes is known for a long time, and it has a bidirectional association. On one hand, diabetes is a modifier factor of chronic periodontitis, and, on the other hand, periodontitis is a complication of diabetes [42,48,49]. Several studies showed a higher prevalence of periodontitis in diabetic patients, as well as a higher periodontal disease severity in diabetic patients [50–52]. The pathophysiological mechanisms involved appear to be a result

of chronic hyperglycemia resulting in decreased macrophage and neutrophil function, accumulation of advanced glycosylation, and inflammation [53]. In contrast, there is also evidence that concomitant presence of periodontitis impairs glycemic control in diabetics, thereby increasing the risk of other complications in diabetes [54–56]. Proinflammatory mediators, such as TNF- $\alpha$ , IL-1, and IL-6 that are increased in both diseases, represent a fundamental linkage (Figure 2) [52,53,57]. In addition, the interindividual variability in both diseases is likely to be influenced by genetic, epigenetic, and environmental factors [52].

Periodontal treatment has been shown to be associated with an improved glycemic control [58–60]. However, in spite of a modest reduction in HbA1c observed as a result of periodontal therapy in subjects with type 2 diabetes, there is limited confidence in the conclusion due to a lack of multicenter trials of sufficient sample size [60,61].

### **Chronic periodontitis and obstetric complications**

Maternal infections associated with systemic inflammatory states, where we may include chronic periodontitis, appear, according to the literature, to contribute to a higher risk of obstetric complications, such as premature births and low birth weight. During pregnancy, the hormonal changes increase vascular permeability in the gingival tissues that facilitate the diffusion of pathogenic microorganisms and their



products into the circulation and to the placenta. Here, they may stimulate immune and inflammatory responses leading to a high secretion of proinflammatory cytokine levels in the fetal tissues and can lead to the premature rupture of membranes and lead to uterine contractions, which in turn can cause miscarriage or premature delivery [62]. Several meta-analysis and systematic reviews reaffirm the association of periodontitis with this complication [62–66]. One of the mechanisms implicated may be mediated by elevated levels of proinflammatory cytokines (Figure 2) [62,67–69].

In addition, some studies have also demonstrated the presence of periodontal pathogenic microorganisms in the amniotic fluid in women with periodontitis, and a correlation between the severity of periodontitis and the risk of preterm birth was found [62,70,71].

Several studies have sought to determine if there is a benefit of periodontal treatment in women at risk for obstetric complications, and although there is no consensus among the various studies [72], it seems to be good practice to apply preventive strategies in these women [73–75].

### **Chronic periodontitis and cancer**

An increased risk of various neoplasms has been associated with chronic periodontitis, namely oral cancers [76] and squamous cell carcinoma [77]. However, a deficient control of variables such as the history of tobacco and alcohol use, and oral human papillomavirus infection limits these results [78]. There is also an increasing interest in the link between periodontal disease and overall cancer risk, with systemic inflammation serving as the focus for biological plausibility. In a recent meta-analysis provided support for a positive association between periodontal disease and risk of oral, lung, and pancreatic cancers. However, future studies should include sufficiently large sample sizes, improved measurements for periodontal disease, and thorough adjustment for smoking and other risk factors [79]. Interestingly, currently, there is a large body of evidence demonstrating that inflammation profoundly affects all phases of cancer, from initiation at the single-cell level, to early growth, progression, and dissemination [80,81]. Another emerging concept is that cancer, like most diseases, is a systemic rather than a local disease. Systemic inflammation in a functional relationship with energy metabolism and genetic instability predisposes individuals to cancer and regulates the neoplastic disease [80]. Cytokines that are known to be elevated in chronic periodontitis, such as TNF- $\alpha$ , IL-1, and IL-6, have been shown to promote breast cancer and other cancers (Figure 2) [81,82].

### **Periodontitis and chronic respiratory diseases**

There is emerging evidence for an association between periodontal disease and pneumonia or chronic obstructive pulmonary disease (COPD). The oral cavity is a reservoir for pulmonary infection and there is some evidence that chronic periodontitis may be associated with risk for pneumonia [83–85]. It is likely that oral bacteria present in the dental plaque are shed into saliva and are then aspirated into the lower respiratory tract and the lungs to cause infection.

Additionally, cytokines and enzymes induced from the periodontally inflamed tissues by the oral biofilm may also be transferred into the lungs where they may stimulate local inflammatory processes preceding colonization of pathogens [86]. Several works demonstrated that application of strategies to reduce oral microbial burden are associated with a lower risk to develop pneumonia [83,87,88]. COPD is a group of diseases characterized by the pathological limitation of airflow in the airway, including chronic bronchitis, and emphysema [89]. COPD and chronic periodontitis share common risk factors such as cigarette smoke, age, and poor socioeconomic status [90]. Moreover, some studies supported an association between chronic periodontitis and COPD although large-scale prospective epidemiological studies are needed [78,91]. COPD and chronic periodontitis share some proinflammatory mediators that may facilitate disease progression of both pathologies (Figure 2) [90,92]. Interestingly, in a pilot trial, it has been shown that periodontal therapy in COPD patients with chronic periodontitis may improve lung function and decrease the frequency of COPD exacerbation [93].

### **Conclusion**

Like to other human body borders, such as the gut, maintaining a healthy oral mucosa may also have a positive impact on the host health and might be preventive for other systemic inflammatory disorders. Thus, it is important to encourage further integrated studies to investigate the interrelationship between inflammation, oral mucosal, and systemic chronic diseases.

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### **Declaration of interests**

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

### **ORCID**

Elsa Maria Cardoso  <http://orcid.org/0000-0002-6937-6474>

Maria Cristina Manzanares-Céspedes  <http://orcid.org/0000-0002-4585-4953>

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