Chapter

Cytokines' Involvement in Periodontal Changes

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Abstract

The bacterial challenge on the periodontal tissues triggers an inflammatory reaction, driven by pro-inflammatory cytokines, that eventually leads to the periodontal structures' damage. The pathogenic mechanisms of this inflammatory reaction are complex and are influenced by the type of host-immune response and certain local and systemic factors. These factors can influence periodontal inflammation, through the action of the various pro-inflammatory cytokines. Periodontal disease and certain systemic conditions can have a mutual association, as the pathogenic mechanisms of these diseases can involve similar molecular and cellular elements. The concept of 'periodontal medicine' comprises these pathogenic connections, focusing on the key role that periodontal health has on the general homeostasis and well-being.

Keywords: periodontal disease, cytokines, inflammation, systemic conditions, associations

1. Introduction

Periodontal disease is defined as an immune, inflammatory disease with a triggering bacterial factor [1]. Its initial phase is characterised by damage to soft gingival tissue (inflammation of gums, gingivitis, plaque accumulation), followed by degradation of the periodontium (chronic inflammation, colonisation by periodontal pathogenic anaerobes) and the surrounding connective tissue matrix of teeth, along with alveolar bone loss, local citrullination, bone resorption and rapid loss of teeth, in the destructive phase [2].

It is considered a multifactorial disease with progressive evolution and pathophysiological mechanisms that involve the association of environmental factors (smoking, stress), microbial factors (several bacterial species, for example, *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, *Aggregatibacter actinomycetemcimtans*), and genetic polymorphism (human leukocyte antigen-antigen D, HLA-DR, HLA-DRB1; IL-1, IL-6 and IL-10 gene polymorphism) with

the inflammatory and immune response (both innate and adaptive immunity) of the host (**Table 1**) [3, 4]. These mechanisms will lead to defective host defences, which will contribute to changes in tissue homeostasis, inflammation and bone loss, the main features of periodontal disease (**Figure 1**) [2].

General function	Type	Specific function	Periodontal implication
Pro-inflammatory	IL-1β	Increases production of other pro-inflammatory mediators (PGE2, IL-6); stimulates neutrophil activity	Key role in the pathogenic processes; enhances alveolar bone-resorption; fuels the inflammatory reaction
	IL-1α	'Alarmin' for tissue damage and immune system; interacts with TNF-α; induces protease synthesis	Enhances alveolar bone-resorption by signalling the presence of bacterial antigens and enhancing the inflammatory response
	IL-6	Regulates cell growth and differentiation: osteoblasts, B and T lymphocytes	Impairs osteoblast growth and function; increases osteoclast formation from monocytes
	IL-18	Increases neutrophil activity and interferon gamma production	Influences lymphocyte Th1/Th2 differentiation; interacts with IL-1β
	IL-33	Activates Th2 and mast cells; stimulates production of IL-5, IL-13 by Th2 cells	Induction of RANKL; induces periodontal damage by stimulation of Th2 cells
	TNF-α	Major regulator of immune cells' activity; involved in the acute phase reaction	Stimulates damage (by osteoclasts) and prevents repair of periodontal tissues (by fibroblast death); starts IL-1β, PGE_2 synthesis
	PGE_2	Increases production of other pro-inflammatory mediators (MMPs); induces fever	Contributes to bone resorption by increasing osteoclast activity
	MMPs (-1, -8, -9)	Enzymatic degradation of collagen (and other extra-cellular matrix proteins). Stimulated by IL-1β and TNF-α. Influences immune cell migration and adhesion	Periodontal damage by impairment of collagen type I production and degradation of structural collagen; causes activation of osteoclasts and damage to connective tissue
Anti-inflammatory	IL-1Ra	Inhibits IL-1β, IL-1α activity by preventing cellular signalling	Limits alveolar bone-resorption; regulates response to antigens (LPS)
	IL-10	Decreases cytokine production by immune cells; reduces inflammatory response	Down-regulates periodontal inflammation by reducing cytokine synthesis in immune cells
	IL-4	Stimulates tissue repair and regulates immunity; regulates differentiation of Th2 cells	Decreases production of Th2 cells, with important implications to periodontal damage
	TGF-β	Enhances epithelial regeneration/repair	Stimulates gingival fibroblast activity

Table 1.
Mediators' role in general and periodontal inflammatory reactions [3].

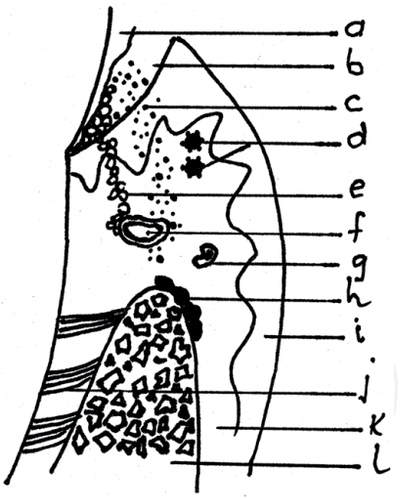

Figure 1.
The periodontium and its inflammatory reaction in periodontal disease: a—bacterial plaque deposits; b—gingival sulcus; c—inflammatory mediators (interleukins—ILs, matrix-metalloproteinases—MMPs, tissue inhibitors of MMP—TIMPs); d—lymphocytes type B and T; e—polymorphonuclear cells; f—blood vessel; g—macrophage cells; h—osteoclast cells; i—gingival epithelium; j—periodontal ligament; k—gingival connective tissue; and l—alveolar bone.

Pathophysiological processes are explained by the participation of a wide range of locally released soluble factors such as pro-inflammatory cytokines, prostaglandin E2 and reactive oxygen species, inflammatory mediators that can be highlighted by various methods within gingival tissues and within the gingival crevicular fluid (GCF) [5]. The association between elevated TNF-α and IL-6 concentrations and disease activity was also highlighted [6]. It has been shown that IL-1β and interferon-gamma (IFN-γ) have elevated concentrations in active periodontal lesions [7]. IL-12, a key-acting cytokine mediating Th1 differentiation, also implicated in cell-mediated immunity, has been observed to stimulate pro-inflammatory proteins involved in bone resorption [8].

A deficiency in the synthesis and release of anti-inflammatory cytokines can also occur, like type Th2 cytokines (IL-4, IL-5, IL-13), IL-10 and transforming growth factor beta 1 (TGF-β1), which confirms the existence of an imbalance between pro- and anti-inflammatory mechanisms at periodontal level [9]. Along with TNF-α, IL-1β and IL-6, the release of the cytokines IL-8, IL-11, and IL-17 has also been revealed within GCF, which has potent osteoclastogenesis stimulating effects and also reduces osteoprotegerin synthesis in osteoblasts and stromal cells [10].

Periodontal disease can be influenced by certain local factors, such as orthodontic therapy and the existence of coronal or prosthodontic restorations, and by certain systemic diseases, this may interfere with the periodontal inflammatory reaction, by means of pro-inflammatory cytokines. These diseases include diabetes mellitus (type 1 and 2), cardiovascular diseases, rheumatoid arthritis and hepatic and renal conditions. The interactions between periodontal tissues and their pathology and these systemic diseases have been reunited under the concept of 'periodontal medicine' [11]. Considering this concept, the chapter aims to exhibit the major implications of cytokines into the pathogenic mechanisms of periodontal disease and its local and systemic influencing factors.

2. Methodology

The design of the chapter has been created in order to reflect the role of cytokines in periodontal pathogenic processes, as both local and systemic risk factors for

periodontal disease have been taken into consideration. The information is divided between the influence of local elements—orthodontic and restorative treatments, and systemic ones—diabetes mellitus type 1 and 2, cardiovascular, rheumatic, hepatic and renal diseases. Relevant scientific information has been sourced from the existing scientific literature and structured so as to pursue the established purpose of the chapter.

3. Local influences on the periodontal inflammatory reaction

3.1 Orthodontic influences

The orthodontic dental movement is the consequence of the application of controlled mechanical forces on the teeth [12], the periodontal ligament (PDL) being the one that mediates the task to which the teeth and the alveolar bone are subjected and creates the conditions for the cells to participate in bone remodelling [13]. Orthodontic forces distort the PDL matrix, causing the cellular form and cytoskeleton configuration to change, with neuropeptides release from the afferent nerve terminals [14], while the orthodontic forces can induce a biomolecular-level release of growth factors, prostaglandins and pro-inflammatory cytokines as IL-1, IL-6, IL-8 and TNF-α, that affect alveolar bone remodelling [15]. At present, the molecular mechanisms underlying bone formation, induced by stretching forces, are not fully understood [16]. The initial phase of orthodontic dental movement always involves an aseptic acute inflammatory reaction [17], which lasts for 1–2 days and is predominantly exudative, followed by a chronic, mainly proliferative process [18] and increased release of cytokines [19], such as TNF-α, TNF-β, IL-1, PDGF, INF-γ and RANKL [15, 20].

Inflammatory cytokines are involved in all phases of inflammation during orthodontic treatment [21]; pro-inflammatory and anti-inflammatory cytokines act synergistically or antagonistically on each other [22]:

- *IL_1 family*: all 3 ligands of the IL-1 family (IL-1α, IL-1β, and IL-1RA) are involved in bone metabolism and orthodontic dental movement [22], as well as IL-1 gene polymorphisms [23]. IL-1β along with TNF-α is a key pro-inflammatory cytokine in acute-phase inflammation [24]. IL-1β gathers leukocytes and activates fibroblasts, endothelial cells, osteoclasts and osteoblasts in order to stimulate bone resorption and to stop bone formation [25]. IL-1β is also a PGE inducer and, along with mechanical stress, synergistically regulates the formation of PGs in periodontal cells [26]. The levels of IL-1β and PGE2 are higher in the tension zones compared to compression zones, which supports the hypothesis that during the initial stage of orthodontic treatment, this cytokine would originate from osteoclasts in response to mechanical stress [27].

- *IL-1RA* acts by limiting the inflammatory conditions [28] mediated by IL-1 and bone resorption [22], and therefore positive correlations exist between decreasing IL-1RA levels in GCF and faster bone resorption during orthodontic dental movement and consequently a higher dental movement speed [29].

  The tooth movement speed is influenced by stress and by levels of IL-1RA, IL-1β and IL-1 gene polymorphisms from GCF. These factors provide a better predictive model for the efficiency of dental movement: activity index [AI = experimental (IL-1β/IL-1RA)/control (IL-1β/IL-1RA)], IL-1RA concentration in GCF and IL-1β genotype [29].

- *IL_6*: IL-6 has a stimulating effect on bone remodelling and osteoclast formation [30] and also in the inflammation associated with orthodontic dental movement [31].

- *IL_8*: IL-8 has a role in the neutrophils' recruitment and activation in the presence of inflammation [32], in improving RANKL expression and consequently in increasing the osteoclast production and their activation [33]. Immediately after the application of mechanical forces, IL-8 has an increased level in both pressure and tension zones [34], but later on, the stimulation of IL-8 secretion only continues in the tension zones; this differential regulation probably plays a major role in the initial stage of bone remodelling [34].

- *TNF-α*: TNF-α binds with macrophage colony-stimulating factors to induce osteoclast differentiation [35].

- *IFN-γ*: IFN-γ increases during late stages of orthodontic dental movement [35], controlling massive osteoclastogenesis [36] related to the increased volume of trabecular bone [37].

The levels of cytokines in the GCF vary with the type and intensity of the applied force, speed of tooth movement, the age of the orthodontic device owner [24] and growth [38]. Equivalent force systems during orthodontic dental movement induce an individualised production of different cytokines [39]. Light continuous forces tend to maintain relatively high levels of IL-1β [29], needed for the continuation of periodontal remodelling, longer periods allowing a reduced frequency of reactivations [38]. A strong force may increase the risk of root resorption and hyalinization of PDL and may also modify the cytokines' level, causing unwanted tissue reactions and the need for multiple reactivations [40]. The increase of IL-1β's level in GCF, as a result of the increased applied force, was also associated with intense pain during orthodontic dental movement [38], probably due to the correlation between IL-1β and substance P [41]. Most studies did not detect differences between the levels of cytokines in the tension and pressure zones [29, 34], probably due to the continuous circulation of GCF in the periodontal ligament. Consequently, it can be concluded that GCF cytokine levels cannot be specific indicators of periodontal remodelling in tension and pressure zones [42].

External apical root resorption (EARR), secondary to orthodontic dental movement, is a frequent clinical complication, and treatment variables, environment factors and/or inter-individual genetic variations may give susceptibility or resistance to its occurrence [43]. Among pro-resorptive cytokines, IL-6 promotes osteoclastic function [44] and amplifies the production of fibroblasts from gingival fluid and periodontium [45], having increased levels in patients with severe dental root resorption [46]. IL-7 acts indirectly on osteoclastogenesis by induction of TNF-α [47]. The increase of IL-6, IL-7 and TNF-α level might be a sign of a continuous remodelling of the periodontal tissues during the lag phase of tooth movement and a mechanism of cellular prohibition [48].

Regarding anti-resorptive cytokines, the levels of IL-4 and IFN-γ increase closely following IL-1β's elevation. This cytokine's expression type may result as an active combined remodelling of periodontal tissue, during the first stages of dental movement and also of cellular prohibition mechanisms, preventing activation and additional differentiation of osteoclastic cells [48] and suppressing osteoclastogenesis, unlike T cells of RANKL that induce osteoclastogenesis [49]. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is also an anti-resorptive cytokine that prevents bone resorption together with IL-4, IL-10, IL-13, IL-18 and IFN-γ [50].

3.2 Restorative influences

The interplay between periodontology and restorative dentistry exists on many levels and functions, in both directions [51]. For example, interproximal restorations, fixed prosthesis and artificial crowns can be involved in the occurrence and progression of gingival inflammation and periodontal destruction [51]. The presence of dental restorations or other appliance, near or below the gingival margin, which reach deep into the gingival sulcus or within the junctional epithelium, may induce localised inflammation that could lead to future periodontal complications [51].

The most reliable mechanism by which the subgingival margins of restorations lead to gingival inflammation and loss of attachment is the increase of plaque accumulation. In these conditions, the rate flow of gingival fluid will increase, because the gingival fluid protects oral tissues (including the junctional epithelium) against the bacterial invasion, acting as a defensive barrier, within the gingival sulcus [52]. IL-1, prostaglandin E2 (PGE_2) and the elements that affect collagen and bone (matrix metalloproteinases (MMPs)) that are detected in gingival fluid can be used as possible indicators for the diagnosis of periodontal disease and its progression [2]. The placement of restorative posts can induce trauma to periodontal structures, mostly in the case of metallic posts and less for the fibre ones, leading to periodontal inflammation [53]. IL-1 family cytokines regulate the activity of other pro-inflammatory cytokines, such as PGE2 and MMPs, their gingival fluid levels being proportionate with the degree of bone loss [10].

The placement of the gingival margins of restorations depends on the position of the decayed portion of the tooth and the extent of caries. The materials used in restorations must not be injurious to periodontal tissues, as they should have highly polished surfaces, the periodontium reacting to the roughness of the material and its accumulation of plaque by inflammation. However, it has been shown that the composition of restorative materials could also initiate periodontal changes, by monocyte activation and changes of the gingival fluid levels of cytokines [54]. It has been observed that periodontal inflammation can occur in areas of the gingival tissue which are adjacent to ceramic, composite or amalgam coronal restorations, even if there are no signs of bacterial plaque accumulation. This may be explained by the stimulation of periodontal neurogenic inflammatory reactions that is caused by these restorative materials. However, these findings are controversial and require further research, as it has been reported that only class V composite fillings can trigger such forms of gingival inflammation, in the areas of their vicinity [55].

Ceramic materials have the lowest plaque retentive capacity, but inner materials of porcelain-fused-to-metal (PFM) crowns can impact periodontal tissues [56]. Certain non-noble metals could have a negative impact on periodontal tissue (Ni-Cr alloy, Co-Cr alloy). It seems that the Au-Pt alloy is least harmful for the periodontium. The spaces between the margins of the restoration, as well as their contour are other contributing factors to gingival inflammation and periodontal destruction, referred to as iatrogenic factors. Restoration margins have been reported as key factors for periodontal health [57]. Another feature referring to periodontal damage is the dental impression that needs to offer a clear image and perspective of the prepared teeth, the neighbouring teeth and the associated gingival tissue. Impressions of tooth preparations with an elastic material that extends subgingivally could damage soft tissues. In order to prevent this, the retraction cord is frequently used during impression taking [58]. Successful restorative and prosthetic treatments require a healthy periodontium, as a start point of therapeutic protocols [51].

4. Systemic pathologic influences on the periodontal inflammatory reaction

4.1 Type 2 diabetes

The relationship between type 2 diabetes mellitus (T2DM) and chronic periodontitis is bidirectional [59]. The deleterious effect of chronic hyperglycemia on the occurrence and progression of periodontitis has been observed in patients suffering from both diseases [59]. Among the factors involved in the pathogenesis of periodontitis in patients with T2DM are the advanced glycation end products, chronic inflammation, altered secretion profile of cytokines, decrease of the immune response to infection and also the exacerbation of bacterial flora at periodontal level [59].

Recent evidence has suggested the role of periodontitis in the pathogenesis of insulin resistance, the adverse effects of periodontitis on glycemic control, and the contribution to the occurrence and progression of chronic diabetic complications [60]. The link between periodontitis and T2DM is potentially explained by the increase of pro-inflammatory cytokines, such as IL-1β, IL-8, IL-6, TNF-α, IL-12, and leptin and decrease of anti-inflammatory cytokines such as IL-4, IL-11, adiponectin and fibroblast growth factor-21 [60, 61].

The assessment of cytokine levels within the gingival crevicular fluid indicated that subjects with T2DM and chronic periodontal disease have significantly higher levels of IL-1β, IL-6 and TNF-α than healthy participants with similar periodontal conditions [59]. The levels of IL-8 within the gingival crevicular fluid and plasma have been evaluated with contradictory results in the context of T2DM and chronic periodontitis, multiple studies reporting that the IL-8 level is higher in patients with T2DM and chronic periodontitis compared to non-diabetic subjects with or without chronic periodontitis [60, 62].

The systemic inflammatory response depends on the ratios of pro-inflammatory to anti-inflammatory cytokines. The patients with T2DM and chronic periodontitis tend to have higher ratios of pro-inflammatory to anti-inflammatory cytokines compared to periodontally and systemically healthy controls [63]. Thus, TNF-α/IL-4, IL-1β/IL-4, IL-23/IL-4, IL-6/IL-4, TNF-α/IL-5, IL-17/IL-5 and IL-6/IL-5 ratios were higher in T2DM patients with chronic periodontitis than in healthy subjects [64].

The literature regarding the systemic plasma cytokine profile's characteristics in patients with T2DM and chronic periodontitis is not consistent. Some reports indicated lower levels of cytokines, including IL-4, IL-5, IL-6, TNF-α, IL-1β, IL-17, IL-13, IFN-γ, IL-2, IL-23 and IL-12 and higher levels of IL-8 in serum samples of T2DM patients with chronic periodontitis than for the control group [60, 63]. There are other studies showing that the systemic levels of some cytokines, such as IL-4, IL-8, IL-6, IL-10 and TNF-α, did not differ between diabetic and non-diabetic subjects with periodontitis [62, 64].

The improvement of glycemic control after periodontal therapy may be explained by the fact that periodontal treatment relives the periodontal inflammatory reaction and further decreases systemic pro-inflammatory cytokines' involvement in the pathogenesis of insulin resistance [65]. Reduction of the pro-inflammatory cytokines such as IL-1β and IL-6 in gingival crevicular fluid and improvement of glycemic control after periodontal therapy was reported in T2DM patients [66]. Furthermore, a significant decrease in serum levels of IL-6 and TNF-α and also a reduction of HbA1c in patients with T2DM were reported after periodontal therapy, indicating the impact of periodontal intervention on periodontal and systemic inflammation related to insulin resistance [65, 66]. Recent findings

show that reducing periodontal inflammation by periodontal therapy may contribute to an increase of systemic anti-inflammatory cytokines, such as adiponectin and fibroblast growth factor-21 levels, and to a decrease of leptin levels, thus improving insulin sensitivity [65].

As high levels of pro-inflammatory cytokines have been reported at periodontal level, associated with increased risk of destructive effects within the periodontal tissues [67], it was shown that diseases characterised by insulin resistance like T2DM are also associated with the increase of cytokines [68, 69]. Chronic periodontitis may influence systemic cytokines in T2DM. The literature documents the role of cytokines TNF-α, IL-1β, IL-4, IL-6 and IL-10 in chronic periodontitis and T2DM [70].

Pathogenic links between periodontal disease and diabetes involve elevations in IL-1β [71], TNF-α, IL-6, RANKL-b, oxidative stress and Toll-like receptor (TLR) expression. It has been demonstrated that prolific circulatory mediators have higher levels in the association of diabetes with a form of periodontal disease, especially TNF-α, C-reactive protein (CRP) and mediators of oxidative stress, which in turn can affect the control of diabetes. Moreover, complete and correct periodontal treatment can improve serum levels of CRP and TNF-α in patients affected by diabetes [65, 72].

The release of inflammatory mediators that can be detected in GCF stimulates the secretion of metalloproteinases, initiates bone resorption processes and plays an important role in the evolution and prognosis of periodontal disease. Inflammatory cytokine and chemokine levels in GCF decreased after initial periodontal therapy [73]. In periodontitis, concentrations of pro-inflammatory cytokines TNF-α and IL-8 increased not only in periodontal tissues [74] but also in serum samples [62].

4.2 Type 1 diabetes

The existence of a bidirectional relationship between periodontal disease and type one diabetes (T1D) has long been considered [75]. Periodontal breakdown is a pivotal aggravating factor for the health status in subjects with T1D, mainly because this preserves a chronic systemic inflammatory condition, contributing therefore to diabetic complications [75]. In fact, periodontitis has been considered to be the sixth complication of diabetic disease, diabetic metabolic impairment being in turn able to point toward a poor periodontal health status. Being not only a metabolic misbalance, but also tightly associated to an important dysfunction of the immune system, several facets of the systemic immune response, such as antigen challenge or polymorphonuclear leukocyte and T-lymphocyte function are altered in diabetic subjects [76].

Hyperglycemia can lead to immune system disorders; hence, the effects mediated by cytokine alterations in patients with T1D might be significant. IL-1β levels in gingival fluid and those of IL-6 in saliva have been correlated with glycosylated haemoglobin [77]. The changes in the cytokine amount on the systemic level are crucial in the pathogenesis of diabetes and can condition the islet cell turnover and apoptosis, with subsequent disease progression toward devastating complications, as macro- and microvascular modifications [78].

Regarding the involvement of cytokines in the immune-inflammatory response in subjects with T1D and periodontal breakdown, the literature highlights the enhancement of IL-1β, IL-6 and prostaglandin E2 in the gingival fluid of these patients, compared to systemically healthy subjects, with comparable periodontal alteration [79, 80]. The results on experimental murine models of induced diabetes include data on a broader range of mediators: IFN (interferon), chemokines such as macrophage inhibiting protein (MIP-2) and monocyte chemo-attractant protein (MCP-1), most likely mediated via TNF-α [81].

The importance of TNF for enhancing the immune response, generated by bacterial plaque challenge, in T1D and T2D, has been experimentally shown for murine models with chronic periodontitis, but without a clear relation between the TNF-α levels found in oral tissues and those found in oral fluids of T2D periodontal subjects [81]. Along with these pro-inflammatory mediators, research has also been carried upon chemokines' performance, growth factors and soluble adhesion molecules, which possess immune-regulatory capacity [79]. The simultaneous action of multiple mediators in evaluating oral immune response in periodontal patients with T1D has also been assessed [82].

Monocytes can have a hyper-inflammatory phenotype in patients with T1D, and these cells are susceptible to the action of lipopolysaccharides (LPS) of the periodontal bacteria, and respond through generation of increased amounts of IL-1β, TNF-α and PGE2, compared to non-diabetic subjects [79]. This inflammatory phenotype of monocytes represents one of the relevant links between periodontal pathogenesis and diabetes mellitus [79].

Research on other cell populations involved in mediating the immune response advocates that T cells accumulation around insulin-sensitive cells is important in metabolic changes correlated to diabetes, via their capacity to moderate macrophage activity [83]. There are a number of distinct subclasses of T cells, with remarkable plasticity, their role being strongly correlated to the local cytokine amount. However, although important in maintaining the Th1/Th2 cell balance in the pathogenesis and progression of periodontitis, data on the underlying mechanisms and their role in homeostasis of periodontal status in patients with diabetes are still to be elucidated [76].

Gathering the whole data related to the modulation of locally expressed mediators, the T1D-periodontitis association would be of particular relevance in the curative management plan, through conduction of long-term studies. Further research is necessary to better understand the cytokine expression in periodontal disease and type 1 diabetes.

4.3 Cardiovascular diseases

Cardiovascular disease (CVD) constitutes an extensive cluster of conditions that deter the physiological function of the heart and/or blood vessels and includes (a) coronary heart disease—angina/myocardial infarction; (b) ischaemic cerebrovascular disease—transient ischaemic attack—TIA and (c) peripheral vascular disease. In both cardiovascular disease and periodontal disease, a systemic inflammatory overload is present in the organism, which can be exacerbated by factors such as smoking, obesity or diabetes mellitus that eventually leads to an altered dishomeostatic status [84]. Due to the ulceration and inflammation of subgingival epithelial layer, oral pathogens and their by-products can access the blood stream, increasing the risk and aggravating the evolution of any pre-existing heart disease [85].

Atherosclerosis is commenced by deterioration of the endothelial tissue of vessels. Following impairment, endothelial pro-inflammatory signals drive not only the expression of adhesion molecules such as E-selectin, ICAM-1, P-selectin and VCAM-1, but also of IL-8 and thrombin that act as chemoattractants and determine an upsurge in the aggregation of platelets and migration of leukocytes [86]. Furthermore, these pro-inflammatory signals trigger the proliferation of smooth muscle cells and the apoptosis of endothelial cells. In this context of complex interactions, leukocytes migrate to the injured site and release additional pro-inflammatory cytokines (IL-1α and β, IL-6, IL-17, IL-22 and TNF-α), reactive oxygen species, as well as proteinases that break down the extracellular matrix of the endothelium [87].

High concentrations of low-density lipoproteins (LDL) in plasma accumulate in the aortic wall beneath the intima layer of the endothelium and are oxidated into oxLDL. Increased blood pressure activates endothelial cells which advocate the activation of adhesion molecules that favour the migration of monocytes. In the aortic wall, these cells transform into macrophages that absorb the oxidated LDL and develop into foam cells filled with lipids. This circumstance further promotes the dispersion of pro-inflammatory molecules which stimulate the invasion and activation of supplementary inflammatory cells and facilitate their confinement in the plaque, precipitating subsequent build-up of inflammation factors [88].

Periodontal microorganisms can alter the mentioned mechanisms by virtue of a direct interaction (for example by the invasion of endothelial, smooth muscle cells, leukocytes and platelets), but also an indirect interplay by stimulating the release of paracrine factors that eventually affect normal cellular function [89]. In addition to direct invasion, microorganisms can release products into the circulation and induce pro-atherogenic responses in endothelial cells [90]. Research has highlighted that vesicles pertaining to the outer membrane such as gingipains from *P. gingivalis* and free soluble components deriving from *A. actinomycetemcomitans* cause irritation to endothelial cells and promote inflammation [91]. Effusion of pro-inflammatory cytokines (IL-1, IL-6 and TNF-α) and other chemokines from the affected periodontal tissues leads to the generation of acute phase proteins (C reactive protein, fibrinogen, amyloid A, etc.) by the liver [92]. As a result of this injury, the activation of the adaptive immune system occurs as a typical response to chronic bacteraemia. Pathogen-associated molecular patterns (PAMPs) of periodontal pathogens determine the production of antibodies and elicit a cross-response between endothelial cells and the altered LDL to exacerbate the migration of lipids into cells inside the blood vessel walls [93]. Antigen-presenting cells, for example, dendritic cells and effector T lymphocytes, bear a substantial part in the generation of proatherogenic cytokines, for example, IL-20, IL-18 and IFN-γ, and are consequently also relevant in the progression of atherosclerotic plaques. A noteworthy role among the proatherogenic cytokines has been assigned to IL-12 due to the fact that when this certain molecule was absent early lesion development was inhibited. However, late progression was unaffected [94].

Considering the recent epidemiological, experimental and clinical evidence presented in the literature on this subject matter [86], the issue of an interrelationship between periodontal disease and cardiovascular disease is clearly supported. In spite this, the exact nature of this relationship, whether it is a direct or causal one, remains to be edified through interventional and longitudinal studies.

4.4 Rheumatoid arthritis

Rheumatoid arthritis (RA) is considered to be an autoimmune, progressive, inflammatory and chronic disorder, in which the human immune system reacts in an erroneous manner to the articular structures. This response is characterised by an inflammatory immune cell infiltrate (activation of innate immunity, followed by the emergence of adaptive immune responses) in the early phase, followed by a destructive phase characterised by degenerative phenomena, such as denaturation of normal synovial structures by hyperproliferation, reactive fibro-vascular proliferation, bone destruction and cartilage degradation. This explains the occurrence of swelling and pain within and around joints [95].

Over the past two decades, RA has been described as a disease model in which various pathophysiological mechanisms have been studied to better explain the inflammatory process, but also the modality of involvement of the human immune system, through two types of specific responses [95]. These research projects

culminated with the introduction into patients' treatment regimens of the chimeric anti-TNF-α monoclonal antibodies (infliximab, 75% human and 25% mouse peptide sequences) [96], a recombinant human TNF receptor (p75)–Fc fusion protein (etanercept) and biological therapy with fully human anti-TNF-α monoclonal antibodies [97].

Major cytokines, such as TNF-α and interleukins (IL-17 and IL-1β), function by promoting inflammatory responses, causing inflammation of the synovium and inducing cartilage degradation. Other soluble mediators, such as cytokines released by the Th2 lymphocyte subpopulation (the most frequently studied and for which statistically significant results were obtained, would be IL-4, IL-10, IL-13) are mainly anti-inflammatory molecules [95, 98]. In addition, IL-13 could have potential clinical importance because it can suppress both secretion and actions of IL-17 [98].

Over the past two decades, the existence of links or associations between RA and periodontitis has been investigated [99]. RA could be a triggering risk factor for periodontitis as there is a high incidence of RA in patients with periodontal disease, and RA patients have more chances to experience moderate to severe periodontal changes, as compared to healthy subjects. It has also been found that calcifications and soft tissue injuries have the same characteristics, leading to the conclusion that the destructive inflammatory chronic lesions are similar [100].

New theories have highlighted that periodontal disease is a risk factor for RA, with several similarities existing between RA and periodontitis [101–103]:

- both diseases are multifactorial, chronic immune-inflammatory diseases with progressive evolution;

- pathophysiological mechanisms involve the association of environmental factors, microbial factors, genetic susceptibility (it was found that the HLA-DRB1 subtype is associated with both fast progressive periodontitis as well as RA);

- locally, the cellular composition of the inflammatory reactions is similar, it includes both the T and B subtypes of lymphocyte populations, but also the cells involved in the activation of lymphocytes such as dendritic cells;

- for both diseases, it was found that the changes occurring in early phases, as well as those in destructive phases are characterised by degenerative phenomena and periodontal degradation, but also the chronic systemic inflammation is determined and mediated by the interruption of balance between the pro-inflammatory and the anti-inflammatory cytokines; and

- change in connective tissue and bone homeostasis is irreversible, consisting in the deterioration of collagen-rich structures, a process in which they intensively participate and have collagenolytic effects as matrix metalloproteinases and other enzymes (elastase, bacterial cysteine proteases, enzymes associated with neutrophils).

4.5 Liver diseases

One of the most damaging hepatic diseases is chronic hepatitis C (CHC), occurring after the infection with the hepatitis C virus (HCV), which replicates within hepatic and peripheral blood cells [104]. It is considered that worldwide, more than 200 million persons are affected by this disease, making it a major public health concern [105]. As the hepatic inflammation progresses and becomes chronic,

healthy liver tissue is replaced by fibrotic tissues, which is unable to perform normal hepatic functions, leading to cirrhosis [106]. During chronic hepatic inflammation important cytokine profile changes can be observed in affected patients, with increased levels of pro-inflammatory markers, such as TNF-α, being found in their serum samples [107].

Cytokine levels, measured in either gingival fluid or serum samples, can be used to assess the progression and severity of both periodontal and hepatic disease [108]. In periodontal disease, the secretion rate of gingival fluid increases, as well as its content in pro-inflammatory cytokines [109]. The levels of these cytokines can be determined, as an indirect indicator of the disease's severity and progression rate [110]. Being easy to sample, the gingival fluid has allowed extensive research on its pro-inflammatory cytokine content [111]. Similarly, the evolution of chronic hepatitis C can be monitored by the assessment of some cytokine's levels (such as IL-18 and IL-33) in the serum samples of affected patients [112, 113]. Moreover, the same pro-inflammatory cytokines, such as IL-1, Il-6 and interferon-gamma, can express elevated levels during chronic hepatic inflammation (as in chronic hepatitis C), as well as during chronic periodontal inflammation (as in chronic periodontal disease) [114]. The similar profiles of these cytokines suggest that the two inflammatory reactions could be driven by the same pro-inflammatory markers, endorsing extensive research on their possible common pathogenic mechanisms [108].

Another frequently encountered hepatic condition, particularly within developed regions, is non-alcoholic fatty liver disease (NAFLD). Affecting almost 24% of the global population [115], the disease is mainly caused by genetic or behavioural factors, such as a misbalanced diet, rich in lipids and sugars, lack of physical activity or can occur during other systemic conditions like obesity and diabetes mellitus [116]. The accumulation of fat leads to hepatic steatosis, which, in time, can develop life-threatening complications, as liver cirrhosis or hepatic cancer [117]. NAFLD has been associated with metabolic disorders, as insulin resistance [118], as the adipocytes of the fatty tissue will produce increased levels of TNF-α [119]. This cytokine can alter cellular sensitivity to insulin, therefore decreasing normal glucose metabolism. As a result, serum glucose will rise, increasing the risk of diabetes mellitus [118].

TNF-α is also intensively involved in periodontal inflammation. This cytokine has been shown to express increased levels in the gingival fluid of periodontal patients [120] and has similar pro-inflammatory mechanisms to IL-1β [121]. Its main damaging role during periodontal inflammation is the disruption of the normal reparatory function of fibroblasts and the stimulation of bone-resorption osteoclasts [122]. TNF-α may represent a key cytokine that links the pathogenic mechanisms that are common between periodontal disease and insulin resistance, insulin resistance and NAFLD, and consequently between periodontal disease and NAFLD [123].

The relationship between periodontal disease and hepatic conditions could be considered as functioning into two directions. Firstly, periodontal disease can impact the development and outcome of hepatic conditions. The main explanation of the root cause of the association between periodontal disease and hepatic conditions seems to be the bacterial challenge that leads to periodontal inflammation [124]. Pre-existing hepatic conditions, as chronic hepatitis, NAFLD or cirrhosis can be aggravated by the impact of bacterial attack on the periodontal tissues [125]. Important periodontal pathogens, like *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* stimulate the synthesis of pro-inflammatory cytokines by periodontal cells [126]. These cytokines, including TNF-α and IL-1 family ones, will be carried by the vascular system and reach the liver. Here, they can have damaging effects on the hepatocytes, if there is a pre-existing hepatic condition, by adding to the distress of the already impaired hepatic tissue [127]. Consequently, the liver

functions will be more difficult to perform and the conditions will aggravate, as a result of a bacterial periodontal challenge [128].

Conversely, hepatic conditions can impact the evolution and manifestations of periodontal disease, by means of increased cytokine production [129]. Various liver diseases, as NAFLD, CHC and liver cirrhosis, trigger the increased production of pro-inflammatory cytokines, including TNF-α, IL-1 family, IL-6, which also have a proven active role in the promoting of the periodontal inflammatory reaction [130]. These cytokines, originating from the affected hepatic tissue, enter the blood stream and reach the periodontal tissues. When a periodontal bacterial challenge occurs, they contribute to the exacerbation of the inflammatory reaction, inflicting damage on the periodontal tissues, together with the periodontal-originating pro-inflammatory cytokines. Therefore, an exaggerated inflammatory response is triggered, causing important loss of periodontal structures in patients who also suffer from chronic liver diseases [131, 132].

4.6 Renal diseases

Chronic kidney disease (CKD) is an official public health concern, with 10–12% of the population affected in terms of mortality and morbidity [133, 134]. CKD is characterised by the use of certain markers that indicate the degree of kidney malfunction, notably the glomerular filtration rate (GFR), which indicates the kidney's functioning efficiency. CKD is diagnosed when multiple standard criteria are met, including a GFR lower than 60 mL/min, albumin levels higher than 30 mg/g of creatinine and the existence of morphological kidney changes. When the GFR drops below 15–20 mL/min, it can be considered that end-stage renal disease has occurred [135, 136].

Various harmful stimuli are triggers for inflammation, the physiological protecting mechanism of the body. In CKD, as in several other chronic debilitating disorders, inflammation becomes maladaptive, uncontrolled and persistent. In this group of patients, a majority of the patients with minimum Stage 3 CKD have increased levels of C-reactive protein (CRP) [137], this prevalence being even higher either in final stage CKD or in dialysis patients [138]. For the evaluation of inflammatory state in clinical practice, a series of specific markers are used. One of the most important inflammation indicators is the CRP, which can also be found in its high sensitive form (hs-CRP) in elevated levels in the serum samples of patients with chronic renal failure, along other pro-inflammatory cytokines [139]. Moreover, another pro-inflammatory cytokine, IL-6, could be a reliable indicator of the risk of cardiovascular diseases and mortality in subjects with end stage renal disease (ESRD) [140].

Malnutrition, a severe consequence of CKD, inflicts important changes in most ESRD patients, in terms of anthropometric and serologic aspects, most of which have an irreversible character, even with proper nutritional supplementation. In addition, malnutrition also comprises a chronic inflammatory reaction, driven by pro-inflammatory cytokines (IL-1, IL-6, TNF-α, IFN-γ, etc). This immune response can accelerate the muscular protein catabolism, on the one hand, by elevating the hepatic synthesis of positive acute phase proteins and, on the other hand, by suppressing the production of negative acute phase proteins [141].

ESRD and haemodialysis (HD) itself lead to an inflammatory status, influenced by numerous factors. The main factor of morbidity and mortality in dialysis patients is considered chronic inflammation, a major determinant of 'dialysis syndrome'. Inflammation in dialysed patients is characterised by enhanced production of CRP, TNF-α, IL-6, IL-2 and chemokines, such as IL-8, and it may vary over time and during this process [142].

The bacteria of the subgingival biofilm can reach the systemic blood circulatory system, causing lesions to the arterial endothelium and triggering a series of pathogenic events that can eventually lead to atherosclerosis [85]. This mechanism can explain certain pathogenic connections between local and systemic conditions. These connections may have a bidirectional nature, deriving from the similar local and systemic inflammatory reactions that these conditions manifest [143]. For instance, a renal inflammatory response (glomerulonephritis) can be triggered by various acute and chronic infections. This is supported by the increased prevalence of periodontal pathology in patients with renal diseases, suggesting the high relevance of the periodontal pathology in the onset of renal inflammatory responses [144].

Recently, research has focused on the contribution of inflammation, determined by periodontitis, to the overall inflammatory systemic burden in patients with CKD and dialysis. In this context, plasma levels of certain inflammatory cytokines may be relevant to malnutrition, morbidity and mortality of these patients, as well as to their quality of life [145]. Individuals with ESRD experience reduced quality of life and many of them also associate low oral health [145].

5. Conclusion

Through the intense implication of cytokines, the periodontal inflammatory reaction can exhibit a variety of clinical manifestations, in terms of onset, evolution, treatment and prognosis. The local and systemic factors, which can influence the development of periodontal inflammation, often have molecular and cellular implications, and cytokines become the means through which different pathologies can have mutual impact. The cytokine standpoint on periodontal disease and its connective systemic conditions offers wide and promising perspectives on further developments of more precise methods of diagnosis and more efficient therapeutic protocols.

Conflict of interest

None.

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