REVIEW

Periodontitis as an inflammatory trigger in hypertension: From basic immunology to clinical implications

Piotr Szczepaniak[1], Tomasz P Mikołajczyk[1], Marta Cześnikiewicz-Guzik[2], Tomasz J Guzik[1, 3]

[1]Department of Internal and Agricultural Medicine, Jagiellonian University Collegium Medicum, Kraków, Poland
[2]Department of Periodontology, Oral Pathology and Dental Prophylaxis, Jagiellonian University Collegium Medicum, Kraków, Poland
[3]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

Correspondence to:
Prof. Tomasz Guzik, MD, PhD, Department of Internal and Agricultural Medicine, Jagiellonian University Collegium Medicum, Skarbowa 1, 31–121 Kraków, Poland, phone: +48 12 633 00 03, e-mail: t.guzik@uj.edu.pl

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ABSTRACT

Hypertension and periodontitis are both highly prevalent co-morbidities worldwide, and their occurrence increases with age. Multiple observational epidemiological studies have shown that periodontitis is associated with an increased cardiovascular disease (CVD) occurrence. Large systematic reviews and metanalyses further show that periodontitis increases the risk of hypertension and is associated with increased systolic and diastolic blood pressure. Genetic and clinical evidence, utilizing mendelian randomization and randomized clinical trials, support the causal role of periodontitis in hypertension. The mechanisms of this link remain unclear. Critical components of immune and inflammatory pathogenesis of periodontitis considerably overlap with immune mechanisms of hypertension. Clinical studies support that both C-reactive protein (CRP) levels and white blood cell counts (WBC) mediate the relationship between periodontal disease and high blood pressure. In particular, activation of Th1, Th17, T regulatory cells, and proinflammatory monocytes has been shown to be essential in both conditions. Immunosenescent dysregulated CD28null T cells have been implicated, along with key effector cytokines such as interleukin 6 (IL-6), TNF-alpha (TNF-α), interferon-gamma (IFN-γ), and interleukin 17 (IL-17). A better understanding of the relationships between hypertension and periodontitis is essential not only for possible utilization of this knowledge for a non-pharmacological approach to improving blood pressure control. It may also provide valuable pathogenetic clues linking inflammation and hypertension, which has become particularly relevant in the light of links between hypertension and autoimmune disorders or, more recently, COVID-19.

Key words: hypertension, inflammation, periodontitis

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INTRODUCTION

Hypertension is highly prevalent worldwide and leads to the development of coronary heart disease, stroke, and other renal and cardiovascular diseases (CVD). It has been estimated that in 2019 hypertension was present in 626 million women and 652 million men aged 30–79 years [1–3]. In similarly, the incidence of periodontitis increases with age and amounts to as much as 60% in adults over 65 years of age [4–5]. As a result, periodontitis is one of the most common causes of systemic inflammation that could potentially affect a wide range of chronic comorbidities including cardiovascular disease. Various immune and inflammatory diseases have been linked to hypertension [6, 7]. Indeed, periodontitis is associated with increased occurrence of CVD in general and, as has been recently established, is particularly strongly linked to hypertension [8]. Evidence of epidemiological associations between hypertension and periodontitis is ample, but the mechanisms behind this relationship remain unclear. Numerous observational studies over the years have been challenged due to confounding factors, which are difficult to control, that predispose to both diseases. Studies published in the last decade provide a much clearer view not only of the clinical relevance of this relationship but also of the possible causal relationship between these two comorbidities.

EPIDEMIOLOGICAL EVIDENCE LINKING PERIODONTITIS AND HYPERTENSION

Association between severe periodontitis and hypertension has been reported throughout the years [9–12]. In a meta-analysis of 40 studies, hypertension was related with moderate-severe periodontitis (odds ratio [OR], 1.22;

95% confidence interval [CI], 1.10–1.35), as well as severe periodontitis (OR, 1.49; 95% CI, 1.09–2.05) [13]. Analysis of large registries further supports these conclusions. Munoz Aguilera et al. [14] have provided evidence that periodontitis increases the odds of hypertension by 20%–60% in large populations from surveys based in the USA (n = 3460) and Korea (n = 4539). Periodontitis was related to the occurrence of hypertension and higher systolic blood pressure (SBP) compared to people without periodontitis. These observations have been further extended to several periodontitis-related phenotypes that may have clinical relevance. For example, Pietropaoli et al. have shown that unstable periodontitis and gingivitis linked to gingival bleeding were associated with an increased risk of uncontrolled/high blood pressure [15]. SBP was significantly higher in patients with unstable periodontitis than in patients with gingivitis (increase by 5.3 mm Hg), as well as people with stable periodontitis (increase by 2.1 mm Hg). Gingival bleeding was correlated with an increased risk of high/uncontrolled BP (OR, 1.42; 95% CI, 1.19–1.68), which is particularly interesting considering that gingival bleeding is a very simple clinical marker of oral involvement [15].

PERIODONTITIS CAUSES HYPERTENSION

Evidence of the causal relationship between periodontitis and hypertension comes from genetic evidence and randomized clinical trials of intensive periodontal therapy. The Mendelian randomization analysis in the UK Biobank (nearly 400 000 individuals), indicated a significant potentially causal relationship between periodontitis-linked single nucleotide polymorphisms (SNPs) and blood pressure phenotypes [16]. The identified SNPs included *SIGLEC5*, *DEFA1A3*, *MTND1P5*, and *LOC107984137* and had been identified using Genome-Wide Association Studies (GWAS) [16]. Evidence from randomized clinical trials further shows that supra- and sub-gingival instrumentation combined with instillation of chlorhexidine in gingival pockets (intensive periodontal treatment [IPT]) improved endothelial function and its cardiovascular complications. Metanalysis performed in hypertensive and prehypertensive individuals revealed a significant blood pressure decrease in successfully periodontal treatment [17]. Direct data from the largest so far randomized study utilizing ambulatory blood pressure monitoring, has clearly shown that IPT was associated with lowering blood pressure in hypertensive patients with periodontitis. The difference in SBP change between subjects randomized to IPT or conventional periodontal treatment (CPT) was 11.1 mm Hg [16]. Other studies further support these conclusions [16, 18–21]. In another trial performed in 107 patients [22], IPT was associated with reductions of endothelial microparticles (EMP) which coincided with blood pressure-related effects and persisted for up to 6 months after IPT [22]. We have recently published a detailed systematic review and metanalysis of all randomized studies reporting the effects of periodontal therapy on hypertension and related cardiovascular outcomes [17]. Sharma et al. [17] reported an improvement in the cardiovascular health of patients with hypertension after IPT. Comparing the effects of CPT and IPT, a decreased level of CRP and an improvement in endothelial function after IPT were observed. Importantly, the systematic review and meta-analysis demonstrated similar reductions of both SBP and DBP to the levels reported by individual trials. In the prehypertensive and hypertensive patients, IPT decreased diastolic blood pressure (DBP) (decrease by 8.43 mm Hg) and SBP (decrease by 11.41 mm Hg) compared with CPT, while in the non-hypertensive populations, blood pressure remained unchanged [17]. In conclusion, the combination of genetic and clinical trial data strongly suggests that periodontitis may be causal in hypertension and that intensive periodontal treatment can support anti-hypertensive therapy and reduce cardiovascular risk.

SYSTEMIC INFLAMMATION AS A MEDIATOR BETWEEN PERIODONTITIS AND HYPERTENSION

There is increasing evidence that hypertension can be caused and modulated by inflammatory responses [23–25]. Blood pressure can be regulated by various immune-targeted therapies [26, 27] or diets [28]. Systemic inflammatory cytokines and CRP serve as biomarkers linking periodontitis and hypertension (Figure 1). The mediation analysis in large epidemiological survey studies discussed above has suggested that CRP and white blood cell counts (WBC) mediated partly the association between periodontitis and hypertension [14]. Similar results were observed in another population [29]. In a study of 500 participants, higher blood pressure, elevated high-sensitivity CRP, and white cell counts were obtained in patients with periodontitis compared to the control group [29].

Recently published studies have provided evidence that periodontitis, as a chronic inflammatory disease, is associated with the prevalence of hypertension [5, 13–17, 30–32]. Poor oral health is linked to systemic inflammation and increased probability of the development of hypertension. In a meta-analysis of several interventional studies, Sharma et al. [14] also reported that the blood pressure-lowering effect was accompanied by the reduction of CRP levels [17]. Specific mediators of this relationship are still under investigation. Interestingly, the improvement of the periodontal status in humans is accompanied by the reduction of immunosenescent CD57+CD28nullCD8+ T cells bearing the activation marker CD38 [16]. These immunosenescent T cells were originally implicated in the pathogenesis of hypertension [33, 34]. Also, the levels of circulating pro-hypertensive cytokines, such as interferon-gamma (IFN-γ), interleukin 17A (IL-17A), TNF-alpha (TNF-α), and interleukin 6 (IL-6), were diminished with the improvement of both periodontal status and blood pressure [16] suggesting their possible involvement. To better

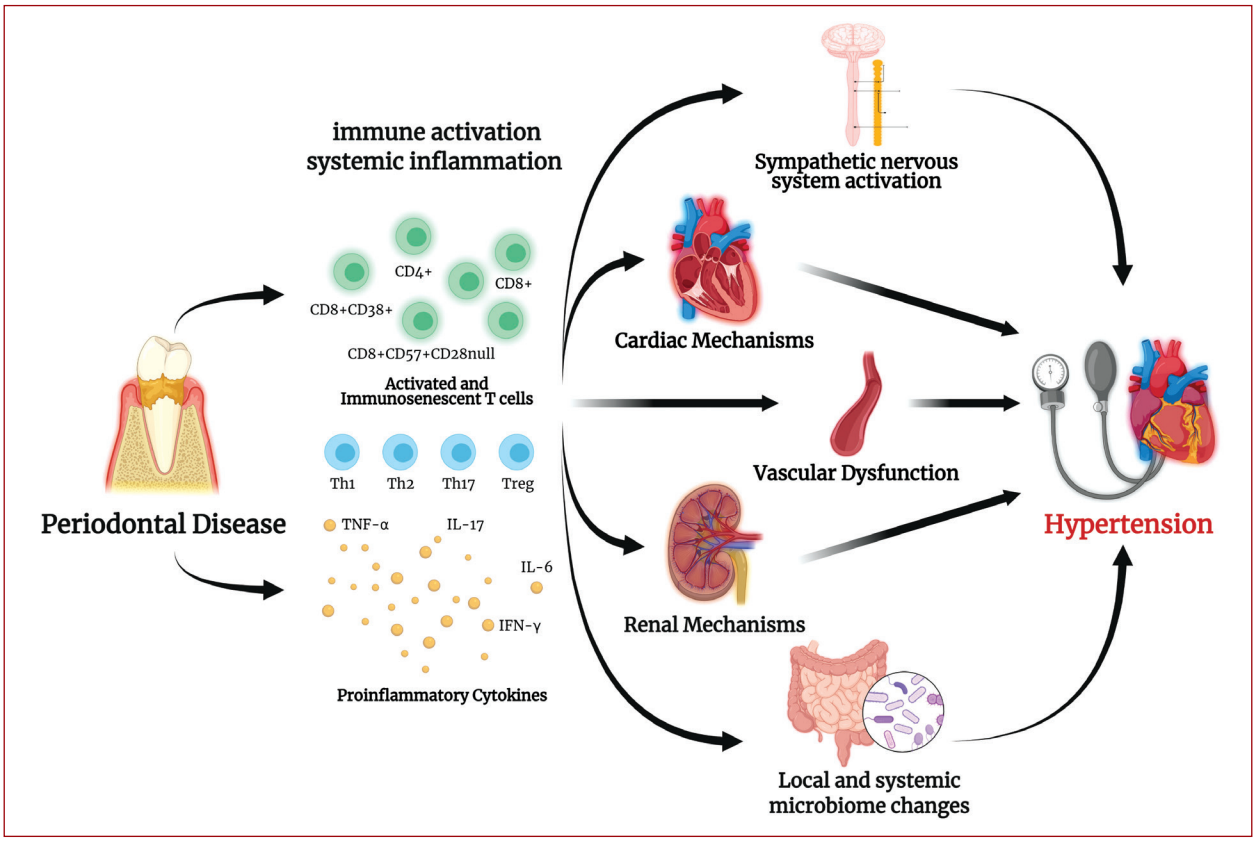

Figure 1. Potential inflammatory mechanisms linking periodontitis and hypertension. This figure has been created with BioRender
Abbreviations: IFN-γ, interferon γ; IL, interleukin; Th, T helper cells; TNF-α, tumor necrosis factor α; Treg, T regulatory cells

understand the possible mechanisms linking periodontal inflammation with hypertension, it is essential to look closely at the immune pathogenesis of periodontitis itself.

IMMUNE MECHANISMS OF PERIODONTITIS

Periodontal disease (PD) is initially caused by the accumulation of biofilm on the teeth. Consequently, it promotes localized inflammation called gingivitis. This stage of inflammation is reversible and represents the mildest form of PD. Further development of inflammation encompasses deeper layers of the periodontium, causing the loss of the connective tissue and bone. The involvement of these tissues is characteristic of periodontitis. In most cases, this stage of inflammation is irreversible [35]. For a long time, a lot of evidence suggested that bacteria are the primary etiology of periodontal diseases. Bacteria implicated in periodontitis are predominantly anaerobic, gram-negative, and may include *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia*, *Bacteroides forsythus*, *Campylobacter rectus*, *Peptostreptococcus micros*, *Eubacterium nodatum*, *Streptococcus intermedius,* and *Treponema sp.* [36]. Nowadays, periodontitis is perceived as a result of the imbalance of the microbial biofilm, known as dysbiosis, rather than the presence of a single pathogen [36]. The pathogenesis of PD is more complex and depends on many additional environmental factors as well as the susceptibility of the host [37, 38]. It is known, that exacerbated immune responses to the biofilm in the periodontal tissue result in the destruction of the structural component of the periodontium [35]. In this context, both bacteria and activated host immunity coincide to trigger immune responses resulting in bone loss [39]. Initially, chemotactic factors released by the activated immune cells are responsible for the recruitment of leukocytes into the inflamed tissues [34, 40].

Neutrophils: Neutrophils are the most abundant leukocytes, which are the first line of antimicrobial defense. These cells act as professional phagocytes, that recognize, engulf, and kill extracellular pathogens. In this way, neutrophils link the innate and adaptive immune responses and help the resolution of inflammation and healing of the tissue [41]. Neutrophils in the periodontal pocket form the wall against the plaque biofilm. This mechanism may initially be protective. However, it is known that neutrophils cannot engulf the large structure of the biofilm and during this process called frustrated phagocytosis, they release enzymes, products of the oxidative burst, and other noxious contents to the surrounding milieu. In this arm of the response, neutrophils have a predominantly destructive effect on the pocket and surrounding tissue [41]. Neutrophils contain the membrane-bound intracellular granules called primary (azurophilic), secondary (specific), and tertiary (gelatinase),

as well as secretory vesicles. Granule proteins contribute to reactive oxygen species (ROS) production. In this process, myeloperoxidase (MPO) produces singlet oxygen, hydroxyl radical (•OH), and hypochlorous acid (HOCl) from chloride and H_2O_2 [42]. This initiates degradation of the proteins and induction of DNA damage resulting in the killing of most prokaryotes [43]. Neutrophil-derived molecules with antimicrobial activities include lysozyme, lactoferrin, elastase, azurocidin (hCAP 37kDa), cathelicidin (LL-37), and human neutrophil peptides (HNPs; α-defensins) [44]. Neutrophils can also release decondensed chromatin with histones and granules into the extracellular space. The formation of neutrophil extracellular traps (NETs) aims to fight microorganisms [45]. During the process of transmigration into the tissue, neutrophils produce chemokines, and they alter their surface expression markers, presenting a higher expression of integrins and proteases. Also, delayed apoptosis is commonly observed because of this process [46]. The measurements of the specific surface cell markers revealed that the potential changes in their expression are likely due to the momentary activity of the cells rather than reflecting specific cell subsets [45]. It is suggested that the oral neutrophils, in comparison to cells isolated from peripheral blood, are terminally migrated cells, which are exposed to high osmotic stress, as well as a high load of bacteria and their toxins [45]. Recently published data provided evidence that neutrophils were elevated in periodontitis tissue when compared to healthy tissue. This effect was also accompanied by increased infiltrates of plasma cells and naïve B cells [38]. It has been postulated that the infiltration of different subpopulations of immune cells in periodontitis is the result of the host immunity against periodontal disease [38].

Th1/Th2 subsets: In the next stage of the immune responses, macrophages, monocytes, and dendritic cells known as the antigen-presenting cells (APCs) are observed in the inflamed tissue. Such imbalances may provide essential links to cardiovascular pathology [47]. Although the content of dendritic cells and macrophages in the periodontal tissue is decreased in comparison to healthy tissue [38], their role in capturing and presenting antigens to lymphocytes is essential. In the periodontal lesions, T cells and both CD4+ and CD8+ subsets are found in the dense inflammatory infiltrate [48]. Interestingly, those cells revealed memory/activated phenotype, presenting CD45RO+/CD29+ markers [38, 48]. CD4+ T cells play a crucial role in antigen recognition since the bacteria involved in periodontitis are extracellular pathogens [48]. Based on the profile of cytokine production, CD4+ cells are divided into T helper 1 (Th1) and T helper 2 (Th2). Th1 and Th2 polarized cells have been shown to play different roles in periodontal diseases. In general, Th1 cells produce IFN-γ and IL-2, while Th2 subsets produce IL-4, IL-5, IL-6 [49]. Th1 cells induce the production of IL-1 and TNF-α, which can initiate bone resorption by activating osteoclasts and promoting differentiation of the osteoclast precursors [48]. It is interesting to note that activated T cells have the expression of the osteoprotegerin ligand (OPG-L) that promotes osteoclast differentiation. Moreover, Th1 cells predominantly express OPG-L. T cells' recruitment into the inflamed tissue is regulated by chemokines and their receptor as well as by the adhesion molecules. In diseased gingiva, Th1 cells with high expression of C-C motif chemokine receptor 5 (CCR5) and C-X-C motif chemokine receptor 3 (CXCR3) have been found [48]. Interestingly, in the inflamed periodontal tissue, elevated levels of Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES) and Macrophage inflammatory protein 1 alpha (MIP-1α) chemokines (both are CCR5 ligands), as well as Interferon gamma-induced protein 10 (IP-10, CXCR3 ligand), were observed [48]. In the gingival tissue, an increased number of mononuclear cells, which express α4 and α6 integrins, has been found. As a result, the lymphocyte migration was increased [50]. It has been observed that T cells express the leukocyte function-associated antigen 1 (LFA-1, CD11a) in the gingival tissue and gingival crevicular fluid. Also, the pocket epithelium in the gingiva expresses the intercellular adhesion molecules 1 (ICAM-1, CD54). It has been shown that the expression of ICAM-1 in the pocket epithelium is associated with the migration of CD11a+CD25+CD4+ cells in the affected periodontally gingival tissue [51]. Lymphocytes can also adhere to gingival fibroblast using CD44/hyaluronate, LFA-1/ICAM1, and very late antigens 4/5 (VLA-4/5) [52]. Th1 lymphocytes and especially IFN-γ positive cells are associated with bone resorption [53]. IFN-γ positive T cells induced osteoclastogenesis from monocytes through the expression of NF-κB ligand (RANKL) [53]. Infection of dental pulp with *Porphyromonas gingivalis*, caused inflammation and alveolar bone destruction in Th1 biased mice, while Th2 biased mice developed minimal lesions. Moreover, inflammatory granulomas, associated with Th1 response, were infiltrated with osteoclast and had high expression of IFN-γ, IL-1α and IL-1β [54]. Another study has revealed osteoclast activity in granulomas, and this was correlated with Th1 response [55] that can also affect cardiac pathology [56].

In turn, Th2 response was associated with minimalized bone loss [57]. The protective effect was dependent on IL-4/IL-13 induced Signal transducer and activator of transcription 6 (STAT6) pathway [57]. It is interesting to note that the development of periodontitis is mediated by an imbalance between Th1 and Th2 responses which can be affected by various immune and non-immune triggers [55, 58–63]. On the other hand, cells isolated from peripheral blood of patients with early-onset periodontitis were characterized by decreased Th1 cytokine expression, while peripheral cells derived from patients with adult periodontitis were predominantly Th2/Th0 polarized [64]. Also, the progression of periodontal disease may be regulated by the local cytokines and the dominance of Th2 response and could

be an exacerbating factor [65]. This observation suggests that cytokines released by the cells infiltrating the gingival tissue affect the progression of gingivitis to chronic and destructive periodontitis with Th2 predominance. Thus, Th2 cells could be associated with progressive lesions while Th1 could be related to stable lesions [61, 65]. In contrast, it has been shown that IFN-γ cells increased with the severity of inflammation in human gingival tissue [66]. Some of the published studies revealed a comparable presence of Th1 and Th2 in periodontitis in humans [67, 68]. Taking together the above data, more research is needed to fully explain the role of Th1/Th2 subsets in the pathogenesis of periodontitis. Th1 cells are particularly important from the standpoint of the possible link to cardiovascular disease as these cells are present in perivascular tissues [69], and Th1 effector cytokines can modify cardiac and vascular remodeling and pathology [70-71].

Th17 lymphocytes: Th17 cells express RAR-related orphan receptor gamma (RORγ) and produce a whole range of cytokines such as IL-17A, IL-17F, IL-21, IL-22, and IL-26 [72]. Th17 development and differentiation are initiated in the presence of IL-2, IL-1β, IL-21, and IL-23 [73]. IL-17 is considered an important regulator of granulopoiesis, and neutrophils are known to provide antimicrobial defense against periodontitis. IL-17RA$^{-/-}$ mice were characterized by enhanced periodontal bone destruction. Moreover, IL-17RA$^{-/-}$ mice revealed both reduced neutrophil migration to the bone and serum chemokine levels [74]. This observation suggests the protective role of IL-17 to the bone [74]. In rheumatoid arthritis (RA), both human and animal studies have provided evidence that IL-17 plays a pathogenic role in bone destruction [75, 76]. IL-17, in a dose-dependent manner, induced the expression of osteoclast differentiation factor (ODF) mRNA in osteoblasts. Kotake et al. have shown that IL-17 is the crucial cytokine for osteoclastic bone resorption in patients with RA [77, 78]. It is important since periodontal diseases represent the most common form of bone loss. PD is also a risk factor for chronic obstructive pulmonary disease (COPD), diabetes, atherosclerosis, and increased preterm labor, and low birth weight [79, 80]. It is well documented that IL-17 upregulates the expression of RANKL leading to the loss of RANKL/OPG balance and stimulating osteoclastogenesis and erosion of bone [81, 82]. IL-17 also stimulates the expression of osteoclastogenic cytokines such as IL-6, IL-8, IL-1, and TNF [83]. The significant overexpression of IL-21 and Th17 related cytokines such as IL-1β, IL-6, IL-17, and IL23, has been observed in the tissue affected by periodontitis [84].

In conclusion, the Th17 response plays a crucial role in bone loss.

Regulatory T cells (Tregs): Regulatory T cells play an important role in suppressing the activation and expansion of other T cells thus maintaining immune homeostasis and tolerance [85]. It has been shown that Tregs can directly inhibit APC [86]. Taking into account the site of Tregs development, two subsets can be distinguished. Natural Tregs (nTreg) develop in the thymus. Second subsets, named induced or peripheral Treg (pTreg), differentiate from naïve CD4+ T lymphocytes at the periphery [86]. The main Tregs phenotypic marker is the transcription factor Forkhead Box P3 (Foxp3). Regulatory T cells are also characterized by the high expression of the α chain of the high-affinity IL-2 receptor (CD25) [86]. Tregs have been found in chronic lesions in periodontitis [87]. Initially, during periodontitis, Tregs accumulate at the infected tissue, limiting the immune response and promoting the survival of the pathogens [87]. On the one hand, immune responses have to be controlled to avoid the dissemination of the microorganisms, and, on the other hand, tissue damage has to be protected [86]. Patients with chronic periodontitis presented the increased content of CD4+CD25+ T cells in the inflammatory gingival tissue. These cells were characterized by the expression of Foxp3, cytotoxic T lymphocyte-associated protein 4 (CTLA-4), CD103, CD45RO, and glucocorticoid-inducible TNFR (GITR). In patients with chronic periodontitis, the levels of CCL17, CCL22, and CCR4 were increased in gingival biopsies, in comparison to controls. Simultaneously, the affected tissue presented high expression of TGF-β and IL-10 [87]. Tregs can inhibit osteoclastogenesis and regulate bone metabolism by releasing cytokines such as IL-10, TGF-β, IL-4, and by using CTLA-4 molecules to direct contact with cells [88]. Nakajima et al. have also described increased infiltration of Tregs in periodontitis compared with gingivitis [89]. Moreover, C57Bl/6 mice infected with *Aggregatibacter actinomycetemcomitans* developed the inflammatory response and alveolar bone resorption. In this model, the migration of Tregs, as well as Th2, was associated with temporal attenuation of disease progression. The blockade of CCR4 ligand, CCL22, in wild type (WT) mice resulted in increased bone loss. A similar effect was observed in CCR4$^{-/-}$ mice. Moreover, the adoptive transfer of CCR4+Tregs into CCR4$^{-/-}$ reverted the exacerbated PD phenotype resulting in bone loss and inflammation reaching levels similar to the ones observed in WT. Despite numerous data reporting increased infiltration of Tregs in periodontal diseases [87, 89, 90], the reduced content of Foxp3+CD25+ cells has been demonstrated as well [91]. To conclude, the decreased content of Tregs or lack of their function contribute to an exacerbated immune reaction in the periodontium leading to the progression of periodontitis.

MECHANISTIC LINKS BETWEEN PERIODONTITIS AND HYPERTENSION

The mechanisms linking hypertension and periodontitis may include systemic inflammatory and local immune mechanisms, chronic pain, sympathetic activation, and gut microbiota (Figure 1) [28]. As discussed above, increasing understanding of the immune mechanisms of hypertension has pointed our attention to all components of perio-

dontitis immunopathogenesis discussed above with Th1, Th17, and T regulatory T cell taking center stage [16, 23, 92]. This has been extensively studied in both animal-model and human studies [93, 94]. Most recently, Mendelian randomization provided strong evidence linking immune cells with hypertension. Lymphocyte, monocyte, or neutrophil counts positively correlate with increased SBP, DBP, and pulse pressure in the large population of UK Biobank [94]. Moreover, recent epidemiological evidence revealed the link between lifetime exposure to oral inflammation and future cardiovascular risk [8]. Angiotensin II (Ang II), salt, and other pro-hypertensive stimuli cause the increase of the expression and accumulation of immune cells including Th17, effector T cells producing Th1 type cytokines [93, 95]. In line with this, animal studies indicated that hypertension was exacerbated by exposure to *Porphyromonas gingivalis antigens*, which are commonly present in periodontal diseases [30]. Recently, we observed an increase in the expression of Th1 cytokines such as IFN-γ, TNF-α, and T-Box Transcription Factor 21 (TBX21) in aortas of *P. gingivalis*/IL-12/aluminum oxide immunized mice. In this model, IL-4 and TGF-β expressions were unchanged. Moreover, this phenotype was accompanied by the enhanced elevation of blood pressure and endothelial dysfunction [30]. Circulating in the blood CD4+ T cells, which have been immunized with *P. gingivalis* antigens, were characterized by the higher expression of CD69 and CCR5 molecules in comparison to controls [30]. It is interesting to note that the cells activated on the periphery can migrate into the heart, kidney, brain, and blood vessel adventitia and periadventitial fat [34, 96]. Simultaneously, we observed that Ang II dependent inflammation was associated with increased expression of RANTES in perivascular adipose tissue (PVAT). This effect was accompanied by increased T cells content in PVAT. Infiltrating T cells were characterized by high expression of CCR1, CCR3, and CCR5 molecules. Furthermore, RANTES$^{-/-}$ were protected against leukocyte, and especially T cell infiltration, and this effect was associated with improvement of vascular function [97]. Thus, periodontal disease initiates systemic inflammation that affects the cardiovascular system by inducing activation of the immune cells and their infiltration into the inflamed tissue leading finally to the end-organs damage.

How activated immune cells can cause hypertension is still unclear. Most mechanisms link to the effects of effector cytokines on endothelial dysfunction [98] and renal expression of key ion transporters such as ENAC, which can then directly regulate blood pressure and contribute to hypertension. Indeed, interferon gamma, a key cytokine in both hypertension and periodontitis, has been shown to directly induce endothelial dysfunction in the vasculature [97].

Understanding the mechanisms of the immune system and hypertension may be crucial in preventing cardiovascular diseases in people with periodontitis. More studies are needed to investigate this relationship.

CONCLUSION

A better understanding of the relationships between hypertension and periodontitis is essential not only for possible utilization of this knowledge for a non-pharmacological approach to improvement of blood pressure control. It may also provide valuable pathogenetic clues linking inflammation and hypertension, which has become particularly relevant in the light of links between hypertension and autoimmune disorders or more recently, COVID-19 [99].

Article information

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