TOPIC: "*Hot topics in hypertension: periodontal disease and hypertension*"

TITLE: Periodontitis and hypertension: is the association causal?

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Fundings: none specific

Conflicts of interest: none

Abstract

High blood pressure (BP) and periodontitis are two highly prevalent conditions worldwide with a significant impact on cardiovascular disease (CVD) complications. Poor periodontal health is associated with increased prevalence of hypertension and may have an influence on blood pressure control. Risk factors such as older age, male gender, non-Caucasian ethnicity, smoking, overweight/obesity, diabetes, low socioeconomic status, and poor education have been considered the common denominators underpinning this relationship. However, recent evidence indicates that the association between periodontitis and hypertension is independent of common risk factors and may in fact be causal in nature. Low-grade systemic inflammation and redox imbalance, in particular, represent the major underlying mechanisms in this relationship. Neutrophil dysfunction, imbalance in T cell subtypes, oral-gut dysbiosis, hyperexpression of proinflammatory genes, and increased sympathetic outflow are some of the pathogenetic events involved. In addition, novel findings indicate that common genetic bases might shape the immune profile towards this clinical phenotype, offering a rationale for potential therapeutic and prevention strategies of public health interest. This review summarizes recent advances, knowledge gaps and possible future directions in the field.

Keywords

Hypertension; Periodontal Diseases; Inflammation; Public Health

Introduction

Cardiovascular diseases (CVD) represent the most common non-communicable diseases linked to mortality worldwide, accounting for about one third of global deaths [1]. Their occurrence is strongly associated with hypertension, a leading cardiovascular risk factor affecting over 1 billion individuals [2]. Although predominantly lacking an identifiable aetiology, several dysfunctional pathways have been associated with high blood pressure (BP), including low-grade chronic inflammation and redox imbalance [1] (**Figure 1**).

Periodontitis is a chronic multifactorial inflammatory disease associated with dysbiotic plaque biofilms and characterized by progressive destruction of the tooth-supporting apparatus, and is estimated to affect nearly one in two persons worldwide [3]. The clinical spectrum of periodontal diseases varies from simple gingival inflammation (i.e. gingivitis) to more severe forms of the disease including alveolar bone resorption leading ultimately to tooth loss (i.e. periodontitis). A relapsing-remitting behaviour mainly due to fluctuations in local microflora dysbiosis and host inflammatory response dictates the development of periodontal diseases [4] (**Figure 1**). There is evidence of an association of periodontitis with nearly 60 extra-oral conditions [5], including, but not limited to, cardiovascular risk factors and diseases like hypertension, obesity, atherosclerosis, diabetes and stroke. In recent years, it has become evident that the observed association between periodontitis and hypertension is more than a simple sharing of common risk factors. Indeed, novel findings support the biological role of common genetic bases in this relation, offering a rationale for potential therapeutic and prevention strategies of public health interest. This review summarizes recent advances, persistent gaps and possible future directions in the field.

Periodontitis and hypertension: the common background

Periodontitis and hypertension share specific demographics and risk factors such as older age, male gender, non-Caucasian ethnicity, smoking, overweight/obesity, diabetes, low socioeconomic status, and poor education [6–12]. According to 2015–2016 data from the National Health and Nutrition Examination Survey (NHANES), the prevalence of hypertension increases from 7.5% in the age group 18–39 years to 63.1% among individuals aged ≥60 years [13]. Similarly, the prevalence of periodontitis increases from about 30% in the age range of 30–44 years to about 60% among seniors aged 65 years and over [14]. Despite both conditions being common in older individuals, the association of PD and hypertension is independent of age, as it is observed also among young and middle-aged adults [15,16].

Individuals of Afro-American ethnicity are particularly susceptible to both high/uncontrolled BP and periodontitis [6,17–19]. According to the 2020 American Heart Association (AHA) Heart Disease and Stroke Statistics, the prevalence of hypertension among US non-Hispanic Black men and women aged ≥20 years is 58.6% and 56%, respectively, i.e. +10–15% higher than other ethnic groups [20]. Similarly, data from the 2009 to 2014 NHANES data revealed a prevalence of periodontitis of approximately 57% among non-Hispanic Black US adults aged ≥30 years, i.e.about +20% compared with non-Hispanic Whites [14]. Besides the possible role of socioeconomic factors, the hypothesis of a genetic predisposition behind this association should not be discarded. Abnormalities in the renin-angiotensin-aldosterone system (RAAS) and increased levels of the pressor peptide endothelin-1 (ET-1) appear to contribute to increased prevalence and severity of hypertension in Blacks [19,21]. Interestingly, gene

variantsof the angiotensin converting enzyme (ACE) and angiotensin II type-I receptor (AT1R) have been observed in patients with periodontitis [22], and interactions of the ET-1 and ACE genes with that of the pro-inflammatory cytokine tumor necrosis factor β (TNF-β) have been described as potentially involved in modulating susceptibility to periodontitis [23].

Socioeconomic status, strictly related to education and income, represents a central determinant of health status awareness and access to healthcare [24], and this issue extends to the field of oral health [25]. The association between socioeconomic status and global health is complex. For instance, socioeconomic indicators like smoking, dietary habits, frequency of dental visits, and oral hygiene practice explain only in part the socioeconomic disparities in oral health [26,27]. In keeping with this, income disparities do not fully explain nor simply confound the association between periodontitis and high/uncontrolled BP. In fact, the association between periodontitis and high BP/uncontrolled hypertension was confirmed among high-income NHANES participants enrolled in the 2009-2014 campaigns after controlling for common denominators[28]. Specifically, in the presence of periodontitis, individuals with poverty-to-income ratio ≥4 (mean 4.8±0.3) had 6 mmHg higher systolic BP and 26% higher odds of systolic BP ≥130 mmHg compared with those without the disease [29]. Although high BP and periodontitis share common pathogenetic mechanisms with metabolic diseases like obesity and diabetes, including insulin resistance and oxidative stress, the epidemiological associations reported between hypertension and periodontitis are confirmed in these diseases and independent of these factors [15,16,30].

Clinical evidence on the association between PD and hypertension

An updated, comprehensive meta-analysis of studies published up to December 2018 has recently summarised the available data on the odds of hypertension in the presence of periodontitis [31]. The systematic review included different outcome measures and reported on the changes in BP after periodontal therapy [31]. Using the definition of hypertension as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg, or the use of anti-hypertensive medications, participants with moderate-severe and severe periodontitis had an increased 20 to 50% odds of hypertension [31]. The magnitude of this association was similar to that observed in studies where a lower threshold for the definition of hypertension was applied. Specifically, periodontitis was associated with about 20% higher odds of BP ≥130/80 mmHg compared with the absence of the disease in treated hypertensive adults ≥30 years enrolled in 2009 to 2014 NHANES campaigns [15]. An earlier systematic review and meta-analysis on longitudinal and cross-sectional studies found that moderate to severe periodontitis was associated with hypertension (BP ≥140 and/or 90 mmHg, or use of antihypertensive medications) with an odds ratio (OR) of 1.50 (95% CI, 1.27-1.78), which increased to 1.64 (95% CI, 1.23-2.19) in a sensitivity analysis including only studies with secure diagnosis [32]. Interestingly, observational and intervention studies indicate that the systolic BP component is more consistently associated with periodontitis than diastolic BP both in terms of magnitude and strength of the association [15,16,31,33]. According to observational evidence from 29 cross-sectional and case-control studies (including >200000 individuals), participants with periodontitis exhibited higher 4.5 and 2 mmHg systolic and diastolic BP, respectively [31]. Indeed, intervention studies on populations at different baseline risk - including healthy individuals and those with pre-hypertension, refractory hypertension, diabetes mellitus, or coronary heart disease -

indicated a reduction in systolic BP after periodontal therapy of 3 to 12.5 mmHg, whereas the benefit on diastolic BP was inconsistent, with some studies reporting no changes and other showing a maximum reduction in this parameter by about 10 mmHg [34–39]. While it is not possible to exclude a role for age-related arterial stiffness behind this finding, it must be noted that the same is confirmed among individuals aged 30 to 45 years [15][35], supporting the possibility of an age-independent increase in arterial stiffness in periodontitis patients [35]. In the only two intervention studies where ambulatory BP measurement was performed — one prospective cohort pilot study on 26 individuals with refractory hypertension and generalized chronic periodontitis treated according to their needs [36]; and a single-centre, parallel-group, randomized clinical trial (RCT) on 101 hypertensive individuals with moderate-severe periodontitis that compared intensive versus conventional care [40] —, both systolic and diastolic BP significantly decreased after periodontal treatment. In the pilot study by Vidal et al, where participants' mean age was 53.6±8.0 years, also arterial stiffness was reduced by periodontal treatment [36]. In the RCT by Czesnikiewicz-Guzik et al, a subgroup analysis indicated that the benefit of treatment on BP was less evident at older age (cutoff at 58 years) [40].

Eight RCTs in the past fifteen years have examined the effects of periodontal therapy on BP [3,41], and only one trial defined BP changes after periodontal treatment as the primary outcome [37]. This study randomized 95 patients with prehypertension and periodontitis to intensive (n=48) and control (n=47) periodontal treatment for 4 consecutive weeks. After 6 months, systolic and diastolic BP were significantly reduced in the intensive group compared with the standard group by about 12.6 and 9.6 mmHg [37]. A previous smaller RCT on 40 otherwise healthy individuals with severe periodontitis randomized to standard or intensive periodontal treatment found that systolic BP was reduced by a mean of 7 mmHg six months after therapy [34]. A similar benefit was also found among patients with coronary heart disease (n=30) compared with controls (n=25) [39]. Conversely, 4 RCTs on a total of 462 patients did not detect significant benefits of periodontal treatment on BP [42–45]. As previously reported there is still insufficient evidence supporting a beneficial role of periodontal therapy in reducing BP [3,41]. To date, 9 studies are found to be registered on clinicaltrials.gov regarding PD and hypertension. Of them, the only two trials exploring BP changes as the primary outcome in hypertensive patients are from the authors of this review [46]. In particular, the *PERIOTENSION* Trial aims at testing the effects of professional care or domestic oral hygiene with electric toothbrush on BP control in treated hypertensive patients.

Plausible biological link between periodontitis and hypertension

A cornerstone paper by Tonetti et al (2007) reported the results of the largest trial investigating the effects of professional periodontal treatment on endothelial function involving systemically healthy individuals [45]. Participants with severe periodontitis were randomised to usual care or intensive periodontal treatment, and measured flow-mediated dilatation of the brachial artery, as well as biomarkers of inflammation, coagulation and endothelial activation before and after treatment. Changes in BP were also a secondary outcome reported. An early increase in the levels of inflammatory mediators and BP, as well as endothelial dysfunction were observed shortly after treatment. Six months later, however, the endothelial function had significantly improved in parallel with the improvement in periodontal variables, and mean systolic BP was about 1.3 mmHg lower in the intensive compared

with the standard treatment group, although this difference was not statistically significant [45]. This is not unexpected, as endothelial dysfunction is only one of the mechanisms leading to hypertension, with an important role of renal and central control mechanisms [47–49]. Nevertheless, periodontitis can act as a source of inflammation and oxidative stress and it might contribute in the long term to functional and anatomic vascular changes, leading to arterial stiffness, increased vascular resistance and volume overload, with ultimate rise in BP [41,47].

Hypertension is considered a condition of low-grade inflammation at least in part involving the activation of the adaptive immune system [50,51]. Recent studies demonstrated a central role for T cells in the development of hypertension [50–52]. Specifically, following hypertensive stimuli, activated T cells accumulate in the perivascular tissue, where they release cytokines (i.e. TNF alpha, IL-6, IL-17) that, in turn, contribute to the development of high BP [50,53]. New evidence is pointing out to a few subsets of T cells particularly involved in vascular pathology. CD8 T cell senescence is an important feature of hypertension [54]. Indeed, in the most recent interventional study, intensive periodontal treatment contributed to the decrease of the percentage of activated CD8 cells and CD28 null CD57+ cells [40]. Additionally, T_H17 cells may play a significant role in pathomechanism of hypertension. IL-17 mediates the increase in superoxide production which scavenges NO from the vessel wall contributing to NO-mediated vasodilation, and contributes to inflammatory cells recruitment to the perivascular tissue [55]. Interestingly, the dysbiosis-dependent expansion of T_H17 cells appears central also in the development of periodontitis, and people naturally deficient in T_H17 cells are less likely to develop periodontitis [56,57]. Another subset of T cells of relevance in both conditions is represented by regulatory T cells (Tregs). In contrast with T_H17 cells, Tregs have a protective effect in hypertension by the antagonism of angiotensin II and the reduction in circulating activated T cells [58], and attenuate the severity of periodontitis through the expression anti-inflammatory cytokines, such as IL-10 and TGF-β [59]. Neutrophils are also involved in both periodontitis and hypertension. Defects in neutrophil chemotaxis, phagocytosis and killing have been described in aggressive forms of periodontitis [60,61], and the proper functioning of these cells appears central for a good periodontal health [62–64]. An interesting study has recently revealed that a high-salt diet, which is a common environmental trigger of hypertension, can impair antibacterial responses of neutrophils through salt-induced hyperglucocorticoidism and consequent glucocorticoid-mediated immunosuppression [65]. Specifically, mice on a high-salt diet experienced exacerbated local and systemic infections due to a reduced capacity of neutrophils to kill ingested bacteria. Neutrophils from healthy human volunteers on a high-salt diet for 1 week showed similar hormonal perturbations and impaired antibacterial neutrophil function [65].

A recent publication by our group indicated that the association of severe periodontitis with BP depends not only on the active periodontal inflammation, but also on its combination with chronic disease parameters [66]. The combination appears to amplify the magnitude of the association, suggesting that different molecular pathways of inflammation might concur in shaping the systemic impact of periodontitis [66].

Local dysbiosis is considered one of the pathogenetic events in periodontitis, and there is evidence indicating that systemic inflammatory pathways associated with periodontitis are triggered by periodontal pathogens [67,68]. As an example of their impact on the cardiovascular system, periodontal pathogens have been detected in relevant

extraoral sites including atheromas [69] and aortic/intracranial aneurysms [70,71]. A study on 653 dentate men and women enrolled in the oral infections and vascular disease epidemiology study (INVEST) indicated that the levels of subgingival periodontal bacteria had a direct relationship with both systolic and diastolic BP, as well as with the prevalence of hypertension [72]. Further, antibody titers to periodontal bacteria, which can be considered a host-related phenotype of periodontal microbiota, have been associated with hypertension [33]. Specifically, higher systolic (+3 mmHg) and diastolic (+2 mmHg) BP and greater odds (+10-13%) of high/uncontrolled BP were found among 7,928 adults enrolled in NHANES in association with antibodies to *Campylobacter rectus*, *Veillonella parvula*, and *Prevotella melaninogenica* (*hypertension-associated oral pathogens*, HOP) [33]. In this study, antibodies titers to HOP, but not to other periodontal bacteria, progressively increased across BP categories as defined by guidelines [73]. In particular, normotensive participants showed significantly lower serum IgG levels to HOP compared with patients with stage 1, 2 or treated hypertension, but this was not observed for antibodies against other periodontal bacteria [33].

In September 2019, the first evidence of a significant relationship between periodontitis-linked single nucleotide polymorphisms (SNPs) and BP was published [40]. The examined SNPs were detected in genes involved in the immune function, i.e. those of defensin alpha 1 and alpha 3, and CD170, supporting the pathogenetic hypothesis of a common proinflammatory milieu (**Figure 1**). These cornerstone findings add to the available evidences regarding the common genetic background of CVD and periodontitis [74–77], and pave the way to future mechanistic studies on this topic.

Periodontitis and cardiovascular risk: current recommendations and gaps in the evidence

The most up to date evidence regarding the associations between periodontitis and CVD derives from the workshop organized by the European Federation of Periodontology (EFP) and the World Heart Federation (WHF) in February 2019 [3]. According to its final recommendations, periodontitis is acknowledged as an established, novel cardiovascular risk factor that affects the management of people who suffer from or are at increased risk for CVD. In the light of this, the consensus document concludes that an active management of traditional cardiovascular risk factors, including hypertension, is required in the presence of periodontitis, and that restoring or preserving a good periodontal health is of crucial importance for achieving global health. However, a definition is lacking regarding the possible systematic approach to periodontal treatment in specific settings, i.e. uncomplicated hypertension, given the limited evidence in this field that can be attributed to practical issues, including ethical concerns in conducting periodontal sham therapy in RCTs. Specific solutions and answers to these open questions are, therefore, eagerly awaited.

Estimated surface of periodontium equals that of the palm of a hand (**Figure 2**). The effect of the local inflammation of this substantial size occurring during generalized periodontitis might contribute significantly to systemic inflammation (**Figure 2**) [78]. The global benefit of maintaining or achieving periodontal health not only adds to that from traditional measures undertaken to reduce CVD risk, but it can be of importance for the efficacy of antihypertensive treatment [15], and in the management of refractory hypertension, potentially through the reduction of systemic inflammation [36] (**Figure 2**). In fact, the effects of periodontal treatment on BP reduction could be

compared in magnitude to that from lifestyle modifications with established effect on BP, and achieving BP control is more likely in the presence of periodontal health [15]. For instance, lowering salt intake by 1 teaspoon reduces systolic BP by about 3 mmHg [79]. Similarly, the benefit of reducing sugar intake on BP is estimated to be of about 4 to 8 mmHg [80–82], while limiting alcohol intake might contribute to BP reduction by 2 to 4 mmHg [32]. Further, regular aerobic and aquatic exercise may significantly decrease systolic BP by about 5 and 8 mmHg, respectively [83,84]. All these non-pharmacological measures are part of a correct lifestyle approach to reduce the CVD burden. In this context, the appropriate administration of periodontal therapy would contribute to the reduction of low-grade systemic inflammation and the achievement of good global health.

Conclusions

The central role of immunity and inflammation in CVD, together with the substantial evidence linking periodontitis with systemic diseases, have led to consider this condition as an emerging cardiovascular risk factor. Achieving and maintaining periodontal health contributes to the global wellbeing of individuals, irrespective of their baseline risk. Whether periodontal treatment in patients with hypertension would translate into a cost-effective approach for cardiovascular risk reduction is yet to be determined; however, this intriguing possibility deserves further investigation.

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Figure legends

Figure 1. Common pathogenetic events in periodontitis and hypertension. Immunity/inflammation and redox status are interconnected with both conditions. Some of the keystone pathogenetic features in this relationship are listed.
ROS=reactive oxygen species.

Figure 2. Plausible events in the association of periodontitis with elevated/uncontrolled blood pressure. See text for details.
BP=blood pressure