

Periodontitis is associated with Hypertension. A systematic review and Meta-analysis.

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Abstract

Recent evidence suggests a link between periodontitis (PD) and hypertension, but the nature of this association remain unclear. The overall aim of this review was to critically appraise the evidence linking these two common disorders. Systematic search was conducted for studies published up to December 2018. Prevalence of hypertension in patients with PD (moderate/severe groups) versus those without PD (non-PD) was the primary outcome. Additional outcomes included adjusted mean difference in systolic (SBP) and diastolic (DBP) blood pressure (BP) levels in PD vs non-PD, assessment of biomarkers in PD and hypertension and BP changes after periodontal therapy. From eighty-one studies selected, 40 were included in quantitative meta-analyses. Diagnoses of moderate-severe PD (OR= 1.22; 95% CI, 1.10, 1.35) and severe PD (OR=1.49; 95% CI, 1.09-2.05) were associated with hypertension. Prospective studies confirmed PD diagnosis increased likelihood of hypertension occurrence (OR=1.68; 95% CI, 0.85-3.35). Patients with PD exhibit higher mean SBP (WMD of 4.49 mmHg; 95% CI, 2.88, 6.11) and DBP (2.03 mmHg; 95% CI, 1.25-2.81) when compared to non-PD. Lastly, only 5 out of 12 interventional studies confirmed a reduction in BP following periodontal therapy, ranging from 3-12.5 mmHg of SBP and from 0-10 mmHg of DBP. Periodontitis is associated with increased odds of hypertension (SORT C) and higher SBP/DBP levels. The evidence suggesting that PD therapy could reduce BP is inconclusive. Although additional research is warranted on this association, these results suggest that oral health assessment and management of periodontitis could not only improves oral/overall health and quality of life but also be important in patients with hypertension.

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Introduction

Hypertension, defined as values ≥ 140 mmHg Systolic Blood Pressure (SBP) and/or ≥ 90 mmHg Diastolic Blood Pressure (DBP), is the most prevalent of all cardiovascular diseases (CVDs)(1). Almost 45% of the worldwide population is affected and the estimate increases steeping with age (2). The incidence of adverse cardiovascular (CV) events such as stroke, myocardial infarction, sudden death, heart failure and peripheral artery disease as well as of end-stage renal disease is strongly associated with hypertension (3, 4). According to the world health organisation (WHO) report in 2014, hypertension accounts for 51% of deaths from stroke and 45% of overall CV mortality and this is true at all ages and in all ethnic groups (2). Blood pressure values are an important predictor of cardiovascular risk (5, 6). Despite available treatments, essential hypertension remains poorly controlled with high rates of no treatment and under-treatment (7). Hence, it is still one of the major modifiable risk factor for CVDs that requires urgent management (8). Hypertension is a complex multifactorial disease with no simple mechanism entirely explaining the blood pressure rise (9). Endothelial dysfunction (as manifested by changes in endothelin and nitric oxide), oxidative stress, and inflammation are implicated in the development of hypertension. Despite a prominent role of the immune system has been observed in experimental models (10) and clinical studies (11) studying the onset of hypertension, the exact mechanisms initiating these responses remain unclear (12).

Periodontitis is a chronic multifactorial inflammatory disease caused by a dysbiotic microflora and resulting in progressive destruction of the dental surrounding tissues and leading to tooth loss. It is associated with masticatory dysfunction and negative impact on the patient's quality of life (13). It is estimated that periodontitis affects over 50% of the worldwide population and its severe form is considered the 6th most prevalent disease of humankind (14, 15). Periodontitis is a major public health problem that considerably increases morbidity and costs of oral health care (16, 17). There is consistent observational evidence that periodontitis is associated with an increased risk for future CVDs independent of traditional risk factors such as smoking and obesity (17, 18). The interplay between the bacterial burden and host response is the most plausible biological mechanism linking periodontitis a number of chronic systemic diseases, such as diabetes mellitus, CVDs and neurological diseases such as Alzheimer (17, 19, 20). An ulcerated epithelial lining of the gingival pocket, subsequent to a local inflammatory response to the dental biofilm could amount to a sizeable area in patients with generalized periodontitis (21). These patients often present with systemic inflammation and endothelial dysfunction (22), which improves following successful periodontal treatment (23).

Several studies appear to support a relationship between severe periodontitis and hypertension (24-27). Limited evidence also suggests that successful periodontal treatment could improve arterial blood pressure (28, 29). However, little is still known about the direction and nature of the association between these two conditions. The overall aim was to conduct a robust critical appraisal of the evidence on the relationship between periodontitis and hypertension. Specific research questions were designed based on the following PECO outline: Population: Individuals >16 years old; Exposure: Presence of periodontitis with/without treatment; Comparison: Individuals with no periodontitis; Outcome(s): Any measure of prevalence and/or levels of hypertension and/or changes in blood pressure following periodontal therapy. In this analysis we addressed several key questions:

- Are patients with periodontitis more likely to have hypertension (compared to those without periodontitis)?
- Is the degree of hypertension influenced by the severity and/or extent of periodontitis (linear association)?
- Is the mean SBP/DBP higher in patients with periodontitis versus those without periodontitis?
- Does periodontal therapy modify the levels of blood pressure?

Material and Methods:

The systematic review protocol was registered in PROSPERO on 28/11/2017 with ID: CRD42017081455. A PRISMA statement is attached to follow the reporting of this systematic review (Appendix 1).

Primary and secondary outcomes:

The primary outcome of this systematic review was OR/RR and CI for hypertension in individuals with periodontitis.

The secondary outcomes included prevalence of hypertension in patients with periodontitis vs patients without periodontitis as well as prevalence of periodontitis in patients with or without hypertension; reports of mean SBP/DBP levels in periodontally-healthy and diseased patients; systemic biomarkers associated with periodontitis and hypertension and changes in BP measurements following periodontal therapy.

Inclusion/Exclusion Criteria

To obtain an estimate of the association between periodontitis and hypertension, inclusion criteria were set to be broad and inclusive. Prospective and retrospective studies were included (randomized controlled trials, controlled clinical trials, cohort studies, case-control studies and cross-sectional studies). Eligibility criteria included individuals from age 16 years onward, with periodontitis (chronic and/or aggressive forms) considered as the exposure. Manuscripts including information related to primary and secondary outcomes were included.

Case report, case series and reviews and animal studies were excluded. Individuals under 16 year's old and pregnant women were also excluded. Lastly, studies that did not have any reports of the primary or secondary outcomes were disqualified.

Search methods for identification of studies:

Five electronic databases were searched up to the 10th December 2018 with no year restrictions (Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (OVID), EMBASE, Web of science, LILACS). The search included no language restrictions and attempts were made to translate non-English language papers. In addition, SIGLE database was examined for relevant unpublished trials. Performed detailed search strategies deemed appropriate for each database using a combination of controlled vocabulary (MeSH terms and free text terms). Supplementary table with all terms is available (Appendix 2).

MeSH terms in all trees and subheadings: "periodontal diseases", "periodontics", "hypertension", "blood pressure".

Keywords: "periodont\$", "gingiv\$", "((blood or bleed\$) adj4 prob\$)", "(ging\$ adj disease)", "hypertens\$", "((elevat\$ or high\$ or rais\$) adj3 (diastolic or systolic or arterial or blood) adj pressure)", "bloodpressure".

Hand searching of bibliographies of papers and review articles retrieved articles not found through other search methods.

Data management:

The eligibility assessment of titles and abstracts (when available) of all reports identified were independently screened by two reviewers based on inclusion/exclusion criteria (EMA & JS). If agreement could not be reached, the study was moved to the next stage and inclusion was based on full text screening. Full reports were obtained and assessed independently and in duplicate (EMA and JS) for studies seeming to meet the inclusion criteria or for which insufficient information in the title and abstract precluded to make a clear decision. Disagreements were resolved by discussion and if necessary, a third reviewer was consulted (FD). When authors were not reporting on an effect estimate they were contacted to request additional information. Excel sheets were created to document information regarding decision for included and excluded articles. Kappa statistic was used to assess the agreement between the reviewers based on full text screening.

The main categories of data grouped according to study design and reported in evidence tables were study characteristics data; population; exposure (case definition for periodontitis); outcome (case definition for hypertension); effect (OR/RR with CI); and publication conclusions.

Regarding the exposure, multiple case definitions for periodontitis were found. A lack of consistent case definitions contributed to the difficulty in assessment and interpretation of the data retrieved. In order to collate studies looking at similar definitions, results were therefore grouped using two case definition thresholds: confident and non-confident case definition of periodontitis based on the following criteria (adapted from a previously reported definition) ((30).

Confident case definition of periodontitis: The following criteria were considered as a confident case definition for periodontitis: Generalized chronic periodontitis (at least 30% sites with CAL \geq 4 mm) (31); at least 2 sites on different teeth with clinical attachment level (CAL) 6 mm and at least 1 site with probing pocket depth (PPD) 4 mm (CDC/AAP periodontitis definition) (32); presence of proximal attachment loss of $>$ 3mm in two or more nonadjacent teeth (sensitive definition) or presence of proximal attachment loss of $>$ 5 mm in $>$ 30% of teeth present (33); at least 5 sites with CAL \geq 6 mm (34).

Non-confident case definition of periodontitis: For non-confident case definition the following reported criteria were considered: Community periodontal index (CPI) score 3/4 in at least 1 quadrant; "Alveolar bone loss" without other measurements of PPD/CAL; unclear diagnostic criteria for periodontitis.

Regarding the outcome, hypertension was defined as SBP \geq 140 mm Hg / DBP \geq 90 mm Hg or the use of anti-hypertensive medications (1, 2). However, reports of BP levels and other cases definitions were also documented for, such as self-reported hypertension and other thresholds (high normal/prehypertension).

Assessment of bias individual studies:

Quality assessment of all included studies were undertaken independently and in duplicate by two reviewers as part of the data extraction process. For bias assessment of randomised controlled trials, non-randomised studies of interventions, and observational studies we used the revised Cochrane tool (ROB-2.0 tool) (35), the ROBINS-I tool (36) and the Newcastle-Ottawa (NOS) tool (37) respectively.

Data Synthesis:

Descriptive statistics were performed to summarise the evidence retrieved and to determine the quantity of data, checking further for study variations in terms of study characteristics and results. This assisted in confirming the suitability of further synthesis methods.

Meta-analysis A was conducted and referred to the following primary outcome: ORs for hypertension among people with or without a diagnosis of periodontitis. The ORs with adjustment for the confounding variables (i.e. age, gender, smoking, socioeconomic status, systemic disease, medication, body mass index etc.) was chosen with hypertension as the dependent variable and periodontitis as the independent variable. Pooled estimates of OR and corresponding 95% confidence intervals, were calculated for dichotomous data. In presence of significant heterogeneity ($p < 0.1$), the pooled estimates of effects were calculated using random effects models rather than fixed effects models. Meta-analysis B referred to the secondary outcome (mean SBP/DBP). The pooled mean SBP/DBP difference and 95% confidence intervals were estimated for continuous data. RevMan[®] 5.3 and JMP[®] 13.0.0 were used for all the statistical analyses.

To evaluate whether the methodological quality of the included studies influenced the direction or the magnitude of the results, we performed a separate sensitivity analysis by study design and either disease severity or case definition (Fig. 2-Fig. 3C and Appendix 5).

Publication bias:

Possible publication bias was assessed for studies included in the different meta-analyses A and B using the methods described by Begg and Egger (38, 39).

Heterogeneity:

The significance of any discrepancies in the estimates from different trials was assessed by means of Cochran's test for heterogeneity and the I² statistic. As alluded above, sensitivity analyses were also planned to explore, quantify and control for sources of heterogeneity between studies.

Strength of recommendation:

The quality and strength of the evidence was assessed with The SORT (Strength of Recommendation Taxonomy). The authors discussed the outcomes of the systematic review, pertinent sources of evidence, clinical recommendations and future areas requiring research (40).

Results:

The electronic search from combination of all databases identified 5575 potentially relevant articles after removal of duplicates, resulting in 182 publications eligible for full text screening. Eighty-one publications met inclusion criteria (Figure 1). The evidence tables created according to study design, included the main study characteristics (Appendix 3). The studies included in the systematic review have been conducted in 26 different countries from all continents involving a large variety of different populations. Authors achieved an almost perfect agreement with a percentage of 97.24%; Cohen's k: 0.94.

A variety of case definition of periodontitis were identified (as shown in evidence tables, Appendix 3). For hypertension diagnosis, the studies generally reported more uniformed criteria based on levels of SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg or use of antihypertensive medication (41). Nevertheless, some studies reported lower cut offs for hypertension (i.e. SBP ≥ 130 mm Hg and/or DBP ≥ 85 mm Hg) (42) or hypertension prevalence was based on medical records, self-report or national classification codes for disease. Similarly, different methods for measuring blood pressure were described in the studies included (Appendix 3). For additional or missing data, of all the authors contacted, only 3 provided additional information regarding the direction of the association and/or mean SBP/DBP following periodontal therapy (43-45).

Study quality for observational studies as assessed by the Newcastle Ottawa scale varied across the studies, ranging from a score of 3/9 to 9/9 (Appendix 4). The assessment revealed several

potential sources of bias including to the adequacy of case definition for cases and controls, the representativeness of the cases, no appropriate description of the sample size calculation, lack of adjustment for potential confounders or inappropriate statistical test. The assessment of randomised controlled trials with the Rob 2.0 tool revealed a low (5 studies) to high (2 studies) risk of bias for the studies included (Appendix 4). The main reasons for high risk of bias in randomised controlled trials arise from the randomization process, blinding of participants and personnel. Study quality for non-randomized trials revealed moderate and serious risk of bias for the two studies assessed with the Robinsin I tool (Appendix 4).

Primary outcome

Twenty studies included in 5 meta-analyses (A) of cohort, cross sectional and case-control studies (Fig. 2-Fig. 3C and Appendix 5) compared the odds of having hypertension if an individual had periodontitis versus periodontally healthy individuals using a periodontal case definition as the exposure measure.

Statistically significant heterogeneity was confirmed with a Tau-squared test (ranging from 0.32 to 0.03), Chi-squared test ranging from (ranging from <0.00001 to 0.008) and I2 test (ranging from 63% to 92%) for the different analyses completed. Due to this level of heterogeneity observed in the studies, random effect meta-analysis was performed.

Odds ratios ranged from 0.90 to 4.20 for all studies, depending on case definition applied, severity of periodontitis and adjustment of the models. Precision of the estimates in the studies varied considerably as appreciated in the varying span of the confidence intervals. Two studies (24, 46) reported ORs for moderate to severe periodontitis separately and one study (47) reported OR for men and women also separately, therefore these different ORs were included independently.

The analysis of three cohort studies predicted the occurrence of hypertension (OR=1.68; 95% CI, 0.85-3.35), but this was not statistically significant ($p=0.14$) (Appendix 5). Three studies were excluded from this meta-analysis due to one of them reported RR (48) and the other two appeared to be duplicated data (45, 49). Diagnosis of moderate-severe periodontitis in 15 cross-sectional and case-control studies was associated with higher odds of hypertension (1.22, 95% CI 1.10, 1.35), which was statistically significant ($p=0.0001$) (Fig. 2). A meta-analysis of 8 cross-sectional and case-control studies confirmed that patients with severe periodontitis had increased odds (1.49, 95% CI 1.09, 2.50; $p=0.01$) of diagnosis of hypertension (Figure 3A). Additionally, meta-analyses of studies according to confident

versus non-confident case definitions of periodontitis were performed. Seven studies with confident definition of periodontitis confirmed higher odds of hypertension (1.53, 95% CI 1.11, 2.10; $p=0.009$) compared to a meta-analysis of 8 studies with a non-confident definition of periodontitis (1.33, 95% CI 1.14, 1.55; $p=0.003$) (Figures 3B and 3C).

Secondary outcomes:

Prevalence: Thirty studies reported prevalence of hypertension in patients with periodontitis versus patients without periodontitis or gingivitis (Appendix 6). Twenty-five of these studies showed a higher prevalence of hypertension in patients with a diagnosis of periodontitis (range=7-77%) versus those without periodontitis (range=4-70%) and one study only confirmed higher prevalence in men (50). These findings were not confirmed in 4 studies (51-54). In addition, a consistent increased prevalence of periodontitis in patients with hypertension (range=29-61%) versus those without hypertension (range=17-39%) was reported in all the 7 publications that included this outcome (Appendix 6).

Mean blood pressure: Thirty-one studies reported average mean SBP/DBP in patients with (range SBP=113-172/DBP=66-101mmHg) and without periodontitis (range SBP=109-143/DBP=65-94mmHg) (Appendix 7). The meta-analysis B, of mean SBP/DBP of 26 studies was performed resulting in statistically significant heterogeneity, confirmed with a Tau-squared test (ranging from 14.38 to 2.92), Chi-squared test ranging from (<0.00001) and I² test (ranging from 96% to 98%). Patients with periodontitis exhibited higher SBP (WMD of 4.49mmHg, 95% CI 2.88, 6.11; $p<0.00001$) and DBP (WMD of 2.03mmHg, 95% CI 1.25, 2.81; $p<0.00001$) when compared to patients without periodontitis (Figures 4 and 5).

Biomarkers: Three studies were included in the review as reporting biomarkers associated with hypertension and periodontitis (55-57). One study analysed serum levels of neutrophilic enzymes in 95 patients (55). They included a test group of patients with hypertension and periodontitis and 2 control groups: a healthy group (without periodontitis or hypertension) and a hypertensive group. The authors observed that circulating levels of matrix metalloproteinases (MMP)-8, MMP-9, myeloperoxidase and neutrophil elastase (NE) were increased in patients with hypertension and periodontitis but not in the controls. Another study examining the gingival crevicular fluid (GCF) levels in patients with hypertension (21 patients) and without hypertension (26 patients) measuring levels of 8-isoprostane, interleukin (IL)-1B, monocyte chemoattractant protein (MCP)-1, tumour necrosis factor (TNF) α , C-reactive protein (CRP), and MMP-8 (56). They reported that independent of

hypertension present or absent, an increased level of these biomarkers was observed when patients had periodontal pockets. In addition, patients with hypertension presented with almost twice as much periodontal clinical attachment loss (CAL) as controls (Mean + SEM in HTN= 0.87±0.13 vs non-HTN= 0.49±0.11). Albush and co-workers assessed levels of vascular thrombotic markers in 40 hypertensive patients with periodontitis (57). Platelet count, fibrinogen, Von Willebrand factor antigen (vWF:Ag) and D-Dimer levels increased after 48h of treatment (scaling of the teeth including subgingival root debridement for half of the patients and surgical periodontal therapy for the other 20) and decreased after 6 weeks ($p<0.05$), with no significant differences between groups ($p>0.05$). Acute increase in endothelial-activation markers including E-selectin, vWF, haemoglobin and haematocrit, D-dimer levels and neutrophils counts was also reported 24 hours following periodontal therapy in several publications (22, 44, 58). Reductions in inflammatory biomarkers were observed in 11 interventional studies following periodontal therapy (22, 28, 29, 44, 59-65).

Response to treatment: The search located 12 interventional clinical trials reporting the effect of periodontal therapy on blood pressure either as a primary [(65)] or secondary outcome (the remaining 11 studies) (See Appendix 3 for a detailed description of the studies and treatment modalities). Eight studies were RCTs, 3 were non-RCT and 1 was a pilot study. These studies comprised a varied sample of individuals, including people medically healthy in 6 studies (22, 28, 44, 58, 59, 62) pre-hypertension (65), refractory hypertension (29), hypertension (59), metabolic syndrome (63), coronary artery disease (60) and type 2 diabetes (64). Five of the 12 interventional studies included in the analysis confirmed a reduction in SBP following periodontal therapy (range=3-12.5 mmHg), and an inconsistent reduction of DBP (range=0-10 mmHg) (28, 29, 61, 64, 65). Six studies reported no changes in blood pressure measures following non-surgical and/or surgical periodontal therapy (44, 58-60, 62, 63), however, only 2 studies reported actual blood pressure values (59, 60) and one author provided values upon request (44). One study (22) reported an increase in blood pressure in the test group one day after periodontal therapy.

Publication bias:

Study publication bias was examined using funnel plots for both meta-analyses A and B (Appendix 8). Egger's test was only calculated for the meta-analyses A of moderate to severe periodontitis (Appendix 8). Visual assessment of the Funnel of moderate-to severe periodontitis revealed studies were slightly skewed to the right, which was confirmed with the Egger's test showing a statistically significant difference ($p=0.0054$); publication bias was therefore suspected in this analysis. Nevertheless, all the other funnel plots for meta-analyses A displayed symmetrical

appearance. Similarly, visual assessment of the Funnel plots for mean SBP and DBP analysis revealed symmetrical appearance. Egger's test estimated for meta-analyses B revealed a not statistically significant result ($p=0.5582$) for the mean SBP meta-analysis and a statistically significant difference ($p=0.0224$) for the mean DBP meta-analysis. On this basis, publication bias was suspected in the mean DBP meta-analysis.

Reporting on strength of recommendation:

The quality, quantity and consistency of the evidence from observational and interventional studies on the relationship between periodontitis and hypertension was thoroughly assessed for a SORT recommendation. Accordingly, we conclude that diagnosis and treatment of periodontitis is positively associated with hypertension (SORT C) (40).

Discussion:

The results of this systematic review support a positive association between periodontitis and hypertension. Based on the quantitative analyses of all studies included, patients with moderate to severe periodontitis have greater (20%) odds of having hypertension when compared to patients without periodontitis. In addition, a positive linear association was observed, confirming that the more severe periodontitis is, the higher the likelihood (49%) of having hypertension. This finding was further corroborated, when the studies with a confident case definition for periodontitis were analysed, confirming even greater odds (50%) of diagnosis of hypertension were found. The magnitude of association between periodontitis and hypertension reported in this review (OR 1.22 to 1.53) is in agreement with that recently reported (27). In this recent review, however Martin-Cabezas and co-workers included observational studies without specifying the exposure and outcome of the analysis. In the current systematic review, we also included three cohort studies (66-68) confirming a temporal association between periodontitis and incidence of hypertension although this was not statistically significant and we excluded a number of studies in this analysis in order to avoid bias due to duplication of data was suspected.

This systematic review also confirmed an increased prevalence of periodontitis in patients with hypertension (as defined by $SBP \geq 140$ and $DBP \geq 90$ mm Hg). Clinical and experimental evidence suggest that this direction of the association could be mediated through hypertension causing microcirculatory changes in of the gingival tissue leading to ischemia, increased inflammation and/or altered microbial composition of the dental biofilm (25, 69, 70). This finding combined with the increased prevalence of hypertension in patients with periodontitis could be even more significant

within the context of the new revised guidelines issued by the AHA for the definition of hypertension (71). A reduced threshold of SBP/DBP for the case definition of hypertension was expressed (stage 1 as SBP=130–139/DBP=80–89 mm Hg, and stage 2 agreeing to stages 1 and 2 in the JNC 7 report; i.e. SBP \geq 140/DBP \geq 90 mm Hg), which has been reported in a recent cross-sectional study to double the prevalence estimates of hypertension in countries like China and US (72). This could result in even greater odds of hypertension in patients with periodontitis and vice versa. Future research should consider the impact of these thresholds for case definition of hypertension in terms of increased prevalence and treatment thereof.

In this systematic review, for the first time, we attempted to provide an estimate of the mean arterial BP in patients with periodontitis versus controls. Very interestingly, more than 80% of the included studies reporting levels of blood pressure showed consistently increased levels of systolic and diastolic BP in patients with periodontitis. Further, the exploratory meta-analysis B revealed that patients with periodontitis showed a higher MWD of 4.49mmHg of SBP and of 2.03 mmHg of DBP. If confirmed in long-term longitudinal studies, periodontitis could represent a novel modifiable risk factor for hypertension at the same strength of diabetes and smoking (73, 74). However, as periodontitis, diabetes and hypertension share common risk factors (such as aging, smoking, and disadvantageous socioeconomic status, among others), residual confounding could affect the magnitude of these associations. Raised arterial blood pressure observed in periodontitis could also explain the moderate but consistent higher risk of CV events (i.e. MI and stroke) reported by several investigators in patients with periodontitis when compared to controls (17). Indeed, an average increase of 5 mm Hg of SBP has been consistently associated with a 25% increased mortality from ischemic heart disease and stroke (75). These assumptions should all be interpreted with caution because of the high heterogeneity observed in the reported scientific evidence. In particular, varying case definitions of periodontitis and hypertension could have undermined the validity of these observations. Nevertheless, due to the high prevalence of both conditions, the clinical implications for public health systems could be very significant.

This systematic review also confirmed a potential positive effect of treating periodontal inflammation on arterial blood pressure. Inconclusive findings were identified in the selected studies, with only 5 out of 12 intervention trials showing a reduction of SBP/DBP in patients with periodontitis. Only one RCT was designed to address the question whether non-surgical periodontal therapy could result in reduced arterial BP levels (65). These authors assessed changes in blood pressure as their primary outcome following non-surgical periodontal therapy. They included 107 pre-hypertensive

participants and reported an absolute difference of SBP=12.57mmHg 95% CI 10.45-14.69, $p<0.05$ and of DBP=9.65mmHg 95% CI 7.06-12.24, $p<0.05$ after periodontal therapy. As treatment of hypertension has been repeatedly advocated as a key intervention to improve general health, quality of life and reduce CV complications (76), periodontitis treatment could represent a novel non-pharmacological therapy to prevent/help manage hypertension. A meta-analysis of RCTs quantified a reduction of 25-30% of coronary heart disease events such as stroke and heart failure with a 10-mmHg reduction in SBP or a 5-mmHg reduction in DBP following antihypertensive drug therapy (77). Future research should address the hypothesis of the treatment of periodontitis could achieve similar reduction in arterial BP and CV outcomes.

The identification of periodontitis as a possible risk factor for hypertension could be explained by a number of plausible mechanisms (Figure 6). Firstly, periodontitis is associated with systemic inflammation, mediators of which, including CRP, IL-6; TNF- α can all affect endothelial function. Clinical evidence suggests periodontitis affects systemic endothelial function and in turn this could impact on hypertension. Our group previously demonstrated that treatment of severe periodontitis improves endothelial function by reduction in systemic inflammation in patients with and without other comorbidities like diabetes (22, 64). Secondly, some reports suggest possible direct effects of oral microbiota related bacteraemia in mediating vascular dysfunction as well. Emerging experimental animal evidence indicates that an immune response to a common periodontal pathogen: *Porphyromonas gingivalis* (*Pg*) results in elevation of BP, vascular inflammation and endothelial dysfunction (78). Another possibility may be that cells, including T cells, B cells as well as monocyte/macrophages, primed in inflamed periodontium may be more prone to chemotactic recruitment to perivascular adipose tissue and adventitia, a step that has been shown to precede development of vascular dysfunction, hypertension and atherosclerosis (79, 80). This review therefore raises an important question regarding the causal nature of the association between periodontitis and hypertension. It should also be noted that similarly to periodontitis, any other chronic infection could have an impact in hypertension...

Strengths and weaknesses

This systematic review was designed to comprehensively investigate the possible role of periodontitis as a possible novel risk factor for hypertension. A number of limitations however should be highlighted starting with the limited value of systematic reviews of observational studies for ascertaining causality (81). Moreover, observational studies have intrinsic biases (mostly selection and information bias), hence the results of this systematic review should be interpreted within the context

of the methodology used. Nevertheless, this review was broad and inclusive of not only observational but also interventional studies. Besides, because of the link between periodontitis and cardio-metabolic risk factors (17, 82), this review also included data from observational studies on MetS and CVD but the authors acknowledge that some of the data may have been missed due to the difficulties in identifying the outcomes within the published reports. Moreover, studies looking at hypertension have inherent problem of the effect of blood pressure measurement technique on the outcome as well as variable degree of reporting of actual criteria of hypertension. Therefore, we have focused on a clear definition of hypertension basing mainly on blood pressure values and anti-hypertensive medications. With the exception of a single study (29) most studies have used office rather than ambulatory blood pressure; our quantitative analysis of the effect of periodontitis on blood pressure values adds to the strength of the selected evidence. One of challenges encountered was to establish the direction of association when studies were included in the quantitative analyses (i.e. dependent and independent variables in the model). This was mainly due to unclear description in the published manuscripts. When a consensus could not be achieved among the reviewers (EMA, JS), a third author was consulted (FD) or attempts were made to contact the authors for clarification (43). Another important limitation of this systematic review is the high level of heterogeneity in the case definitions for both, periodontitis and hypertension (34, 83). To overcome this, data was further analysed according to an arbitrary level of confidence in a given case definition of periodontitis. In fact, when an arbitrary confident diagnosis was confirmed, the observed magnitude of association between periodontitis and hypertension was greater. Lastly, it has been reported that antihypertensives such as calcium channel blockers can cause gingival enlargement in 6.3% to 83% of patients (Hallmon & Rossmann 1999), which should not be confounded with periodontitis.

Conclusions:

Periodontitis could be associated with increased risk of hypertension in a linear fashion. Further, management of periodontitis could impact on the management of hypertension. Our findings highlight the potential to improve CV outcomes by addressing poor oral health in the general population. Longer and larger studies are needed however to determine whether periodontal treatment benefit patients in terms of CV health, ultimately resulting in reduced morbidity and mortality.

Translational Implications:

- To raise awareness of the association between periodontitis and hypertension.

- Patients with periodontitis should be informed by oral health professionals of the risk of developing hypertension.
- Oral health advice should be given to all patients with hypertension.
- Prevention and management of periodontitis improves oral/overall health and quality of life and could prevent/improve hypertension.
- Larger observational studies should include internationally recognised case definitions for periodontitis and hypertension.
- More RCT with reduction of blood pressure as the primary outcome.
- Reporting of patient related outcome measures within the study designs.

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Figures Legends:

Figure 1: Prisma Flow Chart

Figure 2: Forest Plot Cross-sectional and Case-control studies (moderate to severe adjusted)

Figure 3A: Forest Plot Cross-sectional and Case-control studies (severe only group adjusted)

Figure 3B: Forest Plot Cross-sectional and Case-control studies (Confident definition adjusted)

Figure 3C: Forest Plot Cross-sectional and Case-control studies (Non-confident definition adjusted)

Figure 4: Forest Plot Mean SBP

Figure 5: Forest Plot Mean DBP

Figure 6: Mechanistic diagram

Appendices Legends:

Appendix 1: Prisma statement

Appendix 2: Search strategy

Appendix 3: Evidence tables

Appendix 4: Forest Plot Cohort studies

Appendix 5: Bias assessment

Appendix 6: Prevalence

Appendix 7: Mean blood pressure

Appendix 8: Publication bias

Appendix 9: Protocol

Appendix 10: Statement of authors contributions