Association between periodontitis and arterial hypertension: A systematic review and meta-analysis

Rodrigo Martin-Cabezas [a] Narendra Seelam [a] Catherine Petit [a] Kévimy Agossa [b] Sébastien Gaertner [c] Henri Tenenbaum [a,d] Jean-Luc Davideau [a,d] and Olivier Huck [a,d] *Strasbourg, France*

Background Several studies have shown that periodontal diseases are associated with hypertension (HT). However, heterogeneity among populations, diagnosis criteria, and shared risk factors represent some difficulties in terms of interpretation. Therefore, the aim of this study was to determine the magnitude of the association between periodontal diseases and HT.

Methods and results A systematic review and meta-analysis, including studies published up to June 2016, have been performed. Sixteen studies assessing the association between periodontal diseases and HT have been included. The meta-analysis considering all included studies (moderate to severe periodontitis) showed that the presence of HT was associated with the presence of periodontal diseases (OR, 1.50; 95% CI, 1.27-1.78). To reduce potential bias, a stratified analysis has been performed illustrating the impact of inclusion criteria and adjustments on the magnitude of the association. Interestingly, when only studies with secure diagnosis of severe periodontitis and HT were considered, an OR=1.64 (95% CI, 1.23-2.19) has been measured.

Conclusions Periodontal diseases are associated with a higher risk of HT especially for severe periodontitis. However, no conclusions could be made regarding the causative involvement of periodontal diseases mainly due to the reduced number of available prospective studies and remaining questions regarding underlying biological mechanisms. (Am Heart J 2016;180:98-112.)

Periodontal diseases, including gingivitis and periodontitis, are chronic inflammatory diseases affecting gums and are associated with destruction of tooth supporting tissues caused by long-term accumulation of dental biofilms and calculus.[1] Periodontal diseases are common oral diseases with high prevalence worldwide.[2] Severe forms of periodontitis affect around 11% of the world population.[3] Prevalence of periodontitis is more important in males with a peak incidence around 60 years of age.[1] The disease progresses slowly for decades and is influenced by several risk factors such as age, smoking, or systemic conditions that worsen host-immune response.[4]

Recent studies have shown that periodontal diseases represent a potential risk factor for several systemic conditions, including cardiovascular diseases (myocardial infarction and stroke) or even erectile dysfunction.[5] Despite increasing evidences, the association between such diseases and cardiovascular events remains controversial[6] and potential impact on cardiovascular risk factor should be considered to explain this link. Interestingly, recent studies have suggested an association between periodontitis and hypertension (HT).[7]

Arterial HT is a chronic medical condition where the blood pressure (BP) in the arteries is elevated. Hypertension is currently defined as values >140 mmHg systolic BP (SBP) and/or >90 mmHg diastolic BP (DBP).[8] It is a common condition in both developed (333 million) and undeveloped (639 million) countries[9] with overall prevalence of around 30% to 45% in the general population and a steep increase with aging.[8] However, prevalence rates vary markedly in different regions showing the influence of several risk factors such as genetic background, environment and lifestyle.[8] It is quantitatively the most important risk factor for premature CVD, being more common than other major risk factors such as cigarette smoking, dyslipidemia and diabetes.[10] It accounts for an estimated 54% of all strokes and 47% of all ischemic heart diseases events globally.[11]

From the [a]Université de Strasbourg, Faculté de Chirurgie Dentaire, Department of Periodontology, Strasbourg, France, [b]University of Lille, Dental Faculty, Department of Periodontology, [c]Service Hypertension, maladies vasculaires et pharmacologie clinique, Hôpitaux Universitaires de Strasbourg, Strasbourg, France, and [d]INSERM 1109 «Osteoarticular & Dental Regenerative Nanomedicine», Fédération de Médecine Translationnelle de Strasbourg (FMTS), Strasbourg, France.

Funding sources: This study was supported by author's own institution and grant API 2014 HUS N°5883.

Submitted March 30, 2016; accepted July 22, 2016.

Reprint requests: Olivier Huck, PhD, DDS, Dental Faculty, Department of periodontology, 8 rue Sainte-Elisabeth, 67000 Strasbourg, France.

E-mail: huck.olivier@gmail.com

0002-8703

http://dx.doi.org/10.1016/j.ahj.2016.07.018

The risk for both coronary disease and stroke doubles with each 20/10 mmHg incremental increase in BP above 115/75 mmHg in individuals aged 40 to 69 years.[12]

Several studies over the past 15 years described a potential influence of periodontal diseases on HT. This relationship may be explained by common risk factors or by dissemination of infectious and inflammatory components from periodontal lesions through bloodstream, immune response or glucose and lipids metabolism.[7] However, despite the increased evidence, neither a consensus has yet emerged on the existence or relevance of such an association nor on the level of impact of one disease over the other.[13]

The aim of the present study was to evaluate, through a comprehensive systematic review and a meta-analysis, the magnitude of the association between periodontal diseases and HT in adult population.

Methods

Protocol and search strategy

This systematic review was conducted in accordance with the PRISMA guidelines. The following databases: MEDLINE, Cochrane Central Register of Controlled Trials, Science Direct and ISI Web of Science databases were searched from 2000 up to June 2016. The search was limited to publications in the English language. Hand searching comprised of checking bibliographic references of included articles and related review articles. A typical search strategy, using Boolean operators and an asterisk symbol (*) as truncation, was employed to identify papers using MesH, keywords and other free terms: *((Periodontitis OR Periodontal disease OR Periodont* OR probing pocket depth OR periodontal pocket OR gingivitis) AND (hypertension OR hypertensive patient OR arterial hypertension OR blood pressure OR hypertens*)).*

Eligibility criteria

A study was considered eligible for inclusion in this systematic review if it was an original research publication in peer-reviewed journals that met the following criteria: (1) all types of longitudinal studies or case–control studies and cross sectional studies, (2) conducted in humans, (3) assessed both the exposure and the outcome variables (i.e. periodontal status and HT).

Studies were excluded if: (1) was focused on medical subgroups, (2) only reported the effect of therapy in any of the variables, (3) was based on tooth loss per year, (4) was a duplicate or ancillary study. Reviews were excluded after reference checking.

Screening and selection of papers

Selected publications were reviewed independently by three blinded reviewers (R.M., N.S. and O.H.) and categorized as suitable or not for inclusion in this review and meta-analysis. Full reports were obtained and reviewed independently for studies appearing to meet the inclusion criteria or for which there was insufficient information in the title and abstract to allow clear decision.

In the case of disagreements, decisions were reviewed and any disagreement between the authors was resolved after additional discussion.

Search outcomes and evaluation

Selected studies have assessed the presence/absence of periodontal disease (ranging from healthy patients to gingivitis and to chronic moderate and severe periodontitis) as exposures in the analysis of HT.

Risk of bias in individual studies

Risk of bias was evaluated through a process of quality analysis performed by two reviewers (RM, NS) and confirmed by another author (OH). The quality assessment for cross-sectional and cohort studies included in the meta-analysis was based on the Newcastle-Ottawa Scale (NOS) tool evaluating the following criteria:

- Adequacy of case definition (periodontitis)
- Representativeness of the cases
- Selection and definition of controls
- Comparability of cases and controls with respect to confounding factors
- Assessment of outcome (HT)

Definitions of periodontitis and HT

Due to the use of several definitions in the included studies, we set the following diagnostic thresholds, as part of an assessment of methodological quality and external validity, adapted from Nibali et al[14]:

Diagnosis of periodontitis

Moderate periodontitis

- At least 2 sites on different teeth with periodontal clinical attachment level (CAL)≥4 mm or 1 site with probing pocket depth (PPD)≥4 mm[15]
- Diagnosis of generalized chronic periodontitis (at least 30% sites with CAL≥4 mm)[16]
- Community periodontal index (CPI) score of 3 in at least 1 quadrant
- PPD≥4 mm et<6 mm or CAL≥3 mm et<5 mm[17]

Severe periodontitis:

- At least 2 sites on different teeth with CAL≥6 mm and at least 1 site with PPD≥4 mm[15]
- At least 5 sites with CAL≥6 mm[18]
- CPI score of 4 in at least 1 quadrant.
- PPD≥6 mm or CAL≥5 mm[17]

Secure diagnosis of periodontitis:

- Center for Disease Control and Prevention/American Academy of Periodontology (CDC/AAP) periodontitis definition[15]
- Diagnosis of generalized chronic periodontitis (at least 30% sites with CAL≥4 mm)[16]
- At least 5 sites with CAL≥6 mm[18]
- In cases where no CAL or PPD is reported, radiographic alveolar bone loss ≥30% of root length or ≥5 mm in at least 2 teeth
- Community periodontal index (CPI) score of 4 in at least 1 quadrant

Insecure diagnosis of periodontitis:

- "Alveolar bone loss" (not clearly defined or less than definition above)
- CPI score 3 in at least 1 quadrant
- Unclear diagnostic criteria for periodontitis or not employing secure criteria above/self-reported

Diagnosis of HT

Secure:

- SBP≥140 mmHg/DBP≥90 mmHg or use of antihypertensive medication[19]
- Refractory hypertension

Insecure:

- Unclear diagnostic criteria/Self-reported/Medical records

Data extraction and analysis

To be included in the meta-analysis studies have to assess, as primary or secondary outcome, the OR for HT among people with or without a diagnosis of periodontitis. In the case of no reported OR and if data regarding population size and prevalence among groups were available, OR was calculated.[20-23] Data were extracted using a standardized form. ORs adjusted for confounding factors (age, gender, smoking, BMI, etc.…) were computed for analysis and were used as outcome in the meta-analysis. Heterogeneity between the studies was tested and evaluated through Q and I^2 test. A P value of Q statistic <0.1 was defined as an indicator of heterogeneity and data were considered heterogeneous for I^2 value higher than 40%. The inverse of variance for the log ORs were used as weights and fixed or random effect model was applied accordingly. The analyses were undertaken using Review Manager (Version 5.2. The Cochrane Collaboration, 2013, Oxford, UK).

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents. This study was supported by authors' institutions and grant API 2014 HUS N°5883.

Results

Study selection

The search strategy identified 1483 potentially relevant publications. After screening of titles and abstracts, inappropriate papers were excluded resulting in 91 publications (Figure 1). Sixty-seven articles were excluded after full reading, yielding 25 articles included in this review according to the inclusion/exclusion criteria with 16 studies contributing to the meta-analysis. Screening of reviews (n = 3) did not give any additional information.

Study characteristics

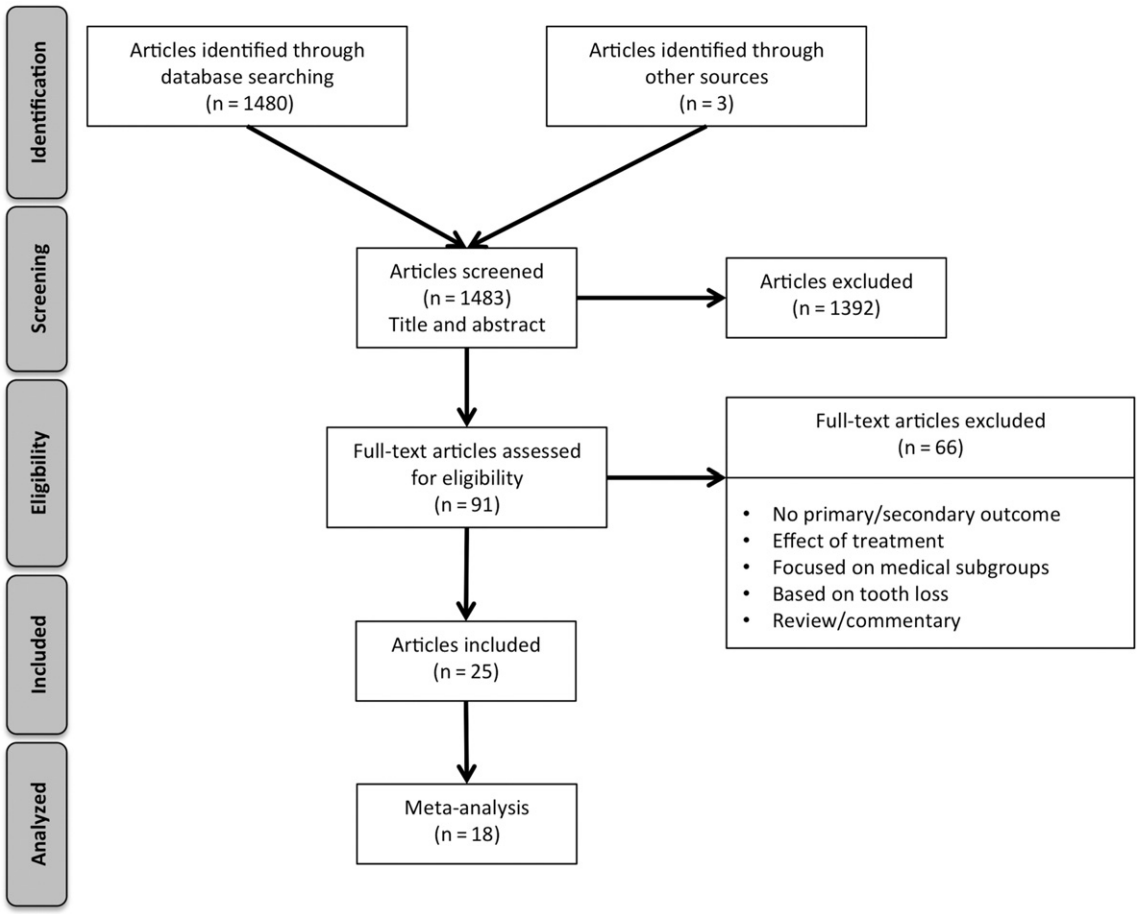
All selected studies are presented in Table I. The included studies were 20 cross-sectional, 3 case-control and 2 longitudinal studies published in the English language between 2002 and 2016. The included studies have been conducted in 14 different countries across Asia, Europe, America and Africa. Size of the included population varied across the studies, ranging from 81[24] to 1,025,340 participants.[25] In all included studies, several definitions have been used regarding periodontal diseases (ie, CDC/AAP case definition, CPITN, etc.).

Study outcomes

Periodontal status and HT. Despite contradictory results, most studies reported a significant association between periodontal diseases and HT strengthening the positive evidence of such association. Several studies analyzed the relationship between periodontitis and HT reporting ORs ranging from 0.039 (95% CI 0.02-0.09)[33] to 7.24 (95% CI 1.6-38.36)[23] with an impact depending on periodontitis severity.[41,44] A cross-sectional study among 4254 participants in Sweden demonstrated a linear trend between severity of periodontal status (healthy; gingivitis; moderate or severe periodontitis) and HT (OR for trend = 1.32; 95% CI, 1.13-1.54) after adjusting for confounding factors (age, gender, number of teeth and smoking status).[44] However, another study comprising 182 adults from Puerto Rico,[36] using a multivariate analysis, did not show any association between severe periodontitis and HT history (OR, 0.99; 95% CI, 0.40-2.48). The same authors, in a prospective study among U.S. health professionals,[39] have not found any association between self-reported periodontitis and the risk of HT in a 20 years follow-up study (Incident HT) despite an association between alveolar bone loss and a relative risk for incident HT of 1.02.

Periodontal status and BP. Several studies suggest a consistent association between periodontal diseases and increased BP. Severe periodontitis was associated with high BP (OR, 2.93; 95% CI, 1.25-6.84), after adjusting for

Figure 1



Search strategy.

age, gender, smoking, and binge drinking. This association was stronger when restricted to those with HT or taking anti-hypertensive medications, (OR, 4.20; 95% CI, 1.28-13.80).[36] Another study with 12,000 participants from the 3rd National Health and Nutrition Examination Survey (NHANESIII) examined the associations between periodontal measurements and BP levels by applying an extensive adjustment process.[41] Mean SBP was reported higher among participants with moderate and severe periodontitis compared to mild form of the disease independently to age. A positive linear relationship between SBP and increased severity of periodontitis was further identified in middle-aged subjects. After adjusting for age, sex and ethnicity, a 10% rise in extent of gingival bleeding, CAL and PPD were associated with a 0.7, 0.2, and 0.6 mmHg elevation of SBP respectively. The fully adjusted model of the study revealed a consistent association of SBP only with gingival bleeding, a marker of acute periodontal inflammation.[41] However, in the study of Buhlin et al[46] evaluating the risk factors for CVD in patients with periodontitis, no positive association between periodontal status and BP was observed.

Risk of bias across studies. Qualitative and quantitative assessments of the included studies contributing to the meta-analysis assessed by the NOS varied considerably among included studies, ranging from a score of 5/9 (high risk of bias) to 9/9 (low risk of bias). The variability in the NOS quality among the studies was mainly related to the adequacy of case definition (periodontitis), the representativeness of the cases and the selection and definition of controls.

Meta-analysis. Sixteen studies were included in the meta-analysis. The outcome measure was the ORs (95% CI) assessing the relationship between periodontitis and HT. ORs (95% CI) and adjustments are reported in Table II. Two studies[20,27] were based on a similar Korean cohort. Therefore, the most recent study[20] was included in the meta-analysis. Two other studies[28,40] based only on patients with HT were not included in the meta-analysis to avoid potential bias.

Table I. Studies characteristics'

Study Country	Type of study	Sample size (N)	Periodontal disease	Hypertension (HT)	Principal findings
Łysek et al, 2016[26] Poland	Cross-sectional	99	CPI score 3-4	Peripheral BP of 140/90 mmHg and central BP of 130/90 mmHg	After adjustments, patients from the CPI 3-4 group were found to have almost 3 times higher ORs for HT.
Ahn et al, 2015[27] Korea	Cross-sectional	14,625	CPI score 3-4	Average SBP over 140 mmHg or DBP over 90 mmHg or medicated for hypertension	There was an association after adjusting for confounding factors: Prevalence Risk =1.09; 95% CI, 1.03-1.15 for pre-hypertension Prevalence Risk =1.10; 95% CI, 1.04-1.16 for HT (P = .001)
Lee et al, 2015[25] Korea	Cross-sectional	1,025,340	Dental records[16]	Medical records: Korean Classification of Disease	Significant and positive correlations were found between periodontitis and HT (OR, 1.07; 95% CI, 1.05-1.08; P < .001)
Kawabata et al, 2015[28] Japan	Longitudinal prospective	2588	PPD≥4 mm or CPI score 3-4 ± BOP ≥30%	SBP≥140 mmHg or DBP ≥90 mmHg	The risk of having HT after 3 years was associated with periodontal disease PPD ≥4 mm + BOP ≥30% at baseline (OR: 2.74; 95% CI, 1.19-6.29; P = .02) after adjusting confounding factors
Darnaud et al, 2015[29] France	Cross-sectional	102,330	Modified gingival index (MGI)	SBP ≥140 mmHg and/or DBP ≥90 mmHg	SBP and DBP were significantly higher (P < .0001) for dental plaque, dental calculus, gingival inflammation and functional masticatory units. SBP was also significantly higher (P < .0001) in patients with more of 10 missing teeth. In subset ≥65 years old, no significant association was found between oral variables and risk of HT In subset <65 years old HT was also associated with high level of dental plaque [OR, 1.90; 95% CI, 1.55-2.33], dental calculus [OR, 1.18; 95% CI, 1.07-1.29] and gingival inflammation [OR, 1.56; 95% CI, 1.35-1.80, P = .07]
Choi et al, 2015[20] Korea	Cross-sectional	19,560	CPI score 3-4	BP ≥140/90 mmHg or the use of antihypertensive medication	Individuals with HT had higher levels of periodontitis (P < .05)
Shamsuddin et al, 2015[23] Malaysia	Cross-sectional	90	Mild, moderate and severe periodontitis[30]	Medical reports	There was a high prevalence of HT in patients with moderate to severe chronic periodontitis compared to patients with mild form of periodontitis.
Machida et al, 2014[31] Japan	Cross-sectional	414	PPD ≥4 mm Severity: Page & Eke, 2007[15]	Self-reported	Moderate/severe periodontitis was related with presence of HT (OR, 1.99; 95% CI 1.07-3.71, P = .030)
Ollikainen et al, 2014[32] Finland	Cross-sectional	1296	Number and % of teeth with PPD ≥4 mm or PPD ≥6 mm	SBP ≥140 mmHg or DBP ≥90 mmHg or the use of antihypertensive medication	There were no consistent associations between the number of teeth with deepened (≥ 4 mm) (OR 0.98; 95% CI 0.95-1.01) or deep (≥ 6 mm) (OR 1.01; 95% CI 0.90-1.12) periodontal pockets

Table I (*continued*)

Study Country	Type of study	Sample size (N)	Periodontal disease	Hypertension (HT)	Principal findings
					or the number of bleeding sextants and HT after adjusting for confounding factors.
Chrysanthakopoulos & Chrysanthakopoulos, 2014[33] Greece	Cross-sectional	3360	Number and % of PPD ≥5 mm and CAL ≥6 mm in two or more teeth	Self-reported	The presence of deep periodontal pockets (>5 mm) (OR 1.268 95% CI 0.85-1.51, *P* = .000) and the presence of severe CAL (>6 mm) (OR 1.472 95%CI 0.58-3.76, *P* = .000) were found to be significantly associated with HT after adjustment
Iwashima et al, 2014[34] Japan	Cross-sectional	1643	CPI score	SBP ≥140 mmHg and/or DBP ≥90 mmHg or the use of antihypertensive medication	After adjustment, no individual oral health markers were significantly associated with HT. The combined effect of health markers showed that subjects with ≥3 disorders had 1.82 times higher odds of HT and they had highest SBP compared with those with no component
Boland et al, 2013[35] USA	Case-control	2475	Dental records	Medical records	Periodontitis was associated to HT (OR, 1.2; 95% CI 1.10-1.37, *P* < .001) after adjustment for age, gender, ethnicity and tobacco abuse
Rivas-Tumanyan et al, 2013[36] Puerto Rico	Cross-sectional	182	Page & Eke, 2007[15]	Self-reported SBP ≥140 mmHg or DBP ≥90 mmHg	No association between severe periodontitis and HT history (OR, 0.99; 95% CI, 0.40-2.48). Severe periodontitis was associated with high BP (OR, 2.93; 95%1.25-6.84) after adjustment
Megat Mohd Zainoddin et al, 2013[22] Malaysia	Cross-sectional	370	Mild, moderate and severe chronic periodontitis[37]	Medical records and self-reported	An association between HT and periodontitis has been observed. However, no specific influence of severity of periodontitis on HT has been measured.
Kumar et al, 2012[38] India	Cross-sectional	465	Russell's periodontal index	Medical records	79.14% of the patients under study presented with Russell's periodontal index score ranging from 2-4.9. There is association between HT and gingival/periodontal pathology.
Rivas-Tumanyan et al, 2012[39] USA	Longitudinal prospective	31,543	Self-reported	Self-reported	No associations between incident HT and periodontal disease at baseline (RR = 1.04; 95% CI, 0.98-1-10) or periodontitis during follow-up (RR = 1.01; 95% CI, 0.96-1.05) after adjusting for potential confounders
Yamori et al, 2011[24] Tanzania	Cross-sectional	81	CPI score	Severely hypertensive (SBP> 180 or DBP> 110) Normal to border line hypertensive (SB< 160 or DBP< 100)	The severity of periodontitis was significantly correlated with SBP and DBP. Periodontitis was significantly associated with an increased risk of HT.
Vidal et al, 2011[40] Brazil	Case-control	137	Generalized chronic periodontitis[16] Severe periodontitis[18]	Refractory hypertension: BP remains above 140x90 mmHg, even when the patient is engaged in a treatment program and uses three	Significant association with arterial HT were severe chronic periodontitis (OR, 4.04; 95% CI, 1.92-8.49) and generalized chronic periodontitis (OR, 2.18; 95% CI, 1.04-4.56)

(continued on next page)

Table I (*continued*)

Study Country	Type of study	Sample size (N)	Periodontal disease	Hypertension (HT)	Principal findings
				or more classes of anti-hypertensive drugs including a diuretic	
Tsakos et al, 2010[41] USA	Cross-sectional	13,994	Page & Eke 2007[15]	SBP ≥140 mmHg and/or DBP ≥90 mmHg or the use of antihypertensive medication	Gingival bleeding was the only measure significantly associated with raised SBP and an increased OR of HT after adjustment. Individuals with 10% greater gingival bleeding extent had 1.1 (1.0-1.1, $P < .05$) times higher odds for diagnosis of HT after full adjustment
Nesse et al, 2010[21] Netherlands	Cross-sectional	1276	CPI score 3-4	Self-reported	HT does not seem to be associated with periodontitis when controlling for confounders
Desvarieux et al, 2010[42] USA	Cross-sectional	653	Page & Eke, 2007 [15] % of sites with PPD ≥3 mm	SBP ≥140 mmHg or DBP ≥90 mmHg or the use or self-reported history	The prevalence of HT among participants defined as "healthy" or having either moderate or severe periodontitis was 72%, 58% and 66% (p for linear trend = 0.64), respectively
Engstrom et al, 2007[43] Sweden	Case-control	390	PPD ≥5 mm	DBP> 90 mm Hg	Patients with periodontal pockets ≥5 mm had 76% larger probability of being a case than those who had no pockets (OR 1.76; 95% CI 1.14-2.72)
Holmlund et al, 2006[44] Sweden	Cross-sectional	4254	PPD ≥5 mm Periodontal Severity Index (PSI) Value: 1-1.9: Mild periodontal disease 2-2.9 Severe periodontal disease	Drug treatment for hypertension	Periodontitis was significantly related to the prevalence of HT (OR 1.32 95% CI 1.13-1.54 $P < .0005$) after adjustment (age, gender, smoking), but only significant in subjects >60 years when the total sample was stratified into age groups. The number of diseased pockets was associated to HT (OR 1.01 95% CI 1.01-1.02 $P < .0001$) after adjustment (age, gender and smoking) and remains significant for patients ≥40 years old after age stratification.
Khader et al, 2003[45] Jordania	Cross-sectional	603	PPD, recession and CAL averages	Self-reported	HT was significantly ($P = .000$) associated with increased CAL and recession. HT increased the mean CAL by 1.20 mm and gingival recession by 0.85 mm
Buhlin et al, 2002[46] Sweden	Cross-sectional	2839	Self-reported	Self-reported	Significant association between self-reported bleeding gums (OR 1.77 95% CI 1.26-2.48 $P = .001$), deep pockets (OR 1.20 95% CI 0.82-1.76 $P = .35$) and high BP.

CPI, Community Periodontal Index; *PPD*, Probing pocket depth; *BOP*: Bleeding on probing; *CAL*, Clinical attachment loss.

The meta-analysis was primarily conducted considering all included studies (moderate to severe periodontitis) with most adjusted ORs (Figure 2). Analysis showed an association between both conditions with an OR of 1.50 (95% CI, 1.27-1.78; $P < .001$). To reduce the impact of common risk factors but also in function of diagnosis criteria, several sub- analyses have been performed. When only studies displaying adjusted ORs with common

Table II. ORs of studies included in the meta-analysis

Study	Severity	Secure/ Insecure	OR	95% CI	Adjustment
Łysek et al, 2016[26]	Moderate to severe	Insecure	4.10	1.78-9.86	Age, gender
			3.38	1.30-9.42	Age, gender, smoking, diabetes, antihypertensive drugs, hypercholesterolemia, BMI, left ventricular ejection fraction
Lee et al, 2015[25]	Moderate to severe	Insecure	1.96	1.94-1.98	Unadjusted
	Moderate to severe	Insecure	1.07	1.05-1.08	Age, gender, household income, insurance status, health status, residence area, cerebral infarction, angina pectoris, myocardial infarction, diabetes mellitus, rheumatoid arthritis, erectile dysfunction, osteoporosis, obesity
Choi et al, 2015[20]	Moderate to severe	Insecure	2.34	2.20-2.50	Unadjusted
Shamsuddin et al, 2015[23]	Moderate to severe	Insecure	7.24	1.6-38.36	Unadjusted
Machida et al, 2014[31]	Moderate to severe	Insecure	2.46	1.39-4.36	Unadjusted
			1.99	1.07-3.71	Age, gender, BMI, smoking, number of teeth present, PCR and duration of maintenance phase
	Severe	Insecure	1.70	1.02-2.84	Unadjusted
			1.46	0.82-2.59	Age, smoking, alcohol consumption, vegetable consumption, coffee consumption, coffee consumed with sugar, number of teeth present, and BOP.
Ollikainen et al, 2014[32]	Moderate to severe	Insecure	1.03	1.00-1.06	Unadjusted
			0.98	0.95-1.01	Age, gender, BMI, educational level, physical activity, alcohol consumption (g/week) and serum lipid composition (triglycerides, HLD-C, LDL-C)
	Severe	Insecure	1.16	0.98-1.38	Unadjusted
			1.00	0.97-1.04	Age, gender, BMI, educational level, physical activity, alcohol consumption (g/week) and serum lipid composition (triglycerides, HLD-C, LDL-C).
Chrysanthakopoulos & Chrysanthakopoulos, 2014[33]	Severe	Insecure	0.039	0.02-0.09	Unadjusted
			1.472	0.58-3.76	Age, gender and smoking
Iwashima et al, 2014[34]	Severe	Secure	1.83	1.03-2.63	Age and gender
			1.71	1.17-2.50	Age, gender, body mass index, diabetes, dyslipidemia, estimated glomerular filtration rate, smoking status, daily alcohol intake, daily fruit intake, daily sugar-sweetened soft drink intake, physical activity, and nocturnal sleep duration
Boland et al, 2013[35]	Moderate to severe	Insecure	1.2	1.12-1.36	Unadjusted
			1.2	1.10-1.37	Age, gender, ethnicity and tobacco abuse
Rivas-Tumanyan et al, 2013[36]	Severe	Secure	2.35	1.08-5.14	Adjusted for age and gender
			2.93	1.25-6.84	Age, gender, smoking, heavy and binge drinking, diabetes, physical activity within the past month, overweight or obesity (BMI ≥25 kg/m2), consumption of fruits and vegetables, whole wheat bread and high-fiber cereal, utilization of preventive dental services and daily flossing
Megat Mohd Zainoddin et al, 2013[22]	Moderate to severe	Insecure	1.99	1-3.85	Unadjusted
Tsakos et al, 2010[41]	Moderate	Secure	2.6	2.1-3.2	Unadjusted
			0.9	0.7-1.1	Adjusted for ethnicity, gender and age.
			0.9	0.7-1.2	Adjusted for ethnicity, gender, age, C-reactive protein, creatinine and Naþ/Kþ ratio
			0.9	0.7-1.2	Adjusted for ethnicity, gender, age, C-reactive protein, creatinine, Naþ/Kþ ratio, BMI, alcohol consumption, smoking, and chronic conditions.
			0.9	0.7-1.2	Ethnicity, gender, age, C-reactive protein, creatinine, Na+/K+ ratio, BMI, alcohol consumption, smoking, chronic conditions, education and poverty
	Severe	Secure	3.5	2.4-5.1	Unadjusted
			1.3	0.8-2.2	Adjusted for ethnicity, gender and age.
			1.4	0.8-2.4	Adjusted for ethnicity, sex, age, C-reactive protein, creatinine and Naþ/Kþ ratio
			1.3	0.7-2.1	Adjusted for ethnicity, gender, age, C-reactive protein, creatinine, Naþ/Kþ ratio, BMI, alcohol consumption, smoking, and chronic conditions.

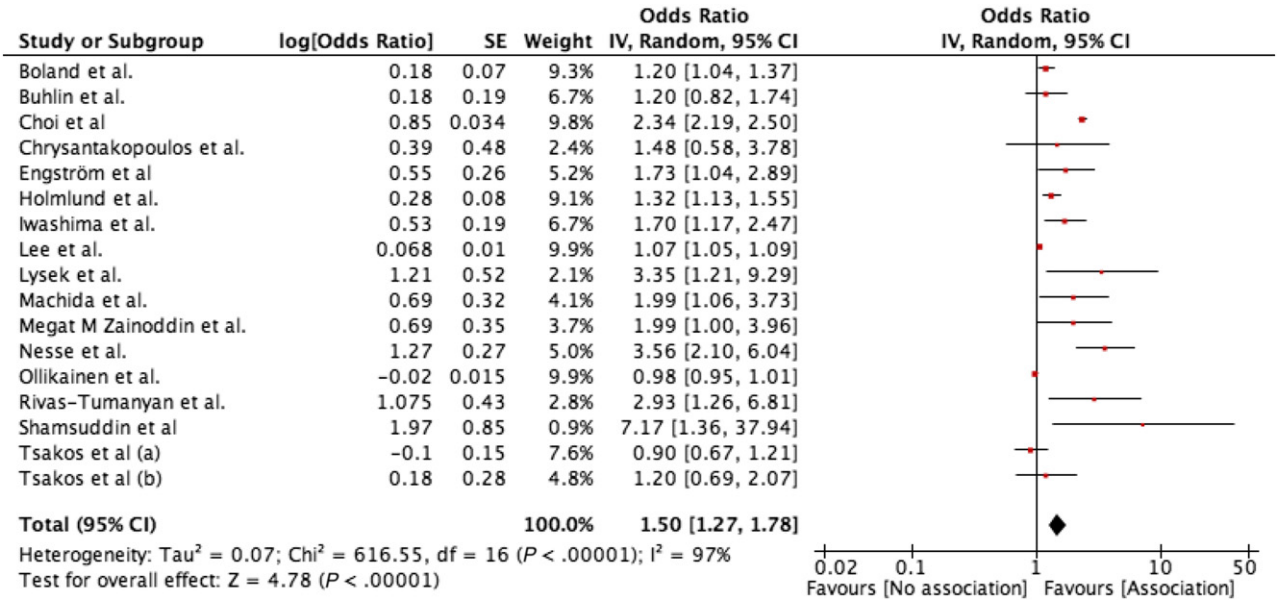
(continued on next page)

Table II (*continued*)

Study	Severity	Secure/ Insecure	OR	95% CI	Adjustment
			1.2	0.7-2.1	Ethnicity, gender, age, C-reactive protein, creatinine, Na+/K+ ratio, BMI, alcohol consumption, smoking, chronic conditions, education and poverty
Nesse et al, 2010[21]	Moderate to severe	Insecure	3.56	2.08-6.07	Unadjusted
Engström et al, 2007[43]	Moderate to severe	Insecure	1.74	1.03-2.93	Age, gender, smoking, snuff and number of teeth
Holmlund, et al, 2006[44]	Moderate to severe	Insecure	1.32	1.13-1.54	Age, gender and smoking
Buhlin et al, 2002[46]	Moderate to severe	Insecure	1.20	0.82-1.76	Age, gender, smoking, income level, civil status and education

BMI, Body Mass Index; *PCR*, Plaque Control Record; *BOP*, Bleeding on probing.

Figure 2



Forest plot for association between periodontitis and HT considering all studies with most adjusted ORs.

risk factors, including, at least sex and age, were input in the analysis, a reduced OR was estimated (OR, 1.16; 95% CI,1.07-1.26; $P < .001$) (Figure 3). When studies with diagnosis regarding periodontal diseases and/or HT based on self-report methods were excluded, the estimated OR decreased to 1.15 (95% CI,1.05-1.25; $P = .002$) (Figure 4). Same estimated OR was observed when only cross-sectional studies were considered (Figure 5). This result can be compared to estimated ORs obtained when only studies with unadjusted ORs were considered (OR, 1.67; 95% CI,1.26-2.22; $P < .001$) highlighting the impact of adjustment on the magnitude of such association (Figure 6).

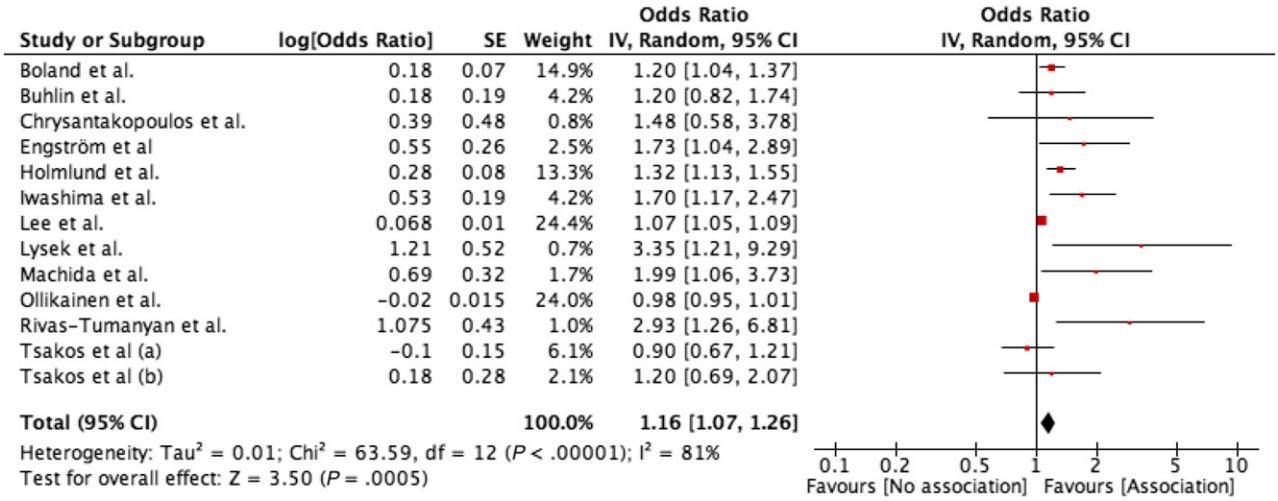
To determine potential influence of the severity of periodontal diseases on the magnitude of the association, an analysis has been conducted considering only severe periodontitis. Interestingly, this analysis estimated an association with an increased magnitude (OR, 1.40; 95% CI,1.01-1.94; $P < .05$) (Figure 7).

These trend of results were also obtained when studies using self-reported diagnosis methods (concerning HT and periodontitis) were not considered (OR, 1.57; 95% CI,0.75-3.29; $P = .23$) however without reaching level of significance (Figure 8).

To strengthen our analysis, included studies were classified as secure or insecure according to the diagnosis criteria used. Regarding the diagnosis classification (Secure/ Insecure) (Table II), only three among the sixteen included studies were qualified as "secure".[34,36,41]

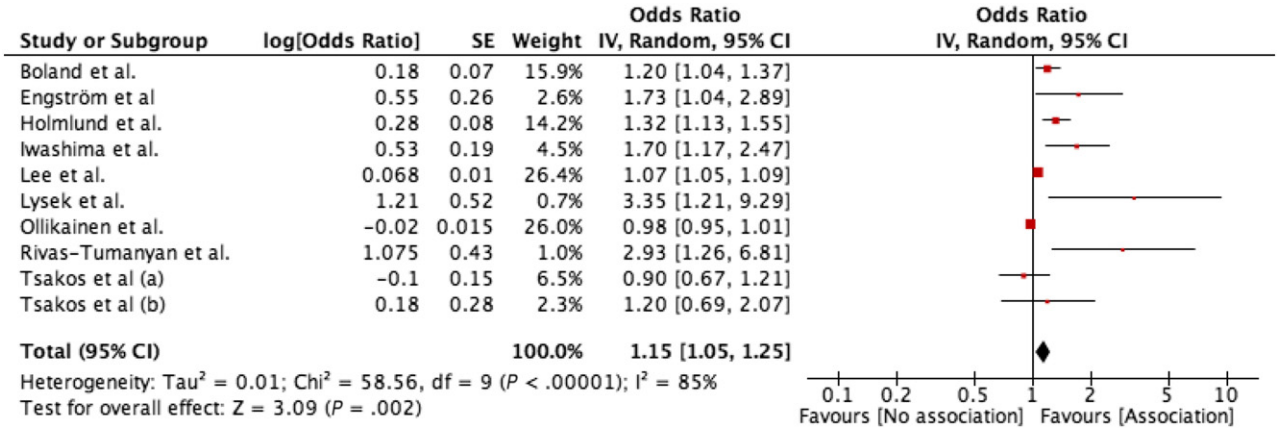
When studies including moderate to severe periodontitis with secure diagnosis were considered, an association between periodontitis and HT was measured (OR, 1.40; 95% CI, 0.90-2.18; $P = .14$) (Figure 9). The strength of this association was more important for severe

Figure 3



Forest plot for association between periodontitis and HT (only adjusted ORs were considered).

Figure 4



Forest plot for association between periodontitis and HT adjusted without studies using self-report methods to diagnose periodontitis and/or HT.

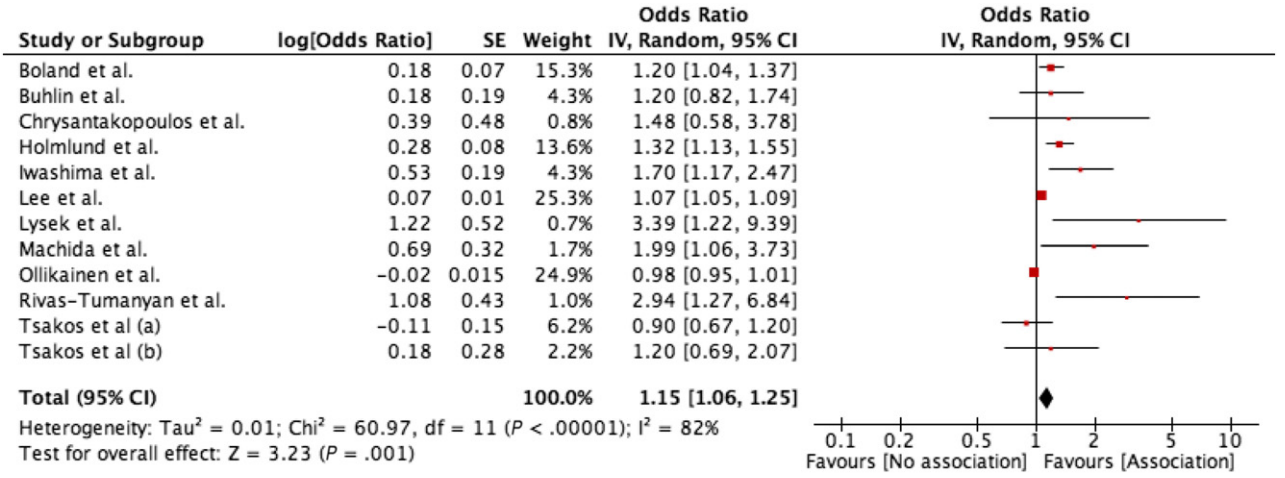
periodontitis with secure diagnosis (OR, 1.64; 95% CI, 1.23-2.19; $P < .001$) (Figure 10).

Discussion

The results from the present meta-analysis support the association between HT and periodontal diseases with a range of OR varying from 1.15 to 1.67. Highest OR was calculated when severe form of periodontitis with secure diagnosis criteria was considered (OR, 1.64). This magnitude could be compared with previous results measured for a well described risk factor of HT such as abdominal obesity (OR, 1.51).[47] Periodontitis has already been linked to several systemic diseases/conditions such as stroke (RR, 1.63),[48] rheumatoid arthritis (RR, 1.13)[49] and metabolic syndrome (OR, 1.71)[14] showing the impact of periodontal health at the systemic level. Regarding the causality of the association, several hypotheses have been proposed to explain this association including endothelial dysfunction, oxidative stress and worsening of systemic inflammation in response to bacteremia or inflammatory mediator dissemination from periodontal lesion.[50] For instance, some studies showed that the presence of periodontitis was associate to modifications of arterial stiffness[51] and to systemic modulation of cytokines level.[52] However, the precise biological mechanisms involved remain under investigation.

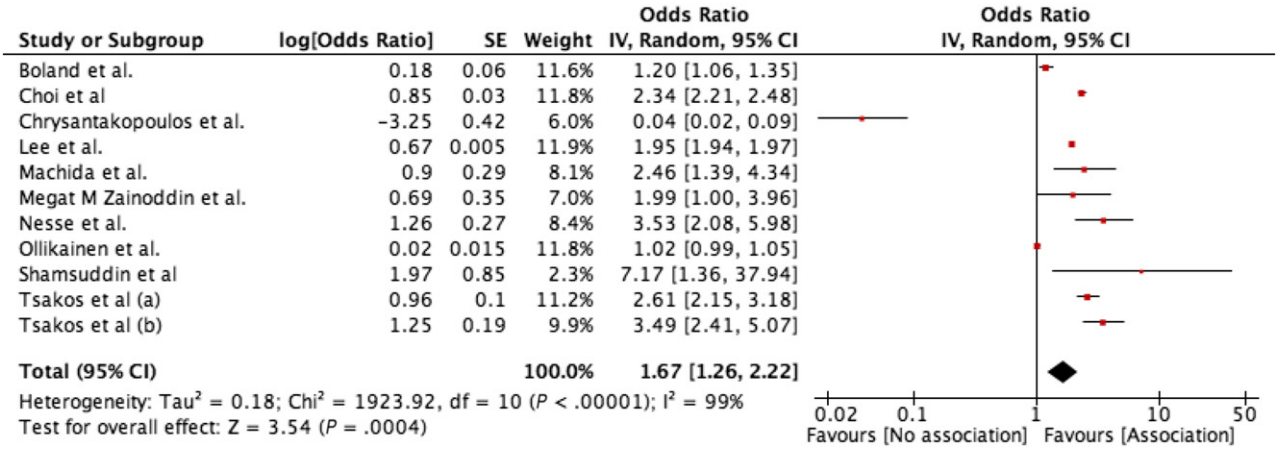
Heterogeneity of the definitions and diagnostic criteria used in the included studies could modify the magnitude

Figure 5



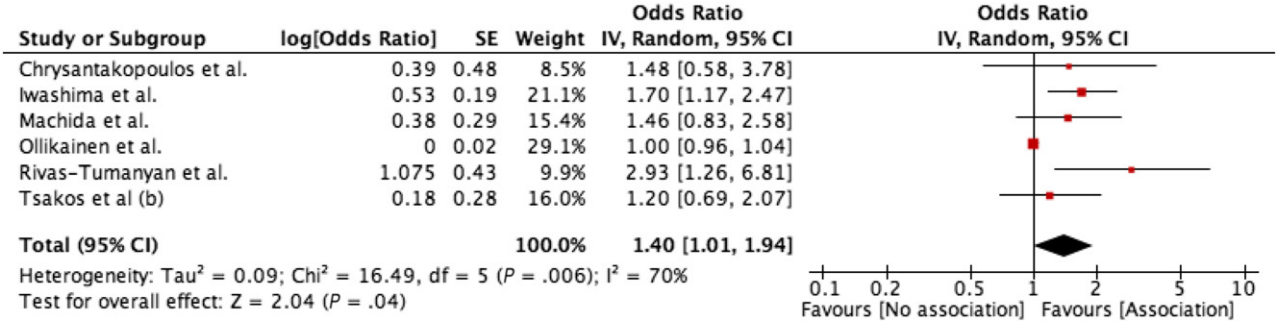
Forest plot for association between periodontitis and HT considering only cross-sectional studies.

Figure 6



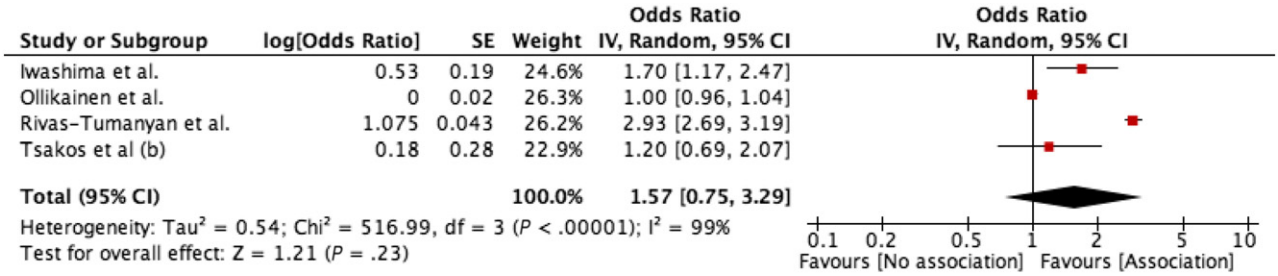
Forest plot for association between periodontitis and HT considering unadjusted ORs only.

Figure 7



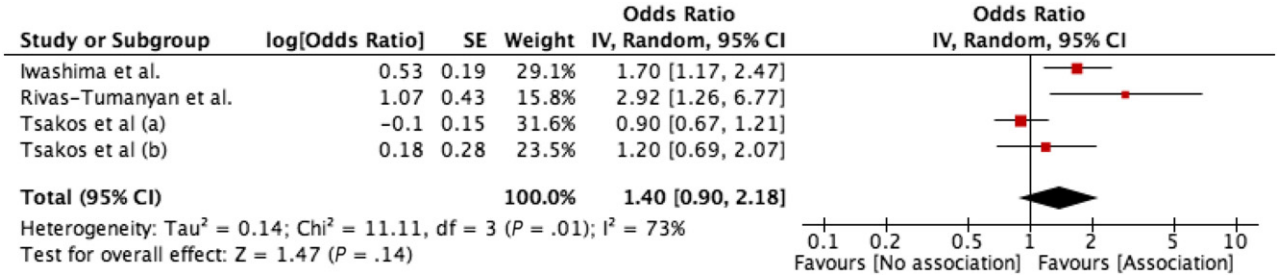
Forest plot for association between severe periodontitis and HT (only adjusted ORs were considered).

Figure 8



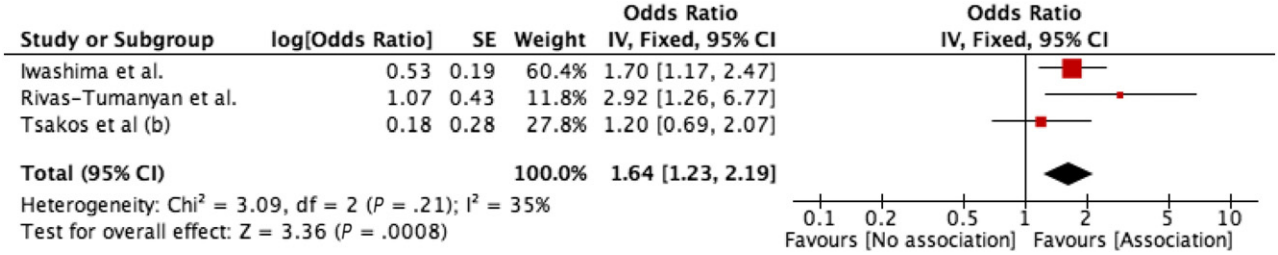
Forest plot for association between severe periodontitis and HT including only studies that did not use self-reported methods for diagnosis (HT or periodontitis) (only adjusted ORs were considered).

Figure 9



Forest plot for association between moderate to severe periodontitis and HT in "Secure" studies.

Figure 10



Forest plot for association between severe periodontitis and HT in "Secure" studies.

of the association and restrict its interpretation. When analysis was conducted only with ORs from studies having used secure diagnostic criteria, as suggested by Nibali et al,[14] an OR of 1.40 was measured for moderate to severe periodontitis. Furthermore, when only severe periodontitis was considered an OR of 1.64 was measured strengthening the association between both diseases. This result has already been observed for other types of associations where the use of more specific case definition leads to higher calculated OR such as for metabolic syndrome[14] or abdominal obesity.[47]

Periodontal treatment aims to suppress bacterial load and to decrease inflammation. To date, only few studies investigated the effect of periodontal treatment on BP as primary outcome.[53,54] However, it has been demonstrated that an effective periodontal treatment reduces significantly the levels of a cluster of inflammatory markers and improves the equilibration levels of lipid markers levels (total cholesterol and LDL-cholesterol) at short-term. Furthermore, it has also been observed that the clinical periodontal improvement could be associated with a reduction of 7 ± 3 mmHg of SBP after 2 months of therapy. These changes in SBP suggest that periodontal treatment could have a positive effect in reducing high BP and also strengthens the association between periodontal

diseases and CV risk factors.[53] In a recent interventional prospective cohort pilot study comprising 26 patients with refractory HT (BP> 140/90 mmHg and patient under treatment using 3 or more classes of anti-hypertensive drugs including a diuretic drug) and generalized chronic periodontitis, non-surgical periodontal therapy significantly reduced all CV risk markers including CRP, IL-6 and fibrinogen. Median values of SBP and DBP were reduced by 12.5 mmHg and 10.0 mmHg, respectively 6 months after periodontal therapy suggesting that reduction in clinical parameters of PD led to the improvement of BP levels.[54] This could be correlated to some observational studies evaluating the potential cardiovascular risk reduction associated to a reduction in BP. A reduction in SBP of 10-12 mmHg or in DBP of 5-6 mmHg resulted in a decrease in the incidences of stroke, coronary artery disease (CAD), congestive heart failure, and cardiovascular death of 35%- 40%, 20%-25%, 45%-55%, and 20%-25%, respectively.[55] This evidence clearly suggests that lowering BP reduces CV morbidity and mortality.[55] The effects of periodontal treatment on BP reduction could be compared to other risk factors of high BP such as lifestyle modifications for which evidence-based data are available to support BP reductions. For instance, lifestyle limiting alcohol intake might help reduce BP by 2 to 4 mmHg. Increasing physical activity, and reducing sodium intake to <6 g of sodium chloride daily helps reduce BP by 4-9 mmHg and 2-8 mmHg respectively.[56]

Quality of evidence and limitations

This systematic review and meta-analysis included strict inclusion and exclusion criteria. However, the main limitation of these studies was the lack of prospective follow-up studies and the heterogeneity among studied populations, periodontal and HT diagnosis criteria. The need of prospective studies appears mandatory to clearly determine the association as periodontal diseases evolve on a chronic mode during years with, at some point acute manifestations. Therefore, as already mentioned by Tsioufis et al, the bacterial load and the inflammatory status, at the moment of the clinical parameters measurement, may influence the result.[7]

In most of the studies, periodontal status was clinically evaluated through PPD and/or clinical attachment level measurement. Nevertheless, several definitions of periodontal diseases have been used across studies and only a few have distinguished severe forms of periodontitis. Consideration of even light and moderate periodontitis could reduce the strength of the association between both diseases as showed in this meta-analysis. Regarding the diagnosis of HT, evaluation method was also different among studies. Some of them assessed only the presence of HT with questionnaire or self-report. This may have resulted in under-diagnosis of HT and, therefore, underestimation of the magnitude of the association between periodontitis and HT. Nevertheless, all studies did not adjust OR with same cofounding factors leading to potential bias.

Conclusion

The identification of modifiable risk factors for the progression of damage caused by HT is of high priority at a global level as it continues to be a major cause of morbidity, mortality, and a significant contributor to health care expenses.[57] The development and progression of HT is complex and multifactorial and, as demonstrated, periodontal status, obviously presence of severe form of periodontitis seems associated. Thus, effective management is rarely achieved through a single intervention. In this context, periodontal screening of hypertensive patients, at risk, and periodontal treatment may be included in the multidisciplinary management of such patients to, at least, benefit from other determinants of good health.

Disclosure

Authors do not have any conflict of interest related to this study.

Acknowledgements

Authors would like to thank Fareeha Batool for her help in the preparation of the manuscript.

References

1. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet 2005;366:1809-20.
2. Petersen PE. The World Oral Health Report 2003: continuous improvement of oral health in the 21st century—the approach of the WHO Global Oral Health Programme. Community Dent Oral Epidemiol 2003;31(Suppl 1):3-23.
3. Kassebaum NJ, Bernabe E, Dahiya M, et al. Global burden of severe periodontitis in 1990-2010: a systematic review and meta-regression. J Dent Res 2014;93:1045-53.
4. Silva N, Abusleme L, Bravo D, et al. Host response mechanisms in periodontal diseases. J Appl Oral Sci 2015;23:329-55.
5. Zadik Y, Bechor R, Galor S, et al. Erectile dysfunction might be associated with chronic periodontal disease: two ends of the cardiovascular spectrum. J Sex Med 2009;6:1111-6.
6. Stewart R, West M. Increasing evidence for an association between periodontitis and cardiovascular disease. Circulation 2016. [CIRCULATIONAHA.115.020869].
7. Tsioufis C, Kasiakogias A, Thomopoulos C, et al. Periodontitis and blood pressure: the concept of dental hypertension. Atherosclerosis 2011;219:1-9.
8. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013;31:1281-357.

9. Kearney PM, Whelton M, Reynolds K, et al. Global burden of hypertension: analysis of worldwide data. Lancet 2005;365:217-23.
10. Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. Lancet 2014;383:1899-911.
11. Lawes CMM, Vander Hoorn S, Rodgers A. International society of hypertension. global burden of blood-pressure-related disease, 2001. Lancet 2008;371:1513-8.
12. Lewington S, Clarke R, Qizilbash N, et al. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903-13.
13. Linden GJ, Lyons A, Scannapieco FA. Periodontal systemic associations: review of the evidence. J Clin Periodontol 2013;40(Suppl 14): S8-19.
14. Nibali L, Tatarakis N, Needleman I, et al. Association between metabolic syndrome and periodontitis: A systematic review and meta-analysis. J Clin Endocrinol Metab 2013;98:913-20.
15. Page RC, Eke PI. Case definitions for use in population-based surveillance of periodontitis. J Periodontol 2007;78:1387-99.
16. Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol 1999;4:1-6.
17. Holtfreter B, Albandar JM, Dietrich T, et al. Joint EU/USA Periodontal Epidemiology Working Group. Standards for reporting chronic periodontitis prevalence and severity in epidemiologic studies: Proposed standards from the Joint EU/USA Periodontal Epidemiology Working Group. J Clin Periodontol 2015;42:407-12.
18. Preshaw PM. Definitions of periodontal disease in research. J Clin Periodontol 2009;36:1-2.
19. Ong KL, Cheung B, Man YB, et al. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999–2004. Hypertension 2007.
20. Choi HM, Han K, Park Y-G, et al. Associations among oral hygiene behavior and hypertension prevalence and control: The 2008 to 2010 Korea National Health and Nutrition Examination Survey. J Periodontol 2015;86:866-73.
21. Nesse W, Dijkstra PU, Abbas F, et al. Increased prevalence of cardiovascular and autoimmune diseases in periodontitis patients: a cross-sectional study. J Periodontol 2010;81:1622-8. [[Internet] Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=20583916&retmode=ref&cmd=prlinks].
22. Zainoddin NBMM, Taib H, Awang RAR, et al. Systemic conditions in patients with periodontal disease. Int Med J 2013.
23. Shamsuddin SN, Ahmad A, Taib H, et al. Hypertension and its association with the severity of chronic periodontitis: a preliminary study. Arch Orofacial Sci 2015;10:3-9.
24. Yamori M, Njelekela M, Mtabaji J, et al. Hypertension, periodontal disease, and potassium intake in nonsmoking, Nondrinker African Women on No Medication. Int J Hypertens 2011;2011:1-5.
25. Lee J-H, Lee J-S, Park J-Y, et al. Association of lifestyle-related comorbidities with periodontitis: a nationwide cohort study in Korea. Medicine 2015;94:e1567. [[Internet]. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26376407&retmode=ref&cmd=prlinks].
26. Łysek R, Jankowski P, Polak M, et al. Association between central and peripheral blood pressure and periodontal disease in patients with a history of myocardial infarction. Pol Arch Med Wewn 2016;126:41-7.
27. Ahn Y-B, Shin M-S, Byun J-S, et al. The association of hypertension with periodontitis is highlighted in female adults: results from the Fourth Korea National Health and Nutrition Examination Survey. J Clin Periodontol 2015;42:998-1005.
28. Kawabata Y, Ekuni D, Miyai H, et al. Relationship between prehypertension/hypertension and periodontal disease: a prospective cohort study. Am J Hypertens 2015. [hpv117].
29. Darnaud C, Thomas F, Pannier B, et al. Oral Health and Blood Pressure: The IPC Cohort. Am J Hypertens 2015;28:1257-61.
30. Flemmig TF. *Periodontitis. 737 N. Michigan Avenue, Suite 800 Chicago, IL 60611–2690 USA: American Academy of Periodontology. 1999:32-8.*
31. Machida T, Tomofuji T, Ekuni D, et al. Severe periodontitis is inversely associated with coffee consumption in the maintenance phase of periodontal treatment. Nutrients 2014;6:4476-90.
32. Ollikainen E, Saxlin T, Tervonen T, et al. Association between periodontal condition and hypertension in a non-smoking population aged 30-49 years: results of the Health 2000 Survey in Finland. J Clin Periodontol 2014;41:1132-8.
33. Chrysanthakopoulos NA, Chrysanthakopoulos PA. Association between indices of clinically-defined periodontitis and self-reported history of systemic medical conditions. J Invest Clin Dent 2014. [n/a–n/a].
34. Iwashima Y, Kokubo Y, Ono T, et al. Additive interaction of oral health disorders on risk of hypertension in a Japanese urban population: the Suita Study. Am J Hypertens 2014;27:710-9. [[Internet] Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=24343779&retmode=ref&cmd=prlinks].
35. Boland MR, Hripcsak G, Albers DJ, et al. Discovering medical conditions associated with periodontitis using linked electronic health records. J Clin Periodontol 2013;40:474-82.
36. Rivas-Tumanyan S, Campos M, Zevallos JC, et al. Periodontal disease, hypertension, and blood pressure among older adults in Puerto Rico. J Periodontol 2013;84:203-11.
37. Kim J, Amar S. Periodontal disease and systemic conditions: a bidirectional relationship. Odontology 2006;94:10-21.
38. Kumar P, Mastan K, Chowdhary R, et al. Oral manifestations in hypertensive patients: A clinical study. J Oral Maxillofac Pathol 2012;16:215-21.
39. Rivas-Tumanyan S, Spiegelman D, Curhan GC, et al. Periodontal disease and incidence of hypertension in the health professionals follow-up study. Am J Hypertens 2012;25:770-6.
40. Vidal F, Figueredo CMS, Cordovil I, et al. Higher prevalence of periodontitis in patients with refractory arterial hypertension: a case–control study. Oral Dis 2011;17:560-3.
41. Tsakos G, Sabbah W, Hingorani AD, et al. Is periodontal inflammation associated with raised blood pressure? Evidence from a National US survey. J Hypertens 2010;28:2386-93.
42. Desvarieux M, Demmer RT, Jacobs DR, et al. Periodontal bacteria and hypertension: the oral infections and vascular disease epidemiology study (INVEST). J Hypertens 2010;28:1413-21.
43. Engström S, Gahnberg L, Högberg H, et al. Association between high blood pressure and deep periodontal pockets: a nested case-referent study. Ups J Med Sci 2007;112:95-103.
44. Holmlund A, Holm G, Lind L. Severity of periodontal disease and number of remaining teeth are related to the prevalence of myocardial infarction and hypertension in a study based on 4254 subjects. J Periodontol 2006;77:1173-8. [[Internet] Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=16805679&retmode=ref&cmd=prlinks].
45. Khader YS, Rice JC, Lefante JJ. Factors associated with periodontal diseases in a dental teaching clinic population in northern Jordan. J Periodontol 2003;74:1610-7.
46. Buhlin K, Gustafsson A, Pockley AG, et al. Risk factors for cardiovascular disease in patients with periodontitis. Eur Heart J 2003;24:2099-107.

47. Ostchega Y, Hughes JP, Terry A, et al. Abdominal obesity, body mass index, and hypertension in US adults: NHANES 2007-2010. Am J Hypertens 2012;25:1271-8.
48. Lafon A, Pereira B, Dufour T, et al. Periodontal disease and stroke: a meta-analysis of cohort studies. Eur J Neurol 2014;21. [1155–61– e66–7].
49. Fuggle NR, Smith TO, Kaul A, et al. Hand to mouth: a systematic review and meta-analysis of the association between rheumatoid arthritis and periodontitis. Front Immunol 2016;7:80.
50. Macedo Paizan ML, Vilela-Martin JF. Is there an association between periodontitis and hypertension? Curr Cardiol Rev 2014;10:355-61.
51. Schmitt A, Carra MC, Boutouyrie P, et al. Periodontitis and arterial stiffness: a systematic review and meta-analysis. J Clin Periodontol 2015.
52. Buhlin K, Hultin M, Norderyd O, et al. Risk factors for atherosclerosis in cases with severe periodontitis. J Clin Periodontol 2009;36:541-9.
53. D'Aiuto F, Parkar M, Nibali L, et al. Periodontal infections cause changes in traditional and novel cardiovascular risk factors: results from a randomized controlled clinical trial. Am Heart J 2006;151:977-84.
54. Vidal F, Cordovil I, Figueredo CMS, et al. Non-surgical periodontal treatment reduces cardiovascular risk in refractory hypertensive patients: a pilot study. J Clin Periodontol 2013;40:681-7.
55. Grossman E. Blood pressure: the lower, the better: the con side. Diabetes Care 2011;34(Suppl 2):S308-12.
56. Cook NR, Cutler JA, Obarzanek E, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). BMJ 2007;334:885-8.
57. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206-52.