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Periodontitis and arterial stiffness: a systematic review and meta-analysis.

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ABSTRACT

Introduction and Aims: Patients with periodontitis have a higher risk of cardiovascular diseases, although a causal relationship between these conditions remains unclear. Arterial stiffness is considered a marker of arteriosclerosis and a risk factor for cardiovascular diseases. A systematic review of the literature on clinical studies using pulse wave velocity to assess arterial stiffness in patients with periodontitis was carried out to answer the following questions: 1) Do patients with periodontitis have impaired arterial stiffness compared to non periodontal diseased subjects? 2) Is periodontal treatment effective as a mean to improve arterial stiffness in patients with periodontitis?

Literature Review: Literature search was done on different databases up to September 2014.

All clinical studies (excluding case reports) using pulse wave velocity in patients with periodontitis were retrieved for a full-text evaluation. A total of 10 studies were included.

Patients with periodontitis have increased arterial stiffness compared to controls (pulse wave velocity mean difference 0.85 m/s; 95%CI: 0.53-1.16; $p < 0.00001$). The only 2 interventional studies showed contradictory results on the effects of periodontal treatment on pulse wave velocity.

Conclusion: Patients with periodontitis appears to have higher values of pulse wave velocity compared to controls. The effect of periodontal treatment on arterial stiffness remains unclear.

CLINICAL RELEVANCE

Scientific rationale: Epidemiological studies demonstrated an association between periodontitis and cardiovascular diseases. Our study was designed to systematically review the current literature in order to assess whether patients with periodontitis have altered arterial stiffness, a marker of arteriosclerosis and a cardiovascular risk factor.

Principal findings: The meta-analysis (based on 7 articles, 1517 patients) indicates that patients with severe periodontitis show significantly greater pulse wave velocity, a measure of arterial stiffness, than controls.

Practical implications: The present findings contribute to describe the cardiovascular profile of patients having periodontitis. Moreover, they support further clinical investigations to assess the impact of periodontal therapy on cardiovascular risk.

INTRODUCTION

Over the last two decades, an increasing number of publications have focused on the relationship between periodontitis and cardiovascular diseases.(Tonetti et al., 2013, Kinane et al., 2008) Indeed, patients with severe periodontitis show an increased risk for developing hypertension, coronary disease, and atherosclerosis.(Friedewald et al., 2009, Humphrey et al., 2008, Tonetti et al., 2013) Chronic systemic low-grade inflammation induced and sustained by periodontitis has been advocated as the possible explanatory mechanism of this association.(Kiechl et al., 2001, Schenkein and Loos, 2013, Demmer et al., 2013) Moreover, bacterial DNA of major periodontal pathogens, such as *Aggregatibacter actinomycetemcomitans* (*Aa*) and *Porphyromonas gingivalis* (*Pg*), has been identified in atheromatous plaques, supporting a role of these bacteria in the occurrence of cardiovascular events.(Figuro et al., 2011, Spahr et al., 2006, Rosenfeld and Campbell, 2011, Lockhart et al., 2012)

Arterial stiffness is also a key component in the development of cardiovascular diseases.(Laurent et al., 2006) Since it can be detected before the occurrence of clinically apparent cardiovascular disease, arterial stiffness acts as a marker of arteriosclerosis and a predisposing factor for the future development of cardiovascular disease, e.g. atherosclerosis. Indeed, increased arterial stiffness is associated with modifications in nitric oxide production, impaired endothelial function, and reduced vasodilation. The degree of arterial stiffness can be evaluated noninvasively by measuring the pulse wave velocity (PWV).(Lane et al., 2006, Tomiyama and Yamashina, 2010) PWV allows calculating the pulse wave propagation velocity between two sites, commonly the carotid and femoral pulses, or the carotid and radial pulses, although brachial-ankle PWV has also been used. Aortic (carotid–femoral) PWV, which remains the “gold-standard” measurement of arterial stiffness (Mancia et al.,

2013, Sethi et al., 2014), has been shown to be predictive of cardiovascular mortality above all classical risk factors.(Ben-Shlomo et al., 2014, Shokawa et al., 2005, Vlachopoulos et al., 2010) It is therefore of interest to study the relationship between periodontitis and PWV measures. The aim of the present systematic review, and possibly meta-analysis, was (1) to determine whether arterial stiffness is altered in patients with periodontitis compared to patients without periodontitis; and (2) to assess whether periodontal treatment results in an improvement of arterial stiffness measured by PWV.

REVIEW OF CURRENT LITERATURE

METHOD

Study design

A systematic review of studies focusing on arterial stiffness assessed by PWV in patients with periodontitis was undertaken. As currently recommended, we followed the PRISMA statements checklist for reporting a systematic review.(Moher et al., 2009)

Eligibility criteria for study inclusion

For the purpose of conducting a systematic review, we assessed all studies in which the primary objective was to evaluate arterial stiffness by PWV in patients with periodontitis.

Randomized controlled clinical trials (RCT), case-control studies, cross-sectional studies, cohort studies, and prospective clinical series were eligible for inclusion. Hereafter, the eligibility criteria (by applying the PICO framework):

Patients: Adult patients with periodontitis, with or without other comorbidities (e.g. diabetes, hypertension). No restriction was applied for the definition and severity of periodontitis.

Intervention: Any type of periodontal treatment.

Comparator: Controls could be represented by patients without periodontal disease or with gingivitis or mild periodontitis.

Outcomes: The primary outcome had to be the measure of arterial stiffness by means of PWV assessment.(Mancia et al., 2013, Sethi et al., 2014, Ben-Shlomo et al., 2014) All PWV techniques (i.e. carotid-femoral pulses; carotid-radial pulses; brachial-ankle) were considered. For inclusion, PWV should have been measured and compared between patients with and without periodontitis, and/or before and after periodontal treatment.

Search strategy

Literature search for articles published up to and including September 2014 was performed by using the following online available databases: MEDLINE (through PubMed), EMBASE, Cochrane Oral Health Group Specialized Register, ProQuest Dissertations, and Thesis Database. A specific research equation was formulated for each different database, using the following key words and MeSH terms: periodontal disease, periodontitis, periodontal treatment, scaling and root planing, endothelial function, endothelial dysfunction, pulse wave velocity, arterial stiffness. In addition, reference lists from eligible studies and relevant review articles (not included in the systematic review) were crosschecked to identify additional studies. A grey literature search was also performed by using the OpenGrey database. Studies meeting the selection criteria were reviewed if written in English, French or Italian.

Study selection and quality assessment

The titles and abstracts of the retrieved studies were independently and blindly screened for relevance by two reviewers (AS and MCC). To enhance sensitivity, records were removed only if both reviewers excluded at the title level. All disagreements were resolved by discussion with a third review author (PhB). Subsequently, both reviewers performed a full-text analysis of the selected articles.

The two reviewers independently assessed the risk of bias using appropriate tools according to the study design. Precisely, for RCT the Cochrane criteria described in the Cochrane Handbook for Systematic Reviews of Interventions were used (Higgins et al., 2011), and for non-randomized studies, the Newcastle-Ottawa Scale (NOS) was used (Stang, 2010).

Additionally, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to grade the “body of evidence” merging from this review. (Guyatt et al., 2008)

Data extraction and analysis

Data from the studies included in the systematic review were processed for qualitative and possibly quantitative analyses. Outcome measures of PWV (mean values and standard deviation) were extracted for periodontal patients and controls as well as before and after periodontal treatment. If necessary and possible, outcome variables were calculated by the authors based on the data available in the individual selected studies. If the standard error (SE) was provided instead of standard deviation (SD), the SD was calculated based on the sample size ($SE=SD/\sqrt{N}$). The 95% confidence interval (CI) was then calculated as $SE \times 1.96$ (upper bound) and $SE \times -1.96$ (lower bound). If possible, mean differences in PWV between patients with and without periodontitis were used to perform the meta-analyses. Weighted

mean difference and 95%CI values were calculated using Review Manager (RevMan, version 5.1, by Cochrane Collaboration, Copenhagen). Heterogeneity was assessed using I^2 statistics.(Harbour and Miller, 2001, Higgins et al., 2011) The pooled estimates of the mean differences were calculated using random effects models to take into account potential inter-study heterogeneity and to adopt a more conservative approach. The pooled effect was considered significant if $p < 0.05$.

RESULTS

Search and selection

Overall, our searches identified 46 articles, of which 15 were rejected after removing duplicates. Out of the remaining 31 articles, 17 were excluded after reading the title and abstract because of non-relevant study design or type of patients, or because the publication was not pertinent to the review questions. After full-text reading, other 4 articles were excluded because not pertinent to the review questions. The flow chart of the study identification and inclusion/exclusion process is shown in Figure 1. The excluded studies and the reasons for exclusion are reported in Supplement Table ST1. In total, 10 articles were found eligible for the systematic review (qualitative analysis) and 7 for the meta-analyses (quantitative analysis).

Study characteristics

Eight observational(Franek et al., 2012, Franek et al., 2009, Hanaoka et al., 2013, Jockel-Schneider et al., 2014, Miyaki et al., 2006, Kapellas et al., 2014a, Shanker et al., 2013, Vieira et al., 2011) and two interventional(Kapellas et al., 2014b, Vidal et al., 2013) studies were included: seven cross-sectional studies, one case-control study, one prospective interventional cohort pilot study, and one randomized controlled clinical trial.

Overall, 2569 subjects were studied: 1496 patients with severe/advanced periodontitis and 1073 patients without periodontal disease or with gingivitis/mild periodontitis (controls). Regarding the type of periodontitis (Armitage, 1999), 1192 patients in 9 studies (Vieira et al., 2011, Kapellas et al., 2014a, Miyaki et al., 2006, Franek et al., 2012, Shanker et al., 2013, Kapellas et al., 2014b, Jockel-Schneider et al., 2014, Vidal et al., 2013, Franek et al., 2009) were diagnosed with severe chronic periodontitis; 18 patients in one study (Jockel-Schneider et al., 2014) with aggressive periodontitis; 619 patients in 2 studies (Franek et al., 2009, Franek et al., 2012) with gingivitis. Two studies (Franek et al., 2009, Miyaki et al., 2006) used the CPITN index to assess periodontitis presence and severity, one study (Hanaoka et al., 2013) used the serum levels of IgG against *Pg* (the most common bacteria associated with advanced periodontitis), other studies applied the common clinical periodontal parameters, like periodontal pocket depth, clinical attachment level, gingival inflammation and bleeding.

Arterial stiffness was measured through the detection of PWV using carotid-femoral PWV in two studies (Vieira et al., 2011, Vidal et al., 2013), brachial-ankle PWV in two studies (Miyaki et al., 2006, Hanaoka et al., 2013), carotid-radial PWV in three studies (Franek et al., 2009, Shanker et al., 2013, Franek et al., 2012), aortic PWV in one study (Jockel-Schneider et al., 2014), and carotid-dorsalis pedis PWV in two studies. (Kapellas et al., 2014b, Kapellas et al., 2014a) Detailed information regarding the study design, sample size, type of population, study duration, periodontal assessment, outcome measures, periodontal treatment, and main findings of each included study are summarized in Tables 1a and 1b.

Relationship between periodontitis and arterial stiffness

Overall, 5 studies(Vieira et al., 2011, Miyaki et al., 2006, Shanker et al., 2013, Kapellas et al., 2014b, Jockel-Schneider et al., 2014) reported a significant association between periodontitis and arterial stiffness, with a direct proportional relationship between the severity of the periodontal disease and the increasing values of PWV.(Vieira et al., 2011, Kapellas et al., 2014b) However, in some studies(Kapellas et al., 2014b, Miyaki et al., 2006, Vieira et al., 2011) this association was attenuated or no longer significant when adjusting for common confounders, such as age, gender, smoking, or diabetes. Miyaki et al.(Miyaki et al., 2006) observed that mild periodontitis have a weaker relationship with arterial damage (assessed by PWV) than severe periodontitis. In the study by Hanaoka et al.(Hanaoka et al., 2013) patients with high levels of *Pg*-IgG tended to have higher PWV values compared to patients with low levels of *Pg*-IgG, but this result was not statistically significant. Conversely, two other studies found no statistically significant difference for PWV between patients with and without periodontitis.(Franek et al., 2009, Franek et al., 2012) However, both studies were conducted in periodontal patients with comorbidities, such as essential hypertension(Franek et al., 2009) and type-2 diabetes.(Franek et al., 2012)

Effect of periodontal therapy on PWV

The effect of non-surgical periodontal therapy on PWV measurement was assessed in two trials.(Kapellas et al., 2014b, Vidal et al., 2013) Contradictory results were found. The prospective cohort pilot study by Vidal et al. 2013(Vidal et al., 2013) was conducted in a small sample of patients with refractory hypertension and advanced chronic periodontitis; it showed a significant reduction of all cardiovascular risk markers, including PWV (decreased by 0.9 m/sec), after periodontal treatment. Conversely, the randomized controlled trial by Kapellas et al. 2014(Kapellas et al., 2014b) found no significant difference in PWV

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measurements between the treatment groups at 3 months (mean difference, 0.06 m/s [95%CI, -0.17 to 0.29]; $p=0.594$) or 12 months (mean difference, 0.21 m/s [95%CI, -0.01 to 0.43]; $p=0.062$) after treatment. Detailed information is shown in Table 1b.

Quantitative assessment

Seven out of eight observational studies were included in the quantitative assessment. The study by Miyaki et al. could not be included in the meta-analysis because of the definition of groups using the presence/absence of atherosclerosis instead of the periodontal status like the other studies (Miyaki et al., 2006).

A series of meta-analyses were performed by pooling together all available mean values of PWV measured at baseline and compared between patients with periodontitis (test) and patients with gingivitis/mild periodontitis or healthy subjects (controls). Overall, the calculated weighted mean difference and 95% confidence interval values showed that patients with severe periodontitis have higher PWV compared to controls (0.85 m/s; 95% CI: 0.53-1.16; $p<0.00001$; I^2 : 51%). Notably, sensitivity analyses aimed to calculate PWV by the specific technique used (e.g. carotid-femoral, carotid-radial, carotid-dorsalis pedis, brachial-ankle or brachial PWV) showed that patients with severe periodontitis have always significantly higher values of PWV, with weighted mean differences that ranged between 0.69 and 1.04 m/s (Figures 2). When analyzing subjects with or without comorbidities separately (i.e. diabetes; hypertension; hypercholesterolemia), the meta-analysis showed that the weighted mean difference for PWV between patients with periodontitis without comorbidity ($n=441$) and healthy controls ($n=666$) is 1.12 m/s (95% CI: 0.76-1.48; $p<0.00001$; I^2 : 41%) (Jockel-Schneider et al., 2014, Kapellas et al., 2014a, Shanker et al., 2013); this difference is less important but still statistically significant when comparing

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patients with periodontitis (n=165) versus controls (n=245) in populations with comorbidities (PWV 0.51 m/s; 95% CI: 0.17-0.84; p=0.003; I²: 0%)(Franek et al., 2012, Franek et al., 2009, Hanaoka et al., 2013, Vieira et al., 2011). Sensitivity analysis has also been performed by the type of exposure (i.e. periodontal disease). The meta-analysis of the studies comparing PWV between patients with severe periodontitis (n=177) versus healthy controls (n=222) showed a mean difference of 0.84 m/s (95%CI: 0.53-1.15; p<0.00001; I²: 62%)(Franek et al., 2012, Jockel-Schneider et al., 2014, Kapellas et al., 2014a). The meta-analysis of the studies comparing PWV between patients with severe periodontitis (n=365) versus patients with non-severe periodontitis (gingivitis or mild periodontitis)(n=627) showed a mean difference of 0.89 m/s (95% CI: 0.59-1.18; p<0.00001; I²: 71%)(Franek et al., 2009, Shanker et al., 2013, Vieira et al., 2011). Finally, when considering only cross-sectional studies in the meta-analysis, the weighted mean difference in PWV between patients with periodontitis and controls was 0.74 m/s (95% CI: 0.49-0.98; p<0.00001; I²: 34%).

Study quality assessment

Two reviewers (AS and MCC) scored the methodological qualities of the included studies. The only one RCT included(Kapellas et al., 2014b) was qualified at low risk of bias. The remaining studies were assessed at low (7 studies(Franek et al., 2012, Franek et al., 2009, Hanaoka et al., 2013, Miyaki et al., 2006, Kapellas et al., 2014a, Shanker et al., 2013, Vieira et al., 2011)) or high (2 studies(Vidal et al., 2013, Jockel-Schneider et al., 2014)) risk of bias. Detailed information regarding the quality assessment of the included studies is reported in Supplement Tables ST2 and ST3.

Based on the GRADE system(Guyatt et al., 2008), 2 studies(Vidal et al., 2013, Jockel-Schneider et al., 2014) were judged at very low grade of evidence, and 8 studies(Miyaki et al., 2006, Franek et al., 2009, Franek et al., 2012, Vieira et al., 2011, Hanaoka et al., 2013, Shanker et al., 2013, Kapellas et al., 2014b, Kapellas et al., 2014a) were judged at low grade of evidence. The RCT by Kapellas et al.(Kapellas et al., 2014b) was judged as a high quality study, but the important concerns about inconsistency and directness of the results downgraded the level of evidence from high to low.

DISCUSSION

This is the first systematic review linking periodontitis to arterial stiffness. The present findings indicate that, despite the heterogeneity of the available studies, there is a significant association between periodontitis and PWV. Indeed, patients with severe periodontitis have higher PWV compared with patients without periodontitis or with gingivitis/mild periodontitis, both in population with and without comorbidities (e.g. hypertension, diabetes). This was also confirmed by sensitivity analyses when data were pooled according to the type of PWV measurement used, supporting that periodontal disease correlates with both central (carotid-femoral PWV or brachial-ankle PWV) and peripheral (other PWV measurements) arterial stiffening. These results suggest that severe periodontitis (and periodontal inflammation) might represent an under-recognized factor increasing patient's cardiovascular risk.

The increase in PWV observed in case of severe/advanced periodontitis might be clinically relevant.(Vieira et al., 2011, Kapellas et al., 2014a) Indeed, it has been shown in a recent review by Vlachopoulos et al.(Vlachopoulos et al., 2010) that an increase in PWV of 1 m/s implies an estimated 14% increased risk for cardiovascular events and a 15% increased risk

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for cardiovascular and all-cause mortality. In our study, when considering the “gold standard” carotid-femoral PWV, patients with severe periodontitis exhibit an average increased PWV of 1.04 m/s compared to controls. Moreover, when considering populations with severe periodontitis in absence of comorbidity, the difference in PWV increases up to 1.12 m/s. These results support the hypothesis that patients with severe periodontitis may present with a greater burden of subclinical arterial damage, and they may be at increased risk of cardiovascular morbidity and mortality.

Interestingly, the difference in PWV between patients with periodontitis and controls decreases at 0.51 m/s when studying populations with comorbidities, such as essential hypertension, diabetes, atherosclerosis, and familial hypercholesterolemia. These conditions are known to potentially influence PWV and the arterial status in general; thus it can be argued that these comorbidities act as confounders by blunting the association between periodontitis and PWV, and superimposing or masking PWV changes related to periodontal inflammation. However, the role of hypertension or diabetes remains under debate, since the contribution of risk factors other than age and blood pressure to carotid-femoral PWV is considered to be rather small or insignificant.(Cecelja and Chowienczyk, 2009)

It can also be argued that the different methods, conditions and devices used to measure PWV may have an influence on the absolute PWV values. The way PWV was assessed was systematically described in the selected studies, which overall used standardized protocols of measurement that insure PWV reproducibility. However, PWV was measured over different arterial territories. As known, the carotid-femoral PWV is clinically the most relevant measurement of aortic stiffness mostly because of the large body of evidence demonstrating its association with incident cardiovascular disease independently of traditional risk factors in various populations.(Reference Values for Arterial Stiffness, 2010, Ben-Shlomo et al., 2014,

Vlachopoulos et al., 2010) However, this is not the only PWV measurement method available, rather several others have been developed in different countries. To overcome potential bias in the measurement, cut-off values have been proposed, but most of the included studies were performed before standardization. The proposed cut-off value (Mancia et al., 2013) of 10 m/s in case of hypertensive patients can nevertheless be used for estimating the risk of subjects included in the two retained studies that used carotid-femoral PWV. (Shanker et al., 2013, Vieira et al., 2011) Patients with severe periodontitis display mean values very close to the 10 m/s threshold, although not all patients were hypertensive. Nonetheless, if considering the PWV threshold for healthy people in the same age range, the periodontal patients evaluated in the included studies have mean PWV values definitely higher (PWV cut-off value for 40-49 years category: 7.2 m/s). Taking these data together, it appears that patients with severe periodontitis have PWV mean values superior to the estimated reference thresholds for arterial stiffness and they may be at an increased risk of arterial dysfunctions and asymptomatic organ damages. However, it remains under debate whether these reference values must be (or not) determined as a function of age and blood pressure, and whether it is possible to sort out all the potential influences on PWV. (Reference Values for Arterial Stiffness, 2010)

The present systematic review also aimed to assess whether periodontal treatment results into an improvement of arterial stiffness. However, the available evidence is weak and based only on two interventional studies. (Kapellas et al., 2014b, Vidal et al., 2013) On one side, Vidal et al. 2013 reported a significant reduction in PWV values 6 months after periodontal non-surgical treatment. On the other side, Kapellas et al. 2014b found only a trend toward reduction in PWV values at 3 months after treatment, although intima-media thickness was significantly decreased. It must be noted, however, that the therapy used by Kapellas et al.

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resulted only in a modest improvement of periodontal parameters in the short-term and that the duration of follow-up might be too short to expect major changes.(Boutouyrie et al., 2011) Although no conclusion can be drawn, the effectiveness of periodontal treatment must be taken into account when evaluating the influence of periodontal inflammation improvements on PWV changes. Because of its dose-dependent relation with PWV, periodontal disease may induce early vascular changes, although the mechanisms of interaction have yet to be determined. Arterial stiffness has both structural and functional determinants. Structural determinants include the breakdown of elastin and increased deposition of collagen, which are known to influence long-term changes in arterial stiffness.(Laurent et al., 2006) Conversely, short- to mid-term changes in arterial stiffness are more likely due to changes in arterial function. In relation to periodontitis, the changes in PWV observed after periodontal therapy do more likely reflect changes in arterial function rather than structural modifications.(Elter et al., 2006, Holtfreter et al., 2013, Seinost et al., 2005, Tonetti et al., 2007)

Recently, a systematic review has demonstrated the association between periodontitis and increased carotid intima-media thickness (IMT).(Orlandi et al., 2014) Periodontal treatment was also found effective in improving endothelial function in patients with severe periodontitis.(Elter et al., 2006, Holtfreter et al., 2013, Seinost et al., 2005, Tonetti et al., 2007) Both endothelial dysfunction and increased IMT are early pathophysiologic features of arteriosclerosis and atherosclerosis, and are considered as independent predictors of cardiovascular events.(Widlansky et al., 2003, Suwaidi et al., 2000, Quyyumi, 2003, Heitzer et al., 2005) However, IMT has been recently challenged for its predictive value(Bots et al., 2014) and endothelial function is difficult to test in routine practice. On the contrary, arterial

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stiffness has been constantly associated with undisputed prediction of cardiovascular events and it is easy to perform.

Study limitations

The present systematic review and meta-analysis has some limitations. Firstly, PWV measurements were heterogeneous and involved different arterial territories. Although we tried to control it by performing sensitivity analyses, standardization in PWV measurements and cut-off values is awaited in future clinical trials. Heterogeneity was also observed in the definition and assessment of periodontitis, which remains a source of potential selection and interpretation bias. Moreover, the included studies were often conducted on specific populations (e.g. Indigenous Australians) or on patients with comorbidities (e.g. patients with hypertension), factors that limit the external validity of the findings. Finally, due to the limited number of studies available, the cross-sectional design of the majority, and, the overall level of evidence, caution should be paid in the interpretation of results.

Conclusion

The present systematic review and meta-analysis support an association between severe periodontitis and increased PWV. The measurement of arterial stiffness provides a cardiovascular marker of the cumulative impact of both known and unknown risk factors, which may include periodontitis. Further investigations are awaited to elucidate the relationship between periodontitis and arterial stiffness, as well as to assess the impact of periodontal treatments on PWV.

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Figure Legends

Figure 1. Flowchart of literature search and study selection.

Figure 2. Meta-analysis of PWV measurements. The forest plot calculates the weighted mean difference [95%CI] in PWV between patients with severe periodontitis and controls (including no periodontitis or gingivitis/mild periodontitis). Data are shown by type of PWV measurement and all type together as calculated from 7 observational studies.

Tables

Table 1a. Summary of the included observational studies assessing the relationship between periodontitis and arterial stiffness measured by pulse wave velocity (PWV).

Authors and Year	Study Design	Sample Size (n)	Study Population	Periodontal Assessment	Definition of periodontitis	Outcome Measures	Main Findings
Miyaki et al., 2006(Miyaki et al., 2006)	Cross-sectional study	291	Adult male employees of a Japanese chemical company divided into two groups: with (n=145) and without (n=146) atherosclerosis	Community periodontal index of treatment needs score (CPITN), average PD, and gingival bleeding index	CPITN scores of 0, ≥ 1 , ≥ 3 and ≥ 4 were defined as healthy, having periodontal disease, having advanced periodontal disease and having severe periodontal disease, respectively	Brachial-ankle PWV	Odds ratio of atherosclerosis in relation to the CPITN score = 1.41 [95% CI: 1.16–1.73]. After adjustment for age, systolic blood pressure and smoking, no relationship between CPITN and atherosclerosis (adjusted OR: 0.91 [0.68–1.20]). The authors found no relationship between mild periodontitis and

							atherosclerosis (assessed as PWV \geq 1400 cm/s)
Franeck et al., 2009(Franeck et al., 2009)	Cross-sectional study	99	Patients with essential hypertension divided into two groups: with chronic periodontitis (CPITN score 3 and 4) (n=50) and without chronic periodontitis (n=49)	Community periodontal index of treatment needs score (CPITN)	Severe periodontitis : CPITN 3–4 No or moderate periodontitis : CPITN 0–2	Carotid-radial PWV	Patients with severe periodontitis have similar values of PWV than subjects with mild forms or without periodontitis.
Vieira et al., 2011(Vieira et al., 2011)	Cross-sectional study	79	Subjects with heterozygous familial hypercholesterolemia divided into two groups: with severe periodontitis (n=33) and with non-severe periodontitis (n=46)	Periodontal examination assessing PD, gingival recession, CAL	Severe periodontitis : \geq 3 sites, not on the same tooth, with clinical CAL \geq 7 mm and \geq 1 interproximal site(s) with PD \geq 5mm	Carotid-femoral PWV	Patients with severe periodontitis have higher values of PWV compared to the non-severe periodontitis patients. After adjustment for traditional atherosclerosis risk factors, no association was found between severe

							periodontitis and PWV > 12 m/sec.
Frane et al., 2012(Frane k et al., 2012)	Cross-sectional study	121	Subjects with type 2 diabetes mellitus divided into three groups: healthy (n=16), with gingivitis (n=87), and with periodontitis (n=18).	PD, BOP	Healthy subjects: PD \leq 3 mm and BOP extent scores < 10% Gingivitis: patients with PD \leq 3 mm and BOP extent score > 10% Periodontitis: patients with PD \geq 4mm	Carotid-radial PWV	PWV was similar between groups.
Hanaoka et al., 2013(Hanaoka et al., 2013)	Cross-sectional study	127	Adult patients with ischemic heart disease divided into two groups: with high level of <i>Pg</i> -IgG (n=64) and with low level of <i>Pg</i> -IgG (n=63)	Periodontal examination assessing PD, BOP, radiographic bone loss, number of teeth, serum antibody levels against <i>Pg</i> (<i>Pg</i> -IgG)	No specific definition. The presence of periodontitis was assessed based on the level of <i>Pg</i> -IgG.	Brachial-ankle PWV	Mean PWV did not differ between patients with high levels of <i>Pg</i> -IgG, who showed high values in the periodontal parameters, compared to the patients with low levels of <i>Pg</i> -IgG. However, PWV tended to correlate with <i>Pg</i> -IgG levels.

Shanker et al., 2013(Shanker et al., 2013)	Case-control study	814	Patients attending a rural charitable hospital in India divided into two groups: with gingivitis (n=532) and with periodontitis (n=282)	Presence of swollen or bleeding gum, gingival recession, tooth mobility, tooth loss and bone loss	Gingivitis: presence of swollen or bleeding gums and gum recession. Periodontitis: presence of tooth mobility, tooth decay, bone loss or tooth loss.	Right and left brachial PWV and carotid-radial PWV	Patients with periodontitis showed higher values in all PWV measurements compared to patients with gingivitis
Kapellas et al., 2014(Kapellas et al., 2014b)	Cross-sectional study	269	Indigenous Australian adults with periodontitis recruited from community medical and dental health clinics. Based on periodontal pocketing quartiles, patients were divided into 4 groups of periodontal disease severity.	Periodontal examination assessing PD, gingival recession, CAL, gingival bleeding	Periodontitis : ≥ 2 interproximal sites with $CAL \geq 4$ mm or ≥ 2 interproximal sites with $PD \geq 5$ mm	Carotid-dorsalis pedis PWV	PWV increased linearly through quartiles of increasing severity of periodontitis.
Jockel-Schneider et al.	Cross-sectional	158	Patients seeking dental care at the School of	Periodontal examination	Periodontitis: $CAL \geq 6$ mm in a minimum of 2 different sextants	Aortic PWV	Significantly higher PWV values were recorded in

<p>al., 2014(Jockel-Schneider et al., 2014)</p>	<p>study</p>	<p>Dental Medicine of the University of Wuerzburg divided into three groups: healthy (n=66), with severe chronic periodontitis (n=74), with aggressive periodontitis (n=18)</p>	<p>assessing number of teeth, PD, CAL</p>	<p>and a minimum of 6 interproximal sites on 6 different teeth</p>	<p>patients with severe chronic periodontitis and severe aggressive periodontitis compared to the periodontal healthy controls.</p>
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BOP stands for bleeding on probing; CAL for clinical attachment level; PD for pocket depth; PWV for pulse wave velocity

Table 1b. Summary of the included interventional studies assessing the relationship between periodontitis and arterial stiffness measured by pulse wave velocity (PWV).

Authors and Year	Study Design	Sample Size (n)	Study Population	Study Duration	Periodontal assessment	Definition of periodontitis	Outcome Measure	Periodontal Treatment	Main Findings
Vidal et al., 2013(Vidal et al., 2013)	Prospective cohort pilot study	26	Adult patients with refractory hypertension and generalized advanced chronic periodontitis	6 m	Medical history, visible plaque index, PD, CAL, BOP	Armitage 1999 criteria	Carotid-femoral PWV	Non-surgical periodontal treatment	Effective periodontal treatment reduced all cardiovascular risk markers, including PWV that significantly decreased by 0.9 m/sec.
Kapellas et al., 2014(Kapellas et al., 2014b)	Randomized controlled clinical trial	273	Adult Aboriginal Australian with moderate periodontitis	12 m	Number of teeth, PD, CAL, calculus score, plaque score, gingival index	Moderate periodontitis : ≥ 2 interproximal sites with	Carotid-dorsalis pedis PWV	Non-surgical periodontal treatment	No significant differences between treatment groups in PWV at 3 months (mean difference:

			and without a history of cardiovascular disease divided into two groups: test (n=138) and control (n=135)			CAL \geq 4 mm or \geq 2 interproximal sites with PD \geq 5mm			0.06 m/s [95% CI, -0.17 to 0.29]; p=0.594) or 12 months (mean difference: 0.21 m/s [95% CI, -0.01 to 0.43]; p=0.062)
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BOP stands for bleeding on probing; CAL for clinical attachment level; PD for pocket depth; PWV for pulse wave velocit



