Systematic Review

Treatment of periodontitis improves the atherosclerotic profile: a systematic review and meta-analysis


Abstract

Aim: Systematic review and meta-analyses to study the robustness of observations that treatment of periodontitis improves the atherosclerotic profile.

Material and Methods: Literature was searched in Medline-PubMed, Cochrane CENTRAL and EMBASE, based on controlled periodontal intervention trials, including also a non-intervention group. Data were extracted and meta-analyses were performed.

Results: From 3928 screened studies, 25 trials met the eligibility criteria. These trials enrolled 1748 periodontitis patients. Seven trials enrolled periodontitis patients that were otherwise healthy, 18 trials recruited periodontal patients with various co-morbidities, such as CVD or diabetes. None of the trials used hard clinical endpoints of CVD. However, improvement of endothelial function has been consistently reported. Meta-analyses demonstrated significant weighted mean difference (WMD) for hsCRP (-0.78 mg/l, 95% CI: -0.78; -0.22), IL-6 (-0.48 ng/l, 95% CI: -0.90; -0.06), TNF-α (-0.75 pg/ml, 95% CI: -1.34; -0.17), fibrinogen (-0.47 g/l, 95% CI: -0.76; -0.17), total cholesterol (-0.11 mmol/l, 95% CI: -0.21; -0.01) and HDL-C (0.04 mmol/l, 95% CI: 0.03; 0.06) favouring periodontal intervention. Importantly, periodontitis patients with co-morbidity benefitted most from periodontal therapy; significant WMD were observed for levels of hsCRP (-0.71 mg/l, 95% CI: -1.05; -0.36), IL-6 (-0.87 ng/l, 95% CI: -0.97; -0.78), triglycerides (-0.24 mmol/l, 95% CI: -0.26; -0.22), total cholesterol (-0.15 mmol/l, 95% CI: -0.29; -0.01), HDL-C (0.05 mmol/l, 95% CI: 0.03; 0.06) and HbA1c (-0.43%, 95% CI: -0.60; -0.25).

Conclusions: This systematic review and meta-analyses demonstrate that periodontal treatment improves endothelial function and reduces biomarkers of atherosclerotic disease, especially in those already suffering from CVD and/or diabetes.

Conflict of interest and source of funding

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A large number of studies have reported on the relationship between periodontitis and cardiovascular disease (CVD) (Friedewald et al. 2009, Dietrich et al. 2013). Periodontitis is a common chronic multifactorial infectious disease of the supporting structures of the teeth (root cementum, periodontal ligament and alveolar bone) and a major cause of tooth loss. The severe form of this condition occurs in about 10–15% of the population (Albandar 2011). The increase in relative risk estimates for developing CVD in subjects with periodontitis ranges from 1.24 to 1.34 (Humphrey et al. 2008). These estimates increase to 1.44 in subjects younger than 65 years of age (Janket et al. 2003). In addition, the risk for stroke in periodontitis patients is estimated to be 1.85 compared to healthy subjects (Janket et al. 2003). Several causal mechanisms have been proposed whereby bacterial pathogens, antigens, endotoxins, and/or inflammatory cytokines from periodontal lesions in the oral cavity contribute to the process of atherogenesis as well as to thromboembolic events and thereby increase the risk for CVD (Humphrey et al. 2008, Friedewald et al. 2009). Treatment of periodontitis includes mechanical removal of supra- and subgingival bacterial plaque deposits [scaling and root planing (SRP)] and intensive oral hygiene instructions. Regularly, periodontal surgery is needed to reduce or eliminate residual periodontitis lesions.

A recent narrative review and subsequent statement of the American Heart Association reviewed the literature on the association between periodontitis and CVD (Lockhart et al. 2012). In addition, clinical studies were reviewed, investigating the effect of periodontal therapy on cardiovascular events, and on markers of inflammation and atherosclerosis risk factors. These trials were often uncontrolled, provided conflicting data and many report only short-term results. However, because of the chronic nature of CVD, also longer term results (e.g. 6-month follow-up) of periodontal intervention are relevant. We hypothesized that if periodontitis is somehow causally related to the common atherosclerotic form of CVD, then periodontal treatment (PT) should affect parameters for CVD. The authors of a recent systematic review presented at the joint EFP/AAP workshop on the association between periodontitis and systemic disease, conclude that periodontal therapy causes a progressive and consistent reduction of systemic inflammation (D’Aiuto et al. 2013). However, large heterogeneity between studies exists, suggesting that inter-trial differences, like study duration, risk of bias, populations with or without co-morbidities and/or other CVD risk markers might play a role. In addition, extensive analyses of recent data of important CVD markers are missing. We performed an up to date systematic review of clinical intervention trials to assess the question whether PT affects the cardiovascular risk profile in periodontitis patients compared to no treatment, taking inter-trial differences into account.

Methods

This systematic review was conducted in accordance with the guidelines of Transparent Reporting of Systematic Reviews and Meta-Analyses [PRISMA statement (Moher et al. 2009)]. The focused question was given in the following: What is the effect of periodontal therapy on clinical CVD parameters and/or markers related to atherosclerosis and CVD risk in patients suffering from periodontitis?

Search strategy

Three literature databases were used to search for appropriate papers. These included the National Library of Medicine, Washington, D.C. (Medline-PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE (Excerpta Medical Database by Elsevier). The databases were searched for trials conducted in the period up to June 2013. The structured search strategy was designed to include any publication that evaluated the effect of periodontal therapy on the atherosclerotic profile (for detail on the used search terms, see Box 1 in Data S1). The following eligibility criteria for publications were used:

- Randomized controlled trials (RCTs) or controlled clinical trials (CCTs), containing the following aspects
  a. Human subjects with periodontitis.
  b. Intervention group receiving PT and a non-intervention group receiving no periodontal treatment (NPT).
  c. Outcome variables must be clinical CVD parameters (i.e. clinical event, such as angina pectoris, myocardial infarction, stroke, death) and/or markers related to atherosclerosis and CVD risk, including markers of systemic inflammation and thrombosis, lipid and glucose metabolism and vascular function.

Screening and selection

Two reviewers (WJT and HS) independently screened titles and abstracts for eligible papers. If information relevant to the eligibility criteria was not available in the abstract, or if the title was relevant but the abstract was not available, the paper was selected for full reading of the text. Next, full-text papers that fulfilled the eligibility criteria were identified and included into this study. The two reviewers hand-searched the reference lists of all the selected articles for additional published papers that could possibly meet the eligibility criteria of this study. Papers that fulfilled all of the selection criteria were processed for data extraction.

Heterogeneity of trials

The heterogeneity across the trials was detailed according to the following factors:

- Population characteristics
- Definition of diseases
- Study design
- Type of periodontal intervention

Quality assessment

Two reviewers (WJT and DES) scored the methodological qualities of the included studies, as proposed previously (Van der Weijden et al. 2009). In short, when random alloca-
tion, defined eligibility criteria, blinding of examiners, blinding of patients, balanced experimental groups, identical treatment between groups (except for the intervention) and reporting of follow-up were present, the study was classified as having a low risk of bias. When one of these seven criteria was missing, the study was considered to have a moderate risk of bias. When two or more of these criteria were missing, the study was considered to have a high risk of bias.

**Data extraction**

Data from the papers that met the selection criteria were processed for analysis. Outcomes for clinical CVD parameters and/or markers related to atherosclerosis and CVD risk were extracted with regard to the effects of periodontal therapy in comparison to no periodontal therapy. For the trials that presented intermediate assessments, the baseline and final evaluations were used for this review. All data were extracted by WJT and DES. If outcome data could not be extracted from a paper (e.g. data were presented in a graph, median values were used) the corresponding author of the publication was asked to provide the requested data.

**Data analysis**

A descriptive manner of data presentation was used for all trials included in the analyses. Where appropriate, a meta-analysis was performed for all available trials together. In addition, subanalyses were performed based on trials using a study population with or without co-morbidity. When not reported in the publication, the difference in mean values of a given parameter between baseline and end was calculated for both the PT and NPT groups (Teeuw et al. 2010). Weighted mean difference (WMD) and 95% confidence intervals (CI) values between PT and NPT groups at both baseline and end were calculated using a random or fixed effect model (Review Manager [RevMan] Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Random-effects models were used to calculate a weighted average on the treatment effects across the studies under review. If there were ≤4 trials, fixed effect analysis was used, as the estimate of inter-trial variance is poor for analyses with low numbers of studies (Vany Strydom et al. 2012). With regard to hsCRP levels, additional meta-analysis with special reference to those RCTs that had a low estimated risk of bias were performed, as this is considered to represent the highest level of evidence (Harbour & Miller 2001).

Some of the studies have multiple treatment arms. If the data from the control group were used in more than one comparison, the number of subjects (n) in this group was divided by the number of comparisons. Heterogeneity was tested by chi-squared test and the I² statistic. A chi-square test resulting in a $p < 0.1$ was considered an indication of significant statistical heterogeneity. As a rough guide for assessing the possible magnitude of inconsistency across studies, $I^2$ statistic of 0–40% was interpreted as not to be important, and above 40% moderate to considerable heterogeneity may be present (Higgins & Green 2011).

If the meta-analysis contained sufficient trials to make visual inspection of the plot meaningful (five trials minimum), funnel plots were used as a tool for assessment of publication bias (Sterne et al. 2005). In relation to this meta-analysis the presence of asymmetry in the inverted funnel would suggest a systematic difference between large and small trials in their estimates of treatment effect, as may occur for example because of publication bias.

**Grading the ‘Body of Evidence’**

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) items as proposed by the GRADE working group (Guyatt et al. 2008) was used for grading evidence merging from this review. Two reviewers (WJT and DES) rated the quality of the evidence and strength of recommendations on the following aspects: risk of bias of the individual trials, consistency and precision among the study outcomes, directness of the study results and the detection of publication bias. Any disagreement between the two reviewers was resolved after additional discussion.

**Results**

**Search and selection results**

The combined searches resulted in 3928 potentially eligible manuscripts. Subsequently, 20 publications, representing 25 trials, were identified as eligible for inclusion in this review according to the defined criteria for the study design, participants, intervention and outcome (Fig. 1). Notably, four trials were excluded from analysis because of very specific reasons: one pilot study reported that a major part (62.8%) of the non-treatment study arm had a regular visit to a dentist and a substantial part (20.0%) received PT outside the study centre (Beck et al. 2008). Three more trials were excluded from analysis, because the research populations consist only of pregnant subjects (Offenbacher et al. 2006, Michalowicz et al. 2009, Fiorini et al. 2013). These trials reported the effect of PT on pregnancy outcomes and were therefore not related to CVD.

**General trial characteristics**

Detailed information regarding the population characteristics, the medical and oral status of the subjects, study design and type of periodontal intervention is summarized in Supplementary Table 1 in Data S1. These studies enrolled 1748 periodontitis patients. Some of the trials used an otherwise healthy population (Ide et al. 2003, D’Aiuto et al. 2005, Tonetti et al. 2007, Higashi et al. 2008, Taylor et al. 2010, Kamil et al. 2011, Li et al. 2011), whereas other trials described a population with co-morbidity. The co-morbidity can be divided into following categories: (i) CVD (coronary artery disease (Higashi et al. 2009), coronary heart disease (Bokhari et al. 2012), (ii) a metabolic disorder (diabetes mellitus; Chen et al. 2012, Katagiri et al. 2009, Koromantzos et al. 2012, Sun et al. 2010, 2011, Taylor et al. 2010), metabolic syndrome (Lopez et al. 2012), impaired glucose tolerance (Sun et al. 2010), hypercholesterolaemia (Oz et al. 2007, Taylor et al. 2010), (iii) a combination of CVD and a metabolic disorder (Sun et al. 2010).

All individuals included in PT groups received SRP, whereas subjects of NPT groups received no periodontal therapy. Details on therapy, follow-up time (range 4 weeks–12 months) and authors’ estimated risk of bias are described in Supplementary Table 1 in Data S1. Quality assessment values, including the internal, external and statistical validity, are presented in Supplementary Table 2 in Data S1.

Study outcomes

None of the included trials used a cardiovascular event as the outcome parameter (i.e. clinical event, such as angina pectoris, myocardial infarction, stroke, death). The reported outcome parameters of all trials can be divided into three groups: systemic inflammation and thrombosis, lipid and glucose metabolism and vascular function.

Periodontal intervention and systemic inflammation and thrombosis

In Supplementary Tables 3a–d in Data S1, detailed information is reported on changes in hsCRP, IL-6, TNF-α and fibrinogen. The majority of the trials that showed a decrease in these markers after PT used a population with co-morbidity. Several other inflammatory biomarkers have been used as study outcomes to determine the effect of PT on the systemic inflammation, including IL-1β (Ide et al. 2003), sialic acid (Ide et al. 2003), soluble E-selectin (sE-selectin) (Tonetti et al. 2007), number of white blood cells (Taylor et al. 2010, Bokhari et al. 2012), monocytes (Taylor et al. 2010), neutrophils (Taylor et al. 2010), leucocytes (Tonetti et al. 2007, Taylor et al. 2010, Li et al. 2011) and lymphocytes (Li et al. 2011). Only the levels of sE-selectin (Tonetti et al. 2007) were slightly reduced after PT compared to the NPT group. Some trials also used markers reflecting the pro-thrombotic state, like von Willebrand factor (Tonetti et al. 2007, Taylor et al. 2010), plasminogen activator inhibitor-1 (PAI)-1 (Tonetti et al. 2007, Taylor et al. 2010) and tissue plasminogen activator (Tonetti et al. 2007, Taylor et al. 2010). No remarkable changes could be observed.

Periodontal intervention and lipid and glucose metabolism

In Supplementary Tables 3e–h in Data S1, detailed information is reported on changes in triglycerides, total cholesterol (TC) and high-density and low-density lipoproteins (HDL-C and LDL-C, respectively). No consistent changes for these parameters have been found. Some trials reported on other lipid markers, including very low density lipoprotein (VLDL-C) (Oz et al. 2007), apolipoproteins, lipoproteins (Li et al. 2011) and malondialdehyde-LDL-C (Higashi et al. 2009); however, no statistically significant changes were observed after PT compared to baseline levels and the NPT group.

Six trials, using a diabetes study population, reported absolute changes in HbA1c after PT. Five trials showed a significant reduction in HbA1c after PT compared to baseline levels and the NPT group.

Periodontal intervention and vascular function

The effects of PT on vascular function are contradictory. On one hand, the primary outcome of five trials
was endothelial function. Although assessed with different methods, these trials showed improvement of endothelial function (Higashi et al. 2008, 2009). On the other hand, alternative markers of vascular function, like nitroglycerine-mediated dilation, brachial-artery diameter, reactive hyperaemia ratio (Tonetti et al. 2007), forearm blood flow (FBF), sodium-nitroprusside-dependent FBF, acetylcholine-dependent FBF in the presence of a NOSynthase-inhibitor (Higashi et al. 2008, 2009) and pulse amplitude tonometry (Li et al. 2011), systolic and diastolic blood pressure (Tonetti et al. 2007, Higashi et al. 2008, 2009, Lopez et al. 2012) (Supplementary Table 3j in Data S1) did not change after PT compared to baseline levels of the PT group and/or end levels of the NPT group.

**Meta-analyses**

The effect of PT on primary or secondary markers of inflammation and thrombosis (hsCRP, IL-6, TNF-α, fibrinogen), lipid and glucose metabolism (triglycerides, TC, HDL-C, LDL-C and HbA1c) and vascular function (systolic and diastolic blood pressure) could be analysed in a series of meta-analyses. The WMD and CI baseline to end between PT and NPT groups for each parameter were calculated (Figs 2 and 3; Supplementary Figs 1–16 in Data S1). A significant WMD including all available trials was found for hsCRP (−0.50 mg/l, CI: −0.78; −0.22, p = 0.0005), IL-6 (−0.48 ng/l, CI: −0.90; −0.06, p = 0.03), TNF-α (−0.75 pg/ml, CI: −1.34; −0.17, p = 0.01), fibrinogen (−0.47 g/l, CI: −0.21; −0.01, p = 0.02) and HDL-C (0.04 mmol/l, CI: 0.03; 0.06, p < 0.0001). Notably, subanalyses showed that periodontitis patients with co-morbidity benefited the most from periodontal therapy; significant WMD were observed for hsCRP (−0.71 mg/l, CI: −1.05; −0.36, p < 0.0001), IL-6 (−0.87 ng/l, CI: −0.97; −0.78, p < 0.00001), triglycerides (−0.24 mmol/l, CI: −0.26; −0.22, p < 0.0001), total cholesterol...
observations consisting of both smokers and non-smokers, did not show a significant difference between the PT and NPT groups (WMD hsCRP: -0.29, CI: -0.88; 0.30, p = 0.34; Fig. 4 and Supplementary Fig. 4 in Data S1). Similar results were obtained by differentiating studies according to the average BMI of the study population. Trials which included study subjects with on average normal weight (BMI < 25 kg/m²) (Perk et al. 2012) showed for hsCRP a WMD of -0.44 mg/l (CI: -1.28; 0.40, p = 0.30, Fig. 4 and Supplementary Fig. 5 in Data S1).

In trials which recruited periodontitis patients with cardiovascular and/or metabolic disease, we observed differences in WMD between studies with different follow-up periods (Supplementary Table 5 in Data S1). For example, seven trials (Vidal et al. 2009, Sun et al. 2010, 2011, Joseph et al. 2011, Bokhari et al. 2012) with <6 months duration, showed for hsCRP a WMD of -0.89 mg/l (CI: -1.33; -0.45, p < 0.0001), while another eight trials (Higashi et al. 2008, 2009, Katagiri et al. 2009, Pinho Mde et al. 2009, Chen et al. 2012, Koromantzos et al. 2012, Lopez et al. 2012) with ≥6 months follow-up showed for hsCRP a WMD of -0.22 mg/l (CI: -0.37; 0.07, p = 0.005) (see also Figs. 3 and 4).

Fig. 3. Meta-analysis of hsCRP levels of individual trials using populations with co-morbidity and a follow-up time of <6 or ≥6 months. Weighted mean difference (WMD) and 95% confidence interval (CI) of hsCRP levels between the periodontal treatment groups (experimental) and non-periodontal treatment groups (control). df, degrees of freedom; IPT, intensive periodontal treatment; IV, inverse variance; SD, standard deviation; SPT, standard periodontal treatment.

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with diabetes as shown by a significant reduction in HbA1c levels (WMD −0.43% for PT group compared to NPT group). This was found in six trials of which only one overlapped with our previous study on the effect of periodontal therapy on metabolic control (Teeuw et al. 2010); the latter publication reported a comparable and significant improvement (∆HbA1c: −0.40%). Recently, this observation is confirmed again by a very recent systematic review and meta-analysis (Engebretson & Kocher 2013). In the current analysis, metabolic diseased patients were included, since it is known that patients with elevated levels of HbA1c run a higher risk for CVD. As we discussed before (Teeuw et al. 2010), a decrease of HbA1c with 1.0 percentage point is associated with a 25% reduction of the risk of dying from CVD.

A third important finding of the current study was, that after periodontal intervention, lipid levels (triglycerides, TC, HDL-C) were also significantly improved in periodontitis patients with CVD and/or metabolic disease compared to the NPT group. Similar to hsCRP and IL-6, this was not observed in otherwise healthy subjects with periodontitis. Abnormal lipid levels are strongly associated with increased risk for CVD (Di Angelantonio et al. 2009). Our findings are in contrast with a previous recent systematic review and meta-analysis, which did not show a difference in lipid levels after PT (D’Aiuto et al. 2013). This is most likely explained by the fact that we distinguished trials with populations with and without co-morbidity. In addition, we also included more recent trials.

In all included trials of this systematic review, only biomarkers were available to evaluate the effect of PT on the atherosclerotic profile. Ischaemic events (e.g. myocardial infarction, stroke) and cardiovascular mortality could not be investigated as no such trials have been performed. This is because of the challenges and ethical issues investigators face in designing RCT including an intervention and appropriate control over a follow-up of at least 5–10 years in order to record a substantial number of clinical events. Nevertheless, the current systematic review shows clearly that patients with known CVD or metabolic disease benefit from periodontal therapy, since CRP, IL-6, TNF-α, fibrinogen, triglycerides, TC, HDL-C and HbA1c improved; they can be judged as robust biomarkers of CVD.

It has been widely accepted that low grade systemic inflammation contributes to an elevated risk for CVD. In this respect, elevated hsCRP levels are strongly associated with increased risk (Kaptoge et al. 2010, Ridker et al. 2010). The elevated levels of hsCRP and other inflammatory markers in periodontitis (e.g. IL-6 and TNF-α) (Loos 2005) might be related to the chronicity of periodontitis and the concomitant periodontal inflamed surface area (PISA). The PISA in patients with severe periodontitis may be as large as 39 cm² (Nesse et al. 2008). This breach in epithelial lining opens up the possibility for oral pathogens to enter the circulation and induce systemic inflammation, metabolic dyscontrol and vascular dysfunction. Periodontal therapy reduces PISA and the current meta-analyses are highly suggestive that this reduction results in lower levels of systemic inflammation and improvement of metabolic control.

We noted quite some heterogeneity between trials (Range F: 0–93%, Supplementary Figs 1–16 in Data S1). Ideally, F should be ≤40% and χ²-test should result in ρ ≥ 0.1. Systematic reviews and meta-analyses run the risk that included studies may have some form of bias: (i) variation in medication usage; (ii) difference in follow-up time; (iii) usage of adjunctive antibiotics; and (iv) differences in methodological quality. The risk of bias assessment as performed in the present review included all relevant aspects and was a compilation of items as found in various checklists. Although the effects of publication bias and poor methodological quality may lead to substantial overestimation of the beneficial effects of medical interventions, these effects cannot be estimated precisely in an individual meta-analysis (Sterne et al. 2000). Meta-analysis are then faced with a choice regarding whether one should take a “best available evidence” approach by restricting attention to trials at low risk of bias or an “all available evidence” approach in which all trials are included (Welton et al. 2009). Therefore, we performed also a subanalysis for hsCRP including only studies with a low estimated risk of bias (Supplementary Table 2 and Fig. 3 in Data S1). The results of this subanalysis showed again the important finding that patients with co-morbidity benefit significantly from periodontal therapy.

Conclusions

PT reduces the risk for CVD by improving plasma levels of inflammatory (CRP, IL-6, TNF-α), thrombotic (fibrinogen) and metabolic (triglycerides, TC, HDL-C, HbA1c) markers and endothelial function. This improvement is sustained well over 6 months after therapy and it is greater in those individuals suffering from both periodontitis and co-morbidities like CVD and/or diabetes mellitus. Notably, risk factors for CVD, like overweight and smoking habits may frustrate the favourable effect. Nevertheless, overall our findings emphasize the effectiveness and need for periodontal diagnosis and periodontal therapy in atherosclerotic and diabetic individuals to improve their systemic health. On the basis of our observations and in agreement with a recent consensus report of the joint EFP/AAP workshop on periodontitis and systemic diseases (Tonetti & Van Dyke 2013), we recommend that cardiologists, diabetologist and general physicians ask their patients to be screened by dental care professionals for the presence of periodontitis and if so, to undergo periodontal therapy to improve their cardiovascular risk profile and thereby reducing the risk for future occurrence of CVD events. In addition, we recommend that periodontists and dentists should discuss CVD risk factors, like overweight and smoking, with their patients as part of their PT protocol.

Further intervention trials are needed to evaluate implementation of oral health in cardiovascular and diabetes care on prevention of hard clinical outcomes, like secondary CVD events or death. Because of the ethical considerations for RCTs with non-periodontal treatment arms,
large community based trials may be the most suitable.

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References


Periodontal treatment and atherosclerosis


Supporting Information

Additional Supporting Information may be found in the online version of this article.

Data S1. Supplementary figures and tables.

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Clinical Relevance

Scientific rationale for the study: Periodontal intervention studies are useful to answer the question whether periodontitis is somehow causally related to cardiovascular disease (CVD). We therefore performed a systematic review of clinical intervention trials to assess the question whether periodontal treatment affects the cardiovascular risk profile in periodontitis patients compared to no treatment.

Principal findings: Periodontal treatment improves endothelial function and reduces biomarkers of atherosclerotic disease in periodontitis subjects, especially in those already suffering from CVD and/or diabetes.

Practical implications: The results emphasize the effectiveness and need for periodontal diagnosis and periodontal therapy in atherosclerotic and diabetic individuals to improve their systemic health.