Clinical Trial

Effect of Periodontal Therapy on Arterial Structure and Function Among Aboriginal Australians
A Randomized, Controlled Trial


Abstract—Observational studies and nonrandomized trials support an association between periodontal disease and atherosclerotic vascular disease. Both diseases occur frequently in Aboriginal Australians. We hypothesized that nonsurgical periodontal therapy would improve measures of arterial function and structure that are subclinical indicators of atherosclerotic vascular disease. This parallel-group, randomized, open label clinical trial enrolled 273 Aboriginal Australians aged ≥18 years with periodontitis. Intervention participants received full-mouth periodontal scaling during a single visit, whereas controls received no treatment. Prespecified primary endpoints measured 12-month change in carotid intima-media thickness, an indicator of arterial structure, and 3- and 12-month change in pulse wave velocity, an indicator of arterial function. ANCOVA used complete case data to evaluate treatment group differences. End points could be calculated for 169 participants with follow-up data at 3 months and 168 participants at 12 months. Intima-media thickness decreased significantly after 12 months in the intervention group (mean reduction = −0.023 [95% confidence interval {CI}, −0.038 to −0.008] mm) but not in the control group (mean increase = 0.002 [95% CI, −0.017 to 0.022] mm). The difference in intima-media thickness change between treatment groups was statistically significant (−0.026 [95% CI, −0.048 to −0.003] mm; P = 0.03). In contrast, there were no significant differences between treatment groups in pulse wave velocity at 3 months (mean difference, 0.06 [95% CI, −0.17 to 0.29] m/s; P = 0.594) or 12 months (mean difference, 0.21 [95% CI, −0.01 to 0.43] m/s; P = 0.062). Periodontal therapy reduced subclinical arterial thickness but not function in Aboriginal Australians with periodontal disease, suggesting periodontal disease and atherosclerosis are significantly associated. (Hypertension. 2014;64:702-708.) • Online Data Supplement

Key Words: Aborigines, Australian ■ diabetes mellitus ■ periodontal debridement ■ randomized controlled trial ■ smoking

Periodontal disease is characterized by bacterial infection and chronic inflammation of the tissues around teeth. There is now a large body of evidence, primarily from observational cohort studies and nonrandomized trials, suggesting a possible association among periodontal disease, atherosclerotic vascular disease, and arterial stiffness of peripheral arteries. Despite published data supporting such associations, some recent reviews have concluded that the current evidence does not support a causative relationship between periodontal disease and atherosclerotic vascular disease. However, reviewers cited a lack of evidence from randomized trials investigating periodontal interventions on atherosclerotic disease or cardiovascular events. Currently, no studies have investigated whether treatment of periodontal disease improves arterial function.

Coronary heart disease typically occurs much earlier among Aboriginal and Torres Strait Islanders compared with their non-Aboriginal counterparts. Periodontal disease is more common among Aboriginal Australians according to Australian national survey data.

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A randomized, controlled trial was conducted to determine the effect of a periodontal intervention on the progression of carotid intima-media thickness (IMT), an established noninvasive measure of subclinical atherosclerosis, and central arterial stiffness measured via carotid-dorsalis pedis pulse wave velocity (PWV) in Aboriginal adults.

Methods
A detailed description of the methods is given in the online-only Data Supplement.

Recruitment commenced in June 2010 and completed in January 2012. Participants were recalled at 3 months and 12 months for repeat assessments of periodontal status and cardiovascular end points. Eligibility criteria were as follows: Aboriginal Australian participants aged ≥18 years without a previous history of cardiovascular disease, a minimum of 5 natural teeth, and moderate periodontitis defined as ≥2 interproximal sites with clinical attachment loss ≥4 mm or ≥2 interproximal sites with pocket depth ≥5 mm. Exclusion criteria were as follows: individuals receiving periodontal treatment in the preceding 6 months, those with a history of any cardiovascular condition, rheumatic fever or any other cardiac or medical conditions requiring preventive antibiotic prophylaxis, pregnant women, or people with clinically visible endodontic or orofacial infections.

Interventions
The periodontal intervention consisted of an untimed single episode of nonsurgical periodontal therapy as described in detail elsewhere. Briefly, 2 clinicians conducted the intervention (see online-only Data Supplement) with the use of Gracey hand scalers (Hu-Friedy, Chicago, IL) and piezoelectric ultrasonic device (Kyungwon Ferrite, Gyeonggi-do, Korea) using universal tips. All participants received oral hygiene instruction along with toothbrush and toothpaste.

Arterial Function
The functional outcome was the short-term 3-month change in carotid-dorsalis pedis PWV, whereas 12-month PWV provided long-term information on functional changes. Applanation tonometry was used to measure PWV via a Millar transducer, the SphygmoCor-PVMx device, and software (version 8.2, AtCor Medical, Sydney, Australia).

Carotid Intima-Media Thickness
The long-term structural outcome measure was the 12-month post-baseline change in maximum carotid IMT, as previously described. Briefly, the common carotid arteries are scanned in longitudinal section by high-resolution ultrasound (10-5 MHz linear array transducer; Sonosite MicroMaxx, Bothell, WA) using a standardized scanning protocol that was consistent for all study visits. The scanning protocol consisted of sequential imaging of anterior, lateral, and posterior views of the carotid artery. Carotid IMT was assessed from the view with the greatest wall thickness.

Randomization
Participants were randomized on a 1:1 basis to either intervention or control group using permuted block randomization with variable block sizes, stratified by recruitment site (Darwin, Katherine, Darwin, and Alice Springs correctional facilities). Randomization was allocated by the study clinicians unaware of block sizes following baseline measures. Because of the mode of intervention, clinicians and study participants could not be blinded from allocation grouping.

Sample Size
Sample size was based on the 12-month structural outcome measure, carotid IMT. Estimates of carotid IMT were derived from published data for Aboriginal Australian adults from the same region (mean [SD], 0.67±0.12 mm) and an estimated 10% difference between groups in maximum carotid IMT after intervention, based on prior evidence from a nonrandomized study. Based on a power of 80% and α of 0.05, calculations indicated that a sample size of 144 participants randomized equally would be required. An a priori change of 10% reduction in PWV was proposed to indicate a clinically significant improvement in this surrogate measure of arterial stiffness. Based on carotid-femoral PWV of a similar sample, a mean (SD) of 8.0 (1.7) m/s was used to estimate the sample size.

Statistical Analysis
Primary analyses for both PWV and IMT were based on the complete case approach. ANCOVA measured between-group change for PWV at 3 and 12 months and both mean and maximum IMT at 12 months, with randomization as the factor after adjustment for baseline values as covariates.

Change in carotid IMT from baseline to 12 months was normally distributed; however, cross-sectional measures of carotid IMT at baseline and 12 months were positively skewed. As such, cross-sectional measures were log-transformed for analysis. Differences in proportions and means between completed and lost to follow-up participants were analyzed using χ² and independent t tests. Specific to IMT, subgroup analyses were undertaken within groups stratified according to baseline measures of sex, age, overweight/obesity, diabetes mellitus, smoking status, and severity of periodontal disease. As a secondary analysis to enable inclusion of the baseline data of participants lost to follow-up and 3 participants who had carotid IMT data available from 12 months but not baseline, we constructed a linear mixed model including carotid IMT data from both baseline and 12 months, with the effect of the intervention determined by the interaction between visit number and allocated group.

Ethical Approval
The PerioCardio study was approved by the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research, the Central Australian Human Research Ethics Committee, Northern Territory Correctional Services Research Committee, University of Adelaide Human Research Ethics Committee, and the Aboriginal Health Council of South Australia. Study participants gave informed consent before participating, which included acknowledgment that they could be randomized into the control group they would not receive immediate periodontal therapy. Research was conducted in accordance with the World Medical Association Declaration of Helsinki (version VII, 2008).

Results
Four hundred twenty-two people were initially screened for eligibility, and of those, 312 met the inclusion criteria and underwent oral assessment. Of those, 273 were clinically confirmed periodontitis cases. Reasons for exclusion of 149 people are included in Figure S1 in the online-only Data Supplement. Fifty-one people in the treatment and 53 in the control group were not assessed at the 3-month time point, and 49 and 56 in the treatment and control groups, respectively, were lost to follow-up at the 12-month time point. Follow-up rates did not differ by randomized group (3 months: intervention 63%, control 61%, P=0.70; 12 months: intervention 65%, control 59%, P=0.26). One participant randomized to the treatment group and self-reported experiencing a myocardial infarction during the study period. There were no other adverse events reported.

Participant characteristics stratified by randomized groups are shown in Table 1, and for those participants who attended the 3- and 12-month recalls compared with those who were lost to follow-up, see Table S1. Baseline PWV, IMT, and periodontal parameters were similar in those lost to follow-up compared with those who completed follow-up at 3 months and 12 months.
Pulse Wave Velocity

After the periodontal intervention, PWV values improved to a greater degree at both 3 and 12 months in the control group (3-month between-group ANCOVA Δ = +0.06 [95% confidence interval [CI], −0.17 to 0.29] m/s; \( P = 0.60 \) and 12-month between-group ANCOVA Δ = +0.21 [95% CI, −0.01 to 0.43] m/s; \( P = 0.06 \)) but were not significantly different than the treatment group (Tables 2 and 3). Stratified analysis by sex revealed no significant treatment effects at 3 months; however, there was a tendency for PWV being higher among men in the treatment group after 1 year (Table S5).

Carotid IMT

In the periodontal intervention group, the maximum carotid IMT was less at 12 months than at baseline (mean reduction=−0.02 [SD 0.07] mm; \( P = 0.003 \)). In the control group, maximum carotid IMT was marginally greater at 12 months than at baseline (mean increase=0.002 [SD 0.09] mm; \( P = 0.820 \)). In our primary analysis, the periodontal intervention produced a statistically significant reduction in maximum carotid IMT compared with the control group (−0.02 [95% CI, −0.05 to −0.002]) mm; \( P = 0.031 \). The effect of the intervention on mean carotid IMT was consistent, albeit less marked (−0.01 [−0.03 to 0.004] mm; \( P = 0.134 \)). Analysis incorporating data for 3 participants excluded from the above analysis because of missing carotid IMT data at baseline, in addition to baseline data for all participants lost to follow-up, found similar results (less IMT progression at 12 months; \( P = 0.020 \)).

Subgroup analyses are shown in Table S2, stratifying by sex, age, overweight/obesity, diabetes mellitus, smoking status, and severity of periodontal disease. Briefly, there was some evidence that the intervention was of no benefit, compared with the control, in participants with diabetes mellitus and may have been of greater benefit in current smokers. Closer examination of current smokers suggests that the carotid IMT regression in the intervention group was similar to that seen with the intervention in the entire study population (−0.027 [95% CI, −0.046 to −0.009] mm); however, the current smokers who were randomized to the control group had more marked progression of carotid IMT (0.020 [95% CI, −0.001 to 0.040] mm).

The effect of the periodontal intervention on carotid IMT in a per-protocol analysis, excluding 5 participants randomized to the intervention group who did not complete the periodontal intervention and 23 who had additional periodontal treatment or dental extractions during follow-up, was similar if not slightly strengthened (−0.030 [95% CI, −0.056 to −0.004] mm; \( P = 0.02 \)). As an additional post hoc sensitivity analysis, we examined whether the change in carotid IMT differed among those in the treatment group with improved periodontal status versus those who experienced periodontal disease recurrence. Although underpowered, maximum IMT was lower among those with periodontal improvement compared with those where periodontal disease regressed (mean IMT change; −0.033 [−0.220 to 0.154] mm; \( P = 0.723 \), which was consistent with our main findings).

Periodontal Parameters

Results of changes to the periodontal parameters are shown in Table S3. Periodontal therapy resulted in modest improvements in periodontal parameters in the short-term, which were no longer significant by 12 months (consistent with disease recurrence). Short-term effects of the periodontal intervention on periodontal health at 3 months have been described in detail in a previous publication.12

Discussion

In this randomized, controlled trial of Aboriginal Australians with periodontitis, nonsurgical periodontal therapy significantly reduced progression of carotid IMT during a 1-year period in the absence of changes in PWV.

Carotid IMT measures the extent and severity of localized atherosclerosis in the carotid artery,20 is independently
associated with incidence of cardiovascular events, and is considered to be the best noninvasive marker of global burden of atherosclerosis. Consistent with the pathophysiology of atherosclerosis, carotid IMT generally increases as people age. The increase in carotid IMT in the control group is consistent with the annual progression described in observational cohort studies. Increased IMT is associated with the presence of high counts of periodontitis etiologic bacteria. Prospective analysis of the Oral Infections and Vascular Disease Epidemiology Study cohort for a median of 3 years (range, 2–7 years) has recently reported that natural progression of IMT is significantly lower when either an improvement in periodontal status or when a decrease in the amount of etiologic bacteria is observed or when a decrease in the amount of etiologic bacteria occurs compared with baseline. Progression of carotid IMT derived from sequential measures may be a valid surrogate measure of cardiovascular disease events for use in clinical trials. Maximum carotid IMT is thought to better reflect focal atherosclerosis and may respond to therapy more rapidly and more markedly than mean carotid IMT.

The magnitude of reduction in maximum carotid IMT in response to the periodontal intervention, relative to the control group, is of a similar degree to that observed in other clinical trials in high-risk populations (eg, with a ≥30% reduction in low-density lipoprotein levels because of statin therapy). Furthermore, the magnitude of the reduction in carotid IMT with periodontal intervention in this trial is equivalent to the effects of reversal of 4 years of aging, 8 kg/m² lower body mass index, or 25 mm Hg lower systolic blood pressure.

Carotid-femoral PWV is associated with increased risk of cardiovascular disease in otherwise healthy adults and is the recommended direct measure of arterial stiffness in trials. Arterial stiffness has both structural and functional determinants. Structural determinants include the breakdown of elastin and increased deposition of collagen, which are more likely to influence long-term changes in arterial stiffness. Short- to mid-term changes in arterial stiffness, however, are more likely because of changes in arterial function. Accordingly, the present findings on the effects of periodontal therapy on PWV at 3 months likely reflect changes in arterial function. Findings from our validation study reveal a small absolute difference between PWV derived from carotid-femoral and carotid-dorsalis pedis measurements (Table S7 and Table S9).

Table 2. Change in Pulse Wave Velocity, Carotid Intima-Media Thickness, and Inflammatory Markers (Complete Case Analysis) at 3 Months

<table>
<thead>
<tr>
<th>Cardiovascular Risk Markers</th>
<th>Treatment</th>
<th>Control</th>
<th>ANCOVA Least Squares</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 Mo</td>
<td>Baseline</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>4.84 (5.37)</td>
<td>4.80 (4.80)</td>
<td>4.71 (5.71)</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>3.21 (2.35)</td>
<td>2.58 (2.21)</td>
<td>2.39 (2.45)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.97 (1.12)</td>
<td>4.78 (0.97)</td>
<td>4.82 (0.87)</td>
</tr>
<tr>
<td>Non-HDL cholesterol, mmol/L</td>
<td>3.97 (1.11)</td>
<td>3.79 (0.95)</td>
<td>3.81 (0.90)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.00 (0.30)</td>
<td>0.99 (0.30)</td>
<td>1.01 (0.32)</td>
</tr>
<tr>
<td>ADMA, μmol/L</td>
<td>0.42 (0.13)</td>
<td>0.43 (0.12)</td>
<td>0.43 (0.12)</td>
</tr>
<tr>
<td>HbA1c, mmol/mol</td>
<td>48.02 (19.79)</td>
<td>46.57 (17.28)</td>
<td>44.75 (14.74)</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>8.22 (1.30)</td>
<td>8.15 (1.09)</td>
<td>8.43 (1.34)</td>
</tr>
</tbody>
</table>

Data for baseline/follow-up means presented as mean (SD). Reported values limited to those that have completed data at 12 months post-intervention. ADMA indicates asymmetrical dimethylarginine; CI, confidence interval; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; and PWV, pulse wave velocity.

Table 3. Change in Pulse Wave Velocity, Carotid Intima-Media Thickness, and Inflammatory Markers (Complete Case Analysis) at 12 Months

<table>
<thead>
<tr>
<th>Cardiovascular Risk Markers</th>
<th>Treatment</th>
<th>Control</th>
<th>ANCOVA Least Squares</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 Mo</td>
<td>Baseline</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>4.68 (5.41)</td>
<td>5.28 (6.46)</td>
<td>4.84 (6.18)</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>3.24 (2.27)</td>
<td>1.87 (2.64)</td>
<td>1.99 (2.05)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.01 (1.09)</td>
<td>4.97 (1.14)</td>
<td>5.04 (1.13)</td>
</tr>
<tr>
<td>Non-HDL cholesterol, mmol/L</td>
<td>3.98 (1.11)</td>
<td>3.96 (1.10)</td>
<td>3.97 (1.14)</td>
</tr>
<tr>
<td>HDL Cholesterol, mmol/L</td>
<td>1.03 (0.30)</td>
<td>1.04 (0.31)</td>
<td>1.08 (0.36)</td>
</tr>
<tr>
<td>ADMA, mmol/L</td>
<td>0.42 (0.12)</td>
<td>0.48 (0.11)</td>
<td>0.43 (0.11)</td>
</tr>
<tr>
<td>HbA1c, mmol/mol</td>
<td>48.12 (19.61)</td>
<td>46.81 (19.30)</td>
<td>44.98 (15.40)</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>8.27 (1.30)</td>
<td>8.44 (0.92)</td>
<td>8.37 (1.36)</td>
</tr>
<tr>
<td>Maximum IMT, mm</td>
<td>0.79 (0.19)</td>
<td>0.76 (0.16)</td>
<td>0.79 (0.15)</td>
</tr>
<tr>
<td>Mean IMT, mm</td>
<td>0.64 (0.14)</td>
<td>0.63 (0.14)</td>
<td>0.64 (0.12)</td>
</tr>
</tbody>
</table>

Data for baseline/follow-up means presented as mean (SD). Reported values limited to those that have completed data at 12 months post-intervention. ADMA indicates asymmetrical dimethylarginine; CI, confidence interval; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; IMT, intima-media thickness; and PWV, pulse wave velocity.
Figure S4). Furthermore, the 2 measures of PWV are linearly correlated such that the carotid-femoral PWV may be estimated using measurements of the carotid-dorsalis pedis PWV.

Periodontal disease may be associated with PWV through persistent inflammation. Elevated C-reactive protein levels inhibit release of nitric oxide by the endothelium in patients with arterial disease, and periodontitis stimulates C-reactive protein. Despite modest short-term improvements in periodontal status after therapy in this study, persistent inflammation is thought to remain as evidenced by residual periodontal pocketing and the continuation of moderate gingivitis in the intervention group. In the present study, periodontal disease is likely to be one of several sources of inflammation. Previous research shows that adiposity and cigarette smoking contribute to systemic inflammation and PWV in Aboriginal Australians. Vessel function was not amenable to a single session of periodontal therapy in this instance.

The specific reasons that describe significant improvements in carotid IMT but not PWV remain unclear. It is possible that the significant increase found in plasma asymmetrical dimethylarginine, an endogenous inhibitor of endothelial NO synthesis, in the treatment but not control group at 12 months may have contributed to the lack of improvement in vessel function. We also cannot exclude the possibility of a threshold effect. Inclusion criteria for some periodontal intervention trials that have reported significant improvements to inflammatory markers and endothelial function have only included participants with severe periodontal disease. By comparison, only 3 of the 273 participants in the present study would be eligible using the same classification. Although the predominance of moderate periodontitis in this trial might have attenuated the observed effects of periodontal treatment on arterial end points, inclusion of people with moderate periodontitis means that these results are more readily generalizable to the Aboriginal adult population.

Previous trials provide important contextual information for our findings. Intensive periodontal treatment involving periodontal therapy and removal of teeth combined with localized antibiotic administration improved endothelial function at 60 and 180 days postintervention. Another study including extraction of hopeless teeth for the secondary prevention of cardiovascular disease reported no benefit for subsequent cardiovascular events. Such improvements in endothelial function are consistent with slower progression of carotid IMT, as observed in the current trial, and reduced risk of cardiovascular disease events. Evidence suggests that IMT may be a stronger predictor of future cardiovascular events than endothelial dysfunction, particularly in relation to patients otherwise considered at low risk. Another uncontrolled trial of 35 participants with mild to moderate periodontal disease described the effects of a periodontal intervention on carotid IMT, finding marked reductions in carotid IMT at 6 months and 12 months after periodontal intervention. These reductions, although limited by the lack of a control group and the small sample size, are consistent with those of the current randomized, controlled trial.

No prior trials have investigated change in PWV after periodontal therapy. Associations between periodontal disease and arterial stiffness have been limited to observational studies. Aside from considerable variations in the criteria defining periodontitis between studies, the anatomic sites for arterial stiffness measurement differ, meaning each study measured separate segments of the arterial tree and are thus not directly comparable. Aging, for example, results in a greater collagen content of central arteries relative to elastin, whereas the elastin content of peripheral arteries supported by muscle has a tendency to increase with age.

Loss to follow-up was 35% at both 3 and 12 months, and as such the potential for attrition bias cannot be completely eliminated. There were no significant differences, however, in baseline PWV, IMT, or periodontal parameters when compared between those lost to follow-up and those completing the follow-up visits. Aside from the present study, 2 other randomized trials limited to Aboriginal Australian adult women have been completed and reported comparable loss to follow-up rates. We made concerted efforts to minimize detection bias in this study by not informing examining clinicians of the original study participant group allocation. For outcomes of interest such as PWV, the 2 assessors achieved sufficient reliability, whereas reproducibility of blinded IMT measurements was excellent. In addition, because of staff changes during the study, examiner 1 collected the majority of the annual measurements, increasing consistency (Figure S1).

We have previously demonstrated that modest improvements to periodontal status can be achieved and maintained for ≤3 months after 1-stage periodontal therapy, irrespective of oral hygiene. However, those findings suggest that, without periodontal maintenance to remove newly formed deposits of calculus and disturb the dental biofilm, the short-term response to the periodontal tissues has a tendency to regress.

Perspectives

The present study reveals that conventional periodontal therapy is sufficient to reduce carotid IMT. This finding is robust even when considering subgroup analyses. Future investigations may determine whether a more intensive approach to periodontal therapy, including regular periodontal maintenance schedules, may result in more marked improvements in vascular structure. Extrapolation of these results, if repeated in other studies, may suggest that treatment of periodontal disease is important for cardiovascular disease risk reduction.

Conclusions

In conclusion, carotid IMT regressed in Aboriginal Australian adults with moderate to severe periodontal disease after periodontal therapy, suggesting periodontal disease and atherosclerosis are significantly associated. However, a single session of nonsurgical periodontal therapy may be insufficient to alter the functional aspects of vascular health that contribute to and modify PWV in the short-term. These findings provide some evidence to suggest that periodontal therapy may have a systemic impact beyond the oral environment. Further studies may also seek to reproduce these findings in other populations and assess cardiovascular events.

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Disclosures
None.

References

**Novelty and Significance**

**What Is New?**

- This study shows, using a randomized, controlled trial design, that conventional periodontal therapy attenuates progression of carotid intima-media thickening in a sample at high risk for cardiovascular disease.

**What Is Relevant?**

- If periodontal disease contributes to atherosclerosis, then treatment of periodontitis should be included in patient management.

**Summary**

Periodontal disease and atherosclerosis seem to be significantly associated. These findings should be examined in other populations. Prospective cardiovascular event data are required.
Effect of Periodontal Therapy on Arterial Structure and Function Among Aboriginal Australians: A Randomized, Controlled Trial

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The effect of periodontal therapy on arterial structure and function among Aboriginal Australians: a randomised controlled trial.


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EXPANDED METHODS

The PerioCardio study is a parallel-group, randomised, open label controlled trial investigating the effect of non-surgical periodontal therapy on surrogate markers of cardiovascular disease among Aboriginal Australian adults residing in the Northern Territory, Australia.

Participants were recruited from two regional centres in Australia’s Northern Territory; one the largest urban centre (Darwin) and the other a regional town approximately 300 km south (Katherine). Participants were also recruited from two correctional facilities; one in Darwin and the other in Alice Springs (the second largest regional centre in the Northern Territory, approximately 1,500 km south of Darwin).

Changes to original study protocol

The original study protocol can be found online [ANZCTR number: 12610000817044].

Three changes to the protocol were made during the study period. Firstly, the age for inclusion was reduced from 25 to 18 years. Eight study participants aged 22 through 24 years were subsequently included. Secondly, the periodontal intervention was altered from two sessions of half-mouth mechanical debridement, to a single, full-mouth untimed session due to operational issues relating to the availability of dental clinical facilities and study participant preference. Thirdly, change in carotid IMT from baseline to 3-month recall was not assessed following cardiologist advice as the timeframe was considered too short to represent true changes to common carotid structural wall.

Participant enrolment and allocation

Enrolment of study participants was conducted by non-dental research staff. We attempted to minimise the effect of detection bias at each recall appointment by not informing examining clinicians of the original study participant group allocation. One of the dental clinicians (KK) and one investigator not involved in data collection (MRS) were responsible for assessing outcomes using de-identified data.

Oral assessment methods to measure periodontal status

Periodontal probing depth (PD) and gingival recession was measured at four sites at every tooth excluding third molars. These included the mesio-buccal, mid-buccal, disto-buccal and disto-lingual. Oral plaque scores were recorded for six index teeth (if present) based on published criteria which included the most anterior molar in each quadrant, tooth 11 and tooth 31. The same six index teeth were assessed for calculus presence. A single gingival bleeding on probing score was collected for each tooth periodontally assessed and was scored based on the Gingival Index criteria.

Statistical methods to analyse periodontal parameters

Extent of PD and CAL were calculated as the percentage of sites examined based on the methods of Carlos and colleagues. For ordinal measures of calculus and plaque assessed on six index teeth, the mean number of each was calculated. Extent of visible plaque
(equivalent to Plaque Index (PI) values ≥2) determined degree of accumulation relative to total plaque. A modified Gingival Index score was calculated by dividing the number of teeth with gingival bleeding by the number of teeth periodontally assessed.

**Periodontal Intervention**

The periodontal intervention consisted of an untimed single-visit full-mouth non-surgical removal of sub and supragingival calculus and plaque biofilm following administration of local anaesthesia if requested by participants. The time required to provide the intervention varied from 45 minutes through to three hours depending on treatment complexity. Two clinicians, one oral health therapist (provider 1) and one dentist (provider 2) (Figure 1) conducted the intervention with the use of Gracey hand scalers (Hu-Friedy, Chicago, USA), and piezoelectric ultrasonic device (Kyangwon Ferrite, Gyeonggi-Do, Korea) using universal tips. The same intervention was offered to those randomised to the control group following completion of annual assessments. Oral hygiene instruction was provided to participants along with toothbrush and toothpaste upon completion of the baseline assessments for the control group and following the periodontal therapy for the treatment group.

**Vascular measures**

**PWV**

Validation of the carotid-dorsalis pedis PWV against carotid-femoral PWV was conducted on an age and gender-matched control group of participants not involved in the primary study, details of which are included below. A pressure tonometer was placed transcutaneously over the carotid followed by the DP arteries. The subtraction method was used to determine the path length between measurement sites, and the resultant PWV score was calculated using the ‘foot-to-foot’ method.

**IMT**

A minimum of three loops were acquired from each of the left and right common carotid arteries, for later batch analysis using semi-automated and validated software in a central reading laboratory (Carotid Analyzer, Medical Imaging Applications, USA), by an observer blinded to participant details, including randomization status. The single thickest section of intima-media on the far wall of the common carotid artery over a 1 cm long portion (0-1 cm proximal to the bulb) was measured from each frame, and averaged over the entire loop. Two loops were obtained from each side (left/right carotid), and averaged to obtain the maximum carotid IMT.

The spatial resolution of high-resolution ultrasound is generally considered to be 100-150 microns. The use of automated analysis systems, however, can effectively provide measures of carotid IMT with greater accuracy, in the order of 0.01 for the mean IMT from a given frame and 0.025 mm for the IMT of a single point, as a result of analysis of grey-levels between pixel pairs and by averaging the IMT along a 1cm long segment of the arterial wall.
Cardiovascular risk assessment

Non-fasting venous blood samples were collected via the antecubital vein. Samples were transported to a local commercial pathology clinic for analysis of lipid profile: total cholesterol (TC), high-density lipoprotein (HDL) and glycated haemoglobin (HbA1c). Direct methods were used to determine lipid profile using an ADVIA 2400 Chemistry System (Siemens, Tarrytown, USA). NonHDL cholesterol was the difference between TC and HDL. Serum and plasma was stored at -80°C until batch analysis. Serum high-sensitivity C-reactive protein (hsCRP) was measured by particle-enhanced immunonephelometry using the BN II system. HbA1c was determined by turbidimetric inhibition immunoassay with a COBAS INTEGRA (Roche Diagnostics, Indianapolis, USA). Plasma asymmetric dimethylarginine was assessed using high-performance liquid chromatography with simultaneous UV and fluorescence detection as previously described. Plasma IL-6 was measured via commercial ELISA assay (Human IL-6 Quantikine kit, R&D Systems Inc., Minneapolis, USA).

Brachial blood pressure was measured while seated using an automated device (Welch Allyn Medical Products, Skaneateles Falls, USA). Three measurements of systolic and diastolic pressure were collected with three minutes between readings. The mean values of the final two recordings were used as sitting blood pressure. Height was measured to the nearest 0.1cm using a stadiometer. Weight was measured to the nearest 0.1 kilogram using a portable weight scale (Tanita HD-351, Arlington Heights, USA) with participants lightly clothed. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (metres).

Self-reported questionnaire

Information on socio-demographic characteristics, tobacco smoking and self-reported health status was obtained via questionnaire. Individuals with self-reported diabetes or HbA1c ≥47.5 mmol/mol were defined as having diabetes for this analysis.

Reproducibility of Measurements

Both clinicians were trained in the collection of PWV and calibrated for periodontal assessment procedures prior to study commencement. For the periodontal assessments, five healthy volunteers were subsequently examined by both clinicians each blinded to the assessment of the other. Periodontal measurements were standardised to within 1mm. Where differences in the assessments occurred, agreement was attained via discussion. Inter-examiner reliability between the two clinicians during the study was assessed using volunteers not involved in the present trial. Precise agreement on the number of sites with PD ≥2 mm was used as a cut-point with weighted kappa statistic of 0.75 (95% CI 0.70 to 0.80) representing very good agreement. For PWV, inter-observer repeatability was tested throughout the study on 20 volunteers and was rated as ‘moderate’ (intra-class correlation = 0.72). Intra-observer repeatability was equally comparable between the two examiners and rated ‘good’; examiner 1: ICC = 0.86, examiner 2: ICC = 0.83. Inter-reader reproducibility for IMT measurement, derived from 20 measures assessed by two experience readers, was excellent (ICC = 0.99 (95% CI 0.98, 1.00).
Sample Size

To account for an *a priori* participant attrition of 25%, the original baseline sample size was set at 200 participants. Following one year of recruitment, almost 40% of the initial sample was lost to follow-up necessitating an increase in the sample. A final sample size of 273 persons was subsequently recruited to ensure that the required sample size would be attained.

Statistical analysis

Specific to IMT, sub-group analyses were undertaken within groups stratified according to baseline measures of sex, age, overweight/obesity, diabetes, smoking status and severity of periodontal disease. As a secondary analysis to enable inclusion of the baseline data of participants lost to follow-up and three participants who had carotid IMT data available from 12-months but not baseline, we constructed a linear mixed model including carotid IMT data from both baseline and 12-months, with the effect of the intervention determined by the interaction between visit number and allocated group.

A gender-specific comparison of baseline characteristics was undertaken due to significantly more males being completed at the 3-month follow-up (Table S4) and gender-stratified change to the two primary outcomes, PWV and IMT (Table S5). A baseline-carried-forward approach was also conducted as an additional sensitivity analysis (Table S6).

Data were analysed using a combination of SAS version 9.3 (Cary, North Carolina, USA) and IBM SPSS Statistics (version 21.0; IBM Corp., Somers, NY). Statistical significance was inferred at two-sided *P*-value <0.05.

Validation of carotid-dorsalis pedis PWV with carotid-femoral PWV

METHODS

Participants

We recruited 30 non-Indigenous Australians, aged ≥18 years, with no history of rheumatic heart disease, prior myocardial infarction, stroke or coronary revascularisation, as a comparator group for the PerioCardio study. All participants provided written informed consent, and the study was approved by the joint Menzies School of Health Research - Northern Territory Department of Health Human Research Ethics Committee.

Pulse wave velocity

PWV was measured using applanation tonometry (SphygmoCor-PVMx device, AtCor Medical, Sydney, Australia), as previously described. Both carotid-femoral and carotid-dorsalis pedis PWV were systematically measured in that order, and calculated via computer algorithm using the mean time difference between the R-wave and pressure wave at the measurement sites and the arterial path length between the recording sites and the suprasternal notch.
Cardiovascular risk factors

Cardiovascular risk factors were assessed as per the PerioCardio study protocol, as described in detail above and elsewhere. In brief, blood pressure was taken three times from seated subjects using an automated device (Welch Allyn Medical Products, Skaneateles Falls, NY, USA). The average of the last two measures was used. A non-fasting blood sample was collected by routine venous blood sampling techniques. Total cholesterol was assayed by enzymatic methods, and high-density lipoprotein cholesterol was measured directly (ADVIA chemistry system, Siemens, Tarrytown, USA). Smoking status was assessed by questionnaire, and pack years calculated. Weight was measured to the nearest 0.1 kg and height to the nearest 0.1 cm.

Statistical analysis

Of the 30 participants, three participants were excluded due to technical issues or poor measurement quality of carotid-femoral PWV, leaving 27 participants for this analysis. The two PWV measures were compared by paired samples t-test, Pearson correlation and Bland-Altman plot. Total cholesterol: HDL-cholesterol ratio (TC:HDL) was calculated. Associations of PWV with cardiovascular risk factors were by Pearson correlation. Statistical analyses were performed using SPSS version 21 (SPSS Inc, Chicago, IL, USA). Statistical significance was inferred at \( P < 0.05 \).

EXPANDED RESULTS

Periodontal parameters

Periodontal therapy improved periodontal parameters 3-months post-intervention, described in detail elsewhere. The periodontal intervention resulted in a significant improvement in periodontal health at 3-months (mean pocket depth: \(-0.16\) mm [95% CI -0.25, -0.07] in the intervention group relative to control, \( P = 0.008 \)). There was some evidence for a sustained improvement in periodontal health at 12-months post intervention (mean pocket depth: \(-0.09\) mm [95% CI -0.19, 0.01] in intervention group relative to control, \( P = 0.08 \)). In summary however, the single-visit non-surgical periodontal intervention did not result in sustained improvements in periodontal status long-term (Table S3).

There was no significant correlation between the 12-month change in maximum IMT & the 3-month change in the extent of periodontal pocket depths \( \geq 4 \)mm (Pearson’s \( r = 0.07 \), \( P = 0.39 \); Figure S5).

Blood lipids, ADMA & hsCRP

There were no significant differences to total cholesterol, nonHDL cholesterol, HDL cholesterol or hsCRP following the intervention (Table 2). In contrast, ADMA was significantly higher in the treatment group 12-months post-intervention (12-month change \( 0.05\mu\text{M/L} \) [95% CI 0.004, 0.10], compared to control, \( P = 0.03 \)) but not at 3-months (Table 2). Periodontal treatment did not alter hsCRP in the treatment group, however there was a non-
significant reduction in the control group following the 3-month assessments (3-month change +0.78 mg/L [95% CI -0.40 to 1.97], p=0.19).

Validation of carotid-dorsalis pedis PWV with carotid-femoral PWV

RESULTS

Participants were non-diabetic, aged between 20-66 years (mean 40 years [SD 15]), 16 of 27 were male, and had generally good cardiovascular risk profiles (mean systolic blood pressure 114 mm Hg [SD 9], BMI 24.6 kg/m² [SD 4.0]), TC:HDL 3.8 [SD 1.2]). Two of the participants were current smokers, while a further 10 were ex-smokers.

The two measures of PWV were significantly correlated (r = 0.496, P = 0.008). Carotid-dorsalis pedis PWV was higher than carotid-femoral PWV (7.4 m/s [SD 1.0] vs 6.8 m/s [SD 1.1], P = 0.005). Agreement between the two PWV measures was similar across the spectrum of measures (Figure S4). Carotid-femoral PWV could be estimated from carotid-dorsalis pedis PWV using the equation:

\[
\text{Carotid-femoral PWV} = 0.565 \times \text{carotid-dorsalis pedis PWV} + 2.601,
\]

where PWV is measured in m/s.

In general, the two PWV measures shared similar associations with risk factors (Table S7). Pulse Wave Velocity was most strongly associated with age and systolic blood pressure; with carotid-femoral PWV being more strongly associated with age, and carotid-dorsalis pedis more strongly associated with systolic blood pressure. Associations of PWV with TC:HDL and body mass index were similar. Neither measure of PWV differed by gender (carotid-femoral PWV: -0.3 m/s [95% CI -1.2, 0.6] in males vs females, P = 0.47; carotid-dorsalis pedis PWV: 0.3 m/s [95% CI -0.5, 1.1] in males vs females, P = 0.46).

EXPANDED DISCUSSION

Inflammation contributes to endothelial dysfunction \(^{12}\) and impaired function of the endothelium has been reported in people with periodontitis.\(^ {13}\) Accumulating evidence suggests both conventional non-surgical \(^ {14}\) and intensive periodontal therapies involving dental extractions, antibiotics and/or surgery can improve endothelial-dependent vasodilation.\(^ {15-17}\) The intensive interventions in these aforementioned studies resulted in marked reduction in systemic inflammation. In contrast, the one-stage non-surgical periodontal intervention provided in the present investigation did not significantly alter inflammation, potentially consistent with the lack of a short-term effect of the intervention on PWV in the present study.

The original study protocol planned for the intervention to be spread over two appointments, whereby two quadrants were to be treated at each session.\(^ {8}\) The intention was
to reduce discomfort for study participants and the physical burden on clinicians. However, participant preference towards a single session led to modification of the intervention protocol early in the study. A single session had the added advantage of ensuring that study participants randomised to the treatment arm completed their assigned therapy in a timely manner and this alteration ensured that 128 of 138 in the intervention group were completed. In relation to short-term periodontal tissue responses, Cochrane systematic review evidence indicates that single sessions of non-surgical periodontal treatment yield comparable outcomes to multiple visits. Therefore, it was not expected that the alteration from an intervention administered over two appointments would differ in terms of efficacy to an intervention administered in a single session, with regards to short-term changes in periodontal health.

Access to and the provision of dental services for Indigenous Australian adults in the Northern Territory is challenging. For example, those living in rural or remote locations may have dental practitioners visit as little as twice yearly and due to seasonal conditions, some locations can become temporarily inaccessible by road for weeks or months. Dental service attendance for Indigenous Australians living in Darwin is heavily weighted towards problem-associated visiting patterns. Reasons for this have not been extensively investigated. Among the PerioCardio study sample, almost 75% reported their last visit to a dentist was for a problem which is similar to that reported in Western Australia. Further, one-third of the PerioCardio study sample was recruited from correctional facilities in Darwin and Alice Springs. By way of explaining the unmet treatment need, at the time of the PerioCardio study, participants in the Darwin correctional facility had, on average, four teeth with untreated caries. For these individuals, sourcing an appointment was dependent on having a problem in the first instance and preventive services were extremely limited if non-existent. Measures from the Northern Territory government have since been implemented to improve access to dental services in this population. With this considered, a periodontal treatment regimen requiring multiple appointments for initial treatment and additional appointments for periodontal maintenance was, in real terms, not suitable in this setting.

It was not expected that the periodontal therapy provided in this study would be sufficient to completely eliminate periodontal disease, especially after one year. Nevertheless, it was expected that the response of the intervention to the periodontal tissues would have been greater than that observed. Teeth were scaled using ultrasonic and manual scalers until a smooth surface was confirmed with a dental explorer. Oral hygiene was discussed and reinforced immediately following the periodontal therapy and again upon follow-up visits. Despite these efforts, there were negligible and clinically insignificant changes to oral hygiene at both recall appointments for both study arms. The smaller-than-expected periodontal treatment effect in the treatment group at 3-months can be partially attributed to the lack of improvement in oral hygiene, which contributed to the perpetuation of periodontal inflammation as evidenced by a Gingival Index >1 for all periods of the study. There was no correlation between the 3-month change in pocket depth and the 12-month change in carotid IMT, although it is likely that the pocket depth variable does not fully
capture the improvements in periodontal disease due to the treatment, both with regards to pathology and time course.

Several operational issues impacted on the delivery of the study which would have precluded the provision of periodontal maintenance even if it was initially included within the study protocol. Firstly, the PerioCardio study was conducted around existing services provided by government departments and Aboriginal medical services. As such, access to dental facilities was not available at all times and a subsequent increase in the number of staff employed by the Northern Territory dental service during the study meant that access to dental facilities had to be arranged on a daily basis and was dependent on clinic availability on a given day. Secondly, scheduling participants for appointments was often complicated by changes to residential addresses and contact details, the management of which was often an overwhelming task for investigators and staff involved. Finally, failure to attend scheduled appointments was a regular occurrence for many study participants which negatively impacted on completion rates. In all likelihood, adoption of a periodontal maintenance regimen as opposed to a one-stage approach for this study protocol would have led to few participants completing the required number of appointments due to the aforementioned factors.

At the time of recruitment many study participants were unaware of their periodontal disease status. There was no limitation on external periodontal treatment, and as such all participants were free to receive periodontal treatment through their usual service providers during the course of the study. Only a few however, accessed periodontal therapy external to the study. For example, only six participants randomised to the treatment group and seven participants in the control group sought additional periodontal treatment during the 12-month follow-up period. At the completion of the 12-month study visit, control group participants were invited to receive the periodontal treatment. Of the 79 control participants who attended the 12-month follow-up, only 24 opted to receive periodontal therapy.

There are few alternatives available for a control-arm in a periodontal intervention other than the community care approach, such as that utilized in this study. An alternative study design would be to treat all study participants at baseline, with periodontal maintenance in the intervention group throughout the duration of the study, however this would likely dilute the overall effect size of our arterial outcome measures, which may be especially problematic given the relatively short time duration of the follow-up. Accordingly, adoption of the community care approach was the pragmatic option in this study.
REFERENCES


Table S1: Baseline Characteristics of Completed versus Lost to Follow-up (baseline data reported)

<table>
<thead>
<tr>
<th>Participant characteristics</th>
<th>3 month</th>
<th>12 month</th>
<th>P value</th>
<th>3 month</th>
<th>12 month</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>40.3 (10.3)</td>
<td>40.2 (10.4)</td>
<td>40.3 (10.1)</td>
<td>0.93</td>
<td>42.2 (10.5)</td>
<td>38.0 (9.4)</td>
</tr>
<tr>
<td>Gender – Male [%]</td>
<td>158 [57.3]</td>
<td>107 [63.3]</td>
<td>51 [49.0]</td>
<td>0.02</td>
<td>96 [57.1]</td>
<td>62 [59.0]</td>
</tr>
<tr>
<td>Female [%]</td>
<td>115 [42.7]</td>
<td>62 [36.7]</td>
<td>53 [51.0]</td>
<td>72 [42.9]</td>
<td>43 [41.0]</td>
<td></td>
</tr>
<tr>
<td>Current Smoker [%]*</td>
<td>161 [66.0]</td>
<td>102 [66.7]</td>
<td>59 [64.8]</td>
<td>0.77</td>
<td>97 [64.7]</td>
<td>64 [68.1]</td>
</tr>
<tr>
<td>Former/Never smoker [%]*</td>
<td>83 [34.0]</td>
<td>51 [33.3]</td>
<td>32 [35.2]</td>
<td>53 [35.3]</td>
<td>30 [31.9]</td>
<td></td>
</tr>
<tr>
<td>Mean HbA1c (mmol/mol)</td>
<td>45.0 (15.8)</td>
<td>46.5 (17.6)</td>
<td>42.1 (11.1)</td>
<td>0.02</td>
<td>46.6 (17.7)</td>
<td>41.9 (10.9)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.98 (1.03)</td>
<td>4.90 (1.01)</td>
<td>5.14 (1.07)</td>
<td>0.08</td>
<td>5.03 (1.11)</td>
<td>4.91 (0.88)</td>
</tr>
<tr>
<td>nonHDL cholesterol (mmol/L)</td>
<td>3.95 (1.03)</td>
<td>3.90 (1.02)</td>
<td>4.03 (1.06)</td>
<td>0.33</td>
<td>3.97 (1.12)</td>
<td>3.90 (0.87)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.04 (0.32)</td>
<td>1.00 (0.30)</td>
<td>1.11 (0.33)</td>
<td>0.01</td>
<td>1.05 (0.35)</td>
<td>1.01 (0.26)</td>
</tr>
<tr>
<td>Mean hsCRP (mg/L)</td>
<td>4.89 (5.35)</td>
<td>4.78 (5.52)</td>
<td>5.11 (5.05)</td>
<td>0.65</td>
<td>4.72 (5.74)</td>
<td>5.19 (4.62)</td>
</tr>
<tr>
<td>Mean IL-6 (pg/mL)</td>
<td>2.79 (2.27)</td>
<td>2.82 (2.42)</td>
<td>2.72 (1.95)</td>
<td>0.73</td>
<td>2.66 (2.24)</td>
<td>3.00 (2.32)</td>
</tr>
<tr>
<td>ADMA (µM/L)</td>
<td>0.43 (0.12)</td>
<td>0.42 (0.12)</td>
<td>0.43 (0.10)</td>
<td>0.76</td>
<td>0.43 (0.12)</td>
<td>0.42 (0.12)</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>29.12 (7.18)</td>
<td>29.67 (6.39)</td>
<td>28.15 (8.35)</td>
<td>0.13</td>
<td>29.06 (6.15)</td>
<td>29.20 (8.77)</td>
</tr>
<tr>
<td>Mean PWV (m/s)</td>
<td>8.34 (1.25)</td>
<td>8.32 (1.32)</td>
<td>8.38 (1.11)</td>
<td>0.72</td>
<td>8.32 (1.32)</td>
<td>8.39 (1.10)</td>
</tr>
<tr>
<td>Mean carotid IMT ( mm)†</td>
<td>0.63 (0.12)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.64 (0.13)</td>
<td>0.62 (0.10)</td>
</tr>
<tr>
<td>Maximum carotid IMT ( mm)†</td>
<td>0.78 (0.16)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.79 (0.17)</td>
<td>0.76 (0.14)</td>
</tr>
<tr>
<td>Mean systolic BP (mmHg)</td>
<td>124.9 (16.7)</td>
<td>124.7 (14.4)</td>
<td>125.4 (20.1)</td>
<td>0.76</td>
<td>125.1 (16.9)</td>
<td>124.6 (16.4)</td>
</tr>
<tr>
<td>Mean diastolic BP (mmHg)</td>
<td>80.2 (10.3)</td>
<td>80.1 (10.2)</td>
<td>80.4 (10.6)</td>
<td>0.82</td>
<td>80.3 (10.5)</td>
<td>80.0 (10.1)</td>
</tr>
<tr>
<td>Mean number of teeth</td>
<td>26.34 (5.96)</td>
<td>26.38 (6.08)</td>
<td>26.27 (5.80)</td>
<td>0.89</td>
<td>25.94 (5.83)</td>
<td>27.11 (6.01)</td>
</tr>
<tr>
<td>Extent CAL ≥3mm</td>
<td>46.79 (25.46)</td>
<td>52.24 (25.18)</td>
<td>55.02 (26.24)</td>
<td>0.38</td>
<td>53.07 (26.59)</td>
<td>53.68 (23.89)</td>
</tr>
<tr>
<td>Extent PD ≥4mm</td>
<td>14.00 (13.96)</td>
<td>14.29 (14.48)</td>
<td>13.51 (13.07)</td>
<td>0.66</td>
<td>13.79 (13.71)</td>
<td>14.20 (14.20)</td>
</tr>
</tbody>
</table>

Data for means presented as mean (SD); difference in means via independent samples t-test.
Proportions presented as column N [%]; Difference in proportions via χ² test.†
*Reported values limited to those that have completed data (n=244).
†Diabetes via self-report (n=41) or when HbA1c ≥ 6.5% (n=21).
‡Geometric mean (IQR) for non-normally distributed variables.
Table S2: Periodontal Therapy and Change in Carotid Intima-Media Thickness –
Subgroup Analyses.

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Effect of periodontal therapy on carotid IMT, mm (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Males (n=93)</td>
<td>-0.031 (-0.061, -0.000)</td>
</tr>
<tr>
<td>Females (n=72)</td>
<td>-0.019 (-0.053, 0.016)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Younger (≤40.5 y)(n=81)</td>
<td>-0.026 (-0.055, 0.002)</td>
</tr>
<tr>
<td>Older (&gt;40.5 y)(n=84)</td>
<td>-0.022 (-0.057, 0.013)</td>
</tr>
<tr>
<td>Adiposity</td>
<td></td>
</tr>
<tr>
<td>Healthy weight (n=39)</td>
<td>-0.025 (-0.063, 0.014)</td>
</tr>
<tr>
<td>Overweight (n=62)</td>
<td>-0.027 (-0.064, 0.010)</td>
</tr>
<tr>
<td>Obese (n=64)</td>
<td>-0.028 (-0.067, 0.010)</td>
</tr>
<tr>
<td>Diabetes status</td>
<td></td>
</tr>
<tr>
<td>Diabetic (n=44)</td>
<td>-0.001 (-0.048, 0.047)</td>
</tr>
<tr>
<td>Non-diabetic (n=121)</td>
<td>-0.032 (-0.058, -0.006)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Current smoker (n=95)</td>
<td>-0.047 (-0.075, -0.019)</td>
</tr>
<tr>
<td>Never or ex-smoker (n=52)</td>
<td>-0.013 (-0.054, 0.027)</td>
</tr>
<tr>
<td>Severity of periodontal disease</td>
<td></td>
</tr>
<tr>
<td>Moderate (n=112)</td>
<td>-0.030 (-0.057, -0.004)</td>
</tr>
<tr>
<td>Severe (n=53)</td>
<td>-0.015 (-0.058, 0.029)</td>
</tr>
</tbody>
</table>

Data are mean (95% CI) for change in maximum carotid IMT with periodontal therapy, relative to control group, adjusting for baseline maximum carotid IMT (log transformed) by ANCOVA.
Table S3: Periodontal parameters at baseline and 12 months (Complete-Case Analysis)*

<table>
<thead>
<tr>
<th>Periodontal health measures</th>
<th>Treatment Baseline</th>
<th>Treatment 12 month</th>
<th>Control Baseline</th>
<th>Control 12 month</th>
<th>ANCOVA least squares mean Δ (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent CAL ≥3mm</td>
<td>53.07 (25.84)</td>
<td>46.37 (25.71)</td>
<td>53.07 (27.59)</td>
<td>50.37 (24.20)</td>
<td>-4.00 (-8.01, 0.02)</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean PD mm</td>
<td>2.38 (0.53)</td>
<td>2.26 (0.52)</td>
<td>2.41 (0.60)</td>
<td>2.37 (0.55)</td>
<td>-0.09 (-0.19, 0.01)</td>
<td>0.08</td>
</tr>
<tr>
<td>Extent PD ≥4mm (%)</td>
<td>13.38 (12.67)</td>
<td>11.69 (12.82)</td>
<td>14.26 (14.86)</td>
<td>13.61 (13.65)</td>
<td>-0.16 (-0.33, 0.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>Extent PD ≥5mm (%)</td>
<td>4.45 (6.36)</td>
<td>4.24 (6.82)</td>
<td>5.45 (8.67)</td>
<td>5.25 (8.25)</td>
<td>-0.63 (-2.09, 0.84)</td>
<td>0.40</td>
</tr>
<tr>
<td>Extent CAL ≥3mm &amp; PD ≥4mm</td>
<td>13.18 (12.50)</td>
<td>11.27 (12.28)</td>
<td>14.18 (14.62)</td>
<td>13.10 (13.19)</td>
<td>-1.27 (-2.87, 0.32)</td>
<td>0.12</td>
</tr>
<tr>
<td>Mean index teeth with calculus</td>
<td>4.11 (1.67)</td>
<td>2.97 (1.94)</td>
<td>4.06 (1.64)</td>
<td>3.94 (1.76)</td>
<td>-1.02 (-1.48, -0.56)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean gingival bleeding score</td>
<td>1.44 (0.67)</td>
<td>1.35 (0.74)</td>
<td>1.43 (0.68)</td>
<td>1.50 (0.67)</td>
<td>-0.13 (-0.32, 0.05)</td>
<td>0.16</td>
</tr>
<tr>
<td>Mean index teeth with plaque</td>
<td>5.22 (1.25)</td>
<td>5.18 (1.37)</td>
<td>5.39 (1.06)</td>
<td>5.29 (1.23)</td>
<td>-0.06 (-0.05, 0.17)</td>
<td>0.30</td>
</tr>
<tr>
<td>Extent visible plaque (%)</td>
<td>28.66 (36.22)</td>
<td>28.54 (36.31)</td>
<td>25.25 (33.29)</td>
<td>32.14 (38.49)</td>
<td>-6.12 (-16.30, 4.05)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Data for means presented as mean (SD).
Reported mean (SD) values limited to those that have completed data 12-months post-intervention.
CAL= Clinical attachment loss; PD = probing pocket depth.
Mean gingival bleeding: modified from Löe & Silness scoring system (number of teeth with BOP / number of teeth periodontally assessed); Maximum score for index teeth with calculus & plaque=6;
Extent visible plaque limited to scores ≥2 indicative of moderate/abundant plaque visible with the naked eye.
Table S4: Baseline Comparisons Stratified by Gender.

<table>
<thead>
<tr>
<th>Participant characteristics</th>
<th>Male (n=158)</th>
<th>Female (n=115)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>37.90 (9.28)</td>
<td>43.19 (10.71)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Current smoker [%]*</td>
<td>96 [69.1]</td>
<td>65 [61.9]</td>
<td>0.24</td>
</tr>
<tr>
<td>Former/Never smoker [%]*</td>
<td>43 [30.9]</td>
<td>40 [38.1]</td>
<td></td>
</tr>
<tr>
<td>Diabetes [%]†</td>
<td>24 [15.2]</td>
<td>17 [14.8]</td>
<td>0.93</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>44.8 (15.5)</td>
<td>45.2 (16.3)</td>
<td>0.86</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>126.3 (12.7)</td>
<td>123.0 (20.9)</td>
<td>0.13</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>81.2 (9.7)</td>
<td>78.8 (10.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.88 (0.96)</td>
<td>5.12 (1.12)</td>
<td>0.08</td>
</tr>
<tr>
<td>nonHDL cholesterol (mmol/L)</td>
<td>3.96 (0.98)</td>
<td>3.92 (1.11)</td>
<td>0.78</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>0.92 (0.27)</td>
<td>1.20 (0.31)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>3.29 (3.97)</td>
<td>7.05 (6.18)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>2.74 (2.44)</td>
<td>2.84 (2.01)</td>
<td>0.74</td>
</tr>
<tr>
<td>ADMA (μM/L)</td>
<td>0.41 (0.10)</td>
<td>0.45 (0.13)</td>
<td>0.04</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27.69 (5.34)</td>
<td>31.08 (8.78)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean PWV (m/s)</td>
<td>8.42 (1.19)</td>
<td>8.23 (1.32)</td>
<td>0.24</td>
</tr>
<tr>
<td>Mean IMT (mm)‡</td>
<td>0.64 (0.17)</td>
<td>0.61 (0.15)</td>
<td>0.02</td>
</tr>
<tr>
<td>Maximum IMT (mm)‡</td>
<td>0.78 (0.18)</td>
<td>0.74 (0.17)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean number of teeth</td>
<td>27.42 (5.10)</td>
<td>24.95 (6.68)</td>
<td>0.001</td>
</tr>
<tr>
<td>Extent PD ≥ 4mm (%)</td>
<td>16.63 (14.87)</td>
<td>10.24 (11.42)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Continuous variables are mean (SD); Categorical values presented as column N [%].
*Reported values limited to those that have completed data (n=244).
†Diabetes via self-report (n=41) or when HbA1c ≥47.5 mmol/mol (additional 21).
‡Geometric mean (IQR) for non-normally distributed variables.
PWV: pulse wave velocity; BP: blood pressure; HDL: high-density lipoprotein; hsCRP: high-sensitivity C-reactive protein; HbA1c: Glycated haemoglobin; ADMA: Asymmetric dimethylarginine.
Table S5: Change in Maximum IMT and Pulse Wave Velocity Stratified by Gender

<table>
<thead>
<tr>
<th>Gender &amp; outcome</th>
<th>Treatment</th>
<th>Control</th>
<th>ANCOVA least squares mean Δ (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 month</td>
<td>Baseline</td>
<td>3 month</td>
</tr>
<tr>
<td>Males - PWV (m/s)</td>
<td>8.15 (1.30)</td>
<td>8.06 (1.07)</td>
<td>8.44 (1.19)</td>
<td>8.13 (1.21)</td>
</tr>
<tr>
<td>Females - PWV (m/s)</td>
<td>8.32 (1.31)</td>
<td>8.15 (1.09)</td>
<td>8.42 (1.68)</td>
<td>8.18 (1.17)</td>
</tr>
<tr>
<td>Males - max. IMT (mm)</td>
<td>0.77 (0.18)</td>
<td>0.76 (0.16)</td>
<td>0.81 (0.16)</td>
<td>0.81 (0.15)</td>
</tr>
<tr>
<td>Females - max. IMT (mm)</td>
<td>0.79 (0.20)</td>
<td>0.77 (0.17)</td>
<td>0.74 (0.11)</td>
<td>0.75 (0.13)</td>
</tr>
</tbody>
</table>

Data for baseline/follow-up means presented as mean (SD). Reported values restricted to those that have completed data post-intervention.
Table S6: Baseline-Carried-Forward analysis

<table>
<thead>
<tr>
<th>Risk markers</th>
<th>Treatment</th>
<th>Control</th>
<th>ANCOVA least squares</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 3 month</td>
<td>Baseline 3 month</td>
<td>mean Δ (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Extent CAL ≥3mm</td>
<td>53.10 (24.84)</td>
<td>45.44 (25.61)</td>
<td>-5.55 (-9.04, -2.06)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean PD mm</td>
<td>2.39 (0.52)</td>
<td>2.23 (0.47)</td>
<td>-0.12 (-0.19, -0.05)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Extent PD ≥4mm (%)</td>
<td>13.40 (12.84)</td>
<td>10.07 (10.82)</td>
<td>-2.39 (-4.04, -0.73)</td>
<td>0.01</td>
</tr>
<tr>
<td>Extent PD ≥5mm (%)</td>
<td>4.40 (6.90)</td>
<td>3.87 (6.75)</td>
<td>-0.01 (-0.03, 0.01)</td>
<td>0.16</td>
</tr>
<tr>
<td>Extent CAL ≥3mm &amp; PD ≥4mm</td>
<td>13.21 (12.68)</td>
<td>9.90 (10.76)</td>
<td>-2.28 (-3.91, -0.66)</td>
<td>0.01</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>8.23 (1.22)</td>
<td>8.23 (1.08)</td>
<td>0.06 (-0.16, 0.28)</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>Baseline 12 month</td>
<td>Baseline 12 month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extent CAL ≥3mm (%)</td>
<td>53.10 (24.84)</td>
<td>47.26 (25.21)</td>
<td>-3.81 (-6.74, -0.89)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean PD mm</td>
<td>2.39 (0.52)</td>
<td>2.29 (0.51)</td>
<td>-0.08 (-0.14, -0.01)</td>
<td>0.03</td>
</tr>
<tr>
<td>Extent PD ≥4mm (%)</td>
<td>13.40 (12.84)</td>
<td>11.68 (12.69)</td>
<td>-1.34 (-2.94, 0.27)</td>
<td>0.10</td>
</tr>
<tr>
<td>Extent PD ≥5mm (%)</td>
<td>4.40 (6.90)</td>
<td>4.34 (7.39)</td>
<td>0.01 (-0.03, 0.05)</td>
<td>0.47</td>
</tr>
<tr>
<td>Extent CAL ≥3mm &amp; PD ≥4mm</td>
<td>13.21 (12.68)</td>
<td>11.45 (12.51)</td>
<td>-1.30 (-2.87, 0.28)</td>
<td>0.11</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>8.23 (1.22)</td>
<td>8.37 (0.96)</td>
<td>0.19 (-0.01, 0.40)</td>
<td>0.07</td>
</tr>
<tr>
<td>Max. IMT (mm)</td>
<td>0.78 (0.18)</td>
<td>0.77 (0.17)</td>
<td>-0.015 (-0.029, -0.006)</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean IMT (mm)</td>
<td>0.64 (0.14)</td>
<td>0.63 (0.13)</td>
<td>-0.007 (-0.018, 0.003)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Data for means presented as mean (SD).
CAL= Clinical attachment loss; PD = probing pocket depth; PWV=Pulse Wave Velocity; IMT=Intima-Media Thickness.
Table S7. Correlation of cardiovascular risk factors with carotid-femoral and carotid-dorsalis pedis pulse wave velocity.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Carotid-femoral PWV</th>
<th>Carotid-dorsalis pedis PWV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation coefficient</td>
<td>P-value</td>
</tr>
<tr>
<td>Age</td>
<td>0.52</td>
<td>0.01</td>
</tr>
<tr>
<td>SBP</td>
<td>0.56</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI</td>
<td>0.18</td>
<td>0.37</td>
</tr>
<tr>
<td>Pack years</td>
<td>0.38</td>
<td>0.06</td>
</tr>
<tr>
<td>TC:HDL</td>
<td>0.33</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Results from Pearson correlation.
FIGURES

Assessed for eligibility (n=422)

Excluded (n=149)
  - Not available for study period (n=54)
  - Non-periodontitis (n=39)
  - Medical contraindications (n=32)
  - <5 permanent teeth (4)
  - Declined to participate (n=18)
  - Undergoing periodontal care (n=2)

Screening

Randomized (n=273)

Allocated to Treatment group (n=138)
  - Received allocated intervention (n=128)
    - Did not receive allocated intervention (n=10)
    - Refused to have treatment (n=2)
    - Failed to attend treatment appointments (n=8)

Allocated to Control group (n=135)
  - Received allocated intervention (n=135)

Allocation

Care providers performing the intervention (n=2)
Number of participants treated by each provider
  - Provider 1 (n=98), Provider 2 (n=40)

3 Month Follow-up
(n=169)

Excluded from analysis (n=51)
  - Did not attend (n=48)
  - Refuse to participate further (n=2)
  - Other (n=1)
Received additional dental treatment (n=4)
  - Extractions (n=4)
Number of participants treated by each examiner
  - Provider 1 (n=51), Provider 2 (n=36)
Analysed at 3 months (n=87)

Excluded from analysis (n=53)
  - Did not attend (n=45)
  - Refuse to participate further (n=5)
  - Other (n=3)
Received additional dental treatment (n=6)
  - Extractions (n=4)
  - Periodontal (n=2)
Number of participants treated by each examiner
  - Provider 1 (n=50), Provider 2 (n=32)
Analysed at 3 months (n=82)

Annual Follow-up
(n=168)

Excluded from analysis (n=49)
  - Did not attend (n=43)
  - Refuse to participate further (n=4)
  - Other (n=1)
  - Refused ultrasound scan (n=1)
Received additional dental treatment (n=8)
  - Extractions (n=2)
  - Periodontal (n=6)
Number of participants assessed by each examiner
  - Provider 1 (n=79), Provider 2 (n=13)
Analysed at 12 months (n=89)

Excluded from analysis (n=56)
  - Did not attend (n=42)
  - Refuse to participate further (n=7)
  - Other (n=7)
Received additional dental treatment (n=13)
  - Extractions (n=8)
  - Periodontal (n=5)
Number of participants assessed by each examiner
  - Provider 1 (n=69), Provider 2 (n=10)
Analysed at 12 months (n=79)

Figure S1: Study Flow Diagram
Figure S2: Periodontal therapy and 12-month change in carotid intima-media thickness. Scatter plot of change in maximum carotid intima-media thickness from baseline to 12-months post randomization adjusting for baseline carotid intima-media thickness, stratified by randomized group. $P$-value for effect of intervention by analysis of covariance adjusting for baseline carotid intima-media thickness. Carotid intima-media thickness regressed in the intervention group ($P = 0.003$), but did not change significantly in the control group ($P = 0.82$). Line and error bars represent mean and standard deviation.
Figure S3: Change in pulse wave velocity from baseline to 3-months (top panel) & baseline to 12-months (bottom panel). Reported values in box refer to differences in within-group change and corresponding (95% CI). Positive values denote greater difference in control group.
Figure S4: Agreement between carotid-femoral pulse wave velocity and carotid-dorsalis pedis pulse wave velocity. A) Bland-Altman plot, and B) individual participant data for carotid-femoral pulse wave velocity and carotid-dorsalis pedis pulse wave velocity. Dotted lines on Bland-Altman plot represent mean difference ±2SD.
Figure S5: Change in extent of periodontal disease and change in maximum carotid intima-media thickness (mm).