Relationship of Periodontal Disease to Carotid Artery Intima-Media Wall Thickness
The Atherosclerosis Risk in Communities (ARIC) Study

James D. Beck, John R. Elter, Gerardo Heiss, David Couper, Sally M. Maunderio, Steven Offenbacher

Abstract—Periodontitis has been linked to clinical cardiovascular disease but not to subclinical atherosclerosis. The purpose of this study was to determine whether periodontitis is associated with carotid artery intima-media wall thickness (IMT). Cross-sectional data on 6017 persons aged 52 to 75 years were obtained from the Atherosclerosis Risk in Communities Study 1996 to 1998 examination. The dependent variable was carotid IMT ≥1 mm. Periodontitis was defined by extent of attachment loss ≥3 mm: none/mild (<10%), moderate (10% to <30%), or severe (≥30%). Covariates included age, sex, diabetes, LDL cholesterol, HDL cholesterol, triglycerides, hypertension, smoking, waist-hip ratio, education, and race/study center. Odds of IMT ≥1 mm were higher for severe periodontitis (OR 2.09, 95% CI 1.73 to 2.53) and moderate periodontitis (OR 1.40, CI 1.17 to 1.67) compared with no periodontitis. In a multivariable logistic regression model, severe periodontitis (OR 1.31, CI 1.03 to 1.66) was associated with IMT ≥1 mm, while adjusting for the other factors in the model. These results provide the first indication that periodontitis may play a role in the pathogenesis of atheroma formation, as well as in cardiovascular events. (Arterioscler Thromb Vasc Biol. 2001;21:1816-1822.)

Key Words: periodontitis ■ periodontal disease ■ mouth diseases ■ carotid artery diseases ■ atherosclerosis ■ ultrasonics

Studies have suggested that periodontitis is associated with coronary heart disease and cerebrovascular disease.1–11 Periodontitis is a chronic infection by Gram-negative bacteria that affects the supporting structures of the teeth.12 A mechanism has been proposed whereby periodontitis creates a burden of bacterial pathogens, antigens, endotoxins, and inflammatory cytokines that contribute to the process of atherogenesis and thromboembolic events. In response to infection and inflammation, certain persons may exhibit greater expression of local and systemic mediators and may thereby be at increased risk for atherosclerosis. The atherosclerosis process may result in decreased arterial patency and/or decreased compliance of the vessel. Ultimately, atherosclerotic lesions may fissure and/or rupture, resulting in occlusion of the vessel lumen, precipitating a myocardial infarction or stroke.13

Until now, study of the periodontitis–cardiovascular disease relationship has concentrated on clinical cardiovascular events, but the relationship of periodontitis to subclinical measures of atherosclerosis has not been examined. The intima-media wall thickness (IMT) of the carotid artery, as measured by B-mode ultrasound, is a measure of preclinical atherosclerosis that has been shown to be associated with coronary heart disease, both prevalent14 and incident,15–18 and with incident stroke.19,20

We report on a novel study of the relationship of periodontitis to increased carotid IMT in individuals free of coronary heart disease, drawn from the Atherosclerosis Risk in Communities (ARIC) cohort. A significant association between periodontitis and carotid IMT may provide evidence of a role for periodontitis in the pathogenesis of atheroma formation.

Methods

The ARIC study, supported by the National Heart, Lung, and Blood Institute, is a prospective investigation of the etiology and natural history of atherosclerosis and clinical cardiovascular disease in 4 US communities (Jackson, Miss; Washington County, Maryland; suburban Minneapolis, Minn; and Forsyth County, North Carolina).21 The Jackson cohort was composed entirely of blacks. A sample of 15 792 community-dwelling residents aged 45 to 64 years at baseline took part in an evaluation of cardiovascular risk factors and their sequelae. The ARIC clinical examination included B-mode ultrasound of the carotid arteries to determine wall thickness and atherosclerotic lesions, anthropometry including waist-to-hip ratio, blood pressure, cognitive function, ECG, clinical chemistries, plasma lipids, medications, and health questionnaires,22

The Dental ARIC, an ancillary study funded by the National Institute of Dental and Craniofacial Research, was conducted at ARIC visit 4 in 1996 to 1998. The aims of the Dental ARIC study were to determine the prevalence, extent, and severity of periodontal conditions in the dentate ARIC population and to describe the associations between those conditions and prevalent coronary heart disease.
disease, carotid artery IMT, presence of carotid artery lesions, and atherosclerosis risk factors.

The Dental ARIC consisted of an oral examination; collection of gingival crevicular fluid, oral plaque, and serum; and interviews. Persons requiring antibiotic prophylaxis for periodontal probing were excluded. Clinical measures collected included probing pocket depth and gingival recession on 6 sites for all teeth. Attachment level (AL) was calculated from the sum of pocket depth and gingival recession scores. The dental examiners were calibrated against a standard examiner, as well as each other. Attachment level, a valid measure of historical periodontal destruction, was derived from percentage of sites with AL ≥3 mm from the periodontal examination. Because buccal sites often exhibit AL that consists primarily of gingival recession from causes not related to periodontitis, a correction was made requiring that buccal sites exhibiting at least 3 mm of AL also have AL less than or equal to that found at the adjacent mesiobuccal and distobuccal sites. Numerous periodontitis case definitions have been used to define periodontitis as an outcome. On the other hand, there is almost no information available on the appropriate definition for periodontitis when it is to be used as an exposure for another disease or condition. Our previous work has indicated that mild periodontitis likely does not have systemic effects and that evidence of a more extensive infection is needed when periodontitis is an exposure. Empirically, when studying dose-response effects, we have found that individuals with ALs in the highest quintile or quartile appear to be at excess risk. We also considered it important to have a referent group with little or no periodontal disease, rather than comparing the "cases" to a group that included individuals with moderate levels of disease. In middle-aged and older adults, almost no one is free from evidence of attachment loss, so we allowed a small percentage of sites (<10%) to be included in the periodontally healthy/mild disease group. Thus, we categorized as follows: none/mild (<10% of sites with AL ≥3 mm); may include subjects with no clinical manifestations of periodontal disease, gingivitis, or slight periodontal disease, moderate (10% to ≤30% of sites with AL ≥3 mm), or severe (≥30% of sites with AL ≥3 mm). Extent of AL of ≥3 mm was also divided into quintiles (<3.7%, 3.7% to <8.7%, 8.7% to ≤16.7%, 16.7% to 30.9%, and ≥30.9%) for assessment of a dose-response relationship with IMT. The dependent variable was carotid artery IMT ≥1 mm, derived by dichotomizing IMT at 1 mm. The 1-mm cut point was chosen because of its clinical and prognostic significance, as it has been associated with the subsequent development of coronary heart disease and stroke. Carotid IMT was measured by B-mode ultrasound on ~50% of the participants at visit 3 (1993 to 1995) and on the remaining participants at visit 4 (1996 to 1998). IMT was measured at both visits 3 and 4 on blacks and on an additional sample of whites. IMT at visit 4 was used for most participants, and visit 3 IMT was used when IMT at visit 4 was not available. Analyses are based on the mean IMT of the far wall for 1-cm lengths of the right and left carotid bifurcation and internal and common carotid arteries on bilateral scans. Not all participants had IMT measured at all 6 sites, so IMT at missing sites was imputed by maximum likelihood methods described elsewhere. Participants fasted for 12 hours before the clinical examination, and blood was collected for plasma lipids (including HDL cholesterol [HDL-C], LDL cholesterol [LDL-C], and triglycerides) and for serum glucose. Diabetes mellitus was defined as fasting serum glucose ≥126 mg/dL, 200 mg/dL if nonfasting, or pharmacological treatment for diabetes. Methods for waist-to-hip ratio and blood pressure have been described previously.

Participants were defined as never smokers, former smokers, or current smokers by interview. The former and current categories were further divided into light or heavy smokers, with light smokers reporting more than 0 but fewer than 20 pack-years of smoking and heavy smokers reporting ≥20 pack-years of smoking. This scheme resulted in a 5-level categorization of smoking that simultaneously took into account both the intensity and the recency of smoking.

Education was divided into basic (<12 years), intermediate (12 to 16 years), or advanced (17 to 21 years) levels and was included to control for socioeconomic status. Age (in years) at visit 4 was included, and a variable representing race/ethnicity (black or white) and ARIC center was designed to control for the ethnic, regional, and examiner differences in the ARIC cohort. Persons who were not black or white and the few blacks in the Maryland and Minneapolis centers were excluded from analysis due to small numbers.

Statistical analyses and data management were performed with SAS (SAS Institute, Cary, NC) and S-Plus (Data Analysis Products Division, Math Soft, Seattle, Wash). Statistical significance was set at 0.05, and the unit of analysis was the person. Frequency distributions, means, empirical distribution functions, and standard errors were determined to describe the data. Bivariate relationships were calculated with t tests or Kolmogorov-Smirnov (KS) tests for continuous variables and Cochran Mantel-Haenszel χ2 statistics and odds ratios with 95% CI for categorical variables. Multivariable modeling was performed with binary logistic regression. Potential confounders were specified a priori and were entered into the models without regard to statistical significance.

Results

Periodontal examiners at the ARIC centers were calibrated to a standard examiner, and the percent agreement for AL within 1 mm between each examiner and the standard examiner ranged from 83.2% to 90.2%. Weighted κ-statistics ranged from 0.76 to 0.86, indicating excellent agreement with the standard examiner. Intraclass correlation coefficients ranged from 0.76 to 0.90, indicating excellent to outstanding agreement.

Thirteen percent of ARIC participants refused the entire visit 4 examination. At the end of visit 3, 86.2% of visit 1 participants had a medical contraindication to probing. Among those screened, 15% were edentulous, and 17% were ineligible because they had a dental contraindication to probing. Among those eligible, 13% refused the dental examination. A total of 11,656 ARIC participants were seen for visit 4, and 6,797 underwent the periodontal examination. Individuals who were not black or white (n = 47), who were missing IMT data (n = 111), or who had myocardial infarction (n = 557) as defined by self-report, review of hospital records, or ECG findings were excluded from the analysis. A final sample of 6,017 subjects formed the study sample.

Severe periodontitis and moderate periodontitis were both associated with higher unadjusted mean IMT compared with no periodontitis (0.82 versus 0.74 and 0.77 versus 0.74 mm, respectively; P = 0.0001). Figure 1 illustrates that the empirical distribution of mean IMT was shifted for subjects with severe periodontitis (2-sample KS test, P < 0.001), and the shift was evident above IMT of 1 mm. The empirical distribution was also shifted for moderate versus no periodontitis and for severe versus moderate periodontitis (KS test, P < 0.001).

Figure 2 shows mean IMT (95% CI) for successively higher quintiles of AL ≥3 mm, adjusted for age, sex, race, and ARIC center. Whereas mean IMT was seen to increase

[Figure 1: Distribution of carotid IMT by periodontitis case status in the ARIC Study visit 4 (n = 6017).]
monotonically for each category of AL, only the fourth and fifth quintiles of mean IMT were significantly higher than the lowest group (P<0.05 and P<0.0001, respectively). Mean IMT for severe periodontitis remained significantly higher than for no periodontitis or moderate periodontitis, but moderate periodontitis was not significantly different from no periodontitis (Figure 2).

Severe periodontitis was associated with slightly more than twice the odds of IMT ≥1 mm, and moderate periodontitis was associated with 1.5 times the odds of IMT ≥1 mm, unadjusted for the other covariates (Table 1). Other categorical variables that were significantly and positively related to IMT ≥1 mm included male sex, <12 years of education, former and current heavy smoking, diabetes, and hypertension. Continuous variables associated with IMT ≥1 mm at P<0.05 were extent of AL ≥3 mm, age, LDL-C, triglycerides, and waist-to-hip ratio. HDL-C was significantly lower in persons with IMT ≥1 mm.

In a multivariable binary logistic regression model for IMT ≥1 mm (Table 2), periodontitis was associated with 1.31 (CI 1.03 to 1.66) times the odds of IMT ≥1 mm, and moderate periodontitis was associated with 1.10 (CI 0.89 to 1.35) times the odds of IMT ≥1 mm compared with no periodontitis, while controlling for the other factors in the model. Covariates significantly related to IMT ≥1 mm in the multivariable model included male sex, 5-year increments of age, LDL-C per 10 mg/dL, diabetes, hypertension, basic versus advanced education, former and heavy current smoking, and standardized waist-to-hip ratio. HDL-C, triglycerides, intermediate education, and former and current light smoking were included in the model but were not statistically significant. All biologically plausible interactions of the covariates with periodontal status and IMT ≥1 mm were evaluated, but none was found to be statistically significant.

**Discussion**

Although studies have reported associations of oral disease with coronary heart disease, incident coronary heart disease, and stroke disease,1-11 the present study focused on the relationship of periodontal disease with a noninvasive measure of atherosclerosis in individuals free of myocardial infarction. To the best of our knowledge, this is the first study designed to assess this association. These findings suggest that periodontitis, in addition to its suspected relationship to cardiovascular events, may also play a role in the pathogenesis of atheroma formation.

We found that individuals with severe periodontal disease had 1.3 times the odds of having thick carotid arterial walls (≥1 mm) compared with individuals with less severe disease, after adjustment for traditional risk factors for atherosclerosis. These findings support those of Mattila et al,4 who reported on associations between dental infections and atherosclerosis in 100 patients (88 males and 12 females) who were referred for coronary angiography. In a multivariable analysis, a significant association was found between dental infection and severe atheromatosis, which remained significant once adjusted for total age, triglycerides, cholesterol, HDL-C, smoking, hypertension, social class, and body mass index.

The multivariable-adjusted periodontal disease–atherosclerosis association found in the present study should be classified as moderate in magnitude, consistent with associations reported for clinical atherosclerosis in other disease studies.2-5,7,8,10 An assessment of such a putative association in observational cross-sectional studies is open to alternative interpretations. For this reason, many researchers favor a statistical adjustment for potential confounding by factors associated with both the hypothesized exposure and the outcome. The ARIC study offers the opportunity to include numerous potential confounders in the analysis, and we included in an a priori manner those suspected to affect the periodontitis-IMT association. In addition, we not only evaluated morbid conditions, such as hypertension, hypercholesterolemia, and diabetes, but also considered whether individuals were being treated for those conditions. We found that treatment status did not contribute to the model. Furthermore, we constructed a smoking variable that tested both recent smoking and cumulative dose (pack-years), because both have been found to affect periodontal disease. Thus, although residual confounding is always a possibility, we have evaluated and adjusted for a wide range of potential confounders of this association. Even though this is an adjusted association of moderate magnitude, the prevalence of both periodontal disease and atherosclerosis means that periodontal disease may be responsible in part for considerable morbidity if the association observed in the present study is both replicated and found to be of a causal nature. For reference, the strength of the periodontal disease–atherosclerosis association is comparable to many of the traditional risk factors in the present study, including male sex, diabetes, hypertension, and smoking.

We examined the presence of a monotonic (dose-response) association in 2 ways (Figure 2). With adjustment for age, sex, and race/center, severe periodontitis was statistically different from noncases, but moderate periodontitis was not. This may suggest a threshold effect rather than a graded dose response, indicating that periodontal infections affecting ≥30% of the sites in the mouth may be needed to generate an infectious burden that has systemic effects. This is consistent with our previous findings from a longitudinal study,12 which indicated a dose-response trend but with only extensive baseline disease being statistically significant in a multivariable model. With respect to this threshold, a number of our previous publications have defined severe periodontal disease as having ≥60% of sites with ≥3 mm of AL and also have
found that this threshold was significantly associated with various systemic conditions, including heart disease. We modified the manner in which we calculated AL for this and future studies, because middle-aged individuals exhibit gingival recession that may be due in part to trauma rather than inflammatory disease. Buccal sites are most likely to exhibit this pattern, often due to overzealous brushing. Thus, we only considered buccal sites to have attachment loss due to periodontal disease when they had attachment loss that was no greater than the immediately adjacent mesiobuccal and distobuccal sites. This decision reduced the prevalence of AL in the present study, as well as the threshold used in the present study (30% of sites with AL ≥3 mm is roughly comparable to the threshold used in previous studies [60% of sites with AL ≥3 mm]).

It has been suggested that the observed associations in studies of the periodontitis–systemic health relationship may be due to confounding by inadequate control for socioeconomic status. This could occur when socioeconomic status is associated with both conditions, and individuals with cardiovascular disease are more likely to be one social class. In these analyses, education was chosen as the best indicator of social class based on its performance in previous ARIC publications and because of limitations in the available measures of household income and occupation due to missing values. To ensure that the issue of socioeconomic status was adequately addressed, variables for household income and for 8 categories of occupational class were added to the model that already contained education. As a result of these additional measures, the ORs for severe periodontitis and for
TABLE 2. Multivariable Logistic Regression Model for Periodontal Disease and IMT ≥1 mm in the ARIC Study Visit 4*

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periodontitis†</td>
<td></td>
</tr>
<tr>
<td>None/mild (&lt;10% of sites with AL ≥3 mm)</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>Moderate (10% to &lt;30% of sites with AL ≥3 mm)</td>
<td>1.10, 0.89–1.35</td>
</tr>
<tr>
<td>Severe(≥30% sites with AL ≥3 mm)</td>
<td>1.31, 1.03–1.66</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.46, 1.18–1.81</td>
</tr>
<tr>
<td>Age per 5-year increment</td>
<td>1.57, 1.44–1.70</td>
</tr>
<tr>
<td>Lipids (per 10 mg/dL)</td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>1.05, 1.03–1.08</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.97, 0.90–1.04</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.01, 1.00–1.02</td>
</tr>
<tr>
<td>Type II diabetes‡</td>
<td>1.54, 1.22–1.95</td>
</tr>
<tr>
<td>Hypertension§</td>
<td>1.80, 1.50–2.16</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>Advanced (17–21 years)</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>Intermediate (12–16 years)</td>
<td>0.91, 0.75–1.10</td>
</tr>
<tr>
<td>Basic (&lt;12 years)</td>
<td>1.21, 0.93–1.58</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>Former light</td>
<td>1.12, 0.87–1.39</td>
</tr>
<tr>
<td>Current light</td>
<td>1.33, 0.71–2.50</td>
</tr>
<tr>
<td>Former heavy</td>
<td>1.72, 1.36–2.19</td>
</tr>
<tr>
<td>Current heavy</td>
<td>2.00, 1.50–2.67</td>
</tr>
<tr>
<td>Waist-hip ratio (standardized)</td>
<td>1.14, 1.02–1.28</td>
</tr>
</tbody>
</table>

*n=5953. Includes persons who had determination of periodontitis status at visit 4 and IMT at visit 3 or 4. Adjusted for race and ARIC field center.
†Excludes buccal sites where AL≥adjacent sites.
‡Fasting blood glucose ≥126 mg/dL, nonfasting ≥200 mg/dL, or self-reported history of diabetes, or evidence of diabetes medication.
§Systolic ≥140 or diastolic ≥90 mm Hg.

Another potential weakness involved the use of visit 3 IMT data (which occurred before the measurement of periodontal status) to supplement visit 4 IMT values. The ARIC plan for collecting IMT data was to examine half the participants in visit 3 and half in visit 4. However, 2 ARIC sites obtained additional funds to examine all participants at both visits. Thus, most of the IMT data came from visit 4. Clinical measures of attachment loss (AL) remain evident, even if the disease is no longer active. Thus, AL is a measure of the cumulative periodontal disease experience of the individual (until the tooth is lost). Therefore, individuals with serious periodontal disease in visit 4 also would have exhibited periodontal disease during visit 3. In addition, longitudinal ARIC findings indicate that IMT changes take place slowly (ranging from 25 to 41 μm over 3 years, depending on smoking status),38 so it is likely that visit 3 IMT scores closely approximated visit 4 scores. Thus, misclassification due to the timing of the exposure and outcome is unlikely. Finally, analyses using only visit 3 data resulted in very similar estimates of association.

The decision to exclude individuals with reported or detected myocardial infarction was made because once a clinical or silent myocardial infarction has occurred, the atherosclerosis detected by ultrasound can no longer be termed subclinical disease. However, the exclusion of myocardial infarction subjects had little effect on the multivariable OR between severe periodontitis and IMT ≥1 mm (OR 1.28, CI 1.03 to 1.60 with myocardial infarction subjects; OR 1.31, CI 1.03 to 1.67 without myocardial infarction subjects). Likewise, the exclusion of reported and detected stroke (n=215) in addition to myocardial infarction was contemplated; however, such exclusion actually strengthened the relationship between severe periodontitis and IMT ≥1 mm (OR 1.30, 1.02 to 1.67 with stroke and myocardial infarction excluded; OR 1.31, CI 1.03 to 1.66 with only myocardial infarction excluded). Lastly, serious periodontal disease is likely to have played a significant role in tooth loss leading to edentulism,39–41 and some studies have shown that individuals who require antibiotic prophylaxis before periodontal treatment often have more serious periodontal disease.42 Thus, these exclusions may have tended to dilute the associations found.

There are additional circumstances that may have attenuated the strength of the associations found in the present study. Danesh43 pointed out that epidemiological studies of oral disease and heart disease were somewhat less convincing than studies of other infections because the dental studies did not quantify the presence of microorganisms. For years, a multitude of microorganisms have been associated with periodontal disease, and recently, the World Workshop on Periodontal Disease44 indicated that there was enough evidence to classify Porphyromonas gingivalis, Bacteroides forsythus, and Treponema denticola, as causal. Although no population-based epidemiological studies have included microorganisms or measures of the host response to those organisms, periodontal organisms have been identified in atheromas45,46; they have been shown to invade the coronary endothelium,47,48 and they are found more frequently in myocardial infarction patients than in controls.49 To adequately test the mechanisms involved in these associations, future studies...
must evaluate the roles of pathogens and the host inflammatory response as they relate to atherosclerosis and cardiovascular events. The Dental ARIC study will be able to provide such information when analyses of stored oral plaque, serum, and gingival crevicular fluid are completed.

If replicated, these findings have profound clinical and public health implications. The prevalence of both periodontitis and atherosclerosis is very high; hence, even associations of modest magnitude have a large impact. The cost to society directly attributable to atherosclerotic sequelae is very large. Periodontitis is treatable; moreover, it is preventable. Pending experimental confirmation of the association shown by this study, another widely prevalent and preventable contributor to the burden of cardiovascular disease would be added to the options available to clinicians and public health practitioners for the control of the epidemic of cardiovascular diseases.

Acknowledgments
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References
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