Early Carotid Atherosclerosis in Subjects With Periodontal Diseases

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Background and Purpose—There is growing experimental evidence implicating chronic inflammation/infection as an atherosclerotic risk factor. In this study, the involvement of periodontal disease in the development of early atherosclerotic vascular lesions has been evaluated.

Methods—In randomly chosen 82 patients with periodontal disease and 31 periodontally healthy individuals subjected to a clinical oral examination in 1985, atherosclerotic risk factor analysis and carotid ultrasonography was performed during reexamination 16 years later. Common carotid artery intima-media thickness (IMT) and lumen diameter were measured and intima-media area (cIMA) was calculated. The relationship between IMT and cIMA as dependent variables and periodontal disease, age, gender, body mass index, heredity for atherosclerosis, diabetes mellitus, hypertension, plasma cholesterol, smoking, and education as independent variables was evaluated in a multiple logistic regression model.

Results—The mean values of IMT and cIMA were significantly higher in patients with periodontal disease than in controls, both at the right (P<0.01 and P<0.001, respectively) and left side (P<0.001 for both variables). When the means of the bilateral measurements of these 2 ultrasonographic variables were tested, multiple logistic regression analysis identified periodontal disease as a principal independent predictor of the common carotid artery cIMA (odds ratio [OR], 5.20; P=0.003) and IMT (OR, 4.64; P=0.004).

Conclusions—The present results indicate that periodontal disease is associated with the development of early atherosclerotic carotid lesions. (Stroke. 2005;36:1195-1200.)

Key Words: atherosclerosis ■ carotid arteries ■ periodontitis

Periodontal disease is characterized by a chronic infection and inflammation in the periodontal tissue leading to the destruction of the bone surrounding the teeth and, ultimately, to dental loss. The fact that chronic inflammation is one of the characteristic features of periodontal disease is of special interest because, in recent years, evidence has been accumulated implicating low-grade inflammatory process in the pathogenesis of atherosclerosis and subsequent ischemic heart disease. Accordingly, chronic infection and inflammation are now being increasingly considered as new risk factors for the development of atherosclerotic cardiovascular disease and the results of recently conducted studies demonstrate that periodontal disease may increase systemic levels of inflammatory mediators and thus potentially contribute to the inflammation-associated atherosclerotic process.

Possible proatherogenic role of chronic infection in periodontal disease has not yet been conclusively established but periodontal pathogens as, for example Bacteroides forsythus (Tannerella forsythensis), Porphyromonas gingivalis, and Prevotella intermedia, have been identified in atherosclerotic plaques, as well as in human aortic and coronary endothelium. There are also data suggesting synergism between inflammatory and infectious factors in increasing the risk for atherosclerotic vascular disease.

Hitherto, studies on a possible connection between periodontal disease and atherosclerosis have focused on the prevalence of overt atherosclerotic disease or clinical cardiovascular events in patients affected by this disease. The results of these studies strongly suggest that there is an association between periodontal disease and increased incidence of coronary artery disease, myocardial infarction, and cerebrovascular events. However, the evidence from these observational studies does not allow any causal interpretation of the role of periodontal disease as an atherosclerotic risk factor because of the inability of the usually used cross-sectional approach to determine whether periodontitis occurred before the onset of the atherosclerotic disease. Furthermore, for the determination of causality, periodontal disease should not only precede the occurrence of clinically overt atherosclerotic disease but also contribute to its development.

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disease but also relate to the development of atherosclerotic vascular changes already at subclinical stage of the disease. In fact, an association of periodontal disease with early atherosclerotic changes in carotid arteries in patients free from signs of overt atherosclerotic cardiovascular disease has been recently reported by Beck et al., but the basically cross-sectional design of that study does not provide any conclusive information concerning temporal relations between periodontal disease and the onset of the atherosclerotic process. Therefore, in this study, we assessed the role of periodontitis in the development of atherosclerosis by evaluating in a prospective way the relationship between periodontal disease and subclinical signs of carotid atherosclerosis in patients with documented periodontitis of at least 16 years’ duration.

Materials and Methods

Participants
The baseline cohort was selected in 1985 using the registry file of all inhabitants of the Stockholm metropolitan area and consisted of 3273 adults aged 30 to 40 years and born on the 20th of any month between 1945 and 1954. This sample represented >93,000 inhabitants of the Stockholm area in the concerned age group. All selected individuals were informed about the purpose of the study and were offered a dental examination. In total, 1676 members of the cohort, 838 men and 838 women, agreed to participate and underwent an initial dental examination. The initial dental screening revealed that 286 participants had at least 1 site with tooth pocket depth of ≥5 mm and were considered to have periodontal disease. After at least 16 years, 82 subjects were randomly chosen from the group of individuals in whom the presence of periodontal disease was documented in 1985 and confirmed between 2001 and 2003. At the same time, 31 periodontally healthy subjects were randomly selected from the group of 1390 individuals who were found to be free from periodontitis in 1985 and confirmed as being healthy between 2001 and 2003.

The study was approved by Ethics Committee of the Karolinska University Hospital at Huddinge. All subjects gave their informed consent to participate.

Clinical Examination and Questionnaire
In all subjects, the following oral clinical parameters were recorded at baseline in 1985 and at the end of the study between 2001 and 2003: the number of remaining teeth excluding third molars, gingival inflammation around every tooth with Gingival Index, as well as oral hygiene status using the dental Plaque Index on 6 surfaces of all teeth excluding third molars. Pocket depth and attachment level were determined with a periodontal probe and recorded to the nearest millimeter of 6 sites of each tooth on all teeth excluding third molars. Wisdom teeth were also excluded because of the frequent occurrence of pseudo-pockets around these teeth.

At the time for the oral examination at the end of the study, blood was collected after 12 hours of overnight fasting for the analysis of total plasma cholesterol. Blood pressure was measured and 12-lead electrocardiogram was also recorded.

At the beginning and in the end of the study, the subjects answered a questionnaire concerning health problems, medication, occurrence of stroke or coronary artery disease in siblings or parents before the age of 65, dental visits, use of tobacco, marital status, socioeconomic data, and education.

Radiograms
A full-mouth set of 14 Ektaspeed periapical radiograms was obtained in each patient, using an EGGen film-holder and an Oralix Roentgen equipment (65 kVp/7.5 mA) equipped with a cone of rectangular section, permitting a modified parallel long cone technique, with a focus-film distance of ~30 cm. At each measureable interproximal surface, except on third molars, alveolar bone height was determined in percentage of the root length from radiograms magnified five times, using the computerized measuring system described by Wouters et al. Radiograms were obtained at baseline and at the end of the study. Dental examinations were performed by one of the authors (B.S.) and the radiograms were evaluated by 1 of the other authors (P-O.S.), blinded to the results of dental examination.

Carotid B-Mode Ultrasonography
Carotid ultrasonography was performed at the time of reexamination between 2001 and 2003. Carotid arteries were examined bilaterally with a duplex scanner (Aspen, Acuson) using a 7-MHz linear array transducer. All recordings were performed by the same trained sonographer with the subjects in supine position, and the head slightly turned away from the sonographer. The scans were videotaped for subsequent analyses by a computer system with automated tracing of echo interfaces. Measurements of distances between the wall echoes within a 10-mm-long section of the common carotid artery were made in late diastole defined by a simultaneous electrocardiographic recording. The far wall of common carotid artery, 0.5 to 1.0 cm proximal to the proximal delimitation of the carotid bulb, was used for measurements of the intima-media thickness (IMT) and lumen diameter. The IMT was defined as the distance between the leading edge of the lumen-intima echo and the leading edge of the media-adventitia echo. The lumen diameter was defined as the distance between the leading edge of the intima-lumen echo of the near wall and the leading edge of the lumen-intima echo of the far wall. The mean values of the IMT and lumen diameter within each 10-mm-long section were calculated unless presence of plaques was observed in the region of interest, in which case the measurements of the IMT were abandoned. Carotid plaque was defined as a localized intima-media thickening of >1 mm and at least a 100% increase in thickness compared with adjacent wall segments. To compensate for the stretching effect of arterial distension (secondary to increased arterial pressure) on the wall thickness, the cross-sectional intima-media area (cIMA) was calculated by using the formula [lumen diameter/2 + IMT]² – [lumen diameter/2]². The differences between repeated measurements of IMT and lumen diameter, using the automated analyzing system, were 3.2% and 0.6% (coefficient of variation), respectively (with IMT of 0.48 to 1.04 mm and a lumen diameter of 4.34 to 7.91 mm).

Statistical Methods
Analysis of variance (ANOVA), χ² tests, and multiple logistic regression analysis with backwards elimination of nonsignificant variables were performed using the SPSS software package, version 13.0 (SPSS Inc). All probability values are 2-tailed, and confidence intervals were calculated at the 95% level.

Results
The demographic data and risk factors of the studied periodontal disease patients and controls are presented in Table 1. As can be seen from Table 1, the study groups did not differ regarding age, gender distribution, and the occurrence of hypertension. There were only 3 patients with diabetes mellitus and all 3 also had periodontal disease. The relative number of individuals with higher education was greater in controls, whereas smoking dominated in the patient group. In addition, significantly more patients with periodontal disease had hereditary risk factors for atherosclerotic disease and these patients had also higher plasma cholesterol levels.

The results of oral examination performed between 2001 and 2003 are presented in Table 2. As can be seen from Table 2, there were statistically highly significant differences between the patients and the controls in all dental
variables considered, indicating a significantly poorer dental status in the patients.

The measured (IMT and lumen diameter) as well as calculated (cIMA) ultrasonographic B-mode variables were significantly greater in the patients than in controls (Table 3) bilaterally. In a multiple logistic regression model for cIMA and IMT, periodontal disease appeared to be a principal independent predictor associated with 5.2-times the odds of increased cIMA (Table 4) and 4.6-times the odds of increased carotid wall thickness (Table 5). Except for male gender, which related significantly to cIMA, and age, which showed weak relationship to both cIMA and IMT, other factors considered in the model exerted no significant independent influence on these 2 variables.

### Discussion

This study addresses the issue of periodontal disease as a risk factor for atherosclerosis by evaluating the relationship between periodontitis and the occurrence of early atherosclerotic changes in carotid arteries in patients without any symptoms of overt atherosclerotic disease. The present results clearly identify periodontal disease as a principal independent predictor of carotid arterial wall thickness and calculated cross-sectional arterial wall area, ie, 2 ultrasonographic measures of preclinical atherosclerosis.

Some comments should be made concerning reliability of the obtained results. First, in this study, the patients and the controls were randomly chosen to avoid selection bias and to ensure normal distribution of the sampled variables. Thus, even if the number of study subjects was limited, the examined group is representative of the ethnically homogenous Swedish adult population. Second, all dental examinations were performed by one and the same experienced dental examiner, whereas dental radiograms were evaluated by another experienced examiner blinded to the results of dental examination. Similarly, carotid sonography was performed and evaluated by the same experienced and blinded sonographer; hence, the methodological bias was minimized. Third, the basically longitudinal prospective design of the present study with a cohort of patients, all of whom had documented periodontitis for at least 16 years at the time of the re-examination, ensures a temporal link associating periodontitis and atherosclerosis in the carotids. Finally, because the randomly selected controls included individuals who presented with different distribution of established atherosclerotic risk factors than that found in the patient population, it can be argued that this might have influenced the obtained results. However, it should not be forgotten in this context that at least one of these factors in the patient group, ie, the higher concentration of total cholesterol, apart from being atherosclerotic

### Table 1. Demographic Data and Risk Factors

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=82)</th>
<th>Controls (n=31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, women/men</td>
<td>41/41</td>
<td>17/14</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>54.3±3.0</td>
<td>53.2±2.8</td>
<td>NS</td>
</tr>
<tr>
<td>Education, compulsory/higher</td>
<td>31/48</td>
<td>3/28</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking, yes/no</td>
<td>31/51</td>
<td>3/28</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.3±4.3</td>
<td>23.5±3.0</td>
<td>NS</td>
</tr>
<tr>
<td>Heredity for atherosclerotic disease, yes/no</td>
<td>38/42</td>
<td>4/26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, yes/no</td>
<td>3/92</td>
<td>0/31</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, yes/no*</td>
<td>19/61</td>
<td>5/31</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma cholesterol, mmol/L</td>
<td>5.9±0.9</td>
<td>5.4±0.7</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* Systolic pressure >140 mm Hg, diastolic pressure >90 mm Hg, or ongoing antihypertensive therapy.

### Table 2. Clinical Oral and Radiographic Data in Patients With Periodontal Disease and Controls on Re-examination Between 2001 and 2003

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=82)</th>
<th>Controls (n=31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of missing teeth</td>
<td>2.7±3.6</td>
<td>0.6±0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of teeth with pocket depth ≥5 mm</td>
<td>7.8±5.8</td>
<td>0.1±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pocket depth, mm</td>
<td>2.8±0.8</td>
<td>1.9±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Loss of attachment, mm</td>
<td>3.6±1.4</td>
<td>2.1±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gingival Index²⁹</td>
<td>1.3±1.0</td>
<td>0.2±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dental Plaque Index²⁹</td>
<td>0.7±0.7</td>
<td>0.2±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentage bleeding on probing</td>
<td>38.0±25.8</td>
<td>15.1±12.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentage of remaining bone on radiographs</td>
<td>84.2±9.5</td>
<td>93.3±1.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
risk factor per se, may be the result of periodontitis-related alteration in lipid metabolism.\textsuperscript{13} In any case, the current statistical analysis was performed with adjustment for several demographic variables and established cardiovascular risk factors, such as age, gender, education, heredity for atherosclerosis, body mass index, diabetes mellitus, hypertension, plasma cholesterol, and smoking; therefore, none of them could confound the observed association between periodontal disease and subsequent development of subclinical atherosclerosis.

Regarding the methodological aspect of the study, it can be emphasized that the B-mode-derived carotid IMT is a well-established variable reflecting early atherosclerosis and its value in the studies of early stages of this disease and various vascular risk factors has been well-documented.\textsuperscript{33,34} However, the thickness of the carotid intima-media complex may vary depending on varying degree of stretching of the arterial wall, the systolic increase of the arterial lumen diameter with the subsequent stretching of the arterial wall resulting in, for example, \(5\%\) to \(7\%\) decrease in the measured IMT.\textsuperscript{35} The same narrowing effect on IMT may occur from age and blood pressure-dependent increase of the arterial lumen or compensatory vasodilatation triggered by atherosclerotic changes of the arterial wall, thus increasing the accuracy of the present ultrasonographic measurements. cIMA has been shown to correlate better with atherosclerotic coronary lesions than IMT.\textsuperscript{36}

The present results add new information to the growing evidence of the association between periodontal disease and atherosclerosis. This evidence has been provided mostly by the results of studies focused on the incidence of clinically overt atherosclerotic cardiovascular disorder such as coronary artery disease and its sequelae\textsuperscript{14–18} or cerebrovascular events\textsuperscript{19–24} in patients with periodontitis. A recently published meta-analysis confirms that periodontal disease appears to be associated with a 19\% increase in risk for future coronary heart disease and stroke.\textsuperscript{37} However, the current results clearly demonstrate that there exists a significant association between periodontal disease and atherosclerotic process already at its early and subclinical stage. In this respect, the obtained results are in accord with the results reported from the dental ARIC study by Beck et al.\textsuperscript{25} The association between periodontitis and the development of subclinical carotid atherosclerosis was, however, stronger in the present study, with periodontal disease being the principal independent predictor of increased carotid arterial intima-media complex. This may be caused by the fact that the patients of Beck et al were \(10\) years older than the patient population examined in this study and the potential effect of at least age, but probably also because other cardiovascular risk factors might be more manifest in the older population. In addition, the definition of periodontal disease in the present and the dental ARIC study was not

### TABLE 3. Ultrasonographic B-Mode Variables

<table>
<thead>
<tr>
<th>Common carotid artery IMT (mm)</th>
<th>Patients (n=78*) Mean±SD</th>
<th>Controls (n=31) Mean±SD</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right side</td>
<td>0.66±0.12</td>
<td>0.58±0.09</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Left side</td>
<td>0.68±0.12</td>
<td>0.58±0.08</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Common carotid artery lumen (mm)</th>
<th>Patients (n=78*) Mean±SD</th>
<th>Controls (n=31) Mean±SD</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right side</td>
<td>6.00±0.63</td>
<td>5.65±0.53</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Left side</td>
<td>5.87±0.64</td>
<td>5.56±0.41</td>
<td>=0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Common carotid artery cIMA (mm(^2))</th>
<th>Patients (n=78*) Mean±SD</th>
<th>Controls (n=31) Mean±SD</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right side</td>
<td>13.80±3.56</td>
<td>11.40±2.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left side</td>
<td>14.20±3.47</td>
<td>11.10±1.90</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\*In 4 cases, measurements of the B-mode variables listed in the Table could not be successfully performed because of a local plaque formation or other technical reasons.

### TABLE 4. The Results of Multiple Logistic Regression Analysis of the Relationship Between Common Carotid Artery cIMA (Bilaterally) as a Dependent Variable and Several Independent Variables (Periodontal Disease, Age, Gender, BMI, Heredity for Atherosclerotic Disease, Hypertension, Diabetes Mellitus, Plasma Cholesterol, Smoking, Education)

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Explaining Variable</th>
<th>(\beta)</th>
<th>(\chi^2)</th>
<th>(P)</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common carotid artery cIMA (bilaterally)</td>
<td>Periodontal disease</td>
<td>1.65</td>
<td>8.59</td>
<td>0.003</td>
<td>5.20</td>
<td>1.73–15.67</td>
</tr>
<tr>
<td></td>
<td>Gender (male)</td>
<td>1.39</td>
<td>8.34</td>
<td>0.004</td>
<td>4.00</td>
<td>1.50–10.31</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.21</td>
<td>6.43</td>
<td>0.01</td>
<td>1.24</td>
<td>1.05–1.50</td>
</tr>
</tbody>
</table>

BMI indicates body mass index.
entirely similar and the structural vascular wall changes reflected by carotid IMT seem to have been more pronounced in the patients of Beck et al, with the latter fact increasing the possibility of a significant contribution of other well-established risk factors in the process of carotid atherosclerosis. However, the difference and, at the same time, important advantage of the present study as compared with the cross-sectional study of Beck et al lies in its prospective nature, that is to say the currently studied patients having been exposed to periodontitis for at least 16 years before re-examination. The correct time sequence and the strength of the observed association suggest for the first time to our knowledge a causal link between periodontal disease and atherosclerotic process already in its early phase. This may create a basis for prophylactic measures that, in the view of prevalence of atherosclerotic disease and the costs it incurs to the society, appear to be highly motivated.

Acknowledgments

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