Dental and Periodontal Status and Risk for Progression of Carotid Atherosclerosis

The Inflammation and Carotid Artery Risk for Atherosclerosis Study Dental Substudy

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**Background and Purpose**—Dental and periodontal disease are potentially involved in the pathogenesis of atherosclerosis. We investigated whether dental and periodontal status is associated with the presence and future progression of carotid stenosis.

**Methods**—We randomly selected 411 of 1268 participants from the prospective Inflammation and Carotid Artery Risk for Atherosclerosis Study and evaluated dental and periodontal status and oral hygiene at baseline measuring three World Health Organization-validated indices: DMFT (decayed, missing, filled teeth), SLI (Silness-Löe Index), and CPITN (community periodontal index for treatment needs), respectively. The degree of carotid stenosis was measured by duplex ultrasound at baseline and after median 7.5 months (range 6 to 9 months) to identify patients with progressive carotid stenosis.

**Results**—DMFT ($P=0.01$), SLI ($P=0.048$), CPITN ($P=0.007$), and edentulousness ($P=0.007$) were associated with the baseline degree of carotid stenosis. Atherosclerosis progression was observed in 48 of 411 patients (11.7%). DMFT (adjusted odds ratio [OR] = 1.11, 95% CI = 1.01 to 1.22, $P=0.032$) and SLI (adjusted OR = 1.77, 95% CI = 1.09 to 2.79, $P=0.021$), but not CPITN (adjusted OR = 1.51, 95% CI = 0.89 to 2.45, $P=0.16$) were significant predictors of disease progression, irrespective of traditional cardiovascular risk factors and the baseline degree of stenosis. Edentulous patients had a significantly increased risk for disease progression as compared with patients with teeth (adjusted OR = 2.10, 95% CI = 1.06 to 4.16, $P=0.33$).

**Conclusion**—Dental status, oral hygiene, and particularly tooth loss are associated with the degree of carotid stenosis and predict future progression of the disease. *(Stroke. 2006;37:2271-2276.)*

Key Words: atherosclerosis ■ carotid ■ dental ■ periodontal ■ plaque
utive patients who underwent duplex ultrasound investigations of the extracranial carotid arteries from March 2002 until March 2003 at our institution and who were neurologically asymptomatic with respect to carotid obstructions defined as absence of ipsilateral cerebrovascular events for at least 12 months before inclusion. Exclusion criteria were symptomatic carotid artery disease necessitating revascularization therapy, current infectious or inflammatory diseases, recent operations or endovascular interventions (within 14 days), patients with bilateral carotid occlusions, bilateral stent implantation, or bilateral carotid endarterectomy.

In the current study, we aimed to directly evaluate clinically relevant progression of atherosclerotic stenosis instead of measuring surrogate markers of carotid disease (like intima-media thickness). The main indications for performing carotid ultrasound investigations were carotid bruits, known atherosclerotic disease in other vessel areas (coronary or peripheral artery disease), and patients scheduled for major cardiac surgery, thus meeting the requirements of a study population of patients likely to exhibit carotid atherosclerosis and potentially progression of disease.

ICARAS Dental Substudy
We enrolled 1363 eligible patients in the ICARAS protocol. Of these, 95 patients (7%) had to be excluded as a result of missing duplex-ultrasound follow-up data (28 deaths; 67 refused the repeated duplex ultrasound investigation), leaving 1268 patients for the final ICARAS analysis. Of these, we randomly selected 450 patients for inclusion in the dental substudy using computer-generated random digits; 411 (91%) followed the invitation to participate and were included. Baseline demographic data and clinical characteristics of these 411 patients as compared with the entire ICARAS study population of 1268 participants are given in Table 1.

**Study End Point**
Study end point was uni- or bilateral progression of carotid atherosclerosis in the extracranial internal carotid arteries from baseline...
to a follow-up investigation after 6 to 9 months. We used the following categories to quantify the degree of internal carotid artery stenosis at baseline and follow up: 0% to 29%, 30% to 49%, 50% to 69%, 70% to 89%, 90% to 99%, and 100%. Progression of atherosclerotic disease was defined as an increase of the degree stenosis by at least one category. Progression of stenosis in either one or both internal carotid arteries was considered as indicative of progressive disease.

As a secondary objective, biomarkers of inflammation (high-sensitivity C-reactive protein, serum amyloid A, fibrinogen) were measured at baseline and follow up as reported previously and were correlated with the indices of dental and periodontal disease.

Color-Coded Duplex Sonography and Grading of Internal Carotid Artery Stenosis

The protocol for baseline and follow-up ultrasound investigations has been reported. In summary, duplex grading of the carotid stenosis was done by measurement of the peak-systolic and end-diastolic velocities in the internal and common carotid arteries by investigators blind to clinical data and dental indices. The accuracy of ultrasound compared with angiography was assessed previously in our laboratory in 1006 carotid arteries. Predictive values ranged from 70% to 98%, and interobserver agreement was excellent with respect to the absolute degree of stenosis (κ=0.83, 95% CI=0.79 to 0.88) as well as with respect to progression of the disease (κ=0.85, 95% CI=0.80 to 0.89).

Dental Status

Four specifically trained dentists performed all dental examinations; dentists were blind to all clinical and ultrasound data. All patients were investigated by two observers in consensus. We prospectively selected three World Health Organization-approved dental indices to quantify dental disease: DMFT (decayed, missing, filled teeth) as a measure of dental status, SLI (Silness-Löe plaque index) as a measure of oral hygiene and dental plaque, and CPITN (community periodontal index of treatment needs) as a surrogate marker of periodontal disease.

DMFT describes dental status and the amount of dental caries in an individual as a means to numerically express the caries prevalence. The score is obtained by calculating the number of decayed (D), missing (M), and filled (F) teeth (T). We calculated DMFT for 32 teeth.

SLI is the measurement of the state of oral hygiene by the SLI index is based on recording both soft and mineralized deposits on teeth 12, 16, 24, 36, and 44. Each of the surfaces (buccal, lingual, mesial, and distal) is given a score from 0 (no plaque) to 3 (abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin). The index for the patient is obtained by calculating the mean for all investigated teeth and surfaces. In patients with complete edentulosity, SLI was obtained from the patients as a separate category, we found that edentulous patients had a significantly increased risk for progressive disease (ad-
justed OR = 2.69, 95% CI = 1.62 to 4.17, \( P = 0.046 \) as compared with patients with a CPITN between 1 and 2 (normal).

Similarly, edentulous patients had a significantly increased risk for disease progression as compared with patients with their own teeth irrespective of the CPITN score (adjusted OR = 2.10, 95% CI = 1.06 to 4.16, \( P = 0.046 \) ) as compared with patients with a CPITN between 1 and 2 (normal).

Similarly, edentulous patients had a significantly increased risk for disease progression as compared with patients with their own teeth irrespective of the CPITN score (adjusted OR = 2.10, 95% CI = 1.06 to 4.16, \( P = 0.33 \)).

**Inflammation**

Baseline/follow-up levels for high-sensitivity C-reactive protein (hs-CRP) were 2.5 (IQR = 1.1 to 5.5)/2.2 (IQR = 10 to 0.43) mg/L; for serum amyloid A were 6.0 (IQR = 3.8 to 10.6)/5.2 (IQR = 3.8 to 8.6) mg/L; and for fibrinogen were 376 (IQR = 328 to 429)/376 (IQR = 336 to 436) mg/dL, respectively. None of the dental indices was significantly associated with hs-CRP, serum amyloid A, and fibrinogen levels at baseline or follow up in univariate analysis (Spearman all \( P > 0.1 \)). To further assess a potential association between inflammation and dental indices, acute-phase parameters (in quartiles) were entered into the fully adjusted multivariable logistic regression models showing a significant association with disease progression, eg, adjusted ORs for the risk of disease progression for increasing quartiles of hs-CRP were 1.42, 2.41, and 2.97 as compared with the lowest quartile (\( P = 0.025 \)). However, the effect sizes of DMFT, SLI, and CPITN remained unchanged (data not shown).

**Prolonged Follow Up**

Being aware of the limitations of a short-term follow-up period, we performed a second follow-up investigation in a subset of 345 of 450 patients after median 11.7 months (range = 10.5 to 14 months) observing disease progression in 53 of 345 patients (15%). Adjusted ORs for disease progression for DMFT (1.14, 95% CI = 1.01 to 1.32, \( P = 0.048 \)), SLI (1.92, 95% CI = 1.04 to 3.05, \( P = 0.038 \)), CPITN (1.42, 95% CI = 0.81 to 2.92, \( P = 0.21 \)), and edentulousness (2.55, 95% CI = 1.57 to 4.35, \( P = 0.052 \)) were comparable as in the 7.5-month sample.

**Discussion**

We found that dental and periodontal disease was significantly associated with progression of carotid atherosclerosis. DMFT, as a measure of global teeth status, and SLI, an indicator of dental plaque, were predictors of prevalent and
TABLE 2. Multivariable Logistic Regression Analysis Assessing the Risk for Progression of Atherosclerotic Lesions Measured by Duplex Ultrasound in the Carotid Arteries of 411 Patients From Baseline to Follow Up (median=5 months, range=6 to 9 months)

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMFT index</td>
<td>1.11</td>
<td>1.01 to 1.22</td>
<td>0.032</td>
</tr>
<tr>
<td>SLI index</td>
<td>1.77</td>
<td>1.09 to 2.88</td>
<td>0.021</td>
</tr>
<tr>
<td>CPITN index</td>
<td>1.51</td>
<td>0.89 to 2.45</td>
<td>0.16</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.00</td>
<td>0.97 to 1.04</td>
<td>0.68</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.85</td>
<td>0.43 to 1.70</td>
<td>0.64</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>1.02</td>
<td>0.96 to 1.10</td>
<td>0.58</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>1.10</td>
<td>0.53 to 2.27</td>
<td>0.80</td>
</tr>
<tr>
<td>Present smoking</td>
<td>1.10</td>
<td>0.59 to 2.45</td>
<td>0.74</td>
</tr>
<tr>
<td>Former smoking</td>
<td>1.03</td>
<td>0.22 to 1.69</td>
<td>0.92</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.06</td>
<td>0.42 to 2.64</td>
<td>0.90</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.21</td>
<td>0.59 to 2.34</td>
<td>0.38</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>1.34</td>
<td>0.65 to 2.77</td>
<td>0.43</td>
</tr>
<tr>
<td>History of stroke</td>
<td>2.32</td>
<td>1.04 to 5.21</td>
<td>0.041</td>
</tr>
<tr>
<td>Baseline degree of stenosis</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>0% to 29%</td>
<td>1.0</td>
<td>. . .</td>
<td></td>
</tr>
<tr>
<td>30% to 49%</td>
<td>0.93</td>
<td>0.18 to 4.88</td>
<td></td>
</tr>
<tr>
<td>50% to 69%</td>
<td>2.99</td>
<td>0.58 to 17.0</td>
<td></td>
</tr>
<tr>
<td>70% and above</td>
<td>4.56</td>
<td>1.05 to 25.7</td>
<td></td>
</tr>
<tr>
<td>Statin treatment</td>
<td>0.75</td>
<td>0.32 to 1.78</td>
<td>0.52</td>
</tr>
</tbody>
</table>

progressive disease. CPITN, a marker of periodontitis, was not associated with progressive disease; however, this likely was confounded by the impact of missing teeth in the study population.

There are several possible explanations for the association between dental and periodontal disease and development and progression of atherosclerosis. First, it may merely reflect confounding by traditional risk factors such as smoking, obesity, or diabetes, which are equally important determinants for both dental and vascular diseases. Furthermore, unmeasured confounders like socioeconomic aspects may substantially modify the observed associations. We tried to account for these problems by statistical adjustment for traditional risk factors without detecting relevant effect modifications. Second, dental disease and atherosclerosis may reflect the individual’s susceptibility to develop a disease in response to specific endogenous or exogenous stimuli. In this context, the individual’s propensity to develop an exuberant inflammatory reaction was considered particularly important.2 Third, inflammation in the periodontal tissue may exaggerate an inflammatory vascular disease, thus promoting the progression of atherosclerosis; although in the present study, dental indices were not associated with baseline and follow-up levels of inflammatory biomarkers, a significant correlation between inflammation and progressive disease has been demonstrated.11,12 Fourth, the infectious theory may hold true when transient bacteremia from periodontal foci leads to inoculation of pathogens in atherosclerotic plaques. It remains uncertain whether an immune response to pathogens or the pathogen itself triggers progression of atherosclerotic disease.14,15 Unfortunately, pathogen levels or immune response to pathogens were not available in these patients.

The association between DMFT and atherosclerosis mainly relied on the positive association between the number of missing teeth and progressive disease, whereas the number of decayed or filled teeth showed no significant associations. It was reported previously in patients with cardiovascular morbidities that tooth loss is a marker of periodontal disease and that tooth loss is related to prevalence of carotid plaque.19 We confirm this observation in the present study and found that edentulousness was a significant predictor not only of prevalent, but also of progressive carotid stenosis. Putting these findings together, it seems that missing teeth resulting from advanced periodontal disease rather than as a result of destructive caries are associated with atherosclerosis progression. Treated caries, as suggested previously,16 does not seem to play a major role in promoting atherosclerosis.

The SLI index showed a significant association with prevalent and progressive carotid atherosclerosis. The development of dental and arterial plaque may partly share common pathophysiological features. It remains to be investigated whether interventions targeting oral hygiene may also beneficially affect the prevalence of atherosclerotic disease.

Infectious periodontitis, a trigger for systemic inflammation, was previously suggested to correlate with carotid intima media thickness, a surrogate marker of atherosclerosis. However, in the present study, the CPITN index as a measure of the degree of periodontitis was not significantly associated with future disease progression. Consistent with our observation, the Atherosclerosis Risk in the Communities Study previously demonstrated no significant association between clinical signs of periodontal disease and coronary artery calcification.17 However, in the present study, this lack of association may have been confounded by the impact of missing teeth; severe periodontitis likely was a major determinant for tooth loss in these patients15 and the most severely diseased patients therefore may have been missed by the CPITN.

Limitations

We only investigated clinical measures of dental and periodontal disease. Microbiologic aspects and the importance of infectious markers of periodontal disease, which have been demonstrated to be more specific than clinical signs of periodontitis,14,15 have not been covered in this study. With respect to caries, we have only measured DMFT, which is weakened by the fact that missing teeth might be either the result of caries or periodontitis, which cannot be differentiated by this index. For evaluation of periodontal disease, the CPITN index was used as recommended by the World Health Organization; however, a complete periodontal status of all patients was reported previously in patients with cardiovascular morbidities that tooth loss is a marker of periodontal disease and that tooth loss is related to prevalence of carotid plaque.19 We confirm this observation in the present study and found that edentulousness was a significant predictor not only of prevalent, but also of progressive carotid stenosis. Putting these findings together, it seems that missing teeth resulting from advanced periodontal disease rather than as a result of destructive caries are associated with atherosclerosis progression. Treated caries, as suggested previously,16 does not seem to play a major role in promoting atherosclerosis.

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Furthermore, specific limitations of the applied indices have to be recognized. DMFT has been suggested to be less suitable for populations with high levels of caries,18 which seems not relevant for the present population. The accuracy of the SLI is mainly limited by a lack of sensitivity for milder forms of inflammation and by the necessity to perform
probing. Finally, CPITN is generated as a measure from different clinical indicators (inflammation, calculus, pockets), which may be better recorded separately, and very severe stages of periodontitis may be underestimated (like total loss of attachment) or even missed (like edentulous patients) by this index.

**Conclusion**

Dental status, oral hygiene, and particularly tooth loss are associated with the degree of carotid stenosis and predict future progression of the disease.

**References**


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