Oral Health and Peripheral Arterial Disease

Hsin-Chia Hung, DDS, DrPH; Walter Willett, MD, DrPH; Anwar Merchant, DMD, DrPH; Bernard A. Rosner, PhD; Alberto Ascherio, MD, DrPH; Kaumudi J. Joshipura, ScD

**Background**—Many studies have reported the association between poor oral health and coronary heart disease or stroke, but few of them evaluated peripheral arterial disease (PAD). Hence, in this study we examined the associations between oral health and PAD.

**Methods and Results**—In the prospective study of 45 136 eligible male health professionals free of cardiovascular diseases at baseline, we identified 342 cases of PAD during a 12-year follow-up period. We evaluated the association between different measures of oral diseases and the occurrence of PAD. Baseline number of teeth was not related to the risk of PAD, but cumulative incident tooth loss was significantly associated with elevated risk of subsequent occurrence of PAD. The relative risk for history of periodontal disease was 1.41 (95% CI, 1.12 to 1.77) and for any tooth loss during the follow-up period was 1.39 (95% CI, 1.07 to 1.82), controlling for traditional risk factors of cardiovascular disease. Among men with a history of periodontal diseases, the relative risk of tooth loss increased to 1.88 (95% CI, 1.27 to 2.77), whereas no association was found between tooth loss and PAD among those without periodontal diseases (RR, 0.92; 95% CI, 0.61 to 1.38). We further explored the potential induction period of tooth loss and found that tooth loss in the previous 2 to 6 years was most strongly associated with PAD.

**Conclusions**—We found that incident tooth loss was significantly associated with PAD, especially among men with periodontal diseases. The results support a potential oral infection–inflammation pathway. *(Circulation. 2003;107: 984–990.)*

**Key Words:** peripheral vascular disease ■ infection ■ periodontitis ■ tooth loss

Several studies have reported that people with periodontal disease or with few or no teeth experience an elevated risk of cardiovascular diseases (CVD), even though control of confounders may have been incomplete in several studies. Because of the high prevalence of tooth loss, these findings could have a significant public health impact.

Chronic infection with inflammation and change in diet have been proposed as 2 pathways linking tooth loss and CVD. Peripheral arterial disease (PAD) of the legs is a state of insufficient tissue perfusion to meet metabolic demand. The most common symptom, intermittent claudication, which is defined as pain felt during walking or other exercise, is caused by insufficient blood supply caused by increased metabolic demand. When tissue perfusion is not enough to meet the demand at rest, revascularization is necessary to avoid tissue loss. PAD shares a common underlying pathological change, atherosclerosis, with coronary heart diseases and stroke. However, only 1 study of dental diseases has focused on PAD. In the Veteran Affairs Dental Longitudinal Study of 1030 subject followed up for 25 to 30 years, Mendez et al3 reported that those with clinically significant periodontal disease at baseline had a relative risk of 2.27 (95% CI, 1.32 to 3.9).

Baseline number of teeth and incident tooth loss are both good indicators of oral health status. Baseline number of teeth represents tooth loss at various time points in the past, including the distant past, and has a wider range (0–32) than incident tooth loss during follow-up, hence, it is more likely to be associated with diet (Figure). Incident tooth loss probably reflects the dynamic oral health status and periodontal disease closer to the follow-up period and hence may be more closely associated with inflammatory mediators. We evaluated the associations between tooth loss and PAD in the Health Professionals Follow-up Study. We also examined the association between history of periodontal disease and PAD and further explored the relative importance of the diet and inflammation pathways by comparing the strength of the relationships between baseline number of teeth and incident tooth loss with occurrence of PAD and by evaluating the tooth loss–PAD association among men with and without periodontal disease.
Pathways for the relationship between incident tooth loss and number of remaining teeth at baseline and PAD. Solid arrow indicates association; dotted arrow, weak association.

**Methods**

**Study Population**

The Health Professionals Follow-up Study is a prospective cohort of 51,529 male health professionals 40 to 75 years of age, including 29,683 dentists. Initiated in 1986, the study required participants to complete detailed mailed questionnaires that included a comprehensive diet survey, questions on lifestyle practices, and a medical history. After 1986, we mailed the follow-up questionnaires every 2 years to update information on potential risk factors and medical history. After 1986, we mailed the follow-up questionnaires every 2 years to update information on potential risk factors and medical conditions.

We excluded 1595 men who reported daily energy intake outside the plausible range of 3360 to 17,640 kJ/d or who left ≥70 of the 131 dietary questions blank in 1986. We further excluded 4840 men who reported intermittent claudication, myocardial infarction, angina, stroke, coronary artery bypass grafting, or angioplasty and those with no information on remaining number of teeth on the 1986 questionnaire. The total number of eligible men in the analysis was 45,094. We received questionnaires from or confirmed the deaths of >94% of eligible participants. Remaining nonrespondents not listed in the National Death Index were assumed to be alive.

**Assessment of PAD**

Participants who reported intermittent claudication or surgery for arterial diseases of the leg in the biennial follow-up questionnaires from 1988 to 1998 were mailed a letter to confirm their self-reported PAD status and request permission to obtain the medical record. For those participants whose medical records were obtained, we verified the diagnosis on the basis of these criteria: (1) ankle-brachial systolic pressure index <0.80, (2) medical or surgical treatment for PAD, (3) angiogram or Doppler ultrasonic reports of >50% narrowing of the femoral or popliteal arteries, or (4) reported symptoms and positive diagnosis made by physicians. If any of the above were documented, we confirmed this as a definite PAD case. For participants whose medical records we were unable to obtain, diseases were verified on the basis of their reply to the confirmation letter or through telephone contact. If they confirmed their PAD diagnosis, we considered them as probable PAD cases.

**Assessment of Tooth Loss and Periodontal Disease**

The questions on remaining number of teeth and history of periodontal disease were asked in 1986. Starting in 1988, participants reported the number of teeth lost and periodontal disease diagnosed in the previous 2 years on biennial questionnaires; we assumed that a missing value on incident tooth loss was zero lost teeth, because fewer than 10% of participants experienced tooth loss every 2 years.

The validity of self-reported periodontal disease with bone loss was described in 2 previous reports, and the results were good compared with x-ray diagnosis. Self-reported number of teeth was highly correlated with the actual number of teeth on clinical examination in a general population (correlation coefficient, 0.97). There is no validation study of self-reported incident tooth loss, but we expect this to be well reported, especially in our population of health professionals.

**Data Analysis**

We recorded 342 cases of PAD (255 definite and 87 probable cases) during the follow-up period, from the date of returning 1986 questionnaires to the diagnosis of PAD, death, or January 31, 1998, whichever came first. Men who reported PAD events or who were deceased were excluded from subsequent follow-up. Thus, each participant could contribute only 1 end point, and the cohort at risk included only those free of PAD.

For the analysis of baseline number of teeth, men with 25 to 32 teeth constituted the referent group to compute the RRs of PAD for men with 0 to 10, 11 to 16, and 17 to 24 teeth. To evaluate the association between periodontal disease and PAD, we compared the risk of developing PAD in subsequent follow-up among those who reported a history of periodontal disease with those who did not report any history of periodontal disease using the data from 1986 as well as updated information. For the analysis of incident tooth loss, we further excluded edentulous participants in 1986, because they could not lose teeth during the follow-up period. For this analysis, we were able to use only data from 1988 to 1998, during which time 294 PAD cases occurred. Because we started the questions on the number of teeth lost in 1988. Different approaches for analyzing the associati were performed. (1) We used tooth loss in the previous 2 years to predict the occurrence of PAD in the subsequent 2 years. Those reporting at least 1 tooth lost were counted as exposed. (2) We evaluated the association between cumulative incident tooth loss and the PAD. Those with any incidence of tooth loss from 1986 onward were defined as the exposed group in all subsequent follow-up to compare against those without tooth loss for risk of developing PAD. (3) To explore the induction period between tooth loss and PAD in the subsequent 2-year follow-up period, we used tooth loss in the previous 0 to 2, 2 to 4, 4 to 6, and 6 to 8 years to predict the occurrence of PAD. For example, in the model using tooth loss in the previous 2 to 4 years to test the induction period of 2 years, we used tooth loss from 1986 to 1988 and 1988 to 1990 to predict the occurrence of PAD in 1990 to 1992 and 1992 to 1994, respectively, and for a model of tooth loss in the previous 4 to 6 years to test the induction period of 4 years, we used tooth loss in 1986 to 1988 and 1988 to 1990 to predict the incidence of PAD in 1992 to 1994 and 1994 to 1996.

In the multivariate model, we adjusted for age (5-year categories); smoking (never, former, current, 1 to 14, 15 to 24, and ≥25 cigarettes per day); alcohol consumption (5 categories); BMI (5 categories); physical activity (quintiles); family history of myocardial infarction; multivitamin supplement use; vitamin E use; history of hypertension, diabetes, and hypercholesterolemia; and profession (dentists or nondentists). For the analyses of incident tooth loss, we also adjusted for remaining number of teeth in 1986. These variables were updated on the basis of the biennial questionnaires, and we used Cox proportional hazards models with time-dependent variables to conduct these analyses.
Results

Table 1 presents the means of the age-adjusted traditional CVD risk factors, periodontal diseases, and cumulative incident tooth loss by categories of baseline number of teeth. Those with smaller numbers of teeth appeared to have worse profiles of CVD risk factors. After adjustment for age, men with 0 to 10 baseline number of teeth had the lowest mean physical activity (17.0 Met/wk) and the highest percentage of current smoking (21.3%) and hypertension (22.9%). Men with intermediate numbers of teeth (11 to 16 and 17 to 24) had higher rates of new periodontal diseases and incident tooth loss than those with ≥25 teeth and 0 to 10 teeth.

Table 2 presents the associations between baseline number of teeth, incident tooth loss, and periodontal diseases and incidence of PAD. Baseline number of teeth was not significantly associated with PAD.

Men with incident tooth loss in the previous 2 years had a relative risk of 1.08 (95% CI, 0.78 to 1.51) for PAD in the subsequent 2 years in the multivariate-adjusted model. Men with any tooth loss since 1986, compared with those without any tooth loss, had a significantly higher RR of 1.51 (95% CI, 1.16 to 1.97) for PAD after adjustment for age and smoking. After adjustment for other traditional CVD risk factors, the RR still remained significant in this model (RR, 1.39; 95% CI, 1.07 to 1.82). When further adjusted for baseline and newly diagnosed periodontal disease, the RR was slightly attenuated to 1.32 but still statistically significant. The multivariate-adjusted RR for updated history of periodontal disease and PAD was 1.41 (95% CI, 1.12 to 1.77) and for baseline history, 1.32 (95% CI, 1.03 to 1.68). When we used only definite PAD cases instead of all PAD cases, the RRs increased from 1.41 to 1.48 for updated history of periodontal diseases, remained 1.32 for baseline history of periodontal diseases, and decreased from 1.39 to 1.30 for cumulative incidence of tooth loss, but their 95% CIs overlapped substantially. Thus, there was no consistent bias toward the null by including probable cases. In the multivariate analyses of subsets of data for 1990 to 1998, 1992 to 1998, and 1994 to 1998, adjusting for tooth loss in other time periods, we found that tooth loss in the previous 2 to 4 and 4 to 6 years seemed to be more related to PAD than was tooth loss in recent or distant 2-year periods (Table 3). However, most of these associations were not statistically significant.

We conducted the analyses relating periodontal disease with PAD separately among subgroups of people classified into 2 groups according to factors such as diabetes history and multivitamin use (Table 4). We found that the association between history of periodontal disease and incidence of PAD varied by multivitamin use, aspirin use, current smoking status, history of diabetes, age, and dental profession, although tests for interaction were not statistically significant.
Similar analyses were conducted and similar findings were seen for cumulative tooth loss. There was a stronger association between tooth loss and PAD among men with a history of periodontal diseases. Cumulative incident tooth loss had an RR of 1.88 (95% CI, 1.27 to 2.77) for PAD among men with periodontal diseases and an RR of 0.92 (95% CI, 0.61 to 1.38) among those without periodontal diseases. The P value for the test for interaction between tooth loss and periodontal disease was 0.09.

**Discussion**

In this study, men with a history of periodontal diseases or with any tooth loss during follow-up had a significantly higher risk of PAD than men without any periodontitis or without any tooth loss, but there was no apparent association between number of teeth at baseline and PAD.

The Figure describes potential mechanisms through which tooth loss and periodontal disease could be associated with PAD. Tooth loss could affect chewing ability, leading to altered diet, which could affect PAD risk. Alternatively, periodontal disease could result in an increased inflammatory response and consequently increased PAD risk. Periodontal disease could also be the cause of tooth loss. Periodontal disease is the principal reason for extraction after age 40 years.16–19

We assessed tooth loss at baseline and during follow-up in this prospective study. The baseline measure of tooth loss would probably exert an effect by causing a change in diet. Moreover, if teeth were missing at baseline, they were no longer at risk of periodontal infection contributing to inflammation. Baseline tooth loss was not associated with PAD risk in this study, indicating that altered diet as a result of tooth loss probably did not explain PAD risk in this population.

Conversely, a history of periodontal disease and incident tooth loss were significantly associated with PAD risk in this cohort. Because the most common cause of tooth loss in older adults is periodontal disease, incident tooth loss partly reflects antecedent periodontal disease. These findings suggest that the association between periodontal disease and incident tooth loss and PAD is probably mediated via the oral infection—inflammation pathway. Alternatively, a common risk factor such as genetic predisposition to inflammation (proinflammatory trait) leading to increased risk of periodontal disease and atherosclerosis might also explain the association.7,12,17

Tooth loss and atherosclerosis share several common risk factors, which could be partially responsible for the association between tooth loss and PAD.12,17 In this study, we adjusted for these common risk factors, and the homogeneity in socioeconomic status and health-related behavior among these health professionals would further minimize the effect from other unmeasured factors. Hence, the results are unlikely to be explained by the confounding effects from these common risk factors.

Until now, most prospective studies used only baseline measurements of oral diseases, which could be predictors of additional oral diseases during follow-up and hence might be associated with subsequent CVDs. However, the association between baseline oral diseases and CVD is likely to be attenuated over an extended follow-up period unless diet is the primary mediator, because oral health is dynamic and can change naturally or be modified through treatment and behavior modification. Although the differences are small and could be caused by chance, our finding that the relative risk of updated history of periodontal disease (RR, 1.41; 95% CI, 1.27 to 1.77) on PAD was slightly higher than baseline history (RR, 1.32; 95% CI, 1.03 to 1.68) suggests that it might be important to consider updated measurements on oral health in studies with a long follow-up period. Mendez et al18 reported an RR of 2.27 between baseline periodontal disease and PAD, which is higher than the association in our study.

One explanation for this difference could be the difference in populations, a relatively high and homogeneous socioeconomic status in our study compared with a population of

**TABLE 3. Multivariate-Adjusted RR (95% CI) for Incident Tooth Loss and History of Periodontal Disease to Predict the Occurrence of PADs in Different Time Periods**

<table>
<thead>
<tr>
<th>Cases in 1990–1998 (n=245)</th>
<th>Tooth Loss in Previous 2 Years</th>
<th>Tooth Loss in Previous 2–4 Years</th>
<th>Tooth Loss in Previous 4–6 Years</th>
<th>Tooth Loss in Previous 6–8 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.47</td>
<td>(1.05–2.07)</td>
<td>0.95* (0.62–1.45)</td>
<td>1.49* (1.05–2.12)</td>
</tr>
<tr>
<td>Cases in 1992–1998 (n=198)</td>
<td>1.43</td>
<td>(0.97–2.12)</td>
<td>0.93* (0.58–1.49)</td>
<td>1.42* (0.95–2.11)</td>
</tr>
<tr>
<td></td>
<td>1.35</td>
<td></td>
<td>0.68* (0.34–1.37)</td>
<td>1.34* (0.83–2.19)</td>
</tr>
<tr>
<td>Cases in 1994–1998 (n=134)</td>
<td></td>
<td></td>
<td>1.35</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.82–2.24</td>
<td></td>
</tr>
</tbody>
</table>

The multivariate model includes age, smoking amount, alcohol consumption, BMI, physical activity, family history of myocardial infarction, multivitamin supplement use, vitamin E use, history of hypertension, diabetes, hypercholesterolemia, and profession.

*RR additionally adjusted for tooth loss in other 2-year periods.
veterans in their study. Second, the use of a self-reported history of periodontal disease in our study compared with radiographs in their study to measure the severity of periodontal disease might explain the smaller relative risks in our study.

We found an association between cumulative tooth loss and PAD but no association between PAD and tooth loss in recent 2-year periods. We further explored the potential induction periods for incident tooth loss and found that tooth loss in the previous 2 to 6 years was more strongly associated with PAD than tooth loss in the previous 2 years or 6 to 8 years. The association between tooth loss and PAD was somewhat lower after 6 years, suggesting that 6 years may be too distant and 2 years may be too recent for tooth loss to have an impact on PAD. Alternatively, it is possible that these differences may be chance findings; hence the need for future studies with repeated measurements of oral diseases. Such studies are necessary to understand the clinical effect of dynamic oral diseases on systemic diseases and the potential effect of treating oral diseases in reducing the risk of CVD.

In conclusion, we found that incident tooth loss was significantly associated with PAD, especially among men with periodontal diseases. Periodontal disease was also independently associated with PAD. The results support a potential oral infection–inflammation pathway for PAD. However, further studies using updated information on oral health are needed to corroborate our findings.

**Acknowledgments**

This research was supported by National Institutes of Health grants DE-12102, CA-55075, and HL-35464 and the Office of Dietary Supplements.

**TABLE 4. Stratified Multivariate-Adjusted RR (95% CI) of PADs According to History of Periodontal Disease and Cumulative Tooth Loss**

<table>
<thead>
<tr>
<th>Stratified Variables</th>
<th>Updated History of Periodontal Disease* (Reference = No Periodontal Disease)</th>
<th>Cumulative Tooth Loss† (Reference = No Tooth Loss During Follow-Up)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of PAD Cases</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Periodontal diseases</td>
<td>Yes</td>
<td>119</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>127</td>
</tr>
<tr>
<td>Multivitamin use</td>
<td>Yes</td>
<td>142</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>133</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>Yes</td>
<td>112</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>230</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Yes</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>280</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>201</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>141</td>
</tr>
<tr>
<td>Dentist</td>
<td>Yes</td>
<td>204</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>138</td>
</tr>
<tr>
<td>Age, y</td>
<td>≤ 60</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>&gt; 60</td>
<td>276</td>
</tr>
<tr>
<td>Smoking</td>
<td>Ever</td>
<td>263</td>
</tr>
<tr>
<td></td>
<td>Never</td>
<td>79</td>
</tr>
</tbody>
</table>

The multivariate model includes age, smoking amount, alcohol consumption, BMI, physical activity, family history of myocardial infarction, multivitamin supplement use, vitamin E use, history of hypertension, diabetes, hypercholesterolemia, and profession except the stratified variables.

*Data from 1986 to 1998.
†Data from 1988 to 1998 and additionally adjusted for No. of teeth at baseline.
‡RR comparing PAD risk between men with and without periodontal disease among multivitamin supplement users.
§RR comparing PAD risk between men with and without tooth loss during follow-up among men who reported periodontal disease at baseline.

iMen who did not take multivitamins or any other supplements.
References

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Circulation. published online February 10, 2003;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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