Gender Differences in the Relationship Between Periodontal Disease, Tooth Loss, and Atherosclerosis

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Background and Purpose—Males carry a disproportionate burden of cardiovascular disease. Because males also bear a higher burden of periodontal disease, we investigated the existence of gender differences in the postulated relationship between periodontal infections, tooth loss, and subclinical atherosclerosis.

Methods—A total of 1710 randomly enrolled participants between the ages of 45 and 75 with no history of myocardial infarction or stroke received a clinical periodontal examination, carotid scan using high-resolution B-mode ultrasound, and extensive measurements for conventional cardiovascular risk factors (age, education, smoking, alcohol, body mass index, diabetes, systolic blood pressure, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, and triglycerides) as well as markers of healthy lifestyle and social network.

Results—In both genders, measures of current and long-term periodontitis worsened as tooth loss increased. In males but not females, an ≈10% difference in carotid artery plaque prevalence was observed between the lowest and highest tertiles of tooth loss (P<0.05) and long-term periodontitis (P=0.05) after multivariate adjustment. Similar patterns were observed for intima–media thickness. The influence of gender on carotid artery plaque prevalence was most evident among the younger age group (<59 years). Between genders, carotid plaque prevalence differed by 10%, 15%, and 25% across increasing levels of tooth loss, and by 5%, 15%, and 25% across increasing levels of long-term periodontitis.

Conclusions—Our data suggest that tooth loss and long-term periodontitis are related to subclinical atherosclerosis in men but not women. Gender variations in cardiovascular morbidity or mortality may be explained partly by the differential contributions of novel risk factors across genders. (Stroke. 2004;35:2029-2035.)

Key Words: atherosclerosis | gender | infection | periodontal disease | tooth loss

Cardiovascular diseases (CVDs) are the most common causes of death and disability in industrialized nations. Males carry a disproportionate burden of CVD, in part because of differences in lifestyles and hormonal balances.1 With the emergence of novel risk factors for CVD, it is tempting to inquire whether the male differential might be explained partly by the uneven distribution of those factors across genders, or rather, whether the proportional contribution of the pathways differs across genders.

The relationship between oral health, specifically periodontal disease, and CVD has been a subject of mounting research recently2 and is biologically plausible and supported by data on transient bacteremia and elevated inflammatory markers.3 Because males tend to carry a disproportionate burden of periodontal infections,4 we investigated the modifying role of gender in the relationship between periodontal infections, tooth loss, and subclinical atherosclerosis. We studied whether: (1) a relationship of periodontal infections, tooth loss, and subclinical atherosclerosis exists in the European population of Eastern Germany; (2) this relationship differs by gender; and (3) the differences in CVD rates across gender are explained partly by varying distributions in periodontal infections.

Materials and Methods

The Study of Health in Pomerania (SHIP) is a cross-sectional population-based survey in Germany involving the cities of Greifswald, Stralsund, and Anklam, and 29 surrounding villages. The 1995 population in this catchment area was 212 157. First, the 3 cities of the region (17 076 to 65 977 inhabitants) and the 12 towns (1516 to 3044 inhabitants) were selected, and then 17 of 97 smaller towns (<1500 inhabitants) were drawn randomly. Second, from each of these, German subjects with main residency in the area were drawn at random, proportional to each community population size and stratified by age and gender. Thus, a representative sample of 7008 adults aged 20 to 79 years was invited to participate. This
2-stage cluster sampling method was adopted from the World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Project in Augsburg, Germany, and yielded 12 5-year age strata (20 to 79 years) for both sexes. After removing 746 individuals (126 who died, 615 who moved away, and 5 with severe medical problems), 6262 inhabitants were invited. The final observed sample included 4310 individuals, reflecting an overall participation rate of 68.8%.

For this article, we selected subjects aged 45 to 75 years with no history of myocardial infarction or stroke (n = 2124). Among them, 1983 had carotid artery ultrasound performed to measure carotid artery plaque and intima–media thickness (IMT). Subjects were removed because of missing tooth count (n = 4), missing periodontal measurements resulting from crowns (n = 128), or absence of teeth in the quadrants measured (n = 12). Ninety had incomplete lipids (n = 62) or risk factor data (n = 28), and 9 refused. Thus, 1740 subjects remained for analyses. Data collection occurred between October 1997 and May 2001 after written consent. The study was approved by the institutional review board of the University of Greifswald.

**Dental History and Oral Examination**

The oral health examination included an examination of the oral cavity to assess tooth count and location. Flossing and brushing were reported. The periodontal probe PCP 11 (Hwendung) was used to assess probing depth (PD), gingival recession, and clinical attachment loss (AL) for all examined teeth. Measurements were taken at 4 sites per tooth (mesiobuccal, midbuccal, distobuccal, and midlingual). All periodontal findings were registered according to the half-mouth method on the right or left side in alternate subjects. In this article, we categorized dentate subjects according to the extent of current (as measured by PD) and long-term (as measured by AL) periodontal disease. Disease was defined at a particular level of severity at each site, namely ≥ 5 mm for PD and ≥ 4 mm for AL. Disease extent was defined by the percentage of periodontal sites meeting the above severity criteria for PD and AL. The percentage of sites was calculated within each mouth by dividing the number of sites with PD ≥ 5 mm by the total number of sites measured, and similarly for AL. Tooth loss was categorized as terciles (0 to 8, 9 to 15, 16 to 31) among the dentate and edentulous.

Calibrated licensed dentists performed the entire examination. Each 6 to 12 months, calibration exercises were performed on a subset of persons not connected with the study, yielding an intra-class correlation of 0.82 to 0.91 per examiner and an inter-rater correlation of 0.84 relative to AL.

**Ultrasound Examination**

Certified examiners scanned the extracranial carotid arteries bilaterally with B-mode ultrasound using a 5-MHz linear probe array transducer and a high-resolution instrument (DIASONICS VST; Gateway Scientific) with the participant in the horizontal position. Plaque occurrence was diagnosed during the examination in the common carotid arteries (CCAs), the bifurcation, and the internal carotid artery (ICA) and external carotid artery (ECA). Plaques were present if a focal widening of the vessel wall relative to adjacent segments was found (as evidenced by protrusion into the lumen or localized roughness with increased echogenicity or an area of focal increased thickness of the intima–media layer). Plaque presence was defined as ≥ 1 plaque in any of the carotid arteries. In addition, scans from the distal straight portion (1 cm in length) of both CCAs were recorded, and the mean far-wall IMT was calculated by averaging the 10 consecutive measurement points (in 1-mm steps) from the bulb of both sites by trained and certified readers.

**Risk Factor Assessment**

All participants received an extensive medical examination, a computer-guided interview, and a self-administered questionnaire. In short, patients were queried by computer-aided face-to-face interviews on sociodemographic characteristics and medical histories regarding hypertension, diabetes, angina pectoris (rose question-naire), history of myocardial infarction and stroke, as well as rehabilitation history, heart surgery, congestive heart failure, peripheral vascular disease, alcohol use, and current smoking.

Smoking was categorized as never, former, occasional, and current smoker. Continuous assessment was calculated as total pack years of cigarette smoking. The following information was collected: smoking duration (age at smoking cessation minus age at initiation) and the maximum quantity of cigarettes smoked per day during a year. Occasional smoking was defined as <1 cigarette per day. The smoking questionnaire was validated.

Diabetes was defined as self-reported physician diagnosis of diabetes and pharmacological treatment for diabetes or hemoglobin A1c values ≥ 7%. Height and weight were determined using calibrated scales. Blood pressure was measured using a calibrated semiautomatic sphygmomanometer (HEM-705CP; Omron Corp), and the average of 3 measurements was used in analysis. Hypertension was defined by self-report of diagnosed hypertension or use of antihypertensive medications, mean systolic blood pressure ≥ 140 mm Hg, or mean diastolic blood pressure ≥ 90 mm Hg.

Nonfasting blood samples were taken and sent for complete blood count to 2 laboratories. The laboratories participated in the official Germany Institute for Standardization and Documentation in the Medical Laboratories round-robin tests for quality assurance in analytical labs semiannually throughout the data collection period. Moreover, duplicate blood samples were collected and analyzed for internal quality assurance protocol in each examination center once per week. Hemoglobin A1c was measured by cation-exchange chromatography (high-performance liquid chromatography) with spectrophotometric detection (Diamat Analyzer; Bio-Rad). Total cholesterol was measured enzymatically (cholesterol esterase/peroxidase, high-density lipoprotein-cholesterol enzymatically after magnesium chloride precipitation, and low-density lipoprotein-cholesterol after dextrane–sulfate precipitation.

**Assessment of Cultural, Life Style, and Social Network Variables**

All participants were white. The self-administered questionnaire included education level and social network. Education was categorized as < 9, 9 to 10 years, and ≥ 11 years of schooling. Social variables were assessed with 12 questions and covered marital status, number of friends and children, contact with them, and the expressed desire to have more friends or family and the availability of support for personal problems or transportation.

Leisure physical activity was assessed as reporting > 2 hours per week, 1 to 2 hours per week, < 1 hour per week, and no activity and was then converted into METS, an established measure of metabolic output. Alcohol intake during the previous week and weekend was queried for type and frequency of alcohol consumption. The mean daily alcohol consumption for the last week (grams of pure alcohol per day) was calculated by the beverage-specific quantity/frequency method: number of days with alcohol intake (subdivided into 3 beverage types: beer, wine, and spirits).

**Statistical Analysis**

All analyses were performed in PC-SAS for Windows 8.0. Linear and logistic regression models were used. The number of missing teeth per mouth was modeled continuously and categorically. We estimated the proportion of individuals with any carotid plaque and odds ratios between tooth loss categories using logistic regression. For IMT, adjusted means were compared. We defined age continuously and categorically by 10-year intervals in preliminary analyses. The 2 definitions produced similar results, and all models presented are adjusted for age as a categorical variable. Physical activity, diastolic blood pressure, and social variables in this highly homogeneous population did not meet the criteria for confounding (namely, that inclusion in the model led to ≥10% change in the coefficient of interest) and were thus excluded from final analyses.
Results

General Characteristics

Fifty-two percent of the 1740 participants were females. Males were older (60.8 versus 59.8 years; \( P = 0.006 \)). After age adjustment, 64% of subjects (males 69%, females 60%; \( P < 0.0001 \)) had plaque detected in at least 1 carotid artery: 32% in the ICA (males 37% versus females 27%; \( P < 0.0001 \)), 21% in the ECA (males 24% versus 19% females; \( P = 0.006 \)), 56% in the carotid bifurcation (males 61% versus females 51%; \( P < 0.0001 \)), and 9% in the CCA (males 13% versus females 5%; \( P < 0.0001 \)). Mean IMT values were also higher in males (0.81 ± 0.005 mm) versus females (0.74 ± 0.005 mm; \( P < 0.0001 \)). Males smoked more than females (\( P < 0.0001 \)).

Eighty-four percent of the participants (n=1463) were dentate and had an average of 19.0 ± 7.0 teeth. After age adjustment, dentate males tended to have more teeth (19.2 ± 7.0) than females (18.7 ± 7.0; \( P = 0.12 \)).

The percentage of periodontal sites with PD ≥5 mm was 10% in males versus 6% in females (\( P < 0.0001 \)). For AL ≥4 mm, these values were 49% and 37% (\( P < 0.0001 \)), respectively. Additional characteristics of the population are in Table 1.

Relationship Between Tooth Loss and Clinical Measures of Periodontal Disease

The greater the number of teeth lost, the higher the extent of severe periodontal disease. Across increasing levels of tooth loss, there was a consistent increase in the age-adjusted proportion of sites with severe AL (from 24% to 64%) and PD (from 9% to 25%), the increase being statistically stronger in males (Table 2).

Conventional Measures of Periodontal Disease, Tooth Loss, and Carotid Atherosclerosis

Atherosclerosis was related to AL and tooth loss in males but not females (Tables 3 and 4). Plaque was 10% more prevalent among males in the highest tertile of AL compared with those in the lowest tertile (\( P = 0.05 \)). Also, among males with 0 to 8 missing teeth, 66% had carotid artery plaque, whereas among those with ≥16 missing teeth, prevalence of carotid artery plaque was ≈75% (\( P < 0.05 \)). Similar patterns were observed for IMT, with males showing adjusted means of 0.80 ± 0.01, 0.80 ± 0.01, 0.81 ± 0.009, and 0.84 ± 0.01 mm (\( P = 0.04 \) for linear trend) across increasing levels of tooth loss and adjusted means of 0.80 ± 0.01, 0.79 ± 0.009, and 0.82 ± 0.009 mm across tertiles of percentage AL ≥4 mm (linear trend \( P = 0.11 \); Figure 1). This gender difference was even stronger with a cut-off of AL ≥5 mm: in males, IMT thickness increased from 0.79 ± 0.1 to 0.80 ± 0.009 and 0.82 ± 0.009 mm across increasing tertiles of AL (\( P = 0.05 \) highest/lowest tertile) as opposed to women (0.74 ± 0.009, 0.74 ± 0.009, and 0.73 ± 0.009 mm). Adjustment for brushing and flossing did not alter these conclusions.

Among the entire population, the relationship was effectively unchanged whether the smoking adjusting variable was...
Table 2. Age-Adjusted Mean (±SE) Percentage of Sites With Deep Pockets and Severe Attachment Loss (Measures of Current and Long-Term Periodontal Disease, Respectively) in Relation to Tooth Loss (of 64 Possible Sites)

<table>
<thead>
<tr>
<th>Variable</th>
<th>0–8 Missing Teeth</th>
<th>9–15 Missing Teeth</th>
<th>16–31 Missing Teeth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>(n=475)</td>
<td>(n=504)</td>
<td>(n=484)</td>
</tr>
<tr>
<td>Mean no. of periodontal sites investigated</td>
<td>46±0.5</td>
<td>31±0.6</td>
<td>15±0.6</td>
</tr>
<tr>
<td>Percentage of sites with pocket depth ≥5 mm</td>
<td>4±1.0</td>
<td>9±1.0</td>
<td>18±1.0</td>
</tr>
<tr>
<td>Percentage of sites with attachment loss ≥4 mm</td>
<td>28±1.7</td>
<td>48±1.8</td>
<td>73±1.8</td>
</tr>
<tr>
<td>Women</td>
<td>(n=504)</td>
<td>(n=537)</td>
<td>(n=510)</td>
</tr>
<tr>
<td>Mean no. of periodontal sites investigated</td>
<td>43±0.6</td>
<td>29±0.5</td>
<td>14±0.6</td>
</tr>
<tr>
<td>Percentage of sites with pocket depth ≥5 mm</td>
<td>3±0.8</td>
<td>5±0.7</td>
<td>10±0.8</td>
</tr>
<tr>
<td>Percentage of sites with attachment loss ≥4 mm</td>
<td>21±1.8</td>
<td>32±1.5</td>
<td>56±1.7</td>
</tr>
</tbody>
</table>

P for attachment loss, gender/tooth loss interaction = 0.01; P for pocket depth, gender/tooth loss interaction = 0.05.

Discussion

To our knowledge, this is the first report of gender differences in the relationship between periodontal disease, tooth loss, and subclinical atherosclerosis. Furthermore, this article provides the first European confirmation of the relationship between tooth loss and subclinical atherosclerosis reported previously in this journal.11

A recent publication in this journal reported on gender differences in the relationship of periodontal disease with clinical end points.12 Therefore, our data support this report at a subclinical level.

The fact that women had substantially less-documented periodontal disease but had lost an equal number of teeth raises a number of possibilities: they might have lost their teeth for reasons independent of periodontal disease; for reasons related to periodontal diseases but accelerated by other conditions; or tooth removal may be pursued more aggressively in women. A number of studies have reported on the relationship between osteoporosis, periodontal disease, and tooth loss.13,14 It is possible that women might be more likely to experience tooth loss because of their osteoporosis compared with men with similar levels of periodontal disease. In such instances, tooth loss might not be as reliable a marker of past periodontal disease in these postmenopausal women. Further, Splieth et al have shown that dentists in this

Table 3. Prevalence and Odds Ratio of Carotid Artery Plaque Across Levels of Periodontal Disease*

<table>
<thead>
<tr>
<th>0–20% of Sites</th>
<th>21–57% of Sites</th>
<th>≥57% of Sites</th>
<th>Edentulous</th>
</tr>
</thead>
<tbody>
<tr>
<td>With AL ≥4 mm</td>
<td>With AL ≥4 mm</td>
<td>With AL ≥4 mm</td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>Odds Ratio (95% CI)</td>
<td>Prevalence</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>Men</td>
<td>n=184</td>
<td>259</td>
<td>296</td>
</tr>
<tr>
<td>Model 1</td>
<td>54%</td>
<td>1.00</td>
<td>65%</td>
</tr>
<tr>
<td>Model 2</td>
<td>61%</td>
<td>1.00</td>
<td>67%</td>
</tr>
<tr>
<td>Model 3</td>
<td>64%</td>
<td>1.00</td>
<td>69%</td>
</tr>
<tr>
<td>Women</td>
<td>n=303</td>
<td>259</td>
<td>201</td>
</tr>
<tr>
<td>Model 1</td>
<td>48%</td>
<td>1.00</td>
<td>57%</td>
</tr>
<tr>
<td>Model 2</td>
<td>57%</td>
<td>1.00</td>
<td>58%</td>
</tr>
<tr>
<td>Model 3</td>
<td>59%</td>
<td>1.00</td>
<td>60%</td>
</tr>
</tbody>
</table>

*Periodontal disease defined as the percentage of sites per mouth with attachment loss ≥4 mm.
Model 1 unadjusted.
Model 2 adjusted for age and region.
Model 3 adjusted for age, region, smoking, diabetes, systolic blood pressure, high blood pressure, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, natural log (triglycerides), education, and body mass index.
population extract teeth at an early stage of disease, a practice that may differ by gender.

The gender differences reported here might be attributable to treatment bias, practice differences, or sociocultural determinants. Smoking patterns, for example, were different across genders. Although we were careful to adjust for smoking, confounding by smoking cannot be unequivocally excluded. However, the fact that our findings were similar in the subgroup of never smokers makes this possibility less likely.

Other explanations (interaction with obesity and interleukin-6) are possible. Also, because males in this study had 50% more periodontal disease compared with females, it is possible that females did not reach a threshold of inflammation that might have otherwise been associated with severe periodontal infections and carried over to subclinical atherosclerosis until a later age. Also, because younger females seem to have no increased carotid plaque associated with periodontal disease but catch up with men as they age, the possibility of a protective hormonal role cannot be excluded.

Whether the gender differential observed in this study is caused by early tooth extraction, early tooth loss, or true mechanistic differences between the genders as it relates to atherosclerosis cannot be determined cross-sectionally. However, the fact that gender differences were noted for

| Table 4. Prevalence and Odds Ratio of Carotid Artery Plaque Across Tooth Loss Categories |
|-----------------------------------------------|----------------|--|------------------|------------------|
|                                                | 0–8 Missing Teeth | 9–15 Missing Teeth | 16–31 Missing Teeth | Edentulous       |
|                                                | Prevalence (95% CI) | Odds Ratio | Prevalence (95% CI) | Odds Ratio | Prevalence (95% CI) | Odds Ratio |
| Men                                            |                   |             |                   |             |                   |           |
| Model 1                                         | 56% (1.00)       | 65% (1.44 (0.99,2.09)) | 81% (3.39 (2.26,5.11)) | 86% (4.94 (2.83,6.62)) |
| Model 2                                         | 63% (1.00)       | 66% (1.09 (0.73,1.62)) | 78% (2.06 (1.33,3.19)) | 76% (1.91 (1.02,3.57)) |
| Model 3                                         | 66% (1.00)       | 67% (0.99 (0.65,1.51)) | 75% (1.66 (1.04,2.65)) | 74% (1.50 (0.78,2.88)) |
| Women                                           |                   |             |                   |             |                   |           |
| Model 1                                         | 46% (1.00)       | 52% (1.26 (0.89,1.78)) | 67% (2.40 (1.65,3.50)) | 77% (3.99 (2.50,6.38)) |
| Model 2                                         | 57% (1.00)       | 57% (0.96 (0.66,1.41)) | 60% (1.12 (0.73,1.71)) | 64% (1.44 (0.85,2.45)) |
| Model 3                                         | 60% (1.00)       | 57% (0.87 (0.58,1.29)) | 59% (0.95 (0.60,1.49)) | 61% (1.06 (0.60,1.88)) |

Model 1 unadjusted.
Model 2 adjusted for age and region.
Model 3 adjusted for age, region, smoking, diabetes, systolic blood pressure, high blood pressure, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, natural log (triglycerides), education, and body mass index.

Figure 1. A, Tooth loss and IMT by gender adjusted for age, region, smoking, diabetes, systolic blood pressure, high blood pressure, LDL-C, HDL-C, triglycerides, education, and BMI. P for linear trend < 0.04. B, Tertile of % of sites with attachment loss > 4 mm and IMT by gender, adjusted for age, region, smoking, diabetes, systolic blood pressure, high blood pressure, LDL-C, HDL-C, triglycerides, education, and BMI. Linear trend without edent P = 0.11, with edent P = 0.007. LDL-C indicates low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-C; BMI, body mass index.
IMT and plaque lends credence to the possibly intrinsic role of gender.

This study shares with others the limitations inherent to cross-sectional data. First, because of a lack of time sequence, the relationships reported here should not be interpreted as causal. Second, only half-mouth examinations were performed, and we had no information on previous periodontal treatment. However, half-mouth examinations and previous undocumented treatment are thought to underestimate the extent of periodontal disease, thus likely moving our estimates toward the null. Nevertheless, because all teeth were counted, tooth loss findings are not affected by this limitation. Finally, absent the collection of antibodies to periodontal pathogens or high-sensitivity C-reactive protein, we were limited in our mechanistic exploration of the inflammatory aspect of this relationship.

Previous findings from the multiethnic Oral Infections and Vascular Disease Epidemiology Study (INVEST) imply that tooth loss is a marker of past periodontal disease in certain populations. Our results in the vastly different SHIP population seem to support the robustness of this hypothesis. The high atherosclerosis values among the male edentulous (with historically worse periodontal disease) compared with the lower values among female edentulous (historically periodontally healthier) also raise the possibility that the damage may be more preventable rather than reversible once a threshold is reached.

As new factors emerge for CVD, questions should be asked not only regarding their contribution to CVD risk but also, we submit, regarding their potential differential contribution to the gender gap in CVD. In this population, the gender differences in atherosclerosis prevalence seemed to be related not only to the distribution but to the differing contributions of periodontal infections to atherosclerosis across genders.

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