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Relationship between Tooth Loss and Peripheral Arterial Disease among Women

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Abstract

Aim—We assessed the longitudinal association between tooth loss and peripheral arterial disease (PAD) within the Nurses' Health Study.

Materials and Methods—After excluding participants with prior cardiovascular diseases, 277 out of 79,663 women were confirmed as PAD cases during 16-years of follow-up. Number of teeth and recent tooth loss were reported initially in 1992. Subsequent tooth loss was recorded in 1996 and in 2000. We evaluated the associations of baseline number of teeth and recent tooth loss with risk of PAD, adjusting for age, smoking, diabetes, hypertension, high cholesterol, aspirin use, family history of myocardial infarction, BMI, alcohol consumption, physical activity, post-menopausal hormone use, and use of vitamin E, vitamin D, multivitamin, and calcium.

Results—Incident tooth loss during follow-up was significantly associated with higher hazard of PAD (HR=1.31 95% CI: 1.00–1.71). However, the association appeared inverse among never smokers. There was no dose-response relationship between baseline number of teeth and PAD.

Conclusions—Tooth loss showed a modest association with PAD, but no dose-response relationship was observed.

Keywords

Inflammation; Periodontal Disease; Atherosclerosis; Risk factor; Cardiovascular disease(s)

Introduction

Peripheral arterial disease (PAD) is a potentially life- and limb-threatening condition affecting 6% of adults aged 40 years and older (approximately 16.5 million persons), and 12–20% of the US population 65 years and older (approximately 8 million individuals) (Lane et al., 2008, Lockhart et al., 2012). PAD occurs when atherosclerotic deposits accumulate in peripheral vessels, restricting blood circulation in arteries leading to the extremities. PAD shares a common underlying pathological change, atherosclerosis, with coronary heart disease and stroke. These atherosclerotic vascular diseases (ASVD) are the leading cause of death (>25% of all deaths) and are a major public health burden for the global population (Collaborators, 2015).

Periodontal disease is a chronic inflammatory disease characterized by the destruction of the tooth-supporting connective tissues in response to sub-gingival infection with various periodontal pathogens (Pihlstrom et al., 2005). Periodontal bacteria can upregulate local and systemic cytokines and other inflammatory mediators, which can subsequently lead to endothelial dysfunction and plaque formation (Haynes and Stanford, 2003, Reyes et al., 2013). Periodontal pathogens have been found within atherosclerotic plaques, where they may play a role in the development and progression of atherosclerosis leading to ASVD (Haraszthy et al., 2000). The chronic inflammatory process of periodontal disease could also contribute to the pathogenesis of atherosclerosis, and subsequently to ASVD (Tonetti and Van Dyke, 2013). Untreated periodontitis ultimately leads to tooth loss, which can have its own deleterious effects on masticatory ability and diet quality, which in turn may have important consequences on cardiovascular and other systemic diseases (Joshi et al., 1996). Consistent with these mechanisms, periodontitis has been associated with an increased risk of cardiovascular disease and coronary heart disease (Demmer and Desvarieux, 2006, Burt and Eklund, 2005).

Studies of periodontitis and PAD are limited. A cross-sectional analysis of the NHANES population showed that periodontal attachment loss of 3 mm or more was significantly associated with PAD (OR = 2.25, 95% CI: 1.20–4.22) (Lu et al., 2008). In a case-control study, periodontal disease defined as clinical attachment loss ≥4 mm in at least 30% of the 6 measured sites was strongly associated with risk of PAD (OR = 8.18, 95% CI: 1.21–35.23) (Soto-Barreras et al., 2013). A small case-control study from Japan suggested that periodontitis patients had a 5-fold higher risk of developing PAD compared with periodontally healthy controls (OR = 5.45, 95% CI: 1.57–18.89) (Chen et al., 2008). A recent cross-sectional study also showed that severe periodontitis was associated with PAD (OR = 2.03; 95% CI: 1.05–3.93) (Ahn et al., 2016).

Only two studies, both among men, have longitudinally assessed the association between oral health and PAD. In the Veteran Affairs Dental Longitudinal Study, mean alveolar bone loss > 20% at baseline compared to ≤20% was associated with PAD, with a relative risk of 2.27 (95% CI: 1.32–3.90) (Mendez et al., 1998). Among Health Professionals Follow-up Study (HPFS) participants, self-reported periodontal disease was associated with an increased risk of PAD (RR = 1.41, 95% CI: 1.12–1.77) (Hung et al., 2003). In the same

study, loss of one or more teeth during follow-up was associated with higher PAD risk (RR = 1.39, 95% CI: 1.07–1.82).

No longitudinal study has evaluated the association between tooth loss and PAD among women. Because of the importance of a potential relationship between dental health and PAD, we conducted a longitudinal analysis of the relation between baseline number of teeth, recent tooth loss and incident PAD.

Materials and Methods

The study was approved by the Partners Human Research Committee and University of Puerto Rico Human Research Subjects Protection Office Institutional Board and is reported following STROBE guidelines. We utilized data from the Nurses' Health Study (NHS) which started in 1976, and consisted of 121,701 married registered nurses, between 30 and 55 years of age, from the 11 most populous states. Every 2 years, participants completed detailed questionnaires. PAD information was collected starting in 1990, and PAD cases were confirmed through 2008. Oral conditions were included in the 1992 questionnaire. Hence, we included a 16-year follow-up period from 1992 to 2008. We excluded participants who were deceased before 1992 (n=2987), had history of heart disease (n=6658), prior stroke (n=374), coronary artery bypass graft (n=92), intermittent claudication (n=278), or had missing information for baseline number of teeth (n=28,188), teeth lost in the previous 2 years (n=695), age (n=27), or smoking (n=2739). A total of 79,663 eligible women were included in the analytic dataset.

PAD

Nurses reported cases of physician-diagnosed peripheral artery disease on questionnaires every two years, including lower limb claudication but not varicose veins. Medical records were then obtained to confirm self-reported PAD. Expert reviewers blinded to periodontal status reviewed records for evidence of diagnosis and/or treatment for PAD. Participants were classified as PAD cases if they underwent revascularization or amputation for atherosclerotic peripheral artery occlusion in a lower limb, had an angiogram or Doppler ultrasound reporting 50% obstruction of at least one artery plus symptoms in the ipsilateral limb, had a measured ankle-brachial systolic blood pressure index < 0.90 at rest, or had a definite physician's diagnosis of PAD documented in the medical record.

Number of teeth and tooth Loss

We used self-reported number of teeth in this study, which is expected to be reliably reported within our educated population of nurses. Number of teeth present is reported accurately even by lower SES populations, and self-reported number of teeth is highly correlated with actual number of teeth on clinical examination ($r = 0.78\text{--}0.97$) (Pitiphat et al., 2002, Douglass et al., 1991). Although misclassification may exist in incident tooth loss, as respondents maybe unclear about the timing of tooth loss, we anticipate this misclassification to be random and unrelated to outcome (as the exposure measures were obtained before the outcome occurred), and such misclassification is generally expected to lead to an underestimation of the effect estimate (Zucker and Spiegelman, 2004). Baseline

number of teeth (categorized as 0, 1–10, 11–16, 17–24, 25–32) and number of teeth lost in the past 2–4 years (categorized as 0, 1, 2, 3, 4, 5–9 or 10) were self-reported in 1992, 1996, and 2000. Baseline periodontal status is not available in the study data set. Hence, we have focused on evaluating tooth loss and baseline number of teeth as independent risk factors for PAD. Participants did not report causes for tooth loss, but we anticipate that tooth loss is primarily driven by periodontal disease within this higher age group.

Data Analysis

Cox proportional-hazards regression was used to model associations between measures of oral diseases and occurrence of PAD. The proportional hazard assumption held after analyzing Kaplan-Meier curves. Participants were followed until PAD emergence, death, or through the follow-up period (2008).

To explore the association between tooth loss and PAD, separate models were run for baseline number of teeth (17–24, 11–16, 1–10 and 0 vs. 25–32) and PAD, and 1 tooth loss at follow-up and PAD, adjusting for age, smoking status, diabetes, hypertension, high cholesterol, aspirin use, family history of myocardial infarction, BMI, alcohol consumption, physical activity, post-menopausal hormone use, and use of vitamin E, vitamin D, multivitamin, and calcium. These potential confounders were included based on risk factors for tooth loss, PAD, or both, based upon previous studies. We also conducted analyses to compare the risk of PAD among women who lost 1–2, 3–4 or 5 teeth versus women with no tooth loss.

We classified participants as never, past and current smokers, but since smoking is strongly associated with PAD, we also accounted for the number of cigarettes smoked and time since quitting smoking. Past smokers were divided into groups that smoked 1–14 cigarettes daily and quit 18.5 years ago or less, smoked 1–14 cigarettes and quit more than 18.5 years ago, smoked 15 or more cigarettes and quit 18.5 years ago or less, and smoked 15 or more cigarettes and quit more than 18.5 years ago. Current smokers were classified as currently smoking 1–14, 15–24, or 25 or more cigarettes per day. Alcohol intake was divided into 5 categories of grams of alcohol consumed daily: 0, (0, 5), [5, 15), [15, 30) and 30 or more. Adjustment for physical activity was made using quintiles of total Metabolic Equivalent of Tasks (METs) per week, and obesity was assessed using five categories of BMI: <18.5, [18.5–25), [25–30), [30–40), 40. Post-menopausal hormone use was categorized as never, past and current use. Variables were updated on the basis of the biennial questionnaires, and we used Cox proportional hazards models with time-dependent variables.

We further conducted stratified analyses to investigate whether the associations between number of teeth and tooth loss with PAD varied by age (at or below median vs. above the median of 65.6 years *in 1992*), smoking (ever vs. never), diabetes, hypertension, BMI (18.5 BMI 25 vs. BMI > 25), hypercholesterolemia, family history of myocardial infarction, physical activity (at or below the median vs. above), and by use of aspirin, multivitamin, vitamin E, vitamin D, calcium, and/or post-menopausal hormones.

Results

Table 1 shows age-adjusted hazard ratios for PAD by baseline number of teeth and incident tooth loss. Edentulous women, followed closely by women with 1–10 teeth, had the highest percentage of current smokers, least years since quitting smoking, and most packs of cigarettes consumed per year; they also drank less alcohol, had the highest BMI, had less physical activity, highest proportion of hypertension, diabetes, and post-menopausal hormone use, and a lower percentage of Vitamin E, multivitamin, and calcium use.

Table 2 shows the hazard ratios of PAD by number of teeth at baseline and incident tooth loss. In the multivariate models, women with 11–16 teeth at baseline had significantly increased hazard of PAD (HR=1.51, 95%CI: 1.01–2.26) compared to women with 25–32 teeth; however, women with 10 or 17–24 teeth did not show a significantly higher hazard. Losing one or more tooth during follow-up was associated with elevated hazard of PAD overall (HR=1.31, 95%CI: 1.00–1.71), as well as in a subgroup of women who were dentate at baseline (HR=1.30 95%CI: 0.99–1.71; results not shown in the tables). Compared to women who did not lose any teeth during the follow-up, the risk for PAD was strongest among women who lost 1–2 teeth (HR=1.40, 95% CI: 1.04–1.88), but lower among women who lost 3–4 teeth (HR = 1.27, 95% CI: 0.70–2.30), and null among those who lost 5 or more teeth (HR=1.09, 95% CI: 0.57–2.09). In the stratified analysis, tooth loss during follow-up was associated with an increased risk of PAD (HR=1.85, 95%CI: 1.39–2.45) among ever smokers, but with a decreased risk of PAD (HR=0.35, 95%CI: 0.12–0.98) among never smokers. We also evaluated interaction (Table 3), and the $p = 0.002$ for the multiplicative interaction, but the relative excess risk due to interaction (RERI) and the attributable proportion due to interaction (AP) are virtually 0 and the synergy index (S) is essentially 1, so we can conclude that there is no additive nor biological interaction as suggested in the literature (Andersson et al., 2005, Knol and VanderWeele, 2012, VanderWeele and Knol, 2014).

Discussion

This is the first large longitudinal study among women evaluating associations between tooth loss and PAD. Both fewer baseline number of teeth (11–16 versus 25–32) and recent tooth loss were associated with increased PAD risk, but there was no dose response. Our analyses adjusted for important confounders. However, given the strong association of smoking with both PAD and tooth loss, the potential for residual confounding may be an important limitation of our study, in spite of rigorous adjustment for smoking. Smoking can play a role as both a confounder and effect modifier (Lockhart et al., 2012). The strong association among smokers in our study may indicate residual confounding or a synergistic effect of smoking with the pro-inflammatory milieu of periodontitis. A significant protective association between tooth loss and PAD among never smokers was observed, possibly reflecting an unusual pathobiology unrelated to inflammation. However, only 51 PAD cases occurred among never smokers, limiting power and interpretation. The incidence of PAD was low throughout NHS, with only 277 of the over 70,000 women with confirmed PAD diagnosis, more generally limiting the power of our study despite its large sample size.

Important reasons exist to clarify the association of tooth loss with risk of PAD among women. Of particular importance given the inflammatory milieu of periodontitis and tooth loss, several studies have observed sex differences in the role of inflammation in the development of PAD. For example, in comparably sized nested case-control studies of the NHS and HPFS, CRP at baseline was less strongly associated with subsequent risk of PAD among women ($p=0.07$) than among men ($p=0.005$) (Bertoia et al., 2013). At the same time, CRP levels at the time of PAD revascularization appear to be higher among women than among men, and these levels predict subsequent graft patency only among women (Hiramoto et al., 2012).

In multivariate analyses, the intermediate category of 11–16 teeth showed a significant association with increased PAD risk compared to people with 25 or more teeth; however, women with 10 or 17–24 teeth did not show a significantly higher risk. Our results are consistent with a previous study in Health Professionals (Hung et al., 2003), which also found that participants with 11–16 teeth had the highest risk of developing PAD compared to those with fewer than 11 teeth or those with 17–24 teeth.

Recent tooth loss showed a small association with PAD, but again no dose-response existed. The association between tooth loss and PAD could be explained by antecedent periodontal disease, antecedent caries, or dietary changes following tooth loss. Since tooth loss limits chewing capacity and affects food choices, it can lead to detrimental changes in diet and could also impact cardiovascular disease (CVD) (Al-Shammari et al., 2005). Prior infection or inflammation may likely be a cause of tooth loss and may also explain the association between tooth loss and PAD.

The lack of a dose-response for baseline number of teeth may be explained as follows. Edentulous people are free of recent periodontal disease and not at risk of periodontal disease or tooth loss and people with few teeth have fewer teeth at risk; for these reasons, they may be at lower risk of PAD. Another explanation for the relatively lower risk of PAD among participants with 10 teeth is a greater likelihood of prostheses (Hessari et al., 2008), which would enable them to have a better diet. Although prosthetic data is not available to evaluate this, we hypothesize that individuals with 17–24 teeth, compared to 11–16 teeth, take better care of their oral health (resulting in less periodontitis) as well as their general health, which could result in reduced PAD risk (Hung et al., 2003). Good oral hygiene might have a direct effect in reducing oral inflammation. Intensive oral hygiene has been shown to slow periodontal deterioration and improve oral inflammation, (Lee et al., 2009), thus reducing systemic inflammation and the risk of PAD. However, in a report from the Health Professionals' Follow-up Study, there was no association between oral hygiene and periodontitis after controlling for potential confounders (Merchant et al., 2002).

One biological pathway connecting periodontal disease to CVD risk is inflammation, which has a key role in the pathogenesis of atherosclerosis (Libby et al., 2002). Tooth loss may also impact CVD risk through detrimental dietary changes (Joshi et al., 1998, Soto-Barreras et al., 2013). Since variation in baseline number of teeth did not show a consistent association with PAD, the diet pathway is less likely. In this study, recent tooth loss showed a more consistent association with PAD compared with baseline number of teeth. This is

likely due to the fact that recent tooth loss in middle age is more likely to reflect severe periodontal disease and chronic inflammation, as opposed to variation in number of teeth at baseline, which also reflects dental caries from earlier years. Number of missing teeth at baseline gives a general idea of cumulative oral conditions of persons throughout their life, but might not represent recent oral inflammation, whereas recent tooth loss is a more contemporary assessment of both function and inflammation (Hung et al., 2003).

Conclusions

In conclusion, we found a significant longitudinal association between recent tooth loss and PAD among women, although this relation differed by smoking status. Given the current prevalence of periodontal disease and tooth loss globally (Eke et al., 2016, Eke et al., 2012, Bourgeois et al., 2007, Muller et al., 2007, Peltzer et al., 2014, Dye et al., 2015), further efforts to obtain and maintain good oral health may importantly reduce the number of persons developing PAD. However further longitudinal studies are needed to examine the relation of periodontal disease to risk of cardiovascular disease.

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Conflict of Interest and Sources of Funding

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Clinical Relevance

Scientific Rationale

This study is one of the few longitudinal studies to assess the relationship between tooth loss and peripheral arterial disease, and is the first among women. The data used in the analyses are part of the Nurses' Health Study (NHS) cohort and includes information from around 80,000 participants.

Principal Findings

We found a significant longitudinal association between recent tooth loss and peripheral arterial disease among women.

Practical Implications

Given the high prevalence of periodontal disease globally, further public health efforts to obtain and maintain good oral health can reduce the number of persons developing peripheral arterial disease.

Age-adjusted Baseline Risk Factors of PAD by Baseline Number of Teeth and Incident Tooth Loss

Table 1

	Baseline Number of teeth					No tooth loss during follow-up (n=67411)	1 tooth lost during follow-up (n=12252)
	25–32 (n=50232)	17–24 (n=16289)	11–16 (n=4222)	1–10 (n=5038)	0 (n=3882)		
Age	57.1	59.8	61.0	61.8	62.3	58.2	59.4
Smoking status (%)							
Never smoker	49.2	40.1	34.0	30.0	27.7	45.8	36.7
Past smoker	40.1	42.9	41.6	42.3	39.4	41.0	41.1
Current smoker 1–14 cigs	4.9	6.6	8.6	8.7	10.6	5.6	8.4
Current smoker 15–24	4.1	7.0	10.7	12.3	14.4	5.3	9.3
Current smoker 25+	1.7	3.4	5.1	6.6	7.9	2.3	4.5
Year since quitting smoking	14.9	12.1	9.8	8.4	7.7	13.6	10.3
Pack of cigarettes per year	10.1	15.0	19.0	22.4	25.2	12.3	17.6
Alcohol consumption (g/d)	5.4	5.1	4.7	4.9	4.3	5.2	5.2
BMI (kg/m ²)	25.7	26.5	26.8	26.9	27.1	26.0	26.6
Physical activity (METs)	19.9	18.4	17.6	17.3	16.0	19.2	18.4
Family history of MI (%)	19.5	20.2	20.9	19.6	21.0	19.8	20.1
Hypertension (%)	21.3	24.7	25.0	24.6	26.5	22.3	24.7
Diabetes (%)--	2.6	3.9	4.5	4.8	5.7	3.0	4.7
High cholesterol (%)	31.9	32.9	31.7	30.6	29.6	31.7	32.4
Post menopause hormone use (%)							
Never used	45.3	48.8	50.9	51.3	53.2	46.8	50.8
Past use	37.8	32.9	29.9	29.3	26.7	35.7	30.9
Current use	17.0	18.3	19.2	19.4	20.1	17.5	18.3
Aspirin use (%)	46.9	46.0	43.5	45.0	44.1	46.4	45.4
Vitamin D use (%)	2.0	1.7	1.5	1.8	1.7	1.9	1.6
Vitamin E use (%)	18.5	17.1	15.8	16.3	14.7	17.8	16.9
Multivitamin use (%)	43.7	42.0	41.6	40.2	40.5	43.0	42.0
Calcium use (%)	37.3	32.9	31.1	27.9	26.7	35.5	31.2

Table 2

Hazard Ratios and 95% CI of PAD by Number of Teeth at Baseline and Tooth Loss during Follow-Up

	Cases/10K person-time	HR (95% CI)	HR (95% CI)
Number of teeth			
		Model 1 *	Model 2 **
25–32 (<i>Ref.</i>)	3.33	1.00	1.00
17–24	4.42	0.86 (0.63, 1.17)	0.88 (0.65, 1.21)
11–16	9.22	1.42 (0.95, 2.12)	1.51 (1.01, 2.26)
1–10	6.38	0.83 (0.54, 1.29)	0.86 (0.55, 1.34)
0	7.28	0.86 (0.54, 1.38)	0.87 (0.54, 1.41)
Tooth loss			
	Cases/10K person-time	Model 1 *	Model 2 **
0 (<i>Ref.</i>)	3.51	1.00	1.00
1 tooth loss	6.84	1.28 (0.98, 1.66)	1.31 (>1.00, 1.71)
Tooth loss during follow-up in 3 categories (<i>Ref</i> = 0)			
	Cases/person-time	Model 1 *	Model 2 **
0	3.84	1.00	1.00
1–2	7.16	1.38 (1.03–1.85)	1.40 (1.04–1.88)
3–4	9.92	1.24 (0.69–2.24)	1.27 (0.70–2.30)
5+	10.16	0.99 (0.52–1.89)	1.09 (0.57–2.09)

* Adjusted for age, smoking and diabetes.

** Adjusted for age, smoking: never, past 1–14 cigs quit 18.5 year, past 1–14 cigs quit 18.5 year, past 15+ cigs quit 18.5 year, past 15+ cigs quit 18.5 year, current 1–14 cigs, current 15–24 cigs, current 25+ cigs; diabetes, hypertension, high cholesterol, obesity <18.5, [18.5–25], [25–30], [30–40], 40, aspirin use, family history of myocardial infarction, alcohol consumption (5 categories), physical activity (quintiles), use of post menopause hormones, multivitamin, vitamin E, vitamin D and calcium supplements.

Table 3

Tooth Loss and smoking interaction for PAD

	No tooth loss		1 tooth loss [†]	
	Cases/subjects	HR (95% CI) *	Cases/subjects	HR (95% CI) **
Never-smoker	47/27454	1.00	4/5136	0.35 (0.12–0.98)
Smoker	139/31377	2.48 (1.77–3.49)	79/8350	1.85 (1.39–2.45)

* HR (95% CI) for Smokers vs Never smokers among persons with no tooth loss

** HR (95% CI) for tooth loss vs no tooth loss within smoking strata

Measures of interaction on additive scale:

$$\text{Relative excess risk due to interaction RERI}_{HR} = 1.85 - 0.35 - 2.48 + 1 = 0.02 \sim 0$$

$$\text{Attributable proportion due to interaction AP} = \text{RERI}/R_{11} = 0.02/1.85 = 0.01 \sim 0$$

$$\text{Synergy index S} = 1.85 - 1 / [(0.35 - 1) + (2.48 - 1)] = 0.85 / (-0.65 + 1.48) = 0.85 / 0.83 = 1.02 \sim 1$$

[†]P-value for multiplicative interaction = 0.002