Tooth Loss, Systemic Inflammation, and Prevalent Stroke Among Participants in the Reasons for Geographic and Racial Difference in Stroke (REGARDS) Study

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Abstract

Background and Purpose —Periodontal disease results in tooth loss, may contribute to systemic inflammation, and is associated with stroke. We examined cross-sectional associations between tooth loss, inflammation markers, stroke, race, and geographic region among participants in the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study of whites and blacks   45 years.

Methods —We studied 24393 participants. Associations of tooth loss and inflammation markers (C-reactive protein (CRP), white blood cell count (WBC) and albumin) were examined by linear regression, and associations of tooth loss with geographic region, race, and prevalent stroke by logistic regression.

Results —Compared to whites, blacks had an odds ratio of 1.48 (95% confidence interval 1.37–1.60) of having more teeth lost. There were no geographic differences in tooth loss. Compared to no tooth loss, those with 17–32 teeth lost had 1.17 mg/L higher CRP ($p < 0.0001$) and 0.18×10^9/L higher WBC ($p = 0.008$), did not differ in albumin, and had an odds ratio of prevalent stroke of 1.28 (1.09–1.49). Those with 1–16 teeth lost did not differ in CRP and WBC, had 0.03 g/dL higher albumin ($p = 0.004$), and had no increased stroke prevalence. CRP or WBC did not attenuate associations between tooth loss and stroke.

Conclusions —Tooth loss, which varied with race, but not region of residence, was associated with inflammation markers and stroke. The latter association was not confounded by inflammation markers.

Keywords

Tooth Loss; Inflammation factors; Stroke; region of residence; race

Introduction

Periodontal disease, a major cause of tooth loss in adults, is an infectious condition and an inflammatory disorder.[1,2] Accumulating evidence supports a causal association between periodontal infection and atherosclerosis.[3,4] One possible mechanism is through the association of oral bacteria with platelet aggregation, a key event in the development of thrombosis. In addition, atheroma can be enhanced by exposure to periodontal pathogens.[5] Periodontal disease is associated with higher C-reactive protein (CRP) levels, higher white blood cell count (WBC), and levels of other acute phase proteins.[2,6] Inflammation markers are in turn related to the development and progression of atherosclerosis. A recent small clinical trial suggested that intensive periodontal treatment reduced CRP level,[7] and another small trial showed that full-mouth tooth extraction reduced both CRP and WBC.[8] Tooth loss is associated with noninvasive measures of atherosclerosis, such as carotid wall thickening, stenosis, and carotid plaque prevalence.[9,10] Periodontal disease and/or tooth loss were associated with stroke and transient ischemic attack (TIA) in previous studies.[11] Based on these findings, it is hypothesized that chronic infection due to periodontal disease has a causal relation to atherosclerosis mediated by changes in inflammation and the immune response, with subsequent causative relationships to stroke and heart disease.[2,12]

Higher stroke mortality rates in the Southeastern United States "Stroke Belt" have persisted for many years,[13,14] and stroke mortality rates among blacks are higher than in whites.[15,16] We hypothesized that tooth loss, as a surrogate for periodontal disease, would be associated with higher levels of inflammation markers and with stroke, and would be more common in blacks than whites and in the Stroke Belt compared to the rest of the United States. We also hypothesized that inflammation markers confound the association between tooth loss and stroke. We examined these hypotheses using cross-sectional baseline data from the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study.

Materials and methods

The REGARDS Study, a national, population-based, longitudinal study of black and white adults aged 45 years and over, was designed to determine causes for excess stroke mortality in the Southeastern U.S. and among blacks.[14] The "Stroke Belt" refers to a region of high stroke mortality in the Southeastern US that includes eight states. Approximately 50% of the REGARDS study participants were selected from the Stroke Belt and approximately 50% from the remaining 40 contiguous states. REGARDS collected baseline data in a multistep manner, including a telephone contact, telephone interviews (collecting data on demographic factors, socio-economic status (SES), and stroke risk factors) and in-home visits (including physical examination, electrocardiogram (ECG), and blood collection).[14]

Subjects

At the time of the analysis (December 2007), 30101 participants had completed the telephone interviews and an in-home visit. Excluding those with missing data on tooth loss (n=1152), income (n=3501), diabetes (n=852), hypertension (n=115), smoking status (n=67), education (n=12), race (n=7), and age (n=2) resulted in 24393 participants included in these analyses. Further excluding those with missing data on outcomes or covariates (WBC and albumin were added in an ancillary study after approximately 8000 participants had been evaluated) resulted in 22972, 15863, and 16837 participants in the analyses of the associations between tooth loss and CRP, WBC, and albumin, respectively; 22862 in the analyses of the associations between tooth loss and stroke; and 23506 participants in the analyses of the associations between tooth loss and region of residence.

Laboratory Analysis

All samples were collected by trained personnel using standardized procedures in participants' homes (or locations of their choice) after a 10–12 hour fast and centrifuged within 2 hours of collection. Serum or plasma was separated and shipped overnight in transfer vials on gel ice packs to the central laboratory. CRP was measured in plasma during enrollment utilizing a validated, high-sensitivity, particle-enhanced immunonepholometric assay (N High Sensitivity CRP, Dade Behring Inc., Deerfield, IL). WBC was measured the day after sample collection by automated cell counting (Beckman Coulter, Inc., Fullerton, CA). Total cholesterol, HDL-cholesterol, triglyceride, albumin, and glucose were measured the day after sample collection in serum (Johnson & Johnson Clinical Diagnostics, Rochester, NY).

Definitions of variables

Tooth loss was defined as number of teeth lost due to gum disease (obtained from responses to "*Have you lost any of your teeth due to gum disease?*" and "*How many teeth have you lost due to gum disease?*"), with results categorized into classes of none, 0, 1–16 (half or less), or 17–32 teeth lost. Prevalent stroke was defined as a positive response to either "*Were you ever told by a physician that you had a stroke?*" or "*Were you ever told by a physician that you had a mini-stroke or TIA, also known as a transient ischemic attack?*" Region of residence was dichotomized as residence in the Stroke Belt or the other 40 contiguous states. Coronary heart disease (CHD) was defined as self-reported myocardial infarction (MI), coronary artery bypass graft, angioplasty or stenting, or evidence of MI by electrocardiogram. Diabetes was defined as fasting glucose>126 mg/dL, non-fasting glucose>200 mg/dL, or taking medicine or insulin for diabetes. Per the US third report of the National Cholesterol Education Program (NCEP) Expert Panel,17 hyperlipidemia was defined as use of lipid-lowering medication, total cholesterol 240 mg/dL, LDL cholesterol 160 mg/dL, or HDL cholesterol 40 mg/dL. Hypertension was defined as systolic blood pressure 140 mm Hg, diastolic blood pressure 90 mm Hg, or taking medicine for hypertension. Smoking status was based on telephone interviews and categorized as never smoking, past smoking, or current smoking. Body mass index (BMI) was calculated as kg/ m^2. Atrial fibrillation was based on ECG.

Analysis

All analyses were performed with SAS for Windows (version 9.1). CRP was log-transformed (denoted by logCRP) to normalize its distribution and results were exponentiated for presentation. Linear regression was used to investigate the associations between tooth loss and CRP, WBC, and albumin. Logistic regression was used to investigate the association between tooth loss and stroke, and ordinal (or ordered) logistic regression was used to investigate the association between tooth loss and region of residence, treating tooth loss categories as ordinal response. Analyses were unadjusted and adjusted for demographic factors (race, age, and sex), socio-economic status (income and education), and other stroke risk factors, depending on the model.

Results

Baseline characteristics by tooth loss are shown in Table 1. Of the 24393 participants, 85.9%, 7.6%, and 6.5% had no teeth lost, 1–16 teeth lost, and 17–32 teeth lost, respectively. Tooth loss was more likely for those in the Stroke Belt and among participants who were black, older, female, had lower socioeconomic status, were past or current smokers, and had CHD, stroke/TIA, diabetes, hyperlipidemia, and hypertension (Table 1). ANOVA and multiple comparisons (or post hoc tests) indicated that CRP and WBC were higher and albumin was lower in those with the highest tooth loss category compared to those with no

tooth loss (Table 1), and that CRP and WBC were also higher in those with 1–16 teeth lost compared to those with no tooth loss. Albumin did not differ between the 1–16 tooth loss and no tooth loss groups.

Associations between tooth loss and region of residence or race are shown in Table 2. The association between tooth loss and region of residence was not significant (p > 0.05) in univariate analysis. While there was a significantly elevated risk of tooth loss in the Stroke Belt in the demographic-adjusted model (odds ratio (OR) = 1.09; 95% confidence interval (CI) 1.01–1.17; p = 0.0254), this difference was not present after adjustment for socio-economic status. Compared to whites, the OR of having a higher category of tooth loss for blacks was 1.84 (95% CI 1.71–1.98) in univariate analysis. The OR was higher after adjustment for demographic factors and was attenuated by further adjustment for SES. In the fully adjusted model, including adjustment for CHD, diabetes, hyperlipidemia, hypertension, smoking status, and BMI, the OR was 1.48 (95% CI 1.37–1.60; Table 2).

Results for associations between tooth loss and inflammation markers are shown in Table 3. CRP increased step-wise with increasing tooth loss. Those with 1–16 teeth lost had a mean CRP 1.15 mg/L higher than those without tooth loss (p < 0.0001), and those with 17–32 teeth lost had a mean 1.48 mg/L higher than those without tooth loss (p < 0.0001). Adjusting for demographic factors and SES modestly attenuated these differences. In the fully adjusted model (with further adjustment for CHD, diabetes, hyperlipidemia, hypertension, smoking status, and BMI), the difference in CRP between those with no tooth loss and those with 1–16 teeth lost was not significant, but the difference remained significant for those with 17–32 teeth lost (1.17 mg/L; p < 0.0001). A similar association was observed between tooth loss and WBC. Associations of albumin with tooth loss were smaller than for CRP or WBC, were in the opposite direction expected in the fully adjusted model, and were limited to those with 1–16 teeth lost (Table 3).

Associations between tooth loss and stroke are shown in Table 4. In univariate analyses, the ORs of prevalent stroke for those with 1–16 teeth lost and those with 17–32 teeth lost, compared to those with no teeth lost, were 1.25 (95% CI 1.06–1.46) and 2.06 (95% CI 1.78–2.38), respectively. The ORs were attenuated by adjustment for demographic factors and SES, and were decreased to 1.13 (95% CI 0.96–1.34) and 1.27 (95% CI 1.09–1.49), respectively, by further adjustment for CHD, diabetes, hyperlipidemia, hypertension, smoking status, atrial fibrillation, and logCRP. In addition, based on a simple model with adjustment only for race, age, and sex, adding logCRP or WBC did not attenuate the odds of prevalent stroke.

Discussion

Our analyses confirmed previous reports that tooth loss, as a measure of periodontal disease, was significantly associated with inflammation markers[2,6–8] and prevalent stroke.[1,18–21] In addition, we found that tooth loss was more likely in blacks than whites, but was not more common in the Stroke Belt after accounting for socioeconomic status. Since tooth loss is more prevalent among black participants and is also associated with the risk of stroke and stroke risk factors, periodontal disease may be contributing to the racial disparity in stroke. In support of this, blacks were reported to have more tooth loss caused by oral bacteria,[22] which induces platelet activation and is associated with platelet aggregation, and through this association, blacks may be more prone to developing thrombosis and atherosclerosis than their white counterparts.[5] Even if tooth loss was associated with stroke risk, the lack of a regional difference in the prevalence of tooth loss would suggest that it is not playing a role in the geographic disparities in stroke. However, it is well known that tooth loss is associated with lower SES and that black have lower average SES than white. This

contributes to the racial disparity in tooth loss and also leaves uncertainty whether SES, race, or both, might have been contributing to the racial disparity in stroke. We have attempted to address this concern by assessing the impact of race after covariate adjustment for SES, using income and education as surrogates. While income and education may not completely quantify SES, the racial differences do persist after the adjustment.

Because noninvasive measures of atherosclerosis, such as carotid wall thickening or stenosis, are risk factors for ischemic stroke, and the extent of tooth loss has been correlated with carotid plaque prevalence,[9] one might expect an association between tooth loss and stroke. Our analysis of the REGARDS baseline data provided positive evidence of the association, and the finding is consistent with existing literature. [1,18–21] We found, however, that adjustment for CRP or WBC did not weaken the association of tooth loss and stroke. This finding might imply that there are potential mediators other than inflammation between tooth loss and stroke.

In addition, our finding of a lack of geographic variation in tooth loss is concordant with the longitudinal data from NHANES I, where Eklund (1994) found no geographic differences in the incidence of total tooth loss during the 10 years between the surveys comparing the southern and other regions of the US.[23] Noting that the southern area in NHANES I covered all 8 southern states in the Stroke Belt, the REGARDS baseline data and NHANES I data are consistent with respect to tooth loss.

The strengths of this study are the use of a large national cohort with substantial representation of blacks and use of a central laboratory. The limitations of this study should also be noted. Analyses were limited due to the cross-sectional design. In addition, we obtained information about prevalent stroke/TIA from the responses of participants and used self-report of the number of tooth lost due to gum disease as a surrogate for periodontal disease. These may have introduced measurement errors and contributed underestimated associations. However, data from INVEST support the use of this surrogate for periodontal disease.[24] Furthermore, since this study is large, the "noise" in self-reported tooth lost can be partially overcome by the large sample size.

In summary, tooth loss was positively associated with CRP, WBC, and stroke/TIA. Inflammatory markers CRP and WBC did not confound associations between tooth loss and stroke. While disparities in periodontal disease may contribute to racial disparities in stroke, more precise measures of oral health and SES are needed to fully assess this relationship.

Acknowledgments

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Table 1

Baseline characteristics by number of teeth lost, (% or mean±SD (n))

| | Sample size | Number of teeth lost | | | P value* |
		0	1–16	17–32	
Total	24393	85.9	7.6	6.5	
Region					0.0009
Other regions	10937	85.9	8.1	6.0	
Stroke Belt	13444	86.0	7.2	6.9	
Race					<.0001
White	14489	89.0	6.2	4.8	
Black	9904	81.5	9.6	8.9	
Age					<.0001
45–54	3233	90.0	7.1	2.9	
55–64	9574	86.4	8.4	5.2	
65–74	7708	84.5	7.3	8.2	
75–84	3460	84.0	6.7	9.4	
85+	418	85.6	6.0	8.4	
Gender					0.0004
Male	11417	86.8	7.3	5.9	
Female	12976	85.2	7.8	7.0	
Income					<.0001
<$20K	4900	78.4	8.7	12.9	
$20K-$34K	6670	84.3	7.7	8.0	
$35K-74K	8327	87.8	7.9	4.2	
$75+	4496	92.9	5.6	1.5	
Education					<.0001
LT HS	2795	77.6	7.5	14.9	
HS	6178	83.2	8.2	8.6	

		Number of teeth lost			
	Sample size	**0**	**1–16**	**17–32**	**P value**[*]
Some College	6617	86.4	8.0	5.6	
College+	8803	90.2	6.9	2.9	
CHD					<.0001
No	18935	87.0	7.5	5.5	
Yes	5458	82.2	8.0	9.9	
Stroke/TIA					<.0001
No	22042	86.6	7.5	6.0	
Yes	2351	80.1	8.7	11.2	
Diabetes					<.0001
No	19170	87.4	7.3	5.3	
Yes	5223	80.5	8.6	10.9	
Hyperlipidemia					<.0001
No	9820	87.4	7.5	5.2	
Yes	14201	84.9	7.7	7.4	
Hypertension					<.0001
No	10269	88.6	7.0	4.4	
Yes	14124	84.0	8.0	8.0	
Smoking					<.0001
Never	10991	89.9	5.8	4.3	
Past	9824	84.4	8.4	7.2	
Current	3578	78.0	10.8	11.2	
		% (mean±SD)			
CRP (mg/L)	23518	2.2±3.3(20227)	2.5±3.2(1776)	3.2±3.3(1515)	<.0001
WBC (10⁹/L)	16307	5.9±2.0(14072)	6.0±2.1(1215)	6.3±2.7(1020)	<.0001
Albumin (g/L)	17308	4.2±0.3(14930)	4.2±0.3(1293)	4.1±0.3(1085)	<.0001

[*] The P values were based on chi-square test or analysis of variance.

[†]LT HS =Less Than High School, HS = High School.

Table 2

Associations between tooth loss and region and race

	n	Univariate analysis*			Logistics regression models †													
					DF Model			DF+SES Model				DF+SES+RF Model						
		OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value					
Region																		
Other regions	10541																	
Stroke Belt	12965	1.01	0.93 1.08	0.8823	1.09	1.01 1.17	0.0254	1.02	0.94 1.10	0.6918	1.03	0.95 1.11	0.4978					
Race																		
White	14029																	
Black	9477	1.84	1.71 1.98	<.0001	1.90	1.76 2.04	<.0001	1.55	1.43 1.68	<.0001	1.48	1.37 1.60	<.0001					

*
Logistic regression models with Region or Race alone as predictor;

†
DF=demographic factors; SES=socio-economic status (income and education); full model adjusted for race, age, sex, SES, smoking status, diabetes, and logCRP.

Table 3

Association between inflammation markers and tooth loss and race

Marker	Tooth loss	Univariate analysis*			Linear regression models [†]								
					DF Model		DF+SES Model		DF+SES+RF Model				
		n	Reg. Coef.	P value	Reg. Coef.	P value	Reg. Coef.	P value	Reg. Coef.	P value			
CRP (g/dL)	**0 lost**	19749											
	1–16 lost	1740	1.15	<.0001	1.08	0.0054	1.07	0.0201	1.02	0.4268			
	17–32 lost	1483	1.48	<.0001	1.38	<.0001	1.27	<.0001	1.17	<.0001			
WBC (×10⁹/L)	**0 lost**	13681											
	1–16 lost	1188	0.17	0.0092	0.26	<.0001	0.22	0.0005	0.07	0.2374			
	17–32 lost	994	0.45	<.0001	0.57	<.0001	0.43	<.0001	0.18	0.0078			
Albumin (g/dL)	**0 lost**	14515											
	1–16 lost	1263	0.00	0.7137	0.02	0.0412	0.02	0.0161	0.03	0.0044			
	17–32 lost	1059	−0.06	<.0001	−0.02	0.0291	−0.01	0.3308	0.00	0.9663			

*
Linear regression models with tooth loss or Race alone as predictor.

[†]
DF=demographic factors; SES=socio-economic status (income and education); full model adjusted for race, age, sex, SES, coronary heart disease, diabetes, hyperlipidemia, hypertension, smoking status, and BMI.

Table 4

Association between tooth loss and stroke

Number of tooth lost	Univariate analysis[*]					Incremental logistics regression models (n) [†]														
						DF Model				DF+SES Model				DF+SES+RF Model			
	n	Stroke(%)	OR	95%	CI	P value	OR	95%	CI	P value	OR	95%	CI	P value	OR	95%	CI	P value
0	19652	8.72																
1–16	1730	10.64	1.25	1.06	1.46	0.0072	1.23	1.05	1.45	0.0113	1.22	1.04	1.44	0.0153	1.13	0.96	1.34	0.1373
17–32	1480	16.42	2.06	1.78	2.38	<.0001	1.77	1.52	2.05	<.0001	1.53	1.31	1.78	<.0001	1.27	1.09	1.49	0.0022

[*] Logistic regression models with Tooth loss or Race alone as predictor;

[†] DF=demographic factors (race, age, sex); SES=socio-economic status (income and education); full model adjusted for race, age, sex, SES, coronary heart disease, diabetes, hyperlipidemia, hypertension, smoking status, atrial fibrillation, and logCRP.