Title: The Association Between Periodontal Disease and Kidney Function Decline in African Americans: The Jackson Heart Study

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Background: Chronic kidney disease (CKD) remains a prevalent public health problem that disproportionately affects African Americans, despite intense efforts targeting traditional risk factors. Periodontal disease, a chronic bacterial infection of the oral cavity, is both common and modifiable and has been implicated as a novel potential CKD risk factor. We sought to examine to what extent periodontal disease is associated with kidney function decline.

Methods: Retrospective cohort study of 699 African American participants with preserved kidney function defined by an estimated glomerular filtration rate (eGFR) >60ml/min/1.73m^2 at baseline who underwent complete dental examinations as part of the Dental-Atherosclerosis Risk in Communities study (1996-1998) and subsequently enrolled in the Jackson Heart Study (2000-2004). Using multivariable Poisson regression we examined the association of periodontal disease (severe vs. non-severe) with incident CKD defined as incident eGFR<60ml/min/1.73m^2 *and* rapid (5% annualized) eGFR decline at follow-up among those with preserved eGFR at baseline.

Results: Mean age at baseline was 65.4 years (SD 5.2) and 16.3% (n=114) had severe periodontal disease. There were 21 cases (3.0%) of incident CKD after a mean follow-up of 4.8 (SD 0.6) years. Compared to participants with non-severe periodontal disease, those with severe periodontal disease had a 4-fold greater rate of incident CKD [adjusted incidence rate ratio 4.18, 95% CI (1.68 – 10.39), p=0.002].

Conclusion: Severe periodontal disease is prevalent among a population at high-risk for CKD and is associated with clinically significant kidney function decline. Further research is needed to determine if periodontal disease treatment alters the trajectory of renal deterioration.

KEYWORDS:

renal insufficiency, chronic; periodontal diseases; risk factors; African Americans; disease progression

Compared with white individuals, African Americans are disproportionately affected by chronic kidney disease (CKD) and have nearly a four-fold greater risk of progression to end-stage renal disease, a racial/ethnic disparity unparalleled in any other area of medicine.[1, 2] The reasons for this racial/ethnic disparity are not entirely explained by traditional CKD risk factors. Identifying novel, potentially modifiable CKD risk factors among African Americans is critical for identifying interventions aimed at reducing this excess burden of CKD.

Periodontal disease, a chronic infection of the oral cavity, also disproportionately affects racial and ethnic minorities and has been recently implicated as an independent risk factor for CKD.[3-7] To date, two studies have found that severe periodontal disease (as defined by radiographic criteria among a cohort of Pima Indians with diabetes and by periodontal inflammation criteria in a cohort of elderly Japanese adults) is associated with an increased risk of kidney function decline over time.[8, 9] However, the association of periodontal disease with kidney function decline over time among African Americans has not been explored.

In this study, we examine the association of periodontal disease with kidney function decline within a cohort of older African American adults over five years of follow-up. We hypothesized that individuals with severe periodontal disease would experience a greater likelihood of progression to clinically significant decreased kidney function than those without severe periodontal disease.

METHODS

Study Design and Population

We assembled a cohort of African American participants of the dental ancillary study to the Atherosclerosis Risk in Communities study (D-ARIC) who were subsequently enrolled in the Jackson Heart Study (JHS). ARIC is a prospective community-based study of the causes and natural history of preclinical and clinical atherosclerotic disease. It included a probability sampling of eligible participants aged 45 to 64 years from 4 U.S. communities, including Jackson, Mississippi. D-ARIC was performed on a dentate (natural teeth present) subgroup of the ARIC cohort visit 4 (1996 to 1998) and consisted of an oral examination conducted by four study-calibrated dental hygienists.[10] Participants requiring antibiotic prophylaxis for periodontal probing were excluded. Clinical measures collected included bleeding on probing, pocket probing depth, and gingival recession on 6 sites for all teeth. Clinical attachment level (CAL) was calculated from the distance in millimeters from the cementoenamel junction (CEJ) to the bottom of the gingival pocket. Similar to ARIC, JHS is also a prospective community-based cohort study designed to examine risk factors for cardiovascular disease among African Americans living in a tri-county area of Jackson, Mississippi. It enrolled participants and conducted an initial examination between 2000 and 2004. JHS did not include an oral examination.

Because the current study was a secondary analysis of de-identified data, it was exempt from institutional review board (IRB) approval. D-ARIC and JHS had IRB approval and participant consent.

There were 755 D-ARIC (baseline) participants who went on to be enrolled in JHS approximately 5 years later (follow-up) (Figure 1). We excluded 19 participants without serum creatinine measures at baseline (n=12) or follow-up (n=7). Because our primary outcome included incident estimated glomerular filtration rate (eGFR)<60ml/min/1.73m^2, we also excluded an additional 37 subjects who had eGFR<60ml/min/1.73m^2 at baseline. The prevalence of severe periodontal disease by the Centers for Disease Control/American Academy of Periodontology (CDC/AAP) 2003 consensus definition (see below) was similar between these participants and the 699 participants with baseline eGFR≥60ml/min/1.73m^2 included in analysis (18.9% vs. 16.3%, p=0.7).

Predictor

Our primary predictor was periodontal disease. While there is no standard case definition for periodontal disease, the Centers for Disease Control/American Academy of Periodontology (CDC/AAP) 2003 consensus definition has been proposed as a standard definition of periodontal status for use in epidemiological studies.[11] By CDC/AAP criteria, severe periodontal disease was defined as the presence of 2 or more interproximal sites with ≥ 6 mm loss of attachment (AL) (not on the same tooth) and 1 or more interproximal site(s) with ≥ 5 mm probing depth. Moderate periodontal disease was defined as 2 or more interproximal sites with ≥ 4 mm clinical AL (not on the same tooth) or 2 or more interproximal sites with probing depth ≥ 5 mm, also not on the same tooth. Mild periodontal disease was defined as ≥ 2 interproximal sites with ≥ 3 mm AL and ≥ 2 interproximal sites with ≥ 4 mm probing depth (not on the same tooth) or 1 site with ≥ 5 mm.[12]

We examined the association of periodontal disease with kidney function decline categorizing CDC/AAP periodontal disease in several ways: (1) severe vs. non-severe (none, mild, or moderate); (2) any (mild, moderate, or severe) vs. none; and (3) a categorical definition (none, mild/moderate, or severe).

Because periodontal disease is thought to lead to kidney dysfunction via an inflammatory pathway, we also defined periodontal status by the periodontal inflamed surface area (PISA) as a secondary predictor. PISA reflects the amount of inflamed periodontal tissue and was calculated for each participant using clinical attachment level, recession, and bleed on probing.[13] We compared the highest quartile PISA vs. the other three PISA quartiles.

Main Outcome

Our main outcome of interest was incident CKD at follow-up (JHS visit), defined as estimated glomerular filtration rate (eGFR)<60ml/min/1.73m^2 accompanied by rapid eGFR decline (>5% annualized loss). We used calibrated serum creatinine for calculation of eGFR as defined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[14] Our definition of rapid decline is consistent with the Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group definition of CKD progression and has been applied to other studies.[15-17] Creatinine was measured by a multipoint enzymatic spectrophotometric assay and standardized to isotope dilution mass spectrometry (IDMS).[18]

Covariates

All covariates were defined using baseline (D-ARIC) data. Age, gender, smoking status, and annual income were obtained by self-report. Age was considered as a continuous variable. We defined smoking status as "never" or "former/current" and income as less than $25,000 (reference), $25,000-$49,999, ≤ $50,000, or missing. We defined diabetes by fasting blood glucose ≥126mg/dl or self-reported use of hypoglycemic medications or insulin. Glycosylated hemoglobin data were not available. Hypertension was defined by a systolic blood pressure of ≥140 mm Hg, diastolic blood pressure of ≥90 mm Hg, or self-reported use of antihypertensive medications.

Statistical Analyses

We used multivariable Poisson regression to examine the association of periodontal disease defined by CDC/AAP and PISA with incident CKD over the study period. We adjusted for demographics (age and gender); comorbidities and health-related behaviors (hypertension, diabetes, and smoking); and socioeconomic status (income) as potential confounders. We added covariates to the model sequentially to examine incremental effects of each confounder category on the likelihood on incident CKD. Analyses were performed using a statistical software package. [‡‡]

RESULTS

The average age in the study population at baseline was 65.4 (SD 5.2) years. The mean number of teeth examined was 17.9 (SD 7.5, range 2-32) and 86.3% had bleeding with probing around one or more teeth. The prevalence of examined sites with pocket probing depth ≥4mm and ≥5mm was 18.6% (SD 27.3) and 11.2% (SD 21.7), respectively. Mean pocket probing depth was 2.0mm (SD 0.7). The prevalence of examined sites with clinical attachment loss ≥3, ≥4mm and ≥6mm was 59.5% (SD 30.7), 25.3% (SD 31.7), and 8.5% (SD 20.1), respectively. Mean clinical attachment loss was 2.3mm (SD 1.0). By the CDC/AAP definition, 335 (47.9%), 17 (2.4%), 233 (33.3%), and 114 (16.3%) participants had no, mild, moderate, and severe periodontal disease, respectively. Baseline characteristics by severe vs. non-severe periodontal disease are shown in Table 1. Age, income, and eGFR were similar across periodontal disease groups, as was the prevalence of hypertension. The prevalences of men, former or current smoking, and diabetes were significantly higher among those with severe periodontal disease.

Mean time to follow-up visit was 4.8 (SD 0.6) years and did not differ by periodontal disease status (p=0.6). At the follow-up visit, the median eGFR was 75.8ml/min/1.73m^2 (SD 19.2, interquartile range 63.0, 88.6). Thirty-one participants (4.4%) developed incident eGFR<60ml/min/1.73m^2, 74 (10.6%) had rapid eGFR decline, and 21 (3.0%) had incident CKD (both incident eGFR<60ml/min/1.73m^2 and rapid eGFR decline). Incident CKD was found among 10 (3.0%), 0 (0%), 2 (0.9%), and 9 (7.9%) of participants with no, mild, moderate, and severe periodontal disease respectively.

In the unadjusted model, severe periodontal disease was associated with a 3-fold greater rate of incident CKD [IRR 3.82, 95% CI (1.65 – 8.87), p=0.002] than non-severe periodontal disease (Table 2). This association appeared to get stronger with adjustment. In the fully adjusted model, severe periodontal disease was associated with a 4-fold greater rate of incident CKD [IRR 4.18 (1.68-10.39), p=0.002] than non-severe periodontal disease.

In the unadjusted model, any periodontal disease (mild, moderate, or severe) was not associated with greater rate of incident CKD than no periodontal disease (p=1.0). In the unadjusted model, the rate of incident CKD among those with mild/moderate periodontal disease was similar to that of those with no periodontal disease [IRR 0.27 (0.06-1.22), p=0.09] but was 2.6-fold greater among those with severe periodontal disease compared to those with no periodontal disease [IRR 2.63 (1.10-6.31), p=0.03 (Table 3). In the fully adjusted model, the strength of the association of severe periodontal disease with incident CKD compared to those with no periodontal disease increased [IRR 2.96 (1.14-7.67), p=0.02].

By the PISA definition, 9 (5.2%) participants in the highest quartile and 12 (2.3%) in the lower 3 quartiles had incident CKD. The highest PISA quartile group had a 2.5-fold greater rate of incident CKD than the lower 3 PISA quartiles after full adjustment [IRR 2.48 (1.04-5.88), p=0.04] (Table 4).

DISCUSSION

In cohort of African Americans adults, we found that severe periodontal disease was consistently associated with incident CKD relative to less severe disease during a follow-up period of 5 years. In the unadjusted model, severe periodontal disease had a 3.8-fold increased rate of incident CKD, and after adjustment for age, sex, diabetes, hypertension, smoking status, and income, the association remained strong/increased. Interestingly, there appeared to be a threshold effect with respect to the severity of periodontal disease. When using quartiles of total periodontal inflamed surface area (PISA), the strength of association with CKD was attenuated, but remained significant. Furthermore, there was no association of mild/moderate periodontal disease with CKD compared to those without periodontal disease.

Prior investigation of elderly Japanese participants found that those with severe periodontal disease, as defined by the highest PISA quartile, were twice as likely to have worsening eGFR category ($\geq$ 60, 30-59, and $\leq$29 ml/min/1.73m^2) after 2 years of follow-up than those without severe periodontal disease.[8] However, worsening of eGFR category as an outcome may be problematic in that declines of significantly different sizes would be classified similarly, such as those from 50 to 29 and from 31 to 29 ml/min/1.73m^2. Among a prospective cohort of Pima Indian adults with diabetes and eGFR>60ml/min/1.73m^2 at baseline, severe periodontal disease, as defined by missing teeth and alveolar bone loss on panoramic radiograph, was associated with a 2-fold increased risk of incident macroalbuminuria and a 3.5-fold increased risk of incident end-stage renal disease over a follow-up of up to 22 years.[9] Our study extends the current understanding of the association of periodontal disease with kidney function decline to an African-American population both with and without diabetes. An important strength of our study is that a full-mouth periodontal examination was performed, lending confidence in our ability to accurately define the prevalence of periodontal disease in the study population. Furthermore, our finding of an association of periodontal disease with both incident eGFR<60ml/min/1.73m^2 *and* rapid eGFR decline is novel and demonstrates the potential importance of periodontal disease on CKD progression.

Our findings are particularly important because periodontal disease is disproportionately more common among racial and ethnic minorities.[3, 4] The strength of the association we found suggests that periodontal disease may be an important contributor to racial and ethnic disparities in CKD prevalence and progression. One prior study using Taiwanese insurance claim data found that patients with periodontal disease who underwent procedures of subgingival curettage

and/or periodontal flap had a 40% lower likelihood of incident end-stage renal disease (ESRD) as defined by ICD-9 codes than those who did not undergo those procedures.[19] Given the low sensitivity of claims based ascertainment of ESRD, further investigation for the effect of treating periodontal disease on kidney function decline is warranted.[20]

Although periodontal disease is a local bacterial infection of the oral cavity, it is thought to exert an effect on kidney dysfunction via an inflammatory pathway because periodontal pathogens can access systemic circulation and potentially induce kidney injury through an innate immune response.[21, 22] Therefore, it seems reasonable that the greatest association between periodontal disease and kidney function decline would be observed among those with the highest inflammatory burden, i.e. highest PISA quartile rather than among those with evidence of the most "end-stage" periodontal disease as found in our study. This finding suggests that the cumulative experience of periodontal disease may be an important contributor to the potential burden of kidney function decline.

Our study is not without limitations. First, because of the relatively small size of our study population, there were a limited number of outcomes. Therefore, we were restricted to a parsimonious model. Body mass index, for example, has been implicated as an independent risk factor for CKD progression.[23] Obesity was not included as a confounder in our analyses, but was highly prevalent in our study population (nearly half had body mass index$\geq$30kg/m^2) and was not different by periodontal disease status (p=1.0). Second, as with all observational studies, the association of periodontal disease with kidney function decline may be subject to residual confounding. However, given that we have accounted for the most important known confounders for periodontal disease and CKD, only one or more powerful unmeasured confounders could explain the strength of the association we found. Third, no interval periodontal disease treatment data or dental measures at follow-up were available. However, interval treatment or worsening of periodontal status would have likely biased findings toward the null if our hypothesis that severe periodontal disease leads to kidney function decline is true—treated patients would have slower decline in kidney function, while kidney function decline in those with interval worsening of periodontal disease would have been attributed to the milder periodontal disease at baseline. Finally, our study was limited to an older adult African American population, thus may not be generalizable to younger or non-African American cohorts. Further study is needed to determine if associations are similar across other races and age groups.

In conclusion, among a cohort at high-risk for CKD progression, severe periodontal disease was associated with incident clinically significant kidney function decline. Further research is needed to determine if the association is causal and, whether treatment of periodontal disease will alter the decline of eGFR.

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CONTRIBUTIONS:

research idea and study design: VG, EV, BY; data acquisition: VG, JB, MG, WW, AC; data analysis/interpretation: VG, EV, BY; statistical analysis: EV; manuscript drafting: VG; manuscript revision: all authors. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. VG takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted.

DISCLAIMERS/CONFLICTS OF INTEREST:

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Figure 1.

Flow chart of cohort selection

Table 1.

Baseline participant characteristics, by periodontal disease status*

Characteristic	Overall (n=699)	Non-Severe (n=585, 83.7%)	Severe (n=114, 16.3%)	p-value†
Age in years, mean (SD)	65.4 (5.2)	65.4 (5.3)	65.2 (5.0)	0.7
Men, n (% column)	240 (34.3)	169 (28.9)	71 (62.3)	<0.001
Smoking status former/current, n (%)	344 (49.5)	271 (46.6)	73 (64.0)	0.001
Hypertension, n (% column)	405 (58.1)	346 (59.3)	59 (51.8)	0.1
Diabetes, n (% column)	137 (19.7)	103 (17.7)	34 (29.8)	0.003
Income <$25,000, n (% column)	322 (46.1)	264 (45.1)	58 (50.9)	0.5
Estimated glomerular filtration rate (eGFR ml/min/1.73m^2), median (interquartile range)	95.7 (83.2, 110.3)	95.7 (84.4, 110.3)	94.1 (81.4, 110.4)	0.2
Number of teeth examined, mean (SD)	17.9 (7.5)	17.6 (7.5)	19.1 (7.1)	0.05
Any bleeding on probing, n (%	603 (86.3)	489 (83.6)	114 (100%)	<0.001

column)				
Pocket probing depth in millimeters (mm), mean (SD)	2.0 (0.7)	1.8 (0.4)	3.1 (0.9)	<0.001
Prevalence of examined sites with pocket probing depth				
≥4mm, % column (SD)	18.6 (27.3)	9.8 (16.4)	64.0 (26.9)	<0.001
≥5mm, % column (SD)	11.2 (21.7)	3.8 (9.2)	48.9 (27.4)	<0.001
Clinical attachment loss in millimeters (mm), mean (SD)	2.3 (1.0)	2.0 (0.5)	3.8 (1.4)	<0.001
Prevalence of examined sites with clinical attachment loss				
≥3mm, % column (SD)	59.5 (30.7)	53.1 (29.9)	92.2 (13.7)	<0.001
≥4mm, % column (SD)	25.3 (31.7)	15.9 (22.7)	74.0 (25.9)	<0.001
≥6mm, % column (SD)	8.5 (20.1)	2.1 (8.0)	41.8 (28.7)	<0.001

*Defined by Centers for Disease Control/American Academy of Periodontology criteria[12]

†p-value is Kruskal-Wallis (eGFR, prevalence pocket probing depth and clinical attachment loss), t-test (age, number of teeth, mean pocket probing depth and clinical attachment loss), or Chi-square test (all other) of association between periodontal disease status and characteristic

Table 2.

Incidence-rate ratio of eGFR<60ml/min and rapid decline at 5-year follow-up by CDC/AAP* severe vs. non-severe periodontal disease, N=699

Model	Non-Severe (12/585)†	Severe (9/114)†	
	IRR (95% CI)	IRR (95% CI)	p-value
unadjusted	1.0 (reference)	3.82 (1.65 – 8.87)	0.002
+ age, gender	1.0 (reference)	4.46 (1.91 – 10.38)	0.001
+ age, gender, diabetes, hypertension, smoking	1.0 (reference)	3.84 (1.50 – 9.79)	0.005
+ age, gender, diabetes, hypertension, smoking, income	1.0 (reference)	4.18 (1.68 – 10.39)	0.002

*Centers for Disease Control/American Academy of Periodontology criteria[12]

†n events/N subgroup

Table 3.

Incidence-rate ratio of eGFR<60ml/min and rapid decline at 5-year follow-up by 3-level CDC/AAP* periodontal disease, N=699

Model	None (10/335)†	Mild/Moderate (2/250)†		Severe (9/114)†	
	IRR (95% CI)	IRR (95% CI)	p-value	IRR (95% CI)	p-value
unadjusted	1.0 (reference)	0.27 (0.06 – 1.22)	0.09	2.63 (1.10 – 6.31)	0.03
+ age, gender	1.0 (reference)	0.26 (0.06 – 1.11)	0.07	2.95 (1.26 – 6.91)	0.01
+ age, gender, diabetes, hypertension, smoking	1.0 (reference)	0.32 (0.08 – 1.37)	0.1	2.69 (1.02 – 7.09)	0.05
+ age, gender, diabetes, hypertension, smoking, income	1.0 (reference)	0.34 (0.08 – 1.50)	0.1	2.96 (1.14 – 7.67)	0.02

*Centers for Disease Control/American Academy of Periodontology criteria[12]

†n events/N subgroup

Table 4.

Incidence-rate ratio of eGFR<60ml/min and rapid decline at 5-year follow-up by PISA* highest quartile vs. lower 3 quartiles, N=699

Model	Lower 3 quartiles (12/526)†	Highest quartile (9/173)†	
	IRR (95% CI)	IRR (95% CI)	p-value
unadjusted	1.0 (reference)	2.29 (0.98 – 5.33)	0.06
+ age, gender	1.0 (reference)	2.49 (1.09 – 5.66)	0.03
+ age, gender, diabetes, hypertension, smoking	1.0 (reference)	2.42 (1.03 – 5.70)	0.04
+ age, gender, diabetes, hypertension, smoking, income	1.0 (reference)	2.48 (1.04 – 5.88)	0.04

*Periodontal inflamed surface area criteria[13]

†n events/N subgroup

⌗ Stata Version 13.1, Stata Corp, College Station, TX

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Figure 1. Flow chart of cohort selection