

ARIC Manuscript Proposal #1955

PC Reviewed: 7/10/11
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: The Effect of Periodontal Disease on Kidney Function Decline in the Jackson Heart Study

b. Abbreviated Title (Length 26 characters): Periodontal and Kidney

2. Writing Group:

Writing group members: Vanessa Grubbs, Eric Vittinghoff, Neil Powe, Steven Offenbacher, Abhijit Kshirsagar, Michael Griswold, Adolfo Correa, Kirsten Bibbins-Domingo, Herman Taylor, James Beck

I, Vanessa Grubbs, confirm that all the coauthors have given their approval for this manuscript proposal. VG [please confirm with your initials electronically or in writing]

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3. Timeline: We will start analyses by July 2012 and anticipate a first draft to co-authors by yearend. An additional 3 months will be needed to complete a manuscript suitable for submission to the P&P committee.

4. Rationale:

Because chronic kidney disease (CKD) affects an estimated 13% of the general population¹ and consumed roughly 28% of the 2007 Medicare budget, with the greatest expenditures incurred during the month of dialysis initiation,² identifying modifiable factors that slow or prevent CKD progression is essential to decreasing this burden. While poorly controlled diabetes and hypertension are well-established CKD risk factors, efforts to reduce them alone have not yet resulted in a decrease in the prevalence of CKD.¹

Periodontal disease may represent a new focus for slowing or preventing CKD progression; it is independently associated with a 1.5 to 2-fold increased risk of CKD in cross-sectional studies;³⁻⁵ is common, with moderate or advanced periodontal disease affecting approximately 18% of the general US population;⁶ and its treatment has been shown to improve endothelial function.⁷ Further, most forms of periodontal disease are readily prevented and treated with good personal oral hygiene and routine non-surgical periodontal therapy, thus presenting a potentially major opportunity to significantly impact the burden of CKD.

Although periodontal disease is a chronic gram negative bacterial infection of the oral cavity, it is proposed that periodontal disease may lead to kidney function impairment via periodontal pathogens accessing systemic circulation through normal oral health procedures like tooth brushing.⁸ As a result, these pathogens can bind specific receptors in the kidney, launching an inflammatory cascade that may lead to sustained local tissue inflammation and fibrosis, with deterioration of renal function.⁹

African Americans are disproportionately affected by CKD, with younger average age of CKD onset¹⁰ and 4-fold greater incidence of end stage renal disease (ESRD) compared to their White counterparts.¹¹ Given that African Americans also have >2-fold prevalence of periodontal disease¹² relative to the general population, periodontal disease may contribute to the observed disparity.

All Jackson site participants of the ancillary dental study to the Atherosclerosis Risk in Communities study (D-ARIC) went on to be enrolled in the JHS. Because JHS includes repeated measures for kidney function, we have a unique opportunity to examine the association of periodontal disease with kidney function decline over time. Through a longitudinal assessment of the association of periodontal disease and CKD, we can gain important knowledge that may improve the burden of CKD, particularly in the disproportionately affected African-American population.

5. Main Hypothesis/Study Questions:

Aim 1: To examine the effect of periodontal disease on kidney function decline (as measured by estimated glomerular filtration rate (eGFR) or albuminuria) in a population at high risk for rapid CKD progression.

Hypothesis 1: Participants with periodontal disease will have faster kidney function decline than those without periodontal disease.

Aim 2: To examine the extent to which the effect of periodontal disease on kidney function decline varies by access to dental care.

Hypothesis 2: Participants who report less than recommended access to dental care will have faster decline in kidney function than those who report recommended access to dental care.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Clinical predictors: The primary predictor is periodontal status. Uniform criteria for accurately defining periodontal disease have not been established in epidemiologic studies. We will use two methods to define and compare periodontal disease: (1) the Centers for Disease Control and Prevention/American Academy of Periodontology (CDC/AAP) definition, which was created by consensus in 2003 to introduce a standard definition for epidemiologic studies,¹³ and (2) the periodontal inflamed surface area (PISA), which takes into account bleeding on dental probing as a marker of active inflammation.¹⁴ D-ARIC consisted of a complete oral examination—including probing pocket depth, bleeding on probing, and gingival recession at all 6 sites for all teeth present in the mouth—thus allowing complete confidence in our ability to categorize periodontal disease.

Primary outcomes: GFR trajectory using repeated eGFR measurements at baseline (D-ARIC) and JHS Exam 1. GFR will be estimated in two different ways for comparison: 1) creatinine-based MDRD¹⁵ and 2) creatinine-based CKD-EPI equation.¹⁶

Secondary outcome: Development of macroalbuminuria ($\geq 300\text{mg/g}$) among those without macroalbuminuria at baseline.

Potential confounders: We will adjust for age, gender, income, education, smoking status, diabetes (self-report, fasting glucose ≥ 126 , taking anti-diabetes medications, or A1c >6.5), diabetes control (A1c), hypertension (self-report or BP $>140/90$), renin-angiotensin-aldosterone system blockade (ACE inhibitors, angiotensin receptor blockers, aldosterone inhibitors), periodontal antibody titers, and dental care.

Variable Type	Variable Name
Demographics and health related behaviors	Age, gender, income, education
	smoking status
	self-reported dental visit

Exam	Systolic blood pressure, diastolic blood pressure
Co-morbid conditions	Diabetes, Hypertension
Labs	Creatinine
	urine albumin: creatinine (ACR)
	Hemoglobin A1c
Medications	Use of medications angiotensin converting enzyme inhibitors or angiotensin receptor blockers

Statistical analysis:

1. Subjects: All D-ARIC participants who went on to be followed as part of JHS (n=1,140).
2. Models: We will use mixed modeling of the repeated, log-transformed eGFR estimates, calculated using first the MDRD and then the CKD-EPI equation, to examine the effect of periodontal status on decline in GFR. We will adjust for potential confounders including age, gender, co-morbid conditions (e.g. diabetes, diabetes control, cause of CKD, and hypertension), and tobacco use, and assess modification of the effect of periodontal status by socioeconomic status and antibody titers. In addition, for Aim 2, we will assess modification of the effect of periodontal status by access to dental care. To reduce bias due to informative missingness, these models will be jointly estimated with a survival model for time to death or dropout, with the estimated latent log-eGFR trajectories based on the mixed model serving as predictors in the survival model. For the secondary outcome, albuminuria, we use Cox models to examine the effect of periodontal status on development of macroalbuminuria ($\geq 300\text{mg/g}$). In addition to adjusting for aforementioned confounders, we will adjust for reported use of angiotensin converting enzyme inhibitors, as well as dose, both as time-dependent covariates.
3. Minimum detectable effects: Based on renal function and periodontal disease prevalence in the larger D-ARIC cohort,⁵ we estimate that we will have 80% power in two-sided tests with a type I error rate of 5% to detect at least a 4.5 ml/min/1.73m² difference in net decline in eGFR over the 10-year period (0.45 ml/min/1.73m²/year) between participants with and without periodontal disease. We will also have 80% power to detect increases of 8 to 13 percentage points in the incidence of eGFR declines of $\geq 25\%$, depending on the overall incidence of this outcome. For Aim 2, we will have 80% power to detect increments of 11 ml/min/1.73m² in the effect of periodontal status on net decline within subgroups with poor access to dental care, as compared to those with good access, if 50% of participants have poor access; this will increase to 13 ml/min if only 20% of participants have poor access.

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes
 No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and

for DNA analysis RES_DNA = "CVD Research" would be used? Yes No

(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? Yes No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? Yes No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: <http://www.csc.unc.edu/ARIC/search.php>
 Yes No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

Kshirsagar AV, Offenbacher S, Moss KL, Barros SP, Beck JD. Antibodies to periodontal organisms are associated with decreased kidney function. The Dental Atherosclerosis Risk In Communities study. Blood Purif. 2007;25(1):125-32. Epub 2006 Dec 14.

Kshirsagar AV, Moss KL, Elter JR, Beck JD, Offenbacher S, Falk RJ. Periodontal disease is associated with renal insufficiency in the Atherosclerosis Risk In Communities (ARIC) study. Am J Kidney Dis. 2005 Apr;45(4):650-7.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes No

11.b. If yes, is the proposal
 A. primarily the result of an ancillary study (list number* _1996.01_)
 B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____)

*ancillary studies are listed by number at <http://www.csc.unc.edu/aric/forms/>

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from <http://publicaccess.nih.gov/> are posted in <http://www.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

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2. U.S. Renal Data System. *USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. Bethesda, MD2009.
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5. Kshirsagar AV, Moss KL, Elter JR, Beck JD, Offenbacher S, Falk RJ. Periodontal disease is associated with renal insufficiency in the Atherosclerosis Risk In Communities (ARIC) study. *Am J Kidney Dis*. Apr 2005;45(4):650-657.
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9. Anders HJ, Banas B, Schlondorff D. Signaling danger: toll-like receptors and their potential roles in kidney disease. *J Am Soc Nephrol*. Apr 2004;15(4):854-867.
10. Stehman-Breen CO, Gillen D, Steffes M, et al. Racial differences in early-onset renal disease among young adults: the coronary artery risk development in young adults (CARDIA) study. *J Am Soc Nephrol*. Sep 2003;14(9):2352-2357.
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- 15.** Levey AS, Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem.* Apr 2007;53(4):766-772.
- 16.** Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* May 5 2009;150(9):604-612.