ARIC MANUSCRIPT PROPOSAL #775

PC Reviewed: 02/15/01 **Status: A** **Priority: 2**
SC Reviewed: 03/01/01 **Status: A** **Priority: 2**

1.a. Full Title: Relationship of periodontal disease to renal insufficiency: The ARIC Study

b. Abbreviated Title: Periodontitis and renal insufficiency

2. Writing Group

Lead: John R. Elter
Address: Center for Oral and Systemic Diseases
UNC School of Dentistry
Campus Box #7450
Chapel Hill, NC 27599-7450

Phone: (919) 843-9974 Fax: (919) 966-6761
E-mail: john_elter@dentistry.unc.edu
Members of Writing Group:
Abhijit V. Kshirsagar Ronald J. Falk
James Beck Steven Offenbacher
Josef Coresh

3. Time Line

Obtain data set:	February 2001
Begin statistical analysis:	February 2001
Complete statistical analysis:	March 2001
Complete manuscript:	April 2001

4. Rationale

Cross-sectional (1, 2), case-control (3-6), and longitudinal reports (7-11) have shown a strong association of periodontitis, a type of chronic infection, and atherosclerotic cardiovascular disease. The bacterial pathogens causing periodontitis are felt to incite an inflammatory response that damages the endothelium and promotes atherosclerosis (12).

The role of chronic infections in the pathogenesis of chronic kidney disease has not been studied. Yet, cardiovascular disease and chronic kidney disease share many similarities. The two conditions often co-exist (13, 14,) and share many common risk factors (15-17). Furthermore, atherosclerosis of large and medium-sized arteries supplying the kidney has been postulated to contribute to chronic kidney disease (18-21).

The prevalence and incidence of chronic kidney disease have been rising steadily for the last 15 years (17). As chronic infections are felt to promote atherosclerosis, they may have an important role in the pathogenesis of chronic kidney disease. We therefore propose to

study the association of periodontitis and renal insufficiency in the Dental ARIC cohort at visit 4.

5. Main Hypotheses/Study Questions

Our *a priori* hypothesis is that periodontal disease and renal function are inversely related. That is, a high level of periodontitis is associated with a low level of renal function, and that having periodontitis increases the risk of having renal dysfunction compared to not having periodontitis. Furthermore, we hypothesize that there is a graded response between the level of periodontitis and level of renal dysfunction.

6. Data

All variables necessary for the analysis are available in the Dental ARIC cohort of the ARIC Study. The variables include age, race, center, gender, weight, serum creatinine concentration, periodontal pocket depth and attachment level, hypertension status, diabetes status, smoking status, education level, total cholesterol, HDL cholesterol, LDL cholesterol, fibrinogen, white blood cell count.

Outcome variable. The main outcome variable is calculated glomerular filtration rate (cGFR), a newly devised and validated estimate of renal function (22).

$$cGFR = 186 * (\text{Serum creatinine})^{-1.154} * (age)^{-0.203} * 1.212(\text{if black}) * 0.742(\text{if female})$$

We will use calculated glomerular filtration rate as both a continuous variable, and as a categorical variable. All the demographic and medical variables needed for the calculation are available for the Dental ARIC cohort.

Main independent variable. The main independent variable is periodontal disease as defined by the interval variable "extent of periodontal attachment loss (AL) (corrected for PD 4+ mm at buccal sites) at least 3 millimeters". In addition, Periodontal case status will be defined as follows: No periodontitis = extent AL < 3%, mild periodontitis = extent AL 3% - < 30%, and severe periodontitis = extent AL 30%+. Quintiles of extent AL will be used to evaluate a dose-response between periodontal disease and impaired cGFR.

Covariables. The covariables will be a composite of race and ARIC field center, 3 levels of education (to control for SES), hypertension, smoking (current heavy, current light, former heavy, former light, or never), diabetes mellitus, fibrinogen, white blood cell count, and plasma LDL, HDL, and triglyceride levels.

Planned Analysis.

1. Logistic regression with relative odds of impaired renal function (yes/no) with no periodontitis, moderate periodontitis, or severe periodontitis as the independent variable.
2. Linear regression with calculated glomerular filtration rate as a continuous outcome variable and extent of periodontal attachment level as a continuous variable, and categorized into no periodontitis, moderate peridontitis, and severe periodontitis as described under "main independent variable" above.

3. Multivariable models will be adjusted for the *a priori* suspected confounders: race and ARIC field center, education, hypertension, smoking, diabetes mellitus, fibrinogen, white blood cell count, and LDL, HDL, and triglyceride levels.

Time window. This study will be a cross-sectional study of the data obtained from ARIC cohort members at Visit 4.

Inclusions/exclusions. This study will include all Dental ARIC cohort members for whom periodontal measures and serum creatinine were available, and exclude persons reporting being on dialysis. Approximately 6800 persons had periodontal examinations at Visit 4.

7. a. Will data be used for non-CVD analysis in this manuscript? **X Yes**
b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH= "CVD Research" for non-DNA analysis, and for DNA analysis, and for DNA analysis RES_DNA= " CVD Research" would be used? **X No**

8. a. Will DNA data be used in the manuscript? **X No**

References

1. Loesche WJ, Schork A, Terpenning MS, Chen YM, Dominguez BL, Grossman N. Assessing the relationship between dental disease and coronary heart disease in elderly U.S. veterans. Journal of the American Dental Association 1998;129:301-311.
2. Mattila K, Nieminen M, Valtonen V, Rasi V, Kesaniemi Y, Syrjala S, et al. Association between dental health and acute myocardial infarction. Br Med J 1989;298:779-782.
3. Grau AJ, Buggle F, Ziegler C, Schwarz W, Meuser J, Tasman AJ, et al. Association between acute cerebrovascular ischemia and chronic and recurrent infection. Stroke 1997;28:1724-1729.
4. Mattila K, Valle M, Niemenin M, Valtonen V, Hieteniemi K. Dental infections and coronary atherosclerosis. Atherosclerosis 1993;103:205-211.
5. Syrjanen J, Valtonen VV, Iivanainen M, Kaste M, Huttunen JK. Preceding infection as an important risk factor for ischaemic brain infarction in young and middle aged patients. Br Med J Clin Res Ed 1988;296:1156-1160.
6. Kweider M, Lowe GD, Murray GD, Kinane DF, McGowan DA. Dental disease, fibrinogen and white cell count; links with myocardial infarction? Scottish Medical Journal 1993;38:73-74.
7. Beck J, Garcia R, Heiss G, Vokonas PS, Offenbacher S. Periodontal disease and cardiovascular disease. J Periodontol 1996;67(10 Suppl):1123-1137.
8. DeStefano F, Anda R, Kahn H, Williamson D, Russell C. Dental disease and risk of coronary heart disease and mortality. BMJ 1993;306:688-691.
9. Joshipura K, Rimm E, Douglass C, Trichopoulos D, Ascherio A, Willett W. Poor oral health and coronary heart disease. J Dent Res 1996;75:1631-1636.

10. Mattila K, Valtonen V, Nieminen M, Huttunen J. Dental infection and the risk of new coronary events: Prospective study of patients with documented coronary artery disease. Clinical Infectious Diseases 1995;20:588-592.

11. Genco R, Chadda S, Grossi S, al e. Periodontal disease is a predictor of cardiovascular disease in a Native American population. J Dent Res 1997;76(Special Issue):408.

12. Beck JD, Offenbacher S, Williams R, Gibbs P, Garcia R. Periodontitis: a risk factor for coronary heart disease? Ann Periodontol 1998;3:127-141.

13. Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol 1998;9: S16-S23.

14. Cheung AK, Sarnak MH, Yan G. Dwyer JT, Heyka RJ, Rocco MV, Teehan BP, Levey AS, and the Hemodialysis (HEMO) Study. Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. Kidney Int 2000;58: 353-362.

15. Klag MJ, Whelton PK, Randal BL. Blood pressure and end-stage renal disease. N Engl J Med 1996;334:13-18.

16. Rowe J, Andres R, Tobin J et al. The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study. J Gerontol 1976;31:155-163.

17. USRDS, US Renal Data System. USRDS 2000 Annual Data Report. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease. Bethesda, MD, April 2000.

18. Baboolal, K, Evans C, Moore RH. Incidence of end-stage renal disease in medically treated patients with severe bilateral atherosclerotic renovascular disease. Am J Kidney Dis 1998;31:971-977.

19. Caps MT, Zierler E, Pollisar NL, Bergelin RO, Beach KW, Cantwell-Gab K, Casadei A, Davidson RC, Strandness DE. Risk of atrophy in kidneys with atherosclerotic renal artery stenosis. Kidney Int 1998;53:735-742.

20. Mailloux LU, Napolitano B, Bellucci AG, Vernace M, Wilkes BM, Mossey RT. Renal vascular disease causing end-stage renal disease, incidence, clinical correlates, and outcomes: a 20 year clinical experience. Am J Kidney Dis 1994;24: 622-629.

21. Textor SC. Pathophysiology of renal failure in renovascular disease. Am J Kidney Dis 1994;24: 642-651.

22. Levey AS, Green T, Kusek JW, Beck J. A simplified equation to predict glomerular filtration rate from serum creatinine. (Abstract) J Am Soc Nephrol 2000;11:155A.