ARIC MANUSCRIPT PROPOSAL #673 REVISED

PC Reviewed: 01/06/00	**Status:__A__**	**Priority:__2_**
SC Reviewed: 01/06/00	**Status:__A__**	**Priority:__2_**

1a. Title:

The effect of smoking on renal function in the ARIC Study - 9 years of follow-up.

b. Abbreviated Title: Smoking and renal function

2. Working group

Susan L. Hogan, Herman A. Tyroler, Josef Coresh, Romulo E. Colindres, Jianwen Cai, Gerardo Heiss

Contact information for: Susan L. Hogan
CB 7155, 347 MacNider Building
Division of Nephrology and Hypertension
UNC-CH School of Medicine
Chapel Hill, NC 27599-7155

Work) 919-966-2561
Fax) 919-966-4251

e-mail) slh@med.unc.edu

3. Timeline

Data analysis will begin upon approval of the manuscript proposal and acquisition of the data (estimated goal: February 2000) and continue through the spring of 2000. Writing will begin in April of 2000, with completion of a publication-ready manuscript in the late spring or summer of 2000.

4. Rationale:

Although there are structural differences, published evidence suggests a striking similarity between glomerulosclerosis and atherosclerotic lesions in both animals and humans (Grond 1986; Keane, 1988; Avram, 1989; Diamond, 1991; Kamanna, 1993). In summary, both lesions are characterized by a deposition of lipids, an influx of monocytes, formation and accumulation of lipid-laden foam cells and the expansion of the extracellular matrix, subsequently leading to the replacement of normal structures by fibrous tissue. Because of these proposed similarities, it is likely that the risk factors for developing renal dysfunction will parallel the risk factors for developing atherosclerotic disease in other organ systems. Smoking is known to accelerate the development of cardiovascular and cerebrovascular disease through the atherosclerotic process.

Smoking and nicotine have been shown to cause acute changes in renal hemodynamics and the presence of albumin in the urine (Ritz 1998, Halimi 1998, Gambaro 1998). In a cross-sectional study of over 1,500 subjects, smoking was significantly related to urinary albumin

excretion and the prevalence of microalbuminuria, both signs of early renal dysfunction (Cirillo 1998). Smoking has also been shown to be associated with the development of end-stage renal disease (ESRD) in more than 330,000 middle-aged men screened for participation in the Multiple Risk Factor Intervention Trial (MRFIT) (Whelton 1995). Furthermore, smoking has been identified as a prognostic factor for progression of renal insufficiency to ESRD in patients with lupus nephritis (Ward 1992) and other primary renal diseases (Orth 1998). On the other hand, in a population-based case-control study (n=716 ESRD patients, n=361 controls), the risk of ESRD was not associated with a history of smoking (Perneger 1997).

In summary, the majority of the literature to date suggests that there is a relationship between smoking and the development of renal impairment. However, long-term data on changes in renal function in the general population are not available. Therefore, the focus of this manuscript will be to expand the knowledge of the role of smoking in early changes in kidney function. An emphasis will be placed on the potential differing impact of smoking on renal function by diabetic status, including patients with glucose intolerance, and hypertension.

5. Main Hypotheses

Smoking predicts worsening changes in renal function over time in a dose-dependent fashion.

The smoking and renal function relationship is altered by level of glucose metabolism (diabetic status) and hypertension.

6. Design

The ARIC study provides a cohort of approximately 15,800 men and women between the ages of 45 and 64 followed in four US communities (The ARIC Investigators 1989). Serum creatinine concentration, a measure of renal function, has been measured at baseline and at 3 and 9 years of follow-up. Smoking history and changes in smoking habits have been evaluated at each of these visits, including at the 6 year visit. The main outcome of interest will be a change in renal function as measured by serum creatinine concentration.

The outcome will be defined as ARIC participants who have a change $\geq$ 0.4 mg/dl in serum creatinine between the baseline and 9-year follow-up versus those participants who have < 0.4 mg/dl change in serum creatinine. This cut-off is identified a priori as a significant change in renal function. A study of the within-person and day-to-day variability in serum creatinine estimated the 'minimum detectable difference' at which a change in serum creatinine is likely to be real at 0.19 mg/dl (Eckfeldt 1994). We chose a value just over twice that to increase the specificity of the outcome and to allow for the higher variability expected over a longer duration of follow-up. The calculated difference in serum creatinine concentration will be corrected for inter-laboratory calibration differences since the 2 values were quantified at different laboratories. The main exposure for this analysis will be the smoking status (current smoker, previous smoker, or never smoked) and the cumulative smoking history in total lifetime pack-years of smoking.

Time to the outcome (Δ serum creatinine $\geq$ 0.4 mg/dl) will be modeled using survival analysis with smoking and other covariates (age, sex, race, hypertension, diabetes). Logistic

regression will be used if the assumptions for survival analysis are not met. Poisson regression will be also examined because it has been used in a previous analysis of the impact of lipids on renal function in the ARIC data (manuscript in press). Survival analysis will likely be the best method of analysis because it will provide more statistical power and will also take advantage of the two study visits during which renal function was evaluated (at 3 and 9 years follow-up).

Calculated continuous changes in estimated kidney function will also be evaluated including: 1) change in estimated creatinine clearance from baseline to 9-years using the Cockcroft and Gault formula [ml/min = (140 - age) x weight (kg) / Serum creatinine (mg/dl) x 72] in men (times 0.85 in women) (Cockcroft, 1976); and 2) the slope of the reciprocal serum creatinine (across the 3 visits).

Clearly there are potential difficulties and many statistical analysis options for evaluating the renal function outcome of interest. Therefore, Susan L. Hogan and the writing group will work closely with Dr. Jianwen Cai of the UNC Biostatistics Department to assure the appropriate analysis is conducted.

7. Data Requirements

Susan L. Hogan will perform the data analysis as part of her dissertation for her PhD degree through the UNC-CH Department of Epidemiology. The SAS system will be used for the data analysis. Information on the main exposure variable and covariates will be needed from baseline, and 3, 6 and 9 year visits. The specific information needed from each time measured (baseline, 3, 6 and 9 year visits) includes:

Identification information:

Patient identification number (Study ID), visit date, clinic code

Demographics:

Race, gender, date of birth (and age at each visit)

Specific measures from each visit:

Weight
Height
Smoking history and changes in smoking habits since the previous visit
Serum creatinine (not available for the 6 year visit)
Diabetic status
Glucose
Insulin
Systolic and Diastolic blood pressures
Medications – current use at each visit
Co-morbid conditions (current and history of)

Manuscript Requests with Overlap

Proposal #347 "Risk Factors for 9-year Incidence of Decreased Renal Function"
Lead on writing group – Josef Coresh

Proposal #223 "Risk Factors for Decreased Renal Function in the ARIC Study"
Lead on writing group – Josef Coresh

Dr. Coresh is a collaborator on this manuscript proposal so he is aware of the demarcations between the above projects and the proposed work. This proposal is submitted, with his collaboration and approval, for the focused topic regarding the effect of smoking on renal function.

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