ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #223

1. Title:
Risk factors for decreased renal function in the ARIC Study

2. Writing Group:
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To be determined: coordinating center contact and other interested ARIC investigators

3. Timeline:
The data for these analyses are already available as part of ARIC visits 1 & 2. We project that the analyses and writing will take place over the next year.

4. Rationale:
End-stage renal disease (ESRD) incidence and prevalence have been increasing relentlessly as long as national statistics have been available. In 1989, approximately 200,000 people received treatment for ESRD with direct costs of 6 billion dollars (US Renal Data System 1991). The incidence of ESRD has doubled in the past 5 years and continues to increase at an annual rate of 8.3%. Patients treated for ESRD experience a markedly higher risk of morbidity and mortality. Despite these statistics the epidemiology of ESRD is poorly understood with few large prospective studies of the progression of renal disease. MRFIT and HDFP have reported on hypertension and race as risk factors for a rise in plasma creatinine among men. However, much more information is needed.

ARIC provides an excellent opportunity to study risk factors for the early stages of the decline in renal function. The availability of serum creatinine and anthropometric measures at visit 1 and visit 2 provides an estimate of the creatinine clearance of renal function. Measurement of the glomerular filtration rate (GFR) using an intravenous infusion of insulin is considered the gold standard for the measurement of renal function. Measurement using radioactive nuclides, such as ^{125}I-iothalamate and ^{99}Tc-EDTA are nearly as good. However, creatinine clearance based on either a 24 hour urine collection or serum creatinine are still the most widely used estimates of GFR and renal function. Estimates of GFR from serum creatinine must take into account differences in body muscle mass (typically estimated crudely using age, weight and gender). Because of compensatory changes in creatinine metabolism rises in serum creatinine will often lag the initial declines in GFR which in turn lags after the initial histopathological changes in the kidney. Therefore, one must be cautious in using creatinine clearance to estimate renal function in individuals. However, overall creatinine clearance estimates based on serum creatinine has been shown to correlate well with GFR in many studies. Recent studies indicate that given more than 2 years of follow-up measurements of the decline in renal function based on creatinine clearance correlate well with similar measures based on GFR. Therefore, elevations in serum creatinine provide good evidence for decreased GFR and allow for a systematic study of risk factors for renal disease.

The plasma creatinine measures during visit 1 and 2 were conducted by the ARIC central laboratory using a modified kinetic Jaffe method (ARIC PROTOCOL Manual 10, version 1.0 and 2.0) The same method was

used in both visits with reagents and calibration standards provided by a single manufacturer (Coulter Diagnostics). Given adequate quality control data these should provide a solid basis for the proposed study. The data will be explored for laboratory drift and corrections will be made for differences across centers and time of sample collection where needed.

The proposed study will be divided into two analyses. A cross-sectional analysis of risk factors for elevated creatinine at baseline and prospective analysis of risk factors for a rise in plasma creatinine during the 3 years of follow-up. In each analysis an estimated creatinine clearance will e constructed after accounting for the estimated lean body mass. This estimated creatinine clearance will be used as the dependent variable in the regression analysis. Each analysis will also be done using logistic regression with binary definition (yes/no) of decreased renal function (elevated creatinine) or declining renal function (rise in serum creatinine larger than the expected laboratory plus physiologic variation). These parallel analytic approaches will ensure that results are robust to the specific statistical model used.

The following independent variables will be explored as risk factors for the presence and progression or renal disease:

High blood pressure and hypertension - strongly implicated in the pathophysiology of renal disease
Diabetes - known to be associated with an increased risk of renal disease. All analyses will be done stratified on diabetes status and the possibility of interaction between diabetes and other risk factors will be examined. In addition, fasting plasma glucose and insulin will be examined.
Dyslipidemia - elevated cholesterol is suspected as possible risk factors for renal disease but little data in humans is available.
Black race - known to be associated with a markedly increased risk of end-stage renal disease. Socioeconomic factors will be explored as confounders of this association.
Gender - will be used as a stratifying variable as well as possible confounder
Age - will be explored as a confounder as well as being a factor in declining renal function.
Analgesic Use - particularly acetominophen containing compounds have been associated with end-stage renal disease mainly in case-control studies.
Cigarette smoking - limited evidence is available in renal disease but worth exploring given the strong association with atherosclerosis
Other potential confounders - will be explored (see data requirements)

5. Main Hypothesis/Issues to be Addressed:
Hypertension, diabetes, lipids, black race, and analgesic use are associated with the presence as well as progression of decreased renal function.

The associations observed in the cross-sectional analysis will be similar to the associations in the prospective analysis.

6. Data Requirements:
Data analysis will be performed by Dr. J. Coresh at Johns Hopkins School of Hygiene & Public Health in collaboration with Dr. J. Nieto.
Variables needed: plasma creatinine and time of collection, center, age, gender, race, blood pressure, anthropometric data, lipids, lipoproteins and apolipoproteins, medical history data (diabetes), risk factor questions (smoking, alcohol consumption).