

Proteinuria and hypertensive nephrosclerosis in African Americans

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Proteinuria and hypertensive nephrosclerosis in African Americans. Proteinuria is a known risk factor for both renal disease progression and cardiovascular morbidity and mortality in hypertensive populations. African Americans are among the highest risk groups for development of renal disease in the setting of hypertension and suffer a disproportionate burden of end-stage renal disease attributed to hypertension. Population-based studies indicate that African Americans have higher rates of albuminuria compared to non-African Americans in part due to higher rates of hypertension and diabetes in African Americans as compared to non-Hispanic whites for example. The African American Study of Kidney Disease and Hypertension (AASK) Trial was a prospective long-term clinical trial that examined the effect of aggressive blood pressure lowering versus usual blood pressure lowering in three different classes of anti-hypertensives on renal outcomes in approximately 1200 African Americans with hypertensive nephrosclerosis. Two thirds of trial participants had <300 mg protein, and one third had \geq 300 mg of protein in a 24-hour urine specimen at baseline. Those with >300 mg protein excretion compared to those with <300 mg protein excretion at baseline had more rapid decline in renal function and ESRD events. Moreover, lower levels of proteinuria than previously thought may be important for identifying those at higher risk for kidney disease progression. The AASK cohort study, a follow-up to the trial, is now underway. The longer term follow-up will provide new insights into proteinuria and other risk factors for progression of kidney disease in hypertensive nephrosclerosis.

Albuminuria is a relatively common finding among African Americans. Data from the NHANES III survey indicate that about 8% of African Americans have an abnormal rate of albumin excretion. Moreover, this is nearly 50% higher than prevalence among non-African Americans [1]. Also significantly higher urine albumin excretion rates are observed in African Americans in those over age 40 compared with Hispanics and non-Hispanic whites in this age range. This increased prevalence is due in large part to the higher rates of hypertension and diabetes mellitus among this ethnic group [1, 2]. In addition,

the lower rates of blood pressure control among hypertensive African Americans may also contribute to higher prevalence of albuminuria because higher blood pressure can be associated with excessive albumin excretion rate [2–4]. Another factor that may contribute to albuminuria prevalence among African Americans is the higher incidence of focal segmental glomerulosclerosis in this population [5–8]. Albuminuria is a hallmark of FSGS, and may be a harbinger of this relatively common form of human glomerulopathy.

As in other populations, albuminuria is associated with diabetes and hypertension among African Americans, and cardiovascular morbidity and mortality are higher in African Americans compared to Caucasians [1–3]. Hypertensive African Americans with albuminuria are more likely to develop heart failure [9], and African Americans in the ARIC study are more likely to develop cardiovascular complications in the presence of albuminuria.

End-stage renal disease (ESRD) attributed to hypertension occurs at a rate that is five-fold higher among African Americans compared to non-African Americans [10]. The reasons for this discrepancy remain unclear. Therefore, efforts to identify and treat hypertension and proteinuria among this population are an important public health issue. Recent analyses from the NHANES III database and USRDS suggest that the higher incidence of ESRD in African Americans is related to increased rate of progression of chronic kidney disease (CKD), and not increased prevalence. Moreover, two major factors associated with more rapid progression of CKD among African Americans are hypertension and albuminuria [4].

METHODS

The African American Study of Kidney Disease and Hypertension was a multicenter prospective, randomized, controlled trial involving nearly 1100 nondiabetic adult African Americans with longstanding hypertension and reduced glomerular filtration rate. Participants in this trial were deemed to have hypertensive nephrosclerosis as the underlying cause for CKD based on clinical and

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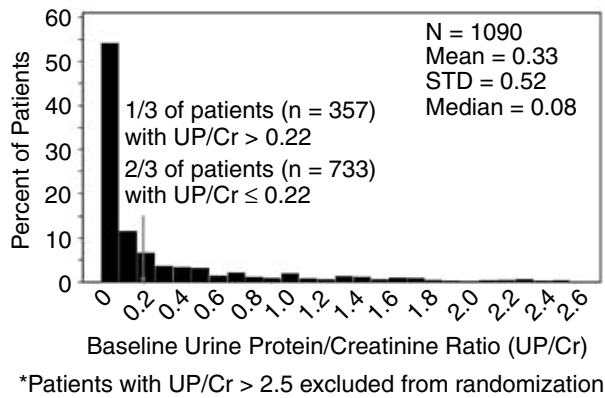


Fig. 1. Distribution of baseline urine protein creatinine ratio for participants in the African American Study of Hypertension and Kidney Disease (AASK) trial.

biochemical characteristics. The study was a 2 × 3 factorial design in which participants were assigned to one of two levels of blood pressure control (lower BP group, mean arterial pressure <92 mm Hg and usual BP group mean arterial pressure 102–107 mm Hg), and one of three different antihypertensive-based regimens administered once daily [10]. These classes included the beta-blocker metoprolol, the dihydropyridine calcium channel blocker amlodipine, and the angiotensin II–converting enzyme inhibitor ramipril. Participants were followed-up to four years with measurements of glomerular filtration rate and urine protein at baseline, and every six months during follow-up. The primary outcome was the rate of decline in glomerular filtration rate estimated by renal clearance of iothalamate. The main secondary outcome was a composite of rapidly declining GFR (50% reduction or >25 mL/min/1.73m² from baseline), ESRD, or death from any cause. An additional secondary outcome was the change in urine protein excretion rate from baseline. Urinary protein excretion rate and creatinine clearance were measured by 24-hour urine collection conducted at baseline, and repeated at six-month intervals during the trial. There was no difference in the primary or secondary outcome for blood pressure groups, or in the rate of decline in GFR among antihypertensive classes. However, those assigned to ramipril had a significantly lower rate of composite outcome and ESRD alone.

RESULTS AND DISCUSSION

As illustrated in Figure 1, approximately two thirds of study participants had a urine protein/creatinine ratio of ≤0.22 g/g, and one third had a ratio >0.22 g/g. Analysis of change in urine protein excretion rate indicated that urine protein increased over time, regardless of group assignment. However, the increase in urine protein excretion was greater in those assigned to the usual compared to the lower BP group and those assigned to amlodip-

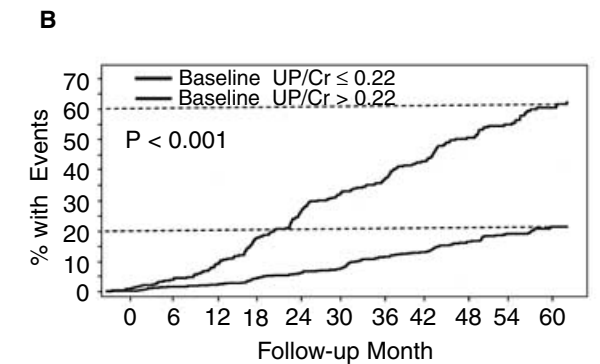
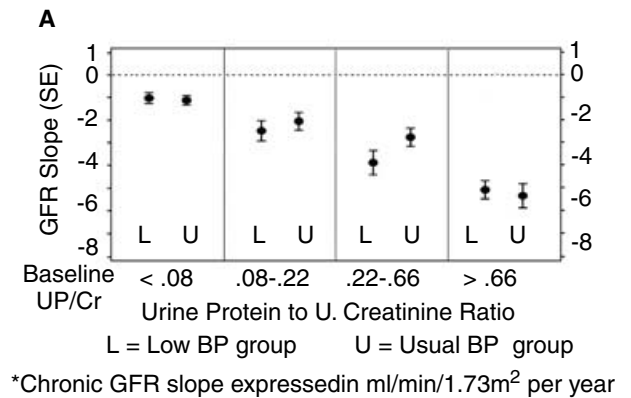


Fig. 2. Association of baseline urine protein creatinine ratio and GFR slope by blood pressure group (A) and % events (rapidly declining GFR or ESRD or death) (B). The rate of decline is illustrated for those assigned to usual (U) and lower (L) blood pressure groups by quartile of baseline urine protein creatinine ratio.

ine compared to ramipril or metoprolol. Further analysis of the relationship of proteinuria to outcomes was investigated. Among AASK participants, those with higher urine protein/creatinine ratios at baseline had faster rate of decline in GFR and higher incidence of the composite end point (Fig. 2) regardless of BP group. It is important to note that MAP was maintained approximately 10 mm Hg lower in the lower BP group compared to the usual BP group. There were no differences in rate of decline in GFR among drug treatment groups for those with baseline urine protein excretion ≤0.22 g/g. In sharp contrast, those with urine protein creatinine ratio >0.22 assigned to amlodipine had a rate of decline in GFR approximately two-fold faster than those assigned to ramipril, and about 1.2 times faster than those assigned to metoprolol (Fig. 3). The rate of decline in glomerular filtration rate was similar among different classes of antihypertensive agents for any level of baseline urine protein excretion, except for those participants with urine protein creatinine excretion rate >0.66 g/g assigned to amlodipine. Among participants with a baseline urine protein creatinine ratio >0.66 g/g assigned to amlodipine, the rate of decline in GFR was doubled compared to those assigned to

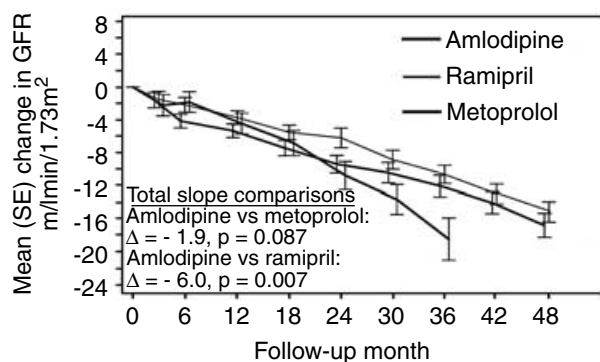


Fig. 3. Relationship between the rate of decline in GFR by drug treatment assignment for those with a baseline urine protein creatinine ratio > 0.22. The rate of decline was more rapid in those assigned to amlodipine.

ramipril. In addition, higher urine protein excretion rate was associated with a three-fold higher event rate for the composite outcome (Fig. 2B). Interestingly, the rate of rise in urine protein excretion among those assigned to amlodipine was attenuated by lower blood pressure assignment, but this did not translate into a slower rate of decline in GFR for the amlodipine compared to the other groups.

To assess whether the urine protein excretion was an independent predictor of ESRD, multivariate analysis was performed controlling for baseline GFR level. In this analysis, the level of baseline urine protein was an independent predictor of subsequent development of ESRD, even among those with the lowest levels of urine protein in the range of <0.08 g/g (unpublished observations). Moreover, after controlling for randomized group, baseline GFR, and change in GFR over the initial six months of follow-up, the change in urine protein from baseline to six-month follow-up was an independent predictor of subsequent development of ESRD. The single measurement of protein excretion rate at six months was also shown to predict the subsequent development of ESRD. And, after controlling for baseline proteinuria, baseline GFR did not predict the rate of decline in GFR. Taken together, these findings suggest that urine protein excretion in African Americans with hypertensive nephrosclerosis is an independent predictor of subsequent decline in kidney function. For the clinician, these analyses from the AASK trial strongly suggest that both lowering blood pressure and protein excretion rate are important for slowing the rate of decline in kidney function and reducing the risk of ESRD.

Future studies are needed to further evaluate the relationship of proteinuria and its reduction with specific interventions on outcomes in patients with hypertensive nephrosclerosis. The African American Study of Kidney

Disease and Hypertension cohort study [14] is a follow-up of participants in the AASK Trial. In the cohort study, albuminuria along additional clinical, biochemical, environmental, and genetic factors will be examined as potential kidney disease progression promoters (AASK cohort). An important question is whether strategies specifically designed to target lowering proteinuria are renoprotective in hypertensive nephrosclerosis. Clinical trials focusing on lowering proteinuria in this population are needed to address this important question.

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