

Racial Differences in Microalbumin Excretion in Healthy Adolescents

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Abstract—It has been suggested that “normal” levels of urine albumin excretion rate (AER) may be predictive of an increased risk for progression of hypertension, cardiovascular morbidity, and mortality. No data are available on the effect of race and gender on AER in normal youth. We evaluated AER in timed urine samples in subjects participating in a study of stress-induced pressure natriuresis. A total of 317 healthy, normotensive adolescents aged 15 to 18 years (155 males and 162 females; 216 blacks and 101 whites) participated in a 5-hour testing protocol, which included a 1-hour period of mental stress preceded and followed by a 2-hour rest period. AER (micrograms per minute) was determined after 60 minutes of rest, and log transformation was used to normalize the data. AER was significantly higher in blacks as compared with whites ($P=0.006$). We also found a race-by-sex interaction, which was driven by the low albumin excretion in white females ($P=0.036$). Indexing urine albumin to creatinine excretion revealed the same pattern. Among blacks, AER was also higher in subjects who demonstrated impaired stress-induced pressure natriuresis versus those with normal sodium excretion ($P=0.024$). AER was related to blood pressure only in African-American males. The relative elevation of AER in normotensive black adolescents and the association with impaired pressure natriuresis and blood pressure is noteworthy. These findings suggest that albumin excretion may be a marker for a population at increased risk for the development of vascular and renal injury even before the manifestation of hypertension. (*Hypertension*. 2008;51:334-338.)

Key Words: albuminuria ■ blood pressure ■ natriuresis ■ risk factors ■ continental population groups

The term “microalbuminuria” describes a urinary albumin excretion rate (AER) that is increased but not to the level of overt proteinuria. Microalbuminuria is associated with an increased risk for cardiovascular and renal disease in diabetic and nondiabetic patients. Typically threshold values of 30 mg/g of creatinine or 20 μ g/min have been used to define an abnormal AER. Recently, several large population studies demonstrated a positive relationship between AER within the “normal” range and cardiovascular morbidity and mortality.^{1,2} In a study of \approx 1500 normotensive nondiabetic adult subjects, investigators found that albumin excretion predicted incident hypertension and progression of hypertension.³ Those individuals in the highest quartile (AER >6.6 mg/g of creatinine for males and 15.24 mg/g of creatinine for females) had a 2-fold increase in their risk of developing hypertension. Moreover, urine albumin excretions as low as 1.7 to 3.8 mg/g of creatinine for males and 3.4 to 7.5 mg/g of creatinine for females were associated with an increased risk for developing hypertension. These authors suggest that higher levels of AER may reflect vascular or renal injury and precede the development of hypertension.

There have been a few studies in adult populations demonstrating that gender and ethnic groups influence albumin

excretion.⁴⁻⁷ Although some data are available on AER in healthy nondiabetic children and adolescents,⁸ little is known about the effect of race or gender on AER in childhood. Similarly, the relationship between blood pressure (BP) and albumin excretion in children with normal BP has not been studied.

We analyzed AER in healthy adolescents with normal casual BP participating in a study of stress-induced pressure natriuresis. We hypothesized that AER would be higher in blacks and would correlate with systolic BP and sodium excretion. We report on our measurements of AER and its association with race, sex, sodium excretion, and BP in 317 black and white (ie, of European-American origin) adolescents.

Materials and Methods

Subjects

Subjects aged 15 to 18 years were recruited from the public school system in Augusta for inclusion in studies of stress-induced pressure natriuresis. Exclusion criteria included any chronic illness, medication use, positive pregnancy test, or BP >95th percentile for age and height. Urinary microalbumin was measured on a subsample of 322 subjects from a cohort of 647 subjects tested in this protocol, all of whom completed the protocol. Of these, 5 were considered not to

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Table 1. Subject Characteristics and Baseline Measurements by Race and Sex

Variable	CA Male	AA Male	CA Female	AA Female	Significant Effects
No.	61	94	40	122	NA
Age, y	16±1	16±1	17±1	16±1	CA>AA†
Height, m	1.77±0.07	1.74±0.07	1.64±0.06	1.62±0.06	CA>AA†, M>F†
Weight, kg	74±16	71±15	59±10	68±19	M>F†
BMI, kg/m ²	24±5	23±4	21±3	25±6	AA>CA†, F>M*
Systolic BP, mm Hg	107±8	111±9	101±8	106±10	AA>CA†, M>F†
Diastolic BP, mm Hg	65±7	68±8	64±9	67±8	AA>CA†
Urinary flow rate, mL/min	4±2	4±3	4±2	4±2	None
Sodium excretion, mEq/h	14±7	14±8	11±5	11±6	M>F†
Creatinine excretion, mg/min	1.46±0.6	1.48±0.7	1.01±0.4	1.20±0.5	M>F†

NA indicates not applicable; AA, black; CA, white; M, male; F, female.

* $P=0.05$.

† $P=0.001$.

have valid readings for AER, leaving a total of 317 subjects for analysis. Consent was obtained from the parent and subject, and the study was approved by the institutional review board at the Medical College of Georgia.

Protocol

Details of the study protocol used at the Georgia Prevention Institute are provided in previous publications.^{9,10} BP, weight, and height were obtained at a screening visit conducted before initiating the study protocol. For 3 days before testing, subjects were provided with a diet that delivered 4000 ± 200 mg of Na^+ and 2600 ± 200 mg of K^+ per day. Overnight urine collections were obtained to monitor compliance with the diet regimen. Compliance was estimated in a subsample of 206 subjects (65%). Of these, 98% ($n=201$) had an acceptable overnight urine volume (100 mL), and of these, 93% ($n=187$) had an acceptable overnight sodium excretion of <120 mEq. Subjects came in on day 4 to complete the research protocol. Because of the potential influence of menstrual blood on urine albumin determination, females were not studied while on their menses.

On the morning of testing, the patients were provided breakfast. A 5-hour protocol was then conducted that involved collecting urine samples every hour. Subjects were seated in a comfortable chair for the entire protocol, and ambulation was only allowed for collection of urine samples. The study consisted of a 2-hour baseline period followed by a 60-minute stress period and then a 2-hour recovery period. The subjects emptied their bladders at the beginning of the baseline period. Timed urine samples were then collected every 60 minutes. The stress consisted of a competitive video game between 2 subjects for a cash prize. BP and pulse were measured every 15 minutes by Dynamap and averaged across the condition for analysis.

Assays

Urine samples for measurement of albumin excretion were obtained at the end of the first hour of baseline (rest). Urine albumin concentration was measured by enzyme-linked immunosorbent assay (Exocell, Inc) with an interassay coefficient of variation of $<5\%$ and a sensitivity of $0.1 \mu\text{g/mL}$. The urinary albumin concentration is used to calculate the AER rate, which is expressed as micrograms per minute. The albumin excretion was also indexed to creatinine excretion to provide the albumin:creatinine ratio (ACR), which is expressed as micrograms per milligram of creatinine. Urine sodium and creatinine were measured by ion-sensitive electrode (NOVA Biomedical), which has have an intra-assay coefficient of variation of $<3\%$ and an interassay coefficient of 4% for both variables.

Analysis

Data analyses were performed using SPSS 14. *T* tests were used to examine group differences in subject characteristics and baseline

data. ANOVA was used to examine the effects of race, sex, and the interaction between race and sex on the variables of interest. A logarithmic transformation was performed on the AER and ACR data before analysis. We also examined differences in log AER as a function of the direction of change in the sodium excretion response to the stress protocol. This factor was not included in the ANOVA model because of the small sample sizes for both white males and females who retained sodium during stress. Pearson correlation coefficients were used to calculate the correlations between log AER and BP throughout the protocol for each of the subgroups. A $P<0.05$ was considered significant.

Results

Subjects

Table 1 provides the subject characteristics for the study by race and sex. Overall, blacks were younger, shorter, and yet had greater body mass index (BMI) and higher casual BP. Males had higher BP, sodium excretion, and creatinine excretion than females at baseline. Urine flow rate did not differ between groups.

AER: Race and Sex

Data for AER by race and sex are presented in Figure 1. The ANOVA revealed a highly significant race effect, with greater log AER in blacks compared with whites ($P=0.006$). The race-by-sex interaction was also significant ($P=0.036$). The interaction was primarily driven by the white females, who had the lowest levels of log AER. Similar but less significant results were observed when age and BMI were included in the model as covariates.

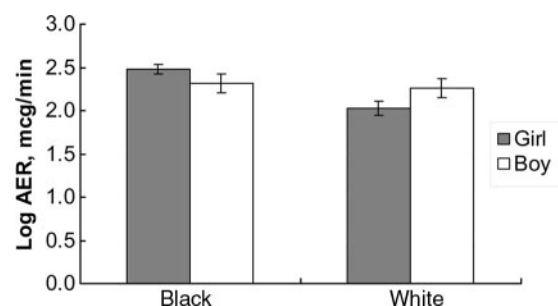


Figure 1. Race and gender differences in urinary microalbumin excretion.

Table 2. Stress-Related Changes (Δ) by Race and Sex

Variable	CA Male	AA Male	CA Female	AA Female	Significant Effects
Δ Systolic BP, mm Hg	9 \pm 8	7 \pm 7	5 \pm 5	5 \pm 7	M>F†
Δ Diastolic BP, mm Hg	7 \pm 5	5 \pm 4	5 \pm 4	5 \pm 5	M>F*
Δ Heart rate, bpm	7.9 \pm 9	5 \pm 7	8 \pm 9	5 \pm 8	CA>AA*
Δ Sodium excretion, mEq/h	5.2 \pm 6.0	3.6 \pm 5.0	2.6 \pm 6.0	2.9 \pm 5.0	M>F*

AA indicates black; CA, white; M, male; F, female.

* $P=0.05$.† $P=0.001$.

We also examined the effects of race and sex on albumin excretion adjusted for creatinine excretion. The results were similar. Blacks had significantly greater log ACR than whites (1.87 ± 0.8 versus 1.65 ± 0.8 $\mu\text{g}/\text{mg}$ of creatinine; $P=0.01$), which approached significance in the overall model ($P=0.09$). The effect of sex was highly significant ($P<0.0001$), with higher levels of log ACR in girls than in boys (2.01 ± 0.7 versus 1.58 ± 0.8 $\mu\text{g}/\text{mg}$ of creatinine) because of lower levels of baseline creatinine excretion in girls (see Table 1). Urine albumin excretion was highest in black females and lowest in white females regardless of whether data are expressed as micrograms per minute or indexed to creatinine.

Stress Protocol

The stress-induced changes in BP, heart rate, and sodium excretion are provided in Table 2. Males had greater changes in BP and sodium excretion, whereas whites had greater changes in heart rate. The stress-induced change in sodium excretion was available for 213 of the 216 black subjects. This included 158 subjects who showed the expected natriuretic response to the stressor and 55 subjects who showed a reduction in sodium excretion from baseline to stress. This pattern is referred to as impaired stress-induced pressure natriuresis (SIPN). These individuals had a significantly higher level of AER ($P=0.024$) than those who showed normal SIPN, as shown in Figure 2. Data on sodium handling during stress was available for 99 of the 101 white subjects. This included 78 subjects who showed normal SIPN and 21 who demonstrated impaired SIPN. The difference in AER between these 2 groups was not significant.

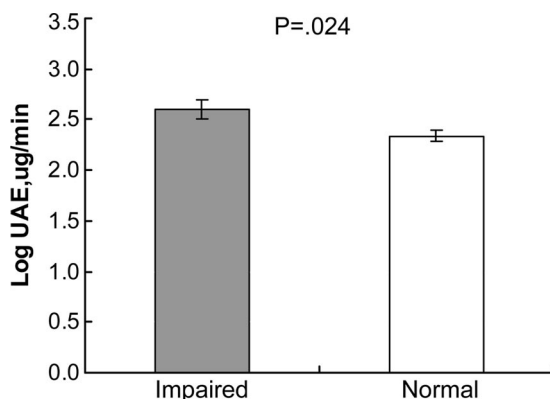


Figure 2. Differences in microalbumin excretion as a function of change in sodium excretion during stress in blacks.

Relationship to BP

The correlations between AER and systolic BP throughout the protocol are provided in Table 3. As can be seen, AER was positively related to systolic BP, but only in black males. Higher correlations were observed during the protocol than was evident for casual systolic BP. The correlations with diastolic BP were not significant in any group.

Discussion

The main finding of this study revealed that healthy, normotensive black adolescents demonstrated an $\approx 10\%$ higher level of AER than healthy, normotensive white adolescents. Furthermore, this relationship was influenced predominantly by differences between black and white females. Black females excreted $\approx 22\%$ more albumin than white females, whereas AER levels were not significantly different for black and white males.

Varying racial and gender differences in AER excretion have been noted in studies of adult populations. In the longitudinal Bogalusa study, investigators found that urine albumin concentrations (milligrams per liter) were highest in young adult black females (19 to 37 years) as compared with white females and all of the males.^{4,6,7} Differences in AER between non-Hispanic blacks and other groups were found when National Health and Nutrition Examination Survey III data in adults were analyzed.⁵ These investigators found that non-Hispanic blacks had higher AER than whites, even after adjusting for age, BP, BMI, and other risk factors. However, they found no difference in albumin excretion (reported as milligrams per gram of creatinine) based on gender after accounting for the difference in creatinine excretion between males and females. Similarly, Murtaugh et al¹¹ documented a greater prevalence of microalbuminuria (25 to 249 mg/g of creatinine) in blacks as compared with whites. Although, overall AER was significantly higher in males versus females, and albumin excretion in black women was similar to

Table 3. Correlations Between Urinary Albumin Excretion and Systolic BP Across the Protocol

Time Period	CA Male	AA Male	CA Female	AA Female
Casual	-0.03	0.245*	0.012	0.014
Baseline	-0.17	0.362†	0.030	0.101
Stress	-0.03	0.384†	0.122	0.078
Recovery	-0.05	0.313†	0.033	0.041

AA indicates black; CA, white.

* $P=0.05$.† $P=0.001$.

that of white men and was highest in black men. The lowest excretion among the groups was found in white women. In contrast, in a small study, Gerber et al¹² reported finding higher AER in whites as compared with nonwhites; however, these data were biased by the pooling of the data on blacks and Hispanic subjects and the limited numbers of hypertensive blacks (1 total).

Increased AER is often attributed to elevated BP. Our data indicate that higher BP is associated with greater AER in black males but not in any of the other 3 groups. This relationship was strongest for BP obtained during the stress period, which accounted for more than twice the percentage of variance (14.7%) of AER as casual BP (6%). Although the relationship between microalbuminuria and hypertension is well recognized, these findings lend support to recent suggestions that even high normal BP may be associated with higher AER. Knight et al¹³ reviewed data from the National Health and Nutrition Examination Survey III survey and found that subjects with high normal BP were twice as likely to have microalbuminuria (>30 mg/g of creatinine) and higher "normal" albumin excretion as compared with those with BP <120/80 mm Hg. They demonstrated that as BP rises above 120/80, the risk for higher albumin excretion increases. Similar results were reported by Murtaugh et al,¹¹ who documented a continuous relationship between BP and albumin excretion, even within the range of nonhypertensive pressures. The link between AER and higher BP has also been confirmed in a young adult population (19 to 32 years).^{6,7} This relationship persisted even when hypertensive subjects were excluded and was not affected by gender.⁶ Data from the Bogalusa Heart Study also demonstrate that higher BPs in childhood were linked with microalbuminuria in young adulthood in blacks but not in whites.⁴ Although we did not see a relationship between BP and AER in black females, their casual BP and BPs throughout the protocol were higher than white females (data not shown). The relatively high AER in black females may be because of the combination of BP with other factors, such as BMI, or other yet-unidentified variables.

An increased sodium load has also been associated with the development of renal damage independent of its effect on BP.¹⁴ Therefore, we examined levels of AER as a function of changes in sodium handling during a 1-hour mental stress task. Previously, we reported that approximately one third of black youth show impaired SIPN.¹⁵ Further studies demonstrated greater impairment of stress-induced pressure natriuresis in black compared with white adolescents.¹⁶ In this study, black subjects with impaired SIPN had more than a 10% higher level of AER than individuals who displayed a normal natriuretic response to stress. These results are consistent with a small study of 22 white hypertensive adults. Bigazzi et al¹⁷ demonstrated a higher AER in patients with essential hypertension who were classified as salt sensitive as compared with those who were salt resistant.

To our knowledge, this is only the second study in which AER is a marker for vascular or renal injury/alterations in a pediatric nondiabetic population. In a small study, Grunfeld et al¹⁸ found significantly higher AER in 33 normotensive children with 1 hypertensive parent as compared with control

children with a negative family history. A report from the Bogalusa Heart Study described above linked childhood BP with AER in adulthood but did not provide data on AER during childhood.⁴

This study has limitations. A postural effect on albumin excretion in some patients cannot be excluded, because we did not use first-morning urine samples for analysis. Intrasubject variability in albumin excretion could also influence our findings, because only 1 sample was analyzed per subject. Because of the observed differences in creatinine excretion based on gender and race, we used timed urine samples and calculated an AER. This approach is consistent with previous reports documenting higher creatinine excretion in males and blacks as compared with females and whites.^{5,19} The use of spot ACRs may contribute to an overestimation or underestimation of albumin excretion. Another issue is the potential effect of age and pubertal development on albumin excretion. Some investigators have shown that age and pubertal status affect AER in normal children and adolescents.^{8,20} Although not specifically assessed, pubertal development was likely complete in this population of older normal adolescents.

Perspectives

It is well established that blacks are disproportionately affected by hypertension and chronic kidney disease. In view of the presumed susceptibility of blacks to vascular and kidney injury, the demonstration here of relative elevation of AER in normotensive black adolescents as compared with white youth is noteworthy. The link between higher BP and impaired sodium natriuresis shown here supports a propensity to develop sustained hypertension with age. Importantly, our findings suggest that target organ effects, such as a relatively high AER, may precede the clinical finding of sustained hypertension in this high-risk population. If these findings are confirmed, high normal AER may be considered a factor that prompts early intervention for blacks with BPs in the prehypertensive range.

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Disclosures

None.

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