Correlates of Urinary Albumin Excretion in Young Adult Blacks and Whites

The Coronary Artery Risk Development in Young Adults Study

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The rate of urinary albumin excretion is an important risk factor for kidney failure, stroke, and cardiovascular disease, perhaps because higher albumin excretion reflects endothelial cell dysfunction. The authors characterized urinary albumin excretion according to blood pressure, diabetes mellitus, and other factors in 2,582 Black and White participants in the Coronary Artery Risk Development in Young Adults (CARDIA) Study who were aged 18–30 years in 1985–1986. Urinary albumin and creatinine concentrations were determined using single untimed samples 10 and 15 years later. The albumin:creatinine ratio was analyzed as a continuous variable and a dichotomous variable (higher albumin excretion, including microalbuminuria (25–249 mg/g) and macroalbuminuria (≥250 mg/g)). Seventy percent of persons with increased albumin excretion were both normoglycemic and normotensive (systolic/diastolic blood pressure <140/90 mmHg and no use of antihypertensive drugs). Even when diabetic subjects, who have greater risk, were excluded, albumin excretion rose continuously as blood pressure increased among Blacks; increases started at systolic/diastolic blood pressures of 130/85 mmHg among Whites. Furthermore, blood pressure measured up to 15 years earlier predicted incident higher albumin excretion at year 15. These findings persisted after adjustment for age, body mass index, smoking, and blood lipid and plasma insulin levels. A risk of higher urinary albumin excretion exists at blood pressure levels below those commonly regarded as hypertension, with a greater risk among Blacks than among Whites.

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; CI, confidence interval; OR, odds ratio; TE, technical error as a percentage of the mean.

Microalbuminuria, the excretion of albumin in the urine at a level above the normal range but below the level of macroalbuminuria, is common in both hypertension and diabetes mellitus. It predicts stroke (1, 2), coronary heart disease (1, 3–5), and cardiovascular disease, as well as total mortality (1, 6) and end-stage renal disease (7–12). Even below the standard cutpoint for microalbuminuria, urinary albumin excretion at a rate regarded as high normal is associated with higher rates of all-cause death and cardiovascular disease in persons without diabetes (13). Elevations in albumin excretion may underlie the relation of renal disease to cardiovascular disease, especially in diabetic nephropathy (14). In fact, the predictive value of microalbuminuria may be a reflection of arterial endothelial cell dysfunction generally (11, 15). As a result, microalbuminuria may be of interest in itself as a subclinical marker of endothelial cell dysfunction, a condition that is believed to promote atherosclerosis.

Therefore, it is important to understand how factors such as blood pressure may lead to a higher rate of urinary albumin excretion. Some studies have suggested that the association between blood pressure and albumin excretion is...
continuous across the range of blood pressures (16–21), although other studies in Whites of European descent have not (22, 23). Only two studies have addressed the level of blood pressure at which microalbuminuria begins to increase (18, 20).

In this paper, we report on urinary albumin excretion based on the urinary albumin:creatinine ratio (24), both as a continuous variable and as the prevalence of higher albumin excretion (micro- or macroalbuminuria) in different population groups. In our analysis, we focused on the relation of albumin excretion to blood pressure, fasting glucose status, and other coronary heart disease risk factors in healthy young Black and White men and women in whom a single untimed urine sample had been obtained on two occasions, 10 and 15 years after the beginning of the study. Furthermore, we examined the utility of blood pressure measurements up to 15 years earlier in predicting the occurrence of higher albumin excretion.

**MATERIALS AND METHODS**

The Coronary Artery Risk Development in Young Adults (CARDIA) Study has as its overarching goal the description of the evolution of cardiovascular disease risk, starting in young adulthood (25). The study recruited 5,115 Black and White men and women aged 18–30 years in 1985–1986 at four clinical centers located in Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. Follow-up examinations were completed 2, 5, 7, 10, and 15 years later. Of the 3,312 persons whose blood pressure and fasting glucose status could be defined because of missing values for blood pressure and fasting glucose status, 235 were excluded because of pregnancy and 27 were excluded because the participant had fasted for less than 8 hours (n = 103). Thus, the final analytical sample included 2,582 participants.

### Examinations

Information on race, sex, and age was provided by self-report. Interviews were used to obtain sociodemographic information such as education, income, medical history, and medication use. Certified technicians measured blood pressure three times after a 5-minute rest, with 1-minute intervals


<table>
<thead>
<tr>
<th></th>
<th>Black males (n = 536)</th>
<th>Black females (n = 615)</th>
<th>White males (n = 780)</th>
<th>White females (n = 651)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age (years)</strong></td>
<td>34.3†‡</td>
<td>34.8†</td>
<td>35.6</td>
<td>35.7</td>
</tr>
<tr>
<td><strong>Mean weight (kg)</strong></td>
<td>88.1†‡</td>
<td>82.0†</td>
<td>84.8†</td>
<td>69.7</td>
</tr>
<tr>
<td><strong>Mean body mass index§</strong></td>
<td>27.8†‡</td>
<td>30.3‡</td>
<td>26.5†</td>
<td>25.4</td>
</tr>
<tr>
<td><strong>Mean systolic blood pressure (mmHg)</strong></td>
<td>115.6†‡</td>
<td>110.4‡</td>
<td>111.5†</td>
<td>102.8</td>
</tr>
<tr>
<td><strong>Mean diastolic blood pressure (mmHg)</strong></td>
<td>76.6‡</td>
<td>74.4‡</td>
<td>73.4†</td>
<td>67.4</td>
</tr>
<tr>
<td><strong>Current smoking (%)</strong></td>
<td>31†‡</td>
<td>24†</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td><strong>Education (% with more than high school)</strong></td>
<td>58†‡</td>
<td>69†</td>
<td>80</td>
<td>84</td>
</tr>
</tbody>
</table>

* SD, standard deviation.  
† Males differed from females within race (p < 0.02).  
‡ Blacks differed from Whites within sex (p < 0.02).  
§ Weight (kg)/height (m)².

### TABLE 2. Numbers of cases of higher urinary albumin excretion (A/kC ≥ 25 mg/g, including microalbuminuria and macroalbuminuria) based on the year 15 measurement (1999–2000), according to the year 10 measurement (1995–1996) and the average of the year 10 and year 15 measurements, Coronary Artery Risk Development in Young Adults Study, 1985–1986 to 2000

<table>
<thead>
<tr>
<th>Yes (n = 126)</th>
<th>No (n = 36)</th>
<th>Yes (n = 37)</th>
<th>No (n = 56)</th>
<th>Yes (n = 126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (n = 2,400)</td>
<td>No (n = 2,363)</td>
<td>2,327</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>Yes (n = 182)</td>
<td>No (n = 56)</td>
<td>0</td>
<td>56</td>
<td>45</td>
</tr>
</tbody>
</table>

* Albumin/(k × creatinine), where k adjusts for race and sex differences in typical daily creatinine excretion (24).  
† UAE, urinary albumin excretion.
between measurements, using a Hawksley random-zero sphygmomanometer (W. A. Baum Company, Copague, New York). Blood pressure categories were defined according to the guidelines set forth by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (26): 1) hypertensive (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of antihypertensive medication); 2) blood pressure ≤139/89—not hypertensive but systolic pressure within 130–139 mmHg or diastolic pressure within 85–89 mmHg; 3) blood pressure ≤129/85—not either of the two previous categories but systolic pressure within 120–129 mmHg or diastolic pressure within 80–84 mmHg; 4) blood pressure <119/79—not either of the three previous categories but systolic pressure within 110–119 mmHg or diastolic pressure within 75–79 mmHg; and 5) blood pressure <110/75—none of the previous categories but systolic pressure less than 110 mmHg and diastolic pressure less than 75 mmHg.

Blood samples were drawn from seated participants after at least 8 hours of fasting. Tourniquet use was limited to 2 minutes to prevent hemococoncentration. Blood samples were centrifuged, aliquoted, and frozen at −70°C within 90 minutes of drawing. Aliquots were stored locally for 1 month and then shipped on dry ice for analysis or long-term storage. Glucose was measured using a Cobas Mira Plus chemistry analyzer (Roche Diagnostic Systems, Inc., Montclair, New Jersey) with the hexokinase ultraviolet method at Linco, Inc. (St. Louis, Missouri) (27, 28). The classification of diabetes was assigned to persons who had a fasting serum glucose level greater than or equal to 126 mg/dl or who were using insulin or oral hypoglycemic medication in any year (29). Given that only 15 of 109 persons taking medication for diabetes (in the entire CARDIA sample) both were taking insulin and had been diagnosed before age 30 years, most diabetics in this study are likely to have had type 2 diabetes. Impaired fasting glucose was defined as a fasting serum glucose level of 110–125 mg/dl in subjects who were not taking medication. Normal fasting glucose was defined as a fasting serum glucose level less than 110 mg/dl in persons who were not taking medication, according to the American Diabetes Association definition (29).

### Measurement of urinary albumin and creatinine levels

A single, untimed (spot) urine sample was collected at both the year 10 and year 15 examinations when convenient during the clinic visit, usually shortly after arrival at the clinic. Albumin and creatinine levels were measured in year 10 at the Regional Kidney Disease Program Renal Laboratory, Hennepin County Medical Center, Minneapolis, Minnesota. Albumin was assessed using a nephelometric procedure with a specific anti-albumin monoclonal antibody, and creatinine was assessed using the Jaffe method. The year 15 samples were analyzed at the Northwest Lipid Research Laboratory in Seattle, Washington, using a nephelometric procedure for albumin and the Jaffe method for creatinine.

### Estimation of albumin excretion rate

We estimated albumin excretion rate using the formula albumin/$k \times$ creatinine (denoted $A/kC$), where $k$ adjusts for race and sex differences in typical daily creatinine excretion (24). For these calculations, albumin and creatinine concentrations are expressed in mg/liter and g/liter, respectively. Thus, $A/kC$ is expressed in mg/g. Briefly, urinary creatinine concentration in men was multiplied by 0.68, which approximated the ratio of albumin:creatinine cutoffs used by Warram et al. (30) to indicate sex-specific elevated albumin
TABLE 4. Geometric mean A/kC* (average of year 10 and year 15 measurements (1995–2000)) and prevalence of higher albumin excretion (A/kC ≥25 mg/g, including micro- or macroalbuminuria), by blood pressure status, Coronary Artery Risk Development in Young Adults Study, 1985–1986 to 2000

<table>
<thead>
<tr>
<th>Systolic/diastolic blood pressure category†</th>
<th>No.</th>
<th>Geometric mean A/kC ≥25 mg/g</th>
<th>% with A/kC ≥25 mg/g</th>
<th>No.</th>
<th>Geometric mean A/kC ≥25 mg/g</th>
<th>% with A/kC ≥25 mg/g</th>
<th>No.</th>
<th>Geometric mean A/kC ≥25 mg/g</th>
<th>% with A/kC ≥25 mg/g</th>
<th>No.</th>
<th>Geometric mean A/kC ≥25 mg/g</th>
<th>% with A/kC ≥25 mg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;110/75 mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whites</td>
<td>419</td>
<td>6.6</td>
<td>6.1</td>
<td>321</td>
<td>7.8</td>
<td>8.6</td>
<td>198</td>
<td>8.9</td>
<td>15.1</td>
<td>100</td>
<td>9.8</td>
<td>16.6</td>
</tr>
<tr>
<td>p value comparing races</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whites</td>
<td>755</td>
<td>5.9</td>
<td>3.0</td>
<td>379</td>
<td>6.5</td>
<td>4.4</td>
<td>185</td>
<td>7.3</td>
<td>4.6</td>
<td>74</td>
<td>7.4</td>
<td>9.3</td>
</tr>
<tr>
<td>p value comparing sexes</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whites</td>
<td>419</td>
<td>6.5</td>
<td>5.2</td>
<td>427</td>
<td>7.4</td>
<td>7.1</td>
<td>262</td>
<td>8.4</td>
<td>10.6</td>
<td>120</td>
<td>9.7</td>
<td>16.2</td>
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<tr>
<td>p value comparing sexes</td>
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</tr>
<tr>
<td>Whites</td>
<td>755</td>
<td>5.9</td>
<td>3.5</td>
<td>273</td>
<td>6.8</td>
<td>5.7</td>
<td>121</td>
<td>7.7</td>
<td>9.4</td>
<td>54</td>
<td>7.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Overall</td>
<td>1,174</td>
<td>6.2</td>
<td>4.5</td>
<td>700</td>
<td>7.1</td>
<td>6.3</td>
<td>383</td>
<td>8.0</td>
<td>9.7</td>
<td>174</td>
<td>8.6</td>
<td>12.8</td>
</tr>
<tr>
<td>p value for comparison with blood pressure &lt;110/75 mmHg</td>
<td>0.002</td>
<td>0.14</td>
<td>&lt;0.001</td>
<td>0.0002</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Albumin (k× creatinine), where k adjusts for race and sex differences in typical daily creatinine excretion (24). k = 1 for White women, k = 0.88 for Black women, k = 0.68 for White men, and k = 0.88 for Black men.

† Blood pressure was classified first by medication status, then by the higher of systolic or diastolic blood pressure. Thus, a person with systolic blood pressure of 109 mmHg and diastolic blood pressure of 77 mmHg who was not on medication was placed in the category ≥110/75 mmHg and <120/80 mmHg.

Mean A/kC levels were similar regardless of whether the pH adjustment was done.

Laboratory methods and technical error

At year 10, samples were pH adjusted for the clinical pH. The sensitivity of the albumin assay was 0.045 mg/liter. No samples had undetectable levels of albumin. A total of 424 split samples were assayed, with 128 samples analyzed for quality assurance. A total of 25 samples were reanalyzed, with no change in the direction of the results. The mean difference, correlation coefficient (r), and technical error as a percentage of the mean (TE) were as follows:

<table>
<thead>
<tr>
<th>Year</th>
<th>TE</th>
<th>r</th>
<th>TE</th>
<th>r</th>
<th>TE</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.06</td>
<td>0.96</td>
<td>0.06</td>
<td>0.96</td>
<td>0.06</td>
<td>0.96</td>
</tr>
<tr>
<td>15</td>
<td>0.02</td>
<td>0.99</td>
<td>0.02</td>
<td>0.99</td>
<td>0.02</td>
<td>0.99</td>
</tr>
</tbody>
</table>

The mean difference was less than 0.045 mg/liter, and the correlation coefficient was 0.99. The technical error was 16.2 percent for creatinine, 10.8 percent for albumin, and 5.9 percent for albumin.
adjustment was made before freezing (8.8 mg/g) or after thawing (9.0 mg/g) ($p$ for difference = 0.6). Therefore, from a technical perspective, we decided that we could combine the data from analyses at year 10 and year 15.

**Statistical methods**

We analyzed continuous $A/kC$ values on the logarithmic scale to focus analytical attention on the central peak of the skewed distribution. For purposes of presentation, the values were transformed back to a linear scale (by exponentiation), yielding geometric means. We conducted linear regression and cross-tabulations to determine the prevalence of higher albumin excretion and its relation with blood pressure, fasting glucose status, and other covariates. With the exception of blood pressure assessments at years 0 and 7, all predictor variables were assessed at year 10. Attenuation of demographic relations was calculated as the regression coefficient for the demographic variable in the full model minus the corresponding regression coefficient in the limited model, divided by the regression coefficient in the limited model. All analyses were completed using the SAS statistical package, version 8.2 (SAS Institute, Inc., Cary, North Carolina).

**RESULTS**

**General characteristics**

Compared with Whites within sex, Blacks were heavier, had higher blood pressure, were more likely to be current smokers, and had lower educational attainment (table 1). Compared with women within race, men were heavier and had higher blood pressure; among Blacks, men were more likely than women to be current smokers and had lower educational attainment. White men had a higher body mass index (weight (kg)/height (m)$^2$) than White women, but Black men had a lower body mass index than Black women.

As in the previously reported data based on year 10 only (24), the geometric mean $A/kC$ based on the average of years 10 and 15 was higher among Blacks than among Whites and higher among men than among women (9.4 mg/g in Black men, 7.2 mg/g in Black women, 6.8 mg/g in White men, and 5.8 mg/g in White women; $p < 0.001$ for all pairwise comparisons except the comparison of White men with Black women ($p = 0.3$)). After adjustment for race and sex, persons who had received no education beyond high school had a higher geometric mean $A/kC$ ($n = 673; 7.9$ mg/g) than persons who had ($n = 1,903; 6.8$ mg/g) ($p < 0.0001$). Average $A/kC$ was slightly higher among participants over 35 years.
TABLE 5. Prevalence of higher urinary albumin excretion (A/kC ≥ 25 mg/g, including micro- or macroalbuminuria) and geometric mean A/kC* (average of year 10 and year 15 measurements (1995–2000)), according to other coronary heart disease risk factors, Coronary Artery Risk Development in Young Adults Study, 1985–1986 to 2000.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Prevalence of higher albumin excretion (%)</th>
<th>p for any difference among categories</th>
<th>Geometric mean A/kC (mg/g)</th>
<th>p for any difference among categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmatic insulin level (mU/ml)</td>
<td>Q1† 2–8 Q2 9–11 Q3 0.12–15 Q4 16–103</td>
<td>Model 1 7.9 6 4.9 8.8 0.03</td>
<td>Model 2 6.4 6.4 5.5 7.2 0.25</td>
<td></td>
</tr>
<tr>
<td>Plasma low density lipoprotein</td>
<td>cholesterol level (mg/dl)</td>
<td>Model 1 7.5 4.9 6.1 8.9 0.03</td>
<td>Model 2 7.6 5.2 6.4 8.3 0.12</td>
<td></td>
</tr>
<tr>
<td>Plasma high density lipoprotein</td>
<td>cholesterol level (mg/dl)</td>
<td>Model 1 6.5 6.6 6.2 8.1 0.58</td>
<td>Model 2 6.6 6.8 6.2 7.8 0.72</td>
<td></td>
</tr>
<tr>
<td>Plasma triglyceride level (mg/dl)</td>
<td>Model 1 4.8 5.7 7.3 9.2 0.02</td>
<td>Model 2 5.4 5.7 7.3 9.2 0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index§</td>
<td>Model 1 15.9–23.1 23.1–26.1 26.1–30.2 30.2–60.3</td>
<td>Model 2 5.6 6.2 4.8 10.8 0.0007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>Current Former Never</td>
<td>Model 1 6.2 6.7 5.1 9.5 0.03</td>
<td>Model 2 7.6 6.7 6.8 7.5 0.05</td>
<td></td>
</tr>
</tbody>
</table>

* Albumin/(k x creatinine), where k adjusts for race and sex differences in typical daily creatinine excretion (24). k = 1 for White women, k = 0.88 for Black women, k = 0.68 for White men, and k = 0.88 for Black men.
† All risk factor categories are quartiles (Q) except those for smoking. The range of risk factor values is given within each risk factor category.
‡ Model 1: Data on each risk factor were adjusted for race, sex, education, age, study center, and each of the other variables in the table.
§ Model 2: Data were further adjusted for fasting glucose status and blood pressure status: 1) systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg or use of antihypertensive medication; 2) blood pressure ≤139/89 mmHg; 3) blood pressure ≤129/85; 4) blood pressure <119/79 mmHg; or 5) blood pressure <110/75 mmHg.
‖ Weight (kg)/height (m)².

of age (n = 1,524; 7.3 mg/g) than among those below age 35 years at the year 10 examination (n = 1,052; 6.7 mg/g) (p = 0.01).

Distribution of albumin excretion values

Based on A/kC at the individual examinations, 2,327 persons consistently had normoalbuminuria and 255 persons had higher albumin excretion at either examination or both examinations (table 2). Based on the average of the year 10 A/kC and the year 15 A/kC, 2,400 of the 2,582 participants included in these analyses had normal albuminuria and 182 had higher albumin excretion (table 2). Thus, 73 persons had higher albumin excretion at one examination only, but their average A/kC was below 25 mg/g.

Based on the average of year 10 A/kC and year 15 A/kC, 18 participants had macroalbuminuria (A/kC ≥ 250 mg/g). An additional six participants had macroalbuminuria at year 15 but not at year 10, and one participant had macroalbuminuria at year 10 but microalbuminuria at year 15. Thus, 25 people had macroalbuminuria based on the maximum A/kC between years 10 and 15.

Associations with fasting glucose status at year 10

Fasting glucose status was a major correlate of albumin excretion after adjustment for sex, age, education, study center, and blood pressure status (table 3): The geometric mean A/kC (based on the average of the year 10 and year 15 measurements) was 25.7 mg/g among diabetic subjects (p < 0.0001 in comparison with normal fasting glucose), 10.0 mg/g among subjects with impaired fasting glucose (p = 0.007 in comparison with normal fasting glucose), and 6.9 mg/g among participants with normal fasting glucose. Relations with prevalence of higher albumin excretion paralleled those with the continuous variable A/kC. There was a nearly 11-fold increase in the odds of higher albumin excretion among diabetic participants compared with participants with normal fasting glucose (odds ratio (OR) = 10.91, 95 percent confidence interval (CI): 5.80, 20.5); the odds of higher albumin excretion among persons with impaired fasting glucose were threefold (OR = 3.05, 95 percent CI: 1.28, 7.3) those of persons with normal fasting glucose. Blacks with normal fasting glucose had a higher A/kC and a greater prevalence of higher albumin excretion than Whites with normal fasting
glucose ($p < 0.0001$). Whites and Blacks with impaired fasting glucose and diabetes had similar $A/kC$’s ($p > 0.4$), but Blacks with diabetes had a greater prevalence of higher albumin excretion ($p = 0.006$). Men had a higher $A/kC$ and a greater prevalence of higher albumin excretion than women, regardless of fasting glucose status.

**Associations with blood pressure at year 10**

Geometric mean $A/kC$ (average of the year 10 and year 15 measurements) increased for each higher category of blood pressure, the increase appearing to be steeper the higher the blood pressure ($p < 0.0001$; table 4, figure 1), after adjustment for sex, age, education, study center, and fasting glucose status. For each standard deviation of increase in systolic and diastolic blood pressure (modeled as continuous variables), the odds of higher albumin excretion increased approximately 1.5-fold (for a 12.3-mmHg increase in systolic blood pressure, $OR = 1.60$, 95 percent CI: 1.38, 1.85; for a 9.9-mmHg increase in diastolic blood pressure, $OR = 1.51$, 95 percent CI: 1.29, 1.76). When systolic and diastolic pressure were modeled together, systolic blood pressure remained an independent predictor of higher albumin excretion ($OR = 1.48$, 95 percent CI: 1.19, 1.84), while diastolic blood pressure had an odds ratio of only 1.10 per standard deviation. Compared with systolic blood pressure, a one-standard-deviation increase of 8.1 mmHg pulse pressure (systolic minus diastolic) was associated with a smaller increase in risk of elevated albumin excretion ($OR = 1.27$, 95 percent CI: 1.10, 1.46).

The tendency for men to have a higher $A/kC$ than women was most apparent for the two highest blood pressure categories. Among hypertensive subjects, approximately 18 percent had higher albumin excretion. The quadratic pattern of relation between higher albumin excretion and blood pressure seen in figure 1 persisted among persons with normal fasting glucose (data not shown). The higher prevalence of higher albumin excretion in Blacks than in Whites in the nonhypertensive range ($<140/90$ mmHg and not on medication; see table 4) also persisted among persons with normal fasting glucose (data not shown).

**Level of albumin excretion predicted from blood pressure measurement prior to year 10**

The prevalence of higher albumin excretion was greater the higher the blood pressure, even for blood pressure measured at year 0, 10 years before urinary albumin was first assessed. In general, the shapes of the relations between blood pressure and higher albumin excretion were similar regardless of when the participant reached the level of blood pressure and regardless of whether blood pressure was modeled using the criteria of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (figure 1) (26) or separately by systolic blood pressure, diastolic blood pressure, or pulse pressure (data not shown). The relation became more stable as the prevalence of subjects in the higher blood pressure categories increased in the later years of the study. In part, the prediction from early blood pressure measurements arose from blood pressure tracking (i.e., the correlations between pairs of blood
pressure measurements at years 0 and 7 versus year 10 were 0.59 and 0.70 for systolic blood pressure and 0.46 and 0.62 for diastolic blood pressure, respectively).

Most people with higher albumin excretion were normotensive and had a normal fasting glucose level at year 10. Of the 182 participants with higher albumin excretion (based on the average of the year 10 and year 15 measurements), 22 had diabetes or impaired fasting glucose but not hypertension; 24 had hypertension but not diabetes or impaired fasting glucose; and eight had both hypertension and either diabetes or impaired fasting glucose. Thus, 54 participants (30 percent) had diabetes, impaired fasting glucose, or hypertension.

Associations of higher albumin excretion with other risk factors measured at year 10

Both the continuous-measure A/\(k\C\) (average of the year 10 and year 15 measurements) and the measure of prevalence of higher albumin excretion had weaker relations with other year 10 coronary heart disease risk factors than they did with blood pressure and fasting glucose status (table 5). Albumin excretion increased with plasma triglyceride level, apparently more rapidly the higher the level of triglycerides; the association was somewhat attenuated after adjustment for blood pressure and fasting glucose status. A U-shaped relation was seen with body mass index, slightly attenuated after adjustment for blood pressure and fasting glucose status. Relations with fasting plasma insulin and low density lipoprotein cholesterol lost statistical significance after adjustment for blood pressure and fasting glucose status. Albumin excretion was unrelated to high density lipoprotein cholesterol or cigarette smoking. The associations of the two measures of albumin excretion with fasting glucose status and blood pressure shown in tables 3 and 4 were little changed by further adjustment for the coronary heart disease risk factors listed in table 5 or in the subset of participants without diabetes or hypertension (data not shown).

Attenuation of demographic associations by risk factor adjustment

A substantial portion of the association of prevalence of higher albumin excretion with demographic factors was explained by adjustment for blood pressure group and fasting glucose status (29 percent of the race difference, 34 percent of the sex difference, 23 percent of the education difference, and 89 percent of the age difference). Nevertheless, the race, sex, and education differences remained statistically significant after this adjustment (\(p < 0.0006\) in each case; \(p = 0.35\) for age). Findings were similar for geometric mean A/\(k\C\).

Findings for incident higher albumin excretion and other definitions of higher albumin excretion

The associations of higher albumin excretion with year 10 blood pressure and fasting glucose status were insensitive to the way in which A/\(k\C\) was combined across years 10 and 15 and, in particular, held for incident higher albumin excretion (figures 2 and 3). The associations were clearest in the analysis based on the maximum A/\(k\C\) between years 10 and 15.

FIGURE 3. Relation of year 10 fasting glucose status to higher urinary albumin excretion (UAE) (A/\(k\C\) \(>\) 25 mg/g) according to four alternative definitions: incident, not persistent, persistent, and present at either examination (see Materials and Methods for details), Coronary Artery Risk Development in Young Adults Study, 1985–1986 to 2000. Data were adjusted for year 10 age, sex, race, education, and blood pressure. Note that the y-axis scale differs between figures 2 and 3.
The association of higher albumin excretion with blood pressure was least apparent in persons whose higher albumin excretion was not sustained at year 15.

DISCUSSION

The healthy young adults studied in CARDIA experienced a significant prevalence of microalbuminuria (6.4 percent) and a lower prevalence of macroalbuminuria (0.7 percent), based on the average of the A/kC’s obtained at years 10 and 15. A/kC increased with both impaired fasting glucose and diabetes and with rising systolic and diastolic blood pressures, regardless of whether the higher albumin excretion outcome was incident (at year 15 only), persistent (at both year 10 and year 15), or prevalent (at either year or both years). Blood pressure was predictive of albumin excretion 10–15 years later. Seventy percent of micro- and macroalbuminuria cases were among persons with both normal fasting glucose and normal blood pressure. Because higher urinary albumin excretion is a subclinical marker for endothelial cell dysfunction in the arterial system and albumin excretion rate is related to higher risk of cardiovascular disease and other chronic diseases (1–6, 8–12, 33–36), the findings of this study imply a significant prognostic value of urinary albumin excretion both below and above the cutoffs used for microalbuminuria, particularly in a population where the opportunity for primary prevention of cardiovascular disease and kidney disease still exists.

There is general agreement that microalbuminuria occurs frequently in subjects with diabetes mellitus (21–23, 37–40). The nearly sevenfold increase in prevalence of micro- and macroalbuminuria among diabetic CARDIA subjects (41 percent) as compared with those with normal fasting glucose (7 percent) is similar to the Pima Indian experience (47 percent in diabetic subjects vs. 8 percent in those with normal glucose tolerance) (41) and agrees with the results of other studies showing an increase in the prevalence of higher albumin excretion among persons with impaired fasting glucose (39, 41–43). These data support the idea that in some people, microalbuminuria may precede the onset of clinically defined diabetes (39).

We confirmed previous reports that the rise of albumin excretion began within the normal range of blood pressure values (16–19, 40, 41, 44–48). These data prospectively demonstrate that a rising blood pressure, even below the range recommended for treatment (26), relates prospectively to the development of higher albumin excretion. The increased prevalence of higher blood pressure and higher albumin excretion at each level of blood pressure among Black participants could be useful in focusing investigations on the disproportionate burden of kidney disease among Blacks as compared with Whites.

With the possible exception of fasting plasma triglyceride level, albumin excretion showed much stronger associations with blood pressure and fasting glucose status than with other coronary heart disease risk factors in this young, healthy cohort. These results agree with those from other reports showing inconsistent relations of age (5, 6, 13, 40–43, 49, 50), smoking (19, 40, 42, 43, 49, 51), body mass index (18, 19, 21, 39, 40, 42), and triglycerides (39, 40, 42, 43, 45, 52) with albumin excretion. The modest strength of the association of these covariates with albumin excretion, differences in the types of participants studied, and different methods of assessing albumin excretion may all have contributed to these inconsistencies in the literature.

The National Kidney Foundation guidelines for assessment of proteinuria (26) recommend screening adults using the albumin:creatinine ratio or an albumin-specific dipstick in a single untimed urine sample. This is consistent with our previous report, in which we adjusted the ratio for race and sex differences in creatinine excretion (thus partially addressing differences in skeletal muscle mass) (24). Although use of the ratio A/kC is likely to misclassify some people’s urinary albumin excretion rate, timed urine samples are also subject to misclassification due to inadequate collection and inaccurate timing.

While most clinical guidelines recommend repeat testing, this is generally not possible in epidemiologic studies. To partially mimic this procedure, we focused on the average of A/kC’s in two untimed urine samples separated by 5 years. Nevertheless, the similarity of findings in this study, whether based on a single untimed urine sample at year 10 only or on incident cases at year 15, implies that considerable epidemiologic information about the causes and consequences of urinary albumin excretion can be obtained in a single untimed urine sample.

In addition to diabetes and hypertension, we found that Black race, male sex, fasting serum glucose level, and blood pressure level within the normotensive range were strong correlates of high normal albumin excretion, microalbuminuria, and macroalbuminuria. Identification of other physiologic, genetic, or environmental factors affecting urinary albumin excretion in normotensive, normoglycemic persons should be a priority. Other investigators have also observed that microalbuminuria is a fairly common occurrence in people who do not have diabetes (1) or who have neither diabetes nor hypertension (49). We add to this the observation that A/kC and microalbuminuria increased at lower levels of normal blood pressure in Blacks than in Whites and that blood pressure measured 10–15 years earlier predicted level of A/kC. The implications of higher A/kC and greater prevalence of micro- and macroalbuminuria in Blacks than in Whites, in men than in women, and at relatively low levels of blood pressure require more attention from both interventional (53–55) and pathophysiologic perspectives.

REFERENCES


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