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Gender- and Race-specific Determination of Albumin Excretion Rate using Albumin-to-Creatinine Ratio in Single, Untimed Urine Specimens

The Coronary Artery Risk Development in Young Adults Study

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Although albumin excretion rate is commonly estimated by using albumin/creatinine ratio (A/C), gender and race differences in creatinine excretion may bias this estimate. The authors optimize the use of an untimed (spot) urine specimen among 3,371 Blacks and Whites aged 28–40 years in the Coronary Artery Risk Development in Young Adults Study in 1995–1996. Using three 24-hour collections during the year 5 examination, they determined $k = 0.68 \times 0.88$ in Black men, 0.88 in Black women, 0.68 in White men, and 1.0 in White women to reflect gender and race differences in creatinine excretion. The authors then computed A/C adjusted for race and sex differences in creatinine excretion (A/kC) by using an untimed urine sample in the year 10 examination. A/kC ≥ 25 mg/g (194 cases of microalbuminuria and 26 cases of clinical grade albuminuria) was more common among Blacks (9.1%) than among Whites (4.2%) and among men (8.2%) than among women (5.0%). Use of the unadjusted A/C underestimated the prevalence of microalbuminuria among men by 52% and among Blacks by 26%. Adjustment of A/C permitted more accurate estimation of albumin excretion rate. Men and Blacks have a higher albumin excretion rate than do women and Whites and may thereby have an increased risk of microvascular and macrovascular disease. *Am J Epidemiol* 2002;155:1114–19.

albumins; creatine; urine

Albumin excretion rate (AER) is optimally determined by urine collection over a known duration of time. However, often a complete, timed urine collection cannot be achieved because of participant burden or logistic challenges; therefore, commonly, the ratio of urinary albumin concentration to urinary creatinine concentration (A/C) from a single urine sample has been utilized to estimate AER (1). A/C eliminates urine volume from the computation and thus decreases variance and bypasses many other errors commonly associated with timed collections. Furthermore, A/C closely approximates excretion rates of total protein or albumin across wide ranges of protein excretion, that is, well into the pathologic range (2). The study of the relation of microalbuminuria with its correlates then becomes the study of A/C with these correlates.

Since urinary creatinine is now in the denominator of A/C, any factor correlated with urinary creatinine excretion will also correlate with A/C, even if it is unrelated to urinary albumin excretion. Factors known to be related to urinary creatinine excretion across the normal kidney include sex, race, age, and muscle mass (3–5). The influence of gender has been addressed by choosing sex-specific cutpoints for the definition of abnormal ranges of A/C (3). However, this sex-specific procedure has not been verified independently, and race-specific cutpoints have not been determined. Using data from the Coronary Artery Risk Development in Young Adults (CARDIA) Study, we developed a method by which both race- and sex-specific differences in A/C, observed in presumably normal populations, could be incorporated into a valid estimate of AER.

MATERIALS AND METHODS

CARDIA has as its overarching goal the description of the evolution of cardiovascular risk, starting in young adulthood (6). The study recruited 5,115 male and female Blacks and Whites aged 18–30 years in 1985–1986 in four clinical centers, located in Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. Follow-up examinations were completed 2, 5, 7, and 10 years later. Information on race, sex, and age was provided by self-

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Abbreviations: A/C, albumin/creatinine ratio; AER, albumin excretion rate; A/kC, albumin/creatinine ratio adjusted for race and sex differences in creatinine excretion; A/sC, albumin/creatinine ratio adjusted for sex differences in creatinine excretion; CARDIA, Coronary Artery Risk Development in Young Adults; TE, technical error.

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report. Interviews were used to assess sociodemographic information such as education, income, medical history, and medication use. Lean mass (kg) was estimated at CARDIA years 5 and 10 from triceps, subscapular skinfolds, and suprailiac skinfolds (7), assuming greater density of lean mass in Blacks than in Whites (8, 9).

To determine the influences of gender and race on creatinine excretion, we analyzed creatinine excretion (mg/24 hours) averaged across the 3 days of urine collected in a subset ($n = 839$) of CARDIA participants at year 5 for a study of sodium excretion (collection started before bedtime and after voiding). Albumin was not analyzed in these urine specimens. Aliquots for each complete day were frozen separately, stored for up to a month at –20°C or lower, and shipped on dry ice to the American Health Foundation, Valhalla, New York. Urine creatinine concentration was measured in the year 5 samples by using the Jaffe method, with determination of 24-hour creatinine excretion over each of the 3 days. Split samples ($n = 162$) analyzed for quality assurance showed a mean difference (standard deviation), correlation coefficient (r), and technical error (TE) as a percentage of the mean of urine creatinine concentration of 1.6 (15.0) mg/dl, $r = 0.98$, TE = 7.5 percent.

At the year 10 examination, 3,950 persons were reexamined, constituting nearly 80 percent of the survivors. Excluded from this analysis were menstruating or pregnant women and participants who refused any aspect of the examination, gave an insufficient urine sample, had not fasted for at least 8 hours, or were missing data. We also omitted 24 people with self-report of kidney transplant ($n = 1$), glomerulonephritis or repeated episodes of pyelonephritis ($n = 22$), or dialysis ($n = 1$), most of whom did not provide a urine sample. After these exclusions, all but three participants (three Black men with values of 1.9, 1.9, and 3.0 mg/dl) had year 10 serum creatinine of less than 1.6 mg/dl. The final sample of 3,371 people had complete data on untimed urinary albumin and creatinine concentrations, age, race, sex, center, education, fasting serum glucose, blood pressure, hypoglycemic medication, and antihypertensive medication.

A single, untimed (spot) urine sample was collected at the year 10 examination when convenient during the clinic visit, usually shortly after arrival at the clinic. The volume of urine was 100 ml or more in greater than 90 percent of the samples. The pH of aliquots of urine for albumin analysis was adjusted to 6.8–7.2. The aliquots were frozen for at least 24 hours locally and sent on dry ice within 1 month to the Regional Kidney Disease Program, Renal Laboratory at Hennepin County Medical Center, Minneapolis, Minnesota. Albumin was measured in year 10 samples by nephelometry based on monoclonal antibodies to human albumin (assay sensitivity, 0.45 mg/liter), and creatinine was determined using the Jaffe method. Split samples ($n = 406$) analyzed for quality assurance showed a mean difference (standard deviation), correlation coefficient (r), and technical error as a percentage of the mean (TE) as follows: albumin: 0.002 (1.1) mg/liter, $r = 0.99$, TE = 28.2 percent; creatinine: –0.01 (25.9) mg/dl, $r = 0.96$, TE = 10.8 percent.

Statistical methods

We calculated two adjusted ratios: A/sC, which accounted for sex differences in creatinine excretion, and A/kC, which accounted for sex and race differences in creatinine excretion. The derivations of s and k are described in Results. Continuous A/C, A/sC, and A/kC were analyzed on the log scale (which focuses analytical attention on the central peak of the distribution); however, for purposes of presentation the values were transformed back to a linear scale (by exponentiation), yielding geometric means. The standard error of the geometric mean was computed in two steps: exponentiate the upper and lower limits of the 95 percent confidence interval for the log scale variable and then divide the difference by the number of standard deviations in the confidence interval, namely, 3.92. Microalbuminuria was defined in each race-sex group as A/kC in the range 25–249 mg/g. Clinical-grade albuminuria was defined as an A/kC 250 mg/g or more (3). The same cutpoints were used when considering A/C and A/sC. Data from participants with normo-, micro-, and clinical-grade albuminuria were included in most calculations, except when noted. Cross-tabulations were conducted to describe the prevalence of micro- or clinical-grade albuminuria. All analyses were completed using the SAS statistical package, version 6.12 (SAS, Inc., Cary, North Carolina).

RESULTS

General characteristics of CARDIA participants at years 5 and 10

Blacks were heavier and had larger mean values for body mass index than did Whites (table 1). Blacks were more likely to be smokers and had lower education levels than did Whites (data not shown).

TABLE 1. Characteristics of participants in the Coronary Artery Risk Development in Young Adults Study by sex and race at the year 10 examination, 1995–1996

	Black men ($n = 725$) (mean (SD†))	Black women ($n = 889$) (mean (SD))	White men ($n = 887$) (mean (SD))	White women ($n = 870$) (mean (SD))
Age (years)	34.3* (3.7)	34.5* (3.9)	35.5 (3.4)	35.6 (3.4)
Weight (kg)	88.3*,** (19.8)	81.7* (22.1)	84.8** (15.2)	69.8 (17.3)
Body mass index (kg/m^2)	27.8*,** (5.6)	30.1* (7.9)	26.6** (4.3)	25.5 (6.0)

* Blacks different from Whites within sex, $p \leq 0.01$.
** Males different from females within race, $p \leq 0.01$.
† SD, standard deviation.

Adjustment for gender and race differences in creatinine excretion in CARDIA year 5

To reduce the influences of gender and race on A/C, the three timed urine collections in year 5 were analyzed to determine the interactions of gender and race on creatinine excretion (table 2). As a result, urinary creatinine excretion (mg/24 hours) at CARDIA year 5 in women was 0.67–0.68 times that in men ($p < 0.0001$), in agreement with the data of James et al. (4) (table 2). Urinary creatinine excretion at year 5 in Whites was 0.89–0.90 times that in Blacks ($p < 0.0001$), again in agreement with the data of James et al. (4) (table 2). Besides age, which was weakly inversely related to creatinine excretion in this narrow age window, the most likely race- and gender-related factor that might cause differences in creatinine excretion relates to body size and, particularly, to lean mass. In CARDIA, values for lean mass/height^2 (mean (standard error)) were 20.5 (0.19) kg/m^2 in Black men, 20.0 (0.18) kg/m^2 in White men ($p = 0.05$ for race difference), 17.8 (0.18) kg/m^2 in Black women, and 16.8 (0.20) kg/m^2 in White women ($p = 0.0003$ for race difference). However, these results concerning lean body mass do not completely explain the gender and race differences in creatinine excretion observed either in year 5 of CARDIA or by James et al. (4) (table 2).

CARDIA year 10 A/kC in the untimed urine, adjusting for creatinine excretion rates

As expected, the application of A/C substantially reduced the variance of the measure of urinary albumin; the natural logarithm of A/C had a coefficient of variation of 45 percent compared with 94 percent for the natural logarithm of urinary albumin concentration. This finding held approximately for each race-sex group (data not shown).

For correction of the gender bias within the year 10 data, urinary creatinine concentration (mg/dl) in men was multiplied by 0.68 (approximately in agreement with the ratio of cutpoints 17 and 25 mg albumin/g creatinine for men and women respectively, used by Warram et al. (3)). For correction of the race bias, urinary creatinine concentration in Blacks was multiplied by 0.88, the average ratios for urinary creatinine excretion (mg/24 hours) found in CARDIA and in the paper by James et al. (4) (table 2). That is, A/kC became albumin/(0.68 × 0.88 × creatinine) in Black men, albumin/(0.88 × creatinine) in Black women, albumin/(0.68 × creatinine) in White men, and albumin/(1 × creatinine) in White women. Application of these adjustments allowed the use of the same cutpoints for microalbuminuria and clinical-grade albuminuria in the four race-sex groups of CARDIA.

Prevalence of microalbuminuria in CARDIA year 10

After adjustment for both gender and race, we observed 3,151 participants with normoalbuminuria (A/kC < 25 mg/g), 194 (5.8 percent) with microalbuminuria (A/kC ≥ 25 but <250 mg/g), and 26 (0.8 percent) with clinical-grade albuminuria (A/kC ≥ 250 mg/g). The application of gender and race adjustments clearly influences the estimates of the prevalence of microalbuminuria (table 3). However, all of the cases that were classified as clinical-grade albuminuria by using A/C were still classified as clinical-grade albuminuria when A/kC was applied. The clinical-grade cases were predominantly Black men ($n = 16$), with five Black women, four White women, and one White man. After adjustment for gender (i.e., using A/sC), five of the Black men with microalbuminuria were reclassified as having clinical-grade albuminuria. The age of the 26 cases with clinical-grade albuminuria (standard error) was 35.2 (0.9) years, similar to that of the rest of the CARDIA cohort, and they had 1.7 (0.4) years less education than did those who had normoalbuminuria. Serum creatinine concentration was 1.18 (0.095) mg/dl in clinical-grade albuminuria ($p = 0.02$ compared with normoalbuminuria) versus 0.94 (0.003) mg/dl in normoalbuminuria and 0.94 (0.013) mg/dl in microalbuminuria.

After adjustment for gender and race, there were 84 cases of microalbuminuria among Black men, 63 among Black women, 48 among White men, and 25 among White women. Adjustment for gender resulted in 16 Black men being reclassified from normoalbuminuria to microalbuminuria. Further adjustment for race reclassified eight more Black men from normoalbuminuria to microalbuminuria. Adjustment for gender reclassified 21 White men from normoalbuminuria to microalbuminuria. Adjustment for race reclassified six Black women from normoalbuminuria to microalbuminuria. Overall, the estimates of microalbuminuria plus clinical-grade albuminuria increased 30 percent with the adjustments for gender and race (table 3), specifically 80 percent in White men, 40 percent in Black men, and 10.9 percent in Black women. The geometric mean of A/kC increased by 25 percent compared with the geometric mean

TABLE 2. Urinary creatinine excretion in the Coronary Artery Risk Development in Young Adults Study (1990–1991) and the paper by James et al. (Am J Hypertens 1988;1:124–31)

	Urinary creatinine excretion (mg/24 hours)								Ratios of means			
	Black men		Black women		White men		White women		White women/ White men	Black women/ Black men	White women/ Black women	White men/ Black men
	No.	Mean (SD*)	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)				
CARDIA* year 5 (3-day collection)	182	2,078 (561)	261	1,386 (386)	191	1,846 (441)	201	1,249 (339)	0.68	0.67	0.90	0.89
James et al. (1-day collection)	695	1,762 (482)	429	1,108 (319)	519	1,554 (339)	416	975 (242)	0.63	0.63	0.88	0.88

* SD, standard deviation; CARDIA, Coronary Artery Risk Development in Young Adults.

TABLE 3. Prevalence of albuminuria ≥25 mg/g according to unadjusted and adjusted ratio of urinary albumin concentration to urinary creatinine concentration in the Coronary Artery Risk Development in Young Adults Study, 1995–1996

	Prevalence of albuminuria ≥25 mg/g (% of subjects in each group)		
	A/C*	A/sC* (corrected for gender differences)	A/kC* (corrected for gender and race differences)
Black	7.2	8.2	9.1
Men	8.3	10.5	11.6
Women	6.4	6.4	7.1
White	3.0	4.2	4.2
Men	3.0	5.4	5.4
Women	2.9	2.9	2.9
Overall	5.0	6.1	6.5

* *s* is a multiplicative factor that adjusts for typical sex differences in creatinine excretion (mg/24 hours). *s* = 1 for women and *s* = 0.68 (equivalent to 17/25) for men. Use of *s* is algebraically equivalent to following the procedure of Warram et al. (J Am Soc Nephrol 1996;7:930–7). *k* is a multiplicative factor that adjusts for typical race and sex differences in creatinine excretion (mg/24 hours). *k* = 1 for White women, 0.88 for Black women, 0.68 for White men, and 0.88 × 0.68 for Black men. A/C, ratio of urinary albumin concentration to urinary creatinine concentration; A/sC, the same ratio adjusted for sex differences in creatinine excretion; A/kC, the same ratio adjusted for race and sex differences in creatinine excretion.

of A/C (table 4): 62 percent in Black men, 47 percent in White men, and 12 percent in Black women. Similar shifts were seen in the 25th and 75th percentiles.

DISCUSSION

There are several methods to assess urinary albumin excretion rate; the standard is a timed urine collection. Timed samples present a burden to the participant and great logistic difficulty to investigators in large, prospective cohorts such as CARDIA. An alternative subsumes an untimed urine collection, used in CARDIA to infer urinary albumin excretion rate from the ratio of urinary concentrations of albumin and creatinine. The logistic advantage of the untimed specimen must be weighed against interpretive problems caused by high variability and/or confounding by other factors. In an untimed sample, unknown hydration status and other conditions not standardized during urine collection increase the variability of urinary albumin concentration. A substantial reduction in variance can be achieved by division of urinary albumin concentration by urinary creatinine concentration. Although others have not always addressed the issue of other factors confounding creatinine excretion (3), division by urinary creatinine concentration introduced confounding with race and sex in the CARDIA data.

Many of these problems in interpreting prevalence of microalbuminuria based on a single urine sample were addressed by Warram et al. (3). After calibration of A/C in an untimed urine against timed albumin excretion rate in a subset of their White participants, they proposed to define microalbuminuria as an A/C of 25 mg/g or more for women and of 17 mg/g or more for men. These cutpoints corresponded to 30 μg/minute albumin excretion rate (3). The definition of microalbuminuria used in this paper expands on theirs. We use their definition for White women. The ratio of the cutpoints 17 and 25 mg/g is 0.68; thus, the procedure in White men that we adopted is algebraically equivalent to that used by Warram et al. (3), namely to adjust their urinary creatinine concentration by multiplying by 0.68, form the ratio of albumin to adjusted creatinine, and use a cutpoint of 25 mg/g. Female-to-male ratios for overnight creatinine excretion of 0.70 (10), 0.67 (11), and 0.63 (4) have been reported, as well as 0.68 in the CARDIA year 5 average of three 24-hour urine samples, all of which are very close to the ratio in the paper by Warram et al. (3) that we have adopted. Although CARDIA data do not include a timed urinary albumin collection (albumin was not mea-

TABLE 4. Geometric mean of albumin/creatinine ratios, standard error, and distribution of albuminuria by race and sex in the Coronary Artery Risk Development in Young Adults Study, 1995–1996

	No.	Geometric mean			Standard error			25th percentile			75th percentile		
		A/C*	A/sC*	A/kC*	A/C	A/sC	A/kC	A/C	A/sC	A/kC	A/C	A/sC	A/kC
Black	1,614	5.2	6.6	7.4	0.16	0.18	0.20	2.8	3.4	3.8	7.2	8.4	9.5
Men	725	5.3	7.6	8.6	0.25	0.35	0.39	2.6	3.7	4.2	6.0	8.8	10.0
Women	889	5.8	5.8	6.5	0.19	0.19	0.21	3.1	3.1	3.5	8.0	8.0	9.0
White	1,757	4.6	5.6	5.6	0.09	0.11	0.11	2.8	3.4	3.4	6.1	7.3	7.3
Men	887	4.3	6.3	6.3	0.12	0.17	0.17	2.7	3.9	3.9	5.4	7.9	7.9
Women	870	5.0	5.0	5.0	0.14	0.14	0.14	2.9	2.9	2.9	6.6	6.6	6.6
Overall	3,371	5.1	6.0	6.4	0.09	0.10	0.11	2.8	3.4	3.6	6.5	7.8	8.2

* *s* is a multiplicative factor that adjusts for typical sex differences in creatinine excretion (mg/24 hours). *s* = 1 for women and *s* = 0.68 (equivalent to 17/25) for men. Use of *s* is algebraically equivalent to following the procedure of Warram et al. (J Am Soc Nephrol 1996;7:930–7). *k* is a multiplicative factor that adjusts for typical race and sex differences in creatinine excretion (mg/24 hours). *k* = 1 for White women, 0.88 for Black women, 0.68 for White men, and 0.88 × 0.68 for Black men. A/C, ratio of urinary albumin concentration to urinary creatinine concentration; A/sC, the same ratio adjusted for sex differences in creatinine excretion; A/kC, the same ratio adjusted for race and sex differences in creatinine excretion.

sured in the 3-day urine collections obtained at year 5, and no untimed urine specimen was obtained at that time), Warram et al. (3) did validate their procedure in relation to timed AER. A/kC should be used cautiously in the elderly in whom creatinine clearance may be reduced.

We report greater geometric mean A/kC and microalbuminuria (criterion A/kC, 25–249 mg/g) among men than among women after adjustment for sex differences in creatinine excretion. We would have inferred that women had only a slightly lower prevalence than did men if we had used the unadjusted criterion for microalbuminuria, A/C of 25 mg/g or more (4.7 percent in women and 5.3 percent in men). Population studies of albumin excretion rate (timed urine samples) (10–12) have also shown that men excrete albumin at a higher rate than women. In contrast, other population-based studies that have been based on A/C (usually in single, untimed urine specimens) that have neither adjusted A/C for gender differences in creatinine excretion nor used sex-specific cutpoints report higher prevalence of microalbuminuria among women than among men (13–16). However, adjustment of creatinine excretion in a manner similar to that used here would lead to higher prevalence of microalbuminuria in men than in women (10, 11, 14, 15). The highly variable measure of albumin concentration in a single urine sample does seem to be a poor differentiator of men from women; various studies have reported that men have either higher (10, 15, 17) or lower (18) prevalence of microalbuminuria. Cirillo et al. (10) pointed out that the sex difference in prevalence of microalbuminuria disappeared when albumin excretion rate was divided by creatinine clearance, a measure of glomerular filtration rate, in effect creating an approximation of fractional clearance of albumin. It remains to be seen whether the difference in albumin excretion between men and women has significance for long-term risk of chronic disease or merely reflects the greater size of men than women.

We similarly removed bias due to differential creatinine excretion in Blacks versus Whites. The factor 0.88 was selected because it characterizes the observed ratio of CARDIA year 5 24-hour urinary creatinine excretion in Whites versus Blacks after adjustment for sex differences and agrees with the values observed by James et al. (4). This adjustment reflects greater lean mass in Blacks than in Whites both in CARDIA data and elsewhere (8, 9). Metcalf et al. (19) reported urinary creatinine concentration 0.83 times lower in New Zealanders of European descent than in Maori and Pacific Islanders, again in agreement with our data, but they classified subjects only by their urinary concentration of albumin. We acknowledge that higher creatinine excretion in Blacks, Maori, and Pacific Islanders could reflect hyperfiltration or other pathophysiologic processes (20), but this seems unlikely to be important in light of the similarity of serum creatinine in normoalbuminuria and microalbuminuria, the lean mass differences among the race-sex groups, and the generally good health of the populations studied.

Ethnic differences in the prevalence of microalbuminuria have also been reported by a number of investigators among both nondiabetic (14, 15, 21) and diabetic (22) subjects. A slightly greater prevalence of microalbuminuria based on unadjusted A/C (>30 mg/mmol) in an untimed urine among healthy Blacks aged 19–32 years (3.8 percent) compared with Whites (3.2 percent) the same age has been previously reported for participants of the Bogalusa Heart Study (14). These values are likely to underestimate the prevalence among non-Whites because they failed to adjust for the higher creatinine excretion in non-Whites (in our data and those in the paper by James et al. (4)). In our study, the prevalence of unadjusted A/C of 25 mg/g or more is 7.2 percent in Blacks and 3.0 percent in Whites, a smaller difference than is found using A/kC (9.1 vs. 4.2 percent).

We were not able to validate our procedure directly by using A/kC with timed urinary albumin excretion at year 10 because we used a spot urine sample at that examination and albumin was not measured in the year 5 timed samples. Nevertheless, the data do extend and confirm the procedure suggested by Warram et al. (3) that was compared with a timed urine specimen. The procedure we suggest to adjust for race follows a similar logic to that suggested by Warram et al. (3). There are several potential confounders for which we did not adjust, including protein intake, exercise (both chronic and preceding the time of the urine collection), urinary tract infections, and acute illnesses. Ellis et al. (23) found no significant effect of inclusion of patients with possible urinary tract infections, suggesting little confounding by the inclusion of a few participants with urinary tract infections on our results. Errors introduced by not strictly controlling for these and other confounding factors are limitations to the precision of A/kC.

Use of an untimed urine sample to estimate the prevalence of microalbuminuria may not be an optimal measure of albumin excretion rate, particularly in a clinical situation, but is all that is possible in many epidemiologic settings. However, the practical challenges of obtaining timed urine collections in the clinical setting have led to widespread adoption of the A/C ratio. Thus, the findings of this study have direct application to the clinical assessment of renal function by measuring albumin excretion. The finding that men have a greater prevalence of microalbuminuria is of interest and should be studied further to see whether it has clinical implications.

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