ORIGINAL INVESTIGATIONS

Race and Creatinine Excretion in Chronic Renal Insufficiency

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● **Black race and the absence of diabetes are associated with higher levels of serum creatinine in patients with end-stage renal disease. We examined whether these factors have a similar influence on creatinine excretion in men with chronic renal insufficiency. The hypotheses were tested in one sample (group A, n = 35) and the findings replicated in a second, independent sample (group B, n = 66). Creatinine excretion normalized to weight (UCr/kg) was compared by race and diabetic status. UCr/kg and creatinine clearance also were compared with the values predicted by the Cockcroft-Gault (CG) formula (based on the regression equation, UCr/kg = 28 − age/5). In each sample, mean UCr/kg was significantly higher in black patients than in nonblack patients (group A, $P = 0.004$; group B, $P = 0.029$), and UCr/kg and creatinine clearance were significantly underestimated by the CG predictions in black patients (group A, $P \leq 0.004$; group B, $P \leq 0.019$), but not in nonblack patients. Diabetes did not significantly influence UCr/kg. The analysis also was performed at two age levels (<50 years or ≥50 years) using groups A and B combined. For black patients younger than 50 (n = 10), observed UCr/kg ($P = 0.059$) and creatinine clearance ($P = 0.025$) exceeded the values predicted by the CG formula; the analysis of nonblack patients younger than 50 years was limited by sample size (n = 1). For patients aged 50 years and older (black, n = 32; nonblack, n = 58), mean UCr/kg was significantly higher in black patients ($P = 0.034$), and UCr/kg and creatinine clearance were significantly underestimated by the CG predictions in black patients ($P \leq 0.002$) but not in nonblack patients. In multiple regression analysis of all patients aged 50 years and older, UCr/kg was independently influenced by both race ($P < 0.05$) and age ($P < 0.04$) (overall model, multiple R = 0.31; $P = 0.012$). The prediction equation was UCr/kg (mg/kg) = 23.6 − age/8.3 + 1.9 × race (race = 0 if nonblack; race = 1 if black). We conclude that the creatinine excretion rate was strongly affected by race but not diabetes in men with chronic renal insufficiency. The CG formula significantly underestimated UCr/kg and therefore creatinine clearance in black patients. These findings may reflect differences between black and nonblack subjects in body composition, muscle metabolism, or diet, and the interaction of these factors with chronic renal insufficiency.**

INDEX WORDS: Creatinine; race; diabetes; chronic renal insufficiency; Cockcroft-Gault; muscle.

IN PATIENTS who are on hemodialysis and essentially anuric, serum creatinine has been found to be approximately 15% to 20% higher (or 2 mg/dL in absolute difference) in black compared with nonblack patients, and similarly in nondiabetic compared with diabetic patients, in a report by Lowrie et al[1] and in our own experience, based on multivariate analyses that also adjust for age and gender. Similar trends have been noted in patients at the onset of uremia.[2,3] These concentration differences are probably the result of different rates of creatinine production. In a study of young adult men on hemodialysis, the amount of creatinine extracted per week by dialysis was found to be approximately 40% higher in black than white men matched for age, weight, and dialysis dose.[4] Black subjects with normal renal function, however, excrete only 5% more urinary creatinine per kilogram of body weight (UCr/kg) than age- and weight-matched white subjects.[5] The influence of race or diabetes on creatinine excretion has not been described in patients with moderate degrees of chronic renal insufficiency.

Clinicians commonly estimate UCr/kg in these patients with a formula that adjusts only for age, the Cockcroft-Gault (CG) formula.[6] In a prospective sample of 35 men with chronic renal insufficiency, we (1) tested the hypotheses that black race and the absence of diabetes are associated with increased creatinine excretion, and that the CG formula underestimates creatinine excretion and clearance in black patients and overestimates these quantities in diabetic patients; and (2) examined the influence of race and diabetes on the age-creatinine excretion relationship. The findings were replicated in a second sample, derived by record review, comprising 66 men with chronic renal insufficiency.

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MATERIALS AND METHODS

Patients

Group A comprised 35 men prospectively enrolled in the study from the renal clinic population during 1995 and 1996. The patients were chosen from consecutive cases that the investigators encountered for whom 24-hour urine collections were needed to monitor their renal conditions. On the initial interview, clinical data were recorded, including age, race, weight, height, medications, and clinical diagnoses. Patients on androgens, or with active malignancy (except localized prostate cancer), wheelchair-bound patients, incontinent patients, and patients with chronic bladder catheters were excluded. Each patient was clearly instructed on how to collect a 24-hour urine specimen properly, and asked to bring it, on the morning of its completion, to the clinical laboratory associated with the study (Special Endocrinology Laboratory) to have blood drawn for a serum creatinine determination. The second sample, group B, was created to attempt to replicate the findings in group A. This sample was derived from a list of the first 150 patients who visited the renal clinic in 1995. From this list, we selected 66 male cases who had (1) at least one "eligible" 24-hour urine creatinine collection on their hospital-computer biochemical database, (2) a concurrent serum creatinine concentration, (3) weight measured at the clinic within 2 weeks of the creatinine collection, and (4) no exclusion criteria. A patient with an eligible urine creatinine value was defined as either having exactly one prior creatinine collection, or, when there was more than one prior collection, having two or more prior creatinine collections that disagreed by less than 20%, and an associated recorded weight. When there were two eligible urine creatinine values, we chose the more recent creatinine value; when there were three or more eligible values, the median creatinine value was chosen. Cases that were already included in the other cohort were excluded from group B. The clinic chart was reviewed for race, age, and history of diabetes. When it could be ascertained on the chart review, incontinent patients with chronic bladder catheters and wheelchair-bound patients were excluded.

Groups A and B were not significantly different in age (group A, 66 ± 12 [SD] years; group B, 67 ± 11 years), race (group A, 40% black, 49% white, 8% Hispanic, and 3% Asian; group B, 42% black, 56% white, and 2% Hispanic), diabetes (group A, 49%; group B, 35%), serum creatinine (group A, 2.9 ± 2.3 mg/dL; group B, 2.6 ± 1.5 mg/dL), creatinine excretion (group A, 1,485 ± 537 mg/24 hr; group B, 1,368 ± 634 mg/24 hr), creatinine clearance (group A, 55 ± 38 mL/min; group B, 50 ± 38 mL/min), weight (group A, 86.3 ± 18.9 kg; group B, 83.5 ± 21.6 kg), and UCr/kg (group A, 17.3 ± 5.2 mg/kg; group B, 16.2 ± 5.6 mg/kg).

Measurements and Derived Quantities

Serum and urine creatinine were determined enzymatically by the creatinine anhydrolase method using dry slide technology on the Ektachem 950 analyzer (Johnson and Johnson, New Brunswick, NJ). UCr/kg was calculated as 24-hour urine creatinine divided by the patient's weight in kilograms. The CG prediction of UCr/kg is a linear transformation of age, calculated as 28 − age/5 (in men).[6] Creatinine clearance (milliliters/minute) was calculated as 24-hour urine creatinine (milligrams/24 hour) divided by serum creatinine (milligrams/deciliter) and multiplied by 100/1,440. Similarly, the CG prediction of creatinine clearance was calculated as (28 − age/5) × weight ÷ (serum creatinine) × (100/1,440). The ratio of observed to predicted UCr/kg was calculated as (UCr/kg) ÷ [(28 − age/5) × weight]; this value also equals the ratio of observed to predicted creatinine clearance.

Data Analysis and Statistics

The hypotheses that race and diabetes influence creatinine excretion were tested separately for groups A and B to enable the relationships found in one sample to be validated in the other. For relationships that were consistent across both groups, the two groups were pooled for graphic display and to increase the precision of the estimates of regression coefficients. The combined data set also was used to increase statistical power for an exploratory analysis performed to detect possible interactions among race, diabetes, and age.

Data are reported as mean values ± standard deviation. Group means were compared using the unpaired *t*-test or ANOVA. Differences between observed and predicted values of UCr/kg or creatinine clearance were tested with the paired *t*-test. The relationships between continuous variables were characterized with Pearson's correlation coefficient (r) and simple or multiple linear regression. Because the CG formula for UCr/kg is simply a linear transformation of age, all correlations reported for age also apply to the CG formula, although the sign of the correlation coefficient must be reversed. For all linear models, residuals and the effect of potentially influential cases were examined, and estimated slopes and intercepts are each presented as regression coefficient ± standard error and/or the 95% confidence interval. Calculations were performed using SPSS for Windows 6.0 (SPSS Inc, Chicago, IL).

RESULTS

Black and nonblack patients did not differ significantly with respect to serum creatinine, creatinine clearance, weight, or proportion of cases with diabetes in either group A or group B. Mean total urinary excretion was higher in black than nonblack patients in group A (1,830 ± 570 mg/24 hr *v* 1,254 ± 373 mg/24 hr; $P = 0.003$) and group B (1,553 ± 734 mg/24 hr *v* 1,231 ± 519 mg/24 hr; $P = 0.041$).

In group A, mean UCr/kg was higher in black than nonblack patients (20.6 ± 5.6 mg/kg *v* 15.1 ± 3.5 mg/kg; $P = 0.004$) despite mean age values that did not differ significantly (63 ± 16 years *v* 69 ± 8 years). UCr/kg exceeded the CG prediction by a mean of 35% in black patients (absolute difference, 5.2 ± 3.9 mg/kg; $P < 0.001$ by paired *t*-test), but by only 7% in nonblack patients (ab-

solute difference, 0.8 ± 3.8 mg/kg; $P = 0.36$ by paired t-test). Similarly, observed creatinine clearance exceeded the CG prediction by a mean of 35% in black patients (absolute values, 64 ± 46 mL/min *v* 48 ± 35 mL/min; $P = 0.006$), but by only 7% in nonblack patients (absolute values, 48 ± 32 mL/min *v* 47 ± 32 mL/min; $P = 0.79$). Overall, UCr/kg correlated with age ($r = -0.55$; $P < 0.001$). When examined by race, however, the correlation was significant in black patients ($r = -0.75$; $P = 0.002$) but not in nonblack patients ($r = -0.04$; $P = 0.85$).

The findings were similar in group B. Mean UCr/kg was significantly higher in black than nonblack patients (17.9 ± 5.6 mg/kg *v* 14.9 ± 5.4 mg/kg; $P = 0.029$). The mean difference observed was 3.1 mg/kg, which exceeded 1.5 mg/kg, the difference predicted by the CG formula based on the younger age of the black patients (62 ± 13 years *v* 70 ± 8 years; $P = 0.008$). UCr/kg exceeded the CG prediction by a mean of 16% in black patients (absolute difference, 2.4 ± 5.0 mg/kg; $P = 0.019$ by paired t-test) but only by 7% in nonblack patients (absolute difference, 0.9 ± 5.5 mg/kg; $P = 0.33$ by paired t-test). Similarly, creatinine clearance exceeded the predicted value by 16% in black patients (absolute values, 53 ± 41 mL/min *v* 45 ± 32 mL/min; $P = 0.012$) but only by 7% in nonblack patients (absolute values, 47 ± 36 mL/min *v* 43 ± 28 mL/min; $P = 0.122$). UCr/kg correlated with age in the entire group ($r = -0.34$; $P < 0.006$). Again, the correlation was significant in black patients ($r = -0.44$; $P = 0.02$) but not nonblack patients ($r = -0.09$; $P = 0.59$).

Diabetic and nondiabetic patients did not differ with respect to age, race, total urine creatinine, or creatinine clearance in either group A or group B. Mean serum creatinine was significantly lower in diabetic patients than in nondiabetic patients in group A (2.1 ± 0.9 mg/dL *v* 3.7 ± 3.0 mg/dL; $P = 0.04$) but not in group B (2.3 ± 0.9 mg/dL *v* 2.7 ± 1.7 mg/dL; $P = 0.25$), and mean weight was higher in diabetic patients than in nondiabetic patients in group B (92.3 ± 20.8 kg *v* 78.8 ± 20.8 kg; $P = 0.014$) but not in group A (85.1 ± 13.5 kg *v* 87.4 ± 23.2 kg; $P = 0.72$). Mean UCr/kg was lower in diabetic patients, but this was not significant in either group A (16.9 ± 5.9 mg/kg *v* 17.6 ± 4.6 mg/kg; $P = 0.71$),

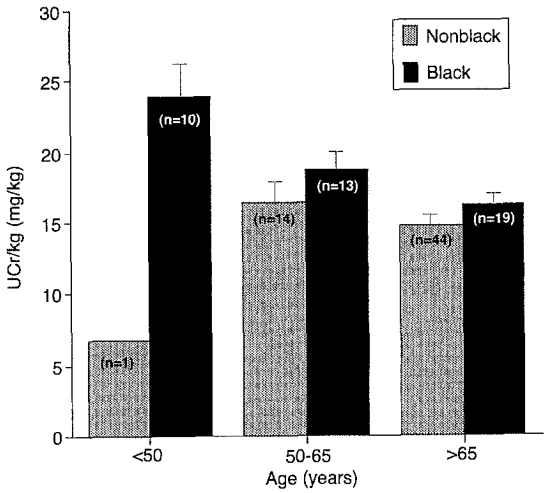

Fig 1. Mean UCr/kg ± SE by age and race. Multiple $R = 0.47$ ($P < 0.001$) for the overall model of UCr/kg by age, race, and age×race (using two-way ANOVA with experimental sum of squares). Significance of individual factors: age, $P = 0.003$; race, $P = 0.02$; and age×race, $P = 0.012$. The mean ages (±SD) of the three nonblack groups were 43 years, 59 ± 4 years, and 73 ± 5 years; the mean ages of the three black groups were 44 ± 7 years, 60 ± 4 years, and 74 ± 7 years.

group B (15.1 ± 4.3 mg/kg *v* 16.8 ± 6.2 mg/kg; $P = 0.26$), or groups A and B combined (15.9 ± 5.1 mg/kg *v* 17.0 ± 5.8 mg/kg; $P = 0.32$). Among all black patients, mean UCr/kg exceeded the CG prediction significantly in patients with ($P = 0.01$) or without ($P = 0.003$) diabetes. Among all nonblack patients, UCr/kg did not significantly exceed the CG prediction in patients with ($P = 0.70$) or without ($P = 0.18$) diabetes. Similarly, in the combined groups, age correlated significantly with UCr/kg in black patients but not nonblack patients irrespective of diabetic status.

The correlation between UCr/kg and age in black patients but not in nonblack patients suggested an age×race interaction. This is illustrated in Fig 1 with age stratified into three categories. Age, race, and age×race were each significant factors in an analysis of UCr/kg using two-way ANOVA. Because of this interaction, the remaining analysis focuses on groups A and B combined and stratified by age, to allow an examination of the relationship of race and creatinine excretion separately at two age levels (<50 years and ≥50 years).

Table 1. Description of Patients Aged 50 Years and Older

	Black (n = 32)	Nonblack (n = 58)	*P* Value
Age (yr)	68 ± 9	70 ± 8	0.382
Diabetes	47%	40%	0.659
Serum creatinine (mg/dL)	3.1 ± 2.4	2.5 ± 1.3	0.212
Urine creatinine (mg/24 hr)	1,512 ± 571	1,246 ± 470	0.020
Weight (kg)	86.5 ± 23.0	82.8 ± 19.4	0.430
UCr/kg (mg/kg)			
Observed	17.2 ± 4.1	15.1 ± 4.7	0.034
Predicted	14.3 ± 1.8	14.0 ± 1.5	
Paired *t*-test	$P < 0.001$	$P = 0.082$	
Creatinine clearance (mL/min)			
Observed	48 ± 35	48 ± 34	0.963
Predicted	40 ± 29	45 ± 29	
Paired *t*-test	$P = 0.002$	$P = 0.112$	

In the 10 black patients younger than 50 years, UCr/kg exceeded the CG prediction by a mean of 25% (absolute values, 24.0 ± 7.2 mg/kg *v* 19.2 ± 1.3 mg/kg; $P = 0.059$), but the difference was not quite significant, probably due to the size of the sample. Similarly, creatinine clearance exceeded the CG prediction by a mean of 25% (absolute values, 86 ± 53 mL/min *v* 65 ± 36 mL/min; $P = 0.025$). Although mean UCr/kg decreased with age (UCr/kg = 35.9[±16.3] − [0.27 ± 0.37] × age; $r = -0.25$, $P = 0.48$), the trend was not significant, again reflecting in part the limited age range and size of the sample. Comparison of mean UCr/kg in black and nonblack patients was not possible since there was only a single nonblack patient younger than 50 years.

In the subset of patients aged 50 years and older, black and nonblack patients were not significantly different in age, diabetes, weight, and creatinine clearance (Table 1). Mean UCr/kg was significantly higher in black than nonblack patients ($P = 0.034$). Observed UCr/kg and creatinine clearance significantly exceeded their respective CG predictions by a mean of 21% for black patients ($P \leq 0.002$ by paired *t*-test), but only by 8% for nonblack patients (Table 1). UCr/kg correlated significantly but weakly with age ($r = -0.24$; $P < 0.03$). There was no age×race interaction: the slope and correlation were similar in the older black patients (Fig 2; $r = -0.27$, $P < 0.13$) and in the older nonblack patients (Fig 3; $r = -0.20$, $P < 0.14$). Figures 2 and 3 also compare the CG formula with the 95% confidence limits of the association observed between UCr/kg and age. The association observed was statistically compatible with the CG prediction for nonblack patients, but not for black patients. By multiple regression, age ($P = 0.036$) and race ($P = 0.049$) were significant independent predictors of UCr/kg for patients aged 50 years and older (Table 2). The model was as follows: UCr/kg = 23.6 − age/8.3 + 1.9 (if black) (multiple $R = 0.31$; $P = 0.012$). The model explained only 8% of the variance in UCr/kg. The estimated independent effect of diabetes after adjusting for race and age was a reduction of 1.20 ± 0.93 mg/kg (±SE) in UCr/kg, which was not significant ($P = 0.20$).

DISCUSSION

This study examined the influence of race and diabetes on the rate of creatinine excretion and on the performance of the CG formula, which adjusts only for age, in two independent samples of men with renal insufficiency. In each sample, the CG formula led to significant underestimates of UCr/kg and creatinine clearance in black patients, and black patients had significantly higher mean UCr/kg than nonblack patients. Stratifying the analysis by age less than 50 years or ≥50 years (for the two samples combined), the underestimation of observed values by the CG predictions in black patients persisted both for patients younger than 50 years and for those aged 50 years and older. For patients aged 50 years and older, mean UCr/kg remained higher in black patients than in nonblack patients (Table 1); for patients younger than 50 years, the black/nonblack comparison was limited by confounding of age and race. In each sample, age and UCr/kg were inversely and significantly correlated in black patients but not in nonblack patients. When the younger patients were excluded, however, the inverse trend with age was similar in black and nonblack patients (Figs 2 and 3). In the patients aged 50 years and older, a mean increase in UCr/kg of 1.93 mg/kg was estimated in black patients

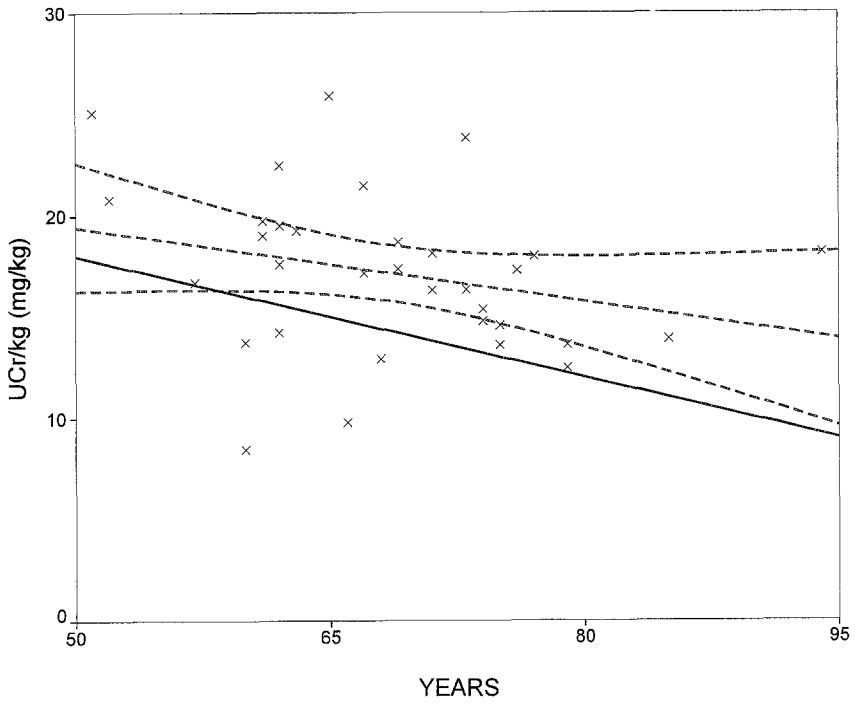

Fig 2. Relationship between UCr/kg and age in 32 black patients aged 50 years and older. The broken lines represent the regression line and 95% confidence interval for the equation UCr/kg = 25.45(±5.32) − [0.121 ± 0.077] × age (r = 0.27; P < 0.13). The solid line represents the prediction of the CG formula.

relative to nonblack patients, adjusting for age by multiple linear regression (Table 2). The regression model in Table 2, if confirmed, could be useful for estimating creatinine clearance in the clinical setting.

In nonblack patients aged 50 years and older, the CG prediction did not differ significantly from the observed values overall, although it appeared to underestimate the observed values in the oldest patients (Fig 3). For example, in the 29 nonblack men aged 70 years and older, UCr/kg exceeded the CG prediction (14.5 ± 4.4 mg/kg v 13.0 ± 0.8 mg/kg; P = 0.05 by paired t-test). Even in the original cohort of 249 Canadian male veterans, presumably nonblack, studied by Cockcroft and Gault,[6] the CG equation fit their original data well, except for the oldest subgroup, aged ≥80 years, whose mean UCr/kg was 12.1 mg/kg, which exceeded the predicted mean of 10.9 mg/kg. Thus, the CG formula may underestimate UCr/kg in elderly nonblack patients.

Differences in creatinine excretion imply differences in muscle mass, creatinine metabolism, or the dietary intake of creatine, creatinine, and protein.[7] There is limited evidence suggesting differences in muscle metabolism and mass. Ama et al[8] found differences in striated muscle metabolism and fiber distribution in matched black and white men, and Ortiz et al[9] reported significantly higher appendicular skeletal muscle mass in black women compared with matched white women. One possible mechanism for a difference in muscle metabolism or mass is endocrinologic. Serum testosterone level tends to be higher in black men than in white men.[10,11] Testosterone promotes the synthesis of creatine, the precursor of creatinine.[7] Although testosterone is anabolic, it is unknown whether a chronic difference in its serum level within the physiologic range can result in a difference in muscle mass.[12]

The magnitude of the creatinine difference by race was greater than 20% in the present study, compatible with observations in hemodialysis patients[1-4] but greater than the 5% difference in creatinine excretion observed by James et al[5] in a healthy worker cohort. It is possible that the

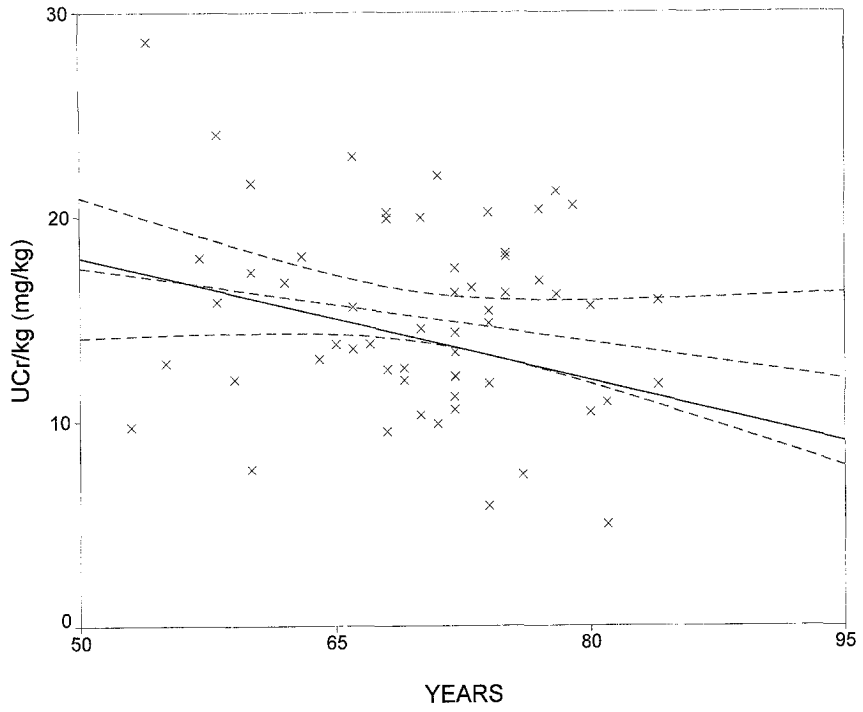

Fig 3. Relationship between UCr/kg and age in 58 nonblack patients aged 50 years and older. The broken lines represent the regression line and 95% confidence interval for the equation UCr/kg = 23.6(±5.68) − [0.122 ± 0.081] × age (r = 0.20; P < 0.14). The solid line represents the prediction of the CG formula.

presence of renal failure and other co-morbid conditions exaggerates differences in muscle mass, creatinine metabolism, or diet that may exist between healthy black and nonblack subjects. Higher serum creatinine concentration statistically explains much of the survival advantage of black patients with end-stage renal disease.[1] It is reasonable to speculate that higher muscle mass is the biologic basis for this statistical association since higher somatic protein stores provide an obvious advantage to dialysis patients, who are at risk of protein-energy malnutrition. Consistent with this view, Daugirdas et al[13] found that urea space during hemodialysis was significantly larger in black patients compared with white patients, adjusting for age, weight, height, and gender. Extrapolating this speculation to men with lesser degrees of chronic renal insufficiency, the higher UCr/kg in black patients in the current study probably reflects, in part, greater muscle mass. The larger black/nonblack difference observed in renal failure compared with the difference reported in normal renal function, in turn, could be explained if nonblack patients are less resistant than black patients to the muscle catabolism that occurs in uremia.[1,14,15]

A stronger age–UCr/kg relationship in black patients compared with nonblack patients was

Table 2. Predictors of UCr/kg in Men Aged 50 Years and Older*

	Coefficient	SE	95% Confidence Interval	P Value
Age (per year)	−0.12	0.057	−0.234 to −0.008	0.036
Black (v nonblack)	1.93	0.97	0.005 to 3.85	0.049
Intercept	23.57	4.02	15.57 to 31.56	<0.0001

* By multiple linear regression: multiple R, 0.31; adjusted R^2, 0.0765; P = 0.012.

not a prior hypothesis of the present study. This anomaly may simply have been the result of the confounding of young age with black race in the study subjects (eg, a stronger correlation could have resulted from the broader age range of the black patients studied). A superficially analogous interaction between age and UCr/kg was reported by James et al[5] in a healthy worker cohort of men and women. These investigators found that compared with younger subjects, UCr/kg was lower in patients aged 60 years or older in all subjects except white men, and that black men showed the greatest decline with age (−20%). In the present study, the steeper decline of UCr/kg with age suggested in young black patients could not be examined in nonblacks, but the more gradual decline in UCr/kg in patients between 50 and 65 years of age and those older than 65 years was similar in black and nonblack patients (Figs 1 to 3).

Diabetic patients with chronic renal insufficiency had a slightly lower creatinine excretion rate, but the reduction was not significant. This is surprising because, for hemodialysis patients, diabetes is associated with 15% to 20% lower serum creatinine levels, adjusting for age, gender, and race.[1] Lower serum creatinine statistically explains much of the survival disadvantage of diabetic dialysis patients,[1] again suggesting that the explanation is lower muscle mass. Serial measurements of creatinine excretion may be necessary to determine the point along the progression to end-stage renal disease when the difference in creatinine associated with diabetes first becomes evident.

In summary, creatinine excretion was influenced by race but not diabetes in two independent samples of men with chronic renal insufficiency. In black patients, UCr/kg and creatinine clearance were significantly underestimated by the CG formula. In men aged 50 years and older, UCr/kg was predicted by the equation 23.57 − age/8.25 + 1.93 (if black).

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