Comparison of Cross-Sectional Renal Function Measurements in African Americans With Hypertensive Nephrosclerosis and of Primary Formulas to Estimate Glomerular Filtration Rate

Julia Lewis, MD, Lawrence Agodoa, MD, DeAnna Cheek, MD, Tom Greene, PhD, John Middleton, MD, Daniel O'Connor, MD, Akinlou Ojo, MD, Robert Phillips, MD, PhD, Mohammed Sika, PhD, and Jackson Wright, Jr, MD, PhD, for the African-American Study of Hypertension and Kidney Disease

• **Renal function measurements were obtained in 1,703 African Americans with presumed hypertensive nephrosclerosis who were screened for entry into the African-American Study of Hypertension and Kidney Disease (AASK). We examined the effect of race on relationships involving renal variables by comparing African Americans enrolled into the AASK with non–African Americans enrolled into the Modification of Diet in Renal Disease (MDRD) study. We examined the effect of gender on renal variables by comparing African American men and women. We compared various methods for estimating glomerular filtration rate (GFR) with iodine 125–labeled (^{125}I)-iothalamate GFR. AASK data were also used to derive a new formula for estimating GFR in African Americans. After adjusting for age, sex, and baseline GFR, African American patients on the AASK study were heavier and had larger body surface areas and body mass indices than either MDRD African Americans or non–African Americans. African Americans had greater serum creatinine levels and urinary creatinine excretions for any given level of GFR. Mean GFR was greater in African American men than African American women (59.7 versus 51.7 mL/min/1.73 m^2), although serum creatinine levels were also greater in men (1.91 versus 1.73 mg/dL). Seventy-eight percent of women with serum creatinine levels between 1.2 and 1.5 mg/dL had GFRs less than 65 mL/min/1.73 m^2. For African Americans in the AASK, GFR was overestimated by the 24-hour creatinine clearance and underestimated by the Cockcroft-Gault formula. A prediction formula developed in the MDRD study more accurately predicted GFR in AASK patients than these measurements. AASK data were also used to derive a new five-term formula for estimating GFR that was slightly more accurate in the African Americans in the AASK than the MDRD formula (median percentage of error, 12.4% for the MDRD formula versus 12.1% for the AASK formula). Important differences exist in renal variables between African Americans and non–African Americans and between African American men and African American women. Formulas using demographic data and readily measured serum values estimate ^{125}I-iothalamate GFR.**

INDEX WORDS: Glomerular filtration rate (GFR); African Americans; African-American Study of Hypertension and Kidney Disease (AASK).

From the Division of Nephrology, Vanderbilt University Medical Center, Nashville, TN; National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; Medical University of South Carolina, Charleston, SC; University of Texas Southwestern, Dallas, TX; University of California, San Diego, CA; University of Michigan, Ann Arbor, MI; Mount Sinai School of Medicine, New York, NY; Case Western Reserve University; and the Cleveland Clinic Foundation, Cleveland, OH.

For the African-American Study of Hypertension and Kidney Disease Study Group. Additional institutions and investigators participating in the clinical trial are listed in the Appendix.

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Address reprint requests to Julia Lewis, MD, Vanderbilt University Division of Nephrology, S-3223 Medical Center North, Nashville, TN 37232-2372. E-mail: julia.lewis@mcmail.vanderbilt.edu

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ACCURATE ESTIMATION of renal function is important not only to identify patients with early renal impairment, but also to follow the course of established renal disease. Although glomerular filtration rate (GFR) is considered the gold standard of renal function measurements, methods available to directly estimate GFR such as iodine 125–labeled (^{125}I)-iothalamate and inulin clearances are time consuming and expensive, require the injection of isotopes, and are technically difficult to perform. Consequently, these methods do not lend themselves to screening large populations of patients at risk for early renal dysfunction. In clinical practice, serum creatinine level, 24-hour creatinine clearance, or a variety of formulas have been used to estimate GFR. Measurement of creatinine clearance requires the collection of urine over a 24-hour period, which is inconvenient for patients and often leads to inaccurate collections.

To avoid these problems, a number of formu-

las have been developed that estimate GFR; the Cockcroft-Gault[2] formula to predict creatinine clearance is the most commonly used. More recently, the Modification of Diet in Renal Disease (MDRD) study data from 1,628 patients screened for participation was used to develop a formula for estimating GFR measured by ^{125}I-iothalamate renal clearance.[3] Demographic and clinical variables included plasma creatinine level, age, sex, race, and serum albumin and serum urea nitrogen levels. This formula proved to be more accurate than 24-hour urine creatinine clearance or Cockcroft-Gault–estimated clearance for predicting GFR measured by ^{125}I-iothalamate clearance.

However, this analysis was limited by the small number of African Americans (12.1%) screened and the low average GFR of screened patients, with few patients in a high-GFR range. To date, no study has compared multiple methods of measuring renal function in an adequate sample of African Americans over a broad range of GFRs. Thus, potentially important differences in renal function estimation between African Americans and non–African Americans have not been evaluated.

The African-American Study of Kidney Disease and Hypertension (AASK) is a multicenter clinical trial designed to evaluate the effects of three major classes of antihypertensive agents and two levels of blood pressure control on the rate of decline in GFR.[3] African Americans are approximately 12% of the US population, but represent 33% of the US end-stage renal disease (ESRD) population.[4] Hypertension is the most common cause of ESRD among African Americans in the US Medicare ESRD program,[4] and African Americans with hypertension are at much greater risk for the development of ESRD than non–African Americans with hypertension.[5-10] Thus, it is critically important to identify African American patients with early renal impairment to target them for aggressive intervention.

Developing an accurate formula to estimate GFR in these patients would facilitate this goal. It would also assist in monitoring renal function subsequent to interventional therapies. In patients screened for the AASK, we had the opportunity to compare serum creatinine level, creatinine clearance, 100/serum creatinine, Cockcroft-Gault–estimated creatinine clearance, and the formula developed from the MDRD study with the renal clearance of ^{125}I-iothalamate in African Americans screened for the AASK trial. These results were compared with those in non–African Americans screened for the MDRD study. Using AASK data, we also developed an equation for estimating GFR. This report describes the results of these renal function measurements that enabled us to characterize renal function parameters in a large group of African Americans.

MATERIALS AND METHODS

AASK Baseline Cohort and Measurement Methods

The overall study design and methods of recruitment for the AASK have been described previously.[11] The study protocol was approved by the institutional review board at each center, and all patients gave written informed consent.

A total of 2,801 patients entered the baseline period, and 1,703 of these patients underwent measurement of GFR, by ^{125}I-iothalamate clearance, and the other variables described and constitute the study group for these analyses. Patients who proceeded to GFR measurement were all African American men and women without diabetes between the ages of 18 and 70 years, with diastolic blood pressure of 95 mm Hg or greater, urinary protein-creatinine ratio less than 2.5, and no clinically apparent reason for renal insufficiency other than hypertensive nephrosclerosis. The initial baseline GFR used to screen for eligibility in the AASK trial was used in this report. In a pilot study conducted before the full-scale trial using similar entry criteria, 97% of patients (38 of 39 patients) randomized had a diagnosis of hypertensive nephrosclerosis on renal biopsy.[12]

GFR was measured as the renal clearance of ^{125}I-iothalamate.[13-15] Four adequate collection periods were obtained for 93% of GFRs; three collection periods were obtained for the remaining 7%. Total urine volume for the collection exceeded 500 mL for 1,702 of the 1,703 patients. The median GFR coefficient of variation over the collection periods was 10.7%. Creatinine clearance was computed from creatinine excretion in a 24-hour urine collection and a single measurement of serum creatinine level.[15] Urea clearance was obtained similarly from 24-hour urea excretion and a single measurement of serum urea nitrogen level. Serum and urine creatinine were measured using a kinetic alkaline picrate assay (Jaffe method). GFR, creatinine, and urea clearances, and estimates of GFR based on all prediction equations were expressed per 1.73 m^2 of standardized body surface area (BSA). Serum and urine specimens were also used for other measurements, including serum albumin (bromcresol-green method) and serum and urea nitrogen (urease method). All measurements were performed in the same laboratory.

Statistics

Patient characteristics and renal function parameters were compared between patient subgroups within the AASK

cohort and between AASK and MDRD patients using two-sample *t*-tests or chi-square tests of the equality of proportions, as appropriate. Analysis of covariance was used to compare biochemistry measurements and other parameters between AASK patients and MDRD African Americans and non–African Americans after controlling for age, sex, and GFR.

We compared the performance of five existing equations and three newly developed equations for predicting GFR in AASK enrollees. The five existing equations were: (1) 100/serum creatinine, (2) Cockcroft-Gault formula, (3) creatinine clearance, (4) the average of creatinine clearance and urea clearance, and (5) a formula based on serum creatinine level, gender, age, race, serum urea nitrogen level, and serum albumin level recently developed from the enrollees of the MDRD study.[3] Each of the three new equations was developed by applying regression analyses to data from the AASK enrollees. For the first of these equations, we investigated the possibility that the performance of the Cockcroft-Gault formula could be improved in African Americans by modifying the coefficients defining the Cockcroft-Gault equation. This was done by using nonlinear least-squares regression to obtain coefficients A, B, and C, based on the following model:

$$(A - \text{age}) \times \text{weight}/(B \times \text{Scr}) \times [C \text{ for women}]$$

where Scr is serum creatinine level, which optimally predicted measured GFR.

Because exploratory data analyses suggested that GFR might be better predicted by a simple multiplicative function of serum creatinine level, sex, and age, we also developed a prediction equation by regressing log-transformed GFR on these three variables. The third new equation was obtained by regressing log-transformed GFR on the same five factors used in the MDRD prediction equation to determine whether different coefficients would lead to improved prediction of GFR in AASK patients. The second and third regression models based on log GFR were then exponentiated to reexpress the results in the original GFR units. Finally, we also applied stepwise regression analysis to a candidate set of 15 potential predictor variables to determine whether GFR could be more accurately predicted in AASK patients using a different set of predictor variables than used in the existing models. The 15 candidate variables were weight, height, serum creatinine level, age, serum urea nitrogen level, albumin level, phosphorus level, calcium level, systolic blood pressure, diastolic blood pressure, bicarbonate level, potassium level, uric acid level, total cholesterol level, and serum sodium level.

We evaluated the agreement of each prediction equation considered with measured GFR by computing R^2 on the log scale (percentage of variability in log GFR explained by the prediction equation) and the 50th, 75th, and 90th percentiles of the percentage of absolute deviations between measured and predicted GFRs. The 50th percentiles indicate the typical size of errors in predicted GFR, and 75th and 90th percentiles indicate the magnitudes of larger errors. In addition, mean and median differences between predicted and actual GFRs were used to assess the bias of each method. Because the three AASK equations were developed using AASK data, we assessed their accuracy based on analyses in which measured GFR for each individual patient was compared with predicted GFRs that resulted from models in which that patient was omitted.

RESULTS

Demographic and Clinical Characteristics

The mean age of patients screened on the AASK was 53.9 years, 35.5% were women, average BSA was 2.02 m^2, and average mean arterial pressure (MAP) was 114.2 mm Hg at baseline (Table 1). Average systolic and diastolic blood pressures were 149.9 and 96.0 mm Hg at baseline, respectively. Similar data are listed in Table 1 for those patients randomized in the AASK. Mean serum blood urea nitrogen, serum

Table 1. Demographic and Clinical Characteristics

Parameter	All AASK Screenees (N = 1,703)	AASK Randomized Patients (N = 1,094)
Age	53.9 ± 10.5	54.5 ± 10.7
Gender (% women)	35.5%	38.8%
MAP (mm Hg)	114.2 ± 15.0	114.0 ± 16.0
BSA (m^2)		
Overall	2.02 ± 0.25	2.01 ± 0.25
Women	1.88 ± 0.22	1.87 ± 0.22
Men	2.10 ± 0.22*	2.10 ± 0.22*
Serum creatinine (mg/dL)		
Overall	1.85 ± 0.88	2.02 ± 0.72
Women	1.73 ± 0.91	1.77 ± 0.56
Men	1.91 ± 0.86*	2.18 ± 0.76*
>55 y	1.71 ± 0.75	1.86 ± 0.64
<55 y	1.99 ± 0.98†	2.20 ± 0.76†
GFR (mL/min/1.73 m^2)		
Overall	56.9 ± 23.4	45.7 ± 13.0
Women	51.7 ± 23.6	43.6 ± 12.6
Men	59.7 ± 22.8*	46.9 ± 13.1*
>55 y	56.7 ± 21.7	46.8 ± 13.0
<55 y	57.0 ± 25.0	44.4 ± 13.0†
Cockcroft-Gault (mL/min/1.73 m^2)		
Overall	54.2 ± 20.0	45.9 ± 14.3
Women	52.8 ± 20.9	46.4 ± 14.7
Men	55.0 ± 19.5	45.6 ±14.1
>55y	50.4 ± 16.2	43.9 ± 12.9
<55 y	58.0 ± 22.6†	48.1 ± 15.5†
Creatinine clearance (mL/min/1.73 m^2)	62.2 ± 29.8	51.5 ± 22.1
Urine creatinine (g/24 h)	1.68 ± 0.67	1.61 ± 0.64

NOTE. All numbers are mean ± SD or percentage.

*Men significantly different from women, $P < 0.01$.

†Younger patients significantly different from older patients, $P < 0.01$.

albumin, and cholesterol levels were 22.0, 4.2, and 211 mg/dL, respectively. Mean 24–hour urinary creatinine excreted was 1.25 g for women and 1.92 g for men ($P < 0.001$). Median and mean levels of 24-hour urinary protein excretion were 0.07 and 0.50 g, respectively. Median and mean values for urinary protein-creatinine ratio were 0.05 and 0.32 g of protein/g of creatinine, respectively. For all screened patients, mean serum creatinine level was 1.85 mg/dL (range, 0.7 to 7.9 mg/dL); GFR, 56.9 mL/min/1.73 m^2; and clearance estimated by Cockcroft-Gault equation, 54.2 mL/min/1.73 m^2 (Table 2). The median absolute percentage of difference between the first two GFRs (measured weeks apart) was 9.3%. African Americans aged older than 55 years had lower serum creatinine levels for any given level of GFR than African Americans aged younger than 55 years (Table 1). African American women had lower mean serum creatinine measurements and a lower mean GFR than African American men (Fig 1).

Comparison of Renal Function Variables in African Americans in the AASK and African Americans and Non–African Americans in the MDRD Study

The MDRD study randomized patients between the ages of 18 and 70 years (mean, 50.6 years) with GFRs between 13 and 55 mL/min/1.73 m^2 and with renal disease of diverse causes, excluding type 1 diabetes. Renal diagnoses among the MDRD screenees were made primarily on clinical grounds and included diabetic nephropathy (3.4%), polycystic kidney disease (22.4%), glomerular disease (26.6%), tubular interstitial nephritis (7.4%), hypertensive nephrosclerosis (16.7%), and unknown renal diagnosis (23.5%). One hundred ninety-seven MDRD screenees were African American (Table 2). The remaining 1,431 non–African American screenees included 1,304 whites, 87 Hispanics, 17 Asian-Americans, and 23 others. All patients screened for the AASK had a clinical diagnosis of hypertension and no other known cause of renal disease other than hypertensive nephrosclerosis. Patients entering the AASK baseline were older and a lower percentage were women compared with the MDRD non–African American patients (Table 2).[3] AASK patients also had higher GFRs than those entering the MDRD study, estimated by iothalamate clearance. AASK participants had greater serum albumin levels and MAPs at baseline than MDRD non–African American patients. After adjusting for age, sex, and baseline GFR, African American patients in the AASK were heavier, with larger BSAs and body mass indices (BMIs) than either MDRD African Americans or non–Afri-

Table 2. Comparison of Selected Clinical and Demographic Factors Between AASK and MDRD Patients

Parameter	AASK Screenees (n = 1,703)	MDRD Black Screenees (n = 197)	MDRD Nonblack Screenees (n = 1,431)
Age* (y)	53.9	48.9†	50.8
Gender (% women)*	35.5	42.6	39.2†
GFR (mL/min/1.73 m^2)*	56.9	43.6†	39.2†
MAP (mm Hg)‡	114.5	103.9†	98.4†
BSA (m^2)‡	2.02	1.96†	1.91†
BMI (kg/m^2)‡	30.7	28.7†	27.0†
Weight (kg)‡	90.2	84.1†	79.3†
Serum creatinine (mg/dL)‡	2.15	2.21	1.90†
Creatinine clearance (mL/min/1.73 m^2)‡	54.1	54.7	57.4†
Cockcroft-Gault (mL/min/1.73 m^2)‡	48.5	47.4	52.0†
Urine creatinine (g/h)‡	1.64	1.59	1.44†
Serum urea nitrogen (mg/dL)‡	25.7	27.8†	28.5†
Serum albumin (g/dL)‡	4.21	4.02†	4.07†
Urine protein/creatinine (g protein/g creatinine)‡	0.45	0.67†	0.64†

*Means or percentages in top 3 rows not adjusted for other factors.
†Significantly different from AASK patients ($P < 0.01$).
‡Means of all but the first 3 rows are statistically adjusted for age, sex, and GFR by analysis of covariance.

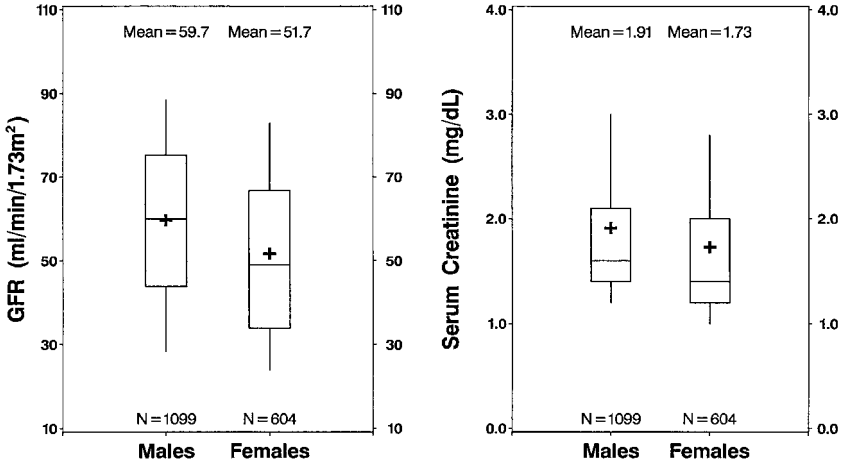

Fig 1. Levels of GFR and serum creatinine in men and women AASK screenees. Shown are box plots indicating the 10th, 25th, 50th, 75th, and 90th percentiles of GFR and serum creatinine level. Both GFRs and serum creatinine levels are significantly greater in men than women.

can Americans.[3] African Americans on the AASK had greater serum creatinine levels and urinary creatinine excretion for any given level of GFR than MDRD non–African Americans. Median absolute percentages of error for GFR versus creatinine clearance were 12% for MDRD non–African Americans and 23.8% for AASK enrollees. Similarly, the median absolute errors for GFR versus the mean of creatinine clearance and urea clearance were 11.8% for MDRD non–African Americans and 22.6% for AASK enrollees. AASK participants had lower serum urea nitrogen levels than MDRD patients. Patients enrolled onto the MDRD study who were not African American but had hypertensive nephrosclerosis did not statistically significantly differ from AASK patients in urinary protein excretions or serum albumin levels. Patients enrolled into the AASK had a poorer correlation of GFR (iothalamate) with creatinine clearance and with the average of creatinine and urea clearance than those in the MDRD study.

Relationship Among Renal Measurements and Prediction of GFR in the AASK and MDRD Study

The relationship between serum creatinine level and ^{125}I-iothalamate GFR on the AASK can be seen in Figs 2 and 3. A single value for serum creatinine can represent a broad range of ^{125}I-iothalamate–measured GFRs. For example, in women with a serum creatinine level of 2.0 mg/dL, the 10th and 90th percentiles for GFR range from 28 to 44 mL/min/1.73 m^2, and at a serum creatinine value of 1.5, the 10th and 90th percentiles are 39 and 61 mL/min/1.73 m^2, respectively. African American women had lower serum creatinine measurements for any given level of GFR than African American men. For example, 78% of women with serum creatinine levels between 1.2 and 1.5 mg/dL had GFRs less than 65 mL/min/1.73 m^2 (Fig 2). Conversely, only 27% of men with serum creatinine levels between 1.2 and 1.5 mg/dL had GFRs less than 65 mL/min/1.73 m^2 (Fig 3). The relationship between measured ^{125}I-iothalamate GFR and creatinine clearance measured by 24-hour urine collection in the African Americans on this study is shown in Fig 4. The 24-hour creatinine clearance often exceeds the measured GFR, presumably because of tubular secretion of creatinine. The discrepancy between measured GFR and creatinine clearance can be extreme, with an iothalamate GFR of 80 mL/min corresponding to creatinine clearances of approximately 15 to 160 mL/min. The relationship of GFR to the reciprocal of serum creatinine and creatinine clearance predicted by the Cockcroft-Gault equation is shown in Table 3. The Cockcroft-Gault equation was calculated as follows:

$$[(140 - \text{age}) \times \text{weight (kilograms)}/(72 \times \text{Scr})](\times 0.85 \text{ for women})$$

The modified Cockcroft-Gault formula for African Americans generated using AASK data was:

$$[(311 - \text{age}) \times \text{weight (kilograms)}/(199 \times \text{Scr})] \times (0.76 \text{ for women})$$

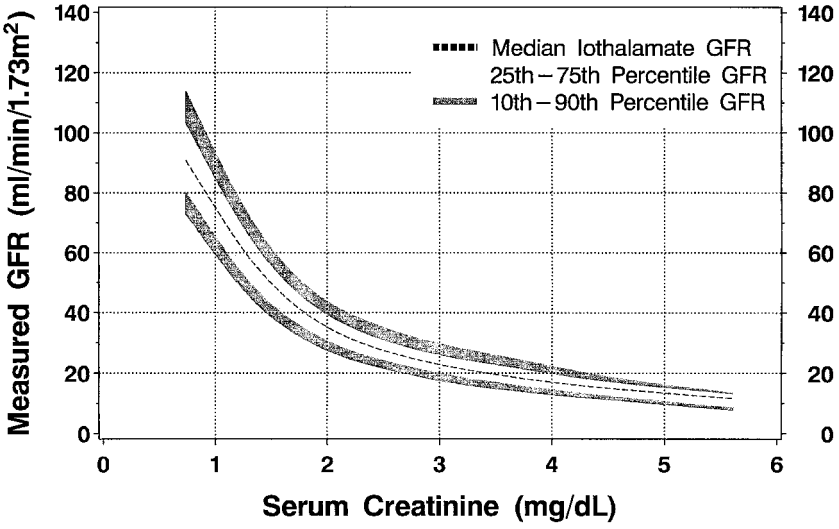

Fig 2. Association of measured GFR with serum creatinine level in male AASK screenees. Boundaries of shaded regions indicate the 10th, 25th, 50th, 75th, and 90th percentiles of GFR as a function of serum creatinine.

This modified Cockcroft-Gault formula performed better than the original Cockcroft-Gault formula (Table 3), although not as well as the formula developed from the screening data in the MDRD study. The formula derived from the MDRD data for predicting GFR was:

$$170 \times (\text{Scr})^{-0.999} \times (\text{age})^{-0.176} \times (0.762 \text{ for women}) \times (1.180 \text{ for blacks}) \times (\text{SUN})^{-0.170} \times (\text{alb})^{+.318}$$

where SUN is serum urea nitrogen level.

The optimal model using these same terms (except for black race), but with values of coefficients derived using AASK data, is as follows:

$$222 \times (\text{Scr})^{-0.974} \times (\text{age})^{-0.267} \times (0.757 \text{ for women}) \times (\text{SUN})^{-0.108} \times (\text{albumin})^{+0.372}$$

The units for this equation are Scr (milligrams per deciliter), age (years), weight (kilograms), SUN (milligrams per deciliter), and albumin (milligrams per deciliter). The coefficients of the AASK model differed significantly from the coefficients in the MDRD prediction equation ($P < 0.001$; Table 3), and the AASK equation was slightly more accurate than the MDRD equation in predicting ^{125}I-iothalamate measured GFRs of patients enrolled onto the AASK ($R^2 = 0.821$;

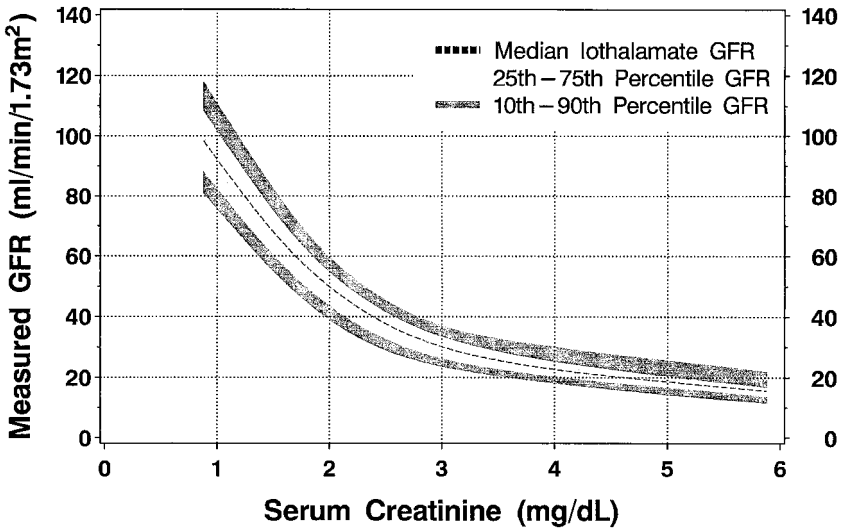

Fig 3. Association of measured GFR with serum creatinine in female AASK screenees. Boundaries of shaded regions indicate the 10th, 25th, 50th, 75th, and 90th percentiles of GFR as a function of serum creatinine.

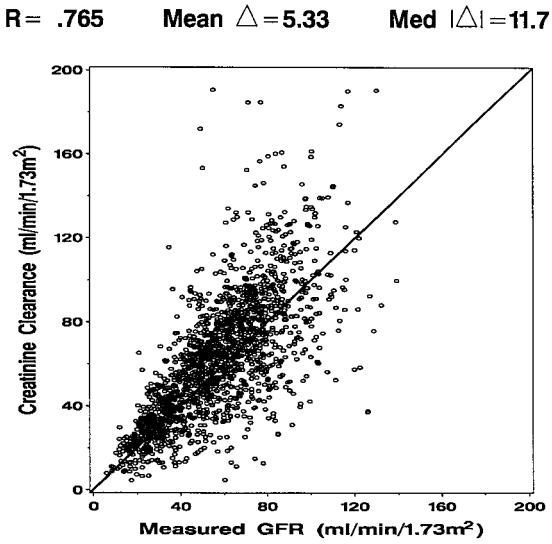

Fig 4. Agreement of creatinine clearance with measured GFR in AASK screenees. The median bias of creatinine clearance as an estimate of GFR is +5.27 mL/min/1.73 m². The median absolute error is 11.7 mL/min/1.73 m².

median absolute percentage of error = 12.1% for the AASK equation versus $R^2 = 0.819$; median absolute percentage of error = 12.4% for the MDRD equation) (Fig 5, Table 3).

Although all five terms included in the AASK prediction equation were statistically significant ($P < 0.001$ for each term), most of the variance in log GFR that was explained by the full equation was accounted for by serum creatinine level, age, and sex. The regression model based on these three terms is:

$$329 \times (\text{Scr})^{-1.096} \times (\text{age})^{-0.294} \times (0.736 \text{ for women})$$

As shown in the bottom row of Table 3, the agreement of this simpler model with GFR was substantially better than the original or modified Cockcroft-Gault formulas or creatinine clearance and nearly as good as the more complex equations derived in the MDRD study and the AASK. In particular, the ratio of percentage of variance of log GFR accounted for by the three- and five-variable models derived in the AASK was 0.989.

Our assessment of the accuracy of the different prediction formulas is based on the measurement methods used for the various variables in this study (eg, kinetic alkaline picrate assay for serum creatinine). If alternate methods are used, the relative accuracy of the formulas may differ from that shown here.

As described in Methods, we used stepwise regression analysis to investigate whether a model with different predictor variables could more accurately predict GFR than the models considered previously. Results indicated that the best fitting models with three variables (serum creatinine level, sex, and age) or five variables (serum creatinine level, sex, age, serum urea nitrogen level, and serum albumin level) included the same variables as the three- and five-variable prediction models shown previously. Inclusion of additional predictor variables did not substantially increase the proportion of variance in log GFR accounted for by the model. As seen in Table 3, the AASK equations were superior to the Cockcroft-Gault equation in multiple key subgroups.

DISCUSSION

This is the first report to compare techniques to estimate renal function in a large cohort of African Americans with hypertensive nephrosclerosis.

In comparing the non–African American popu-

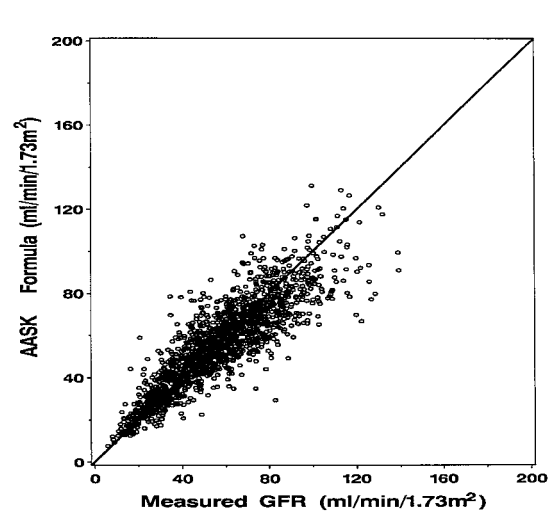

Fig 5. Agreement of five-variable AASK equation with measured GFR in AASK screenees. The median bias of the AASK equation as an estimate of GFR is −0.33 mL/min/1.73 m². The median absolute error is 6.19 mL/min/1.73 m².

Table 3. Agreement of Alternative Methods With Measured GFR in AASK Screenees

Method	Pearson *R*	Pearson R^2	Mean Δ (mL/min/1.73 m²)	Median Δ (mL/min/1.73 m²)	Median |Δ|	Median |%Δ|	75th Percentile |%Δ|	90th Percentile |%Δ|
Cockkroft-Gault	0.848	0.720	−2.67	−1.91	8.34	16.4	27.2	39.6
Modified Cockkroft-Gault	0.873	0.762	−0.36	0.38	7.31	14.3	25.1	38.9
Ccr	0.765	0.586	5.33	5.27	11.74	23.8	38.7	57.7
100/Scr	0.836	0.699	6.32	5.73	9.62	17.8	35.6	59.5
0.5 × (Ccr + Ucr)	0.771	0.594	−11.5	−9.36	11.11	22.6	37.6	52.5
MDRD equation[3]	0.905	0.819	−0.94	−0.82	6.27	12.4	21.0	31.8
AASK equation (Scr, sex, age, serum urea nitrogen, serum albumin)	0.906	0.821	−0.99	−0.33	6.19	12.1	21.2	31.8
AASK equation (Scr, sex, age)	0.901	0.812	−1.05	−0.49	6.19	12.3	21.8	33.1

NOTE. N = 1,703. Pearson *R* and Pearson R^2 computed on log scale. Measures of agreement for the AASK equations were obtained using predicted GFRs computed with the current observations omitted.

Abbreviations: Ccr, creatinine clearance; Ucr, urea clearance; Δ, difference; Med |Δ|, median absolute difference; Med |%Δ|, median percentage absolute difference.

lation studied in the MDRD study with the African American population studied in the AASK trial, after controlling for differences in age, sex, and GFR, important differences in renal function measurements were observed. The Third National Health and Nutrition Examination Study (NHANES III) conducted from 1988 to 1994 found that in a representative sample of 18,723 US citizens, African Americans had greater serum creatinine levels than their non–African American counterparts.[16] These differences were hypothesized to be the result of physiological differences and/or the greater prevalence of renal disease in African Americans. African American screenees in the AASK had greater serum creatinine levels and urinary creatinine excretions for any given level of GFR than MDRD non–African Americans. This would suggest that at least some of the differences noted between African Americans and non–African Americans in serum creatinine values in the NHANES III study may be related to physiological differences in muscle mass, creatinine production, or renal tubular secretion of creatinine and may not reflect abnormalities in renal function. As reported in non–African American women, African American women screenees on the AASK study had lower mean GFRs for any given level of serum creatinine than African American men.[17] Therefore, the patients screened in the AASK provide important insight into two demographic groups that have often been underrepresented in previous clinical nephrology trials: African Americans and women.

Of the 1,703 patients enrolled into this trial, 35.5% were women, making this the largest number of African American women in whom renal function has been carefully assessed. It is presumed that lower serum creatinine to GFR ratios in women compared with men reflect the greater daily production and excretion of creatinine in men associated with greater muscle mass per body weight or BSA. For both men and women, the lower serum creatinine to GFR ratio observed with increasing age also likely reflects decreasing muscle mass with age. However, it is very important clinically to note that African American women and the elderly will have lower GFRs representing worse renal function compared with men and the young with the same creatinine levels. Ten percent of African American women in the AASK trial with a serum creatinine level of 1.5 mg/dL, a level considered normal, will have a GFR less than 39 mL/min/1.73 m², representing moderate renal insufficiency. Even African American women with a serum creatinine level less than 1.0 mg/dL may have renal insufficiency.

The AASK trial documented that serum creatinine level was an imprecise measure of renal function in the African American screenees in this study. Twenty-four–hour creatinine clearance was also a poor measure of renal function and consistently overestimated GFR, presum-

ably in part because of tubular secretion of creatinine. This was in a population of patients who received careful urine-collection instructions as participants in a clinical trial. It is anticipated that the accuracy of 24-hour urine collections would be less in a clinical practice setting. Although the Cockcroft-Gault estimation of creatinine clearance has been found to overestimate iothalamate GFR in non–African American populations, we found the Cockcroft-Gault formula slightly underestimated GFR. The Cockcroft-Gault formula was originally defined in non–African American men.[2] Underestimation of GFR presumably represents increased muscle or dietary creatinine production relative to creatinine excretion in our study. It is unclear whether increased muscle mass or increased animal protein is responsible for the increased creatinine production rate observed in this cohort.

In the MDRD study, an equation was developed using serum creatinine level, demographic characteristics (age, sex, race), serum urea nitrogen level, and serum albumin level. Less than 15% of participants in the MDRD study were African American. Patients screened in the AASK trial were older, had greater BMIs, and fewer were women. The mean GFR was substantially greater in the AASK than the MDRD study.[3,18] The equation derived from the MDRD population for predicting GFR was nearly as accurate in this population as the AASK equation, confirming the accuracy of estimating GFR from easily obtainable clinical parameters and providing an external validation of this equation. Also, when looking at the accuracy of the equations compared with iothalamate GFR, it is important to remember that iothalamate GFRs themselves are variable. The median absolute percentage of difference between the first two GFRs (measured a few weeks apart) was 9.3%. This is almost as large as the median absolute percentage of difference between predicted and measured GFR. The MDRD or the AASK equation should be used to better estimate GFR.

The stepwise regression analysis performed using data from the AASK alone identified the same five variables as the prediction equation developed in the MDRD study. However, the coefficients associated with these variables were different for a best fit with AASK data. This equation for predicting GFRs using demographic and serum variables is the first ever developed for use in African Americans and is far superior to serum creatinine level, 24-hour creatinine clearance, or Cockcroft-Gault–estimated creatinine clearance. We also presented a simpler prediction equation, depending on only serum creatinine level, age, and sex, that predicts GFR in the AASK screenees almost as accurately as the more complex equations derived from the MDRD study or the AASK. This should facilitate the estimation of GFR from simple variables collected in routine clinical practice. The prediction equations presented here have not been shown to be accurate in patients not in a steady state of creatinine balance (eg, patients with acute renal failure).

The importance of being able to accurately assess GFR without complex procedures is especially important in the African American population. First, because the prevalence of ESRD is especially high in this population, it is very important to be able to estimate renal function to detect renal dysfunction early so that appropriate renal-sparing therapy can be applied. Second, renal function can be estimated to accurately time the initiation of renal replacement therapy. Lastly, this is particularly important in African American women and the elderly, in whom serum creatinine levels, even in the normal range, can mask advanced renal failure. In this study, we only examined African Americans with hypertensive nephrosclerosis who were screened for our study and thus cannot comment on the applicability of our results to a broader or different group of African Americans.

We conclude that there are important differences in renal function measurements in African Americans compared with non–African Americans, including greater serum creatinine levels and urinary creatinine excretion rates for a given GFR. The equation we developed gives the clinician the opportunity to estimate GFR more accurately using simple serum measurements and demographic variables.

APPENDIX

National Institutes of Health: Lawrence Agadoa, MD (Program Director), John Kusek, PhD, Steering Committee: Janice Douglas, MD (Chairman). Clinical Centers: University of California, San Diego, CA: Daniel T. O'Connor, MD; Case

Western Reserve University, Cleveland, OH: Jackson Wright, MD, PhD; Emory University, Decatur, GA: Janice Lea, MD; Harbor-University of California at Los Angeles Medical Center, Torrance, CA: Joel Kopple, MD; Howard University, Washington, DC: Otelio S. Randall, MD; Johns Hopkins University, Baltimore, MD: Lawrence J. Appel, MD, MPH; Martin Luther King–Drew Medical College, Los Angeles, CA: Keith Norris, MD; Medical University of South Carolina, Charleston, SC: DeAnna Cheek, MD; Meharry Medical College, Nashville, TN: Marquetta Faulkner, MD; Harlem Hospital Center, New York, NY: Velvie Pogue, MD; Morehouse School of Medicine, Atlanta, GA: William Cleveland, MD; Mount Sinai School of Medicine, New York, NY: Robert A. Phillips, MD, PhD; Ohio State University, Columbus, OH: Lee Hebert, MD; Rush Presbyterian/St Luke's Medical Center, Chicago, IL: George L. Bakris, MD; University of Alabama, Birmingham, AL: Stephen G. Rostand, MD; University of Florida, Gainesville, FL: C. Craig Tisher, MD; University of Miami, Miami, FL: Jacques J. Bourgoignie, MD; University of Michigan, Ann Arbor, MI: Kenneth Jamerson, MD; University of Southern California, Los Angeles, CA: Shaul G. Massry, MD; The University of Texas Southwestern Medical Center, Dallas, TX: John Middleton, MD; Vanderbilt University, Nashville, TN: Julia Lewis, MD; Data Coordinating Center: Cleveland Clinic Foundation, Cleveland, OH: Jennifer Gassman, PhD, Tom Greene, PhD.

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