Evaluation of Serum Creatinine for Estimating Glomerular Filtration Rate in African Americans with Hypertensive Nephrosclerosis: Results from the African-American Study of Kidney Disease and Hypertension (AASK) Pilot Study

ROBERT D. TOTO,* KATHARINE A. KIRK,† JOSEF CORESH,‡ CAMILLE JONES,§ LAWRENCE APPEL,‡ JACKSON WRIGHT,‖ VITO CAMPESE,¶ BABATUNDE OLUTADE,# LAWRENCE AGODOA,** and THE AASK PILOT STUDY INVESTIGATORS

**University of Texas Southwestern Medical Center at Dallas, Dallas, Texas; †Department of Biostatistics, The University of Alabama at Birmingham, Birmingham, Alabama; ‡Welch Center for Prevention, Epidemiology and Clinical Research at The Johns Hopkins University Medical Center, Baltimore, Maryland; §Case Western Reserve University, Cleveland, Ohio; ‖USC Medical Center, Los Angeles, California; ¶Emory University, Atlanta, Georgia; and #The National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), Bethesda, Maryland.*

Abstract. Measurement of GFR is considered the standard for estimating renal function. However, standardized accurate GFR methodology is expensive and cumbersome; therefore, estimates of GFR based on serum creatinine concentration have been employed. The purpose of the study presented here was to assess the accuracy and precision of using serum creatinine measurements to estimate GFR in the screenee cohort of The African-American Study of Kidney Disease and Hypertension (AASK) Pilot Study. GFR was estimated by four methods: 100/serum creatinine, Cockcroft-Gault equation, creatinine clearance from 24-h urine collection, and a new regression equation derived from the pilot study data. These methods were compared with renal clearance of ^{125}I-iothalamate GFR (GFR1) in 193 hypertensive (diastolic blood pressure ≥95 mm Hg) African-American screenees (142 men, 51 women). A second GFR (GFR2) was performed in 98 screenees who were eligible (GFR1 25–70 mL/min per 1.73 m^2) for the pilot study. Accuracy was assessed by the difference of ^{125}I-iothalamate GFR-estimated GFR (Δ GFR), and precision was estimated from the combined root mean squared error (CRMSE) and the coefficient of determination (r^2). The results for accuracy (± SD) and precision were as follows: (*1*)100/Scr, Δ GFR = −0.76 ± 16.5, CRMSE = 16.5, r^2 = 0.69; (2) Cockcroft-Gault, Δ GFR = 9.56 ± 14.9, CRMSE = 17.7, r^2 = 0.66; 3) 24-h creatinine clearance, Δ GFR = 0.79 ± 20.7, CRMSE = 20.7, r^2 = 0.49; 4) New equation Δ GFR = −0.08 ± 12.8, CRMSE 12.7, r^2 = 0.75. In comparison, a second GFR (GFR2, N = 98) had Δ GFR = 1.36 ± 8.48, CRMSE 8.6, r^2 = 0.75. Estimates based on 100/SCr and the new equation were the most precise. It was concluded that GFR estimated by serum creatinine is superior to outpatient 24-h urine creatinine clearance in this population. Serum creatinine values can be used to provide a reasonably accurate estimate of GFR in hypertensive African Americans. (J Am Soc Nephrol 8: 279–287, 1997)

Identification of hypertensive patients with impaired renal function is a high priority because of the high morbidity and mortality associated with this condition (1–3). However, the optimal technique to estimate GFR in patients with hypertensive nephrosclerosis is unclear. Accurate estimates of GFR in patients with hypertensive nephrosclerosis are not available from large-scale clinical trials of hypertension treatment. Indeed, most studies have only employed serum creatinine to estimate renal function (2,4). Although serum creatinine provides only a rough estimate of GFR and is subject to many limitations as a filtration marker (5,6), it is still the most widely used tool for screening populations at risk for progressive renal disease. Regrettably, few studies have assessed the relationship between serum creatinine, 24-h creatinine clearance, Cockcroft-Gault estimation of creatinine clearance, and GFR in patients with renal disease in general and in African Americans with hypertensive nephrosclerosis in particular (7–10).

The United States Renal Data Systems reported that hypertension accounted for 29% of new cases of end-stage renal disease (ESRD) in the general United States population in 1992 (11). Among patients with hypertension, African Americans are at higher risk of developing ESRD than non-African Americans (12–17). To identify individuals with early evidence of renal impairment, accurate estimates of renal function in African-American populations are particularly important. If serum creatinine is shown to be a reliable way to estimate GFR

Received April 11, 1996. Accepted October 25, 1996.
Correspondence to Dr. Robert D. Toto, Professor, Department of Medicine, University of Texas Southwestern Medical Center at Dallas, Dallas, TX 75235-8856.
1046-6673/0802-0279$03.00/0
Journal of the American Society of Nephrology

among African-American patients, it could not only be used as an efficient tool to screen patients in clinical practice but also to measure changes in renal function over time in clinical research trials. On the other hand, if serum creatinine does not reliably estimate GFR among African-American patients, other measures must be employed.

In screenees in the African-American Study of Kidney Disease and Hypertension (AASK) Pilot Study, we compared commonly used estimates of GFR, including 100/serum creatinine, Cockcroft-Gault estimated creatinine clearance, 24-h urine creatinine clearance, and renal clearance of ^{125}I-iothalamate. The AASK is a prospective multicenter randomized controlled trial designed to study the effect of lowering blood pressure (BP) with different antihypertensive regimens on slowing the rate of decline in GFR over time in African Americans with renal insufficiency due to hypertensive nephrosclerosis. The AASK trial is the first large-scale trial in which GFR has been measured by renal clearance of ^{125}I-iothalamate in a large number of African-American patients with hypertensive nephrosclerosis. This report describes the results of the renal function measurements performed on screenees during the screening and baseline periods of the AASK Pilot Study.

Materials and Methods

Patients

The study population for the AASK pilot study consisted of African-American men and women aged 18 to 70 yr with diastolic BP ≥95 mm Hg, a GFR between 25 and 70 mL/min per 1.73 m^2, and no apparent reason for renal insufficiency other than hypertension. Screenees for the trial were identified through a variety of methods, including chart reviews, physician referrals, and mass mailings. The AASK clinical centers used serum creatinine when available as a guide for screening, typically selecting patients with a serum creatinine value between 1.2 and 4.4 mg/dL for women and between 1.4 and 5.0 mg/dL for men. Screenees were excluded from participation if they had known glomerular disease, serious systemic disease, diabetes mellitus, serum K >5.5 mEq/L, chronic continuous use of nonsteroidal anti-inflammatory drugs, history of renal failure requiring dialysis, history of malignant or accelerated hypertension in the preceding 6 months, urine protein (mg/dL)/creatinine (mg/dL) ratio of >2.5, known allergy to any randomized study drug, asthma, congestive heart failure, allergy to iodine, pregnancy or lactation, or history of drug abuse. The study protocol was approved by an Institutional Review Board at each clinical center, and all participants gave written informed consent for the study.

Experimental Design

The pilot study was designed to test the feasibility of conducting a long-term, prospective double-blind randomized trial to determine whether (*1*) pharmacologic treatment to lower BP to one of two levels of BP control (a seated mean arterial pressure <92 mm Hg *versus* 102 to 107 mm Hg) and (*2*) treatment with a calcium channel blocker (CCB)-based, an angiotensin converting enzyme (ACE) inhibitor-based, or a β-blocker (BB)-based treatment regimen would preferentially slow the rate of decline in GFR. At a screening visit, a serum creatinine was obtained (and measured in a central laboratory), and a 24-h urine was collected to measure creatinine clearance and protein excretion rate. Antihypertensive therapy was gradually withdrawn if seated diastolic BP was ≤95 mm Hg to confirm the presence of diastolic hypertension. On the day after the 24-h urine collection, an eligibility GFR measurement (renal clearance of ^{125}I-iothalamate) was performed (GFR1). If the GFR1 value was in the range of 25–70 mL/min per 1.73 m^2, a second GFR measurement was performed within the next 1 to 8 wk (GFR2). During the interval between GFR1 and GFR2, patients were followed-up in the study clinic, and antihypertensive medications were adjusted in an attempt to maintain BP ≤140/90 mm Hg while withdrawing patients from ACE inhibitors, CCB, and BB. After completing GFR2, eligible participants were asked to undergo percutaneous renal biopsy. Participants were then randomized to (*1*) one of two BP control levels and (*2*) one of the three antihypertensive treatment regimens, and they were then followed at least at monthly intervals to achieve the targeted BP and to promote adherence with the medication regime. If BP was not controlled using initial monotherapy with an ACE inhibitor, CCB, or BB, additional medications were added, beginning with diuretics.

Study Procedures

BP measurement. BP, height, and weight were measured at both the screening and the GFR visits. BP was measured at rest in the seated position, using a Huntley-Hawksley random zero sphygmomanometer. Patients were instructed to avoid smoking and drinking caffeinated beverages prior to the BP measurement. The BP measurement was repeated three times, and the average of the last two measurements was calculated and recorded. Each measurement was performed by staff trained and certified to measure BP according to standardized methods.

24-h creatinine clearance. A 24-h urine collection for measurement of creatinine clearance was obtained on the day prior to each GFR measurement. Patients were given both verbal and written instructions on how to collect the urine. They were instructed to begin the collection in the morning after the first void and then to collect all urine until the next morning (including the first morning void). To ensure that collections were complete, patients were told that all urine, including urine voided during defecation, be collected. All urine samples submitted at the time of the G1 measurement were included in the analysis. Adequacy of urine collection was based on the total creatinine in the sample. The patients were to return to the clinic that same morning for a fasting serum sample for creatinine determination. Creatinine clearance was calculated by the standard formula and normalized for body surface area. The CX3 autoanalyzer methodology (Beckman Instruments, Berria, CA) was employed for determination of urine creatinine by the central laboratory; however, serum creatinine was determined by a Hitachi autoanalyzer (Hitachi, Indianapolis, IN). To adjust for the differences in the methods of determining creatinine concentration for serum *versus* urine, the Hitachi method was adjusted to the CX3 method by using a linear equation that minimized the deviations perpendicular to the fitted line. The line was fitted from data obtained in a substudy in which serum creatinine was measured by both methods on the same sample. The equation for the fitted line was CX3 Scr = 1.016 × Hitachi Scr − 0.21, (r^2 = 0.99). The coefficient of variation for serum creatinine with both assays was <6.0% (18).

GFR. GFR was measured by renal clearance of ^{125}I-iothalamate. Water loading was accomplished by instructing participants to consume ~5 mL/kg of body weight of tap water prior to arrival at the clinic on the day of the GFR measurement. After arriving at the clinic, participants ingested an additional 10 mL/kg of body weight of water. Next, the patient ingested two drops of supersaturated potassium iodide to block thyroidal uptake of the ^{125}I-iothalamate. Baseline blood and urine samples were obtained 30 min later, after which the patient was given a subcutaneous injection of 35 μCi of ^{125}I-iothalamate in the subdeltoid area. Approximately 1 h later, the patient

was asked to void, and a blood sample was obtained. Four 30-min urine collections were then performed, with blood samples taken at the end of each period. Urine volume was measured, and the urine flow rate was calculated. Samples of blood and urine were sent to the central GFR laboratory (The Cleveland Clinic, Cleveland Ohio), where they were counted for 10 min in a γ counter calibrated with ^{131}Cs. GFR for each 30-min period was calculated using the logarithmic mean of the plasma ^{125}I-iothalamate counts compared with urine counts during that period. The mean of four periods was used to calculate GFR. In 3.5% of the cases, GFR was calculated using the mean of three samples.

Urine protein excretion. Urine protein was measured from the 24-h urine collections and expressed as milligrams of protein/milligrams of creatinine. Protein was measured by standard automated clinical methods (19).

Data analyses and estimates of GFR. The relationship between GFR (^{125}I-iothalamate clearance) and GFR estimated by several methods was assessed by linear regression analysis. The first, or eligibility GFR, (GFR1) measurement was regressed upon (*1*) 100/serum creatinine; (*2*) 24-h creatinine clearance; and (*3*) creatinine clearance estimated by the Cockcroft-Gault equation (20). In addition, to determine whether other characteristics of the screening population could be used to obtain a better estimate of GFR than was possible from existing equations, we used multiple regression analysis to determine the best linear fit equation (see below) for the relationship between baseline serum creatinine, age, body weight, body mass index (BMI), protein excretion rate, and gender. The regression of the first GFR on the second baseline GFR was also examined to determine intra-individual variability of GFR. The relationship of the second GFR with the other estimates of GFR was examined for the 98 patients who had a second GFR. Correlations were determined by the Pearson correlation coefficient. Three parameters were used to assess the accuracy and precision of the GFR estimates, including the mean difference (Δ GFR) between the estimates and GFR, the coefficient of determination (r^2), and the combined root mean squared error (CRMSE). CRMSE measures both bias (shift of the regression line from identity) and precision (variability about the regression line).

Calculations. Creatinine index was calculated as the 24-h urine creatinine excretion divided by body weight in kilograms. The 24-h creatinine clearance was calculated as urine creatinine concentration $\times$ urine flow rate $\div$ serum creatinine concentration. Cockcroft-Gault creatinine clearance was calculated as [(140 $-$ age) $\times$ weight (in kg)/(72 $\times$ serum creatinine)] for men and as [(140 $-$ age) $\times$ weight (in kg)/(72 $\times$ serum creatinine)] $\times$ 0.85 for women. Urine protein was expressed as the ratio of protein to creatinine in milligrams of protein/milligrams of creatinine. BMI was calculated as weight (kg) $\div$ height (m^2). The CRMSE is calculated as the square root of [(mean difference in GFR estimate $-$ GFR)^2 + (SD of the difference)^2]. Values in tables are mean $\pm$ SD.

Results

Baseline Characteristics

Table 1 illustrates the baseline characteristics of the screenee population included in this study. One hundred ninety-three screenees, 142 (74%) men and 51 (26%) women, completed both a baseline 24-h creatinine clearance and an eligibility GFR (GFR1) measurement. Mean BP was elevated at the time of screening in most patients, and nearly all were taking antihypertensive medications. Mean BMI was increased above normal in both men and women. Renal function of the screenee population was decreased: mean serum creatinine was 1.69 $\pm$ 0.89 mg/dL, 24-h creatinine clearance was 68.0 $\pm$ 27.6 mL/min per 1.73 m^2, and GFR1 was 68.8 $\pm$ 26 mL/min per 1.73 m^2. As shown in Figure 1, eligibility GFR (GFR1) measurement in screenees had a normal distribution. More than half of the screenees gave a history of cigarette smoking at some time in the past.

Table 1. Baseline characteristics of AASK pilot study screenees[a] (N = 193)

Parameter	Mean $\pm$ SD	Range
Age (yr)	53 $\pm$ 10.2	23–70
Gender (% Men)	76	—
Systolic blood pressure (mm Hg)	146 $\pm$ 23	99–224
Diastolic blood pressure (mm Hg)	91 $\pm$ 13	62–133
Mean blood pressure (mm Hg)	110 $\pm$ 15	77–150
Duration of hypertension (yr)	14 $\pm$ 10.5	0.25–50
Body mass index (kg/M^2)		
men	29.0 $\pm$ 5.1	14.8–59.4
women	29.7 $\pm$ 5.8	19.5–41.5
Serum creatinine (mg/dL)	1.69 $\pm$ 0.89	0.61–8.53
24-H creatinine clearance (mL/min/per 1.73 m^2)	68.1 $\pm$ 27.6	9–178
Creatinine clearance by Cockcroft-Gault	59.3 $\pm$ 21.7	12.1–160
Glomerular filtration rate (mL/min/per 1.73 m^2)	68.8 $\pm$ 26	11–126
Urine protein/creatinine ratio (mg/mg)	0.21 $\pm$ 0.47	0.008–2.97
History of cigarette smoking (%)	57.6%	—

[a] Expressed as mean $\pm$ SD except where noted.

Creatinine Index and 24-h Creatinine Clearance

The data in Table 2 illustrate the variability in serum creatinine, total urine creatinine excretion (mg/kg per day, "creatinine index"), and creatinine clearance by age category and gender. The mean creatinine index for all subjects was 19.5 $\pm$ 6.2 (range, 3.34 to 46.0). The average total creatinine excretion was slightly greater in the subjects in the age range from 41 to 50 yr; however, the number of subjects of ages <40 yr old was relatively small (N = 26); consequently, these differences were not significant. As expected, total creatinine excretion was higher in men than in women ($P < 0.001$). The range of creatinine excretion was quite large, and values <10 and >30 mg/kg per day were found in all age ranges and in both sexes. To estimate poor or inappropriate collection efforts, we analyzed our data by calculating the individual creatinine index and compared these values with the range that encompasses 95% of the normal population (mean $\pm$ 2 SD) by age and gender. As shown in Table 3, 10% of the urine collections were deemed undercollections, and 6% were deemed overcollections by this method. In other words, 10% and 6% of the

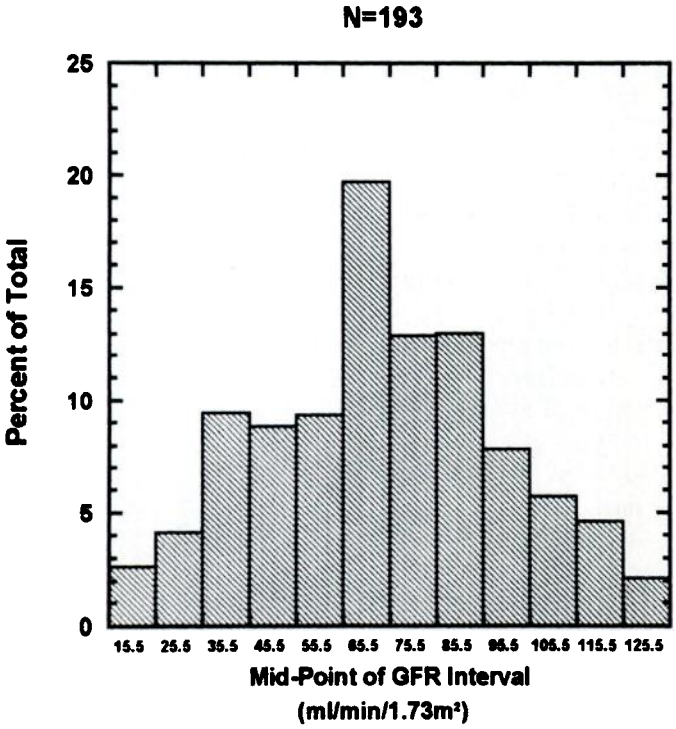

Figure 1. Distribution of screening glomerular filtration rate.

samples submitted to analysis were above and below 2 SD from the normal mean for age and gender, respectively.

Serum creatinine was significantly higher in men compared with women who were screenees; however, mean 24-h creatinine clearance corrected for body surface area was similar for men and women (Table 2). The mean 24-h creatinine clearance was slightly higher after age 40; however, as noted above, only 26 screenees were <40 yr old.

Assessment of Serum Creatinine as a Screening Tool

Figure 2 shows the relationship between GFR (^{125}I-iothalmate clearance) by gender and screening serum creatinine values. The range of serum creatinine values encompassing GFR eligibility (GFR values within the horizontal dotted lines) was wide, ranging from 0.90 to 4.0 mg/dL. Using different cutoff points of serum creatinine, the following yields of eligibility were noted: ≥1.0 mg/dL was 90%, ≥1.5 mg/dL was 74%, ≥2.0 mg/dL was 18%, and ≥3.0 mg/dL was 4%. Serum creatinine values of 1.42, 1.83, 2.33, and 2.94 mg/d identify the 25th, 50th, 75th, and 90th percentiles, respectively, for eligible participants .

Estimates of Glomerular Filtration Rate

The precision and reliability of four different methods of estimating GFR are compared in Table 4: (*1*) 100/Scr; (*2*) Cockcroft-Gault; (*3*) 24-hour creatinine clearance; and (*4*) a new equation using parameters of age, gender, BMI, and serum creatinine in a linear model (Table 4, Figures 3 and 4). As shown in Figures 3a and 3b, there was a very good correlation between GFR estimated by 100/Scr and GFR for both men (r^2 = 0.68) and women (r^2 = 0.75), although the variability increases with lower serum creatinine values. The slope of the regression of GFR on 100/Scr was 0.98 for men and 0.81 for women. The overall mean difference between GFR and estimated GFR was −0.76 ± 15.6 mL/min per 1.73 m^2. This led to a CRMSE between 100/Scr and GFR of 16.5.

GFR estimated from the Cockcroft-Gault equation also correlated well with measured GFR for men (r^2 = 0.70) and women (r^2 = 0.59) (Figure 3c and 3d). In contrast to 100/Scr, mean difference between GFR and the respective Cockcroft-Gault estimate was 9.6 ± 14.9 mL/min per 1.73 m^2, with a CRMSE of 17.7. Thus, on average, the Cockcroft-Gault formula underestimated glomerular filtration rate by almost 10 mL/min per 1.73 m^2.

The 24-h creatinine clearance was more weakly correlated with GFR in both men (r^2 = 0.48) and women (r^2 = 0.54) as compared with 100/Scr and Cockcroft-Gault estimates. The mean difference between 24-h creatinine clearance and GFR was 0.79 ± 20.7 mL/min per 1.73 m^2, and CRMSE was 20.7. Thus, 24-h creatinine clearance had an average bias similar to 100/Scr and less than Cockcroft-Gault, but the precision of the GFR estimate was inferior to both (Table 4, Figure 3). The modeled equation for estimating GFR from age, 1/serum creatinine, gender, and weight or BMI using least squares regression had greater accuracy than and similar precision to 100/Scr, Cockcroft-Gault and 24-h creatinine clearance. The regression equation for estimating GFR was GFR = −0.30 (Age − 52) +

Table 2. Serum creatinine, creatinine index, and 24-h creatinine clearance in AASK pilot study screenees

Age group	*N*	Serum Cr (mg/dL)	Creatinine Index (mg/kg per day)		24-H Creatinine Clearance (mL/min per 1.73 m^2)	
		Mean ± SD	Mean ± SD	Range	Mean ± SD	Range
20–30	4	2.72 ± 1.04	16.4 ± 6.2	10.9–24.1	35.0 ± 21.5	18–65
31–40	22	2.36 ± 1.86	19.5 ± 7.7	3.34–30.5	60.1 ± 37.1	9–135
41–50	62	1.66 ± 0.78	20.5 ± 6.0	9.42–33.2	70.0 ± 25.5	25–131
51–60	70	1.56 ± 0.64	18.8 ± 5.9	8.58–46	70.5 ± 26.9	14–137
61–70	52	1.54 ± 0.46	19.4 ± 6.6	5.85 ± 43.5	68.5 ± 25.3	28–178
Men	142	1.82 ± 0.95	21.0 ± 6.0	8.58–46.0	68.9 ± 28.2	13–178
Women	51	1.34 ± 0.60	15.3 ± 4.9	3.34–30.8	63.70 ± 25.8	9–120
TOTAL	193	1.69 ± 0.89	19.5 ± 6.2	3.34–46.0	68.0 ± 27.6	9–178

Table 3. Analysis of urine collection errors based on urine total creatinine (mg/kg per day)

Age	*N*	Urine Creatinine (mg/kg/24 h)	Below Range (*N*)[a]	%	Above Range (*N*)[a]	%
Men						
21–30	3	19–28	2	67	0	0
31–40	18	18–28	4	22	0	0
41–50	45	12–28	3	6	0	0
51–60	45	12–26	4	10	3	7
61–70	31	9–23	0	0	5	16
Subtotal	142		13	9.1	8	5.6
Women						
21–30	1	11–27	0	0	0	0
31–40	2	12–28	1	50	0	0
41–50	11	11–25	1	9	0	0
51–60	20	11–25	3	15	0	0
61–70	17	8–18	2	12	4	23
Subtotal	51		7	14	4	7.8
TOTAL	193		20	10	12	6

[a] Based on ranges for normal individuals (adapted from Reference 31).

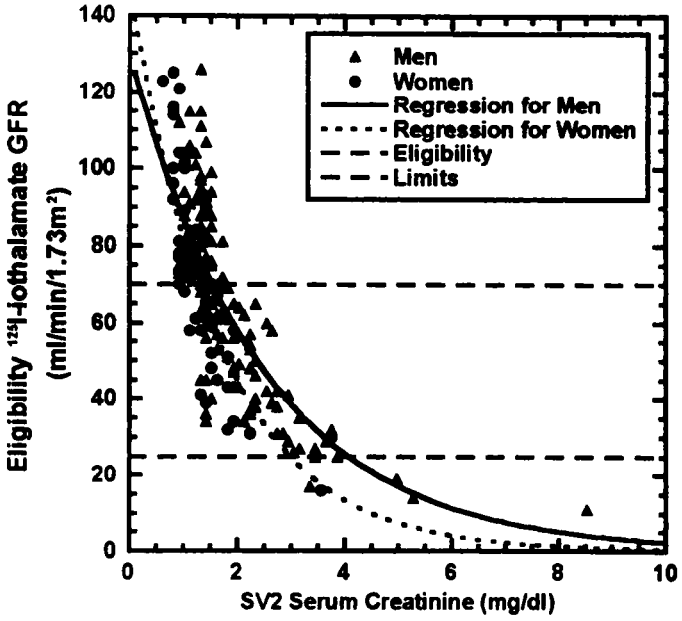

Figure 2. Relationship between screening (G1) glomerular filtration rate (GFR) and screening visit serum creatinine. The eligibility GFR limits are indicated by the horizontal dashed lines at 25 and 10 mL/min per 1.73 m^2.

105/Scr + (Weight − 86) for men, and using BMI as the weight parameter, it was GFR = −0.29 (Age − 52) + 88/Scr − 0.77 (BMI − 30) for women. In men, use of weight in the regression equation was more predictive of GFR than BMI; the opposite was true in women.

Using a Single GFR to Predict a Second GFR

The relationship between GFR1 and GFR2 was evaluated in the 98 randomized participants. The range of GFR values for this comparison is restricted to 25 to 70 mL/min per 1.73 m^2 because only subjects whose first (eligibility) GFR was in this range were allowed a repeat GFR measurement. As shown in Figure 5, there was a strong correlation ($r^2 = 0.75$) between the two measurements. The equation for the relation between GFR2 and GFR1 was GFR2 = −0.40 + 1.0 × GFR1 for men and −3.1 + 1.1 × GFR1 for women). The slope of this line was not significantly different from 1.0, and the CRMSE was 8.6 mL/min per 1.73 m^2. This degree of variability is clinically important but is consistent with previous observations in normal and hypertensive patients (21,22).

Discussion

Accuracy and Precision of Creatinine Clearance Estimates of GFR

A comparison of techniques to estimate renal function in a cohort of African Americans with hypertensive nephrosclerosis has not been reported previously. In other populations (*e.g.*, normal persons and patients with renal diseases), limitations of creatinine as a filtration marker have been well described (5–10,21,23,24). However, in some studies, GFR has been estimated with reasonable precision from serum creatinine, age, gender, and measures of body size in patients with renal disease (7,8,20,25,26). A simple and accurate estimate of GFR is desirable not only for monitoring renal function in clinical trials but also for estimating renal function in clinical practice (27).

The main objective of this study was to determine whether GFR estimates based on serum creatinine and 24-h creatinine clearance are accurate and precise in comparison to actual GFR measurements in African Americans. To our knowledge, this analysis had not been previously performed on a large number of African Americans with hypertension (with or without renal disease). We found that 100/Scr and Cockcroft-Gault methods were comparable with regard to precision. Moreover, both of these methods were more precise than outpatient 24-h urine

Table 4. Measures of precision and reliability of different methods in estimating GFR (^{125}I-iothalamate clearance)[a]

Parameter	Estimators				
	100/Scr (N = 193)	Cockcroft-Gault (N = 193)	Measured Ccr (N = 193)	New Equation (N = 193)	GFR2 from GFR1 (N = 98)
Mean GFR	68.8 ± 25.0	68.8 ± 25.0	68.8 ± 25.0	68.8 ± 25.0	52.7 ± 16.8
Mean estimated GFR	69.6 ± 25.5	59.3 ± 21.7	68.0 ± 27.6	68.9 ± 21.8	51.4 ± 13.9
Mean difference (Δ GFR)[b]	−0.76 ± 16.5	9.56 ± 14.9	0.79 ± 20.7	−0.083 ± 12.8	1.36 ± 8.48
r^2	0.6294	0.6618	0.4868	0.7496	0.7468
CRMSE	16.5	17.7	20.7	12.8	8.60

[a] Values in table are mean ± SD. GFR, glomerular filtration rate; Scr, serum creatinine; Ccr, creatinine clearance; r^2 Pearson coefficient of determination; CRMSE, combined root mean squared error (see Methods section for details).
[b] Mean difference (Δ GFR) = mean ^{125}I-iothalamate clearance − mean estimate.

measurement of creatinine clearance as an estimate of GFR. As shown in Table 3, the CRMSE, a measure of both bias (shift of regression line from the line of identity) and precision (variability about the regression line) of the estimate, was lower for 100/Scr and Cockcroft-Gault as compared with 24-h creatinine clearance. This finding is similar to that reported by Lemann *et al.* in Type I diabetics with nephropathy (7). In contrast, the 24-h creatinine clearance estimate was less biased than either 100/Scr or the Cockcroft-Gault estimates (Figures 2 and 3; Table 3). The relatively poor reliability of estimating GFR from the 24-h creatinine clearance in this and other studies may result in part from inaccuracies in urine collection. In this regard, GFR estimates that correlate poorly with measured GFR may not provide an accurate estimate of an individual's actual level of glomerular filtration.

In contrast to some other studies (7,18) we found that the Cockcroft-Gault formula underestimated GFR by almost 10 mL/min per 1.73 m^2 on average. The Cockcroft-Gault formula for estimating endogenous creatinine clearance was originally developed in white men (3). Previous studies in predominantly white populations show no consistent tendency of the formula to underestimate GFR (7,18,28). In fact, it was found to underestimate GFR in two studies (7,9) and to overestimate GFR in one (10).

Several possible explanations for the finding that Cockcroft-Gault underestimates GFR in an African-American population with renal disease should be considered. Serum creatinine measurements for estimating both creatinine clearance and GFR are subject to several limitations, owing to the altered metabolism of creatinine in patients with renal insufficiency. The steady-state serum creatinine concentration is influenced by dietary protein intake, muscle creatinine production, and both renal and extrarenal creatinine excretion (19,27). Because the estimate of GFR using Cockcroft-Gault underestimated GFR, muscle (or dietary) creatinine production rate possibly increased relative to creatinine excretion (renal and/or extrarenal) in our study cohort. The creatinine production rate can be increased because of increased muscle mass or animal protein intake. Decreased renal excretion could result from reduced tubular creatinine secretion or increased extrarenal creatinine clearance. The fact that measured urinary creatinine clearance was on average similar to GFR suggests that alterations in creatinine production or extrarenal creatinine metabolism may be responsible for the large positive bias noted with the Cockcroft-Gault estimate. Further studies estimating relative contributions of tubular creatinine secretion and estimated creatinine production rate are needed in this patient population.

We also utilized a multiple linear regression analysis in an attempt to improve the reliability of serum creatinine estimates for GFR, taking into account gender, age, and body size measurements in African Americans with hypertension. The new linear equation derived from the data in Figure 4 was somewhat better than using 100/Scr and the Cockcroft-Gault formulae and substantially better than 24-h creatinine clearance (Table 2); however, the variability was still considerable (CRMSE = 12.8). In this patient cohort, the 100/Scr and the new formula had similar degrees of accuracy, and the 100/Scr measurement yielded a more accurate estimate of GFR than the Cockcroft-Gault equation. Hence, the new equation modeled from the AASK pilot study data may prove to be the most accurate and precise of the available methods for estimating GFR in this population. However, validation of this formula is needed to objectively test its predictive ability in an independent patient population with renal disease.

The ability of a single measurement of GFR to predict a subsequent measure of GFR was also assessed in this study. We found that in this patient population, the ability of the first (screening) GFR to predict the second GFR was reasonably good (CRMSE = 8.6). The degree of variability in GFR measurements observed in our study was not different from that noted in previous reports using ^{125}I-iothalamate and other markers of GFR (21,22,29–31). However, this degree of variability is still somewhat high, raising general concerns about measurement of GFR even by a technique considered to be a standard.

Utilizing Serum Creatinine as a Screening Tool for Established Renal Insufficiency

The data in the screened population indicate that serum creatinine was a useful marker for recruiting patients into clinical trials of renal disease. The screening creatinine ranges of 1.2 to 4.0 mg/dL in African-American women and 1.4 to 4.5 mg/dL in African-American men turned out to be very good for identifying participants with GFR values within the range of 25

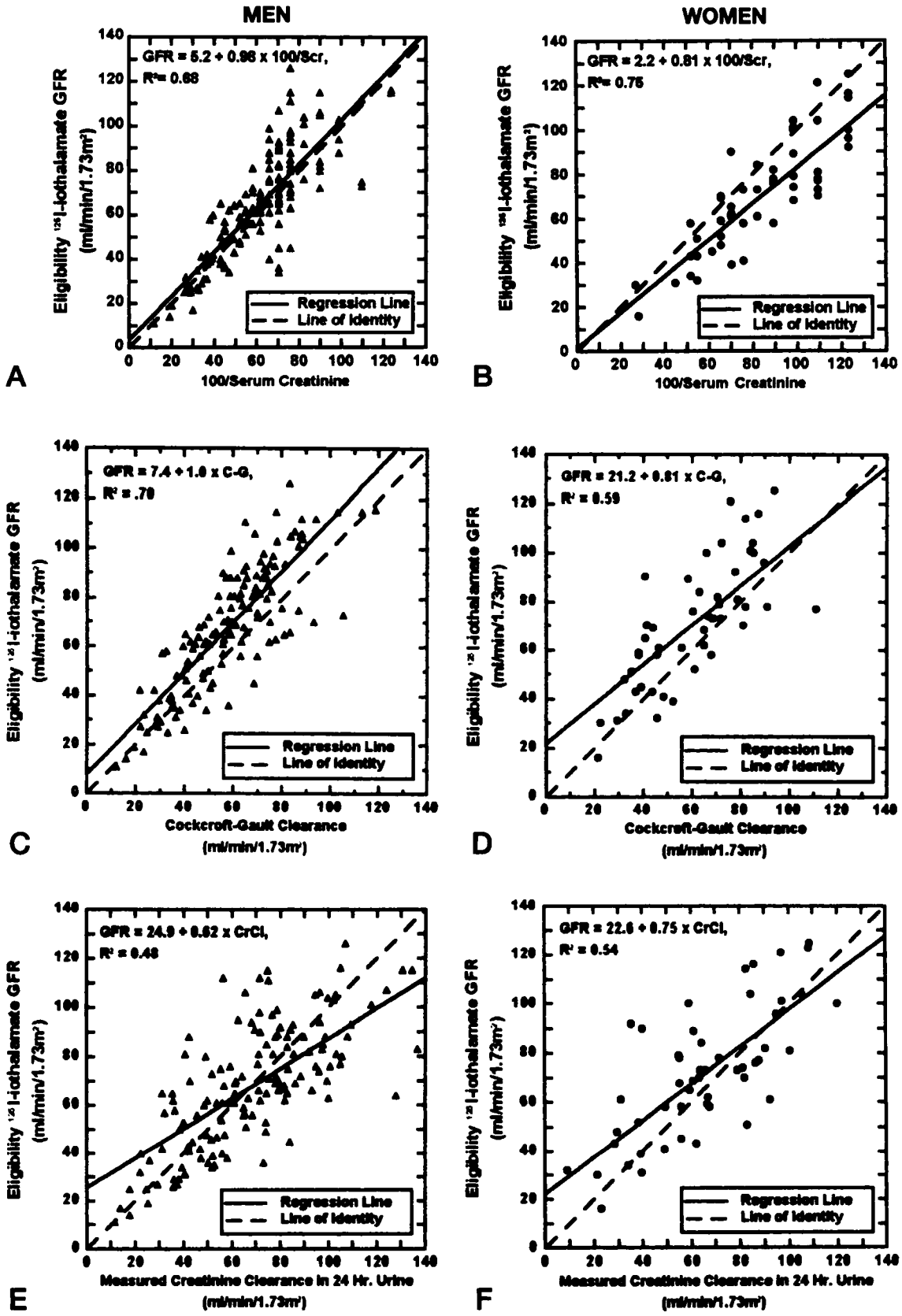

Figure 3. Relationship between eligibility (G1) glomerular filtration rate (GFR) and estimates of GFR by gender.

to 70 mL/min per 1.73 m^2. In fact, all eligible had a serum creatinine in the range of 1.0 to 4.0 mg/dL. Thus, targeting a large number of participants with a screening serum creatinine in this range is a reasonable method for screening and identifying potentially eligible participants.

In summary, we screened 193 African Americans with long-

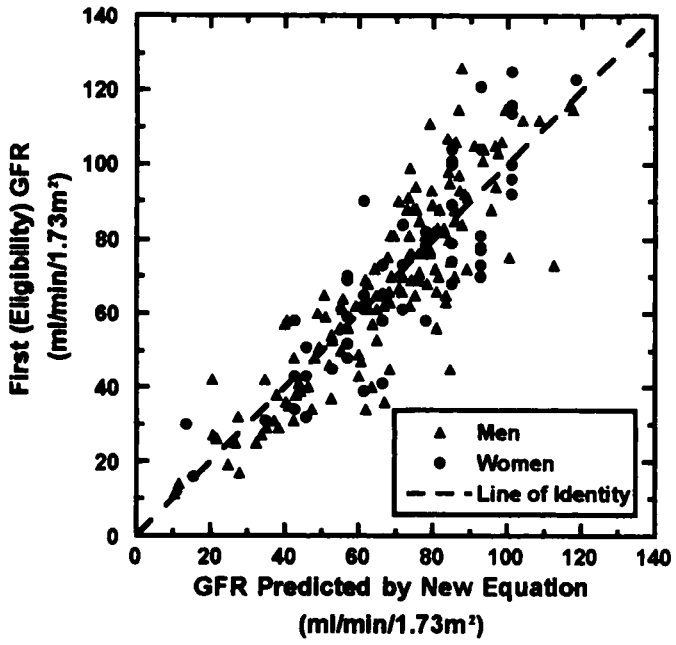

Figure 4. Relationship between eligibility glomerular filtration rate (GFR) and GFR estimated from new equation by gender.

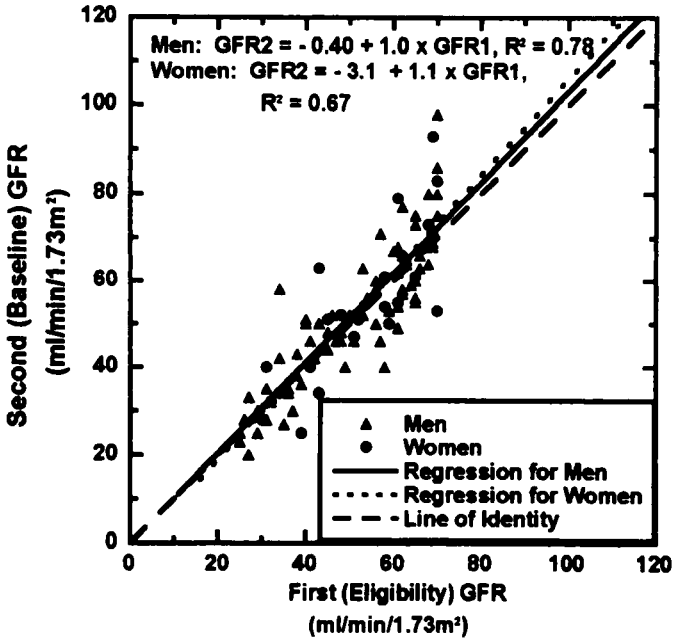

Figure 5. Relationship between second glomerular filtration rate (GFR) and eligibility GFR (G1) in 98 pilot study patients.

standing hypertension and serum creatinine values ranging from 0.60 mg/dL to 8.5 mg/dL. In this population, we found that GFR measured by iothalamate clearance ranged from 11 to 126 mL/min per 1.73 m^2. Estimating GFR with formulae derived from serum creatinine alone or in combination with age, gender, and body measurements provided a reasonable method for screening patients for the presence of a reduced GFR and were more precise than measurements of 24-h creatinine clearance. Both 100/Scr and the Cockcroft-Gault formulae were useful for estimating GFR in African Americans with long-standing hypertension, and estimates based on linear regression analysis from the study population did not substantially improve on those estimates. However, in this cohort, use of the Cockcroft-Gault formula provided a less accurate estimate of GFR as compared with 100/Scr and underestimated GFR by about 10 mL/min. This underestimation may be the result of a relatively high input of creatinine into the extracellular fluid. We conclude that fasting serum creatinine concentration proved to be a useful assay for GFR eligibility, and reciprocal creatinine appears to be reasonably accurate and precise as an unobtrusive technique to estimate GFR in this study population of hypertensive African Americans. Validation of the new equation will be required prior to use in clinical practice or research.

Acknowledgment

This study was supported by NIH Grants DK45386-02 and M01-RR00633.

References

1. Klag M, Whelton P, Randall BL, Neaton JD, Brancati FL, Ford CE, Shulman NB, Stamler J: Blood pressure and end-stage renal disease in men. *N Engl J Med* 334: 13–18, 1996
2. MaGee JH, Unger AM, Richardson DW: Changes in renal function associated with drug or placebo therapy of human hypertension. *Am J Med* 36: 795–804, 1964
3. Toto R, Coresh J, Jones C, Kirk K, the AASK Pilot Study Investigators: Serum creatinine is more precise than creatinine clearance for estimating GFR in African Americans [Abstract]. *J Am Soc Nephrol* 6: 406, 1995
4. Shulman NB, Ford CE, Hall WD, Blaufox D, Simon D, Langford HB, Schneider KA: Prognostic value of serum creatinine and effect of treatment of hypertension on renal function: Results from the Hypertension Detection and Follow-up study. *Hypertension* 13[Suppl I]: I 80–I 93, 1989
5. Mroczek WJ, Davidov M, Gavrilovich MD, Finnerty FA: The value of aggressive therapy in the hypertensive patients with azotemia. *Circulation* 40: 893–904, 1969
6. Breckenridge A, Dollery CT, Parry EHO: Prognosis of treated hypertension: Changes in life expectancy and causes of death between 1952 and 1967. *Q J M* 39: 411–429, 1970
7. Lemann J, Bidani AK, Bain RP, Lewis EJ, Rohde RD, and the collaborative study group of angiotensin converting enzyme inhibition in diabetic nephropathy: Use of the serum creatinine to estimate glomerular filtration rate in health and early diabetic nephropathy. *Am J Kid Dis* 26: 236–243, 1990
8. Walser M, Drew HH, Guldan JL: Prediction of glomerular filtration rate from serum creatinine concentration in advanced chronic renal failure. *Kidney Int* 44: 1145–1148, 1993
9. Trollfors B, Alestig K, Jagenburg R: Prediction of glomerular filtration rate from serum creatinine, age, sex and body weight. *Acta Med Scand* 221: 495–498, 1987
10. Waller DB, Fleming JS, Ramsay B, Gray J: The accuracy of creatinine clearance with and without urine collection as a measure of glomerular filtration rate. *Postgrad Med J* 67: 42–46, 1991
11. The National Institutes of Health: U.S. Renal Data Systems Annual Report, US Renal Data Systems, 1995.
12. Blythe WD, Maddux FW: Hypertension as a causative diagnosis of patients entering end-stage renal disease programs in the United States from 1986–1980. *Am J Kidney Dis* 28: 33–37, 1991

13. Easterling RE: Racial factors in the incidence and causation of end-stage renal disease (ESRD). *Trans Am Soc Artif Intern Organs* 23: 28–33, 1977
14. McClellan W, Tuttle E, Issa A: Racial differences in the incidence of hypertensive end-stage renal disease are not entirely explained by differences in the prevalence of hypertension. *Am J Kidney Dis* 12: 285–290, 1988
15. Rostand SG, Kirk KA, Rutsky EA, Pate EA: Racial differences in the incidence of treatment for end-stage renal disease. *N Engl J Med* 306: 1276–1279, 1982
16. Whittle JC, Whelton PK, Seidler AJ, Klag MJ: Does racial variation in risk factors explain black-white differences in the incidence of hypertensive end-stage renal disease. *Arch Intern Med* 151: 1359–1364, 1991
17. Walker GW, Neaton JD, Cutler JA, Neuwirth R, Cohen JD: Renal function change in hypertensive members of the Multiple Risk Factor Intervention Trial. *JAMA* 268: 3085–3091, 1992
18. van Lente F, Suit P: Assessment of renal function by serum creatinine and creatinine clearance: Glomerular filtration rate estimated by four procedures. *Clin Chem* 35: 2326–2330, 1989
19. Levey AS: Measurement of renal function in chronic renal disease. *Kidney Int* 38: 167–184, 1990
20. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16: 31–35, 1976
21. Bergstrom J, Alvestrand A, Bucht H, Gutierrez A: Progression of chronic renal failure in man is retarded with more frequent clinical follow-up and better blood pressure control. *Clin Nephrol* 25: 1–6, 1986
22. Whelton PK, Klag MJ: Hypertension as a risk factor for renal disease. *Hypertension* 13[Suppl]: I19–I 27, 1993
23. Luke RG: Can renal failure due to hypertension be prevented? *Hypertension* 18[Suppl]: I139–I142, 1991
24. Shemesh O, Golbetz H, Kriss JH, Myers BD: Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int* 28: 830–838, 1985
25. van Lente F, Suit P: Assessment of renal function by serum creatinine and creatinine clearance: Glomerular filtration rate estimated by four procedures. *Clin Chem* 35: 2326–2330, 1989
26. Labeeuw M, Diaz C, Cailette A, Aissa AH, Pozet N: Estimation of GFR from serum creatinine in elderly patients: Comparison of several methods [Abstract]. *Clin Nephrol* 33: 6, 1990
27. Levey AS, Greene T, Schluchter MD, Cleary PA, Teschan PE, Lorenz RA, Molitch ME, Mitch WE, Siebert C, Hall PM, Steffes MW: Glomerular filtration rate measurements in clinical trials. *J Am Soc Nephrol* 4: 1159–1171, 1993
28. Rodby RA, Ali A, Rohde RD, Lewis EJ: Renal scanning 99 mTc diethylene-triamine pentaacetic acid glomerular filtration rate (GFR) determination compared with iothalamate clearance GFR in diabetics [Abstract]. *Acta Radiol* 35: 391–395, 1994
29. Peronne RD, Steinman TI, Beck GJ, Skibinski CI, Royal HD, Lawlor M, Hunsicker LG: Utility of radioisotopic filtration markers in chronic renal insufficiency: Simultaneous comparison of I-Iothalamate, Yb-DTPA, Tc-DTPA, and Inulin. *Am J Kidney Dis* XVI: 224–235, 1990
30. Ruilope LM, Alcazar JM, Hernandez E, Moreno F, Martinez MA, Rodicio JL: Does an adequate control of blood pressure protect the kidney in essential hypertension. *J Hypertens* 8: 525–531, 1990
31. Schuster VL: Renal clearance. In: *The Kidney*, 2nd Ed., edited by Seldin DW, Giebisch G, New York, Raven Press, 1994, pp 365–396.