Transplantation

Measured and Estimated GFR in Healthy Potential Kidney Donors

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• ***Background:*** **Nonradiolabeled iothalamate clearance is an accurate way to determine glomerular filtration rate (GFR). Objectives of this study are to define the normal range of nonradiolabeled iothalamate clearance in potential kidney donors and assess whether creatinine-based GFR estimates are accurate in this population.** ***Methods:*** **Medical records of 365 potential kidney donors were reviewed. GFR was measured using clearance of nonradiolabeled iothalamate. Linear regression analysis was used to determine age- and sex-specific normal range values for GFR and serum creatinine. The abbreviated Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault prediction equations were used to estimate GFR from serum creatinine levels.** ***Results:*** **GFR declined significantly with increasing age ($P < 0.001$) and was lower in women than men ($P < 0.001$). Men at the age of 20 years had an estimated mean GFR of 129 mL/min that declined by 4.6 mL/min/decade. Women at the age of 20 years had a mean GFR of 123 mL/min that declined by 7.1 mL/min/decade. Regression analysis of GFR normalized to body surface area (nGFR) was significant for age ($P < 0.001$), but not sex ($P = 0.826$). A 20-year-old had a mean nGFR of 111 mL/min/1.73 m^2 that declined by 4.9 mL/min/1.73 m^2/decade. Correlation between measured nGFR and estimated GFR was weak ($r = 0.26$ for abbreviated MDRD equation; $r = 0.35$ for Cockcroft-Gault equation).** ***Conclusion:*** **This study of nonradiolabeled iothalamate clearance for the measurement of GFR in potential kidney donors established age-adjusted normal values. In healthy individuals, GFR cannot be estimated accurately using the abbreviated MDRD or Cockcroft-Gault prediction equations.** ***Am J Kidney Dis*** **43:112-119.**

INDEX WORDS: Creatinine; glomerular filtration rate (GFR); iothalamic acid; kidney; living donor; reference values.

RESULTS OF LIVING donor kidney transplantation are superior to those of cadaveric transplantation.[1] Additionally, waiting times for cadaveric kidney transplants continue to increase, now approaching more than 6 years at some transplant centers.[2] Increasing use of laparoscopic donor nephrectomy has made kidney donation more appealing than open surgical procedures. Related and nonrelated donation increasingly is preferred over cadaveric transplantation. To ensure that kidney donation is not performed using donors with even mild renal impairment, many centers obtain a direct measurement of glomerular filtration rate (GFR). Although some centers use a GFR cutoff value of 80 mL/min, others use 60 mL/min in the determination of donor candidacy.[3] It also is pertinent that recipients have double the risk for graft loss when receiving a kidney from a donor with a GFR less than 80 mL/min.[4] Therefore, assurance of normal donor renal function is a critical component of donor evaluation.

Ideally, assessment of renal function should be accurate, simple, safe, and cost-effective. Use of a 24-hour urine collection to estimate GFR with creatinine clearance is the most common technique of donor evaluation.[3] However, creatinine clearance has many deficiencies, including errors from incomplete urine collection and tubular secretion of creatinine. Undercollection and overcollection of 24-hour urine for creatinine clearance measurement is a common problem in donor evaluation.[5] Measurement of inulin clearance is considered the gold standard for GFR estimation, but the process is expensive, requires an intravenous infusion, and has intermittent problems with availability. Iothalamate radiolabeled with iodine 125 also has been used to measure GFR.[6] Clearance of a subcutaneous injection of radiolabeled iothalamate correlates well with clearance of an intravenous infusion of inulin ($r = 0.982$).[6]

More recently, clearance of nonradiolabeled iothalamate, a commonly used radiopaque contrast agent, has been shown to be an accurate,

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safe, and cost-effective method to measure GFR.[7] This method eliminates the risk for radioactivity exposure to patients and laboratory personnel. Furthermore, clearance of nonradiolabeled iothalamate correlates well with clearance of radiolabeled iothalamate ($r = 0.998$).[7] However, use of nonradiolabeled iothalamate for assessment of renal function in healthy subjects has not been evaluated. Therefore, the primary purpose of this study is to determine normal values for GFR by age and sex on the basis of nonradiolabeled iothalamate clearance in a large donor population and compare these findings with those of other GFR normal-value studies in the literature.

Based on Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, estimation of GFR with creatinine-based prediction equations is recommended in evaluating patients with chronic kidney disease.[8] However, application of these formulas in healthy populations has not been well studied. Two of the more popular GFR prediction equations are the Cockcroft-Gault equation[9] and abbreviated Modification of Diet in Renal Disease (MDRD) equation.[10,11] The secondary purpose of this study is to evaluate the performance of these 2 equations in a healthy donor population.

PATIENTS AND METHODS

Patient Selection

Records of potential living donors for kidney transplantation at Mayo Clinic between October 20, 1996, and April 20, 2001, were reviewed retrospectively. Four hundred forty-two patients older than 18 years had nonradiolabeled iothalamate clearance measured for their evaluation. Patients who had a history of a primary renal or systemic disease were excluded. Patients who had elevated blood pressure (>140/90 mm Hg), fasting serum glucose level elevation (>126 mg/dL [>7 mmol/L]), elevated 24-hour urine protein level (>150 mg), or abnormal urinary sediment on urinalysis were excluded. Patients with structural abnormalities on computed tomographic urography or angiography also were excluded. Of the remaining 376 patients, 11 patients had not given consent for the medical record review for research purposes and were not included in the study.

Data Collection

The remaining 365 patients had data for age, sex, race, body surface area, serum creatinine level, and nonradiolabeled iothalamate clearance obtained from their medical records. Serum creatinine was measured with use of the modified kinetic rate Jaffé reaction on an autoanalyzer (Roche-Hitachi 747; Roche Diagnostics Corp, Indianapolis, IN) that was calibrated daily. Details of GFR measurement with use of nonradiolabeled iothalamate have been described previously.[7] Total duration of this clearance test was approximately 2 hours. Briefly, each patient was administered a 300-mg subcutaneous injection of nonradiolabeled iothalamate. Hydration with 4 to 6 glasses of water before the test was performed to maintain urine flow. After a 45-minute equilibrium period, the patient completely voided, confirmed by bladder ultrasonography, and a first plasma sample (P_1) was obtained. After an additional 45 to 60 minutes, the patient again completely voided to provide a urine sample (U_1), and an additional plasma sample (P_2) was obtained. Flow (V) was determined from the urine volume of U_1 divided by time between voiding episodes. Iothalamate concentration (in micrograms per milliliter) was measured in plasma and urine samples (P_1, P_2, U_1) by capillary electrophoresis. GFR (in milliliters per minute) was calculated using the following equation:

$$\text{GFR} = \frac{U_1 \times V}{(P_1 + P_2)/2} \quad (1)$$

GFR normalized to body surface area (nGFR; in milliliters per minute per 1.73 square meters) was obtained using the following equation:

$$\text{nGFR} = \text{GFR} \times \frac{1.73\ \text{m}^2}{\text{weight (kg)}^{0.425} \times \text{height (cm)}^{0.725} \times 0.007184} \quad (2)$$

Data Analysis

The primary goal of analysis is to determine the normal range for GFR, nGFR, and serum creatinine values, taking into account age and sex, if necessary. Potential effects of age and sex were tested by using linear regression analysis on each laboratory value. If sex was significant, a separate analysis was performed for each sex. If age was significant, the regression model was used to estimate percentiles at each age. Percentiles 2.5, 5, mean, 95, and 97.5 were estimated from the regression model using the nonparametric method of O'Brien and Dyck.[12]

The secondary goal of analysis is to estimate nGFR by using the Cockcroft-Gault and abbreviated MDRD equations. Statistical comparison of estimated nGFR with measured nGFR was performed by estimating the bias (mean estimated − measured), precision (percentage of estimated nGFRs within 30% of measured), and correlation.[8]

RESULTS

Demographics

Of 365 study subjects, 205 subjects (56.2%) were women, mean age was 41.1 ± 11.4 (SD) years (range, 18 to 71 years), and mean body surface area was 1.93 ± 0.23 m^2. Two hundred fifty-nine subjects (71.0%) were living related donors, 104 subjects (28.5%) were living unrelated donors, and 2 subjects were not classified.

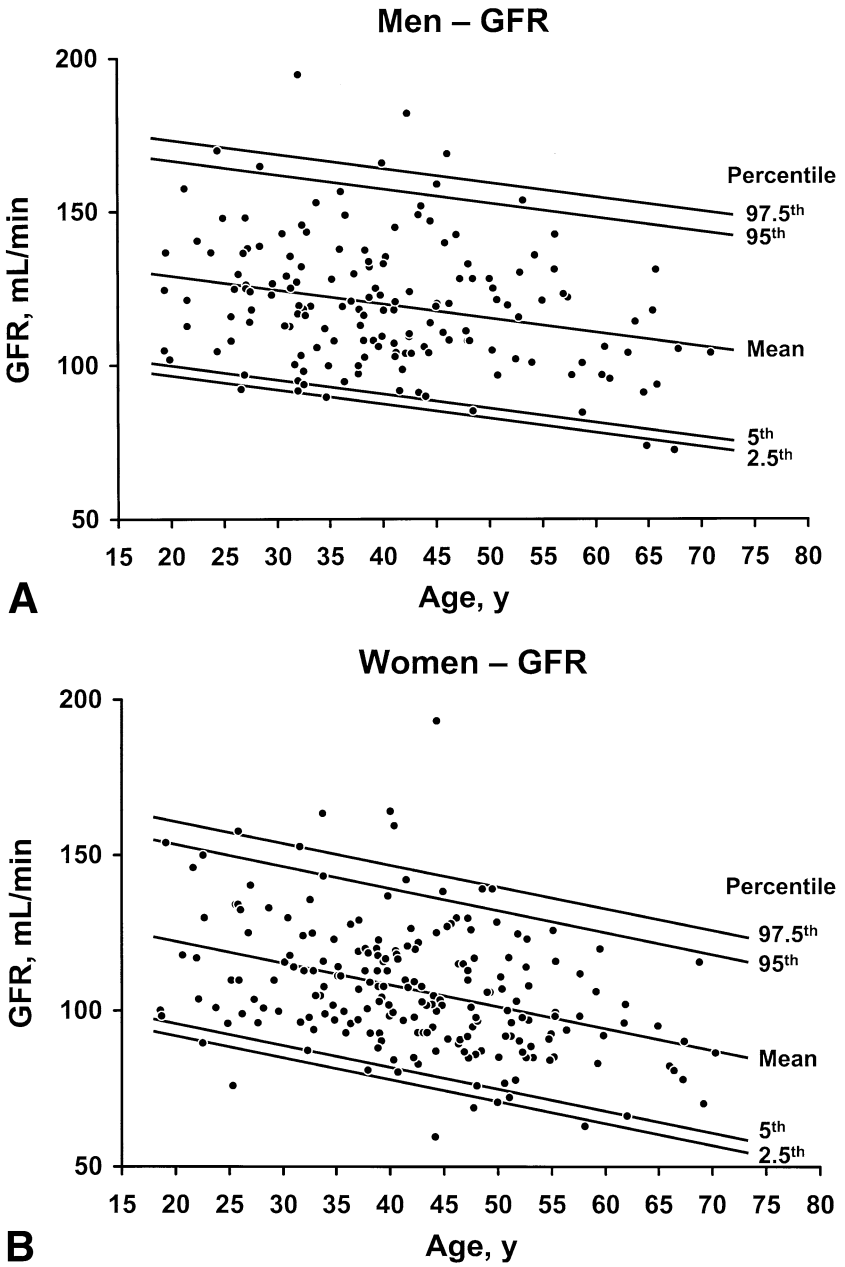

Fig 1. (A) GFR by age in 160 male donors. Estimated 2.5th, 5th, mean, 95th, and 97.5th percentiles at the age of 20 years are 97, 100, 129, 167, and 174 mL/min, respectively. GFR declined at an estimated rate of 4.6 mL/min/decade. (B) GFR by age in 205 female donors. Estimated 2.5th, 5th, mean, 95th, and 97.5th percentiles at the age of 20 years are 92, 96, 123, 153, and 161 mL/min, respectively. GFR declined at an estimated rate of 7.1 mL/min/decade.

Racial distribution was 293 whites (80.3%), 12 Middle Easterners (3.3%), 6 Hispanics (1.6%), 5 African Americans (1.4%), 5 Asian/Pacific Islanders (1.4%), 1 Native American (0.3%), and 43 unknown (11.8%). Mean GFR was 113 ± 22 mL/min (range, 60 to 195 mL/min), and mean nGFR was 101 ± 16 mL/min/1.73 m^2 (range, 67 to 164 mL/min/1.73 m^2). Mean serum creatinine value was 1.04 ± 0.15 mg/dL (92 ± 13 μmol/L; range, 0.7 to 1.6 mg/dL [62 to 141 μmol/L]).

GFR

Figure 1 shows the relationship between age and GFR for men and women. Regression analysis of GFR was significant for both age ($P < 0.001$; $r = 0.33$) and sex ($P < 0.001$; $r = 0.30$). GFR declines by 4.6 mL/min/decade in men and 7.1 mL/min/decade in women, but this difference was not statistically significant ($P = 0.18$). Men at the age of 20 years had a mean GFR of

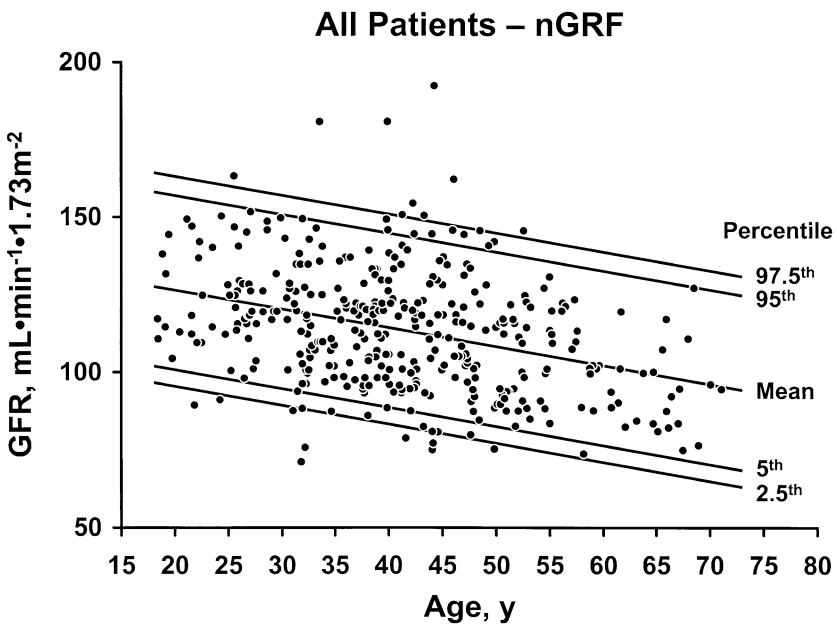

Fig 2. nGFR by age in 365 potential donors. Estimated 2.5th, 5th, mean, 95th, and 97.5th percentiles at the age of 20 years are 87, 91, 111, 136, and 141 mL/min/1.73 m^2, respectively. nGFR declined at an estimated rate of 4.9 mL/min/1.73 m^2/decade.

129 mL/min and 5th percentile GFR of 100 mL/min. Women at the age of 20 years had a mean GFR of 123 mL/min and 5th percentile GFR of 96 mL/min.

nGFR

Figure 2 graphically shows the relationship between age and nGFR for all patients. Regression analysis of nGFR also was significant for age ($P < 0.001$; $r = 0.35$), but not sex ($P = 0.826$). nGFR declines by 4.9 mL/min/1.73 m^2/decade. Twenty-year-olds had a mean nGFR of 111 mL/min/1.73 m^2 and 5th percentile nGFR of 91 mL/min/1.73 m^2. Table 1 lists age-based normal value ranges for nGFR.

Serum Creatinine

Regression analysis of serum creatinine values was significant between men and women ($P < 0.001$), but not for age ($P = 0.269$). Mean creatinine values were 1.16 mg/dL (103 μmol/L) for men and 0.96 mg/dL (85 μmol/L) for women. Percentile 95 creatinine values were 1.4 mg/dL (124 μmol/L) for men and 1.1 mg/dL (97 μmol/L) for women.

GFR Prediction Equations

Of 365 study subjects, only results from 298 white or African-American subjects were analyzed further to be consistent with known racial criteria for MDRD study equations.[10] Twenty-four subjects who lacked weight data, necessary for application of the Cockcroft-Gault equation, also were excluded. Figure 3 graphically shows the relationship between estimated nGFR and measured nGFR with use of the Cockcroft-Gault (Fig 3A) and abbreviated MDRD (Fig 3B) equations. Mean nGFR was 101 ± 16 mL/min/1.73 m^2 for iothalamate clearance, 72 ± 11 mL/min/1.73 m^2 for the abbreviated MDRD equation (bias, −29 mL/

Table 1. nGFR in Healthy Donors

	Percentile				
Age (y)	2.5	5	Mean	95	97.5
20	87	91	111	136	141
25	84	88	109	133	138
30	81	86	107	131	136
35	79	83	104	128	134
40	77	81	102	126	131
45	74	78	99	123	129
50	72	76	97	121	126
55	70	73	94	119	124
60	67	71	92	116	121
65	65	69	89	113	119
70	62	66	87	111	116
75	60	64	84	109	114

NOTE. nGFR expressed as mL/min/1.73 m^2.

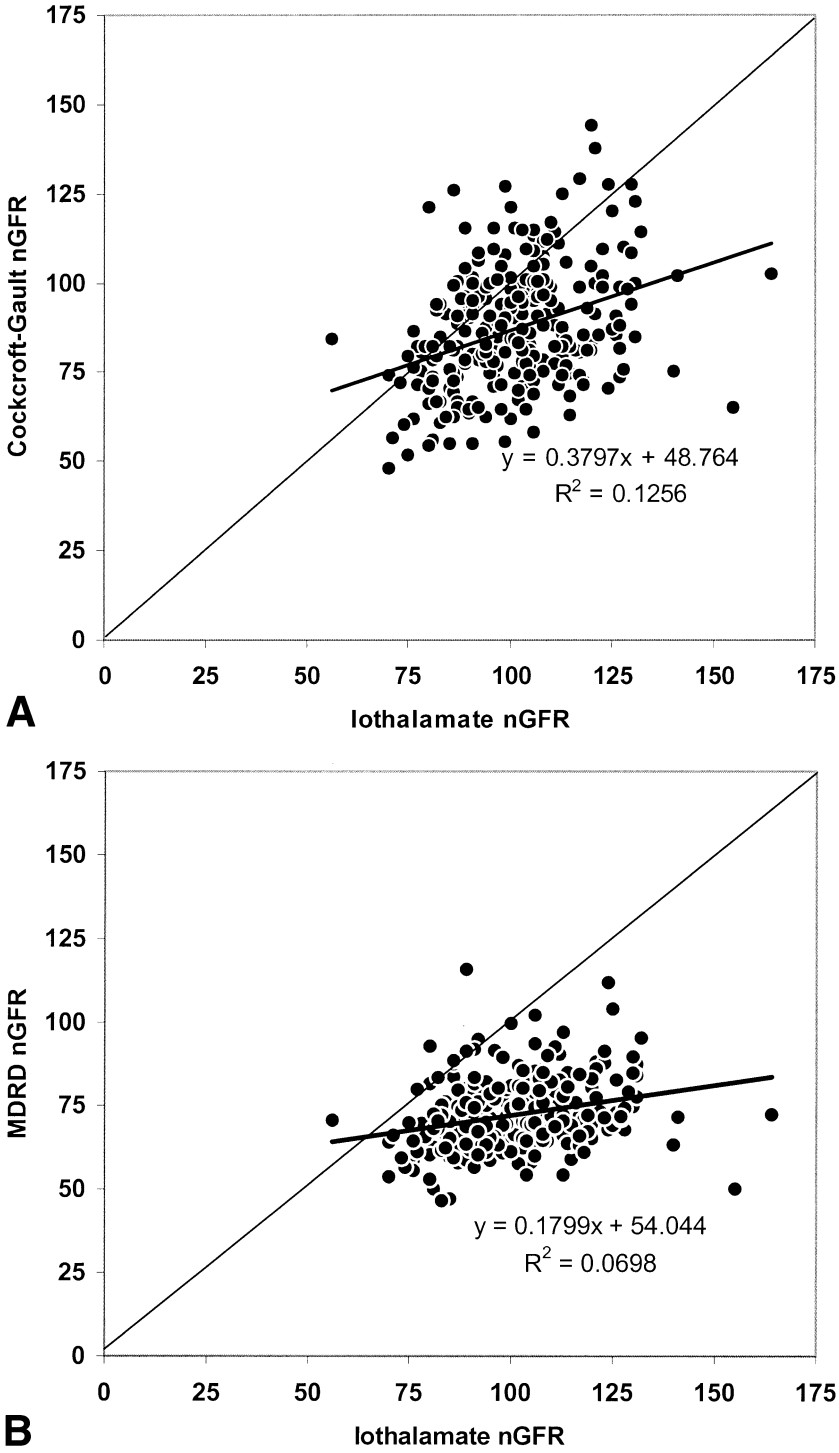

Fig 3. (A) Estimated nGFR (in mL/min/1.73 m^2) using the abbreviated MDRD equation compared with measured nGFR using nonradiolabeled iothalamate clearance in 274 potential donors (r = 0.26; P < 0.001). (B) Estimated nGFR using the Cockcroft-Gault equation compared with measured nGFR (r = 0.35; P < 0.001).

min/1.73 m^2), and 87 ± 17 mL. mL/min/1.73 m^2 for the Cockcroft-Gault equation (bias, −14 mL/min/1.73 m^2). Percentages of estimated values within 30% of iothalamate clearance values were 55% for the MDRD equation and 82% for the Cockcroft-Gault equation. Correlation coefficients between each equation and iothalamate clearance were r = 0.26 for

the MDRD equation and $r = 0.35$ for the Cockcroft-Gault equation.

DISCUSSION

The primary objective of this study is to determine the normal distribution of GFR on the basis of sex and age in a population of ostensibly healthy study subjects evaluated for kidney donation. Results show the expected sex- and age-related differences in GFR.[13-15] The dependence of GFR on sex is consistent with the larger body habitus of men compared with women. However, when GFR is normalized to body surface area, there is no significant difference between men and women, consistent with previous studies.[6,16] The decline in GFR by 0.5 mL/min in men and 0.7 mL/min in women is similar to the 0.75-mL/min decline seen in the Baltimore Longitudinal Study of creatinine clearance.[15]

In an earlier study at Mayo Clinic, inulin clearance was used to define normal values for GFR in 141 healthy donors.[6] Mean nGFR in the inulin study was defined by the linear regression equation nGFR = 118 − 0.4(age − 20) and compares to the present study linear regression equation of nGFR = 111 − 0.5(age − 20). The present study shows GFR continues to decrease linearly by 0.5 mL/min/1.73 m^2 in older donors (age, 60 to 75 years); the inulin study lacked these data. The small difference between these 2 studies could suggest that nonradiolabeled iothalamate clearance underestimates GFR compared with standard inulin clearance. However, this difference may be related to variations in study protocols that effect physiological changes in GFR related to hydration, fasting, and recumbence. High hydration, as performed in this study, has been shown to decrease GFR in healthy adults.[17] Another explanation is supported in a study that shows a decline in mean donor nGFR measured by radioactive iodine–labeled iothalamate clearance from 110 mL/min/1.73 m^2 in 1970 to 95 mL/min/1.73 m^2 in 1990.[18] Thus, results of the present study may simply confirm a decline in mean GFR of donor populations in the 30 years since the older inulin study.

Applying results of this study to define a normal value range assumes the study population is a representative sample of the healthy adult population. Race data were incomplete in this study, but nonwhite racial groups appear to be underrepresented compared with the general US population. Also, many potential donors are relatives of recipients and may have a greater prevalence of subclinical renal disease than the general population, even with rigid screening criteria.[19] In this study, 71% of subjects were relatives of transplant recipients with kidney disease. The mean nGFR of 109 mL/min/1.73 m^2 in 25-year-olds in this study is less than that in other studies. The original normal value study for GFR using inulin clearance in healthy young adults gave mean nGFRs of 127 mL/min/1.73 m^2 in men and 118 mL/min/1.73 m^2 in women.[20] A more recent study of inulin clearance in 24 young normotensive subjects (mean age, 26 ± 3 years) found a mean nGFR of 121 mL/min/1.73 m^2.[13] Thus, applying results of this study to the general population requires both race considerations and recognition of a possible subclinical renal disease selection bias in donor populations.

The constant decline in nGFR of 4.9 mL/min/1.73 m^2/decade for all age groups in this study is contrary to findings in earlier studies that showed an increase in rate of decline after the age of 50 years. A meta-analysis of 8 normal-value studies of nGFR using inulin or chromium 51–labeled edetic acid clearance showed a decline of 4 mL/min/1.73 m^2/decade up to age 50 years and a decline of 10 mL/min/1.73 m^2/decade after the age of 50 years.[16] Only 1 study in this meta-analysis included subjects older than 60 years, and that study did not censor subjects with untreated high blood pressure.[21] Another normal-value study that used iohexol clearance found no change in nGFR with age up to 50 years and a decline of 10 mL/min/1.73 m^2/decade after the age of 50 years. Limited information was provided about how study subjects were screened for kidney disease.[22] In the general population, the prevalence of kidney disease increases with age. Any normal-value study that does not exclude kidney disease would be expected to show an increased rate of nGFR decline with age. Reanalysis of this current study found a decline of 3.5 mL/min/1.73 m^2/decade up to the age of 50 years and 5.5 mL/min/1.73 m^2/decade after the age of 50 years, but this difference was not statistically significant ($P = 0.44$).

Nonradiolabeled iothalamate clearance has several advantages over other methods of measuring GFR in donor populations. Creatinine clearance

is prone to 24-hour urine collection errors and overestimates GFR by 10% to 40% because of tubular secretion of creatinine.[8,23] Serum cystatin C values can be used to estimate GFR independent of age and sex, but its measurement has not been studied as a screening tool in a donor population.[24] In addition to nonradiolabeled iothalamate, other clearance techniques that use exogenous markers have been developed to replace inulin clearance, which is expensive and cumbersome. Clearance techniques with radioactive markers (iodine 125–labeled iothalamate, technetium 99–labeled pentetic acid, chromium 51–labeled edetic acid) give results similar to inulin clearance, but radioactive exposure and infrastructure to handle radioactive materials limit their use.[25] Iohexol is an exogenous nonradiolabeled iodine compound used in clearance estimates of GFR with capillary electrophoresis.[26] However, correlation of iohexol to iodine 125–labeled iothalamate ($r = 0.93$)[26] is lower than correlation of nonradiolabeled iothalamate to iodine 125–labeled iothalamate ($r = 0.998$).[7] Although nonradiolabeled iothalamate clearance has never been directly compared with inulin clearance, its strong correlation with iodine 125–labeled iothalamate clearance is adequate validation for accurately measuring GFR. Nonradiolabeled iothalamate clearance has been used on a regular basis at the Mayo Clinic to assess renal function in potential donors for the past 8 years.

Serum creatinine values in this study compare equivocally with those reported in the Third National Health and Nutrition Examination Survey (NHANES III), a study of the US adult population. Subjects in NHANES III without hypertension or diabetes mellitus had mean serum creatinine values of 1.13 mg/dL (100 μmol/L) for men and 0.93 mg/dL (82 μmol/L) for women.[27] This is only slightly less than the 1.16 mg/dL (103 μmol/L) for men and 0.96 mg/dL (85 μmol/L) for women found in the donor population of the current study. However, variation in serum creatinine measurements attributable to different manufacturer calibration standards can cause bias errors between different laboratories. For example, serum creatinine values were on average 0.23 mg/dL (20 μmol/L) lower at the MDRD study laboratory compared with the NHANES III study laboratory.[28] Consistent with the literature, we found no change in serum creatinine values with age[14] because muscle mass declines at a rate similar to GFR.

Recent K/DOQI guidelines recommend estimating GFR with equations based on serum creatinine values.[8] The Cockcroft-Gault equation[9] and abbreviated MDRD equation[10,11] are both commonly used in adults. Both equations have been advocated,[8] but were designed on the basis of populations with chronic kidney disease. In this healthy population study, these equations appear to underestimate GFR by 29 mL/min/1.73 m^2 with the MDRD equation and 14 mL/min/1.73 m^2 with the Cockcroft-Gault equation. However, calibration bias in serum creatinine measurement is known to be a source of GFR estimation errors between laboratories. For example, there is a serum creatinine bias (difference) of 0.23 mg/dL (20 μmol/L) between the MDRD study and NHANES III study.[28] Mean serum creatinine values in the present study are similar to those reported in the NHANES III study. To test the possible effects of this creatinine bias on the relationship between measured and estimated nGFR, serum creatinine values were decreased by 0.23 mg/dL (20 μmol/L) and reanalyzed using the MDRD equation. Estimated GFR increased to 97 $\pm$ 17 mL/min/1.73 m^2, with a bias of -4 mL/min/1.73 m^2 (previously 72 $\pm$ 11 mL/min/1.73 m^2, with a bias of -29 mL/min/1.73 m^2). The percentage of values within 30% of the iothalamate clearance improved to 89% (previously 55%). However, the correlation coefficient remained low at $r = 0.27$ (previously $r = 0.26$). Thus, in healthy populations, a calibration difference between laboratories can lead to large bias errors in estimating GFR with creatinine-based prediction equations. However, even when correcting for calibration bias, the correlation between estimated and measured GFR remains weak.

Nonradiolabeled iothalamate clearance may be preferred to creatinine-based prediction equations in certain clinical settings. In addition to donor evaluation, patients with chronic kidney disease need accurate GFR measurements.[8] In particular, in diagnosing and monitoring kidney disease in the early stages, nonradiolabeled iothalamate is much more accurate and precise than creatinine-based prediction equations. These prediction equations may be more prone to error in a population with similar and low serum

creatinine levels because epidemiological factors have a more dominant effect on the GFR estimation. There may be too much variation in healthy individuals to determine muscle mass and thus creatinine production from age, sex, race, and weight. GFR estimations of patients in the later stages of kidney disease with exceptional dietary intake (vegetarian, creatine supplements) or decreased muscle mass are not reliable with prediction equations.[8] Clinical trials also would benefit from an accurate and cost-effective[7] method of measuring GFR, as provided with nonradiolabeled iothalamate clearance.

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