

Comparison of Methods for Determining Renal Function Decline in Early Autosomal Dominant Polycystic Kidney Disease: The Consortium of Radiologic Imaging Studies of Polycystic Kidney Disease Cohort

Andrew D. Rule,* Vicente E. Torres,* Arlene B. Chapman,[†] Jared J. Grantham,[‡] Lisa M. Guay-Woodford,[†] Kyongtae T. Bae,[§] Saulo Klahr,[§] William M. Bennett,^{||} Catherine M. Meyers,[¶] Paul A. Thompson,[§] J. Philip Miller;[§] for the the CRISP Consortium

*Divisions of Nephrology, Epidemiology, Radiology, and Biostatistics, Mayo Foundation, Rochester, Minnesota;

[†]University of Alabama, Birmingham, Alabama; [‡]University of Kansas Medical Center, Kansas City, Kansas;

[§]Washington University, St. Louis, Missouri; ^{||}Northwest Renal Clinic, Portland, Oregon; and [¶]University of Pennsylvania, Philadelphia, Pennsylvania

A decline in renal function suggests progression of chronic kidney disease. This can be determined by measured GFR (*e.g.*, iothalamate clearance), serum creatinine (SCr)-based GFR estimates, or creatinine clearance. A cohort of 234 patients with autosomal dominant polycystic kidney disease and baseline creatinine clearance >70 ml/min were followed annually for four visits. Iothalamate clearance, SCr, and creatinine clearance were obtained at each visit. Estimated GFR (eGFR) was determined with the Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault equations. Renal function slopes had a mean residual SD of 10.7% by iothalamate clearance, 8.2% by MDRD equation, 7.7% by Cockcroft-Gault equation, and 14.8% by creatinine clearance. By each method, a decline in renal function (lowest quintile slope) was compared among baseline predictors. Hypertension was associated with a decline in iothalamate clearance (odds ratio [OR] 5.8; 95% confidence interval [CI] 2.3 to 14), eGFR (OR [MDRD] 2.0 [95% CI 1.0 to 4.2] or OR [Cockcroft-Gault] 1.9 [95% CI 0.9 to 3.9]), and creatinine clearance (OR 2.0; 95% CI 1.0 to 4.2). Each doubling of kidney volume at baseline was associated with a decline in iothalamate clearance (OR 2.4; 95% CI 1.5 to 3.7), eGFR (OR 1.7 [95% CI 1.1 to 2.6] or 2.1 [95% CI 1.4 to 3.3]), and creatinine clearance (OR 1.7; 95% CI 1.1 to 2.5). Predictor associations were strongest with measured GFR. Misclassification from changes in non-GFR factors (*e.g.*, creatinine production, tubular secretion) conservatively biased associations with eGFR. Misclassification from method imprecision attenuated associations with creatinine clearance.

J Am Soc Nephrol ●●: ●●●–●●●, ●●●●. doi: 10.1681/ASN.2005070697

To treat patients with early chronic kidney disease (CKD), it is important to identify predictors for a decline in renal function. Both slope and threshold analyses of renal function have been used to infer progression of CKD. There are advantages to using a slope analysis for statistical power and for understanding the mechanisms of a disease (1). In a slope analysis, renal function is measured at multiple time points. For each individual, a straight line or curve can be fit to these measurements to reflect the change in renal function over time. Predictors can be compared between individuals who have a decline in renal function (negative slope) with those who have stable or a rise in renal function (neutral or positive slope).

Measured GFR (*e.g.*, inulin or iothalamate clearance), esti-

mated GFR (eGFR) based on serum creatinine (*e.g.*, Modification of Diet in Renal Disease [MDRD] or Cockcroft-Gault equation) (2–4), and creatinine clearance are commonly used as markers of renal function. These three methods have been used to infer changes in renal function over time (5–10). Reciprocal serum creatinine (1/SCr) has also been used to infer changes in renal function over time (7,11,12).

Measured GFR with an exogenous marker such as inulin or iothalamate is the gold standard method, but expense and inconvenience are important drawbacks. Urine collection errors and tubular secretion of creatinine impair the precision and the accuracy of creatinine clearance as a marker of GFR (13–15). Estimating equations are inexpensive and convenient but have not been accurate in populations that are characterized by normal or near-normal renal function (16–18).

One study concluded that measured GFR should be the preferable method for assessing renal function in clinical trials of patients with renal grafts (19). Another study found that eGFR was similar to measured GFR for assessing renal function change over time in a CKD clinical trial (6). More studies are

Received July 8, 2005. Accepted December 10, 2005.

Published online ahead of print. Publication date available at www.jasn.org.

Address correspondence to: Dr. Andrew D. Rule, Division of Nephrology and Hypertension, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. Phone: 507-266-7961; Fax: 507-266-7891; E-mail: rule.andrew@mayo.edu

still needed to determine the accuracy of estimating equations for following progression of CKD (20). In particular, the association of demographic or clinical predictors with SCr, creatinine clearance, and measured GFR slope need further comparison (1). The objective of this study was to compare methods for a decline in renal function for a cohort with early autosomal dominant polycystic kidney disease (ADPKD).

Materials and Methods

Study Participants

Details of the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) have previously been published. CRISP is a multicenter study of the natural history of ADPKD (21) in adherence to the Declaration of Helsinki. The sites included Kansas University Medical Center, Emory University, the Mayo Clinic, and University of Alabama at Birmingham. A cohort of patients who had ADPKD and were aged 15 to 46 yr were followed annually for four total visits. Eligibility required an ADPKD diagnosis by the criteria of Ravine *et al.* (22) and a measured or estimated (Cockcroft-Gault equation) creatinine clearance >70 ml/min. Eligibility also required a SCr ≤1.6 mg/dl in men and ≤1.4 mg/dl in women. Patients were ineligible when they had other medical conditions besides hypertension that could affect renal function (*e.g.*, diabetes).

Baseline Predictors

During the baseline visit in 2001, patients underwent a 2-d evaluation. A focused history and examination was used to identify relevant characteristics and medical conditions. In particular, current smoking status, history of urinary tract infection (UTI), abdominal pain, and history of gross hematuria were determined. Hypertension was defined by current use of antihypertensive medications or a systolic and diastolic BP ≥140/90 mmHg on multiple occasions. Magnetic resonance imaging was used to determine the cyst volume and total volume of the combined kidneys (21). The day before the baseline visit, a 24-h urine sample was collected to determine the urine albumin to creatinine ratio (ACR).

Renal Function Measurements

Renal function was measured by each method at baseline (2001) and at the follow-up visits in 2002, 2003, and 2004. Details of the measurement of iothalamate clearance have been described previously (21,23). Briefly, after oral hydration, patients received a subcutaneous injection of nonradiolabeled iothalamate. After a 60-min equilibrium period, each patient voided and the first plasma sample was drawn. After a timed 45- to 60-min collection period to determine urine flow (V), a voided urine sample and a second plasma sample were obtained. Postvoid residuals were assessed by ultrasound after each void. The two plasma (P) samples and one urine (U) sample were assayed for iothalamate *via* capillary electrophoresis at the Mayo Clinic. Iothalamate concentrations in the plasma samples were averaged, and GFR was determined using the clearance equation ($U_{\text{iothalamate}}V/P_{\text{iothalamate}}$).

During the feasibility phase, four patients had an iothalamate clearance test at each of the four study sites within a 6-wk period. The mean between-site coefficient of variation was 9.8% but decreased to 4.9% with exclusion of three suboptimal iothalamate clearance tests. A suboptimal test was defined *a priori*: (1) A postvoid residual of at least 20 ml and >20% voided volume; (2) urine flow rate <3 ml/min; or (3) a collection time <30 or >90 min. A suboptimal test occurred at least once in 22% of the study patients. Exclusion of or adjustment for suboptimal tests had no substantive effect on the predictor associations and was not done in the final analyses.

Serum was collected at each visit and assayed for creatinine at each site. All SCr levels were adjusted for calibration bias with the Cleveland Clinic laboratory used for deriving the MDRD equation. For determination of this calibration bias, 90 serum samples were exchanged between the Mayo Clinic laboratory and the MDRD Study laboratory. An additional 31 serum samples were exchanged among all four study sites to determine calibration bias between sites. The final calibration equations were as follows: $SCr = 0.01 + 1.30 \times SCr_{\text{Kansas}}$, $SCr = -0.01 + 1.08 \times SCr_{\text{Emory}}$, $SCr = -0.33 + 1.28 \times SCr_{\text{Mayo}}$, and $SCr = 0.04 + 0.97 \times SCr_{\text{Alabama}}$. GFR was estimated using the MDRD equation $186.3 \times SCr^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) $\times 1.212$ (if black) (3,4) and the Cockcroft-Gault equation $[(140 - \text{age}) \times \text{weight} \times 0.85$ (if female)]/(72 \times SCr) (2). The age and the weight at each visit were used to calculate eGFR. Creatinine clearance was determined with the 24-h urine creatinine at each visit.

Statistical Analyses

Analyses were performed with JMP 5.1 (SAS Institute, Cary, NC). The annual percentage change in renal function (*i.e.*, slope) was determined by regressing logarithmic renal function on time from baseline (in years) for each patient. Whereas higher order curves may be needed for more advanced CKD with longer follow-up (6), a line was adequate for describing changes over time in this study (Figure 1). For iothalamate clearance, the annual percentage change was determined with and without standardizing body surface area (per 1.73 m²) with a formula that used the height and the weight at each visit (24). For SCr-based methods, slopes were determined for the MDRD equation, Cockcroft-Gault equation, and 1/SCr. The creatinine clearance slopes were not standardized (results were similar with standardizing body surface area). The correlation of each renal function slope with unstandardized iothalamate clearance slope was compared.

For each patient, some of the variability in renal function between follow-up visits was due to physiologic variability (*e.g.*, changes from diet and hydration) (25) and assay error. This measurement error or imprecision represents variability that was not accounted for by the overall change in renal function with time (*i.e.*, slope) and was reported as a residual SD (26). The mean within-patient residual SD was compared between renal function methods with the paired Wilcoxon sign-rank test.

Because of imprecision in renal function measurements, a decline in renal function defined simply by a negative slope would lead to substantial misclassification. For obviating this error, a decline in renal function was defined as the lowest quintile slope ($n = 47$) for each method. The agreement between a decline in renal function slope by unstandardized iothalamate clearance compared with each other method was assessed with a κ statistic (0 = agreement no greater than chance, 1 = complete agreement). Logistic regression was used to compare baseline predictors with a declining *versus* neutral or increasing renal function slope. The statistical significance of a decline in renal function with respect to baseline predictors was determined by the Wald test. All odds ratios (OR) were adjusted for study site. Continuous baseline predictors were evaluated per doubling for kidney volume, cyst volume, and urine ACR and per 10 yr for age. Backward elimination model building was used to identify independent predictors ($P < 0.05$) for a decline in renal function by each method. Additional analyses compared renal function slope methods using the *t* test for nominal predictors and Pearson correlation for continuous predictors.

The MDRD equation was developed with cross-sectional data to estimate standardized iothalamate clearance in patients with CKD and decreased renal function (3). With the MDRD equation, there is a static relationship between equation variables (ln SCr, ln age, gender, and

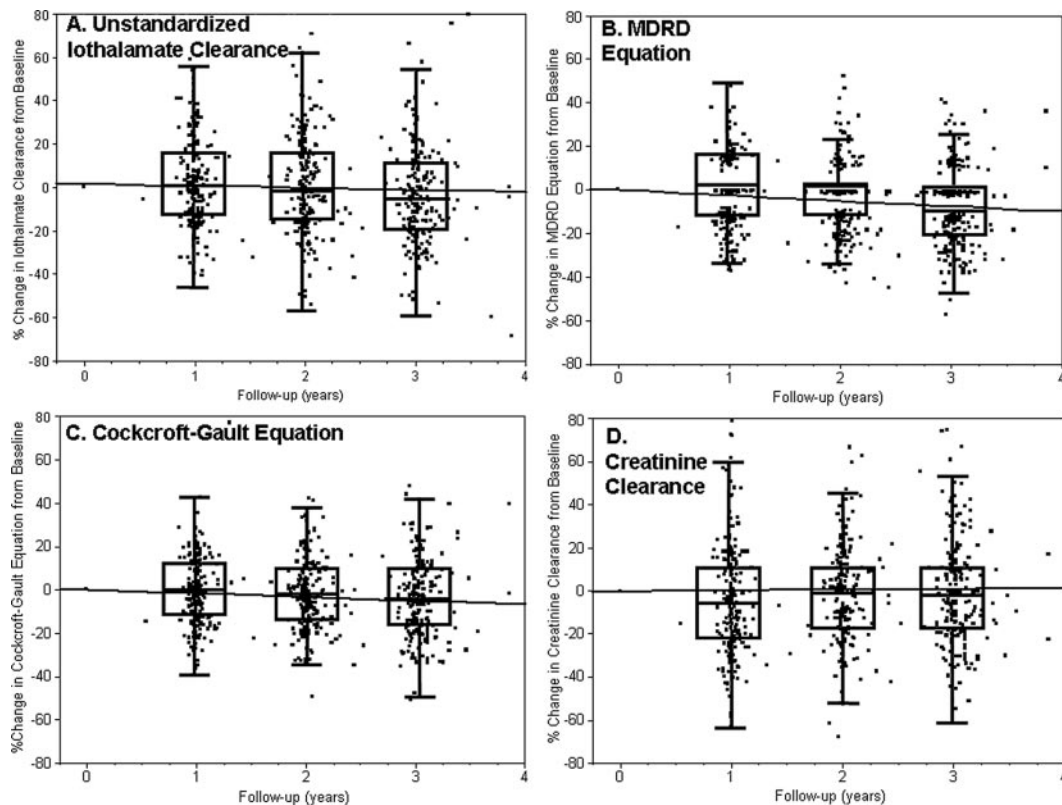


Figure 1. Percentage change in renal function from baseline at each follow-up visit by unstandardized iothalamate clearance (A), Modification of Diet in Renal Disease (MDRD) equation (B), Cockcroft-Gault equation (C), and creatinine clearance (D). The line represents the pooled data regression slope and shows relatively stable renal function for the overall cohort by each method. Box plots for each follow-up visit show more variability in the change in renal function by iothalamate clearance and creatinine clearance than by the MDRD or Cockcroft-Gault equation. This was consistent with greater measurement error by the clearance methods than by the equation methods.

race) and ln measured GFR (standardized iothalamate clearance) based on a linear regression model. Using this same multivariable regression model, the relationship between these variables and standardized iothalamate clearance was compared at each of the four visits. An additional model included a quadratic term for logarithmic serum creatinine $[\ln(\text{SCr})]^2$ to assess curvature (18). Using a smoother function (JMP 5.01, $\lambda = 0.1$), the relationship between iothalamate clearance and SCr was graphically compared between the combined first two study visits and the combined last two study visits.

Results

The baseline characteristics of the CRISP cohort are shown in Table 1. Of 241 patients who enrolled in the study, seven were excluded for having only one study visit. By each renal function method, slopes could be calculated in the remaining 234 patients. By iothalamate clearance, this involved measures from all four visits for 82%, three visits for 12%, and two visits for 6% (missing data trends similar for creatinine clearance and SCr). Figure 1 shows the annual percentage change in renal function from baseline for unstandardized iothalamate clearance, the MDRD equation, the Cockcroft-Gault equation, and creatinine clearance. Individual slopes by each method followed a normal distribution. There was a gradual but statistically significant decline in renal function by unstandardized iothalamate clear-

ance (mean slope = $-1.5\%/yr$; $P = 0.009$; $SD = 9.3\%$), by MDRD equation (mean = $-3.0\%/yr$; $P < 0.001$; $SD = 7.0\%$), and by Cockcroft-Gault equation (mean = $-1.8\%/yr$; $P < 0.001$; $SD = 6.7\%$). This decline was not statistically significant by creatinine clearance (mean = $-0.6\%/yr$; $P = 0.48$; $SD = 13.3\%$). As shown by the box plots and the SD of slopes, there was more slope variability by iothalamate clearance and creatinine clearance than by the estimating equations.

Each renal function method was compared with unstandardized iothalamate clearance. The Pearson correlation with unstandardized iothalamate clearance slope was $r = 0.98$ ($P < 0.001$) for standardized iothalamate clearance slope, $r = 0.30$ ($P < 0.001$) for $1/\text{SCr}$ slope, $r = 0.30$ ($P < 0.001$) for MDRD equation slope, $r = 0.25$ ($P < 0.001$) for Cockcroft-Gault equation slope, and $r = -0.06$ ($P = 0.34$) for creatinine clearance slope. The agreement with unstandardized iothalamate clearance for lowest quintile slope was $\kappa \pm SE = 0.92 \pm 0.03$ for standardized iothalamate clearance, 0.23 ± 0.07 for $1/\text{SCr}$, 0.25 ± 0.07 for MDRD equation, 0.15 ± 0.07 for Cockcroft-Gault equation, and 0.20 ± 0.07 for creatinine clearance.

The precision between renal function methods was compared. The mean residual SD was 10.7% for both unstandardized and standardized iothalamate clearance. For unstandard-

Table 1. Clinical characteristics at baseline for 234 patients with ADPKD^a

Demographics	
age (yr)	34 (25 to 40)
female	60% (140)
white	88% (206)
black	10% (24)
weight (kg)	74 (61 to 91)
height (cm)	170 (163 to 181)
Predictors for a decline in renal function	
hypertension	61% (143)
bilateral kidney volume (ml)	865 (585 to 1340)
bilateral cyst volume (ml)	320 (166 to 727)
albumin to creatinine ratio (mg/g)	25 (11 to 49)
current smoker	17% (40)
history of urinary tract infection	45% (104)
abdominal pain	61% (142)
gross hematuria	32% (76)
Renal function measures	
unstandardized iothalamate clearance (ml/min)	107 (86 to 123)
standardized iothalamate clearance (ml/min per 1.73 m ²)	95 (79 to 115)
SCr (mg/dl)	1.03 (0.82 to 1.21)
MDRD equation ^b (ml/min per 1.73 m ²)	79 (63 to 96)
Cockcroft-Gault equation ^c (ml/min)	101 (82 to 126)
creatinine clearance (ml/min)	109 (89 to 130)

^aResults given as percentage (count) or median (25th to 75th percentiles). ADPKD, autosomal dominant polycystic kidney disease; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine.

^b $186.3 \times (\text{SCr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black}) (4)$.

^c $[(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})] / (72 \times \text{serum creatinine}) (2)$.

ized iothalamate clearance, patients with at least one suboptimal test had a mean residual SD of 13.1%, whereas patients with no suboptimal tests had a mean residual SD of 10.1%. The mean residual SD was 6.9% for 1/SCr, 8.2% for the MDRD equation, and 7.7% for the Cockcroft-Gault equation, and these all were lower (*i.e.*, more precise) than unstandardized or standardized iothalamate clearance ($P < 0.001$ for all). The mean residual SD was 14.8% for creatinine clearance, and this was higher (*i.e.*, less precise) than the unstandardized or standardized iothalamate clearance ($P < 0.001$ for both). Across each study site (Kansas, Emory, Mayo Clinic, and Alabama), the mean residual SD was 10.5, 11.0, 10.0, and 13.8% for unstandardized iothalamate clearance; 6.6, 7.2, 6.7, and 7.7% for 1/SCr; 7.7, 8.4, 7.8, and 10.1% for the MDRD equation; and 18.3, 10.7, 12.3, and 22.1% for creatinine clearance.

Baseline predictors were compared between patients with and without a decline in renal function as defined by the lowest quintile slope (Table 2). Statistically significant predictors of a decline in both unstandardized and standardized iothalamate clearance included hypertension, kidney volume, cyst volume, urine ACR, and history of UTI (all $P < 0.05$). Age was borderline significant ($P = 0.06$). For a decline in 1/SCr, eGFR (MDRD equation or Cockcroft-Gault equation), or creatinine clearance, most of these same predictor associations were present but were attenuated. For estimating equations, constant multipliers (gender and race variables) had no effect on the logarithmic

slopes. In general, predictor associations were similar between a decline in 1/SCr and a decline in eGFR. There were similar differences between methods for associations with renal function slopes as continuous variables (Table 3).

In a multivariable model, independent predictors for a decline in unstandardized iothalamate clearance were hypertension with OR of 3.5 (95% confidence interval [CI] 1.3 to 9.3), kidney volume per doubling with OR of 1.9 (95% CI 1.2 to 3.1), and history of UTI with OR of 2.3 (95% CI 1.1 to 4.6). For this sample size, multiple independent predictors for renal function decline were identified only by the iothalamate clearance. By eGFR, 1/SCr, and creatinine clearance, only one predictor remained statistically significant with backward stepwise elimination.

For further exploration of the discrepancy between measured GFR slope compared with eGFR slope, logarithmic standardized iothalamate clearance was regressed on the same variables used in the MDRD equation (ln SCr, ln age, gender, and race) for each of the four study visits (Table 4). For the SCr, female gender, and black race variables, the strength of association with standardized iothalamate clearance increased progressively from baseline through the follow-up visits. The association between these variables and standardized iothalamate clearance also became more consistent with the MDRD equation with each follow-up visit. Variability in ln GFR also increased progressively from an SD of 0.25 at baseline to an SD of

Table 2. Association between baseline predictors and lowest quintile ($n = 47$) renal function slope by different methods (95% CI)^a

Baseline Predictors	Odds Ratio ^b by Renal Function Method					
	Unstandardized Iothalamate Clearance Slope < -7.1%/yr	Standardized Iothalamate Clearance Slope < -8.0%/yr	1/SCr Slope < -6.7%/yr	MDRD Equation Slope < -8.3%/yr	Cockcroft-Gault Equation Slope < -6.9%/yr	Creatinine Clearance Slope < -7.0%/yr
Hypertension	5.8 (2.3 to 14) ^c	5.8 (2.3 to 14) ^c	2.0 (1.0 to 4.2)	2.0 (1.0 to 4.2)	1.9 (0.9 to 3.9)	2.0 (1.0 to 4.2)
Kidney volume per doubling	2.4 (1.5 to 3.7) ^c	2.3 (1.5 to 3.5) ^c	1.7 (1.1 to 2.6) ^c	1.7 (1.1 to 2.5) ^c	2.1 (1.4 to 3.3) ^c	1.7 (1.1 to 2.5) ^c
Cyst volume per doubling	1.6 (1.2 to 2.0) ^c	1.5 (1.2 to 1.9) ^c	1.3 (1.0 to 1.7) ^c	1.3 (1.0 to 1.7) ^c	1.4 (1.1 to 1.7) ^c	1.3 (1.0 to 1.6) ^c
Urine ACR per doubling	1.3 (1.0 to 1.6) ^c	1.3 (1.1 to 1.7) ^c	1.3 (1.0 to 1.6) ^c	1.3 (1.0 to 1.7) ^c	1.1 (0.9 to 1.4)	1.0 (0.8 to 1.3)
History of UTI	2.2 (1.2 to 4.3) ^c	1.8 (0.9 to 3.4)	0.9 (0.5 to 1.8)	1.0 (0.5 to 2.0)	1.0 (0.5 to 1.8)	1.3 (0.6 to 2.4)
Abdominal pain	1.7 (0.9 to 3.4)	1.2 (0.6 to 2.3)	1.7 (0.9 to 3.5)	1.7 (0.9 to 3.5)	2.0 (1.0 to 4.0)	2.2 (1.0 to 4.5) ^c
Gross hematuria	1.6 (0.8 to 3.1)	1.6 (0.8 to 3.2)	1.2 (0.6 to 2.5)	1.4 (0.7 to 2.8)	1.0 (0.5 to 2.0)	1.2 (0.6 to 2.5)
Current smoker	1.8 (0.8 to 4.0)	1.8 (0.9 to 3.4)	0.9 (0.2 to 4.0)	1.1 (0.5 to 2.6)	1.5 (0.5 to 2.6)	1.8 (0.8 to 4.1)
Age group per 10 yr	1.5 (1.0 to 2.1)	1.3 (0.9 to 1.9)	1.1 (0.7 to 1.5)	0.9 (0.6 to 1.4)	1.3 (0.9 to 1.9)	1.4 (0.9 to 2.0)
Female	1.8 (0.9 to 3.7)	1.6 (0.8 to 3.2)	0.7 (0.3 to 1.3)	0.7 (0.4 to 1.4)	0.6 (0.3 to 1.2)	0.7 (0.4 to 1.4)
Black	1.1 (0.4 to 3.4)	1.1 (0.4 to 3.4)	1.7 (0.6 to 4.8)	1.7 (0.6 to 4.8)	1.8 (0.6 to 5.8)	1.6 (0.6 to 4.2)

^aCI, confidence interval; UTI, urinary tract infection.

^bOdds ratios adjusted for study site. Results were similar when limited to patients who completed all four visits ($n = 192$).

^cStatistically significant ($P < 0.05$, Wald test).

Table 3. Association between baseline predictors and renal function slope by different methods^a

Baseline Predictors	Unstandardized Iothalamate Clearance (ml/min)	Standardized Iothalamate Clearance (ml/min per 1.73 m ²)	1/SCr	MDRD Equation	Cockcroft-Gault Equation	Creatinine Clearance
Nominal predictors (<i>t</i> test)						
hypertensive	-3.1%/y	-3.3%/y	-2.5%/y	-3.5%/y	-2.6%/y	-1.3%/y
normotensive	1.0%/y	0.3%/y	-1.2%/y	-2.1%/y	-0.7%/y	0.6%/y
	($P < 0.001$)	($P = 0.003$)	($P = 0.08$)	($P = 0.11$)	($P = 0.02$)	($P = 0.25$)
UTI history	-2.5%/y	-3.0%/y	-1.8%/y	-2.7%/y	-1.7%/y	-0.8%/y
no UTI history	-0.7%/y	-1.1%/y	-2.2%/y	-3.2%/y	-2.0%/y	-0.7%/y
	($P = 0.11$)	($P = 0.11$)	($P = 0.67$)	($P = 0.61$)	($P = 0.80$)	($P = 0.95$)
abdominal pain	-2.2%/y	-2.4%/y	-2.4%/y	-3.4%/y	-2.4%/y	-2.5%/y
no abdominal pain	-0.5%/y	-1.2%/y	-1.4%/y	-2.3%/y	-1.0%/y	2.4%/y
	($P = 0.16$)	($P = 0.33$)	($P = 0.21$)	($P = 0.24$)	($P = 0.11$)	($P = 0.003$)
gross hematuria	-1.8%/y	-2.2%/y	-2.3%/y	-3.3%/y	-2.2%/y	-1.2%/y
no hematuria	-1.4%/y	-1.8%/y	-1.9%/y	-2.8%/y	-1.7%/y	-0.3%/y
	($P = 0.80$)	($P = 0.75$)	($P = 0.56$)	($P = 0.60$)	($P = 0.61$)	($P = 0.61$)
current smoker	-3.3%/y	-3.6%/y	-2.0%/y	-3.0%/y	-2.2%/y	-3.1%/y
nonsmoker	-1.2%/y	-1.6%/y	-2.0%/y	-2.9%/y	-1.8%/y	0.0%/y
	($P = 0.18$)	($P = 0.21$)	($P = 0.98$)	($P = 0.89$)	($P = 0.72$)	($P = 0.16$)
female	-2.3%/y	-2.8%/y	-1.7%/y	-2.6%/y	-1.3%/y	-0.8%/y
male	-0.4%/y	-0.7%/y	-2.4%/y	-3.4%/y	-2.7%/y	-0.2%/y
	($P = 0.10$)	($P = 0.10$)	($P = 0.38$)	($P = 0.35$)	($P = 0.11$)	($P = 0.70$)
black	-0.7%/y	-1.5%/y	-2.1%/y	-3.0%/y	-1.8%/y	-2.7%/y
white	-1.6%/y	-2.0%/y	-2.0%/y	-2.9%/y	-1.8%/y	-0.3%/y
	($P = 0.63$)	($P = 0.81$)	($P = 0.93$)	($P = 0.94$)	($P = 0.99$)	($P = 0.38$)
Continuous predictors (Pearson correlation with logarithmic renal function slope)						
kidney volume (logarithmic)	$r = -0.33$	$r = -0.30$	$r = -0.25$	$r = -0.23$	$r = -0.28$	$r = -0.19$
	($P < 0.001$)	($P < 0.001$)	($P < 0.001$)	($P < 0.001$)	($P < 0.001$)	($P = 0.003$)
cyst volume (logarithmic)	$r = -0.28$	$r = -0.26$	$r = -0.21$	$r = -0.19$	$r = -0.24$	$r = -0.20$
	($P < 0.001$)	($P < 0.001$)	($P = 0.001$)	($P = 0.004$)	($P < 0.001$)	($P = 0.002$)
urine ACR (logarithmic)	$r = -0.19$	$r = -0.21$	$r = -0.17$	$r = -0.16$	$r = -0.08$	$r = -0.14$
	($P = 0.004$)	($P = 0.002$)	($P = 0.01$)	($P = 0.02$)	($P = 0.26$)	($P = 0.04$)
age	$r = -0.10$	$r = -0.06$	$r = -0.08$	$r = -0.04$	$r = -0.17$	$r = -0.15$
	($P = 0.14$)	($P = 0.39$)	($P = 0.23$)	($P = 0.55$)	($P = 0.01$)	($P = 0.02$)

^aACR, albumin to creatinine ratio.

Table 4. Association between predictor variables and measured GFR at each annual visit with the same multivariable regression model used for the MDRD equation^a

Predictor	% Difference in Standardized Iothalamate Clearance (95% CI)				MDRD Equation (4)
	Baseline	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3	
SCr (per 50% increase)	-22.0% (-26.1 to -17.6%)	-31.8% (-35.1 to -28.3%)	-32.7% (-35.8 to -29.4%)	-32.5% (-35.5 to -29.3%)	-37%
Age (per 50% increase)	-5.4% (-8.9 to -1.9%)	-2.1% (-5.7 to 1.6%)	-6.2% (-10.4 to -1.9%)	-5.6% (-9.8 to -1.1%)	-7.9%
Gender					
female	-9.4% (-14.6 to -4.0%)	-18.4% (-23.0 to -13.4%)	-18.4% (-23.2 to -13.3%)	-24.2% (-28.7 to -19.4%)	-26%
male	Reference	Reference	Reference	Reference	Reference
Race					
black	3.7% (-4.7 to 13.0%)	8.0% (-0.7 to 17.5%)	9.3% (-1.3 to 21.1%)	10.4% (-0.4 to 22.5%)	21%
other	Reference	Reference	Reference	Reference	Reference
Model fit (logarithmic R ²)	0.403	0.579	0.646	0.671	

^aModel also adjusted for study site. Results were similar when limited to patients who completed all four clinic visits ($n = 192$).

0.35 at the final visit (3 yr later). The relationship between ln SCr and ln GFR was relatively linear for the combined first two rounds but developed more curvature for the combined last two rounds (Figure 2). This curvature could be modeled by addition of a quadratic term [$\ln(\text{SCr})^2$] to the regression model shown in Table 4. Inclusion of this quadratic term increased the model fit (R^2) by 0.028 ($P < 0.001$) at baseline, 0.005 ($P = 0.10$) at follow-up visit 1, 0.022 ($P < 0.001$) at follow-up visit 2, and 0.031 ($P < 0.001$) at follow-up visit 3.

Discussion

In a cohort of patients who had ADPKD and baseline normal renal function, predictors for a decline in measured GFR

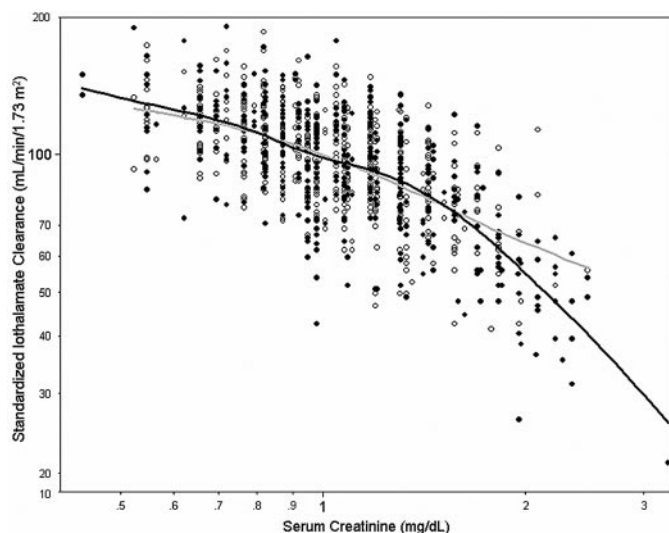


Figure 2. A log-log plot of serum creatinine versus iothalamate clearance for the first two study visits (○) compared with the last two study visits (●). Smoother curves (JMP 5.01, $\lambda = 0.1$) regressed standardized iothalamate clearance on SCr for the first two study visits (gray curve) compared with the last two study visits (black curve). There was more downward curvature in the last two study visits compared with the first two study visits.

(iothalamate clearance) were hypertension, increased kidney volume, increased cyst volume, increased urine ACR, and history of UTI (Table 2). With creatinine clearance, these associations were attenuated from more measurement error (mean residual SD 14.8 *versus* 10.7%; $P < 0.001$). With $1/\text{SCr}$ or eGFR, there was less measurement error (mean residual SD ≤ 8.2 *versus* 10.7%; $P < 0.001$), but predictor associations were weaker instead of stronger compared with measured GFR. Therefore, changes in non-GFR factors conservatively biased associations with the SCr-based methods. This supports the hypothesis that the rise in SCr with a decline in GFR is less than expected as a result of concurrent muscle atrophy, decreased dietary protein, and increased tubular creatinine secretion (17). To a different extent between methods, a decline in renal function can be misclassified from measurement error (precision) or from measurement bias (Table 5).

Many of the predictors that were associated with a decline in renal function have previously been reported for ADPKD. Proteinuria and increased cyst volume have previously been identified as prognostic factors for a decline in measured GFR (27). Kidney volume, proteinuria, and age have been associated with a decline in eGFR (9). In this study, history of UTI was also identified as a prognostic factor for a decline in measured GFR. Whether this was related to renal parenchymal damage from UTI or misdiagnosis of hematuria, leukocyturia, flank pain, or other renal cyst symptoms as a UTI is unclear. In this study, hypertension, kidney volume, and history of UTI were independent prognostic factors for a decline in measured GFR.

In cohorts with baseline normal renal function, it may be preferable to use $1/\text{SCr}$ slope rather than eGFR slope because the relationship between equation variables and measured GFR can be dynamic (Table 4). Furthermore, the mathematical model of the equation can be dynamic with changes in curvature during the follow-up (Figure 2). When a baseline cohort is characterized by normal or near-normal renal function, most of the variability in SCr may reflect creatinine production (*e.g.*, muscle mass). Gender may have a weak effect at baseline (Table 4), as a result of collinearity with SCr (both are markers of muscle mass [28]). However, as disease progression increased

Table 5. Sources of misclassification for a decline in renal function

Renal Function Method	Measurement Error ^a (Decreased Precision)	Measurement Bias (Decreased Accuracy)
Measured GFR (iothalamate clearance)	+ +	0
Estimated GFR ^b (MDRD or Cockcroft-Gault)	+	+ + +
Reciprocal SCr ^b (1/SCr)	+	+ + +
Creatinine clearance	+ + +	+

^aPhysiological variability and assay error.

^bSystematic changes in creatinine production (muscle mass or protein intake), tubular creatinine secretion, or extrarenal creatinine clearance causes bias, whereas random fluctuations contribute to error.

GFR variability in the cohort during the follow-up period (Figure 2), SCr became more a marker of GFR and less a marker of muscle mass. This results in gender having less collinearity with SCr. Subsequently, gender more strongly adjusts for confounding between SCr and GFR (Table 4). This change in the relationship among SCr, gender, and GFR was consistent with previous studies that compared populations that had a normal and narrow range of renal function with populations that had a reduced and wide range of renal function (17,18).

A decline in creatinine clearance had weaker associations with predictors than a decline in iothalamate clearance. The higher within-patient residual SD for creatinine clearance than for iothalamate clearance could explain much of this discrepancy. Incomplete or overcollection of 24-h urine samples can affect precision and accuracy. Some of the change in creatinine clearance over time may reflect changes in creatinine secretion or changes in patient effort for collection of urine samples. Adjustment for study site increased the strength of predictor associations with a decline in creatinine clearance but had no substantive effect on predictor associations by the other methods (unadjusted data not shown). This can be explained by the greater discrepancy between sites with the precision of creatinine clearance than with other methods. Another study that compared longitudinal and simultaneously collected creatinine clearance with measured GFR found substantial discordance between these two methods over time (15).

When slopes or changes in renal function were compared, there were no advantages to standardizing iothalamate clearance for body surface area (Tables 2 and 3). In cross-sectional or threshold analyses (e.g., GFR <60 ml/min per 1.73 m²), standardizing for body surface area attempts to account for differences in physiologic demand for renal function (i.e., larger individuals need more absolute renal function than smaller individuals). In this longitudinal study, however, percentage changes in renal function were compared and each patient served as his or her own control for physiologic demand. Adjustment for body surface area provides an additional source of measurement error with the added height and weight variables. Also, some longitudinal changes in height (e.g., compression fractures) or weight (e.g., obesity or wasting) will be interpreted incorrectly as changes in renal function. This can also explain the discrepancy with predictor associations between the Cockcroft-Gault equation (weight variable present)

and the MDRD equation (weight variable absent; Tables 2 and 3).

In this study, logarithmic slopes (% per year) were used instead of absolute slopes (ml/min per year or ml/min per 1.73 m²/yr) because measurement error decreases as renal function decreases (3). For example, a rise in SCr from 0.9 to 1.0 mg/dl or from 3.3 to 6.0 mg/dl represents a decline in eGFR of 10 ml/min per 1.73 m² for a 60-yr-old white man with CKD (MDRD equation). The former can be attributed easily to measurement error, whereas the latter more likely represents a true decline in GFR. With logarithmic slopes, a rise in SCr from 0.9 to 1.6 mg/dl would be similar to a rise in SCr from 3.3 to 6.0 mg/dl. In this study, associations with baseline predictors were generally more attenuated with analyses by absolute slope. Hypertension was associated with a decline (lowest quintile slope) in unstandardized iothalamate clearance by an OR of 4.0 (95% CI 1.8 to 9.7), MDRD equation by an OR of 1.1 (95% CI 0.6 to 2.2), and creatinine clearance by an OR of 0.9 (95% CI 0.7 to 1.9). Each doubling of kidney volume was associated with a decline in unstandardized iothalamate clearance by an OR of 2.4 (95% CI 1.6 to 3.7), MDRD equation by an OR of 1.1 (95% CI 0.8 to 1.7), and creatinine clearance by an OR of 1.2 (95% CI 0.7 to 1.9).

The stronger predictor associations by measured GFR slope may not be applicable to CKD populations with a more reduced baseline renal function. Lewis *et al.* (6) found predictor associations to be similar by measured GFR slope and eGFR slope. Patients in that study had a baseline measured GFR of 20 to 65 ml/min per 1.73 m², and there was a more substantial overall decline in renal function during follow-up. Different methods for assessing the rate of renal function decline may correlate better in advanced CKD compared with early CKD. However, when the goal is to intervene early in CKD, measured GFR may be superior for identifying the initial decline in renal function.

A potential limitation of this study was protocol differences between renal function methods. Iothalamate concentrations were assayed at a centralized laboratory, whereas SCr and creatinine clearance were assayed at each study site. This was addressed by adjusting for study site in the analyses. There was also good agreement between lowest quintile slope for the MDRD equation with SCr calibrated *versus* MDRD equation without SCr calibrated ($\kappa \pm SE = 0.95 \pm 0.03$). Furthermore, predictor associations did not change substantively with SCr

calibration. Patients in this study all had ADPKD and were younger than the typical patient with CKD. Consequently, generalization to other CKD causes and older populations should be done with caution. However, ADPKD may also be useful as a model for CKD, because the diagnosis can be made with radiologic imaging before a detectable decline in renal function. Finally, only a few predictors for renal function decline were identified in this study, and further studies are still needed to compare renal function methods by other baseline predictors.

Conclusion

Measured GFR decline had the strongest association with predictors. Measurement error with creatinine clearance attenuated associations because of increased misclassification for a decline in renal function. SCr-based methods (1/SCr or eGFR) had less measurement error compared with measured GFR. However, changes in SCr from non-GFR factors (*e.g.*, creatinine production, tubular secretion) led to conservatively biased associations. The cost and the convenience of different methods still need consideration when assessing changes in renal function over time.

Acknowledgments

This study was supported by F32-DK68996, by the CRISP study UO1 cooperative agreements (DK56956, DK56943, DK56957, and DK56961) of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, and the General Clinical Research Center grants MO1-RR00585 (the Mayo Foundation), MO1-RR00052 (University of Alabama at Birmingham), and M01-RR00039 (Emory University) for the Division of Research Resources, National Institutes of Health.

References

- Hsu CY, Chertow GM, Curhan GC: Methodological issues in studying the epidemiology of mild to moderate chronic renal insufficiency. *Kidney Int* 61: 1567–1576, 2002
- Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16: 31–41, 1976
- Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130: 461–470, 1999
- Levey AS, Greene T, Kusek JW, Beck GJ: A simplified equation to predict glomerular filtration rate from serum creatinine [Abstract]. *J Am Soc Nephrol* 11: A0828, 2000
- Lindeman RD, Tobin JD, Shock NW: Association between blood pressure and the rate of decline in renal function with age. *Kidney Int* 26: 861–868, 1984
- Lewis J, Greene T, Appel L, Contreras G, Douglas J, Lash J, Toto R, Van Lente F, Wang X, Wright JT, Group AS: A comparison of iothalamate-GFR and serum creatinine-based outcomes: Acceleration in the rate of GFR decline in the African American Study of Kidney Disease and Hypertension. *J Am Soc Nephrol* 15: 3175–3183, 2004
- Walker WG, Neaton JD, Cutler JA, Neuwirth R, Cohen JD: Renal function change in hypertensive members of the Multiple Risk Factor Intervention Trial. Racial and treatment effects. The MRFIT Research Group. *JAMA* 268: 3085–3091, 1992
- Levey AS, Adler S, Caggiula AW, England BK, Greene T, Hunsicker LG, Kusek JW, Rogers NL, Teschan PE: Effects of dietary protein restriction on the progression of advanced renal disease in the Modification of Diet in Renal Disease Study. *Am J Kidney Dis* 27: 652–663, 1996
- Fick-Brosnahan GM, Belz MM, McFann KK, Johnson AM, Schrier RW: Relationship between renal volume growth and renal function in autosomal dominant polycystic kidney disease: A longitudinal study. *Am J Kidney Dis* 39: 1127–1134, 2002
- Lin JL, Lin-Tan DT, Hsu KH, Yu CC: Environmental lead exposure and progression of chronic renal diseases in patients without diabetes. *N Engl J Med* 348: 277–286, 2003
- Murray S, Martin M, Amoedo ML, Garcia C, Jornet AR, Vera M, Oliveras A, Gomez X, Craver L, Real MI, Garcia L, Botey A, Montanya X, Fernandez E: Rapid decline in renal function reflects reversibility and predicts the outcome after angioplasty in renal artery stenosis. *Am J Kidney Dis* 39: 60–66, 2002
- Ravid M, Brosh D, Ravid-Safran D, Levy Z, Rachmani R: Main risk factors for nephropathy in type 2 diabetes mellitus are plasma cholesterol levels, mean blood pressure, and hyperglycemia. *Arch Intern Med* 158: 998–1004, 1998
- K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Kidney Disease Outcomes Quality Initiative. *Am J Kidney Dis* 39[Suppl 2]: S1–S246, 2002
- Bauer JH, Brooks CS, Burch RN: Clinical appraisal of creatinine clearance as a measurement of glomerular filtration rate. *Am J Kidney Dis* 2: 337–346, 1982
- Petri M, Bockenstedt L, Colman J, Whiting-O'Keefe Q, Fitz G, Sebastian A, Hellmann D: Serial assessment of glomerular filtration rate in lupus nephropathy. *Kidney Int* 34: 832–839, 1988
- Lin J, Knight E, Hogan M, Singh A: A comparison of prediction equations for estimating glomerular filtration rate in adults without kidney disease. *J Am Soc Nephrol* 14: 2573–2580, 2003
- Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG: Using serum creatinine to estimate glomerular filtration rate: Accuracy in good health and in chronic kidney disease. *Ann Intern Med* 41: 929–937, 2004
- Poggio ED, Wang X, Greene T, Van Lente F, Hall PM: Performance of the Modification of Diet in Renal Disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. *J Am Soc Nephrol* 16: 459–466, 2005
- Mariat C, Alamartine E, Barthelemy JC, De Filippis JP, Thibaudin D, Berthouix P, Laurent B, Thibaudin L, Berthouix F: Assessing renal graft function in clinical trials: Can tests predicting glomerular filtration rate substitute for a reference method? *Kidney Int* 65: 289–297, 2004
- Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, Zeeuw D, Hostetter TH, Lameire N, Eknoyan G: Definition and classification of chronic kidney disease: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 67: 2089–2100, 2005
- Chapman AB, Guay-Woodford LM, Grantham JJ, Torres VE, Bae KT, Baumgarten DA, Kenney PJ, King BJ Jr, Glockner JF,

- Wetzel LH, Brummer ME, O'Neill WC, Robbin ML, Bennett WM, Klahr S, Hirschman GH, Kimmel PL, Thompson PA, Miller JP: Renal structure in early autosomal-dominant polycystic kidney disease (ADPKD): The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) cohort. *Kidney Int* 64: 1035-1045, 2003
22. Ravine D, Gibson RN, Walker RG, Sheffield LJ, Kincaid-Smith P, Danks DM: Evaluation of ultrasonographic diagnostic criteria for autosomal dominant polycystic kidney disease. *Lancet* 343: 824-827, 1994
 23. Wilson DM, Bergert JH, Larson TS, Liedtke RR: GFR determined by nonradiolabeled iothalamate using capillary electrophoresis. *Am J Kidney Dis* 30: 646-652, 1997
 24. DuBois D, DuBois E: A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med* 17: 863-871, 1916
 25. Anastasio P, Cirillo M, Spitali L, Frangiosa A, Pollastro RM, De Santo NG: Level of hydration and renal function in healthy humans. *Kidney Int* 60: 748-756, 2001
 26. Perkins BA, Nelson RG, Ostrander B, Blouch KL, Krolewski AS, Myers BD, Warram JH: Detection of renal function decline in patients with diabetes and normal or elevated GFR by serial measurements of serum cystatin C concentration: Results of a 4-year follow-up study. *J Am Soc Nephrol* 16: 1404-1412, 2005
 27. King BF, Reed JE, Bergstralh EJ, Sheedy PF 2nd, Torres VE: Quantification and longitudinal trends of kidney, renal cyst, and renal parenchyma volumes in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 11: 1505-1511, 2000
 28. Walser M: Creatinine excretion as a measure of protein nutrition in adults of varying age. *J Parenter Enteral Nutr* 11[Suppl]:73S-78S, 1987