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The Performance of Three Serum Creatinine-Based Formulas in Estimating GFR in Former Kidney Donors

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Studies addressing long-term consequences of living with one kidney have used serum creatinine-based formulas that have not been validated in former kidney donors. Therefore, we evaluated the performance of Cockcroft–Gault (CG), Modification of Diet in Renal Disease (MDRD) and Mayo Clinic formulas in predicting iohexol glomerular filtration rate (iGFR) after donation in 112 randomly selected former kidney donors. Mean time from donation was 12.2 ± 8.5 years. Serum creatinine was 1.1 ± 0.2 mg/dL and iohexol GFR was 72 ± 12 mL/min/1.73 m^2. The majority, 83.9%, of donors had a GFR >60 mL/min. CG formula overestimated GFR by 3.35 ± 13.6 mL/min and was within 10% of iohexol GFR in only 43.7% of cases. MDRD formula underestimated iohexol GFR by 6.45 ± 9.5 mL/min and was within 10% of actual GFR in half of the cases. In contrast, the Mayo Clinic equation was the most biased at 14.71 ± 12.3 mL/min and was within 10% of measured GFR in only a fifth of the cases. Only MDRD and CG formulas provide estimates of GFR in former kidney donors that are within a clinically acceptable range of actual GFR. In conclusion, the majority of former kidney donors have excellent kidney function and the MDRD formula should be the recommended GFR estimating model in this population.

Key words: GFR, kidney donor, MDRD, uninephrectomy

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Introduction

Transplantation using a live donor offers many advantages when compared to transplantation using a deceased donor (1,2). Live donor transplantation is not without risks and the donor is required to have a major operation that is associated with morbidity and even mortality (3–7). Studies addressing long-term renal outcomes of former kidney donors are scant and have regularly used serum creatinine to assess kidney function with its known limitations in accurately reflecting the glomerular filtration rate (GFR) (8). Using serum creatinine-based GFR prediction models, such as the Cockcroft–Gault (CG), the Modification of Diet in Renal Disease (MDRD) study formulas and the newly introduced Mayo Clinic equation (MCe), is superior to using the serum creatinine alone as an index of renal function (9–11). These formulas, however, have not been validated in people who underwent a uninephrectomy for donation. While there is no reason to believe that these formulas will perform differently in donors than in other populations, to fully and accurately discuss the long-term renal consequences of donation a reliable measurement of renal function should be used (11–13). Herein and for the first time, we report on the performance of the CG, MDRD and MCe formulas in randomly selected former kidney donors who underwent formal iohexol glomerular filtration rate (iGFR) measurement.

Patients and Methods

As of October 2005, 3398 donor nephrectomies have been performed at the University of Minnesota. We generated donor lists that were stratified by gender and years from donation by 3-year intervals, e.g. 3, 6, 9, 12, . . . ,36 years post donation. From these lists and at random, 112 donors were admitted to the General Clinical Research Center and underwent iGFR measurement. If the randomly selected donor refused participation or was discovered to be deceased, another donor was contacted.

GFR was measured using the plasma clearance of non-radioactive iohexol (14). Five milliliters of iohexol solution (647 mg of iohexol; 300 mg of iodine per mL) was injected via a small polyethylene catheter placed in an antecubital vein and serial samples were then taken from the contralateral arm via a second antecubital vein catheter at 120, 150, 180, 210 and 240 min (±15 s). Plasma was stored at −20°C for later HPLC determination of iohexol concentration. The plasma profile was analyzed by a one-compartment model system with all data fitted by a non-linear regression iterative program. This method provides values for GFR that are highly correlated with inulin clearance (the gold standard) method. iGFR was chosen since it does not require timed urine collections where incomplete bladder emptying may lead to significant variability of GFR determinations. The coefficient of variation of this method in our institution is 10%.

Large differences in calibration of the serum creatinine assay across laboratories, and by extension the prediction models that depend on them, influence accuracy and bias of these formulas (15,16). Therefore, we sent 25 samples for creatinine measurement (range 0.6–2.3 mg/dL) to the Cleveland Clinic Core Biochemistry Laboratory where serum creatinine for the MDRD study was assayed using the Beckmann Rate Jaffe'/CXR Synchron method

which is based on the kinetic alkaline picrate reaction and compared them to the University of Minnesota Laboratory, which uses an identical method and instrument (17). The results were virtually identical and the Pearson correlation coefficient between the measurements at the two laboratories was 0.9965. Moreover, the mean difference (Cleveland Clinic Lab − University of Minnesota Lab) was 0.0125 mg/dL with a standard deviation of 0.03 mg/dL. All serum creatinine measurements were after 8–10 h of an overnight fast.

GFR was estimated using the formulas of CG, the MDRD and Mayo Clinic equations. The CG formula predicts creatinine clearance (CG Cl_{cr}): [(140 − age) × weight/(72 × SCr)] × (0.85 if female). We adjusted the creatinine clearance estimate for body surface area by multiplying by (1.73/BSA).

We used the abbreviated MDRD study equation: MDRD-GFR = 186 × $SCr^{1.154}$ × $age^{0.203}$ × 0.742 (if female) × 1.210 (if black) (18). Applying the more extended versions of the MDRD formula showed identical results (data not shown).

The MCe (MCe-GFR) is a quadratic equation that estimates logarithmic GFR from serum creatinine, age and gender:

$$\text{GFR} = \exp\left(1.911 + \frac{5.249}{\text{SCr}} - \frac{2.114}{\text{SCr}^2} - 0.00686 \times \text{age} - 0.205\,(\text{if female})\right).$$

If SCr < 0.8 mg/dL, a value of 0.8 was used (11).

We assessed the performance of the CG Cl_{cr}, MDRD-GFR and MCe-GFR against measured GFR in several ways:

1. Bias: the average prediction error = $\sum$(estimated GFR − iGFR)/n, where n is the number of GFR studies performed and iGFR is iohexol GFR. Relative bias, % deviation from the gold standard, was also calculated.
2. Precision: the value of R^2 from the linear regression of iGFR on estimated GFR.
3. Relative accuracy: the percentage of estimates falling within 10%, 30% and 50% of iohexol GFR.

The equations were compared statistically for each of these measures. The comparisons were made using a paired *t*-test for bias, a bootstrap test for the bias's standard deviation (19), a paired test of proportions for relative accuracy (20) and the Hotelling–Williams test for precision, R^2 (21). The bootstrap test estimates the sampling distribution of differences in the standard deviation of the bias for each pair of formulas using 20 000 bootstrap samples. All of these statistical tests take into account that all equations were calculated for the same set of subjects.

The Bland–Altman plots of these formulas were also performed. This technique examines bias and precision for a new method of measuring a clinical variable compared to an established gold standard, iohexol GFR in this case (22). This sort of analysis plots the (estimated GFR − iohexol GFR) on the y-axis against their average on the x-axis which permits detection of a trend in bias. Graphically, it depicts the mean difference between the two methods bracketed by the observed ±2 standard deviations of the difference between the two methods. Statistical tests for the bias and its standard deviation mentioned above apply to the Bland–Altman analysis. Residual plots for each of three formulas were also constructed; similar to the Bland–Altman plots with exception that the x-axis is iohexol GFR. These plots help determine whether the bias of the measurement varies with the level of GFR.

Results are expressed as mean ± standard deviation; unless indicated otherwise. Statistical significance was assessed with a Bonferroni-adjusted threshold of 0.05/3 since three pairs of formulas were compared. Analyses and graphs were completed using statistical software R and SAS (23,24).

Table 1: Demographics of donors at the time of GFR measurement

Number of donors	112
Age at donation (years)	40.1 ± 10.0
Male	41%
White	98%
BMI (kg/m^2)	28.2 ± 4.9
Time from donation (years)	12.2 ± 8.5
SBP (mmHg)	122 ± 15
DBP (mmHg)	73 ± 9
Hypertension	30.3%
Diabetes	3.7%

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Results

Since the program began in 1963, 3398 donor nephrectomies have been performed at the University of Minnesota. Of these, 154 have died and the vital status of 138 remains unknown; 112 underwent iohexol GFR measurements. On average 2–5% of donors at each 3-year interval participated. The mean time from donation was 12.2 ± 8.5 years, 41% were males and 98.2% were white (Table 1). The baseline demographics of the subjects who underwent GFR measurement were not different than those who did not undergo GFR measurement (data not shown).

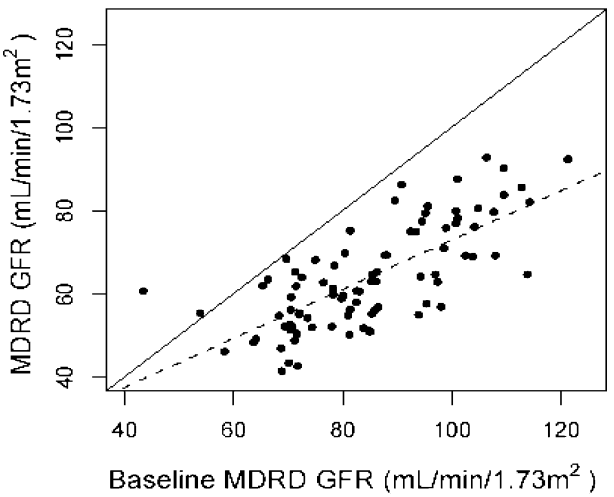

Figure 1: Current MDRD-GFR and MDRD-GFR at time of donation. The solid line indicates unity and the dotted line is the regression line.

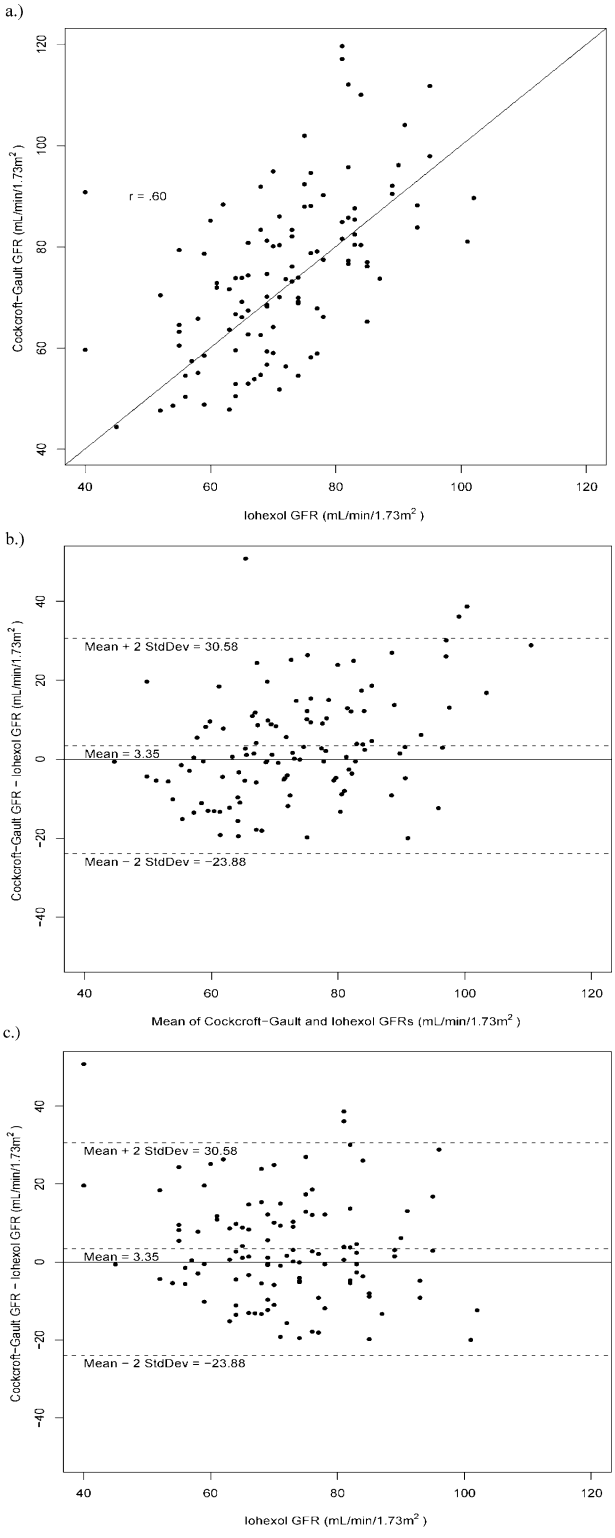

Figure 2: Performance of the CG Cl_{cr} against iohexol GFR. (A) Scatter plot of CG Cl_{cr} on iohexol GFR with line of unity. (B) Bland–Altman plot. (C) Residual plot of CG Cl_{cr} bias against iohexol GFR.

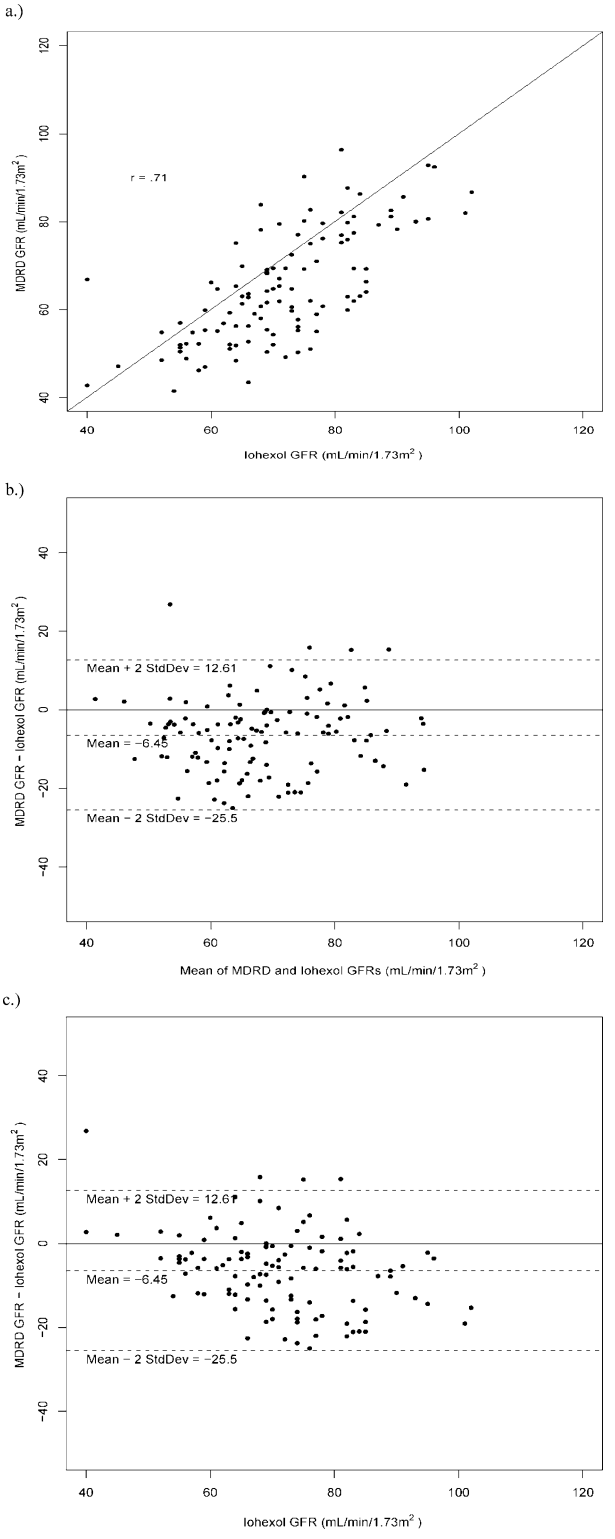

Figure 3: Performance of the MDRD-GFR against iohexol GFR. (A) Scatter plot of MDRD-GFR on iohexol GFR with line of unity. (B) Bland–Altman plot. (C) Residual plot of MDRD-GFR bias against iohexol GFR.

The serum creatinine was 1.1 ± 0.2 mg/dL. GFR was 75 ± 17, 65 ± 13, 86 ± 17 and 72 ± 12 mL/min/1.73 m^2 by the CG Cl_{cr}, MDRD-GFR, MCe-GFR and iohexol GFR, respectively. Most reassuring was the finding that 83.9% of donors had a GFR >60 mL/min.

All kidney donors had a current GFR that is higher than half of their estimated GFR at donation. As a matter of fact, their MDRD-GFR at the time of the iohexol GFR measurement was 76.3 ± 12.2% of the one kidney baseline MDRD-GFR (range 57–140%). There was a direct relationship between baseline and current estimated GFR (Figure 1). We could not perform correlational analysis using iohexol GFR since it was not done at the time of donation. In addition, weight was missing in many subjects precluding analyzing the CG Cl_{cr} at these two time points.

CG estimate

CG Cl_{cr} tended to overestimate iGFR by 3.35 ± 13.6 mL/min, Figure 2A. The relative bias was 5.6 ± 21.5%. It fell within 10%, 30% and 50% of the measured GFR in 43.7%, 86.6% and 99.1% of the cases, respectively (Table 2). With regard to precision, the R^2 estimate was 0.36. Inspecting the Bland–Altman plot of CG Cl_{cr} reveals a very wide ±2SD interval around the mean absolute bias of 3.35 mL/min (−23.88 to 30.58 mL/min), Figure 2B. The residual plot reveals that the bias of the CG Cl_{cr} was constant across the entire GFR range, Figure 2C.

MDRD-GFR

The MDRD-GFR underestimated iGFR by 6.45 ± 9.5 mL/min, Figure 3A. The relative bias was −8.3 ± 14.1%. The MDRD-GFR was within 10%, 30% and 50% of iGFR in 50%, 95.5% and 99.1%, respectively (Table 2). The MDRD-GFR was more precise than CG Cl_{cr}; $R^2 = 0.50$. The ±2SD interval of the Bland–Altman plots was also significantly narrower than the CG Cl_{cr} (−25.5 to 12.61 mL/min), Figure 3B. Similar to the residual plots of the CG Cl_{cr} estimate, there was no change in degree of bias with level of GFR, Figure 3C.

Since the CG Cl_{cr} overestimated iGFR and MDRD-GFR underestimated it, their average yielded the least absolute bias, −1.64 ± 10.5 mL/min, but unfortunately did not improve precision beyond that achieved with the MDRD-GFR alone.

Mayo Clinic equation

The MCe-GFR grossly overestimated iGFR by 14.71 ± 12.3 mL/min, Figure 4A. Its relative bias was highest at 21.4 ± 19.6%. It fell within 10%, 30% and 50% of iGFR in 22.3%, 67.9% and 95.5% of the cases, respectively (Table 2). Its precision was similar to the MDRD formula and both were more precise than the CG Cl_{cr} estimate. The ±2SD interval of the Bland–Altman plot was 49.3 mL/min (−9.98 to 39.4 mL/min), Figure 4B. Again, the residual plots revealed no bias dependence on level of GFR, Figure 4C.

Intrigued by the poor performance of the MCe we compared the three formulas in the manner the MCe was developed, namely, plotting the reciprocal of serum creatinine on the x-axis and iohexol GFR on the y-axis in our donors, Figure 5. It is evident that the curve for the MCe shifts upward at high reciprocal serum creatinine due to the high GFRs of the healthy individuals in their sample. Our donors, of course, had lower GFRs, though they have similar serum creatinine to the Mayo cohort.

The percentage of donors who fit the GFR definition cut-point of CKD (<60 mL/min) was 16.1% by iohexol GFR in contrast to 22.3%, 39.3% and 6.2% by the CG, MDRD and Mayo Clinic models, respectively (Figure 6).

In summary, the MDRD-GFR provided the best GFR estimate followed by the CG Cl_{cr} estimate. The Mayo Clinic formula, on the other hand, performed the poorest (Table 2).

Discussion

This is the single largest and only experience that compared serum creatinine-based formulas with measured GFR in former kidney donors. The CG Cl_{cr} and MDRD prediction models give GFR estimates that are certainly within an acceptable range of measured GFR for routine assessment and screening of kidney function in former kidney donors. The MCe, however, was generally inferior to either model. More importantly, this study clearly demonstrates

Table 2: Overall performance of the CG Cl_{cr}, MDRD and Mayo Clinic formulas in kidney donors

	Bias	Relative bias	R^2	Within 10% of iGFR	Within 30% of iGFR	Within 50% of iGFR
CG Cl_{cr}	3.35 ± 13.6	5.6 ± 21.5%	0.36	43.7%	86.6%	99.1%
MDRD	−6.45 ± 9.5	−8.3 ± 14.1%	0.50	50.0%	95.5%	99.1%
Mayo Clinic	14.71 ± 12.3	21.4 ± 19.6%	0.46	22.3%	67.9%	95.5%
Rank of	CG MDRD Mayo	CG MDRD Mayo	CG MDRD Mayo	CG MDRD Mayo	CG MDRD Mayo	CG MDRD Mayo
performance	1 1 3	1 1 3	3 1 1	1 1 3	1 1 3	1 1 1

Bias (mL/min) = $\sum \frac{\text{estimated GFR} - \text{measured GFR}}{\text{number of GFR measurements}}$; Relative bias = % deviation from iohexol GFR; R^2 = from regressing estimated GFR on measured GFR; iGFR = iohexol GFR.

Rank of performance: 1 = best and ties are assigned the same rank. The rank performance of the variance in bias and relative bias was 2, 1 and 2 for CG, MDRD and Mayo.

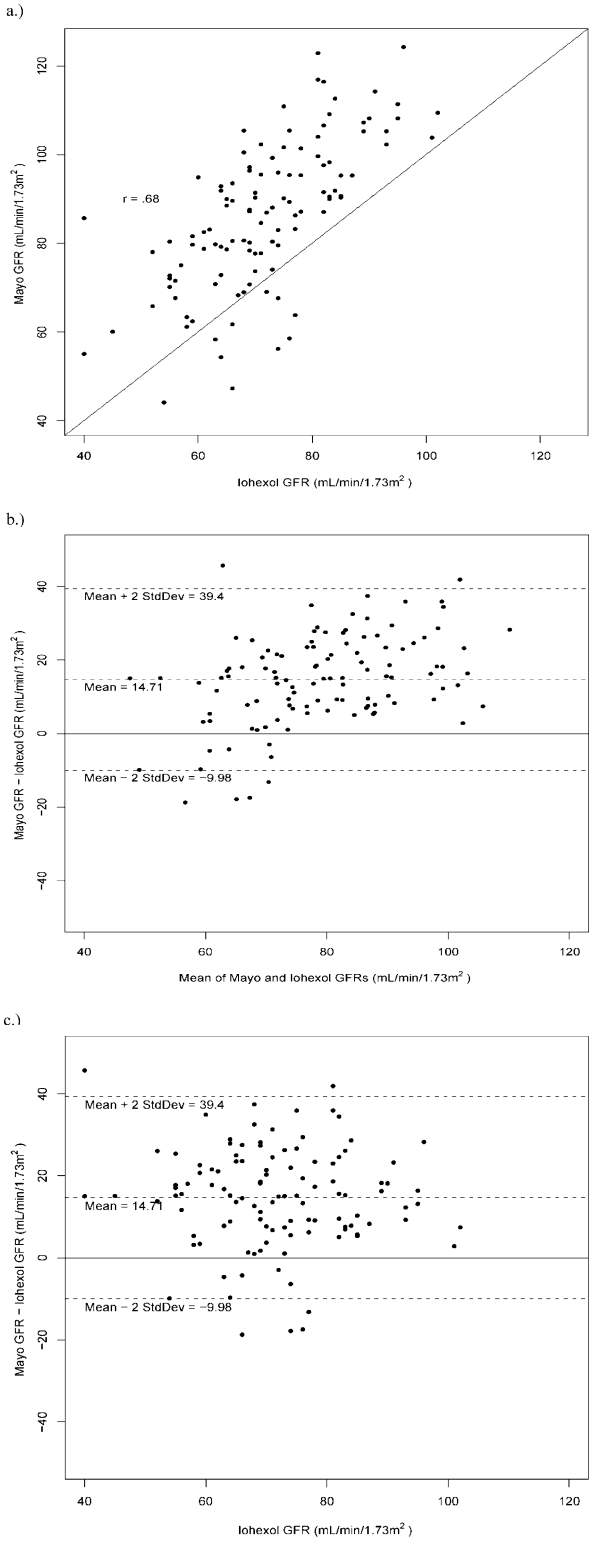

Figure 4: Performance of the Mayo Clinic equation (MCe) against iohexol GFR. (A) Scatter plot of MCe on iohexol GFR with line of unity. (B) Bland–Altman plot. (C) Residual plot of MCe bias against iohexol GFR.

that GFR is preserved in the majority of donors many years after donation.

The CG Cl_{cr} formula was validated in 249 patients ranging in age from 18 to 92 years with a serum creatinine between 0.99 and 1.78 mg/dL in a predominantly male population (96%) with no information about disease status (9). Since the CG formula was designed to predict 24-h creatinine clearance and not GFR, it is not surprising that it performs poorly when used to estimate GFR. The MDRD formula, on the other hand, was developed from 1 628 subjects with a mean age of 50.6 ± 12.7 years (10). It included patients with serum creatinine between 1.2 and 7 mg/dL and purposefully excluded patients with a GFR more than 70–80 mL/min/1.73 m^2 and those with diabetes mellitus. Therefore, its limited utility in the people with history of uninephrectomy from donation, the majority of whom enjoyed a GFR >60 mL/min, is not very surprising. The MCe was developed in 580 healthy individuals and 320 subjects with chronic kidney disease (11). The mean serum creatinine in the latter group was 1.93 ± 0.97 mg/dL. To our knowledge this formula has not been validated in a large cohort other than the one it was derived from and Figure 5 may offer an explanation to why the MCe performs rather poorly.

Why does a need exist for accurate assessment of kidney function in former donors? One needs to consider the possibility that hyperfiltration damage may conspire with the reported normal loss of kidney function with age, may lead to renal damage (25). Numerous but not all cross-sectional studies in healthy humans have shown an age-related decrease in GFR and renal blood flow (26). Histologic studies have also shown that after the fourth decade, the incidence of sclerotic glomeruli increases in otherwise healthy males (27). More importantly, the recent demonstration that even modest reductions in GFR may be associated with an increased risk of cardiovascular disease makes this issue a critical one (28,29). Whether the sole presence of reduction in GFR without the usual clustering of other cardiovascular risk factors leads to an augmented risk has not been proven. In addition, we are unaware of any published data that suggest that kidney donors or individuals with a single kidney have an increased risk of CVD.

Our study has limitations. The overwhelming majority of our donors were white and it included only residents of the greater Minneapolis area. In addition, this is a small study. The utilization of simple random sampling and our additionally planned careful evaluation of at least 20% of all former donors should test the validity of the current findings.

As the number of live donors increases, potential donors need to know the risk of living with one kidney. These data clearly demonstrate that the majority of kidney donors have a very favorable renal course but larger numbers of donors are needed to confirm this finding. Moreover,

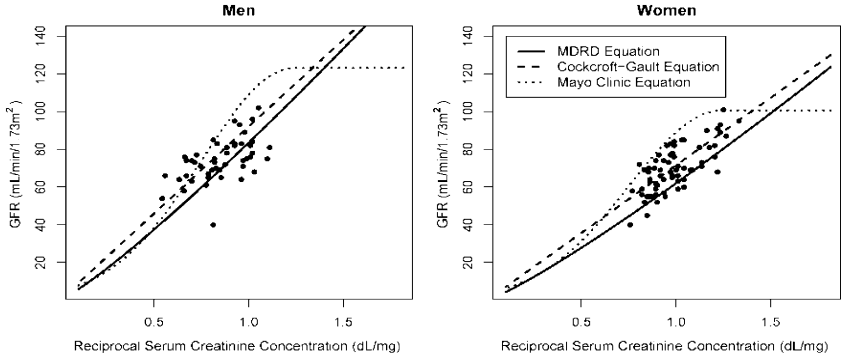

Figure 5: Reciprocal serum creatinine versus GFR for the three prediction models (lines) and iohexol GFR (points) for men and women. The prediction models used median age, weight and body surface area.

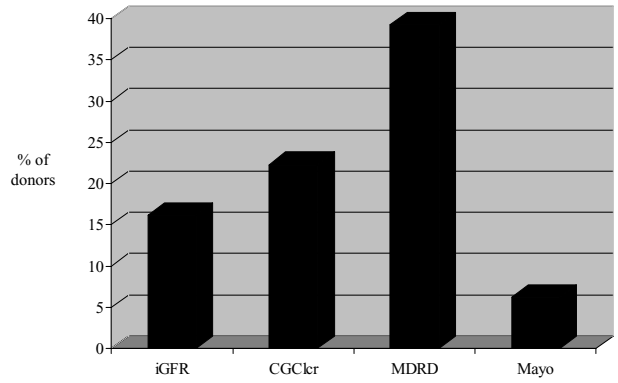

Figure 6: Percentage of donors with GFR < 60 mL/min. iGFR = iohexol GFR; CG Cl_{cr} = Cockcroft–Gault.

using GFR estimation formulas is clearly inferior to measured GFR but with the exception of the MCe, current prediction models are within a reasonable vicinity to actual GFR. Therefore, measuring GFR is probably not warranted in the overwhelming majority of this population and the currently recommended use of the MDRD formula can be extended to people who underwent a uninephrectomy for donation.

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