Imprecision of Creatinine-Based GFR Estimates in Uninephric Kidney Donors

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Background and objectives: To ensure long-term safety of living kidney donors, it is now recommended that they be followed for at least 2 years after donation and that serum creatinine levels be monitored. Such levels are often subjected by clinical laboratories to estimating equations and are reported as estimated GFR (eGFR). The accuracy of such equations in uninephric living donors has yet to be validated. This is especially important in older living donors, who often have senescence-related depression of GFR.

Design, setting, participants, & measurements: We compared urinary creatinine clearance, four-variable Modification of Diet in Renal Disease estimating equation (eGFR), and the recently reported CKD-EPI GFR estimating equation with true GFR measured by the urinary iothalamate clearance (iGFR) in 64 subjects after kidney donation.

Results: Creatinine clearance overestimated iGFR. Both creatinine-based estimating equations were poorly correlated with and underestimated iGFR. More than half of kidney donors had eGFR <60 ml/min per 1.73 m² after donation, a level that categorized them as having stage 3 chronic kidney disease by our current laboratory reporting, whereas only 25% had iGFR <60 ml/min per 1.73 m². This misclassification disproportionately affected older donors age ≥55 years, of whom 80% had eGFR <60 ml/min per 1.73 m². Neither significant albuminuria nor hypertension was observed.

Conclusions: The current practice of reporting eGFR after donation commonly leads to a misclassification of chronic kidney disease, particularly in older donors. To ensure long-term well-being of living kidney donors, more precise estimates of GFR are required, particularly among older potential donors.


The incidence of transplantation from living donors in the United States has nearly doubled over the past decade (1). Since 2001, more than 6000 individuals have made living kidney donations annually, a number that now exceeds that for deceased kidney donors (1). The willingness of transplant teams to accept living kidney donation is largely on the basis of evidence suggesting a safe long-term outcome for the donor (2–4). To ensure such long-term safety, extensive evaluation of donors is routinely performed (5). Such evaluation includes an estimation of GFR, the best overall measure of the functional performance of the kidney.

GFR, measured by the urinary clearance of a true filtration marker (6), is cumbersome and costly and is not available at most transplant centers. Instead, the clearance of endogenous creatinine is typically used as a surrogate measure of GFR. Most centers have arbitrarily selected 80 ml/min per 1.73 m² as a threshold for GFR, below which living donation is not permitted (7). Observations from our own laboratory reveal that for urinary inulin clearance, 80 ml/min per 1.73 m² represents the lower end of the normal range in a large population of healthy individuals younger than 55 years (8). Because creatinine is secreted by the proximal tubule, as well as freely filtered, the creatinine clearance (C\text{crea}) overestimates the GFR and, assuming a lower limit of 80 ml/min per 1.73 m² for this surrogate filtration marker, could well lead to acceptance of kidney donors whose actual GFR is below the normal range. The long-term safety of donation under these circumstances remains to be demonstrated.

Equations derived from the Modification of Diet in Renal Disease (MDRD) study have been widely applied to estimate GFR (eGFR) from serum creatinine and have largely supplanted the urinary C\text{crea} as a method of GFR estimation in practice. Although reporting of eGFR may aid in the early detection of chronic kidney disease (CKD) in persons with elevated serum creatinine concentrations, the application of eGFR to healthy kidney donors may be misleading. Recent studies reported eGFR in a healthy binephric population to be inaccurate (9,10). Moreover, the precision of these equations has not been examined in uninephric kidney donors. In an attempt to refine estimates of GFR, particularly among persons with normal or near normal GFR, a new equation was recently developed (the “CKD-EPI” equation) and is expected to replace the MDRD equation for routine clinical laboratory reporting of eGFR (11). The accuracy of this equation in the living donor population, especially in the elderly, has not been tested.
To ensure the safety of the growing living donor population, United Network for Organ Sharing now requires follow-up and monitoring of the serum creatinine in living kidney donors for at least 2 years after donation (1). Such follow-up of living donors combined with often routine reporting of eGFR by clinical laboratories warrants a careful comparison of such estimating equations against GFR, as determined by clearance of a true filtration marker. In this study, we examined the accuracy of $C_{\text{creat}}$ and the most commonly used abbreviated four-variable MDRD, as well as the new CKD-EPI estimating equation in predicting in living donors after kidney donation the actual GFR, determined by the urinary clearance of the filtration marker, iothalamate (iGFR). Additional analysis compared these results in younger versus older subjects.

**Materials and Methods**

**Patient Population**

All protocols were approved by the Institutional Review Board of Stanford University School of Medicine. The study population was composed of 64 subjects who had previously undergone uninephrectomy for living kidney donation from 5 to 86 months before this study. The median time from donation was 13 months.

A comparison group consisted of a population of 275 patients with various stages of glomerular disease who had undergone inulin clearance as part of a series of studies for progression of glomerular disease. Findings from this group were used to characterize the relationship between serum creatinine and iGFR over the entire range of GFR.

**Measurement of GFR**

All studies were performed in the General Clinical Research Center at Stanford University. GFR was estimated by the urinary iothalamate clearance as described in detail elsewhere (12). Cold iothalamate was given by constant infusion during a state of water diuresis. Four 20-minute urine collections and bracketing plasma were analyzed to determine the iGFR from the urinary clearance of iothalamate. The urinary clearance of endogenous creatinine ($C_{\text{creat}}$) and the urinary albumin/creatinine ratio were determined simultaneously. Mean arterial pressure (MAP) was also determined at the commencement of the clearance study.

An Array 360 System (Beckman Instruments Inc., Brea, CA) was used to measure urinary albumin concentration by rate nephelometry (13). Serum and urinary creatinine levels were determined with a Beckman creatinine analyzer. A second determination of serum creatinine concentration was performed on each patient by the Stanford Hospital clinical laboratory using a similar kinetic assay to minimize noncreatinine peaks. Their age at time of study ranged from 21 to 70 years (median, 48 years). Forty-seven percent were women; 6% were African American, 11% Hispanic, and 19% Asian American. Age at donation ranged from 18 to 67 years (median, 48 years). At screening, all subjects had serum creatinine levels within the normal range and $C_{\text{creat}}$ > 80 ml/min per 1.73 m². The exclusion criteria employed before transplantation include a history of drug or alcohol use, smoking, obesity, hypertension, abnormal glucose tolerance test, body mass index > 30, and proteinuria.

**GFR in Postnephrectomy Donors**

$C_{\text{creat}}$ substantially overestimated iGFR: 91 ± 23 versus 71 ± 16 ml/min per 1.73 m² ($P < 0.0001$), as shown in Figure 1A and Table 1. Whereas the correlation was reasonably strong ($R^2 = 0.62; W = 0.895$), there was a positive bias of +19 ml/min per 1.73 m² (Figure 1B). The interquartile range (IQR) was 11 to 26 ml/min per 1.73 m². The accuracy of $C_{\text{creat}}$, as judged by being within 10% of iGFR, was only 11% (Table 1). $C_{\text{creat}}$ failed to identify 13 of 16 patients whose iGFR fell below a threshold of 60 ml/min per 1.73 m², which has been used to classify stage 3 CKD (Figure 1A) (17).

The eGFR underestimated iGFR in uninephric donors: 61 ± 15 versus 71 ± 16 ml/min per 1.73 m² ($P < 0.0001$). As shown in Figure 2A, the correlation between the two values was relatively weak ($R^2 = 0.38; W = 0.830$). As shown in Figure 2B and Table 1, a negative bias was −10 ml/min with an IQR of −18 to −1 ml/min per 1.73 m². The eGFR was within 10% of iGFR in only 25% of subjects (Table 1). More than half of these subjects (35 of 64) had an eGFR < 60 ml/min per 1.73 m², although only 25% (16 of 64) had iGFR < 60 ml/min per 1.73 m² (Figure 2A).

Similar to the MDRD eGFR, the CKD-EPI equation also underestimated iGFR. Again, the correlation between the two values was relatively weak ($R^2 = 0.42; W = 0.836$), although slightly better than the MDRD eGFR (Figure 3A). A negative bias was −9 ml/min per 1.73 m² with an IQR of −16 to +1 ml/min per 1.73 m² (Table 1). Once again, only 25% of subjects were within 10% of iGFR. More than half of the subjects (33 of 64) had an eGFR < 60 ml/min per 1.73 m² versus only 16 of 64 with iGFR < 60 ml/min per 1.73 m² (Figure 3A).

Two subjects had borderline microalbuminuria, 32 and 38 mg/g creatinine, despite iGFR above 60 ml/min per 1.73 m²: 82 and 62 ml/min per 1.73 m², respectively. Each of the

**Statistical Analyses**

All data are expressed as mean ± SD. Linear regression analysis was used to determine the relationship between $C_{\text{creat}}$ or eGFR and iGFR. Standard assumptions for linear regression were met. The concordance coefficient was calculated to assess the degree of correlation between the various estimating equations and iGFR. Bias and the interquartile ranges were calculated. The precision of the estimating equations was expressed as root mean square error, and accuracy was expressed as % estimating equation within 10% and 30% of iGFR. Residual plots were determined (15,16). Nonlinear regression analysis was used to characterize the relationship between serum creatinine levels and iGFR.

**Results**

Sixty-four kidney donors were studied a median time of 13 months after transplantation, with a range of 5 to 86 months. Their age at time of study ranged from 21 to 70 years (median, 48 years). Age at donation ranged from 18 to 67 years (median, 48 years). At screening, all subjects had serum creatinine levels within the normal range and $C_{\text{creat}}$ > 80 ml/min per 1.73 m². The exclusion criteria employed before transplantation include a history of drug or alcohol use, smoking, obesity, hypertension, abnormal glucose tolerance test, body mass index > 30, and proteinuria.

The abbreviated four-variable MDRD eGFR was calculated as follows (14):

$$\text{eGFR} / 1.73 \ m^2 = 186 \times \text{SCr}^{-1.154} \times \text{Age}^{-0.203} \times 0.742 \ (\text{if female}) \times 1.21 \ (\text{if black})$$

where SCr is the serum concentration performed by the Stanford clinical laboratory.

The CKD-EPI equation was calculated according to the equations published by Levey et al. (11)
remaining 62 subjects had negligible or unmeasurable albuminuria (<30 mg/g creatinine). None of the 64 subjects was hypertensive, with mean MAP of 89 ± 11 mmHg.

**Older Donors and eGFR**

On average, iGFR was significantly lower in older (>55 years) than younger (<55 years) subjects, 58 ± 15 versus 77 ± 15 ml/min per 1.73 m², respectively (P < 0.001). The iGFR was <60 ml/min per 1.73 m² in 52% of older donors versus only 8% of younger donors (Figures 1 through 3 and Table 2), suggesting a substantial incidence of CKD in the former, using the MDRD definition. Among older donors, 80% had eGFR <60 ml/min per 1.73 m², compared with only 38% of the younger group (Table 2). By our current clinical labora-

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**Table 1. Bias, accuracy, and precision of estimating equations**

<table>
<thead>
<tr>
<th>Estimation Method</th>
<th>Median Bias</th>
<th>IQR</th>
<th>Within 10% of iGFR, % (n)</th>
<th>Within 30% of iGFR, % (n)</th>
<th>RMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{creat}</td>
<td>19</td>
<td>11 to 26</td>
<td>11 (7)</td>
<td>53 (34)</td>
<td>10.1</td>
</tr>
<tr>
<td>MDRD eGFR</td>
<td>-10</td>
<td>-18 to -1</td>
<td>25 (16)</td>
<td>84 (54)</td>
<td>12.8</td>
</tr>
<tr>
<td>CKD-EPI eGFR</td>
<td>-9</td>
<td>-16 to 1</td>
<td>25 (16)</td>
<td>84 (54)</td>
<td>12.4</td>
</tr>
</tbody>
</table>

IQR, interquartile range; RMSE, root mean square error.
tory reporting practices, these patients are routinely reported as having CKD stage 3. None of the subjects had eGFR < 30 ml/min per 1.73 m². If the CKD-EPI eGFR was applied, 76% of the older living donors and 36% of younger donors would be reported as having CKD stage 3 (Table 2).

Serum Creatinine versus GFR in Kidney Donors Relative to Patients with CKD

In recent years, we have measured GFR using a true filtration marker (inulin or iothalamate) in 275 patients with chronic glomerular disease. We have used a smoothing spline regression technique to fit the individual points for serum creatinine versus iGFR. The fitted regression line (Figure 4, solid line) confirms the well-known hyperbolic relationship between these two quantities when the data points (gray “x” symbols) span the entire biologic range of GFR. In Figure 4, we have superimposed the corresponding data points after transplantation for our uninephric donors (black circles). Over the moderately depressed iGFR range in uninephric posttransplantation donors, the inverse relationship is only minimal, with a slope -0.0077, an intercept of 1.64, and a relatively weak correlation with $R^2 = 0.209$. The absence of a substantial inverse relationship between serum creatinine and iGFR in the uninephric living donor population explains the poor correlation between eGFR and iGFR in this setting.

Discussion

Living donor kidney transplantation now comprises 40% of all kidney transplantations. Studies of long-term donor safety have concluded that carefully screened living donors are not at increased risk of mortality or significant morbidity (2,3,18). However, the demography of living donors has been steadily changing, with an increasing trend toward the use of older and medically complex living donors (19,20). For example, the number of living donors age 50 years or older almost doubled from 853 in 1998 to 1561 in 2008, corresponding to an increase from 19% to 25% of all living donors (1). Recognizing the increased acceptance of and willingness for living donation by the general population, an effort is being made by the transplant community to better define long-term health outcomes of living donation. An example of this is the recent United Network for Organ Sharing guideline to follow-up and monitor serum creatinine.

Table 2. Prediction of CKD in older and younger donors

<table>
<thead>
<tr>
<th>Method of measurement</th>
<th>GFR &lt; 60 ml/min per 1.73 m²</th>
<th>Age &lt; 55 yr, %</th>
<th>Age ≥ 55 yr, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{creat}}$</td>
<td>3</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>MDRD eGFR</td>
<td>38</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>CKD-EPI eGFR</td>
<td>36</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>iGFR</td>
<td>8</td>
<td>52</td>
<td></td>
</tr>
</tbody>
</table>

$C_{\text{creat}}$, creatinine clearance; iGFR, iothalamate GFR.
levels of living donors in their transplant center for at least two years after donation (21).

The convention in most transplant programs is to select living kidney donors on the basis of a value for GFR that is above 80 ml/min per 1.73 m² (5), and reports of long-term safety of living donors have been on the basis of populations screened by this traditional guideline. We have determined GFR by inulin clearance in healthy individuals. Among those younger than 55 years (n = 133), a value of 80 ml/min per 1.73 m² represents the sixth percentile (8). Among healthy individuals age >55 years (n = 29), however, 80 ml/min per 1.73 m² represents the 49th percentile. Thus, fully one half of potential older donors are predicted to have a GFR below the conventional threshold for donor acceptance, a phenomenon that is not recognized because of an overestimation of GFR by C_{crea} which is used as a surrogate in most transplant centers. The significantly lowered GFR evident in older potential donors reflects the phenomenon of renal senescence, in which GFR depression is associated with a loss of filtration capacity attributable to glomerulopenia (8). We submit that the posttransplantation reduction of iGFR in older donors in this study also likely reflects renal senescence.

A substantial impediment to using iGFR to identify the development of CKD after living kidney donation is that the performance of urinary clearance of a filtration marker is time-consuming and not widely available. As discussed above, creatinine secretion leads to a systematic overestimate of iGFR by C_{crea} (6) and could obscure the detection of subjects whose iGFR may fall to values in the CKD range after transplantation.

On the other hand, using eGFR, either by MDRD or CKD-EPI equations, does not provide a reasonable solution to this dilemma. Underestimation of the iGFR by eGFR during such follow-up of subjects after donation has led to increased categorization by many clinical laboratories of donors with values <60 ml/min per 1.73 m² as having stage 3 CKD (17,22). This study reveals that because of adaptive hyperfiltration, iGFR is actually >60 ml/min per 1.73 m² after donation in most patients ≥55 years of age (Figures 2A and 3A), notwithstanding the finding that the vast majority (80%; Table 2) have an eGFR that labels them as having CKD. Among those older posttransplantation donors with iGFR 50 to 60 ml/min per 1.73 m², the absence of albuminuria and hypertension suggests that a GFR within this range is unlikely to indicate clinically meaningful CKD. Adaptive hyperfiltration after uninephrectomy has been shown to elevate iGFR in the remaining kidney by approximately 33% (23–25). Thus, an older donor with a pretransplantation GFR of 80 to 90 ml/min per 1.73 m² (i.e., 40 to 45 ml/min per 1.73 m² per kidney) would be expected to increase GFR in the remaining kidney to a postdonation value of 50 to 60 ml/min per 1.73 m². We suspect that this range of iGFR is likely to represent an adequate compensatory response to uninephrectomy and to portend a satisfactory long-term outcome in an older donor (26).

There has been increasing debate over the validity of the widespread use of eGFR in the general population (26–31). A particular concern is that eGFR <60 ml/min per 1.73 m² after donation could mislabel perfectly healthy uninephric individuals, converting them to the “worried-well” (27). One possible source of the imprecision of the eGFR in this study is our failure to calibrate the assay of serum creatinine to that of the Cleveland Clinic reference laboratory (32–36). The majority of the samples used in this study were obtained before the calibration of assays across the United States to the sample provided by the National Institute of Standards and Technology (NIST). Another and, we suspect, more important cause of imprecision is the relationship between serum creatinine levels and GFR in those with normal or near normal renal function. The fitted regression line of GFR versus serum creatinine in subjects with chronic glomerular disease (Figure 4, solid line) confirms the well-known hyperbolic relationship between these two quantities when the data points (gray “x” symbols) span the entire biologic range of GFR. Superimposition of corresponding data points for follow-up iGFR after transplantation in our uninephric donors (black circles) demonstrates that over the observed GFR range there is a minimal inverse relationship between serum creatinine and GFR. The failure of the MDRD and other estimating equations to reliably predict GFR from serum creatinine in apparently healthy transplant donors is therefore not surprising. This is in contrast to GFR predictions by MDRD and other estimating equations in persons with moderate or advanced CKD, the population from which the MDRD equation was derived (iGFR 25 to 55 ml/min per 1.73 m²). Inspection of Figure 4 reveals that over the MDRD study range of iGFR, the serum creatinine-to-GFR relationship occupies the steep part of the hyperbolic curve.

Conclusions

We submit that eGFR cannot be expected to accurately predict iGFR when the latter is in the upper part of the biologic range, and that the practice of predicting GFR from eGFR in living donors should be abandoned (26).

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Disclosures

None.

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Access to UpToDate on-line is available for additional clinical information at http://www.cjasn.org/