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ORIGINAL ARTICLE

The performance of three estimates of glomerular filtration rate before and after live donor nephrectomy

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Summary

Serum creatinine-based estimates of glomerular filtration rate (GFR) are inaccurate in healthy individuals. Therefore, their use in assessment prior to live donor nephrectomy has been restricted. There are less data on their use postdonor nephrectomy. This study assessed three GFR estimates against Cr^{51} EDTA radioisotope GFR (iGFR) in the same cohort of patients before and after donor nephrectomy. A total of 206 patients underwent iGFR measurement prior to donor nephrectomy and this was repeated in 187 patients 6–8 weeks postsurgery. The iGFR was compared with the modification of diet in renal disease (eGFR), Cockcroft–Gault (cgGFR) and Mayo Clinic equation (mcGFR) estimates of GFR. Preoperatively, all GFR estimates performed poorly against iGFR; however, mcGFR provided the most reliable estimate. The eGFR underestimated iGFR by 23.60 ± 16.43 ml/min/1.73 m^2, cgGFR by 15.54 ± 18.13 ml/min/1.73 m^2 and mcGFR overestimated by 0.72 ± 18.11 ml/min/1.73 m^2. Postdonation, all estimates again performed poorly, but eGFR and mcGFR outperformed cgGFR. The eGFR underestimated iGFR by 9.13 ± 10.11 ml/min/1.73 m^2, mcGFR by 9.44 ± 13.80 ml/min/1.73 m^2 and cgGFR overestimated by 6.42 ± 14.49 ml/min/1.73 m^2. No GFR estimate performed sufficiently well to supersede iGFR measurement prior to donor nephrectomy. Performance postdonation was little better. In addition, there was no correlation between fall in iGFR and fall in GFR estimates postdonation.

Introduction

The widespread use of estimated glomerular filtration rate (GFR) in clinical practice came about following recommendations by the Kidney Disease Improving Global Outcome (KDIGO) organization in 2004, whose aim was to provide a global definition and classification of chronic kidney disease (CKD). KDIGO recommended the use of estimated GFR using the formula derived from the Modification of Diet in Renal Disease (MDRD) study [1]. This recommendation recognized the drawbacks of using serum creatinine as a measurement of glomerular filtration rate. First, there is significant inter- and intra-individual variability in serum creatinine concentrations because of varying creatinine production. In addition, as GFR declines, tubular secretion of creatinine increases resulting in normal serum creatinine levels even with a GFR of 60 ml/min/1.73 m^2 [2]. Therefore, the use of estimated GFR has important advantages, but does in itself have limitations.

The two principal equations for estimated GFR in clinical use are the MDRD and Cockcroft–Gault equations. Both of these have been shown to underestimate significantly GFR above approximately 60 ml/min/1.73 m^2 and to overestimate markedly GFR below 20 ml/min/1.73 m^2 and in the presence of heavy proteinuria [3–7]. This is a reflection of the original population from which the formulas were derived; the MDRD study included mainly Caucasian, non-diabetics with a GFR of around 40 ml/min/1.73 m^2. In addition, the Cockcroft–Gault equation estimates creatinine clearance rather than GFR and, unlike the MDRD equation, is not normalized to a body surface

area (BSA) of 1.73 m^2. Further debate surrounds which equation performs better, with no consensus from the published literature.

This has implications in the preoperative work up of potential live kidney donors. To maximize donor safety and recipient outcome following live donor nephrectomy, it is vital that preoperative donor GFR is accurately measured. This ensures that the donor is left with sufficient renal reserve and that the recipient benefits from a graft with adequate functional capacity. The current standard for measuring GFR preoperatively remains radioisotope clearance. Unfortunately, this method is expensive, cumbersome and time-consuming, as well as exposing patients to the risks of radioactivity. However, the limitations of estimated GFR equations described above have particular relevance in this patient group. A number of studies have shown creatinine-based estimates of GFR such as the MDRD and Cockcroft–Gault equations to be inaccurate in the setting of live kidney donation [3–5,8,9]. This is not surprising given this is a population of healthy individuals and the equations for GFR estimation were mostly derived in patients with CKD.

In contrast, there are little data, and subsequently little consensus, on the best method of assessing kidney donors' GFR postnephrectomy. Nevertheless, this remains important if we are to identify accurately those with borderline renal function who require close follow-up and attention to cardiovascular risk factors.

This study aimed to compare the performance of creatinine-based GFR estimates with Cr^{51} EDTA radioisotope GFR (iGFR) measurement in the same cohort of patients both before and soon after live donor nephrectomy.

Patients and methods

All 203 patients undergoing donor nephrectomy in Leicester between January 2000 and December 2007 were included in this study. All patients underwent iGFR prior to surgery. iGFR was measured using the plasma clearance of Cr^{51} EDTA. Patients were limited to clear oral fluids for 12 h prior to testing. Following informed consent, 3 MBq of Cr^{51} EDTA was administered via a peripheral vein using a winged needle infusion set. Four timed venous blood samples were then taken at 2, 2.5, 3 and 4 h post injection from the arm contralateral to the infusion. iGFR was calculated using the slope-intercept method and corrected for a BSA of 1.73 m^2 [10].

A blood sample was taken at the same visit and serum creatinine obtained. GFR estimates were performed using the following equations:

4-variable modification of diet in renal disease GFR (eGFR) [11]

$$1.863 \times (S_{Cr}/88.4)^{-1.154} \times age^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$$

Cockcroft–Gault creatinine clearance (cgGFR) [12]

$$\frac{(140 - age) \times weight \times 1.2}{S_{Cr}} \times (0.85 \text{ if female})$$

Mayo Clinic Equation (mcGFR) [3]

$$\exp(1.911) + \frac{5.249}{(S_{Cr}/88.4)} - \frac{2.114}{(S_{Cr}/88.4)^2} - 0.00686 \times age - (0.205 \text{ if female})$$

To allow accurate comparison between iGFR and cgGFR, the cgGFR was normalized for a BSA of 1.73 m^2.

A majority of patients ($n = 187$) underwent repeat iGFR using the same method between 6 and 8 weeks following surgery. Again, height and weight were measured at the same visit and blood sample was taken for serum creatinine estimation. GFR estimates were repeated using the formulae above.

All data were prospectively collected on either the renal unit database or a specific donor nephrectomy database.

Statistical analysis

The performance of each GFR estimation against isotope GFR was assessed in the following ways.

- Bias: $\sum$(estimated GFR − iGFR)/no. of GFR studies performed.
- Precision: coefficient of determination (R^2).
- Relative accuracy: percentage of estimates falling within 10%, 30% and 50% of isotope GFR.

The bias was represented graphically using the Bland–Altman plot [13]. This analysis also calculates the limits of agreement (mean bias ± 1.96 × SD of bias). For any future sample, the difference between measurements using these two assay methods should lie within the limits of agreement approximately 95% of the time.

Unless otherwise stated, data are presented as mean ± standard deviation. Statistical analysis was performed using GRAPHPAD PRISM 5 (GraphPad Software Inc., San Diego, CA, USA). All tests were two-tailed and $P < 0.05$ was taken as statistically significant.

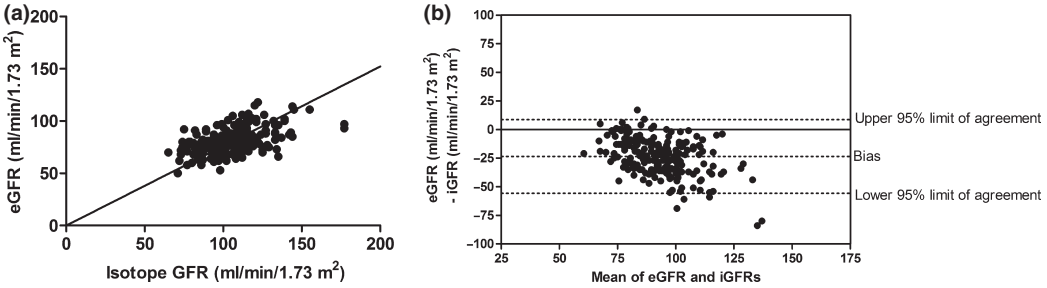
Results

The mean age at donation was 47 (±10.8) years and the mean body mass index 26.6 (±4.6). Men comprised 40% of donors. Mean preoperative iGFR was 105 (±19.0) ml/min/1.73 m^2. Mean postoperative iGFR was 65 (±10.2) ml/min/1.73 m^2.

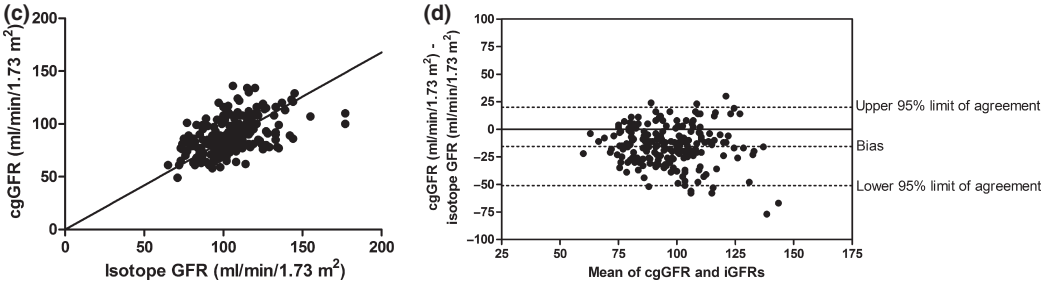
Performance of each of the preoperative GFR estimates against preoperative iGFR can be seen in Table 1 and

Table 1. Performance of serum-creatinine based glomerular filtration rate (GFR) estimates against Cr^{51} EDTA isotope GFR prior to live donor nephrectomy.

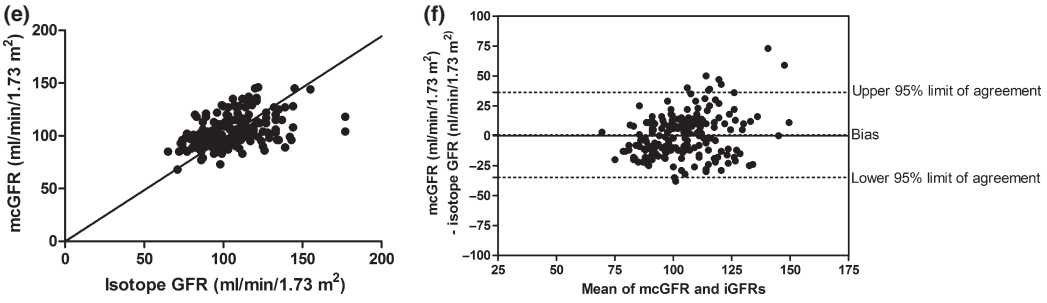
GFR Estimate	Bias	SD of bias	Upper 95% limit of agreement	Lower 95% limit of agreement	R^2	Within 10% of iGFR (%)	Within 30% of iGFR (%)	Within 50% of iGFR (%)
eGFR	−23.60	16.43	8.61	−55.81	0.27	16.3	51.7	81.2
cgGFR	−15.54	18.13	20.00	−51.09	0.25	27.0	54.4	89.3
mcGFR	0.72	18.11	36.23	−34.77	0.19	43.8	90.6	97.0



Performance of pre-operative eGFR vs. iGFR. (a) Scatter plot of eGFR on iGFR with regression line (R^2 = 0.27). (b)Bland-Altman Plot.



Performance of pre-operative cgGFR vs. iGFR. (c) Scatter plot of cgGFR on iGFR with regression line (R^2 = 0.25). (d)Bland-Altman Plot.



Performance of pre-operative mcGFR vs. iGFR. (e) Scatter plot of mcGFR on iGFR with regression line (R^2 = 0.19). (f)Bland-Altman Plot.

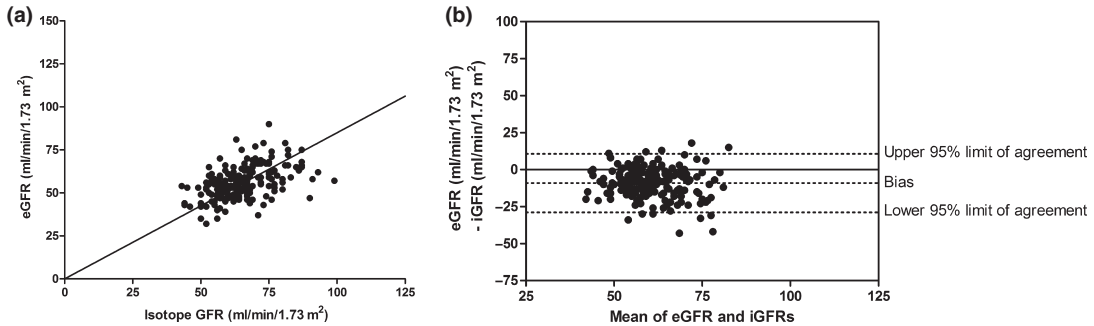
Figure 1 The performance of creatinine-based estimates of glomerular filtration rate (GFR) vs. Cr^{51} EDTA isotope GFR (iGFR) prior to live donor nephrectomy.

Fig. 1. eGFR underestimated iGFR by 23.6 ml/min/1.73 m^2, cgGFR underestimated by 15.54 ml/min/1.73 m^2 and mcGFR overestimated iGFR by 0.72 ml/min/1.73 m^2. Correlation was significant between each GFR estimate and iGFR ($P < 0.001$ for each). Overall, mcGFR appears to best estimate iGFR in this setting, although eGFR was more precise. Interpretation of the Bland–Altman plots demonstrates that the accuracy of all three GFR estimates improve as GFR falls, with the scatter of the data tending to decrease as the mean of the GFR estimates and iGFR (x axis) falls

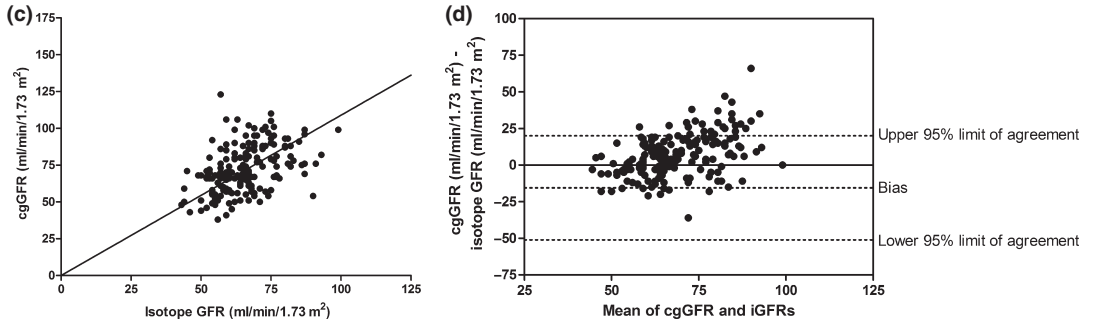
Table 2 and Fig. 2 outline performance of the GFR estimates against iGFR postoperatively. In this setting, eGFR underestimated iGFR by 9.13 ml/min/1.73 m^2, cgGFR

Table 2. Performance of serum-creatinine based glomerular filtration rate (GFR) estimates against Cr^{51} EDTA isotope GFR following live donor nephrectomy.

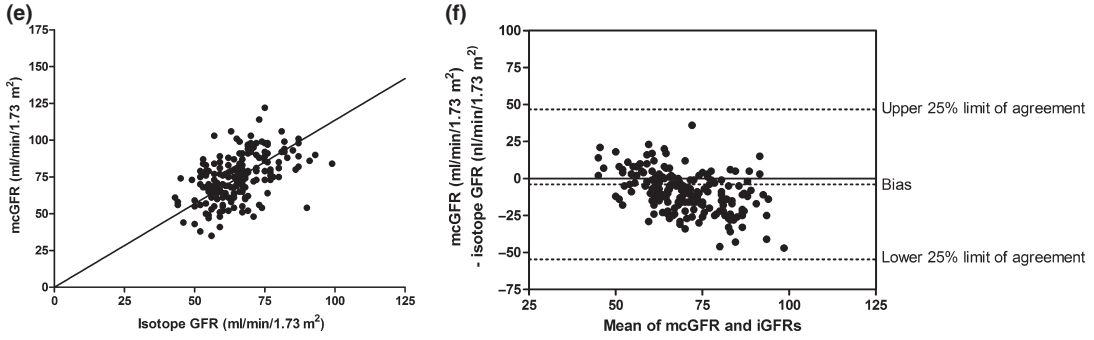
GFR Estimate	Bias	SD of bias	Upper 95% limit of agreement	Lower 95% limit of agreement	R^2	Within 10% of iGFR (%)	Within 30% of iGFR (%)	Within 50% of iGFR (%)
eGFR	−9.13	10.11	10.68	−28.94	0.22	28.8	77.0	92.5
cgGFR	6.42	14.49	34.83	−21.99	0.21	36.4	89.3	98.9
mcGFR	−9.44	13.80	17.61	−36.49	0.24	32.1	85.6	98.9



Performance of post-operative eGFR vs. iGFR. (a) Scatter plot of eGFR on iGFR with regression line (R^2 = 0.22). (b)Bland-Altman Plot.



Performance of post-operative cgGFR vs. iGFR. (c) Scatter plot of cgGFR on iGFR with regression line (R^2 = 0.21). (d)Bland-Altman Plot.



Performance of post-operative mcGFR vs. iGFR. (e) Scatter plot of mcGFR on iGFR with regression line (R^2 = 0.24). (f)Bland-Altman Plot.

Figure 2 The performance of creatinine-based estimates of glomerular filtration rate (GFR) vs. Cr^{51} EDTA isotope GFR (iGFR) following live donor nephrectomy.

overestimated iGFR by 6.42 ml/min/1.73 m^2 and mcGFR underestimated by 9.44 ml/min/1.73 m^2. Again, correlation was significant between each GFR estimate and iGFR ($P < 0.001$ for each). Overall, eGFR and mcGFR best estimated iGFR with eGFR being least biased and most precise, but mcGFR having the best relative accuracy.

To make a combined evaluation of the preoperative and postoperative performances of each GFR estimate,

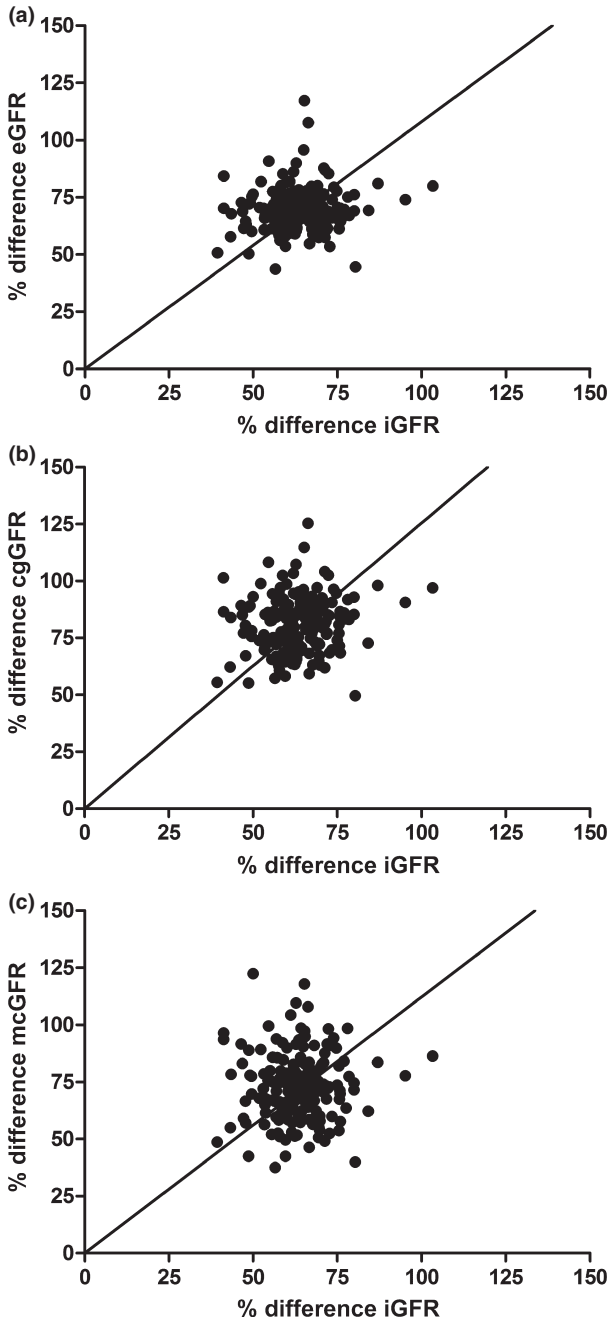


Figure 3 Scatter plots of percentage difference in preoperative and postoperative serum-creatinine based glomerular filtration rate (GFR) estimates vs. Cr^{51} EDTA isotope GFR with regression lines. (a) eGFR (R^2 = 0.01); (b) cgGFR (R^2 = 0.02); (c) mcGFR (R^2 = 0.001).

the postoperative GFR estimates as a percentage of preoperative GFR estimates were compared against that between iGFRs (Fig. 3). On average, postoperative iGFR was 63(±9.2)% of preoperative iGFR; for eGFR this figure was 69(±9.1)%, for cgGFR 81%(±12.0%) and for mcGFR 61(±14.5)%. There was no correlation between postoperative GFR estimates as a percentage of preoperative GFR estimates for eGFR ($R^2 = 0.01$, $P = 0.1019$), cgGFR ($R^2 = 0.02$, $P = 0.0502$) or mcGFR ($R^2 = 0.001$, $P = 0.5496$) against iGFR.

Table 3. Chronic kidney disease (CKD) stage of live donors following nephrectomy as determined by Cr^{51} EDTA isotope GFR and serum-creatinine based GFR estimates.

CKD stage	iGFR	eGFR	cgGFR	mcGFR
1 (GFR > 90)	4 (2)	1 (1)	53 (26)	41 (20)
2 (GFR 60–89)	123 (66)	67 (33)	113 (56)	127 (63)
3 (GFR 30–59)	60 (32)	135 (66)	37 (18)	35 (17)
4 (GFR 15–29)	0	0	0	0
5 (GFR < 15)	0	0	0	0

Figures in brackets are percentages.

Table 3 outlines the proportion of donors fulfilling the criteria for the diagnosis of CKD postnephrectomy using each GFR estimate and iGFR. The differences seen were statistically significant ($\chi^2 = 199.9$, $P < 0.0001$).

Discussion

This is, to our knowledge, the first study to evaluate the performance of GFR estimates against isotope GFR in the same cohort of patients both before and after donor nephrectomy.

Accurate measurement of GFR during workup of patients for donor nephrectomy is vital for two main reasons. First, to ensure that the donor is left with adequate residual renal function and second to ensure that the recipient receives a kidney with adequate functional capacity. This second point is particularly important, as low GFR in the donor has been shown to be an independent risk factor for graft loss [14]. In addition, some donors with falsely low GFR measurements may be inaccurately precluded from donating.

Previous studies have shown that GFR estimates perform poorly against isotope GFR in healthy individuals such as those being assessed for donor nephrectomy. The MDRD formula (eGFR) consistently underestimates GFR by between 9 and 29 ml/min [3–5,8,9], a finding confirmed in this study. The performance of cgGFR against is less consistent, with one study showing that it overestimates iGFR [4] and some that it underestimates it [5,9]. The present study is in agreement with the latter, finding cgGFR to underestimate iGFR in patients predonor nephrectomy. Fewer studies have investigated the performance of mcGFR; however, Rule *et al.* [3] demonstrated that it performed better within the normal serum creatinine range than eGFR, a finding confirmed in this study.

Despite mcGFR providing the best estimate of iGFR in preoperative patients in this study, the precision and

relative accuracy remain poor. Overall, the authors do not feel the performance of mcGFR justifies its use over iGFR measurement in the preoperative assessment of potential live kidney donors.

There is less information in the literature on the role of isotope GFR measurement in patients following donor nephrectomy. Ibrahim *et al.* compared iohexol GFR with eGFR, cgGFR and mcGFR in donors at various time points postnephrectomy, finding eGFR to be the best estimate. This is partly at odds with the findings of the current study, which shows eGFR to be least biased and have the narrowest limits of agreement, but mcGFR to be most precise and have the best relative accuracy.

It is of interest that each GFR estimate performs differently prior to and following nephrectomy, with the cgGFR in particular underestimating preoperatively and overestimating postoperatively. The reasons for this are not clear, but it is presumably a reflection of the GFR in the populations from which the original formulae were derived. Intuitively, one would expect the performances to improve as GFR falls, as is the case with eGFR and cgGFR, which become less biased and more accurate following nephrectomy.

The poor performance of the GFR estimates postoperatively brings into question the current practice of relying on these measures rather than on isotope GFR. The main role of GFR measurement postoperatively is to identify those patients with impaired renal function, who need closer follow-up to ensure no further deterioration in renal function and to manage cardiovascular risk factors. As shown in Table 3, there were significant differences in the CKD staging postnephrectomy depending on which GFR measurement was used. As can be seen, using eGFR would label over twice as many donors as CKD stage III when compared with using iGFR. This has important implications if eGFR is used in the postoperative evaluation of live kidney donors. First, it is likely to create unnecessary worry for those donors inaccurately labelled as stage III. Secondly, it will increase the burden on personnel in nephrology services who are often asked to follow up donors with a low GFR.

However, there is some controversy surrounding the use of CKD staging in live kidney donors. Some argue that they represent an entirely separate group as they seldom develop the metabolic, haematological or micro-inflammatory changes associated with CKD, the decline in renal function does not tend to be progressive and significant comorbidities are generally absent [15]. In addition, it is debatable whether having a single kidney fulfils the definition of kidney damage which has to be present in CKD 1 and 2.

What is not clear is whether kidney donation increases the risk of future cardiovascular events, and whether there is an increased risk of progressive kidney disease. Certainly, the prevalence of hypertension in one large cohort of donors postnephrectomy was 32% and of abnormal proteinuria was 13% [16]. Given the known association between hypertension and proteinuria and future cardiovascular events, one might expect these to be increased in live kidney donors. As no prospective long-term follow-up study of a large group of donors has been performed, the evidence to support or refute this hypothesis is not available.

The other advantage of accurate postdonation GFR measurement is that, with a large enough patient cohort, it allows analysis of factors affecting the reduction in GFR. In this study, percentage difference in iGFR predonation and postdonation varied from 39% to 103%. If we were able to predict those donors at risk of a greater fall in GFR postdonation, it would allow more informed selection of donors.

The strengths of this study are that all data were collected prospectively. It also includes a large number of patients; indeed, this appears to be the largest reported cohort of donors to undergo iGFR measurement postnephrectomy. The method of iGFR measurement is also regarded as very reliable and an acceptable alternative to inulin clearance, the absolute gold standard [17,18].

Weaknesses of the study are that not all patients underwent postoperative iGFR testing and that this measurement was only undertaken at one timepoint. It is possible that findings at, for example, 1 year postdonation would differ from those seen. In addition, this study only used GFR as a measure of renal function, without taking tubular secretion into account. One of the proposed mechanisms of compensation in patients with single kidneys is that tubular secretion increases to counteract the fall in GFR. Measurement of renal clearance of creatinine would have provided more information in this regard. It is also arguable that measuring GFR in absolute values (ml/min) is safer than using a GFR value normalized for BSA (ml/min/1.73 m^2). If a donor with a small BSA is giving a kidney to a recipient with a large BSA, the normalized GFR will mask the situation by overstating the GFR of the donor. This situation will be more detrimental to the recipient, who may not receive a kidney with the necessary functional capacity for their body size. Finally, it can be argued that Cr^{51} EDTA has never convincingly been shown to be as reliable a technique for measuring GFR as inulin clearance. This analysis, however, compares three GFR estimates with a suboptimal, but acceptable measurement technique, which allows at least positioning of the performance of the equations among each other.

In conclusion, this study demonstrates that GFR estimates do not perform sufficiently well to justify their use

in the preoperative assessment of GFR in potential live kidney donors. Postoperative GFR estimates also performed poorly. The authors feel that postnephrectomy iGFR measurement is justified by these findings. This allows accurate identification of those donors with a low GFR, who require closer monitoring of renal function and cardiovascular risk factors. Nevertheless, iGFR measurement does expose donors to radiation and inconvenience. An acceptable compromise may therefore be to perform iGFR in those donors found to have a low estimated GFR postnephrectomy.

Authorship

ADB: designed study, collected and analysed data, wrote manuscript. AHT: collected and analysed data. RE: designed study, collected data. ASB and JM: collected data. MN: designed study, wrote manuscript.

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