Implications of predonation GFR to recipient and donor outcomes

Connie J. Wang¹, James B. Wetmore² and Bertram L. Kasiske²

Correspondence and offprint requests to: Bertram L. Kasiske; E-mail: kasis001@umn.edu

Enthusiasm for living kidney donation has grown considerably over the past two decades as an ever-expanding waiting list demand has outstripped organ supply, while the number of living kidney donations in the USA has more than doubled during that time to nearly 6000 in 2011 [1], this growth is largely attributable to an increase in older donors (those aged 54 and above), who tend, on average, to have lower kidney function. Therefore, the implications of lower predonation kidney function on graft outcomes are increasingly relevant, and require careful scrutiny.

Concern over the use of kidneys from donors with low glomerular filtration rate (GFR) was triggered by a seminal study from Norden et al. [2], which showed that the hazard ratio (HR) for graft loss was more than double when predonation GFR, as measured by ⁵¹Crom EDTA, was <80 mL/min/1.73 m². Despite the small number of patients studied (26 recipients with donor GFR <80 mL/min/1.73 m²), this study became, in part, the basis for requiring a predonation GFR of >80 mL/min/1.73 m². This threshold was subsequently adopted by most transplant centers and many guidelines [3–5]. However, a retrospective study examining 2057 living kidney transplantations from Norden et al. [6], reported in this issue, has yielded different results. These investigators found that the HR’s for graft loss and patient death after 6 years of follow-up were no different between individuals who received donor kidneys with an eGFR above or below 80 mL/min/1.73 m². Furthermore, they were unable to detect an association between increasing eGFR and improved outcomes when they stratified donor eGFR in 10 mL/min/1.73 m² increments (from < 80 to >110 mL/min/1.73 m²). These findings raise questions about current consensus-based predonation GFR recommendations.

Studies of the association between predonation measured GFR (mGFR) and graft outcomes have yielded inconsistent results, likely due to variation in study design, GFR measurement, follow-up duration and outcome ascertainment. Norden et al. [2] observed worse long-term (>5 years) graft survival when predonation mGFR was lower, while Lezaic et al. [7] failed to demonstrate such a difference (Table 1). The studies varied somewhat in their treatment of predonation mGFR: the former used a cutoff of 80 mL/min/1.73 m² [2], while the latter used 50 mL/min/1.73 m², albeit in a single kidney [7]. Four other studies examined the effect of GFR on subsequent allograft function [using eGFR or creatinine clearance (CrCl)]. Three showed an association between low predonation kidney function and worse graft function [8–10], while one did not [11]. Thus, the balance of the historical evidence has suggested that predonation kidney function influences allograft function and, ultimately, graft loss.

The GFR in living kidney donors is most accurately measured by clearance of exogenous markers such as inulin or iothalamate. However, due to the cost and complexity of measuring GFR, many centers forego the direct approach and simply estimate living donor GFR. Common approaches include calculating GFR by the Modification in Diet of Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology (CKD-EPI) equations, calculating CrCl by the Cockroft–Gault (CG) equation and measuring CrCl in a 24-h urine collection.

Efforts to validate these approaches in living donors have been attempted. In a study of 253 living donors, Tent et al. [12] compared the performance of the MDRD, CKD-EPI and CG equations against mGFR; the three equations underestimated predonation mGFR by 15, 4 and 11 mL/min/1.73 m², respectively. Notably, the discrepancy between eGFR and mGFR grew as mGFR increased. Similar findings were reported by Rule et al. [13], who demonstrated significant underestimation of mGFR by eGFR derived from the MDRD equations in a cohort of 365 living donors. Correlation between the measured and calculated GFR was poor (relative risk [RR] = 0.26). Conversely, Issa et al. [14] showed that a 24-h urine collection for creatinine clearance overestimated mGFR...
by >10% and correlated more poorly with mGFR than did eGFR by the MDRD equation. Cystatin C-based equations have subsequently been developed in the hope of improving the accuracy of estimating GFR. However, studies comparing the performance of cystatin C-based equations to Cr-based equations have yielded conflicting results [15].

Overall, eGFR does not perform especially well compared with mGFR in living donors, and should therefore be used with caution. As recommended by the KDIGO guidelines, mGFR should be performed in assessing donor kidney function [16].

Because GFR declines with age, predonation GFR is generally lower in older living donors. As the age of eligible donors is liberalized, the impact of increased donor age, and therefore lower predonation GFR, on graft outcomes is important. Two major questions can be posed: are older kidneys associated with suboptimal allograft outcomes, and, if so, is there still a benefit to transplanting older kidneys into older recipients?

A recent meta-analysis examined 31 studies of older donors (age >60 years) [17]. Iordanous et al. analyzed 5-year death-censored graft survival, composite 5-year patient and graft survival, and 1-year graft function; all were lower in recipients of kidneys from older donors. Statistical significance was achieved in composite 5-year patient and graft survival and 1-year graft function, while a trend was observed in 5-year death-censored graft survival.

Subsequently, four additional studies using large registry databases investigated this question (Table 2). By querying the UNOS/SRTR and ANZDTR databases, respectively, both Gill et al. [18] and Lim et al. [19] reported unadjusted death-censored graft survival as being slightly inferior in recipients of kidneys from living donors >55 years old compared with recipients of kidneys from living donors <55. However, after adjustment for a wide variety of risk factors, the studies differed in their conclusions. In the former [18], the RR for graft loss was no higher for older donors, while in the latter [19] the adjustment resulted in a higher HR for graft loss in the older kidneys (1.5) and a lower HR in the younger kidneys (0.6), when kidneys from deceased standard criteria donors were used as the referent group. Two additional studies sought to examine this question by creating finer strata of donor age. Fuggle et al. [20] (using UKTR data) and Chang et al. [21] (USRDS data) stratified recipients into four and seven donor age groups, respectively. They both found that, except in the group with the oldest donors (age >60 in the former study and >65 in the latter), donor age has little clinically significant impact on the RR of graft loss. However, the RR for graft loss becomes significantly higher when donor age reaches an age threshold (RR = 3.72 in donors >60 [20] and RR = 1.7 in donors >65 [21]).

Therefore, most, but not all, observational studies appear to support the conclusion that increasing donor age is associated with worse graft outcomes, although the definition of older donors varies. However, whether this apparent association of older age with inferior outcomes is caused by lower predonation GFR (because older donors tend to have lower GFR) has not been extensively studied. Insight into this issue was provided by Noppakun et al. [22] in a study of 1063 living kidney transplantations in which the relative age difference between donors and recipients was analyzed. The authors found inferior outcomes resulted when donors were older than recipients, even after adjustment for predonation eGFR. The suggestion of an independent effect of age was supported by Young et al. [23] who showed that the association between graft loss and older donor age was independent of predonation eGFR.

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### Table 1. Studies of the impact of living donor kidney function on graft outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Years</th>
<th>n</th>
<th>Follow-up duration (years)</th>
<th>Donor GFR (mL/min/1.73 m²)</th>
<th>Graft outcomes</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norden et al. [2]</td>
<td>2000</td>
<td>344</td>
<td>5</td>
<td>mGFR &lt;80 versus &gt;80</td>
<td>Graft survival (%)</td>
<td>76 versus 88 S</td>
</tr>
<tr>
<td>Lezaic et al. [7]</td>
<td>2004</td>
<td>70</td>
<td>10</td>
<td>skmGFR &lt;50 versus &gt;50</td>
<td>Graft survival (%)</td>
<td>72 versus 85 NS</td>
</tr>
<tr>
<td>Issa et al. [8]</td>
<td>2007</td>
<td>248</td>
<td>2</td>
<td>mGFR &lt;110 versus &gt;110</td>
<td>GFR (mL/min/1.73 m²)</td>
<td>53 versus 60 S</td>
</tr>
<tr>
<td>Poggio et al. [9]</td>
<td>2006</td>
<td>119</td>
<td>2</td>
<td>mGFR &lt;55 versus &gt;55</td>
<td>GFR (mL/min/1.73 m²)</td>
<td>51 versus 64 S</td>
</tr>
<tr>
<td>Fuggle et al. [10]</td>
<td>2006</td>
<td>206</td>
<td>0.5</td>
<td>CrCl</td>
<td>eGFR (mL/min/1.73 m²)</td>
<td>Correlation S</td>
</tr>
<tr>
<td>Kokado et al. [11]</td>
<td>1993</td>
<td>163</td>
<td>2</td>
<td>mGFR &lt;80 versus &gt;80</td>
<td>Cr (mg/dL)</td>
<td>1.7 versus 1.6 NS</td>
</tr>
</tbody>
</table>

mGFR, measured GFR; skmGFR, single kidney measured GFR; CrCl, creatinine clearance; Cr, creatinine; eGFR, estimated GFR; S, statistically significant; NS, statistically not significant.
Older dialysis patients have a high mortality associated with remaining on dialysis. Therefore, even if older age is associated with inferior graft outcomes, utilization of kidneys from older donors remains a viable option for older recipients for two reasons.

First, the adverse impact of an older kidney is relatively less on older recipients, compared with younger ones. In the study of Noppakun et al. [22], the overall graft survival disadvantage associated with a donor being older than a recipient was observed only in recipients <50 years old. In other words, in older recipients (those >50 years), graft outcomes were not significantly affected by whether the donor was older or younger than the recipients.

Secondly, compared with transplantation from deceased donors, living donation, even using older kidneys, provides superior overall outcomes compared with dialysis. In a study of 23,754 kidney transplant recipients over 60 years old, Gill et al. [18] found that recipients of kidneys from living donors over 55 years old demonstrated graft outcomes similar to those of recipients of deceased SCD kidneys. Indeed, the outcomes were superior to those of recipients who received deceased ECD kidneys. Findings from another study of 6317 kidney transplantations [19] showed that although the use of older donor kidneys was associated with increased graft loss (HR 1.5), this strategy was still generally superior to the use of ECD kidneys.

In the context of recent changes in deceased donor kidney allocation policy, which is projected to result in an estimated 32% reduction of kidney transplantations to recipients over 65 years old [24], the benefit of proper utilization of kidneys from older living donors needs to be further examined in order to expand the donor pool for elderly transplant candidates.

Predonation GFR not only helps determine recipient outcomes, but also has an important role in predicting donor outcomes as well. Following donor nephrectomy, adaptive hyperfiltration in the remaining kidney causes a compensatory increase in GFR. Predonation GFR is one of the critical tests to determine whether the remaining kidney can provide sufficient postnephrectomy GFR for the donor. Not unexpectedly, lower predonation GFR was found to be a significant predictor of lower postdonation GFR by Rook et al. [25], who followed 125 consecutive living donors for 2 months after donation. The odds ratio (OR) for development of postdonation mGFR <60 mL/min/1.73 m² increased as predonation mGFR decreased. Compared with the referent predonation mGFR of >124 mL/min/1.73 m², the OR for postdonation mGFR < 60 mL/min/1.73 m² was 3.0 when the predonation mGFR was ‘only’ 112–123 mL/min/1.73 m², and rose to 9.9 when mGFR was 100–111 mL/min/1.73 m². However, a longer follow-up is needed to determine when the maximum compensatory

<table>
<thead>
<tr>
<th>Study</th>
<th>Database</th>
<th>Year</th>
<th>Donor age (years)</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>Follow-up duration (years)</th>
<th>Graft outcomes</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gill et al. [18]</td>
<td>UNOS/SRTR</td>
<td>2008</td>
<td>&gt;55 versus &lt;55</td>
<td>80 versus 91</td>
<td>4</td>
<td>Graft survival (%)</td>
<td>78 versus 81</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR graft loss</td>
<td>NS</td>
</tr>
<tr>
<td>Lim et al. [19]</td>
<td>ANZDTR</td>
<td>2013</td>
<td>&gt;55 versus &lt;55</td>
<td>81 versus 89</td>
<td>5</td>
<td>Graft survival (%)</td>
<td>90 versus 93</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 Graft survival (%)</td>
<td>68 versus 86</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR graft loss</td>
<td>1.5 versus 0.58</td>
</tr>
<tr>
<td>Fuggle et al. [20]</td>
<td>UKTR</td>
<td>2010</td>
<td>&gt;60 versus &lt;60</td>
<td>NA</td>
<td>3</td>
<td>RR graft loss</td>
<td>3.72</td>
</tr>
<tr>
<td>Chang et al. [21]</td>
<td>USRDS</td>
<td>2012</td>
<td>&gt;65 versus &lt;65</td>
<td>NA</td>
<td>&gt;10</td>
<td>RR graft loss</td>
<td>1.7</td>
</tr>
</tbody>
</table>

UNOS, United Network for Organ Sharing; SRTR, Scientific Registry of Transplant Recipients; ANZDTR, Australia and New Zealand Dialysis and Transplant Registry; UKTR, United Kingdom Transplant Registry; USRDS, United States Renal Data System; RR, relative risk; HR, hazard ratio; NA, not available; S, statistically significant; NS, statistically not significant; NR, not reported.
hyperfiltration is achieved. Additionally, lower postdonation GFR has been reported in older donors in a meta-analysis compared with their younger counterparts [26], but confounding by age remains a concern, since older donors are expected to have lower eGFR.

Whether lower posttransplant GFR translates into a higher risk for ESRD or, ultimately, mortality has profound implications for organ donation, and must be considered in the context of donor age. Although evidence suggesting adverse long-term effects resulting from living kidney donation is lacking, common limitations of many studies, such as donor selection bias, lack of optimal controls and inadequate sample size, in addition to the traditional limitations of retrospective study designs, have all undermined the quality of the evidence [27].

An age-adjusted threshold GFR for living donor safety is an important consideration because the likelihood of developing ESRD is dependent upon remaining years of life. For example, a GFR of 80 mL/min/1.73 m² may be acceptable for a 65-year-old donor, but would be of great concern for a 30 year old, as the latter has a great many more expected years of life.

The present study by Young et al. [6] raises important questions about how much predonation GFR is adequate to provide sufficient GFR to the recipient. The study has numerous strengths, such as a large cohort drawn from multiple centers, substantial follow-up time and well-designed statistical analysis, including provision for competing risks. However, an important limitation acknowledged by the authors is the method used to determine predonation GFR. As discussed, the MDRD equation underestimates mGFR by ≈10 mL/min/1.73 m², which implies that the outcomes compared may in fact have been between recipients of kidneys with a predonation GFR below and above 90 mL/min/1.73 m², instead of 80 mL/min/1.73 m². The use of a higher effective GFR value as a cutoff could potentially result in a failure to demonstrate an association between predonation GFR and outcomes. In addition, the lack of association could also be due to a lack of statistical power to detect potential differences, given the variation of eGFR values.

Predonation GFR, which is best assessed by direct measurement of GFR, is associated with both recipient and donor outcomes. Nevertheless, the predonation GFR threshold that is adequate for recipients and donors remains to be determined. Kidneys from older donors, who likely have lower predonation GFR, may be a good option in selected older recipients.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no financial conflicts of interest.

(See related article by Young et al. Living kidney donor estimated glomerular filtration rate and recipient graft survival. Nephrol Dial Transplant 2014; 29: 188–195.)

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LMX1B mutations with nails and kneecaps: a new paradigm?

Kevin V. Lemley1,2

Correspondence and offprint requests to: Kevin V. Lemley;
E-mail: klemley@chla.usc.edu

1Division of Nephrology, Children’s Hospital Los Angeles, Los Angeles, CA, USA and
2Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Nail–patella syndrome (NPS, OMIM 161200) is a rare pleotropic, genetic disease with both renal and extra-renal manifestations. The vast majority of affected individuals are recognizable by the presence of one or more of a number of characteristic physical findings—including the classical tetrad of absent or hypoplastic finger and toe nails, absent or hypoplastic patellae, elbow dysplasia (usually posterior subluxation of the radial head) and iliac horns. Renal involvement is common, although serious sequelae of NPS, such as nephrotic syndrome or renal failure, are not.

The molecular–genetic basis of clinical disease is inactivating mutations in the LIM-homeodomain transcription factor, LMX1B [1]. Missense, non-sense and frame-shift mutations in the LIM and homeodomain moieties of the gene, as well as partial or complete gene deletions, have been found in affected individuals [1, 2]. Co-transfection studies and the pathogenicity of complete gene deletion support haploinsufficiency as the mechanism of disease causation, rather than a dominant negative effect of the mutations [3]. With respect to the extra-renal findings in classic NPS, LMX1B activity is apparently needed only during fetal development, when it is important for dorsal–ventral pattern specification. After fetal life, LMX1B is not expressed in skeletal and other extra-renal tissues. Quite interestingly, LMX1B seems to play a quite different role in podocytes than it does in the rest of the body [4]. LMX1B starts being expressed in the glomerulus at the S-shaped body stage, when the process of podocyte differentiation starts [5]. At least in the mouse, LMX1B activity seems to be necessary post natally for the proper expression of a number of podocyte-related genes, including CD2AP, NPHS2 [6] and COL4A3/COL4A4 (encoding the α3 and α4 chains of mature type IV collagen) [7]. In contrast, proteins for these putatively LMX1B-regulated genes are present in normal abundance in glomeruli from kidney biopsies of patients with NPS [8]. Understanding this species difference is complicated by the fact that the presence of the cardinal features of NPS requires the homozygous presence of the mutant gene in mice, while it is autosomal dominant in humans.