The Natural History of Residual Renal Function in Transplant Donors

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ABSTRACT

After uninephrectomy, GFR in the remaining kidney increases to 60%–70% of the predonation value, largely because of a substantial increase in renal blood flow. Donor kidney function is then generally maintained over many years. Hypertension and proteinuria are common among living donors but do not appear to negatively affect long-term renal function. Loss of reserve capacity regarding renal function in some subgroups after donation, particularly in obese and older donors, raises questions about limitations of the renal adaptive response and suggests caution in generalization of current outcome data to more marginal donors not well represented in older studies.

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The first successful living donor (LD) kidney transplantation took place in 1954. Ronald Herrick, then 23 years old, donated a kidney to his twin brother, Richard. The donor died 56 years later at age 79. This heroic and historic donation demonstrated that transplantation was possible and that removal of a kidney in a healthy person did not result in harm. Approximately 27,000 LD kidney transplantations are now performed annually worldwide.[1]

PHYSIOLOGIC ADAPTATIONS AFTER UNINEPHRECTOMY IN HEALTHY DONORS

Uninephrectomy, involving the reduction of nephron mass by 50%, in the setting of an unchanged metabolic demand and normal prior renal function, induces a highly predictable increase in single-kidney GFR of 20%–40% within days, resulting in a postdonation GFR of 60%–70% of the predonation value.[2–6] The rapidity and reproducibility of this early increase in GFR after nephrectomy suggest a predominantly hemodynamic response.

In humans, direct measurements of glomerular hemodynamics are not possible. Rat studies show that after uninephrectomy, single-nephron GFR increases, largely because of an increase in glomerular plasma flow, whereas after more extensive nephron loss, GFR is maintained at the expense of a significant increase in glomerular capillary pressure (P_{GC}).[6] The lack of a substantial increase in P_{GC} after uninephrectomy probably explains why renal function is relatively preserved over time compared with subtotal nephrectomy.

Studies in nonhuman primates observed that glomerular pressures are similar to those in the rat, that GFR is dependent on blood flow, and that because filtration fraction and plasma protein concentrations are similar in humans and monkey, these findings also probably apply in humans.[7] The central role of increased perfusion in the early functional adaptation in humans is supported by the observed increase in renal plasma flow (RPF) after nephrectomy, of a magnitude similar to or greater than the percentage change in GFR (Table 1).[2,3,5,8]

To investigate the hemodynamic mechanisms whereby GFR increases after nephrectomy, renal functional reserve capacity (RFR), defined as percentage increase in GFR after infusion of low-dose dopamine or amino acids, was evaluated in 15 LDs before donation and at a mean ± SEM of 1.3±0.3 months and 4.9±0.8 years after donation (Table 1).[9] At both time points, the percentage increase in GFR induced by dopamine was half of that measured before donation, whereas the percentage change induced by amino acid infusion was similar before and after donation. Amino acids increase GFR by preferential dilation of the afferent arteriole, probably increasing P_{GC}, whereas dopamine induces dilation of both afferent and efferent arterioles, increasing GFR by increasing RPF; these two mechanisms are additive when induced simultaneously.[9] Given the preservation of the GFR response to amino acids before and after nephrectomy and the reduction in dopamine responsiveness, researchers have suggested that the adaptive increase in GFR after uninephrectomy is probably largely maintained by an increase in RPF rather than P_{GC}.[8,9] Persistence of

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Table 1. Renal functional reserve measured in the same patients before and after kidney donation

Donor Characteristic	Patients (*n*)	Measurement	Baseline Adaptation (Mean of Predonation Value) (%)	Mean Change from Baseline GFR (%)								Ref
				Low-Dose Dopamine			Amino Acid Infusion			Dopamine + Amino Acid		
				Before Donation	Early[a]	Long-Term[b]	Before Donation	Early[a]	Long-Term[b]	Before Donation	Early[a]	Long-Term[b]
Healthy donors	15	GFR[c]	65	12.9	5.5	7.7	11.9	8.9	10	23.4	15.5	18.3	8,9
		ERPF[d]	69	32.0	19.8	26.1	10.4	5.9	6.3	40.2	24.7	31.0	
		FF	95	−15.3	−12.3	−14.0	0	2.9	4.7	−13.0	−7.4	−9.7	
Weight[e]													
normal	87	GFR[c]	63	10.6±8.7	6.7±8.4	—	—	—	—	—	—	—	14
overweight	70	GFR[c]	63	10.8±10.4	4.8±5.5	—	—	—	—	—	—	—	
obese	21	GFR[c]	62	11.1±11.9	1.3±5.5	—	—	—	—	—	—	—	
Age													14
21–45 yr	62	GFR[c]	63	9.6±8.9	7.1±7.3	—	—	—	—	—	—	—	
6–53 yr	59	GFR[c]	64	12.6±8.9	6.1±7.2	—	—	—	—	—	—	—	
54–75 yr	57	GFR[c]	63	10.1±11.2	2.8±6.1	—	—	—	—	—	—	—	

Ref, reference; ERPF, effective renal plasma flow; FF, filtration fraction.
[a]Early, <3 months after donation.
[b]Long-term, 4.9±0.8 years after donation.
[c]By ^{125}I-iothalamate GFR.
[d]By ^{131}I -hippurate ERPF.
[e]Normal weight: BMI < 25 kg/m^2; overweight, BMI 25–30 kg/m^2; obese, BMI > 30 kg/m^2.

RFR up to 5 years after nephrectomy suggests that the adaptive hemodynamic changes do not negatively affect renal function over this time.[9]

After the initial postdonation decrease in GFR, many studies document a gradual increase in GFR and renal size over the first months, consistent with an adaptive hypertrophic response in the remaining kidney.[9–12] In patients studied ≥6 months after nephrectomy, based on mathematical modeling, an increase in glomerular ultrafiltration coefficient (reflecting glomerular hypertrophy and increased filtration surface area) and/or an increase in P_{GC} probably contribute to the ongoing adaptive hyperfiltration.[12,13] Also consistent with a renal hypertrophic response, the increase in GFR in healthy LDs is accompanied by a proportional increase in tubular maximal reabsorptive function, demonstrating preservation of glomerulotubular balance.[3] Absolute increases in single-kidney uric acid and phosphate clearance, as well as acid excretion, however, cannot be attributed solely to the increase in GFR; these increases therefore reflect additional homeostatic adaptations in tubular function after nephrectomy.[3]

Donor age and obesity are important modulators of adaptation in the single kidney. Despite a similar baseline adaptive renal response after nephrectomy, RFR measured by dopamine infusion 2 months after donation was significantly reduced in obese donors (body mass index > 30 kg/m^2), most markedly among young obese donors, and in older donors (>54 years) (Table 1 and 2).[14] In another study, the calculated ultrafiltration coefficient was reduced in older (≥55 years) compared with younger (≤45 years) donors at 6 months after donation, a finding attributed to age-associated nephron loss.[12] Fewer nephrons in older donors would be consistent with a reduced RFR. The loss of dopamine-induced RFR in older and obese donors suggests that these kidneys are maximally using this pathway to maintain baseline adaptation and are therefore hyperfiltering. Older donors tend to have lower GFRs before donation, which is a predictor of lower postdonation GFR.[4] A few studies have examined outcomes in

Table 2. Groups at potential increased long-term risk after living kidney donation

Living donor group	Outcome
African American versus white (United States)	Increased risk for hypertension (hazard ratio, 1.52)[24,31]
	Increased risk for macroalbuminuria (12% versus 0%)[30]
	Greater decline in GFR after donation with higher BMI [31]
	Increased risk for CKD (hazard ratio, 2.32)[24, 30]
	Greater decline in estimated GFR in AA women at 273 days after donation [32]
	Highest risk for kidney failure among AA males donating before age 35 yr[25]
	Greater proportion of AA donors listed for transplantation[25]
Hispanic versus white (United States)	Increased risk for hypertension (hazard ratio, 1.36)[24]
	Increased risk for CKD (hazard ratio, 1.90)[24]
Australian aboriginal versus white	Increased mortality (12% versus 0%)[27]
	Increased prevalence of CKD and ESRD (81% versus 38%)[27]
	Increased prevalence of hypertension (50% versus 6%)[27]
	Increased prevalence of proteinuria (81% versus 6%)[27]
Canadian aboriginal versus white	Increased prevalence of hypertension (100% versus 45% at 20 yr)[26]
	Increased prevalence of proteinuria (21% versus 4%)[26]
Older versus younger	Lower postdonation GFR in older donors[11,14, 32]
	Reduced renal functional reserve capacity with donor age $>$ 54 yr[14]
Higher BMI	Lower postdonation GFR with increasing BMI[11,14,16]
	Reduced renal functional reserve capacity, especially with donor age $<$ 49 yr[14]
Low birth weight/low nephron number	Unknown
APOL1 variants	Unknown
Postdonation pregnancy	Unclear[17]

AA, African American.

older donors and found that a greater proportion have GFRs below 60 ml/min compared with younger donors, although GFRs appear to remain stable over time.[11,15] Similarly, GFRs tend to be lower in obese donors, especially those with microalbuminuria (which may reflect hyperfiltration injury), but effect on long-term outcomes is not yet clear.[4,11,16] Pregnancy induces a temporary state of renal hyperperfusion and hyperfiltration. Long-term outcomes in donors who undergo subsequent pregnancy are not clear.[17]

EFFECT OF KIDNEY DONATION ON LONG-TERM RENAL FUNCTION

Change in Renal Function over Time

To our knowledge, only a single study has examined longitudinal changes in renal function in a cohort of LDs.[18] GFR was measured by ^{51}Cr EDTA in 47 of 70 donors 10 years apart, at 1.4–20.7 years and 12–31 years after donation. Overall, the GFR increased by a median of 4 ml/min over the 10-year interval.[18] Albuminuria was present in 34% of donors, the mean albumin excretion rate increased over time, but no donor had macroalbuminuria.[18] The percentage of donors with hypertension increased from 36% to 74.5% over the 10-year period.[18] The results of this longitudinal study are consistent with the findings of many cross-sectional studies: that GFRs tend to remain stable over time but that the incidence of hypertension and of proteinuria are increased among LDs.[11,19–21] Of concern, in several studies hypertension was previously undiagnosed or untreated in up to half of patients.[10,18]

The reported stability of GFR over time in LDs may, however, reflect insufficient long-term follow-up. A recent cross-sectional study of 573 donors (52% of the cohort) followed for up to 40 years reported changes in GFR with time.[10] Among donors aged 30 years at time of donation, GFR tended to increase for the first 17 years, stabilize for 8 years, and then decline slowly thereafter. In those who were 50 years old, GFRs increased over the first 15 years and then began to decline.[10] That study suggests decline in renal functional is evident with longer follow-up and older donor age.[10] In eight studies that assessed GFR after a mean of 10 years after donation, 12% of LDs had GFRs between 30 and 59 ml/min and 0.2% had a GFR $<$ 30 ml/min.[19] In LDs, the diagnosis of CKD, defined as a GFR $<$ 60 ml/min, has been debated elsewhere; nevertheless, donor ESRD has been reported at a median of 20 years after donation.[22,23] The risk for ESRD, however, was not increased among 3698 LDs compared with the general population at a mean follow-up of 12.2$\pm$9.2 years, although this conclusion may be confounded by the choice of control group, the duration of follow-up, and the predominance of white participants.[11]

Questions have been raised about the consequences of kidney donation in nonwhite donors (Table 2): The risks for hypertension and CKD are significantly increased in African American and Hispanic donors compared with risks in white persons;[24] African Americans are disproportionately represented among 126 LDs awaiting transplantation;[25] among Canadian aboriginal donors, 100% have hypertension and proteinuria is more common than among white donors at 20 years after donation;[26] and aboriginal Australian donors have significantly more hypertension, CKD, and ESRD compared with white persons at a median of 16.1 years after donation.[27] Whether genetic predisposition to renal disease (perhaps *APOL1* variants) or other factors contribute to the increased risk after kidney donation in these groups remains unclear.

There is a 13-fold variation in nephron number in humans, which may conceivably affect the renal adaptive response after uninephrectomy.[28] Low birth weight and low nephron number are prevalent among Australian aboriginals, for example, which may contribute to the increased risk in this population.[28]

Proteinuria

The pooled incidence of proteinuria across 42 LD studies is 12%, which is significantly higher than in control groups by 11 years after donation.[19] Proteinuria is thought to reflect glomerular hypertension and hyperfiltration in the single kidney and to anticipate renal functional decline. In most studies, however, postdonation GFR remains relatively stable, despite the increasing incidence of proteinuria with time.[11,19,20] The nature and implications of proteinuria in a single healthy kidney may therefore differ from those in renal parenchymal disease. Of note, proteinuria among LDs tends to remain < 0.3 g/d, which even in native CKD presents low risk for renal disease progression.[19,29]

CONCLUSIONS

Studies of long-term outcomes in LDs must be interpreted with caution because most were cross-sectional, had small numbers, had short follow-up, lacked optimal control groups, used calculated rather than measured GFRs, and had an average loss to follow-up of 31%.[21] Given all of these caveats, existing data tend to support preservation of renal function in most kidney donors over time. The healthy single kidney after contralateral nephrectomy undergoes a rapid increase in RPF and a 20%–40% increase in GFR. This GFR is associated with renal hypertrophy and is generally maintained over the long term, possibly at the expense of rising BP and increasing proteinuria. With pressure to approve more donors as transplant waiting lists increase, it is imperative we better understand the renal adaptive process in kidneys from donors who many years ago would have been declined—particularly the young and obese donor, older donors, and those with medical abnormalities (such as hypertension) —and are therefore not represented in long-term follow-up studies, as well as donors of varying ethnic and genetic backgrounds.

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DISCLOSURES

None.

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