Early increase in single-kidney glomerular filtration rate after living kidney donation predicts long-term kidney function

van der Weijden, Jessica; Mahesh, Shekar V. K.; van Londen, Marco; Bakker, Stephan J. L.; Sanders, Jan-Stephan; Navis, Gerjan; Pol, Robert A.; Roodnat, Joke; Kho, Marcia M. L.; Yakar, Derya

Published in:
Kidney International

DOI:
10.1016/j.kint.2022.01.034

Early increase in single-kidney glomerular filtration rate after living kidney donation predicts long-term kidney function

OPEN

Jessica van der Weijden[1], Shekar V.K. Mahesh[2], Marco van Londen[1], Stephan J.L. Bakker[1], Jan-Stephan Sanders[1], Gerjan Navis[1], Robert A. Pol[3], Joke I. Roodnat[4], Marcia M.L. Kho[4], Derya Yakar[2], Thomas C. Kwee[2], Ilja M. Nolte[5], Stefan P. Berger[1] and Martin H. De Borst[1]

[1]*Department of Internal Medicine, Division of Nephrology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands;* [2]*Department of Radiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands;* [3]*Department of Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands;* [4]*Department of Internal Medicine, Division of Nephrology, Erasmus Medical Center, University Medical Center, Rotterdam, The Netherlands; and* [5]*Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands*

Single-kidney glomerular filtration rate (GFR) increases after living kidney donation due to compensatory hyperfiltration and structural changes. The implications of inter-individual variability in this increase in single-kidney GFR are unknown. Here, we aimed to identify determinants of the increase in single-kidney GFR at three-month postdonation, and to investigate its relationship with long-term kidney function. In a cohort study in 1024 donors, we found considerable inter-individual variability of the early increase in remaining single-kidney estimated GFR (eGFR) (median [25th-75th percentile]) 12 [8-18] mL/min/1.73m^2. Predonation eGFR, age, and cortical kidney volume measured by CT were the main determinants of the early postdonation increase in single-kidney eGFR. Individuals with a stronger early increase in single-kidney eGFR had a significantly higher five-year postdonation eGFR, independent of predonation eGFR and age. Addition of the postdonation increase in single-kidney eGFR to a model including predonation eGFR and age significantly improved prediction of a five-year postdonation eGFR under 50 mL/min/1.73m^2. Results at ten-year follow-up were comparable, while accounting for left-right differences in kidney volume did not materially change the results. Internal validation using ^{125}I-iothalamate-based measured GFR in 529 donors and external validation using eGFR data in 647 donors yielded highly similar results. Thus, individuals with a more pronounced increase in single-kidney GFR had better long-term kidney function, independent of predonation GFR and age. Hence, the early postdonation increase in single-kidney GFR, considered indicative for kidney reserve capacity, may have additional value to eGFR and age to personalize follow-up intensity after living kidney donation.

Correspondence: *Martin H. de Borst, Department of Internal Medicine, Division of Nephrology, University of Groningen, University Medical Center Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands. E-mail: m.h.de.borst@umcg.nl*

Received 18 November 2021; revised 30 December 2021; accepted 11 January 2022; published online 26 February 2022

Kidney International (2022) **101,** 1251–1259; https://doi.org/10.1016/j.kint.2022.01.034

KEYWORDS: glomerular filtration rate; living kidney donation; postdonation adaptation; postdonation outcomes; renal functional reserve

In 1930, Ernest Basil Verney postulated that the kidney has reserve forces, a dormant renal reserve intended to cope with extraordinary hemodynamic and metabolic demands.[1] In line with this concept, donor nephrectomy is followed by an adaptive increase in glomerular filtration rate (GFR) by ∼30% in the remaining kidney.[2–4] Although little is known about underlying mechanisms and determinants, early hemodynamic changes and structural adaptations of the remaining nephrons are generally considered to explain this increase.[5] A recent study identified a low nephron number for age as a predictor for long-term risk of chronic kidney disease after living kidney donation.[6] Whether reduced nephron number or cortical kidney volume, which has also been linked with postdonation kidney function,[7,8] are associated with a less pronounced postdonation increase in single-kidney GFR is unknown.

Interestingly, the magnitude of the postdonation increase in single-kidney GFR varies between individuals.[9] Hypothetically, an increased single-kidney GFR could lead to glomerular hypertension, glomerular injury, and loss of kidney function on the long term.[10,11] In contrast, a prior study showed that postdonation hyperfiltration by the remaining kidney is maintained stable by a combination of an increase in kidney plasma flow and in the ultrafiltration coefficient resulting from compensatory glomerular hypertrophy, not glomerular hypertension.[5] So far, the impact of the postdonation increase in single-kidney GFR on long-term postdonation kidney function remains unknown.

At the same time, the optimal estimation of long-term kidney function at living donor screening is key.[12,13] Previous studies identified age and predonation GFR as major predictors of long-term postdonation kidney function,

although these factors together explained only 53% of the variation in postdonation GFR.[9] At least part of the unexplained variability may be accounted for by the postdonation increase in single-kidney GFR.

Therefore, in the present study, we hypothesized that the early postdonation increase in single-kidney GFR predicts long-term postdonation kidney outcomes. We first aimed to identify predonation determinants of this increase and subsequently investigated its capacity to predict long-term kidney function after donation.

METHODS

Study design and participants

An overview of participants and available data is provided in Figure 1 and Supplementary Table S1. Data were used from all adults who donated a kidney between 1984 and 2018 at the University Medical Center Groningen, The Netherlands, and who provided informed consent. Both estimated GFR (eGFR) and measured (mGFR) data (details below) were available for the predonation screening visit and at 3 months postdonation in 1024 donors. Five- and 10-year follow-up of eGFR was available in 693 and 321 donors, respectively. Measured GFR, used for the internal validation of the analyses, was available in 529 and 236 donors at 5 and 10 years postdonation, respectively. The study was approved by the institutional ethical review board (2014/077) and was registered at clinicaltrials.gov under identifier NCT0327284.[14] An independent living kidney donor cohort from the Erasmus Medical Center (Rotterdam, The Netherlands) was used as a replication cohort. Design and study population of this cohort, consisting of 647 donors, are described in Supplementary Methods. All procedures were conducted in accordance with the Declaration of Helsinki, the Declaration of Istanbul, and the Dutch Scientific Guidelines.

Measurements and calculations

Primary analyses involved the eGFR using the (isotope dilution mass spectrometry–traceable) creatinine-based Chronic Kidney Disease Epidemiology Collaboration formula.[15] Internal validation was performed in a subgroup of donors with mGFR data by using radiolabeled iothalamate (^{125}I-iothalamate) clearance, as described in detail previously.[16] Details on serum creatinine and mGFR measurements are provided in Supplementary Methods. The day-to-day variability of ^{125}I-iothalamate–based mGFR is 2.5%.[16,17] The postdonation increase in single-kidney GFR was calculated as the GFR at 3 months postdonation minus 50% of the predonation GFR.[18] To account for left-right differences in kidney volume, we performed a secondary analysis where we recalculated the postdonation increase in single-kidney GFR by using the remaining kidney volume as a percentage of the total volume of both kidneys using computerized tomography (CT). Preoperative kidney CT obtained during the corticomedullary phase (scanned 20–25 seconds after i.v. contrast injection) was automatically segmented; the volumes of the kidney cortex and medulla of both kidneys were calculated separately, and cortical kidney volume of the remaining (nondonated) kidney was used for further analysis. The CT scans were performed routinely in every donor between 2007 and 2016 and were therefore available only in a subgroup of donors.

Other clinical and biochemical measurements were performed as described previously.[14] Diabetes was diagnosed according to the American Diabetes Association criteria.[19] Proteinuria was determined using the protein-creatinine ratio in a spot urine sample.[20]

Statistical analyses

Data are presented as mean ± SD for normally distributed variables and as median (25th–75th percentile) for nonnormally distributed variables. Binary variables are shown as number (percentage). The distribution was tested using histograms and probability plots. The characteristics of the population are presented for the whole cohort and according to tertiles of the postdonation increase in single-kidney GFR. In cross-sectional analyses, we aimed to identify independent predonation determinants of the short-term postdonation increase in single-kidney GFR, including all potential determinants of this parameter.[3,9,21] Variables with univariable P values <0.05 were subsequently included in a multivariable linear regression model. Because we hypothesized that the cortical volume of the remaining kidney would be a major determinant, we performed similar analyses in a subgroup with available CT-based kidney volume data.

Next, in longitudinal analyses, we used multivariable linear regression models to investigate the association between the (short-term) postdonation increase in single-kidney GFR and the eGFR at 5 and 10 years postdonation. We similarly used linear regression analysis to study the associations between the postdonation increase in single-kidney GFR and the development of proteinuria at 5 and 10 years postdonation. Models were adjusted for predonation eGFR and donor age as well-established determinants of long-term postdonation kidney function.[9] Multicollinearity was examined in all models using the variance inflation factor; only variables with a variance inflation factor of <3 were included in the models.

We subsequently assessed the capacity of the postdonation increase in single-kidney GFR to predict an eGFR of <50 ml/min per 1.73 m^2 at 5 and 10 years postdonation beyond established predictors (i.e., age and predonation eGFR). This threshold was selected to make sure that $>10\%$ of donors would reach the end point, allowing for reliable risk prediction. We compared the performance of basic models including GFR and age with or without the postdonation increase in single-kidney GFR by using receiver operating characteristic curve analyses to calculate the area under the curve (AUC) for predicting an eGFR of <50 ml/min per 1.73 m^2 at 5 and 10 years postdonation. Differences in AUCs between models were tested according to DeLong *et al.*[22] In addition, we calculated the net reclassification improvement and the integrated discrimination improvement index by comparing 2 logistic regression models for the risk of reaching a 5- and 10-year postdonation eGFR of <50 ml/min per 1.73 m^2.[23,24] We performed several sensitivity analyses including replication of analyses using the mGFR-based postdonation increase in single-kidney GFR in the same cohort and external validation in a cohort with pre- and postdonation eGFR (see Supplementary Methods).

SPSS version 23 for Windows (IBM Corporation), RStudio version 1.1.463, and GraphPad Prism 6 for Windows (GraphPad) were used to perform the analyses. P values <0.05 were considered statistically significant.

RESULTS

Characteristics of the donor cohort

The characteristics of the study participants are summarized in Table 1. At the predonation screening visit, donors were 52 ± 11 years old, 52% were female, and all donors were White. The mean eGFR was 91 ± 15 ml/min per 1.73 m^2

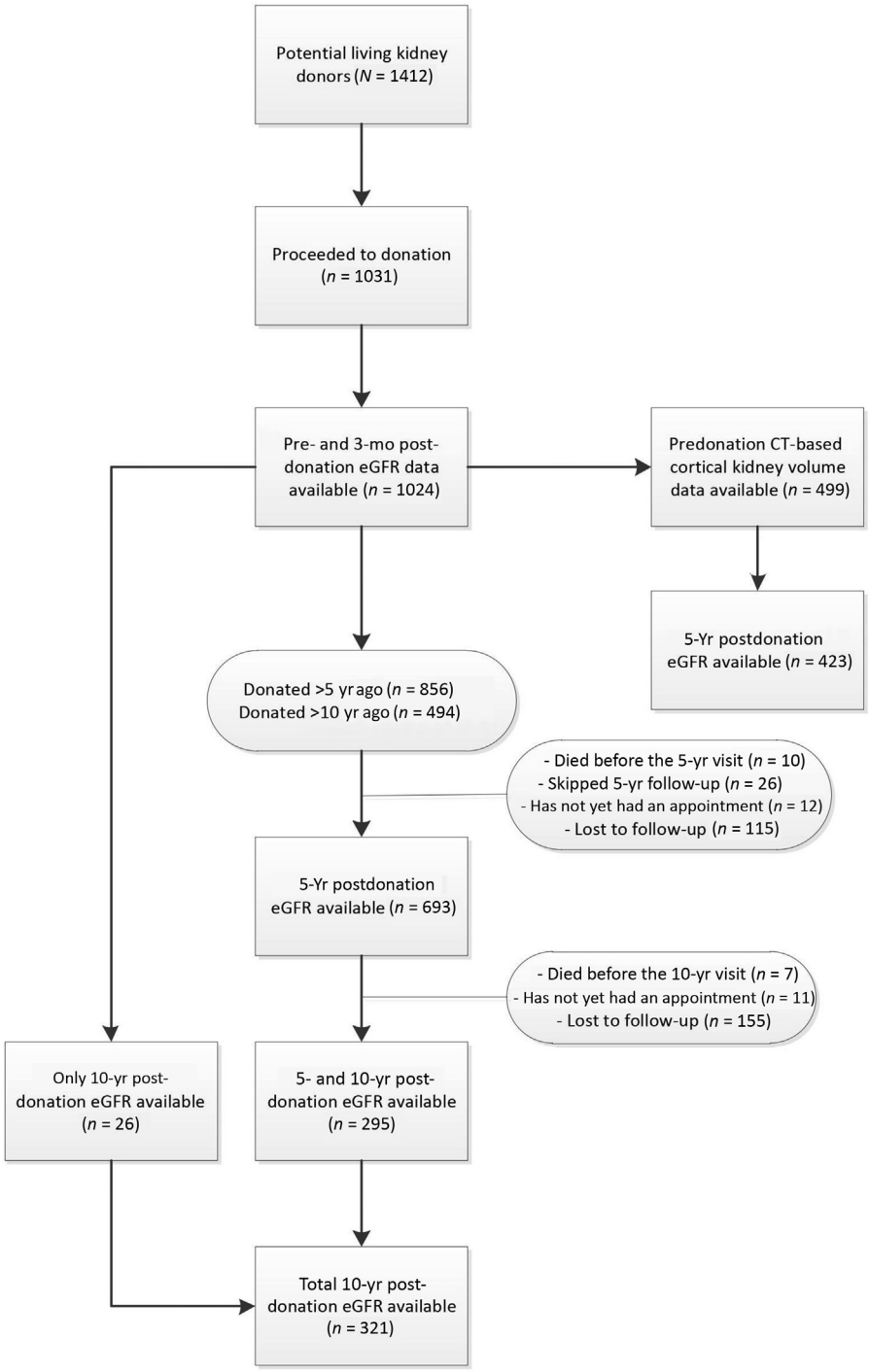

Figure 1 | Overview of the study design and numbers of donors with available data. CT, computed tomography; eGFR, estimated glomerular filtration rate.

predonation, 59 ± 13 ml/min per 1.73 m^2 at 3 months postdonation ($P < 0.001$ vs. predonation), and 62 ± 13 and 63 ± 13 ml/min per 1.73 m^2 at 5 and 10 years postdonation (for both, $P < 0.001$ vs. 3 months postdonation). The median (25th–75th percentile) increase in eGFR beyond 50% of the predonation eGFR at 3 months postdonation was 12 (8–18) ml/min per 1.73 m^2.

Determinants of postdonation increase in single-kidney eGFR

In univariable analyses, age, body mass index, systolic blood pressure, HbA1c, and body surface area were inversely associated and predonation eGFR was positively associated with the postdonation increase in single-kidney eGFR (Table 2). In the final multivariable model, predonation eGFR, age, and body surface area were independent determinants (Table 2).

Table 1 | Characteristics of living kidney donors according to tertiles of Δsk-eGFR

Characteristic	Total	Δsk-eGFR		
		Low (<10 ml/min per 1.73 m^2)	Intermediate (10–16 ml/min per 1.73 m^2)	High (>16 ml/min per 1.73 m^2)
Number	1024	341	341	342
Female sex	531 (52)	160 (47)	189 (55)	182 (53)
White race	1028 (100)	343 (100)	343 (100)	342 (100)
Age (yr)	52 ± 11	56 ± 10	52 ± 10	47 ± 11
Weight (kg)	80 ± 14	82 ± 14	80 ± 14	78 ± 13
Height (cm)	175 ± 9	175 ± 10	175 ± 9	175 ± 10
BMI (kg/m^2)	26 ± 4	27 ± 3	26 ± 3	26 ± 4
BSA (m^2)	1.95 ± 0.20	1.97 ± 0.20	1.95 ± 0.19	1.93 ± 0.19
SBP (mm Hg)	126 ± 13	128 ± 13	127 ± 13	124 ± 12
DBP (mm Hg)	76 ± 9	76 ± 9	76 ± 9	75 ± 9
Hypertension[a]	159 (16)	62 (18)	49 (14)	48 (14)
Use of antihypertensives	142 (14)	64 (19)	39 (11)	39 (11)
ACE inhibitors	54 (5)	25 (7)	10 (3)	19 (6)
ARBs	30 (3)	16 (5)	11 (3)	3 (1)
β-Blockers	53 (5)	21 (6)	15 (4)	17 (5)
Calcium antagonists	27 (3)	12 (4)	8 (2)	7 (2)
Diuretics	43 (4)	20 (6)	10 (3)	13 (4)
Statins	39 (4)	16 (5)	14 (4)	9 (3)
Predonation eGFR (ml/min per 1.73 m^2)	91 ± 15	86 ± 16	90 ± 12	96 ± 14
Predonation mGFR (ml/min)	114 ± 21	108 ± 20	113 ± 21	120 ± 22
Serum creatinine (μmol/l)	75 ± 13	79 ± 13	75 ± 12	72 ± 13
Serum glucose (mmol/l)	5.3 ± 0.6	5.4 ± 0.7	5.3 ± 0.5	5.2 ± 0.5
HbA1c (%)	5.5 ± 0.4	5.5 ± 0.4	5.5 ± 0.4	5.4 ± 0.4
Current smoking	249 (24)	61 (18)	78 (23)	110 (32)
Serum cholesterol (mmol/l)	5.3 ± 1.0	5.4 ± 1.0	5.4 ± 1.0	5.2 ± 1.1
LDL	3.5 ± 0.9	3.5 ± 0.9	3.5 ± 1.1	3.4 ± 0.9
HDL	1.5 ± 0.5	1.4 ± 0.4	1.7 ± 0.5	1.6 ± 0.6
Triglycerides	1.4 ± 0.9	1.4 ± 0.8	1.4 ± 0.9	1.3 ± 0.9
Serum urea (mmol/l)	5.4 ± 1.3	5.8 ± 1.3	5.4 ± 1.2	5.1 ± 1.4
Serum potassium (mmol/l)	4.0 ± 0.3	3.9 ± 0.3	3.9 ± 0.3	4.0 ± 0.4
Serum sodium (mmol/l)	141 ± 3	141 ± 2	141 ± 2	140 ± 3
Sodium excretion (mmol/24 h)	194 ± 74	196 ± 74	196 ± 75	190 ± 74

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BSA, body surface area; DBP, diastolic blood pressure; Δsk-eGFR, postdonation increase in single-kidney glomerular filtration rate; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; mGFR, measured glomerular filtration rate; SBP, systolic blood pressure.
[a]SBP >140 mm Hg and/or DBP >90 mm Hg.
Data are expressed as mean ± SD or n (%).

A secondary analysis in a subgroup of donors with available CT-based cortical kidney volume data (n = 499; characteristics in Supplementary Table S2) identified cortical kidney volume as another independent determinant (Supplementary Table S3).

Postdonation increase in single-kidney eGFR and long-term kidney function

Five- and 10-year eGFR follow-up was available for 693 and 321 donors, respectively; the predonation characteristics of these subgroups are provided in Supplementary Table S4 and were highly similar to the full cohort (Table 1). Five- and 10 years postdonation eGFR values according to postdonation increase in single-kidney eGFR tertiles are provided in Figure 2. The postdonation increase in single-kidney eGFR was associated with eGFR at 5 years after donation both in univariable analysis (Supplementary Table S5) and after adjustment for predonation eGFR and age (St. β = 0.33; $P < 0.001$; Table 3). Adding the postdonation increase in single-kidney eGFR to a model with predonation eGFR and age significantly improved the model R^2 (0.58–0.68; $P < 0.001$; Table 3). Similar results were obtained in the subgroup with data available on 10-year postdonation

Table 2 | Predonation determinants of the postdonation increase in single-kidney eGFR

Variable	Univariable		Multivariable	
	St. β	P	St. β	P
eGFR	0.34	<0.001	0.22	<0.001
Age	−0.33	<0.001	−0.23	<0.001
BMI	−0.11	0.001	—	—
SBP	−0.10	0.001	—	—
BSA	−0.09	0.003	−0.13	<0.001
HbA1c	−0.08	0.02	—	—
Female sex	0.05	0.15	—	—
Sodium excretion	0.05	0.13	—	—

BMI, body mass index; BSA, body surface area; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; St. β, standardized β.
Multivariable model, R^2 = 0.16.

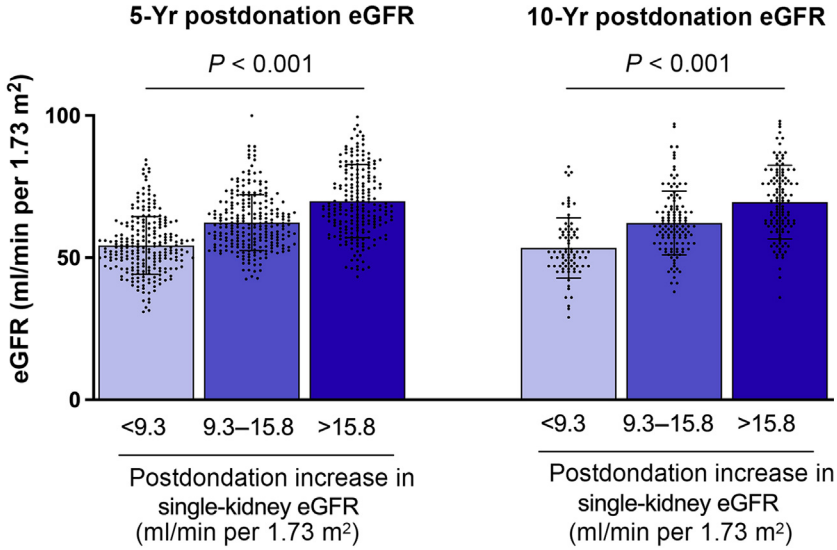

Figure 2 | Five- and 10-year postdonation estimated glomerular filtration rate (eGFR) according to tertiles of the early postdonation increase in single-kidney eGFR. Bars and error bars indicate means and SDs.

follow-up (Table 3). The postdonation increase in single-kidney eGFR was not associated with a protein-creatinine ratio of >15 mg/mmol at 5 and 10 years postdonation (odds ratio 1.02; 95% confidence interval [CI] 0.99–1.04; $P = 0.21$, $n = 650$ and odds ratio 1.01; 95% CI 0.98–1.05; $P = 0.49$, $n = 301$, respectively; Supplementary Table S6).

We next investigated the capacity of the postdonation increase in single-kidney eGFR to improve the prediction of an eGFR of <50 ml/min per 1.73 m^2 at 5 and 10 years postdonation. Of the 693 donors with 5-year postdonation eGFR data available, 108 reached an eGFR of <50 ml/min per 1.73 m^2 at 5 years postdonation (median [range] 46 [31–49] ml/min per 1.73 m^2). Receiver operating characteristic curve analyses demonstrated that predonation eGFR combined with age (model 1, Table 3) strongly predicted a 5-year eGFR of <50 ml/min per 1.73 m^2 (AUC 89%; 95% CI 86%–92%). Addition of the postdonation increase in single-kidney eGFR (model 2, Table 3) improved prediction (AUC 92%; 95% CI 90%–94%; $P = 0.01$ vs. model 1). Addition of the postdonation increase in single-kidney eGFR to a logistic regression model that also included predonation eGFR and age improved the reclassification of donors who reached a 5-year

Table 3 | Multivariable associations of Δsk-eGFR with long-term postdonation eGFR in the main cohort and independent validation cohort

	Main cohort				Independent validation cohort			
Variable	St. β	P	R^2	R^2 change	St. β	P	R^2	R^2 change
5-yr eGFR (n = 693)					**5-yr eGFR (n = 647)**			
Model 1								
eGFR	0.67	<0.001	0.58		0.67	<0.001	0.62	
Age	−0.16	<0.001			−0.16	<0.001		
Model 2								
eGFR	0.59	<0.001			0.59	<0.001		
Age	−0.10	0.001	0.68	<0.001	−0.11	<0.001	0.70	<0.001
Δsk-eGFR	0.33	<0.001			0.30	<0.001		
10-yr eGFR (n = 321)								
Model 1								
eGFR	0.67	<0.001	0.45					
Model 2								
eGFR	0.57	<0.001	0.55	<0.001				
Δsk-eGFR	0.34	<0.001						

Δsk-eGFR, postdonation increase in single-kidney estimated glomerular filtration rate; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; St. β, standardized β.
Age, eGFR, and body surface area were measured predonation. Age was not an independent determinant of 10-yr postdonation eGFR and was therefore withdrawn from the 10-yr postdonation eGFR model. The independent validation cohort had no 10-yr eGFR data available.

Table 4 | Reclassification table of models with vs. without the postdonation increase in single-kidney eGFR for predicting a 5- or 10-yr postdonation eGFR of <50 ml/min per 1.73 m^2

Without the postdonation increase in single-kidney eGFR	With the postdonation increase in single-kidney eGFR (n) <30%	30%–60%	>60%	Total (n)	Correctly reclassified: Increased risk	Correctly reclassified: Decreased risk	Net correctly reclassified
Risk of 5-yr postdonation eGFR < 50 ml/min per 1.73 m^2							
Donors reaching a 5-yr postdonation eGFR of <50 ml/min per 1.73 m^2					25%	9%	16%
<30%	22	12[a]	2[a]	36			
30%–60%	7[b]	16	13[a]	36			
>60%	0[b]	3[b]	33	36			
Total	29	31	48	108			
Donors not reaching a 5-yr postdonation eGFR of <50 ml/min per 1.73 m^2					4%	4%	0%
<30%	507	19[b]	1[b]	527			
30%–60%	17[a]	23	4[b]	44			
>60%	0[a]	6[a]	8	14			
Total	524	48	13	585			
Risk of 10-yr postdonation eGFR < 50 ml/min per 1.73 m^2							
Donors reaching a 10-yr postdonation eGFR of <50 ml/min per 1.73 m^2					42%	8%	34%
<30%	13	6[a]	6[a]	25			
30%–60%	0[b]	8	9[a]	17			
>60%	0[b]	4[b]	4	8			
Total	13	18	19	50			
Donors not reaching a 10-yr postdonation eGFR of <50 ml/min per 1.73 m^2					7%	4%	−3%
<30%	234	14[b]	2[b]	250			
30%–60%	11[a]	4	2[b]	17			
>60%	0[a]	1[a]	3	4			
Total	245	19	7	271			

eGFR, estimated glomerular filtration rate.
[a]Donors who were correctly reclassified by the model including the postdonation increase in single-kidney GFR.
[b]Donors who were incorrectly reclassified by the model including the postdonation increase in single-kidney GFR.
Model predicting a 5-yr postdonation eGFR of <50 ml/min per 1.73 m^2: (i) net reclassification improvement 0.16 ($P < 0.001$) and (ii) integrated discrimination improvement 0.08 ($P < 0.001$).
Model predicting a 10-yr postdonation eGFR of <50 ml/min per 1.73 m^2: (i) net reclassification improvement 0.32 ($P < 0.001$) and (ii) integrated discrimination improvement 0.18 ($P < 0.001$).

eGFR of <50 ml/min per 1.73 m^2 (integrated discrimination improvement 0.08; net reclassification improvement 0.16; $P < 0.001$; Table 4).

Of the 321 donors with 10-year postdonation eGFR data available, 50 reached a 10-year postdonation eGFR of <50 ml/min per 1.73 m^2 (median [range] 46 [29–49] ml/min per 1.73 m^2). Predonation eGFR (model 1, Table 3) predicted a 10-year postdonation eGFR of <50 ml/min per 1.73 m^2 with an AUC of 81% (95% CI 75%–87%). Addition of the postdonation increase in single-kidney eGFR (model 2, Table 3) increased the AUC to 88% (95% CI 83%–94%; $P < 0.001$ vs. model 1). The postdonation increase in single-kidney eGFR also improved the reclassification of donors who reached a 10-year postdonation eGFR of <50 ml/min per 1.73 m^2 (integrated discrimination improvement 0.18; net reclassification improvement 0.32; $P < 0.001$; Table 4).

Sensitivity analyses and internal and external validation

We based our definition of the postdonation increase in single-kidney GFR on the assumption that 50% of kidney mass remains after donation. In a sensitivity analysis, we changed the definition to account for the actual percentage of remaining kidney volume (see Supplementary Methods). The modified postdonation increase in single-kidney eGFR was still associated with 5- and 10-year eGFR (Supplementary Table S7). Next, we internally validated our longitudinal analyses by redefining the postdonation increase in single-kidney GFR based on mGFR (^{125}I-iothalamate), yielding similar results regarding the associations with 5- and 10-year mGFR (Supplementary Table S8). Then, we repeated all analyses using the eGFR-based postdonation increase in single-kidney eGFR in an independent validation cohort of 647 donors with 5-year postdonation eGFR available (characteristics in Supplementary Table S9). Multivariable linear regression also revealed age and predonation eGFR as main determinants of the postdonation increase in single-kidney eGFR in the validation cohort (Supplementary Table S10). The postdonation increase in single-kidney eGFR was similarly associated with eGFR at 5 years in the validation cohort (Table 3). Lastly, we calculated the postdonation increase in single-kidney eGFR based on the postdonation eGFR as a percentage of the predonation eGFR. This relative postdonation increase in single-kidney GFR was also associated with long-term eGFR (Supplementary Table S11).

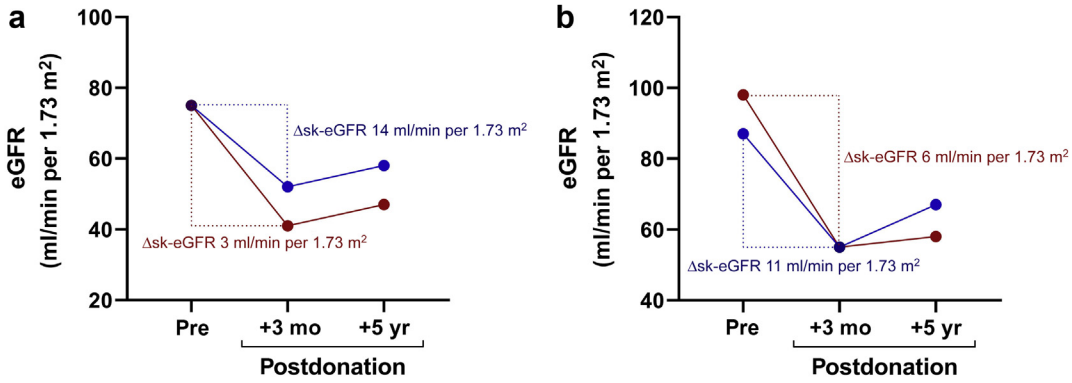

Figure 3 | Examples illustrating application of the postdonation increase in single-kidney estimated glomerular filtration rate (eGFR). (**a**) Two individual patients with identical predonation eGFR (75 ml/min per 1.73 m^2). One patient (blue symbols) had a higher early postdonation eGFR (52 ml/min per 1.73 m^2), resulting from a relatively stronger increase in single-kidney eGFR [Δsk-eGFR = 52 – (75/2) = 14 ml/min per 1.73 m^2]. This patient had a higher long-term eGFR (57 ml/min per 1.73 m^2). The other patient (red symbols) had a lower early postdonation eGFR (41 ml/min per 1.73 m^2), as a result of a less pronounced increase in single-kidney eGFR [Δsk-eGFR = 41 – (75/2) = 3 ml/min per 1.73 m^2]. This patient, despite the identical early postdonation eGFR, had a lower long-term eGFR (49 ml/min per 1.73 m^2). (**b**) Two individual patients with identical eGFR at 3 months postdonation (55 ml/min per 1.73 m^2). One patient (blue symbols) had a lower predonation eGFR (87 ml/min per 1.73 m^2), resulting in a relatively stronger increase in single-kidney eGFR [Δsk-eGFR = 55 – (87/2) = 11 ml/min per 1.73 m^2]. This patient had a higher long-term eGFR (67 ml/min per 1.73 m^2). The other patient (red symbols) had a higher predonation eGFR (98 ml/min per 1.73 m^2), resulting in a less pronounced increase in single-kidney eGFR [Δsk-eGFR = 55 – (98/2) = 6 ml/min per 1.73 m^2]. This patient, despite the identical early postdonation eGFR, had a lower long-term eGFR (58 ml/min per 1.73 m^2).

Practical implications

To illustrate the implications of the postdonation increase in single-kidney GFR beyond predonation and early postdonation GFR, 2 sets of examples are presented in Figure 3. Figure 3a shows the eGFR course for 2 individual patients with an identical predonation eGFR but with different early postdonation eGFR values and subsequently with different eGFR values at 5 years postdonation. Figure 3b shows 2 individual patients with different predonation eGFR values but with an identical eGFR at 3 months postdonation. These patients therefore also had different early increases in single-kidney eGFR and had different long-term eGFR values.

DISCUSSION

This study aimed to investigate the predictive value of short-term postdonation kidney function adaptation, defined as the postdonation increase in single-kidney GFR, for long-term postdonation GFR. Furthermore, we aimed to identify predonation determinants of the postdonation increase in single-kidney GFR. We found that the postdonation increase in single-kidney GFR improves the prediction of long-term postdonation kidney function beyond predonation mGFR and age. Independent determinants of the postdonation increase in single-kidney GFR were age, predonation GFR, and cortical volume of the remaining kidney.

Prediction of long-term postdonation kidney function has been a major goal in transplant nephrology for decades,[25] and several stress tests have been developed to investigate the potential role of the renal reserve capacity in this context. We previously reported that dopamine-induced GFR stimulation before living kidney donation was associated with short-term but not long-term mGFR postdonation.[21] This suggests that predonation dopamine stimulation might reflect only hemodynamic processes that play a dominant role in the early postdonation GFR adaptation, but not long-term adaptation, which might be more a result of adaptive structural changes after kidney donation.[21] The same likely applies to oral/i.v. amino acid administration.[26] In current practice, predonation kidney function and age are often used to estimate postdonation kidney function.[12,13] This study shows that early postdonation GFR adaptation improves the prediction of long-term postdonation kidney function beyond the absolute values of pre- or postdonation GFR and might inform about the reserve capacity of the remaining kidney. In other words, donors with the same pre- or postdonation GFR but differences in postdonation increase in single-kidney GFR displayed differences in long-term kidney function, as shown in the longitudinal analyses of this study. This is in line with the conclusions of a previous study.[27] Possibly, an early increase in GFR reflects a more physiological mechanism of adaptation to acute reduction in kidney mass (i.e., a better renal functional reserve) whereas slow/long-term postdonation increase in GFR may reflect more structural or even pathophysiological changes in the kidney. Of interest, a recent study found that subclinical nephrosclerosis, larger cortical nephron size, and smaller medullary volume observed in intraoperative biopsies in healthy donors predicted recipient death-censored graft failure independently of donor or recipient clinical characteristics.[28] Moreover, another recent study from the same group established an association between nephron number and residual eGFR, defined as postdonation eGFR divided by predonation eGFR.[6] In support of an underlying relationship with residual kidney mass, our study showed that (remaining) kidney volume is an independent determinant of the postdonation increase in single-kidney GFR. The postdonation increase in single-kidney GFR could be used to

guide the intensity of donor follow-up by identifying individuals at risk of decreased GFR on the longer term. The 2017 Kidney Disease: Improving Global Outcomes guideline states that for each donor a personalized plan for follow-up should be made, which describes who should perform follow-up care and how often. It is not specified how this should be personalized. Our study may be useful to guide personalization, as donors with low postdonation increase in single-kidney GFR, similar to dose with low predonation eGFR, might benefit from extended follow-up in the transplant center.

Whether a relatively high postdonation GFR reflects renal reserve or hyperfiltration linked with poor outcome has been a long-standing debate. In various settings, such as diabetic nephropathy, decreased GFR impairment is preceded by hyperfiltration.[11,29] Landmark studies by Brenner and colleagues showed that hyperfiltration is followed by kidney damage and proteinuria in animals.[29,30] However, so far it has been unclear how these observations relate to unilateral nephrectomy in healthy donors. We found that a more pronounced postdonation increase in single-kidney GFR was associated with better, not decreased, long-term GFR, and we found no independent association with the development of proteinuria. Instead, donors with low postdonation increase in single-kidney GFR had worse outcomes on the long-term after donation, possibly because these donors already suffered from nephron loss before donation. Whether donors with a more pronounced postdonation increase in single-kidney GFR retain additional reserve in case of a postdonation "second hit" (e.g., new-onset diabetes) remains unknown.

Donor age and predonation GFR were the main determinants of the postdonation increase in single-kidney GFR, in line with a previous study by our group using the dopamine-based renal functional reserve.[3] The inverse association between age and the postdonation increase in single-kidney GFR could indicate aging-related subclinical kidney injury. Although we analyzed a wide range of variables and identified 3 independent determinants, the multivariable model explained only 16% of variance in the postdonation increase in single-kidney GFR ($R^2 = 0.16$, Table 2), limiting predonation applicability. The inverse association between systolic blood pressure and the postdonation increase in single-kidney GFR that was found in univariable analyses points toward the suggestion that donors with hypertension might suffer from nephron loss and therefore retain less capacity to increase GFR postdonation. However, this association lost significance after adjustment for age, which also applies to sex, body mass index, and HbA1c. The association with (cortical) kidney volume is in line with previous studies connecting kidney volume with (postdonation) GFR.[8,31] Our findings pave the way for future studies that identify underlying molecular mechanisms, define biomarkers, and reveal the clinical potential of the postdonation increase in single-kidney GFR, both in and beyond kidney donation.

Our main cohort is unique in that it consists of a large number of donors with both repeated eGFR and mGFR measurements before and up to 10 years after donation. Although we cannot fully exclude residual confounding, our results were robust upon multivariable adjustment and consistent in internal and external validation cohorts. Limitations of our study include poor generalizability to populations other than White people and the lack of follow-up beyond 10 years precluding conclusions on the potential impact on the risk of kidney failure. The time range in which the postdonation compensatory increase in kidney function is determined varies among studies, and in our center, only 3 months postdonation eGFR and mGFR data were available.[25] Lastly, the postdonation increase in single-kidney GFR cannot be assessed before donation, underlining the need to develop adequate biomarkers in addition to age, cortical kidney volume, and kidney function.

In conclusion, we found that the postdonation increase in single-kidney GFR predicts long-term kidney function independent of predonation GFR, age, and body surface area. Our findings provide novel insights in the prognostic potential of the kidney's reserve capacity.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

We thank T.M. Royaards, Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands, for her contribution to the data collection and management of the replication cohort.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Methods.

Table S1. Overview of available data.

Table S2. Living kidney donor characteristics before donation in a subgroup with and without computed tomography–based (remaining) cortical kidney volume data available.

Table S3. Determinants of the postdonation increase in single-kidney estimated glomerular filtration rate (eGFR) in a subgroup with remaining cortical kidney volume data available ($n = 499$).

Table S4. Living kidney donor characteristics before donation in subgroups with and without 5- and 10-yr postdonation estimated glomerular filtration rate (eGFR) data available.

Table S5. Univariable associations of the postdonation increase in single-kidney glomerular filtration rate (GFR) and predonation parameters with estimated GFR (eGFR) at 5 and 10 years postdonation.

Table S6. Longitudinal association of the postdonation increase in single-kidney estimated glomerular filtration rate (Δsk-GFR) with a protein-creatinine ratio (PCR) of >15 mg/mmol at 5 and 10 years postdonation.

Table S7. Multivariable associations of the postdonation increase in single-kidney estimated glomerular filtration rate (eGFR), based on the remaining versus total cortical kidney volume (Δsk-GFR_{KV}), with eGFR at 5 and 10 years postdonation.

Table S8. Multivariable associations of the postdonation increase in single-kidney measured glomerular filtration rate (mGFR) with mGFR at 5 and 10 years postdonation.

Table S9. Characteristics of the validation cohort.

Table S10. Multivariable linear regression model of predonation variables with the increase in single-kidney estimated glomerular filtration rate (eGFR) in the discovery and validation cohorts.
Table S11. Associations of the relative increase in single-kidney estimated glomerular filtration rate (postdonation increase in single-kidney glomerular filtration rate [Δsk-GFR]) with 5- and 10-year eGFR.
Supplementary References.

REFERENCES

1. Verney E, Camb M, Lond F. The reserve forces of the kidney. *Lancet*. 1930;216:63–69.
2. Delanaye P, Weekers L, Dubois BE, et al. Outcome of the living kidney donor. *Nephrol Dial Transplant*. 2012;27:41–50.
3. Rook M, Bosma RJ, Van Son WJ, et al. Nephrectomy elicits impact of age and BMI on renal hemodynamics: lower postdonation reserve capacity in older or overweight kidney donors. *Am J Transplant*. 2008;8:2077–2085.
4. Sugino N, Duffy G, Gulyassa P. Renal function after unilateral nephrectomy in normal man. *Clin Res*. 1967;15:143.
5. Lenihan CR, Busque S, Derby G, et al. Longitudinal study of living kidney donor glomerular dynamics after nephrectomy. *J Clin Invest*. 2015;125:1311–1318.
6. Merzkani M, Denic A, Narasimhan R, et al. Kidney microstructural features at the time of donation predicts long-term risk of chronic kidney disease in living kidney donors. *Mayo Clin Proc*. 2021;96:40–51.
7. Fananapazir G, Benzl R, Corwin MT, et al. Predonation volume of future remnant cortical kidney helps predict postdonation renal function in live kidney donors. *Radiology*. 2018;288:153–157.
8. Hori S, Tanaka N, Yoneda T, et al. Remnant renal volume can predict prognosis of remnant renal function in kidney transplantation donors: a prospective observational study. *BMC Nephrol*. 2021;22:367.
9. Rook M, Hofker HS, Van Son WJ, et al. Predictive capacity of pre-donation GFR and renal reserve capacity for donor renal function after living kidney donation. *Am J Transplant*. 2006;6:1653–1659.
10. Tonneijck L, Muskiet MHA, Smits MM, et al. Glomerular hyperfiltration in diabetes: mechanisms, clinical significance, and treatment. *J Am Soc Nephrol*. 2017;28:1023–1039.
11. Brenner BM, Lawler EV, Mackenzie HS. The hyperfiltration theory: a paradigm shift in nephrology. *Kidney Int*. 1996;49:1774–1777.
12. British Transplantation Society, The Renal Association. *Guidelines for Living Donor Kidney Transplantation*. 4th ed. British Transplantation Society; March 2018:1–87.
13. Lentine K, Kasiske B, Levey A, et al. KDIGO Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors. *Transplantation*. 2017;101(8S, suppl 1):S1–S109.
14. Mariat C, Mjøen G, Watschinger B, et al. Assessment of pre-donation glomerular filtration rate: going back to basics. *Nephrol Dial Transplant*. 2022;37:430–437.
15. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the Modification of Diet in Renal Disease Study equation for estimating glomerular. *Ann Intern Med*. 2014;145:247–254.
16. Tent H, Rook M, Stevens LA, et al. Renal function equations before and after living kidney donation: a within-individual comparison of performance at different levels of renal function. *Clin J Am Soc Nephrol*. 2010;5:1960–1968.
17. Donker A, van der Hem G, Sluiter W, Beekhuis H. A radioisotope method for simultaneous determination of the glomerular filtration rate and the effective renal plasma flow. *Neth J Med*. 1977;20:97–103.
18. Bertoni E, Rosati A, Zanazzi M, et al. Functional reserve and hyperfiltration after cadaveric renal transplantation. *Transplant Proc*. 2001;33:3363–3364.
19. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes—2020*. *Diabetes Care*. 2020;43(suppl 1):S14–S31.
20. Fisher H, Hsu C, Vitiinghoff E, et al. Comparison of associations of urine protein-creatinine ratio versus albumin-creatinine ratio with complications of CKD: a cross-sectional analysis. *Am J Kidney Dis*. 2013;62:1–7.
21. van Londen M, Kasper N, Hessels NR, et al. Renal functional reserve capacity before and after living kidney donation. *Am J Physiol Physiol*. 2018;315:F1550–F1554.
22. DeLong E, DeLong D, Clarke-Pearson D. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44:837–845.
23. Pencina M, D'Agostino RS, D'Agostino RJ, Vasan R. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:207–212.
24. Pencina MJ, D'Agostino RB, Pencina KM, et al. Interpreting incremental value of markers added to risk prediction models. *Am J Epidemiol*. 2012;176:473–481.
25. Figurek A, Luyckx VA, Mueller TF. A systematic review of renal functional reserve in adult living kidney donors. *Kidney Int Rep*. 2020;5:448–458.
26. Ter Wee P, Rosman J, Van der Geest S, et al. Renal hemodynamics during separate and combined infusion of amino acids and dopamine. *Kidney Int*. 1986;29:870–874.
27. Massie AB, Holscher CM, Henderson ML, et al. Association of early postdonation renal function with subsequent risk of end-stage renal disease in living kidney donors. *JAMA Surg*. 2020;155:e195472.
28. Issa N, Lopez CL, Denic A, et al. Kidney structural features from living donors predict graft failure in the recipient. *J Am Soc Nephrol*. 2020;31:415–423.
29. Hostetter T, Olson J, Rennke H, et al. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol Physiol*. 1981;240:F85–F93.
30. Anderson S, Meyer TW, Rennke HG, Brenner BM. Control of glomerular hypertension limits glomerular injury in rats with reduced renal mass. *J Clin Invest*. 1985;76:612–619.
31. Wang X, Vrtiska TJ, Avula RT, et al. Age, kidney function, and risk factors associate differently with cortical and medullary volumes of the kidney. *Kidney Int*. 2014;85:677–685.