ORIGINAL ARTICLE

Five-year follow-up after live donor nephrectomy – cross-sectional and longitudinal analysis of a prospective cohort within the era of extended donor eligibility criteria

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SUMMARY

To establish the outcome of live kidney donors 5 years after donation, we investigated the risk for progressive renal function decline and quality of life (QoL). Data on estimated glomerular filtration rate (eGFR), creatinine, hypertension, QoL and survival were assessed in a prospective cohort of 190 donors, who donated between 2008 and 2010. Data were available for >90%. The mean age predonation was 52.8 ± 11.5 years, 30 donors having pre-existent hypertension. The mean follow-up was 5.1 ± 0.9 years. Eight donors had died due to non-donation-related causes. After 5 years, the mean eGFR was 60.2 (95% CI 58.7–62.7) ml/min/1.73 m^2, with a median serum creatinine of 105.1 (95% CI 102.5–107.8) μmol/l. eGFR decreased to 33.6% and was longitudinally lower among men than women and declining with age ($P < 0.001$), without any association on QoL. Donors with pre-existent and new-onset hypertension demonstrated no progressive decline of renal function overtime compared to nonhypertensives. No donors were found with proteinuria, microalbuminuria or at risk for end-stage renal disease. After an initial decline postdonation, renal function remained unchanged overtime. Men and ageing seem to affect renal function overtime, while decreased renal function did not affect QoL. These data support further stimulation of living kidney donation programmes as seen from the perspective of donor safety.

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Introduction

Renal transplantation offers a better prognosis and long-term benefit to patients with chronic kidney failure compared with other renal replacement therapies [1,2]. The benefits of live kidney donation have been well described [3–6], and the surgical procedure has been proven to be safe [7–13] with a very low mortality rate [13,14]. In addition, health-related QoL of donors after the procedure has proven to be better than that of the general population [7,8,10,15,16]. Driven by its success, the inclusion criteria of the living donation programme gradually have been extended and older donors and donors with minor comorbidities such as hypertension and obesity have become eligible for donation [17–20].

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However, it must be noted that live donor nephrectomy is performed on people considered to be healthy individuals who do not need any intervention. Therefore, seeking after optimal donor safety remains priority in living kidney donation for the short term as well as the long term. It has been documented that renal function usually may decline directly after donation and recovers within the first year. Previous studies suggest that renal function reached at 1 year postdonation remains stable at least for over the next decade [16,21,22], but then declines with ageing [21]. These studies report on cohorts including low numbers of donors with minor comorbidities, such as hypertension and obesity. Therefore, the outcome of these studies may not apply for donors under the donor eligibility criteria used at present.

Previously, we have reported on the 1-year follow-up of a donor cohort from a randomized study on hand-assisted or laparoscopic donor nephrectomy [10]. Donors were included with hypertension and overweight. We now present data of 5-year follow-up and analysed the effect of potential factors associated with accelerated decline of renal function. In addition, we longitudinally studied the effect of renal function on health-related QoL of live kidney donors.

Patients and methods

Study population

All 190 donors of a randomized controlled trial comparing left-sided hand-assisted and laparoscopic donor nephrectomy conducted between July 2008 and September 2010 at the Radboud University Medical Center, Nijmegen, and the Erasmus University Medical Center, Rotterdam, were selected [10,23]. The pre-, intra- and postsurgery procedures were described previously [10,23]. An amendment to the protocol [23] was written and approved by the internal medical ethics committee to evaluate the 5-year follow-up data of all donors (MEC-2015-653), and a description of the ethical guidelines was followed.

Surgical procedures

Donors were operated in two Dutch tertiary referral centres of which 95 were randomized to hand-assisted and 95 to laparoscopic donor nephrectomy. Both surgical techniques have been described previously [23].

Data collection

Yearly visits to the outpatient clinic or the general practitioner were scheduled. All donors have prospectively been followed since donation. For this study, data were collected from medical records 5 years after the randomized controlled trial had ended. The data collection included serum creatinine, proteinuria, microalbuminuria, blood pressure, weight, hypertension, medication and donor survival. A creatinine-based estimated glomerular filtration rate (eGFR) was measured with the CKD EPI = Chronic Kidney Disease Epidemiology Collaboration equation [24]. Proteinuria was defined as a protein–creatinine ratio of >45 mg/mmol [25] and microalbuminuria as an albumin–creatinine ratio of >30 mg/mmol [26]. Blood pressure was manually measured in an upright position in the examination room on one arm. Hypertension was defined as listed as diagnosis in medical records, the use of antihypertensive medication or repeated high blood pressure measurements. Donor survival was checked in the municipal registry up to 13 November 2015 and, if applicable, the date and reason of death were recorded.

QoL measures

We used a physical and mental instrument to assess the QoL, both represented in the Short-Form Health Questionnaire, a validated and commonly used tool to measure health-related QoL. It contains questions on physical performance and well-being, and mental functioning and emotional well-being, resulting in the physical (PCS) and mental component score (MCS), respectively. The SF-12 can be extracted from a SF-36 [27,28]. The component scores are computed by normative comparison and standardized to the Dutch population [29,30]. Scores below 50 indicate inferior QoL compared to the general Dutch population, and scores above 50 indicate superior QoL. The EQ-5D records QoL in five dimensions: mobility, self-care, daily activities, pain or discomfort and anxiety/depression. The responses on the five dimensions combine to a score between −0.59 (worst imaginable health state) and 1.00 (best imaginable health state) [31]. The SF-36 and EQ-5D questionnaires had been conducted preoperatively at 1, 3 and 6 months, and 1 year [10]. For the current study, SF-12 and EQ-5D questionnaires were sent to all donors who were still alive 5 years after the trial had ended.

Statistical analysis

The difference between baseline and follow-up was compared with paired *t*-tests for continuous normally

distributed variables, Wilcoxon tests for abnormally distributed variables and the chi-square tests for categorical variables.

Mixed modelling, also referred to as multilevel regression analysis, was applied for longitudinal analyses of renal function and health-related QoL. Multilevel regression analysis can efficiently handle data with unbalanced time points and corrects for selective dropout when the dropout is dependent on aspects that are included in the model [32]. First, saturated models were postulated for each of the dependent variables eGFR, creatinine, PCS, MCS and EQ-5D. The saturated models included age, gender, BMI, pre-existent hypertension, new-onset hypertension, PCS, MCS, EQ-5D, time, linear and logarithmic and all interactions with time as fixed effects. The time variables were entered as continuous variables. The deviance statistic [33] using restricted maximum likelihood [34] was applied to determine the most parsimonious covariance structure (unstructured, variance components or intercept only). The saturated model was subsequently reduced by eliminating insignificant fixed effects, taking into account that interaction effects ought to be nested under their respective main effects [35]. The significance of the difference between the saturated model and the parsimonious final model was determined with the deviance statistic using ordinary likelihood. Effect sizes (Cohen's *d*) were computed by dividing the difference between the estimate at time point *t* and the baseline score by the estimated baseline standard deviation. An effect size between 0.20 and 0.50 was considered a small effect, between 0.50 and 0.80 a medium effect and above 0.80 a large effect [36]. All analyses were conducted using SPSS (version 22; SPSS Inc., Chicago, IL, USA). Two-sided *P*-values < 0.05 were considered statistically significant.

Results

Population characteristics

The living kidney donation procedures were conducted in 93 (48.9%) living-related and 97 (51.1%) nonrelated donor–recipient combinations. Thirty-two per cent of the donors ($n = 61$) had (multiple) extended eligibility criteria: pre-existent hypertension ($n = 30$), age >70 years ($n = 10$) and BMI > 30 kg/m^2 ($n = 26$). The follow-up examinations were performed between November 2015 and January 2016. Eight donors had passed away due to non-donation-related causes; three of these eight donors had completed a 5-year follow-up. Five donors were lost to follow-up: one donor lives abroad and four donors were not willing to visit the outpatient clinic for the annual follow-up. Thus, follow-up data were available in more than 90.0% of donors. Mean follow-up of the population was 5.1 ± 0.9 years. Population characteristics are shown in Table 1.

Renal function

Only gender and age turned out to have significant effect on eGFR (Table 2). After 1 year, eGFR values for

Table 1. Population characteristics predonation and at 5-year follow-up.

	Predonation ($n = 190$)		Five years ($n = 176$)		
	n	Mean ± SD/median [IQ-range]/frequencies (%)	*n*	Mean ± SD/median [IQ-range] frequencies (%)	*P*-value
Age (years)	190	52.8 ± 11.5	176	58.0 ± 11.1	–
Gender (male)	190	92 (48.4)	176	82 (46.6)	–
Caucasian	190	183 (96.3)	176	170 (96.6)	–
Creatinine (μmol/l)	190	74 [64–83]	173	104 [91–118]	<0.001
eGFR (ml/min/1.73 m^2)	190	91.9 ± 15.0	173	60.2 ± 12.1	<0.001
BMI (kg/m^2)	190	25.9 [23.8–28.5]	157	26.7 [24.5–30.1]	<0.001
Systolic blood pressure (mmHg)	189	130 [120–144]	167	134 [120–145]	0.407
Diastolic blood pressure (mmHg)	189	79 [73–85]	167	80 [75–85]	0.005
Hypertension*	170	30 (17.6)	169	59 (34.7)	<0.001
Physical component score	178	58.4 [55.8–59.8]	169	52.3 [48.3–55.5]	<0.001
Mental component score	178	54.4 [52.1–56.4]	169	44.2 [40.0–49.0]	<0.001
EQ-5D score	188	1.00 [1.00–1.00]	167	1.00 [0.84–1.00]	0.350

eGFR, estimated glomerular filtration rate.

*Defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or the use of antihypertensive medication.

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Table 2. Parsimonious mixed models predicting renal function and QoL measures.

	Intercept or main effect		Time linear		Time logarithmic	
Model	Estimate	Standard error	Estimate	Standard error	Estimate	Standard error
eGFR (ml/min/1.73 m^2)	90.26***	1.06	18.70***	0.66	−68.40***	1.94
Men	1.99*	0.66			−1.86*	0.83
Age	−0.83***	0.07	−0.13*	0.06	0.48**	0.17
Creatinine (μmol/l)	67.57***	1.25	−19.41***	1.18	67.61***	3.33
Men	15.42***	1.81	−5.74***	1.67	22.70***	4.75
Age	0.16*	0.07			0.15**	0.05
PCS	57.02***	0.52	−2.43**	0.75	2.69	2.08
Men	0.00	0.74	2.71*	1.08	−6.71*	3.02
Age	−0.10***	0.03				
BMI	−0.40***	0.09				
New-onset hypertension	2.30*	0.89				
MCS	52.37***	0.58	−3.39***	0.58	4.34**	1.60
Men	1.80*	0.80				
EQ-5D	0.947***	0.009	−0.023*	0.011	0.063*	0.031
Pre-existent hypertension	0.003	0.020	−0.013*	0.006		
BMI	0.005*				−0.007***	0.002

eGFR, estimated glomerular filtration rate; MCS, mental component score; PCS, physical component score; QoL, quality of life. All models included age, gender, BMI and pre-existent and new-onset hypertension for all models. In addition, PCS, MCS and EQ-5D for outcome renal function, and eGFR and creatinine for outcome QoL. Only significant effects are mentioned.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

women decreased significantly with 31.8% and thereafter remained stable during 5 years after donation (Table 3). Men had at baseline a small but significantly higher eGFR than women, which decreased with 32.5% after 1 year, and decreased further to 35.1% after 5 years. Older patients (e.g. age 10 years older) had lower baseline values, but recovered slightly at the 1- and 5-year follow-up. Overall, the 5-year follow-up measurements of eGFR compared with the predonation measurements demonstrated a mean decline in eGFR of 33.6%. Longitudinal analysis showed no effect of new-onset hypertension and BMI on eGFR (data not shown). Furthermore, no different outcome in eGFR ($P = 0.479$) or eGFR decline ($P = 0.159$) was found in donors with extended eligibility criteria ($n = 61$) as compared with donors without these criteria.

Also for creatinine, gender and age were found to have significant effects on renal function (Table 2). After 1 year, creatinine values for women increased significantly with 40.6%, but this reduced to 35.7% 5 years after donation (Table 3). Men had at baseline a small but significantly higher creatinine level than women, which increased with 45.1% after 1 year and remained stable (43.5%) after 5 years. Older patients had lower baseline values, and these increased slightly at 1- and 5-year follow-up. Overall, the 5-year follow-up measurements of creatinine compared with the predonation measurements resulted in a mean increase of 39.4%. Longitudinal analysis demonstrated no effect of pre-existent and new-onset hypertension, or BMI on creatinine.

The 5-year follow-up mean eGFR of men and women is plotted against age categories ($n = \pm 20$), as depicted in Fig. 1 (See Table S1 for corresponding values). The eGFR of the donors is matched to the eGFR of corresponding age categories of the general population [37]. All age categories for men and women demonstrated significant differences in eGFR.

Ninety-three donors had an eGFR < 60 ml/min/1.73 m^2 at 5-year follow-up without proteinuria (mean protein–creatinine ratio of 11.3 ± 6.9 mg/mmol) or microalbuminuria (mean albumin–creatinine ratio of 2.5 ± 4.5 mg/mmol). These donors were older at the time of donation (mean 58.3 ± 8.6 vs. 47.5 ± 10.6 years, $P < 0.001$) and had a lower eGFR predonation (mean 82.3 ± 11.5 vs. 101.0 ± 10.7 ml/min/1.73 m^2, $P < 0.001$) than donors with a current eGFR of ≥60 ml/min/1.73 m^2. In addition, their eGFR decline was higher at 5-year follow-up, mean 36.9 ± 8.6 vs. 30.0 ± 7.8% ($P < 0.001$) respectively. However, there were no differences at 5-year follow-up in gender ($P = 0.152$) or BMI ($P = 0.920$).

Table 3. Longitudinal analysis of renal function and QoL.

	Estimates			Effect sizes (Cohen's *d*)		
Model	Baseline	1 year	5 years	Baseline–1 year	Baseline–5 years	1–5 years
eGFR (ml/min/1.73 m^2)						
Women	90.3	61.6	61.2	−2.68***	−2.71***	−0.03
Men	92.2	62.3	59.9	−2.80***	−3.02***	−0.22**
Age of 10 years older, additional effect†	−8.3	−6.4	−6.4	0.18**	0.18***	−0.00
Creatinine (μmol/l)						
Women	67.6	95.0	91.7	2.15***	1.89***	−0.26*
Men	83.0	120.4	119.1	2.93***	2.82***	−0.11
Age + 10 years†	1.6	2.6	4.2	0.08**	0.21**	0.13**
PCS						
Women	57.0	56.5	49.7	−0.11	−1.45***	−1.34***
Men	57.0	54.5	51.2	−0.50**	−1.15***	−0.65***
Age of 10 years older, additional effect†	−1.0	−1.0	−1.0			
BMI 5 kg/m^2 higher, additional effect†	−2.0	−2.0	−2.0			
New-onset hypertension†	2.3	2.3	2.3			
MCS						
Women	52.4	52.0	43.2			
Men	54.2	53.8	45.0	−0.06	−1.51***	−1.45***
EQ-5D						
No pre-existent hypertension	0.95	0.97	0.95	0.18	0.02	−0.19
Pre-existent hypertension	0.94	0.95	0.88	0.07	−0.55*	−0.62**
BMI 5 kg/m^2 higher, additional effect†	0.03	0.00	−0.04	−0.21***	−0.54***	−0.33***

eGFR, estimated glomerular filtration rate; MCS, mental component score; PCS, physical component score; QoL, quality of life.

All models included age, gender, BMI, pre-existent, and new-onset hypertension for all models. In addition, PCS, MCS and EQ-5D for outcome renal function, and eGFR and creatinine for outcome QoL. Only significant effects are mentioned.

†This value must be added to the estimate reported above; for example, the eGFR estimate for women at mean age (52.3 years) at baseline is 90.3, and the estimate for 10 years older women (i.e. 62.3 years) is 90.3–8.3 = 82.0.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. Nonsignificant effects are deleted.

At follow-up, none of the donors had proteinuria or microalbuminuria; mean protein–creatinine ratio was 13.5 ± 24.6 mg/mmol and mean albumin–creatinine ratio was 2.0 ± 3.6 mg/mmol. No donors were found at risk for end-stage renal disease or renal replacement therapy. Among the 93 living-related donations, 14.7% of the recipients ($n = 10$) had a hereditary renal disease (e.g. Joubert syndrome, polycystic kidney disease). No significant differences in eGFR or protein–creatinine ratio were found among living-related donors with recipients with a hereditary renal disease and other living-related donors, $P = 0.408$ and $P = 0.490$, respectively.

Effect of hypertension on renal function

Blood and urine renal function measures among nonhypertensive and hypertensive donors are depicted in Table 4. The eGFR overtime for nonhypertensive and hypertensive donors is depicted in Fig. 2.

Thirty donors (17.6%) had pre-existent hypertension compared with 59 donors at follow-up. The 5-year eGFR and serum creatinine of donors with pre-existent hypertension were not significantly different from these values of nonhypertensive donors, $P = 0.062$ and $P = 0.533$, respectively. Donors with pre-existent hypertension were adequately treated after donation and showed no abnormalities at follow-up, having a mean systolic blood pressure of 138.9 ± 17.6 mmHg and a mean diastolic blood pressure of 83.5 ± 9.2 mmHg. Treatment consisted of beta blockers ($n = 16$), diuretics ($n = 12$), calcium chain blockers ($n = 5$), ACE inhibitors ($n = 5$), ATI inhibitors ($n = 5$) and other ($n = 1$). Ten donors used one medication to regulate blood pressure. During follow-up of donors, antihypertensive medication was unchanged in nine, dose adaptation or combined drug treatment in eight, complete drug substitution in five, cessation of medication in three and dose reduction in two. Of two donors, it is unknown whether the medication has altered compared to

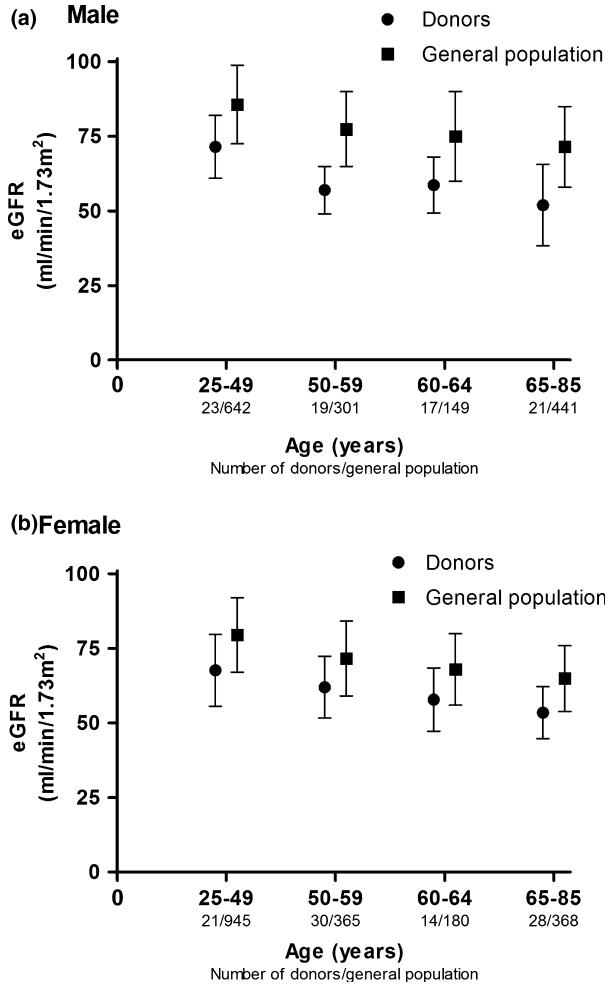

Figure 1 Overview of mean estimated glomerular filtration rate (eGFR) values at 5-year follow-up after live kidney donation of male (a) and female (b) donors with corresponding eGFR of the general population.

predonation use, and of one donor the use of medication is unknown.

Twenty-nine donors developed new-onset hypertension with a mean systolic blood pressure of 141.7 ± 17.3 and a mean diastolic blood pressure of 83.1 ± 7.9 mmHg. They were mostly treated with medication, including beta blockers ($n = 7$), diuretics ($n = 5$), calcium chain blockers ($n = 3$), ACE inhibitors ($n = 10$) and ATI inhibitors ($n = 7$). One donor used three medications, eight donors used two medications, fifteen donors used one medication, four donors did not use medication and of one donor the number of medications is unknown. The 5-year eGFR and serum creatinine of new-onset hypertensive donors were significantly different compared to nonhypertensive donors, $P = 0.001$ and $P = 0.015$, respectively, while the eGFR decline was not significantly different, 36.6% vs. 33.4% ($P = 0.073$), respectively. New-onset hypertensive donors were older at the time of donation (59.0 ± 8.7 vs. 50.4 ± 11.2 years, $P < 0.001$) with a higher BMI (27.6 ± 3.7 vs. 25.9 ± 3.4, $P = 0.021$), and lower eGFR before donation (85.9 ± 13.0 vs. 94.1 ± 14.8 years, $P = 0.007$) compared with nonhypertensive donors. Furthermore, there were more donors with an eGFR < 60 ml/min/1.73 m^2 with new-onset hypertension compared with nonhypertensive donors, 79.3% vs. 43.5% ($P = 0.001$), respectively.

Health-related QoL

Donor response with regard to the QoL questionnaires was almost 90% of the original cohort. PCS and EQ-5D follow-up scores were higher compared with the general Dutch population [29,30]. MCS scores were lower (Table 1). There were no significant differences in PCS, MCS and EQ-5D score at 5-year follow-up between donors with an eGFR < 60 ml/min/1.73 m^2 compared with an eGFR ≥ 60 ml/min/1.73 m^2, $P = 0.993$, $P = 0.754$ and $P = 0.242$ respectively. There was also no significant difference in MCS at 5-year follow-up among living-related donors for recipient ($P = 0.837$) or graft survival ($P = 0.894$).

Longitudinal analysis of health-related QoL

No change in PCS was observed in women after 1 year, but they had a large decrease 5 years after donation. Men had a medium decrease at 1 year with a further reduction at 5 years. Older donors and donors with a higher BMI had lower PCS over the whole period. Donors who developed new-onset hypertension had higher PCS predonation and during follow-up. In all donors, a large decrease in MCS was observed after 5 years. MCS scores remained stable at 1-year follow-up, but showed a large decrease at 5-year follow-up. Men had slightly higher MCS than women predonation and during follow-up. Donors had a small decrease in EQ-5D values after 1 year, but this difference was not significant at the 5-year follow-up. Donors with a pre-existent hypertension had a medium decrease at 1- and 5-year follow-up. Donors with, for example, 5 kg/m^2 higher BMI had relatively lower baseline EQ-5D scores, which reduced further to a medium decrease at 5-year follow-up (Table 3). No significant effect of age or gender on EQ-5D scores was found.

Table 4. Effect of hypertension on renal function of live kidney donors.

Renal function	Nonhypertensives $N = 111$ Mean ± SD/median [IQ-range]	Pre-existent hypertensives $N = 30$ Mean ± SD/median [IQ-range]	New-onset hypertensives $N = 29$ Mean ± SD/median [IQ-range]
Blood			
eGFR (ml/min/1.73 m^2)			
Baseline	94.1 ± 14.8	85.4 ± 12.1	85.9 ± 13.0
1 year	60.7 ± 11.6	54.4 ± 11.3	53.2 ± 10.2
5 years	62.3 ± 12.2	57.6 ± 12.2	54.2 ± 9.7
Creatinine (μmol/l)			
Baseline	74 [56–92]	76 [58–104]	73 [45–101]
1 year	106 [81–131]	112 [94–130]	112 [84–130]
5 years	102 [75–129]	103 [73–134]	119 [84–153]
Urine			
Protein–creatinine ratio			
5 years	8.7 [2.7–14.7]	11.8 [1.8–21.8]	8.5 [5.2–11.8]
Albumin–creatinine ratio			
5 years	0.9 [−0.5 to 2.3]	1.9 [−4.3 to 6.3]	1.4 [0.1–2.7]

eGFR, estimated glomerular filtration rate.

Survival

Eight donors died due to non-donation-related causes. One donor suddenly died at home within 1 year after donation due to an unknown reason after coughing up blood (age 75, unrelated donation); four donors died after 4 years of follow-up, one for unknown reason (negative findings at autopsy; age 24, related donation), one due to sudden cardiac arrest (age 62, unrelated donation), one due to a malignant mesothelioma (age 67, unrelated donation) and one due to a brain tumour (age 65, unrelated donation); two died after 5 years of follow-up, one due to lung cancer (age 56, related donation) and one due to sepsis (age 63, related donation); and finally one died after 6 years of follow-up due to decompensated alcoholic liver cirrhosis (age 66, related donation).

Discussion

This study reports on a prospective cohort of 190 donors that were followed annually after living kidney donation up to 5 years after the randomized trial had ended. Data were available of more than 90% of donors. This study demonstrates a stable renal function 5 years after donation with no progressive decline in function. Also, donors with pre-existent and new-onset hypertension do not have a progressive decline during follow-up. Furthermore, no proteinuria or albuminuria was observed in any of the donors, not even in donors with an eGFR < 60 ml/min/1.73 m^2. This supports the assumption that live kidney donors are a highly selected group of healthy individuals who may safely proceed in life with one kidney and the values on eGFR and creatinine outside the normal range for individuals with two kidneys do not indicate any physiological dysfunction, because secondary signs of kidney disease such as proteinuria are not present. These findings support the recommendation of Matas and Ibrahim [38] that kidney donors with an eGFR < 60 ml/min/1.73 m^2 should not be classified as having chronic kidney disease, especially if there are no other signs of kidney disease present.

Renal function

Our study demonstrates that lower eGFR after donation is longitudinally associated with older age and male gender, and cross-sectionally with lower predonation eGFR levels. All three factors can easily be explained. The CKD-EPI equation [24] used to calculate the eGFR has age and gender embedded in the equation. Therefore, ageing will result in a lower eGFR, while the serum creatinine remains stable. This is comparable to the findings in the general population. Second, muscle mass, which is different between males and females, influences serum creatinine levels and is therefore responsible for the difference in eGFR. Last, there is an expected decline in eGFR levels among donors after donation; therefore, lower predonation eGFR levels will result in lower postdonation levels. Thus, by definition,

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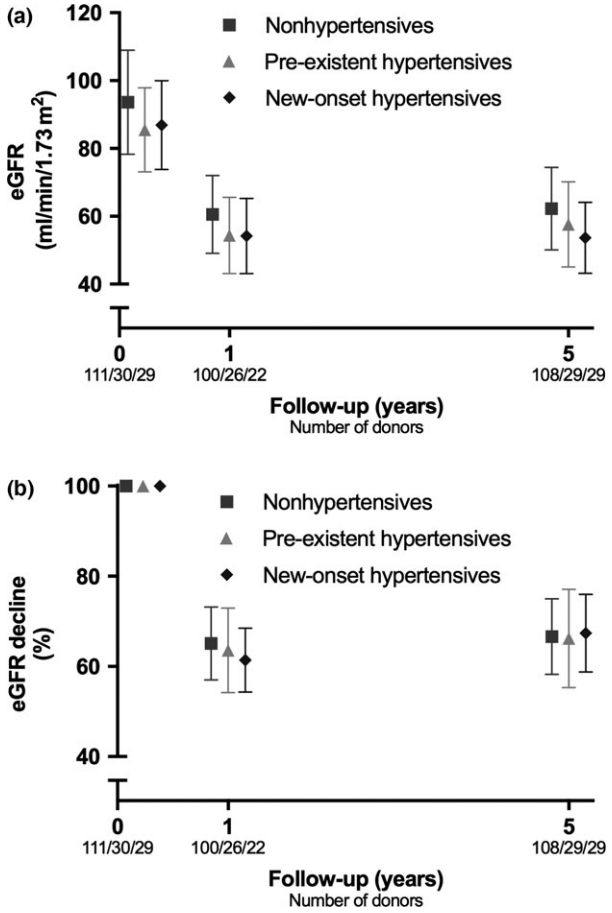

Figure 2 Renal function (a, eGFR overtime; b, eGFR decline) during follow-up of nonhypertensive, pre-existent hypertensive and new-onset hypertensive donors overtime. eGFR, estimated glomerular filtration rate.

donors with lower eGFR levels will have lower eGFR levels at follow-up. In our study, no donors had any signs of glomerular dysfunction such as proteinuria or microalbuminuria, not even donors with an eGFR < 60 ml/min/1.73 m^2.

Other studies reporting on renal function following donation also reported on a stable renal function after 1 year [39–44], with a decline in renal function of 31–40% [43,44]. Despite that our cohort is older compared with most studies and has included a higher number of hypertensive donors with a higher predonation eGFR, the decline fits the lower range. The renal function of the general population age categories [37] was found to be higher than our donor cohort. It should be noted that hypertensives were excluded from their analysis, which could have led to a higher renal function among the general population. Furthermore, the renal function was calculated using the MDRD [45]. Nowadays, the CKD-EPI equation is used, which is more accurate compared with the MDRD equation [24].

Effect of hypertension on renal function

Ageing and hypertension are reported to be associated with progressive decline in renal function in the general population [46–50]. These factors are part of the extended eligibility criteria of live kidney donors indicating that they would even have an increased risk with just one kidney and no renal reserve left. Our study demonstrated that in cross-sectional analysis new-onset hypertensive donors have a significant lower eGFR and higher serum creatinine at 5-year follow-up than nonhypertensive donors, while eGFR decline was similar. More importantly, longitudinal analysis demonstrated no effect of new-onset hypertension on eGFR. Furthermore, the incidence of hypertension is known to increase with age [51], which is supported by our finding that hypertensives were significantly older than nonhypertensives. The used definition of hypertension embeds the use of antihypertensive medication [52], which could include donors who were prescribed antihypertensive medication for a different indication than hypertension, such as a cardiac condition (beta blockers, diuretics or ACE inhibitors). The use of antihypertensive medication can influence the renal function, such as ACE inhibitors, which could decrease or remove proteinuria, or increase serum creatinine, and diuretics, which could increase the serum creatinine, resulting in a lower eGFR. This could have affected our renal function results among hypertensive donors. Reassuringly, as in previous studies [40–44,47,53], we found no evidence of further decline in renal function after 1 year, no proteinuria or albuminuria, and no donors at risk for end-stage renal disease.

Health-related QoL

EQ-5D scores remained at the same level after 5 years of follow-up. Physical and mental component scores decreased after 5 years, but the PCS remained higher than the general population scores [30], and the MCS at 5-year follow-up was lower. The overall decrease in all measures overtime is a phenomenon that has also been observed in the general population [30]. It has been established that QoL depends on both age and gender [30,54]. This was true for the PCS where differences were found in age and gender, but also in BMI. The latter is known to be associated with a decreased QoL among the general population [55,56]. Reassuringly, the PCS was not affected by a decreased eGFR < 60 ml/min/1.73 m^2, which is known to decrease physical functioning [57]. Unfortunately, the

overall decrease for MCS was larger overtime compared to the general population [30]. This could not be explained by age or BMI. MCS was not affected by recipient or graft survival among living-related donors. However, some respondents did report to have mental difficulties due to problems at work, or death of a partner or family member. This might explain the lower MCS for some donors, but this was not a sufficient explanation for the overall lower MCS at 5-year follow-up. This may be explained by assuming that donors are mentally affected by other (medical) conditions not related to donation or life events. It must be noted that while donors are a preselected group of individuals, their QoL follow-up scores are within the range of the general population.

Strengths and limitations

The strength of this study is the extensive predonation and follow-up data from a prospective cohort of live kidney donors, who annually visited a physician and whose changes in medical condition were recorded. Only 2.6% of the donors were lost to follow-up. Previous studies [58,59] have indicated that donors lost to follow-up are healthier than donors attending timed control visits. The QoL questionnaire response was more than 90%, and it seems unlikely that donors who were not satisfied with the results of the donation were less likely to respond to the questionnaire. Therefore, both limitations could not have influenced the outcome of this study in a major way. A limitation that should be mentioned is the lack of a matched control group of nondonors limiting the statements of the decline in renal function, incidence of hypertension and QoL to population-based studies. Furthermore, the relatively small number of donors in our cohort limits us to perform subgroup analysis. Finally, the eGFR used as a measurement for renal function is merely an estimation and could underestimate the renal function for leaner or bigger persons. Furthermore, the eGFR is less accurate in the higher renal function levels. The better the kidney function, the less accurate the predictive value of the eGFR. Also, the eGFR is not validated for individuals with a mono-kidney. A GFR from a 24-h urine sample would be more accurate.

Future perspectives

Of course, it is possible for donors to develop a medical condition that could cause deterioration of the renal function to ESRD [11,12,60]. Two recent studies reported that donors have an increased risk for ESRD than nondonors [61,62]. While their follow-up was longer than our study, the establishment of the results and more importantly the subsequent limitations of these studies should be taken into consideration by transplant professionals before indiscriminately repeating these results to the next potential donor in the consulting room, especially considering the impact of these studies [61,62] among the transplant community. Selection criteria for nondonors were not equal to donors leading to a healthier group of nondonors. Furthermore, due to the low incidence of ESRD, both analyses overadjusted for potential confounders. Both limitations could have led to an overestimation of risk attributable to donation [63]. Reassuringly, both studies reported low absolute risks for ESRD among donors, which should be the main message for potential new donors. One should bear in mind that donors with a decreased renal function are no patients with renal insufficiency. Individuals are categorized as having chronic kidney disease if the eGFR is below 60 ml/min/1.73 m^2. Furthermore, among these individuals, secondary signs of kidney disease such as proteinuria are usually present. It is unfair to categorize donors within this group, unless other signs of kidney disease are present. Annual follow-up of live kidney donors is recommended to detect any loss of renal function. Future studies are indicated to identify those individuals at risk for a progressive loss of renal function after kidney donation [64].

In conclusion, we report a stable renal function after 5 years of follow-up among live kidney donors in the era of extended live kidney donation eligibility criteria, which seems to be maintained after an initial decline postdonation. Ageing, gender and hypertension seem to be associated with a lower renal function among donors, which is similar for the general population. There was no evidence for end-stage renal disease among donors or other additional signs of renal dysfunction. These results reassure the current practice of live kidney donation, and a conscientious follow-up of live kidney donors should be maintained after donation. Future studies are indicated to identify those individuals at risk for a progressive loss of renal function after kidney donation.

Authorship

SJ, LD, JW and JIJ: responsible for the study design. SJ, EM and ID: involved in the acquisition of data. The data were analysed by SJ, EM and RT. All authors involved in the interpretation of data. SJ and LD:

drafted the article. RT, EM, ID, JW and JIJ: revised the work critically. All authors approved the final version of the manuscript for publication and agree to be accountable for all aspects of the work.

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Conflicts of interest

The authors have declared no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. The 5-year follow-up mean eGFR of male and female donors with the eGFR of corresponding age categories of the general population.

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