Increase in 24-Hour Protein Excretion Immediately After Donation Is Associated With Decreased Functional Recovery in Living Kidney Donors

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ABSTRACT

Objectives. In this study, we evaluated the occurrence of proteinuria in living kidney donors during the immediate postdonation period, aiming to determine its clinical significance in renal function recovery.

Patients and methods. We enrolled living kidney donors with predonation protein excretion rate (PER) < 150 mg/24 h. Participants were divided into 2 groups according to immediate postdonation PER (4 days after nephrectomy): non-microproteinuria (non-mPr; PER < 150 mg/24 h), n = 244; and immediate postdonation microproteinuria (ImPr; PER ≥ 150 mg/24 h), n = 605.

Results. Estimated glomerular filtration rate (eGFR) did not differ significantly between groups immediately after nephrectomy but was consistently lower in the ImPr group 1 week to 1 year postdonation (1-year postdonation eGFR: ImPr group, 63.6 ± 12.1 mL/min/1.73 m^2; non-mPr group, 68.6 ± 12.3 mL/min/1.73 m^2; $P = .001$). Immediate postdonation microproteinuria was an independent predictor of eGFR at 1 year postdonation (β [standard error] = -2.68 [1.15], 95% confidence interval -4.94 to -0.42, $P = .02$), along with predonation eGFR, age, and sex. Immediate postdonation microproteinuria was more common in donors who were older or male and occurred in 71.3% of kidney donors, suggesting renal injury in this period.

Conclusions. Although proteinuria generally resolves, its impact persists and can impair renal function recovery. Donors who are older and male are more likely to undergo immediate hyperfiltration after donation.

KIDNEY transplantation, particularly from a living donor, is the treatment of choice for most patients with end-stage renal disease. Kidney donors are thought to have normal life spans, health statuses similar to that of the general population, and excellent quality of life, without excessive risk of end-stage renal disease [1]. However, to follow the ethical principle of "first, do no harm," we must ensure the long-term well-being of living kidney donors. Thus, multiple studies have reported outcomes of living kidney donors to assist in predicting the safety of donor candidates prior to donation.

One of the main outcomes of interest after donation is renal function. Animal studies have shown that acute nephron loss leads to glomerular hypertension and hyperfiltration, which results in kidney injury [2].

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Accumulating experience in kidney transplantation from living kidney donors indicates that carefully selected donors can lead long, healthy lives after donation [3–5]. However, the safety of kidney donors continues to be an issue as transplantation centers are now accepting "medically complex living donors" to increase the availability of organs for donation [6].

Postdonation renal function is approximately 70% of predonation renal function because of adaptive hyperfiltration and hypertrophy in the remaining kidney [7]. In a previous study of renal function recovery after donor nephrectomy, we observed microalbuminuria during the immediate postdonation period, which later resolved [8]. Urinary protein excretion is associated with glomerular injury, and proteinuria itself can also cause tubulointerstitial injury [9]. Although the presence of proteinuria several years after donation has been reported by multiple groups [10], proteinuria occurring immediately after nephrectomy and its clinical significance have not been previously reported. Therefore, in this study we evaluated the effect of proteinuria immediately after donation on renal function recovery.

MATERIALS AND METHODS

This study was approved by the Severance Hospital Yonsei University Health System Institutional Review Board. Of the living kidney donors in our prospectively collected database, we included those who 1. had completed 24-hour urine protein collection both before donation and 4 days after donation, and 2. had a predonation urinary protein excretion rate (PER) < 150 mg/24 h. Study participants were then stratified into 2 groups according to their PER immediately after donation (4 days after nephrectomy): 1. the non-microproteinuria (non-mPr) group, with postdonation PER < 150 mg/24 h, and 2. the immediate postdonation microproteinuria (ImPr) group, with postdonation PER ≥ 150 mg/24 h.

Two surgeons performed all donor nephrectomies by video-assisted mini-incision surgery, as previously reported [11]. In accordance with in-house donor criteria, candidates with an estimated glomerular filtration rate (eGFR) < 80 mL/min/1.73 m^2 at baseline and those with diabetes or hypertension inadequately controlled by a single medication were excluded from donation. Candidates with overt proteinuria (exceeding the microproteinuria range) were also excluded from donation. We evaluated donor characteristics including age, sex, history of hypertension or diabetes, blood pressure, height, weight, body mass index, and body surface area, as well as results of preoperative and postoperative urinalysis, PER, albumin-to-creatinine ratio (ACR), and routine serum chemistry. Pre- and postoperative renal function was evaluated using the Modification of Diet in Renal Disease study equation to calculate eGFR [12]. A 24-hour urine collection was routinely examined at predonation and at 4 days after nephrectomy (on the day before discharge). Follow-up data were collected 1 week, 1 month, 3 months, and 6 months after donation and annually thereafter.

Continuous variables are expressed as mean $\pm$ standard deviation and were compared using the Student t test. Categorical variables are expressed as percentages and were compared using either the χ^2 test or Fisher exact test. A P value $< .05$ was considered significant. All statistical analyses were conducted in SPSS version 23 (IBM Corp, Armonk, NY, United States).

Table 1. Donor Characteristics

	Non-mPr Group (n = 244)	Immediate mPr Group (n = 605)	P Value
Predonation PER, mg/24 h*	74 ± 23	78 ± 26	.015
Postdonation PER, mg/24 h*	109 ± 26	337 ± 255	< .001
Age, y*	38.3 ± 11.3	43.5 ± 11.2	< .001
Male, n (%)*	90 (36.9)	281 (46.4)	.011
Left kidney donation, n (%)	210 (86.1)	541 (89.4)	.166
History of hypertension, n (%)	11 (4.5)	35 (5.8)	.457
History of diabetes, (%)	1 (0.4)	3 (0.5)	.868
BMI, kg/m^2	23.4 ± 2.9	23.5 ± 2.6	.88
BSA, m^2	1.68 ± 0.19	1.71 ± 0.18	.06
Systolic BP, mm Hg*	123 ± 14	125 ± 14	.046
Diastolic BP, mm Hg	76 ± 11	77 ± 11	.64
Serum creatinine, mg/dL	0.79 ± 0.18	0.77 ± 0.17	.18
eGFR, mL/min/1.73 m^2	99.2 ± 18.1	99.6 ± 19.0	.77
ACR, mg/g	6.7 ± 14.0	7.1 ± 11.5	.74
Serum calcium, mg/dL	9.2 ± 0.4	9.2 ± 0.4	.42
Serum uric acid, mg/dL	4.74 ± 1.30	4.87 ± 1.37	.19
Serum cholesterol, mg/dL*	185 ± 35	193 ± 34	.001
Serum triglycerides, mg/dL	119 ± 141	113 ± 66	.39
Serum HDL cholesterol, mg/dL	55 ± 13	55 ± 14	.61
Serum LDL cholesterol, mg/dL*	109 ± 31	116 ± 30	.003
Serum glucose, mg/dL	93.7 ± 9.9	95.2 ± 10.9	.07
HbA1c, %*	5.31 ± 0.29	5.42 ± 0.32	.046

Data are presented as mean ± standard deviation or n (%).

Abbreviations: ACR, albumin-to-creatinine ratio; BMI, body mass index; BP, blood pressure; BSA, body surface area; eGFR, estimated glomerular filtration rate (based on the Modification of Diet in Renal Disease study equation); HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; mPr, microproteinuria; PER, protein excretion rate.

*$P < .05$.

RESULTS

In this study, we included 849 kidney donors who completed pre- and postdonation (4 days after nephrectomy) 24-hour urine collection from February 2007 to June 2018 and had a predonation PER < 150 mg/24 h. Compared with the ImPr group, participants in the non-mPr group were younger (38.3 ± 11.3 years vs 43.5 ± 11.2 years, $P < .001$), more likely to be female (63.1% vs 53.6%, $P = .011$), and had slightly lower systolic blood pressure, PER, and serum levels of total cholesterol, low-density lipoprotein cholesterol, and hemoglobin A1c before donation (Table 1). Four days after donation, 605 participants (71.3%) had microproteinuria (PER ≥ 150 mg/24 h; ImPr group), whereas 244 (28.7%) were free from microproteinuria (non-mPr group).

We used postdonation ACR to evaluate the effect of proteinuria immediately after donation on subsequent renal function recovery. Although predonation ACR did not differ significantly between the 2 groups, mean ACR was markedly higher in the ImPr group on day 2 after donation (12.3 ± 10.3 mg/g vs 30.7 ± 115.0 mg/g, $P = .16$) and on day 3 after donation (10.0 ± 9.5 mg/g vs 24.5 ± 39.8 mg/g, $P < .001$) (Table 2). From 1 week to 1 year after donation, the mean ACR of the ImPr group ranged from 10.4 to 12.7 mg/g but remained consistently higher than that of the non-mPr group. Compared with the non-mPr group, a greater percentage of donors in the ImPr group had an ACR ≥ 30 mg/g

Table 2. Pre- and Postdonation Albumin-to-Creatinine Ratio (mg/g)

	Non-mPr Group (n = 244)	Immediate mPr Group (n = 605)	*P* Value
Predonation	6.7 ± 14.0	7.1 ± 11.5	.74
Postdonation			
2 d	12.3 ± 10.3	30.7 ± 115.0	.16
3 d*	10.0 ± 9.5	24.5 ± 39.8	< .001
1 wk	11.0 ± 12.4	12.5 ± 14.3	.49
1 mo*	7.7 ± 6.5	10.4 ± 14.9	.033
3 mo*	7.6 ± 7.4	10.8 ± 14.2	.016
6 mo	10.3 ± 21.2	10.5 ± 15.3	.95
1 y*	6.2 ± 6.8	12.7 ± 20.9	.003

Data are presented as mean ± standard deviation.
Abbreviation: mPr, microproteinuria.
*$P < .05$.

during the immediate postdonation period (day 2, 7.7% vs 22.0%, $P = .004$; day 3, 5.6% vs 26.1%, $P < .001$) (Table 3). From 1 week to 1 year after donation, the percentage of donors in the ImPr group with an ACR ≥ 30 mg/g appeared to be higher, but this difference was not significant.

We calculated eGFR to evaluate postdonation renal function. Mean eGFR did not differ significantly between the 2 groups before donation (99.2 ± 18.1 vs 99.6 ± 19.0, $P = .77$) or immediately after donation (Table 4, Fig 1). However, from 1 week to 1 year after donation, mean eGFR was consistently 3.2 to 5.0 mL/min/1.73 m^2 higher in the non-mPr group compared with the ImPr group ($P \leq .002$). At the 1-year follow-up, mean eGFR was 68.6 ± 12.3 mL/min/1.73 m^2 in the non-mPr group and 63.6 ± 12.1 mL/min/1.73 m^2 in the ImPr group ($P = .001$).

To determine whether immediate postdonation microproteinuria is associated with subsequent renal function recovery, we carried out linear regression analysis to identify factors predicting eGFR 1 year after donation. In simple linear regression, immediate postdonation microproteinuria was a significant predictor (β = -5.0, $P = .001$), along with age, history of hypertension, body mass index, systolic blood pressure, predonation eGFR, and serum levels of creatinine, uric acid, cholesterol, and glucose. These factors and the sex of the donor were included in a multivariable linear regression analysis using a stepwise selection procedure. Immediate postdonation microproteinuria was retained as a significant predictor (β = -2.68, $P = .020$) after predonation eGFR, age, and sex (Table 5).

We then evaluated donor characteristics to identify factors predicting immediate microproteinuria after donation. In a simple logistic regression analysis, donor age, sex, predonation eGFR, predonation PER, systolic blood pressure, hemoglobin, total cholesterol, and low-density lipoprotein cholesterol were significant predictors. In multivariable logistic regression analysis, age, sex, and predonation eGFR were retained as significant predictors. Donors who were older (odds ratio [OR] 1.062, 95%

Table 3. Pre- and Postdonation Microalbuminuria (% of Donors with Albumin-to-Creatinine Ratio ≥ 30 mg/g)

	Non-mPr Group (n = 244)	Immediate mPr Group (n = 605)	*P* Value
Predonation	2/123 (1.6)	16/492 (3.3)	.549
Postdonation			
2 d*	6/78 (7.7)	68/309 (22.0)	.004
3 d*	4/72 (5.6)	80/306 (26.1)	< .001
1 wk	3/56 (5.4)	23/248 (9.3)	.437
1 mo	1/61 (1.6)	16/269 (5.9)	.331
3 mo	1/59 (1.7)	19/251 (7.6)	.140
6 mo	2/53 (3.8)	19/206 (9.2)	.265
1 y	1/49 (2.0)	11/122 (9.0)	.183

Data are presented as number of donors with microalbuminuria/total donors at follow-up (percentage of donors with microalbuminuria).
Abbreviation: mPr, microproteinuria.
*$P < .05$.

Table 4. Estimated Glomerular Filtration Rate (mL/min/1.73 m^2)*

	Non-mPr Group (n = 244)	Immediate mPr Group (n = 605)	*P* Value
Predonation	99.2 ± 18.1	99.6 ± 19.0	.77
Postdonation			
3 d	67.7 ± 14.5	67.6 ± 15.0	.88
5 d	68.4 ± 15.1	68.2 ± 14.8	.88
1 wk†	64.9 ± 12.6	61.6 ± 11.3	.002
1 mo†	65.9 ± 11.1	62.7 ± 11.2	.001
3 mo†	66.5 ± 11.4	62.9 ± 11.5	< .001
6 mo†	68.5 ± 12.5	64.5 ± 11.8	.001
1 y†	68.6 ± 12.3	63.6 ± 12.1	.001

Data are presented as mean ± standard deviation.
Abbreviation: mPr, microproteinuria.
*Calculated using the Modification of Diet in Renal Disease study equation.
†$P < .05$.

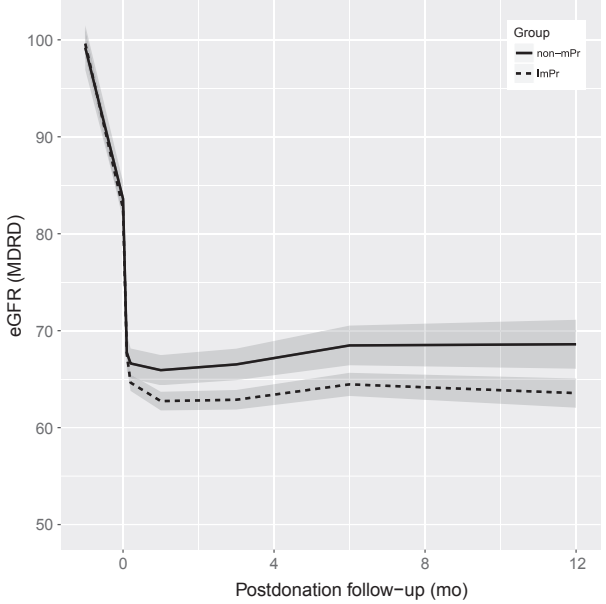

Fig 1. Estimated glomerular filtration rate (mL/min/1.73 m^2), calculated using the Modification of Diet in Renal Disease study equation. Graph presents mean and 95% confidence interval. eGFR, estimated glomerular filtration rate; ImPr, immediate microproteinuria group; MDRD, Modification of Diet in Renal Disease; mPr, microproteinuria group.

Table 5. Multivariable Linear Regression Analysis of Factors Predicting Postdonation eGFR at 1 Year

Independent Variable	β	SE	95% CI	*P* value	R^2
Model 1				< .001	0.379
Predonation eGFR	0.40	0.03	0.35–0.46	< .001	
Model 2				< .001	0.449
Predonation eGFR	0.35	0.03	0.30–0.41	< .001	
Age	−0.29	0.04	−0.37 to −0.20	< .001	
Model 3				< .001	0.460
Predonation eGFR	0.34	0.03	0.29–0.39	< .001	
Age	−0.32	0.05	−0.41 to −0.23	< .001	
Sex (male)	2.76	1.05	0.70–4.82	.009	
Model 4				< .001	0.469
Predonation eGFR	0.35	0.03	0.29–0.40	< .001	
Age	−0.29	0.05	−0.38 to −0.20	< .001	
Sex (male)	2.45	1.05	0.39–4.51	.020	
Immediate postdonation microproteinuria	−2.68	1.15	−4.94 to −0.42	.020	

Excluded variables from model 1: age, sex, immediate postdonation microproteinuria, history of hypertension, body mass index (BMI), systolic blood pressure, serum uric acid, serum cholesterol, and serum glucose; excluded variables from model 2: sex, immediate postdonation microproteinuria, history of hypertension, BMI, systolic blood pressure, serum uric acid, serum cholesterol, and serum glucose; excluded variables from model 3: immediate postdonation microproteinuria, history of hypertension, BMI, systolic blood pressure, serum uric acid, serum cholesterol, and serum glucose; excluded variables from model 4: history of hypertension, BMI, systolic blood pressure, serum uric acid, serum cholesterol, and serum glucose.

Abbreviations: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate (calculated using the Modification of Diet in Renal Disease study equation); SE, standard error.

confidence interval [CI] 1.044–1.080, $P < .001$), male (OR 0.418, 95% CI 0.289–0.606, $P = .004$), or had higher predonation eGFR (OR 1.014, 95% CI 1.005–1.024, $P < .001$) were more likely to have immediate postdonation microproteinuria (Table 6).

DISCUSSION

In a previous study, our group observed microalbuminuria in kidney donors after nephrectomy, which was associated with delayed recovery of renal function. In that study, ACR was highest in the immediate postdonation period, after which microalbuminuria resolved [8]. Because urinary protein excretion is associated with kidney damage, we aimed to determine the effect of immediate postdonation microproteinuria on subsequent kidney function recovery.

The findings from the present study indicate that microproteinuria occurring immediately after donation is associated with impaired renal function recovery during longer-term follow-up. Immediate postdonation microproteinuria was a significant predictor of 1-year postdonation eGFR, along with predonation eGFR, age, and sex. The risk of immediate postdonation microproteinuria was 2.39 times higher for male donors, 1.82 times higher with each additional 10 years of age, and 1.15 times higher when predonation eGFR was 10 mL/min/1.73 m^2 higher.

Previous studies regarding postdonation proteinuria focused on the first several years after donation. A meta-analysis conducted by Garg et al [10] showed that the pooled incidence of proteinuria > 300 mg/day was 10% for donors followed for 7 years. Compared with controls, PER was 66 mg/day higher in donors at an average of 11 years after donation. In contrast, Ibrahim et al [1] reported that the prevalence of microalbuminuria was not increased in donors compared with matched control subjects. At 13.7 ± 9.2 years after donation, 12.7% of donors had albuminuria (microalbuminuria or macroalbuminuria), and donors with albuminuria had a higher GFR (based on iohexol clearance) at follow-up (75.7 ± 13.0 mL/min/1.73 m^2 vs 71.2 ± 11.5 mL/min/1.73 m^2, $P = .04$). Their study indicates that living kidney donors are not at an increased risk of albuminuria and that the development of albuminuria may not have a deleterious effect on the remaining kidney.

Table 6. Logistic Regression Analysis of Factors Predicting Immediate Postdonation Microproteinuria

	Univariate Analysis			Multivariable Analysis		
Independent Variable	β	OR (95% CI)	*P* Value	β	OR (95% CI)	*P* Value
Age	0.040	1.041 (1.027–1.055)	< .001	0.060	1.062 (1.044–1.080)	< .001
Sex (male)	−0.395	0.674 (0.497–0.914)	.011	−0.871	0.418 (0.289–0.606)	.004
Predonation eGFR	0.001	1.001 (0.993–1.009)	.772	0.014	1.014 (1.005–1.024)	< .001
Predonation PER	0.008	1.008 (1.001–1.014)	.015			
Systolic BP	0.011	1.011 (1.000–1.022)	.047			
Hemoglobin	0.101	1.106 (1.002–1.221)	.046			
Total cholesterol	0.008	1.008 (1.003–1.012)	.001			
LDL cholesterol	0.008	1.008 (1.003–1.014)	.003			

Abbreviations: BP, blood pressure; CI, confidence interval; eGFR; estimated glomerular filtration rate (calculated using the Modification of Diet in Renal Disease study equation); LDL, low-density lipoprotein; OR, odds ratio; PER, protein excretion rate.

In contrast to previous studies, we studied microproteinuria in the immediate postdonation period, which despite being common has not been well described. Immediate postdonation microproteinuria is consistent with sudden nephron loss caused by nephrectomy and increased blood flow in the remaining kidney [13]. In the present study, 71.3% of donors had microproteinuria 4 days after donation, with the remaining 28.7% free of proteinuria despite the sudden hemodynamic changes in the remaining kidney. Our analyses showed that immediate postdonation microproteinuria was associated with impaired renal function recovery during the 1-year follow-up. This finding can be explained in 2 ways. First, sudden nephron loss by nephrectomy leads to increased renal blood flow and glomerular hypertension, which can damage the remaining glomeruli [2]. Proteinuria itself may also cause tubulointerstitial injury [9]. This initial acute injury can impair long-term renal function. Second, the presence or absence of microproteinuria after donation may be explained by the donor's renal functional reserve, which represents the capacity to increase GFR in response to certain physiological or pathologic stimuli or conditions [14]. Prior to donation, GFR in kidney donors has been reported to increase 26 $\pm$ 12 mL/min after amino acid and dopamine infusion [15]. A large renal functional reserve may attenuate the negative impact of renal hemodynamic changes after nephrectomy, with less injury to the remaining kidney and no microproteinuria after donation.

We used ACR to evaluate persistent urinary protein excretion during follow-up and found that ACR at 2 and 3 days after donation was higher in the ImPr group compared with the non-mPr group. Although mean ACR in the ImPr group remained below 13 mg/g from 1 week to 1 year after donation, this value was consistently higher than that of the non-mPr group. The resolution of proteinuria may be the result of adaptive hyperfiltration due to compensatory glomerular hypertrophy [13]. The clinical significance of the decreased but persistent elevation of ACR in the ImPr group during later follow-up requires further study. Although the ACR level was < 30 mg/g, which is within the widely accepted normal range, differences in "normal" ACR may also have clinical significance. For example, several studies have reported that ACR > 10 mg/g is clinically important despite being in the normal range [8,16,17].

There are some limitations to our study, including those inherent to the retrospective cohort study design. However, the data were collected in a prospective manner, and longitudinal follow-up data were available, which can offset such limitations. Another limitation is the evaluation of proteinuria using PER (which measures total urinary protein) immediately after donation and ACR (which measures only urinary albumin) during longer follow-up. To overcome this limitation, we compared ACR values during longer follow-up with ACR values in the immediate postdonation period. Currently, testing for albuminuria rather than proteinuria is recommended for the evaluation of chronic kidney disease [18]. However, the mechanism of urinary protein excretion after nephrectomy likely differs from that of chronic kidney disease; therefore, measuring other proteins, such as NGAL or KIM–1, may be needed to provide more information [19].

Despite its limitations, our study is valuable as it is the first to describe the presence and clinical significance of urinary protein excretion during the immediate postdonation period. More than 70% of donors have microproteinuria immediately after donation, which resolves after 1 week. However, the impact of microproteinuria extends beyond the immediate postdonation period, resulting in impaired renal function recovery even 1 year after donation. However, kidney injury does not occur in all donors. Further investigation may provide information needed to prevent proteinuria immediately after donation and improve renal function recovery. This information may be used to screen potential donors at risk for postdonation kidney injury or to prevent postdonation protein excretion with medications such as angiotensin receptor blockers.

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