INTRODUCTION

Following the introduction of kidney transplantation in the 1950s, it has become essential for the improvement of quality of life for end-stage renal disease (ESRD) patients. However, as the demand for donor kidneys has increased, living donors are now a major source for kidney transplantation in Korea [1]. Improved outcomes and reduced waiting times are some of the merits of living donor kidney transplantation [2], but is not without its shortcomings, and the risk of mortality or renal failure of living donors remains a concern [3].
Compensatory hypertrophy has been observed after unilateral or partial nephrectomy [4-6], and the renal functional reserve has also been assessed along with the consequences of hyperfiltration [7-11]. Preoperative factors, such as obesity, hypertension, and proteinuria have been known to influence the renal function after unilateral nephrectomy [12-14]; in addition, old age has been associated with reduced renal reserve [15]. Older or overweight kidney donors have a lower post-donation reserve capacity, but obesity has a greater impact on loss of renal reserve in younger donors, suggesting that younger donors with obesity must be monitored carefully [16]. Most of the previous studies have focused on the risk factors and pathophysiology of renal failure or other comorbidities [10,17-19]. Edgren et al. [4] reported that renal function reached 77% of its initial level in kidney donors after a mean follow-up of 3 years. Several studies on donor renal function have also reported that renal function reaches 70%–75% of its initial pre-nephrectomy renal function [17,20,21].

This study retrospectively reviewed the renal function of living donors after nephrectomy in order to understand the long-term postoperative changes in renal function, and also define the factors related to renal function compensation.

### HIGHLIGHTS

- The immediate postoperative estimated glomerular filtration rate decreased to about 65.5% of its primary function which is affected by the sex and body mass index of the donor.
- In the long term, we found that compensation of renal function occurs over time, regardless of donor factors.

### METHODS

Data for 1,933 living kidney donors from January 1999 to December 2017 at Yonsei University, Severance Hospital, Korea were collected. The follow-up hospital records of 1,175 donors (60.7%) were available. The selection criteria of donors at donor nephrectomy were: (1) pre-nephrectomy serum creatinine level below 1.5 mg/dL, (2) no radiologic abnormality in bilateral kidneys, and (3) no history of hypertension, diabetes or active hepatitis. Donor nephrectomy was performed by conventional open nephrectomy or video assisted mini-laparotomy surgery. The estimated glomerular filtration rate (e-GFR), as determined by the Modification of Diet in Renal Disease (MDRD) study, was used. Hospital records were retrospectively reviewed to evaluate the residual renal function and renal impairment.

Early e-GFR was defined as the e-GFR at the early period (usually within 5 days of nephrectomy) and late e-GFR was defined as e-GFR at the time of the most recent follow-up. The e-GFR ratio was the relative e-GFR represented by the ratio of post-nephrectomy e-GFR versus pre-nephrectomy e-GFR. Renal failure was defined using the Kidney Disease Outcomes Quality Initiative Chronic Kidney Disease classification, the need for dialysis, or e-GFR<15 mL/min/1.73 m².

Donor sex, age, and body mass index (BMI) were analyzed for variables affecting the donor residual renal function after nephrectomy. Patients were categorized and analyzed according to their BMI (BMI <25 kg/m² and ≥25 kg/m² groups; normal and obese groups, respectively) and age (<35 years and ≥35 years) and analyzed [22,23]. Statistical analysis was performed using Student t-test. The relevance between factors was analyzed using linear regression. Multivariate linear regression was used to determine factors significantly related to post-nephrectomy e-GFR. A general linear model was applied to compare the donor factors in combination with follow-up period. A P-value <0.05 was defined as statistically significant.

### Table 1. Donor demographics

| Clinical manifestation | Value                  |
|-----------------------|------------------------|
| Number                | 1,175                  |
| Age at nephrectomy (yr) | 40.1±11.4 (16–69)    |
| Sex (male:female)      | 547 (46.6):628 (53.4) |
| BMI (kg/m²)            | 23.2±2.7 (15.6–33.3)  |
| Living donor type (related:unrelated) | 775 (66.0):400 (34.0) |
| Mean follow-up duration (mo) | 36.3±37.6 (0–193)    |

Values are presented as mean±standard deviation (range) or number (%). BMI, body mass index.
RESULTS

Donor Characteristics and Renal Failure after Donor Nephrectomy

The clinical characteristics of 1,175 donors whose hospital records were retrospectively collected are shown in Table 1. Of the 1,175 donors, two donors developed renal failure and were on dialysis (2/1,175; 0.17%); renal failure occurred at 34 months and 57 months after nephrectomy. The cause of ESRD was hypertension in one case and disease of unknown origin in the other case.

Early Change of Renal Function after Donor Nephrectomy

The mean age at the time of donation was 40.1±11.4 years (16–69 years). The pre-nephrectomy mean e-GFR was 99.2±19.9 mL/min/1.73 m², and the mean serum creatinine was 0.82±0.17 mg/dL. In the immediate post-operative period, the early e-GFR dropped to 64.3±14.2 mL/min/1.73 m², and the serum creatinine increased to 1.21±0.29 mg/dL.

Donor sex and BMI showed statistically significant relevance with early decrease in renal function, and the early e-GFR was significantly lower in males compared to females. The mean early e-GFR was 62.1±12.2 mL/min/1.73 m², 66.1±15.4 mL/min/1.73 m² in males and females, respectively. The decrement of the early e-GFR ratio was statistically greater in males than in females (64.1%±10.2% vs. 66.7%±13.0%, P<0.001). Donor BMI also showed negative correlation with the early e-GFR ratio, and the slope of the relationship between the early e-GFR ratio and BMI was –0.53 (P<0.001) by linear regression analysis.

Late Change of Renal Function after Donor Nephrectomy

The mean follow-up period was 36.3±37.6 months (0–193 months), and the mean late e-GFR was 70.2±13.3 mL/min/1.73 m² (e-GFR ratio, 72.0%±13.5%) (Fig. 1). The late e-GFR ratio significantly increased according to the follow-up period, and the e-GFR increased 1.94%±0.10% of its initial e-GFR per year (P<0.001) (Fig. 2).

Table 2. Early changes of renal function after donor nephrectomy (n=1,175)

| Donor variable | n  | e-GFR by MDRD formula (mL/min/1.73 m²) | e-GFR ratio (B/A, %) | P-value |
|----------------|----|--------------------------------------|----------------------|---------|
|                |    | Pre-nephrectomy (A)                   | Early e-GFR (B)      |         |
| Overall        | 1,175 | 99.2±19.9                           | 64.3±14.2            | 65.5±11.9 | <0.001 |
| Sex            |     |                                       |                      |         |
| Male           | 547 | 97.9±17.7                           | 62.1±12.2            | 64.1±10.2 |       |
| Female         | 628 | 100.4±21.6                          | 66.1±15.4            | 66.7±13.0 |       |
| Age (yr)       |     |                                       |                      |         |
| <35            | 768 | 105.5±18.7                          | 69.0±14.5            | 66.0±11.9 | 0.277  |
| ≥35            | 407 | 95.9±19.3                           | 61.8±13.3            | 65.2±11.9 |       |
| BMI (kg/m²)    |     |                                       |                      |         |
| <25            | 294 | 100.4±20.4                          | 65.6±14.6            | 66.1±12.5 | <0.001 |
| ≥25            | 881 | 95.7±17.9                           | 60.4±12.0            | 63.5±9.4  |       |

Values are presented as means±standard deviation.

Table 3. Stepwise multiple linear regression analysis for early changes in renal function

| Variable | Beta  | Standard error | P-value |
|----------|-------|----------------|---------|
| Constant | 77.219 | 2.956          | <0.001  |
| BMI      | –0.460 | 0.128          | <0.001  |
| Sex      | –2.174 | 0.705          | 0.002   |

R²=0.023, F=9.515, P<0.001. Excluded variable: age. BMI, body mass index.

The early e-GFR ratio in BMI <25 kg/m² and ≥25 kg/m² groups were compared and showed significant difference (P<0.001). However, age was not significantly associated with early e-GFR, and by linear regression analysis, age at donation showed no significant relationship to the early e-GFR ratio. The early e-GFR ratio was analyzed in groups age <35 years and ≥35 years, and there was no significant difference between the two age groups (P=0.277) (Table 2).

Stepwise multiple linear regression was used for verification of donor factors affecting renal function after nephrectomy. Donor BMI and sex showed significant correlation with the early change of renal function (Table 3).
Donor age, sex, and BMI showed no significant correlation with the late e-GFR. The age of the donor at the time of donation had no linear correlation to the late e-GFR ratio. The BMI of the donor at the time of donation also had no correlation with the late e-GFR ratio, although in the immediate postoperative period, a higher donor BMI resulted in a greater decrease in e-GFR. The late e-GFR ratio showed no significant difference in terms of sex, age (<35, ≥35 years), or BMI (<25, ≥25 kg/m²) (Table 4).

The donor variables and the late e-GFR ratio were analyzed by stepwise multiple linear regression. Results showed that the follow-up period was the only significant factor explaining the compensation of the donor renal function. The donor variables: sex, age, and BMI at donation were excluded (P<0.001) (Table 5).

The effects of the donor variables combined with the follow-up period on the late e-GFR ratio were analyzed. Donors <35 years and ≥35 years were analyzed in combination with follow-up time. We found no significant difference in the effects of the two age groups combined with follow-up period on the late e-GFR ratio (P=0.104) (Fig. 3). When BMI was grouped into <25 kg/m² and ≥25 kg/m² groups, there was no significant difference between the effects of the two groups in combination with follow-up period on the late e-GFR ratio (P=0.466) (Fig. 4). There was a statistically significant difference in the late e-GFR ratio between males and females when they were analyzed in combination with follow-up time. Female donors

**Table 4. Late changes of renal function after donor nephrectomy (n=1,173, excluding two cases of renal failure)**

| Donor variable | n  | e-GFR by MDRD formula (mL/min/1.73 m²) | e-GFR ratio (C/A, %) | P-value³) |
|---------------|----|-------------------------------------|----------------------|-----------|
|               |    | Pre-nephrectomy (A) | Late e-GFR (C)      |           |
| Overall       | 1,173 | 99.2±19.9 | 70.2±13.3   | 72.0±13.5 |
| Sex           |      |           |           |           |
| Male          | 545  | 97.9±17.7 | 69.6±13.2  | 72.1±13.2 |
| Female        | 628  | 100.4±21.6| 70.7±13.5  | 72.0±13.7 |
| Age (yr)      |      |           |           |           |
| <35           | 766  | 105.5±18.7| 76.1±14.0  | 73.1±13.4 |
| ≥35           | 407  | 95.9±19.8 | 67.1±11.9  | 71.5±13.5 |
| BMI (kg/m²)   |      |           |           |           |
| <25           | 294  | 100.4±20.4| 71.0±13.5  | 72.0±13.22|
| ≥25           | 879  | 95.7±17.9 | 67.7±12.6  | 72.0±14.4 |

e-GFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; BMI, body mass index.
³P-value calculated by comparison mean (Student t-test) of e-GFR ratio by variables.
showed a greater renal compensation rate compared to male donors (P=0.004) (Fig. 5).

**DISCUSSION**

The safety of the donors has been the primary concern of the transplant society since the introduction of living donor kidney transplantation [24]. Although there are concerns about glomerular hyperfiltration, proteinuria, hypertension, and other cardiovascular risks, several studies have reported that kidney donation is relatively safe and that the survival of donors is similar to that of the general population [25,26]. While the risk of ESRD in donors is higher, the absolute risk remains low [27,28]. The rate of ESRD was 0.17% (2/1,175) in our study.

The e-GFR of the donor decreases immediately after nephrectomy. After nephrectomy, the renal function is partially compensated and is reported to recover 70%–75% of its initial GFR [17,20,21]. ter Wee et al. [29] reported that the GFR of kidney donors increased for years after donation, probably due to compensatory hypertrophy of the remaining kidney. Furthermore, Rook et al. [30] reported that baseline GFR, BMI, and age were independent predictors for renal function impairment after living donor donation. However, this study had a relatively short follow-up period after donation. We studied the factors affecting the rate of compensation and demonstrated that the immediate decrease in renal function was affected by the sex and BMI of the donor. Overweight donors showed a greater decrease in e-GFR after nephrectomy; however, during follow-up, the compensatory rates were similar.

**Table 5.** Stepwise multiple linear regression analysis for late changes of renal function

| Variable            | Beta  | Standard error | P-value |
|---------------------|-------|----------------|---------|
| Constant            | 66.216| 0.495          | <0.001  |
| Post-nephrectomy period | 0.162| 0.009          | <0.001  |

$R^2=0.199$, $F=291.921$, $P<0.001$. Excluded variable: age, sex, and body mass index.
between the normal donors and obese donors.

We compared the donor variables in combination with follow-up period to verify the effect on the compensation of renal function and found that the compensatory rate showed no significant difference according to donor variables, with the exception of donor sex. Sex affected the decrease in e-GRF immediately after nephrectomy, as well as the compensatory rate during follow-up. Previous studies have reported that men have a higher GFR than women before nephrectomy [30,31]. Gossmann et al. [32] found that a higher GFR at the time of donation was the only significant factor for a larger than average loss of GFR. Similarly, our results demonstrated that males had a higher pre-nephrectomy GFR, which may support the greater decrease in postoperative e-GFR. We also showed that males had a lower compensatory rate than females, which may be due to a larger kidney volume and larger muscle mass in males compared to females. Although the compensation rates were statistically different, both sexes showed a compensation rate of over 70%.

In meta-analyses, Kasiske et al. [20] reported an immediate decrease in renal function after nephrectomy, and an increase in GFR was noted per decade during long-term follow-up. Moreover, Garg et al. [33] reported that after an initial decrement in GFR after nephrectomy, the renal function remained stable over 15 years. Our results show a significant linear increment in late e-GFR ratio that was only relevant in terms of the follow-up period. This may imply that donor factors such as sex and BMI only affect the renal function in the immediate postoperative period, but after time, the donor factors have little or no impact on the compensation of the renal function in healthy donors.

There are certain limitations of our study. The data were collected retrospectively and the donors were not asked to come for follow-up testing specifically for this study, only the data available at our center were used. Therefore, the donor pool that was analyzed may not adequately represent the total donor population. Furthermore, the donor pool did not include higher risk donors, such as hypertensive donors or elderly donors, compared to other reports. Therefore, our results may have not fully exhibited the impact of donor factors on the compensation of renal function. In addition, the consequences of hyperfiltration, such as albuminuria and hypertension, could not be evaluated due to our data collection method. Further studies should be carried out in a prospective fashion with an adequate control group in order to study the risk of such comorbidities and the survival of the donors.

In conclusion, we found that in healthy donors with no major comorbidities, donor factors such as sex and BMI may affect renal function immediately after nephrectomy, but that compensation of renal function occurs over time, regardless of donor factors. The compensation rate reaches an average of over 72% of its initial renal function.

ACKNOWLEDGMENTS

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Funding/Support
This study was supported by research grant from the Korean Society for Transplantation (2020-02-01001-003).

ORCID
Yong Pyo Lee https://orcid.org/0000-0002-0343-749X
Soo Jin Kim https://orcid.org/0000-0002-5576-8557
Juhan Lee https://orcid.org/0000-0003-4910-2596
Jae Geun Lee https://orcid.org/0000-0002-6722-0257
Kyu Ha Huh https://orcid.org/0000-0003-1364-6989
Dong Jin Joo https://orcid.org/0000-0001-8405-1531
Soon Il Kim https://orcid.org/0000-0002-0783-7538
Yu Seun Kim https://orcid.org/0000-0002-5105-1567
Myoung Soo Kim https://orcid.org/0000-0002-8975-8381

Author Contributions
Conceptualization: MSK. Data curation: YPL, SJK. Formal analysis: YPL. Funding acquisition: MSK. Methodology: SJK, JL, JGL, KHH, DJJ. Project administration: MSK, SIK, YSK, KHH, JL. Visualization: YPL. Writing—original draft: SJK. Writing—review & editing: YPL, SJK, MSK.

REFERENCES
1. Korean Network for Organ Sharing (KONOS). 2017 Annual data report [Internet]. Seoul: KONOS; 2017 [cited 2020 May 27]. Available from: http://www.konos.go.kr.
2. United States Renal Data System. USRDS 2017 annual data report [Internet]. Bethesda (MD): Atlas of End-
Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2017 [cited 2020 May 27]. Available from https://www.usrds.org/2017/view/.

3. Gaston RS, Kumar V, Matas AJ. Reassessing medical risk in living kidney donors. J Am Soc Nephrol 2015;26:1017-9.

4. Edgren J, Laasonen L, Kock B, Brotherus JW, Pasterнак A, Kuhlbäck B. Kidney function and compensatory growth of the kidney in living kidney donors. Scand J Urol Nephrol 1976;10:134-6.

5. Orecklin JR, Craven JD, Lecky JW. Compensatory renal hypertrophy: a morphologic study in transplant donors. J Urol 1973;109:952-4.

6. Takagi T, Mir MC, Sharma N, Remer EM, Li J, Demirjian S, et al. Compensatory hypertrophy after partial and radical nephrectomy in adults. J Urol 2014;192:1612-8.

7. Saxena AB, Myers BD, Derby G, Blouch KL, Yan J, Ho B, et al. Adaptive hyperfiltration in the aging kidney after contralateral nephrectomy. J Urol 2006;291:F629-34.

8. Srivastava T, Harirharan S, Alon US, McCarthy ET, Sharma R, El-Meanawy A, et al. Hyperfiltration-mediated injury in the remaining kidney of a transplant donor. Transplantation 2018;102:1624-35.

9. Praga M. Synergy of low nephron number and obesity: a new focus on hyperfiltration nephropathy. Nephrol Dial Transplant 2005;20:2594-7.

10. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. J Am Soc Nephrol 2001;12:1315-25.

11. Mjøen G, Hallan S, Hartmann A, Foss A, Midvedt K, Øyen O, et al. Long-term risks for kidney donors. Kidney Int 2014;86:162-7.

12. González E, Gutiérrez E, Morales E, Hernández E, Andrés A, Bello I, et al. Factors influencing the progression of renal damage in patients with unilateral renal agenesis and remnant kidney. Kidney Int 2005;68:263-70.

13. Locke JE, Reed RD, Massie A, MacLennan PA, Sawinski D, Kumar V, et al. Obesity increases the risk of end-stage renal disease among living kidney donors. Kidney Int 2017;91:699-703.

14. Ito K, Nakashima J, Hanawa Y, Oya M, Ohigashi T, Marumo K, et al. The prediction of renal function 6 years after unilateral nephrectomy using preoperative risk factors. J Urol 2004;171:120-5.

15. Esposito C, Plati A, Mazzullo T, Fasoli G, De Mauri A, Grosjean F, et al. Renal function and functional reserve in healthy elderly individuals. J Nephrol 2007;20:617-25.

16. Rook M, Bosma RJ, van Son WJ, Hofker HS, van der Heide JJ, ter Wee PM, 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;8:2077-85.

17. Fehrmann-Ekholm I, Dunér F, Brink B, Tydén G, Elinder CG. No evidence of accelerated loss of kidney function in living kidney donors: results from a cross-sectional follow-up. Transplantation 2001;72:444-9.

18. Lam NN, Lentine KL, Levey AS, Kasiske BL, Garg AX. Long-term medical risks to the living kidney donor. Kidney Int 2015;11:411-9.

19. O’Keeffe LM, Ramond A, Oliver-Williams C, Willeit P, Paige E, Trotter P, et al. Mid- and long-term health risks in living kidney donors: a systematic review and meta-analysis. Ann Intern Med 2018;168:276-84.

20. Kasiske BL, Ma JZ, Louis TA, Swan SK. Long-term effects of reduced renal mass in humans. Kidney Int 1995;48:814-9.

21. Kasiske BL, Anderson-Haag T, Israni AK, Kimmel RS, Kraus ES, et al. A prospective controlled study of living kidney donors: three-year follow-up. Am J Kidney Dis 2015;66:114-24.

22. Seo MH, Lee WY, Kim SS, Kang JH, Kim KK, et al. Korean Society for the Study of Obesity guideline for the management of obesity in Korea. J Obes Metab Syndr 2019;28:40-5.

23. Pottel H, Delanaye P, Weekers L, Selistre L, Goffin K, Ghysens O, et al. Age-dependent reference intervals for estimated and measured glomerular filtration rate. Clin Kidney J 2017;10:545-51.

24. Weitz J, Koch M, Mehrabi A, Schemmer P, Zeier M, Beimler J, et al. Living-donor kidney transplantation: risks of the donor: benefits of the recipient. Clin Transplant 2006;20 Suppl 17:13-6.

25. Ibrahim HN, Foley R, Tan L, Rogers T, Bailey RF, Quo H, et al. Long-term consequences of kidney donation. N Engl J Med 2009;360:459-69.

26. Rizvi SA, Naqvi SA, Jawad F, Ahmed E, Asghar A, Zafar MN, et al. Living kidney donor follow-up in a dedicated clinic. Transplantation 2005;79:1247-51.

27. Muzaale AD, Massie AB, Wang MC, Montgomery RA,
McBride MA, Wainright JL, et al. Risk of end-stage renal disease following live kidney donation. JAMA 2014;311:579-86.
28. Hartmann A, Fauchald P, Westlie L, Brekke IB, Holdaas H. The risk of living kidney donation. Nephrol Dial Transplant 2003;18:871-3.
29. ter Wee PM, Tegzess AM, Donker AJ. Pair-tested renal reserve filtration capacity in kidney recipients and their donors. J Am Soc Nephrol 1994;4:1798-808.
30. Rook M, Hofker HS, van Son WJ, Homan van der Heide JJ, Ploeg RJ, Navis GJ. Predictive capacity of pre-donation GFR and renal reserve capacity for donor renal function after living kidney donation. Am J Transplant 2006;6:1653-9.
31. Goldfarb DA, Matin SF, Braun WE, Schreiber MJ, Mastroianni B, Papajcik D, et al. Renal outcome 25 years after donor nephrectomy. J Urol 2001;166:2043-7.
32. Gossmann J, Wilhelm A, Kachel HG, Jordan J, Sann U, Geiger H, et al. Long-term consequences of live kidney donation follow-up in 93% of living kidney donors in a single transplant center. Am J Transplant 2005;5:2417-24.
33. Garg AX, Muirhead N, Knoll G, Yang RC, Prasad GV, Thiessen-Philbrook H, et al. Proteinuria and reduced kidney function in living kidney donors: a systematic review, meta-analysis, and meta-regression. Kidney Int 2006;70:1801-10.