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ORIGINAL ARTICLE

Factors Affecting Changes in the Glomerular Filtration Rate after Unilateral Nephrectomy in Living Kidney Donors and Patients with Renal Disease

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Abstract
Purpose We evaluated the factors affecting changes in the postoperative glomerular filtration rate (GFR) after unilateral nephrectomy in living kidney donors and patients with renal disease.
Methods We studied 141 subjects who underwent living donor nephrectomy for renal transplantation (n=75) or unilateral nephrectomy for renal diseases (n=66). The GFR of the individual kidney was determined by Tc-99m DTPA scintigraphy before and after nephrectomy. By performing multiple linear regression analysis, we evaluated the factors that are thought to affect changes in GFR, such as age, sex, body mass index (BMI), preoperative GFR, preoperative creatinine level, operated side, presence of diabetes mellitus (DM), presence of hypertension (HTN), and duration of follow-up.
Results In both the donor nephrectomy and the disease nephrectomy groups, GFR increased significantly after nephrectomy (46.9±8.4 to 58.1±12.5 vs. 43.0±9.6 to 48.6±12.8 ml/min, $p<0.05$). In the donor nephrectomy group, age was significantly associated with change in GFR (β=-0.3, $p<0.005$). In the disease nephrectomy group, HTN, preoperative creatinine level, and age were significantly associated with change in GFR (β=-6.2, $p<0.005$; β=-10.9, $p<0.01$; β=-0.2, $p<0.01$, respectively). This compensatory change in GFR was not significantly related to sex, duration of follow-up, or operated side in either group.
Conclusions The compensatory change in the GFR of the remaining kidney declined with increasing age in both living kidney donors and patients with renal disease.

Keywords Tc-99m DTPA scan · Glomerular filtration rate · Unilateral nephrectomy · Age

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Introduction

Owing to a shortage of kidneys for transplantation, the elderly and obese have begun to be accepted as kidney donors [1]. After nephrectomy, the remaining kidney undergoes compensatory adaptation, and its total glomerular filtration rate (GFR) increases by 70% of the preoperative value within 8 to 12 weeks [2]. However, it has been reported that after donor nephrectomy, subjects experience renal insufficiency of about 0.2% to 0.5% [3]. Since renal function is expected to decrease with age, it is important to predict renal function after unilateral nephrectomy, especially in elderly donors. A study has shown that GFR in uninephric subjects exhibits a negative correlation with advancing age [4]. This study had a limitation in that the number of elderly patients was small. Therefore, further studies should be performed to evaluate the renal function in elderly donors because if the remaining kidney of elderly donors undergoes less compensatory change in GFR, other criteria must be established for the selection of elderly living donors [5].

To identify factors determining the risk of renal failure after unilateral nephrectomy, it is necessary to correctly estimate the individual function of each of the kidneys before and after surgery. In a previous study, the GFR of each kidney in binephric individuals was expressed as half of the corresponding two-kidney value [4, 5]. However, this method does not accurately reflect the individual function

of each of the kidneys because creatinine clearance determines the total GFR rather than the individual kidney function. On the other hand, the Tc-99m DTPA scan has been validated and accepted as a method for determining the GFR as a measure of both the overall renal function and the individual function of each of the kidneys [6].

The purpose of this study was to evaluate the factors affecting changes in GFR after nephrectomy in living kidney donors and patients with renal disease by using the results of Tc-99m DTPA scans.

Methods

Subject Population

We retrospectively reviewed 250 individuals on whom a unilateral nephrectomy had been performed at our institution in 2006 by two surgeons, and to include a large number of older subjects, we recruited not only a nephrectomy group comprising living donors, but also a group comprising patients with renal disease. We enrolled 144 of theses 250 individuals; Tc-99m DTPA scans were performed before and after surgery for theses subjects to estimate the GFR values of the remaining kidneys. Three of these subjects were excluded because retrieval data were not available.

Therefore, our study included 141 individuals who had undergone a unilateral nephrectomy either for kidney donation or for resection of renal carcinoma. We divided these subjects into a donor nephrectomy group and a disease nephrectomy group to analyze them separately and to evaluate the factors affecting change in GFR after nephrectomy. The donor nephrectomy group comprised 75 living donors (43 men and 32 women; average age: 37.8±11.1 years; median: 39 years; range: 17 to 58 years), and the disease nephrectomy group comprised 66 patients with renal malignancy (46 men and 20 women; average age: 53.9±12.9 years; median: 53 years; range: 23 to 79 years). Of the 66 patients with renal malignancy, 59 had renal cell carcinoma, and 7 had uroepithelial cancer. Each patient underwent two sequential Tc-99m DTPA scans before and after surgery. None of the study participants had renal disease, tumors, or a history of partial nephrectomy in the remaining kidney. The first study was performed 13.7±3.1 days (range: 1 to 174 days) before nephrectomy for the donor nephrectomy group and 16.7±1.7 days (range: 1 to 54 days) before nephrectomy for the disease nephrectomy group. The second study was performed 6.7±0.2 months (range: 5 to 13 months) after surgery for the donor nephrectomy group and 7.9±0.52 months (range: 3 to 18 months) after surgery for the disease nephrectomy group. We analyzed the factors that are thought to affect changes in GFR, such as age, sex, body mass index (BMI), preoperative GFR, preoperative creatinine level, operated side, presence of diabetes mellitus (DM), presence of hypertension (HTN), and duration of follow-up.

Tc-99m DTPA Scans

Quantitative scans of Tc-99m DTPA uptake in the kidneys were taken using a gamma camera-based Gates method. The subject was injected intravenously with 285 MBq (5 mCi) Tc-99m DTPA, and the Gates analysis was performed 2–3 min after the tracer was injected. The exact injection dose required for quantitation was determined by measuring the syringe uptake immediately before and after injection, and a decay correction was performed from the time of injection to the time of scintigraphy. Regions of interest were assigned for each kidney and perirenal semilunar background region. All GFR values were corrected on the basis of depth and normalized correction. In this study, we used this value as the preoperative or postoperative GFR.

To determine the reproducibility and repeatability of calculating GFR using this Tc-99m DTPA scan, the data of 40 subjects were analyzed twice, and another expert analyzed these data again. The standard deviation (SD) of intraobserver variability was 2.3, and the coefficient of variation (CV) was 5.1%. The SD of interobserver variability was 2.6, and the CV was 5.7%.

Statistical Analysis

The pre- and postoperative GFR values were compared using a paired *t*-test, and the subject characteristics of the two groups were compared using the unpaired Student's *t*-test. Categorical variables were examined using a simple chi-square analysis or a Fisher's exact test when the number of data elements was small. To determine the factors that were most predictive of the post-nephrectomy change in GFR, we performed univariate and multivariate regression analysis. A stepwise linear regression analysis was performed to identify independent variables that determined the post-nephrectomy change in GFR. Variables found to be statistically significant ($p<0.1$) in the univariate analysis were included in the multiple linear regression analysis. The values are expressed as mean ± SD. Two-tailed p-values were used, and $p<0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS software (Statistical Package for the Social Sciences for Windows, version 10.1.3, SPSS Inc., Chicago, IL).

Results

The characteristics of the subjects are summarized in Table 1. The subjects in the disease nephrectomy group

Table 1 Demographic data and characteristics of patients who underwent unilateral nephrectomy for donation of kidney or treatment of underlying renal disease

	Donor group (N=75)	Disease group (N=66)	*p*-value
Age (years)	37.8±11.1	53.9±12.9	<0.001
Sex (M:F)	43:32	46:20	NS
Diabetes	0	4	0.046
Hypertension	0	15	<0.001
Preop. creatinine (mg/dl)	0.8±0.2	1.0±0.2	0.001
Preop. GFR (ml/min)	46.9±8.4	43.0±9.6	0.011
BMI[a] (kg/ m^2)	24.1±3.5	24.3 ± 3.4	NS
Operated side (right:left)	44:31	28:38	NS
Duration of follow-up (day)	6.7±0.2	7.9±0.52	0.046

[a] BMI = body mass index

were significantly older than those in the donor nephrectomy group at baseline (53.9±12.9 years vs. 37.8±11.1 years, $p<0.05$) and had a higher preoperative creatinine level (0.95±0.20 mg/dl vs. 0.85±0.18 mg/dl, $p<0.05$). The donor nephrectomy group did not include subjects with DM or HTN, whereas the disease nephrectomy group included 4 patients with DM and 15 with HTN who had a history of drug treatment ($p=0.046$, $p<0.001$, respectively). The second study after nephrectomy was significantly shorter in the donor nephrectomy group than in the disease nephrectomy group (6.7±0.2 vs. 7.9±0.52, $p<0.05$). There was no significant difference between the groups with regard to sex, BMI, or operated side.

The differences between the groups with respect to post-nephrectomy changes in GFR are shown in Fig. 1. In both the donor nephrectomy and the disease nephrectomy groups, the GFR increased significantly after nephrectomy. In the donor nephrectomy group, the mean GFR of the remaining kidney of the 75 donors was 46.9±8.4 ml/min at baseline and increased to 58.1±12.5 ml/min after nephrectomy. The average percentage increase in the GFR of the remaining kidney in the donor nephrectomy group was 23.9%. In the disease nephrectomy group, the mean GFR of the remaining kidney of the 66 patients was 43.0±9.6 ml/min at baseline and increased to 48.6±12.8 ml/min after nephrectomy. For this group, the average percentage increase in the GFR of the remaining kidney was 13.0%. The mean change in GFR was significantly greater in the donor nephrectomy group than in the disease nephrectomy group (11.1±8.5 ml/min vs. 5.6±7.2 ml/min, $p<0.05$). In both groups, the mean serum creatinine level increased significantly after nephrectomy from 0.85±0.18 mg/dl to 1.16±0.24 mg/dl in the donor nephrectomy group and from 0.95±0.20 mg/dl to 1.30±0.27 mg/dl in the disease nephrectomy group ($p<0.05$).

We performed univariate and multivariate regression analyses to evaluate the factors affecting compensatory changes in the GFR of the remaining kidney (Table 2). In the donor nephrectomy group, univariate and multivariate analyses showed that age was the only factor significantly associated with the compensatory changes in GFR. The multiple regression model had an R^2 value of 11.9% (GFR change = 21.14 – 0.3 · age; $p<0.005$), as illustrated in Fig. 2. In the disease nephrectomy group, univariate analysis showed that DM, HTN, age, BMI, preoperative GFR, and preoperative creatinine levels were significantly associated with the compensatory change in GFR. Multiple regression analysis showed that HTN was the primary predictive factor for compensatory changes in GFR ($\beta=-6.2$, $p<0.005$). The patients with HTN showed fewer compensatory changes in GFR after nephrectomy than those without HTN. Preoperative creatinine level was an independent secondary predictive factor ($\beta=-10.9$, $p<0.01$), and age

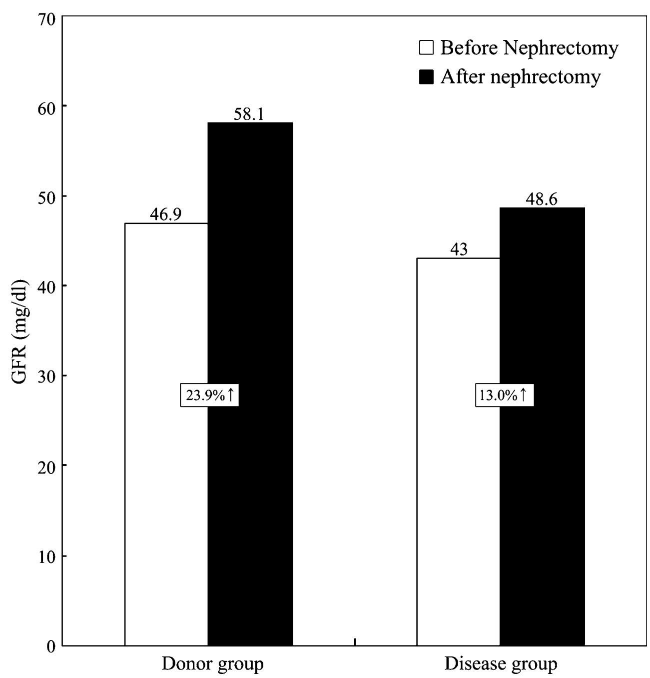

Fig. 1 This graph shows the difference in GFR after nephrectomy between the donor nephrectomy group and the disease nephrectomy group. Both the donor nephrectomy group and the disease nephrectomy group show significantly increased GFR after nephrectomy. The donor nephrectomy group shows a significant increase (greater average percentage) in GFR of the remaining kidney compared to the disease nephrectomy group (23.9% vs. 13.0%, $p<0.05$)

Table 2 Univariate and multivariate analysis of factors affecting compensatory changes in the GFR of the remaining kidney after unilateral nephrectomy

Variable	Donor group		Disease group	
	Univariate *p*-value	Multivariate	Univariate *p*-value	Multivariate
Age	0.001	β=-0.3, *p*=0.002	0.005	β=-0.2, *p*=0.007
Sex	NS[a]		NS	
Diabetes	NA[b]		0.004	
Hypertension	NA		<0.001	β=- 6.2, *p*=0.001
Preop. creatininne	NS		0.004	β=- 10.9, *p*=0.007
Preop. GFR[c]	NS		0.019	
BMI[d]	NS		0.015	
Operated side	NS		NS	
Duration of follow-up	NS		NS	

[a] NS = not significant, [b] NA = not applicable, [c] GFR = glomerular filtration rate, [d] BMI = body mass index

was the third predictive factor (β=-0.2, $p<0.01$; R^2= 34.0%). The multivariate regression analysis also showed that DM, BMI, and preoperative GFR had little or no influence on the outcome of renal function in the disease nephrectomy group when adjusted for HTN, preoperative creatinine level, and age.

Furthermore, the compensatory change in GFR was not significantly correlated with sex, duration of follow-up, or operated side in either group.

Discussion

In this study, patients exhibited a compensatory change in GFR in the remaining kidney after nephrectomy. However, the compensatory hyperfunction declined with increasing age in both the donor nephrectomy and disease nephrectomy groups.

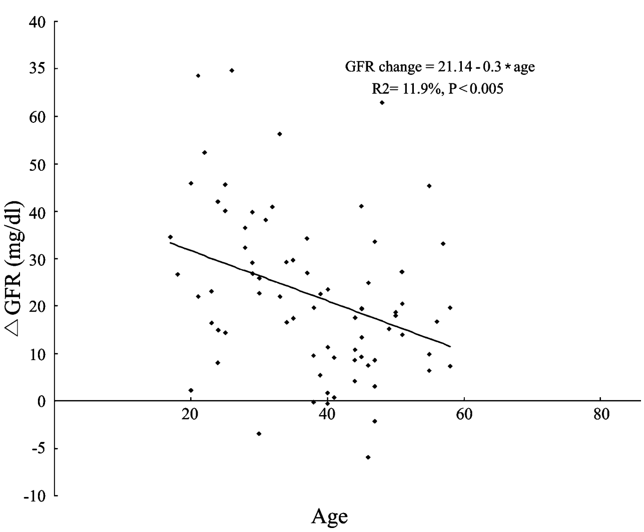

Fig. 2 These plots show the correlation of age and compensatory GFR change in the donor nephrectomy group. In the donor nephrectomy group, older patients undergo a lesser change in the compensatory GFR of the remaining kidney. The multiple regression model shows R2 of 11.9% (GFR change=21.14 – 0.3 age; $p<0.005$)

The elderly have been selected for living kidney donation in some centers; however, the use of elderly living donors is considered controversial because renal function begins to decline in the 3rd decade of life [7, 8]. Furthermore, aging is related to a high prevalence of glomerulosclerosis and global glomerulosclerosis [9, 10]. Therefore, the selection of elderly living kidney donors is an important issue because these donors could develop post-nephrectomy renal failure due to failure of the remaining kidney to compensate for the removed kidney. In a study by Johnson et al., elderly donors had a reduced serum creatinine clearance at a 1-year follow-up after donation. Therefore, additional follow-up should be performed for elderly donors who present for living donor nephrectomy [1]. Despite this concern, many centers currently use living kidney donors of advanced ages.

The regression analysis of our data shows that at the time of nephrectomy, the compensatory change in the GFR of the remaining kidney is less in older subjects. For example, using the multiple regression equation mentioned earlier, it can be estimated that for a 55-year-old individual undergoing nephrectomy, the change in GFR will be about 9 ml/min less than that for a 25-year-old individual after unilateral nephrectomy. In the general population, the GFR decreases with age and begins to fall at the age of 40. After 50 years of age, the GFR declines more rapidly. The decline in GFR between the age of 35 and 55 years is approximately 1 ml/(min•year), and it accelerates to approximately 1.4 ml/(min•year) beyond 55 years of age [11]. Taking into consideration that the compensatory change is lesser among elderly patients, especially those beyond 55 years, age should be an important factor in deciding whether an individual should be selected as a kidney donor.

Studies have reported an age-related decline in renal function among hypertensive subjects [12, 13], and unilateral nephrectomy is associated with an increase in blood pressure [14]. Our data indicated that in the patients with HTN, the

compensatory change in GFR was about 6.2 ml/min less than that in patients without HTN. Hence, it is important to screen for HTN in living kidney donors before nephrectomy, and HTN is an exclusion criterion for kidney donation.

Unlike in the disease nephrectomy group, in the donor nephrectomy group, only age was significantly associated with the compensatory change in GFR. It is thought that living donors are generally selected according to the donor criteria. Thus, donors with any medical disease or high creatinine levels would have been excluded from living kidney donation.

In our study, the multivariate analysis showed that the preoperative GFR value as measured by the Tc-99m DTPA had little or no influence on the outcome of renal function in nephrectomy patients; however, the univariate analysis showed that it significantly affected the compensatory change in GFR. Both the analyses showed that preoperative creatinine levels were significantly associated with the compensatory change in GFR. Estimating creatinine levels is thought to be a more precise method for assessing renal function than using radionuclide techniques. However, radionuclide techniques show a good correlation with a 24-h creatinine clearance ($r=0.91$) [15], and it is possible to determine GFR as a measure of both the overall renal function and the individual function of each kidney [6]. Therefore, a Tc-99m DTPA scan is a useful and simple method for assessing the individual function of each kidney and for monitoring adaptive changes during follow-ups.

In this study, the donor nephrectomy and disease nephrectomy groups differed in terms of duration of follow-up after nephrectomy. The average duration of follow-up was 6.7 ± 0.2 months (range: 5 to 13 months) after nephrectomy for the donor nephrectomy group and 7.9 ± 0.52 months (range: 3 to 18 months) after nephrectomy for the disease nephrectomy group. Previous studies have demonstrated that compensatory changes in the remaining kidney occur within several weeks, peaking at 2–6 months, and stabilize or increase very slightly for more than 10 years after nephrectomy [2, 16]. Thus, the difference in follow-up duration between the donor nephrectomy and disease nephrectomy groups is not important because the average follow-up duration in this study was 6 months for both groups.

In our study, the disease nephrectomy group showed fewer compensatory changes in GFR than the donor nephrectomy group. This effect was attributed to the higher number of older patients in the disease nephrectomy group. Further, a compensatory reaction may have already occurred in the contralateral kidney before nephrectomy. Prassonpoulos et al. have inferred that the compensatory reaction in the remaining kidney occurs before surgery in patients with renal cell cancer because the unaffected kidneys in their patients were 36% larger than the corresponding normal kidney in binephric individuals 1 month before nephrectomy [17].

This study has several limitations. Firstly, it included only 56% of all the nephrectomy patients who were examined using Tc-99m DTPA scans in 2006. Thus, the results may have been subject to selection bias. Secondly, in order to include data on elderly patients, we analyzed patients who underwent unilateral nephrectomy for renal disease. Therefore, the results of this study cannot be extrapolated to healthy donors. However, we performed multiple regression analysis to obtain a regression coefficient associated with increasing age.

In conclusion, age, preoperative creatinine level, and HTN were statistically significant predictive factors affecting the change in GFR after unilateral nephrectomy. Our study showed that the compensatory change in the GFR of the remaining kidney declined with increasing age in both the younger donors and older nephrectomy groups. The compensatory change in the GFR of the remaining kidney determined in this study will help in predicting changes in GFR after unilateral nephrectomy, especially in elderly patients.

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