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Original Article

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Long-Term Follow-up Results of Living Kidney Donors: 20 Years of Experience

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Abstract

Objective: We aimed to retrospectively evaluate the follow-up results of living kidney donors (LKD) at our center since 1997.

Materials and Methods: LKD instances between 1997 and 2016 were evaluated. Followed-up by at least one year post-donation were included. The criterion for progression in renal failure (RF) was more than 25% reduction in the glomerular filtration rate (GFR). The cases were divided into two groups: Group 1 (GFR<60 mL/min/1.73 m^2) and Group 2 (GFR≥60 mL/min/1.73 m^2) according to the GFR values obtained at the last follow-up.

Results: In this study, 205 cases were included. The mean follow-up period was 57±46 (12–215) months. The prevalence of hypertension (all of them were stage 1) and diabetes (83.3% of them were new diagnosis with no end-organ damage) before and after donation was 3.1 and 2.9% vs. 13.3 and 17.5%, respectively (p<0.05). Progressive decline in RF was observed in 29 cases (14%). None of the donors progressed to end-stage renal disease (ESRD). When compared with Group 2, Group 1 patients were older, more frequently hypertensive, and had lower GFR and higher serum uric acid levels.

Conclusion: Despite the loss of GFR due to nephrectomy, the progression to RF is rare in LKD. Baseline GFR, uric acid, and age are associated with RF progression. There is a need for a "national donor follow-up program" in Turkey.

Keywords: Kidney transplantation, live kidney donors, follow-up results, renal failure

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INTRODUCTION

The number of patients waiting for an organ both in Turkey and in the world is increasing day by day. However, the absence of a sufficient increase in the number of cadaveric transplants boosts the demand for living-donor organ transplantation. With regard to living-donor kidney transplantation (LDKT), Turkey is one of the many countries that have most successfully performed this transplant in the world. According to the data from the Transplantation, Dialysis and Follow-up Systems (TTIS) in our country, the number of kidney transplants in 2011 was 2952, while the number of LDKT was 2435. This rate has reached 3342 in 2017 out of which 2649 were LDKT (1). The increase in the number of LDKT is remarkable. Although LDKT is optimal for the treatment of end-stage renal disease (ESRD) when considering both the patients and kidney survival, there may be an increase in the risk factors for living kidney donors (LKDs). According to American data, the incidence of ESRD and cardiovascular risk factors such as hypertension, diabetes, and obesity may increase in kidney donors (2). When considering these risks, it is important to follow-up LKDs. There are not sufficient data on this subject in our country. In this study, we aimed to retrospectively evaluate the follow-up results of LKDs at our center since 1997.

MATERIALS AND METHODS

LDKT performed between January 1997 and December 2016 was retrospectively evaluated. LKDs who were older than 18 years old, had a glomerular filtration rate (GFR) of >70 mL/min/1.73 m^2, body mass index (BMI) ≤35 kg/m^2, no proteinuria (<300 mg/day), and were followed-up for at least one year after donation were included in this study. Kidney donor candidates with a history of hypertension were evaluated with a 24-h ambulatory blood pressure measurement. Those with stage 1 hypertension whose blood pressure was controlled with a single antihypertensive agent, who had no end-organ damage to their eye, and normal echocardiographic findings were considered as kidney donors. Those with type 2 diabetes who were older than 50 years, blood glucose was controlled with a single oral antidiabetic agent, and who had no end-organ damage to their eye and kidney (absence of microalbuminuria, normal fundus) were considered as kidney donors.

The exclusion criterion for participation in this study was accepted as a follow-up period of less than 1 year. The baseline and follow-up data of the cases were retrospectively obtained from their files. The follow-ups of the cases were scheduled as preoperative, postoperative day 1, discharge, first polyclinic visit (between 1 and 3 months), and yearly visits.

The GFR values of the cases were calculated according to the MDRD formula. The criterion for progression in renal failure (RF) was considered as more than 25% reduction in GFR according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines (3). The assessment of progression was performed using GFR values measured at the first (1-3 months) and last visits after donation. The cases were divided into two groups: Group 1 (GFR <60 mL/min/1.73 m^2) and Group 2 (≥60 mL/min/1.73 m^2) according to the GFR values measured at the last visit. Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Statistical Analysis

All the analyses were performed using the Statistical Package for the Social Sciences (SPSS) 15.0 software (SPSS Inc., Chicago, IL, USA) for Windows. The mean and standard deviation (mean±SD) of all the values were calculated. The Student's t-test and chi-squared test were used for intergroup comparisons. Here, p<0.05 was considered to be statistically significant. The Cox regression model was used for the analysis of multiple variables (age, gender, comorbid disease status, basal GFR, and serum uric acid level).

RESULTS

Here, 205 cases were selected from 236 LKDs with a follow-up period of more than 1 year. The mean follow-up period was 57±46 (12-215) months. The mean age of the cases was 48±11 (19-82) years. Further, 101 (49%) cases were female. When the kinship between the kidney transplant donors and recipients was evaluated, 51 (24.8%) received a kidney transplant from their mothers; 42 (20.4%), fathers; 53 (25.8%), siblings; 46 (22.4%), spouse; 11 (5.6%), children; and 2 (1%), unrelated individuals. Out of these cases, 3.1% had a history of hypertension and 2.9% had a history of diabetes (83.3% of them were new diagnosis). Further, 22.9% of the cases were obese (29.9<BMI<35 kg/m^2).

At the baseline, the mean serum levels of urea, serum uric acid, and GFR value were 29±8.6 (14-61) mg/dL, 4.6±1.3 (0.3-9.2) mg/dL, and 103±21 (70-177) mL/min/1.73 m^2, respectively. The average value of proteinuria 122±68 (8–298) mg/day. At the baseline, the mean serum levels of fasting blood glucose, total cholesterol, triglyceride, HDL, and LDL were 95±12, 195±39, 145±88, 41±12 and 125±33, respectively. At the first visit, the mean serum urea level was 35±10 (19-68) mg/dL and the mean GFR value was 67±16 (32-154) mL/min/1.73 m^2. At the last visit, the mean serum urea level was 34±10 (10-106) mg/dL, mean GFR value was 69±18 (19-145) mL/min/1.73 m^2, and mean serum uric acid level was 5.6±1.4 (2.6-9.5) mg/dL. At the last visit, the mean serum levels for fasting blood glucose, total cholesterol, triglyceride, HDL, and LDL were 98±14, 206±44, 162±84, 48±13 and 135±36, respectively. At the last visit, the rates of hypertension and diabetes were 13.3% and 17.5%, respectively. The values of variables at the baseline, first, and last visits are listed in Table 1.

Out of the cases, 3.1% (n=7) had a history of hypertension; angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers, calcium-channel blockers, and diuretic were used in four, two, and one cases, respectively. These cases were older (62±11 years vs. 47±10 years; p=0.01) and had lower baseline GFR values (90±11 vs102±23 mL/min/1.73 m^2; p=0.02). However, there was no significant difference between the two groups in terms of baseline serum urea (30±8.6 vs 29±8.6; p=0.88) and uric acid (4.9±1.8 vs 4.6±1.4; p=0.66) levels. At the last visit, there was no significant difference in terms of serum urea (41±15 vs 34±10; p=0.27) and uric acid (6.4±1.8 vs 5.6±1.4; p=0.16) levels. However, these cases had lower last GFR values (50±12 vs70±18 mL/min/1.73 m^2; p<0.01).

When the cases were compared according to the presence of comorbid diseases (hypertension, diabetes, and obesity where at least one was included), 57 (28%) cases had at least one comorbid disease. These cases were relatively older (50±13 years vs. 47±9.8 years; p=0.08) and had higher baseline serum uric acid levels. However, there was no significant difference between the two groups in terms of baseline GFR values and baseline serum urea levels. Although there was no significant difference between the two groups in terms of kidney function parameters at the last control, there were significant differences, rate of hypertension (27 vs. 8%; p=0.02), obesity (72 vs. 16; p<0.001), and diabetes (30 vs. 13%; p=0.05). There was a remarkable increase in the incidence of new onset diabetes (15%), hypertension (10%), and obesity (8%) during the follow-up period (p<0.05).

Further, 29 (14%) cases had a progressive reduction in RF. None of the cases developed ESRD or required renal replacement therapy. One case died from cardiovascular causes at the age of 67 years, approximately 14 years after nephrectomy.

The cases with progression in RF were relatively older (51±9.9 years vs. 48±11 years; p=0.17) and had higher prevalence of obesity (38 vs. 20%; p=0.08). There was no significant difference between the two groups in terms of other values.

Table 1. Values of variables at baseline, first, and last visits

	Baseline (Range)	First control (Range)	Last control (Range)	p
SBP (mm Hg)	118±14 (80-160)	120±14 (90-180)	124±15 (90-180)	<0.05
DBP (mm Hg)	76±9.5 (50-110)	77±9.0 (50-110)	79±10 (50-110)	<0.05
Serum Urea (mg/dL)	29±8.6 (14-61)	34±9.7 (19-68)	34±10.3 (10-106)	0.83
Serum Uric Acid (mg/dL)	4.6±1.3 (0.34-9.2)	5.4±1.4 (2.2-11.7)	5.6±1.4 (2.6-9.5)	<0.05
GFH (mL/min/1.73m^2)	103±22 (70-177)	67±16 (32-155)	69±18 (19-145)	<0.05
Proteinuria (mg/day)	122±68 (10-290)	-	153±75 (21-694)	0.78
CKD n, (%) Stage of 3-4	0 (0)	75 (36.5)	68 (33.1)	0.25
Hypertension (%)	3	3	13	<0.05
Diabetes Mellitus type 2 (%)	2.9	2.9	18	<0.05
Obesity (%)	22.9	22.9	31	<0.01

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; GFH: Glomerular Filtration Rate; CKD: Chronic Kidney Disease

Table 2. Comparison of baseline and follow-up results between Group 1 and Group 2

	Group 1 GFH<60 mL/ min/1.73m^2 (n:66)	Group 2 GFH≥60 mL/ min/1.73m^2 (n:139)	p
Age (years)	53±11	46±9.7	<0.001
Gender (F/M)	58	46	0.12
Hypertension (%)	9	1	<0.05
Diabetes Mellitus Type 2 (%)	3	3	0.98
Obesity (%)	27	21	0.35
BMI kg/m^2	27.2±3.62	26.7±4.1	0.45
SBP (mmHg)	120±13	117±13	0.15
DBP (mmHg)	78±10	76±9.2	0.12
B.Serum Urea (mg/dL)	33±8.7	28±8.2	<0.001
B. Serum Uric acid (mg/dL)	4.9±1.3	4.4±1.4	<0.01
B.GFH (mL/dak/1.73m^2)	90±15	108±22	<0.001
LC. Serum Urea (mg/dL)	40±12	32±7.9	<0.001
LC. Serum Uric Acid (mg/dL)	6.2±1.3	5.4±1.4	<0.001
LC.GFH (mL/dak/1.73m^2)	52±7.2	78±16	<0.001
LC.Hypertension (%)	23	9	0.02
LC.Diabetes Mellitus type 2 (%)	21	17	0.40
Obesity (%)	31	33	0.73

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; GFH: Glomerular Filtration Rate; CKD: Chronic Kidney Disease; BMI: Body mass index; B: Baseline, LC: Last Control

During the follow-up, 66 (32.1%) cases had GFR<60 mL/min/1.73 m^2 (Group 1). While 65 cases had stage 3 chronic kidney disease (CKD), 1 case had stage 4 CKD. When compared with Group 2, 66 cases (32.1%) with GFR < 60 mL/min/1.72 m^2 (Group 1) were older (53±11 vs. 46±9.7 years, p<0.001), more frequently hypertensive (9 vs. 1%, p<0.05), had lower basal kidney functions (GFR=90±15 vs. 108±22 mL/min/1.73 m^2; p<0.001), and had higher serum uric acid levels (4.9±1.3vs 4.4±1.4; p<0.01). These findings are listed in Table 2.

Since the number of patients with progression in RF was low, none of the variables reached statistical significance in the Cox regression analysis. This analysis was performed to predict the cases with GFR < 60 mL/min/1.73 m^2 at the last visit. In this analysis, the variables of age, gender, comorbid disease status, basal GFR, and serum uric acid level were examined. Age (exp(B):1.46(CI:1.20-1.76); p=0.001), basal GFR (exp(B):0.96 (CI:0.95-0.98); p<0.001), and serum uric acid level (exp(B):1.18(-CI:1.03-1.39); p=0.04) were independently associated with Group 1.

DISCUSSION

In our study, we found no significant progression in RF in the follow-up of LKDs. However, there was a remarkable increase in the incidence of comorbid diseases such as diabetes, hypertension, and obesity during the follow-up period.

So far, most of the studies involving LKDs after donation even in developed countries have been retrospectively conducted or conducted based on the data obtained from national registries. Unfortunately, the number of randomized controlled trials on this subject is insufficient. Although there have been significant increases in the number of LDKT in the last 10 years in our country, there are insufficient studies and data on LKDs. According to the data from the Organ Procurement and Transplantation Network (OPTN), a study evaluating 123.000 LKDs between 1994 and 2016 found that the risk of developing ESRD in patients showed racial differences (4). The risk of developing ESRD within 20 years was 8 per 10.000 white women and 111 per 10,000 black men (4). This risk was found to be very low, particularly in white individuals. Similarly, the study by Ibrahim et al. involving 3.956 white LKDs with a mean follow-up period of 16.5 years revealed that only 28 (0.7%) patients developed ESRD (5). In the meta-analysis of Sha-Sha Li et al. evaluating 62 studies and 114,783 cases, it was revealed that time is very important for the development of ESRD and that this risk increases particularly 10 years after kidney donation (6). This risk was found to be 1.1% (6). In accordance with the literature, we found that our cases had lower progression in chronic RF and did not develop ESRD. The limited duration of the follow-up (57±45 months) may be an important factor responsible for these findings. Although it varies according to ethnicity, age is an important factor for white individuals. In a recent study by Wainright et al. (4), it was found that the risk of developing ESRD increased 1.26 times particularly over 40 years of age. In this study, according to the scoring system for developing ESRD, the risk increased significantly over 10 years of follow-up and over 40 years of age in white individuals. These rates were determined as 5 times for men aged 40-60 years and 3 times for women aged 40-60 years. The risk increased exponentially over 20 years of follow-up and over 60 years of age. In our study, we may have not found the development of ESRD and/or may have found lower progression of RF because the mean age (48±11 years) was relatively low.

Although we did not observe significant progressions in RF during follow-up, we found that the presence of lower predonation GFR increased the risk of having GFR <60 mL/min/1.73 m^2 at follow-up. When the literature is considered, similar results have been shown in many studies (2, 6, 7). The presence of predonation hypertension, particularly in these cases, was remarkable (9 vs. 1%). None of our hypertensive cases had macrovascular and microvascular end-organ damage. They performed ambulatory blood pressure monitoring before donation. This may be related to the presence of hypertension and poor predonation renal histological patterns in patients who have a solitary kidney after donation. In our previous study, we found supportive findings in the zero-hour biopsies of LKDs. Even if kidney histological patterns and GFRs of both the kidney donors with hypertension and white-coat hypertension were similar, we determined that they had poorer kidney histological patterns as compared to nonhypertensive donors (8). As a result, this has indicated that the clinician should be careful when making a donation decision in patients with a history of hypertension and with GFR from 70 to 90 mL/min/1.73 m^2.

Serum uric acid levels are an important parameter in these cases. Because our cases have elevated serum uric acid levels during follow-up, serum uric acid levels at the baseline and follow-up are high in the presence of comorbid conditions, and they independently link to the patients with GFR <60 mL/min/1.73 m^2. Indeed, several large-scale studies have shown that serum uric acid levels are an important marker for predicting newly emerging hypertension, diabetes, metabolic syndrome, and cardiovascular disease in healthy populations (9-12). It is also a crucial parameter in the prediction of progression in CKD patients (13). However, there are insufficient data on this subject in LKDs in the literature. We need to consider pre- and post-donation uric acid levels in these patients.

In our cases, there was a remarkable increase in the incidence of new onset hypertension, diabetes, and obesity post-donation. When we examined the literature, a similar increase was found in such cases. In a study conducted in Canada, when 1.278 LKDs and 6.359 healthy individuals were compared with each other, it was found that LKDs had a 1.4-fold increased risk of developing hypertension (14). In a meta-analysis, the cases had a 6 mmHg increase in the mean systolic blood pressure and 4 mmHg increase in the mean diastolic blood pressure during post-donation follow-up (15). Many pathogeneses may be responsible for the development of hypertension. In these cas-

es, processes such as hyperfiltration in the remaining kidney, activated Renin–angiotensin system, obesity accompanied by increased vascular tone, and diabetes may be responsible for this occurrence (2, 14, 15). There is a need for large-scale studies to clarify this issue. Post-donation is an important problem in diabetes and obesity (2, 5, 16). Many risk factors such as age, gender, ethnicity, family history, presence of diabetes in the recipient, and basal BMI have been attributed to the occurrence of this process (5). There is a need for studies to elucidate the cause–effect relationships for its pathogenesis.

There is a need for a "national donor follow-up program" in Turkey. Further, there are many reasons for which the use of a systematic approach to follow-up for donor safety is imperative. Early detection of complications may prevent poor outcomes. This issue is important not only for kidney health but also for cardiovascular morbidity and mortality. Further, health insurance coverage that can be experienced in the national donor follow-up program should be considered.

This study has certain limitations. Firstly, we did not have a control group and had a small number of cases. Secondly, our follow-up period was relatively short. Thirdly, a donation decision was made after important clinical assessments, particularly in patients with comorbid diseases. For this reason, the above results may not reflect the results of LKDs in all the possible centers. Lastly, only diabetics and hypertensive donors with microalbuminuria were evaluated.

CONCLUSION

Although LKDs have a loss of GFR after donation, progression in RF is rarely seen. Predonation GFR, age, and serum uric acid levels are associated with progression in RF. Early and late follow-ups of these cases are important. Clinicians need to be cautious about hypertension, diabetes, and obesity that can develop after donation.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Informed consent was obtained from all participants included in the study.

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