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

Canlı Böbrek Donörlerinin Uzun Dönem Takip Sonuçları: 20 Yıllık Tecrübemiz

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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.

MATERIAL and METHODS: LKD between 1997 and 2016 were evaluated followed by at least one year post donation were included. The criterion for progression in renal failure (RF) was a more than 25% reduction in Glomerular filtration rate (GFR). The cases were divided into two groups as 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 obtained at the last follow up.

RESULTS: A total of 205 cases were included in the study. 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% 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). A progressive decrease in RF was observed in 29 cases (14%). None of the donors progressed to end stage renal disease. When compared with Group 2, Group 1 cases were older, more frequently hypertensive and had lower GFR and higher serum uric acid levels.

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

KEY WORDS: Kidney transplantation, Live kidney donors, Follow-up results, Renal failure

ÖZ

AMAÇ: Bu çalışmada, merkezimizde 1997 yılı itibariyle böbrek donörü olmuş canlı vericilerin takip sonuçlarını geriye dönük değerlendirmeyi amaçladık.

GEREÇ ve YÖNTEMLER: Merkezimizde 1997-2016 dönemi böbrek nakillerinin canlı donörleri değerlendirmeye alındı. Donasyon sonrası en az bir yıl izlenen donörler çalışmaya dahil edildi. Olgular son kontrolde Glomeruler filtrasyon hızı (GFH) değeri 60'ın altında (grup 1) ve üstünde (grup 2) olmak üzere iki gruba ayrıldı.

BULGULAR: 205 olgu çalışmaya dahil edildi. Ortalama takip süresi 57±46 aydı. Olguların transplant öncesi %3.1'inde hipertansiyon (tamamı evre 1 ve uç organ hasarı olmayan), %2.9'unda diyabet (%83.3'de yeni tanı diyabet ve uç organ hasarı olmayan) mevcut iken, son kontrolde bu oranlar sırasıyla %13 ve %18 olarak saptandı (p<0.05). Yirmidokuz olguda (%14), böbrek fonksiyonlarında progresif azalma gözlendi. Son donem böbrek yetmezliği gelişen olgu yoktu. İzlemde; grup 1, grup 2 ile kıyaslandığında, bu olgular daha yaşlı, daha sıklıkla hipertansif, bazal GFH düzeyi daha düşük ve serum ürik asit değerleri daha yüksekti.

SONUÇ: Canlı böbrek donörlerinde nefrektomiye bağlı GFH kaybı olmakla birlikte böbrek yetmezliğinde progresyon nadirdir. Bazal GFH, serum ürik asit düzeyi ve yaş böbrek yetmezliğinde ilerlemeyle ilişkilidir. Ülkemizde ulusal donör izleme programına ihtiyaç vardır.

ANAHTAR SÖZCÜKLER: Böbrek nakli, Canlı böbrek donörü, İzlem sonuçları, Böbrek yetmezliği

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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 sufficient increases in the number of cadaveric transplants boosts the demand for living-donor organ transplantation. A living-donor kidney transplantation (LDKT), Turkey is one of among countries that the successfully and most performed in the world. According to the data of Transplantation, Dialysis and Follow-up Systems (TTIS) in our country, the number of kidney transplants in 2011 was 2952, while the number of LDKTs was 2435. This rate has reached 3342 in 2017 and 2649 of them were LDKT (1). The increase in the number of LDKT cases is remarkable. When the patient and kidney survival is considered, LDKT is the optimal treatment of end stage renel disase (ESRD). However, the procedure itself carries a number of risks for donors. According to American data, the incidence of ESRD and cardiovascular risk factors such as hypertension, diabetes, and obesity may increasing in the kidney donor population (2). When considering these risks, it is important to follow up living kidney donors. The data on this subject is inadequate in our country. In this study, we aimed to retrospectively evaluate the follow-up results of living kidney donors at our center since 1997.

MATERIALS and METHODS

LDKT cases performed between January 1997 and December 2016 were retrospectively evaluated. Living kidney donors who were older than 18 years, had a glomerular filtration rate (GFR) of >70 ml/min/1.73 m^2 and a body mass index ≤35 kg/m^2, with no proteinuria (<300 mg/day) and who had been followed up for at least one year after donation were included in the study. Kidney donor candidates with a history of hypertension were evaluated with a 24-hour ambulatory blood pressure measurement. Those with stage I hypertension, not accompanied by retinopathy or echocardiographic disorder and successfully controlled with single antihypertensive drug, were accepted as donors. Also,those with Type II Diabetes Mellitus and over 50 years of age, already having had single drug glucose regulation and no retinopathy and proteinuria were accepted as donors.

A follow-up period less than 1 year was the exclusion criterion in this study. The baseline and follow-up data of the cases were obtained retrospectively from their files. The follow-ups of the cases were scheduled as preoperative, postoperative day 1, discharge, first outpatient 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 a more than 25% reduction in GFR according to the KDIGO guidelines (3). Progression was assessed using GFR values measured at the first (1-3 months) and last visits after donation. The cases were divided into two groups as Group 1 (GFR< 60 mL/min/1.73 m^2) and Group 2 (≥ 60 mL/min/1.73 m^2) according to GFR values measured at last visit.

All analyses were performed using the SPSS 15.0 for Windows statistical package. The mean and standard deviation (mean ± SD) of all values were calculated. The Student t-test and Chi-square test were used for intergroup comparisons. A p-value <0.05 was considered statistically significant. The Cox regression model was used for the analysis of multiple variables (variables: age, gender, comorbid disease status, basal GFR, and serum uric acid level).

RESULTS

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

At 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 was 122±68 (8-298) mg/day. At 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, the mean GFR value was 69±18 (19-145) ml/min/1.73 m^2, and the mean serum uric acid level was 5.6±1.4 (2.6-9.5) mg/dL. At last visit, the mean serum levels of 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 the variables at the baseline, first and last visits are shown in Table I.

Of the cases, 3.1% (n:7) had a history of hypertension: angiotensin converting enzyme inhibitors or angiotensin-receptor blockers, calcium channel blockers and diuretics were used by 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 vs. 102±23; 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

Table I: Values of variables at baseline and the first and last visits.

	Baseline (Range)	First follow up (Range)	Last follow up (Range)	P value
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.

visit, similarly 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 vs. 70±18; p<0.01).

When the cases were compared according to the presence of comorbid diseases (where at least one of hypertension, diabetes, and obesity 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 follow-up, there were significant differences with regard to the 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 significant increase in the incidence of new onset diabetes (15%), hypertension (10%) and obesity (8%) during follow-up (p<0.05).

29 (14%) cases had a progressive reduction in renal function. None of the cases developed ESRD or required renal replacement therapy. One donor deceased due to a cardiovascular cause at the age of 67, approximately 14 years after nephrectomy.

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

During follow-up, 66 (32.1%) cases had a 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, the 66 cases (32.1%) with GFR < 60ml/min/1.72m2 (Group 1) were older (53 ± 11 vs. 46 ± 9.7, p <0.001), more frequently hypertensive (9% vs. 1%, p <0.05), and had lower basal kidney functions (GFR= 90 ± 15 vs. 108 ± 22; p <0.001) and higher serum uric acid levels (4.9±1.3 vs. 4.4±1.4; p<0.01). These findings are shown in Table II.

Since the number of patients with progression in RF was low, none of the variables reached statistical significance in the Cox regression analysis. The Cox regression analysis was performed to predict the cases with a GFR below 60 mL/min/1.73 m^2 at the last visit. In this analysis, the variables evaluated were age, gender, comorbid disease status, basal GFR, and serum uric acid level. 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 living kidney donors. However, there was a remarkable increase in the incidence of comorbid diseases such as diabetes, hypertension, and obesity during follow-up.

Most of the studies so far on living kidney donors after donation, even in developed countries, have been conducted retrospectively or are based on the data obtained from national registry systems. Unfortunately, the number of randomized controlled trials on this subject is insufficient. Although there have been significant increases in the number of LDKTs in the last 10 years in our country, there are not enough studies and data on living kidney donors. According to the data from the

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

	Group 1 GFR<60 ml/min/1.73m2 (n:66)	Group 2 GFR≥60ml/min/1.73m2 (n:189)	P value
Age (years)	53±11	46±9.7	<0.001
Gender (F/M)	58	46	0.12
Hypertansion(%)	9	1	<0.05
Diabetes Mellitus Type 2 (%)	3	3	0.98
Obesity (%)	27	21	0.35
BMI kg/m2	27.2±3.62	26.7±4.1	0.45
SBP (mm Hg)	120±13	117±13	0.15
DBP (mm Hg)	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/min/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 follow up.

Organ Procurement and Transplantation Network (OPTN), a study evaluating 123,000 living kidney donors 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 especially in white individuals. Similarly, the study of Ibrahim et al. involving 3,956 white living kidney donors with a mean follow-up period of 16.5 years determined that only 28 (0.7%) patients developed ESRD (5). In the meta-analysis of Li et al. evaluating 62 studies and 114,783 cases, it has been revealed that time is very important for the development of ESRD and that this risk increases especially 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 especially 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 a GFR less than 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 was especially remarkable in these cases (9% vs 1%). None of our hypertensive cases had macrovascular and microvascular end-organ damage. They had measurements of blood pressure as 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 zero-hour biopsies of living kidney donors. 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 compared to non-hypertensive donors (8). This has indicated that the clinician should be careful when making a donation decision in patients with a history of hypertension and with a GFR of 70 to 90 ml/min/1.73 m^2.

Serum uric acid levels are an important parameter in these cases. 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 living kidney donors in the literature. We need to consider predonation and postdonation uric acid levels in these patients.

In our cases, there was a remarkable increase in the incidence of new onset hypertension, diabetes, and obesity postdonation. When we examined the literature, there was a similar increase in these cases. In a study conducted in Canada, when 1,278 living kidney donors and 6,359 healthy individuals were compared with each other, it was found that living kidney donors had 1.4-fold increased risk of developing hypertension (14). In a meta-analysis, the cases had a 6 mmHg increase in mean systolic blood pressure and a 4 mmHg increase in mean diastolic blood pressure during post-donation follow-up (15). Many pathophysiological processes may be responsible for the development of hypertension. In these cases, processes such as hyperfiltration in the remaining kidney, activated Renin-angiotensin system, obesity accompanied by increased vascular tone, and diabetes may be responsible (2,14,15). There is a need for large-scale studies to clarify this issue. Diabetes and obesity in LKDs postdonation is an important problem (2,5,16). Many risk factors such as age, gender, ethnicity, family history, presence of diabetes in the recipient, and basal BMI have been accused of this process (5). Studies to elucidate the cause-effect relationship for the pathogenesis are required.

There is a need of "national donor follow up program" in Turkey. There are many reasons to use a systematic surveillance program for donor safety. At first, early detection of complications definitely prevents poor outcomes. This issue is important not only for kidney health but also for cardiovascular morbidity and mortality. Also, implementation of a novel health insurance coverage for donors should be considered.

This study has some 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, we made a donation decision after important clinical assessments, especially in patients with comorbid diseases. These results may therefore not reflect the results of living kidney donors at all possible centers. Lastly, diabetics and hypertensive donors were only evaluated with microalbuminuria.

In conclusion, although living kidney donors have a loss of GFR after donation, progression to 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.

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