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Original Article

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Clinical Course of Kidney Donors in the Long Term after Transplant: A Single-Center Experience

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Abstract

Objective: The aim of this study was to evaluate the parameters affecting the long-term results and glomerular filtration rate (GFR) of kidney donors for five years and over.

Materials and Methods: Forty-two female and twenty-one male patients were included in this study. The mean age was 54.97±10.28 years and the mean follow-up time was 8.02±4.43 years. In our retrospective study, the follow-up period of the donors, age, sex, weight, height, hypertension (HT), coronary artery disease (CAD), diabetes mellitus (DM), drug use, cigarette and alcohol consumption, socio-economic status, educational level, and laboratory results was recorded. The patients were divided into three groups based on HT. Those diagnosed with HT before transplantation, those diagnosed with HT after transplantation, and those with normotensives.

Results: No correlation was found between GFR and gender, BMI, follow-up period ($p<0.05$ for all). Significant decrease in GFR was detected in HT group before transplantation (GFR 53.12±12.08 mL/min) compared with normotensive group (62.68±9.70 mL/min) ($p=0.021$). There was a positive correlation between age and uric acid ($r=0.362$, $p<0.01$). However, GFR correlated inversely with age and uric acid ($r=-0.514$, $p<0.01$; $r=-0.364$, $p<0.01$, respectively). When we performed multivariate regression analysis of age, uric acid, and blood pressure groups for GFR, only age was detected significantly as an independent risk factor ($p<0.001$).

Conclusion: For kidney donors, age and uric acid have a correlation with GFR. Only age is an independent risk factor for GFR.

Keywords: Age, renal donor, renal failure, renal transplantation, uric acid

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INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem with economic, epidemiological, and social effects (1). Kidney transplantation is the primary treatment option for patients diagnosed with end-stage kidney disease (ESKD). Although transplantation is primarily performed from cadavers, the waiting list is increasing day by day. One of the solutions to reduce the increase in cadaver waiting lists is live transplantation. The number of transplants from living kidney donors in the world and in Turkey is more than those made from cadavers (2). Long-term results in living donor transplants are better than cadaveric transplants. In live transplants, it is essential to protect the donor's health in the near and long term because the donor is a person who has been documented to be healthy in the general population through examinations and analyses. There is no gain other than moral from the transfer. In order to increase the number of donors, the criteria of the 2017 KDIGO Clinical Practice Guideline on the Evaluation and Care Living Kidney Donors states that a donor must have controllable glucose intolerance or have hypertension regulated with one or two antihypertensive drugs without target organ damage (3).

A body mass index (BMI) of 30 kg/m^2 is considered the upper limit value for a donor candidate in many guide-

lines including KDIGO. It is stated that a person with BMI >30 kg/m^2 and without any accompanying metabolic problems can be a donor provided that he/she is informed about the risk of future metabolic diseases and kidney failure. However, with increasing numbers of live transplants, Wainright et al. (4) reported that 45-50 live kidney donors every year were added to the cadaver waiting list in the Organ Procurement and Transplantation Network (OPTN) in 2017. In the light of this information, we planned to investigate our live kidney donors with a follow-up period of five years and longer after transplantation in our center in terms of risk factors, such as sex, age, post-transplant follow-up time, BMI, glomerular filtration rate (GFR), hypertension (HT), microalbuminuria (MAU), diabetes mellitus (DM), and coronary artery disease (CAD) and to evaluate the possible reasons that could be indicators of the development of CKD.

MATERIALS AND METHODS

In this retrospective study, of the 170 kidney donors registered in our system, 63 donors including 42 females and 21 males with a regular follow-up of five years and longer after transplantation were included. Informed consent was obtained from the patients who participated in this study.

The creatinine clearance measured before transplantation was >90 mL/min/1.73 m^2 and MAU was <30 mg/day in all the kidney donors. There was no hematuria. The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital with the decision number 53/10, dated 06.08.2018. Post-transplant follow-up time, age, gender, weight, height, HT, CAD, DM, drug use, cigarette/alcohol consumption, socio-economic status, and educational level were recorded for all donors from their files. For the diagnosis of hypertension, the criteria were that after a 30-minute rest in the sitting position, a mean blood pressure measurement must be >139/89 mm Hg via a mercury sphygmomanometer or there must be history of antihypertensive use. Blood pressure criteria for donors included: 1) Those who were diagnosed and treated for HT before nephrectomy. 2) Those who were diagnosed with HT in the post-transplant follow-up period. 3) Normotensives. For the diagnosis of diabetes, the use of oral antidiabetic drugs or insulin, the value of glycated hemoglobin (HbA1C) ≥6.5% and fasting blood glucose ≥126 mg/dL measured on two separate visits were evaluated. For the diagnosis of CAD, those with a history of myocardial infarction, coronary stent implantation, or bypass surgery were considered. BMI was calculated as weight/(height)^2 in kg/m^2. Laboratory values such as serum urea, creatinine (Cr), uric acid (UA), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), HbA1C, MAU (with albumin/creatinine ratio in spot urine), and spot urine sodium values were recorded from the electronic database. GFR measurement for the study was calculated using the Modification of Diet in Renal Disease (MDRD) (5) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (6). GFR <60 mL/min was also accepted for the diagnosis of chronic kidney failure.

Main Points

- Of all the kidney transplants in Turkey, 78.9% are from live donors, and 41% of these are mothers.
- Almost all the donors in our center have a kinship relationship with the recipients. This means that they share a common genetic heritage, the same environmental factors, and quality of life. Therefore, post-transplant follow-up of the donor, especially long-term follow-up, becomes important.
- In our study, the age of the donor and uric acid level were found to be related to GFR.
- A significant difference was found between the group with pre-transplant hypertension and the normotensive group in terms of GFR.
- Only age is an independent risk factor for GFR in living kidney donors.

The statistical analysis of all data obtained at the end of the study was done with the IBM Statistical Package for the Social Sciences software version 20.0 (IBM SPSS Corp.; Armonk, NY, USA). Of the continuous variables, those with normal distribution were presented as mean±standard deviation (SD), and those without normal distribution were presented as the median (minimum-maximum) value. The evaluation of whether the distributions of continuous variables were parametric or non-parametric was done with the Kolmogorov-Smirnov test. T test was used to evaluate the differences between the two groups in continuous parametric variables, and the chi-squared test was used for categorical parametric variables. The Mann-Whitney U and Spearman Brown tests were used for continuous non-parametric variables. The Fisher exact test was used for categorical non-parametric variables. One way ANOVA was used to analyze categorical variables with more than two subgroups. As post-hoc test, Tukey and LSD were used. Multivariate regression analysis was used for independent risk factors. For statistical significance, a value of $p<0.05$ was accepted.

RESULTS

The mean age of the donors was 54.97±10.28 years, and the mean post-transplant follow-up period was 8.02±4.43 years. The longest post-transplant period was 32 years. Donor demographics and clinical information are shown in Table 1. There were 21 female and nine male donors with a GFR <60mL/min. No significant relationship was found between post-transplant follow-up time and GFR, MAU, ESR, and CRP ($p=0.69$, $p=0.723$, $p=0.512$, $p=0.656$, respectively). According to the post-transplant follow-up period, two groups of donors were created. Group 1 with 53 donors with five to nine years of follow-up; of these, there were 25 donors with GFR <60 mL/min. Group 2 with 10 donors with a follow-up period of 10 years or more; of these, five donors had a GFR <60 mL/min. There was no difference between the two groups ($p=0.559$).

The number of donors with active smoking was 5 (7.9%), those who had quit smoking was 14 (22.2%), and the number of donors who had never smoked was 44 (69.8%). There was no sig-

Table 1. Demographic information, clinical, and laboratory results of living kidney donors participating in the study*

Female/Male ratio (n/n)	42/21
Age (year)	55.5 (27-83)
Height (m)	1.63 (1.50-1.87)
Weight (kg)	72.50 (47-97)
BMI (kg/m^2)	26.48 (18.59-38.14)
Number of hypertensive patients	18
Anti HT 1 drug	10
Anti HT 2 drug	6
Anti HT ≥3 drug	2
CAD	2
DM	2
Number of smoking patients	19
Hb (g/dL)	14.03±0.18
Urea (mg/dL)	34.19±0.99
Creatinine(mg/dL)	1.16±0.03
GFR (mL/dL)	60.42±1.39
Uric acid (mg/dL)	6.21±0.15
Total cholesterol (mg/dL)	208.41±5.29
Triglyceride (mg/dL)	171.5 (43-493)
HDL (mg/dL)	45 (24-83)
LDL (mg/dL)	146.29±4.20
Albumin (g/dL)	4.37±0.04
25(OH) vitamin D (mg/dL)	13.23 (4.45-54.52)
Urine albumin/creatinine ratio	10.07 (2.44-11.25)
Urine sodium	101.5 (28-273)
Sedimentation (mm/hour)	12.5 (2-54)
HbA1C (%)	5.78±0.07
CRP	5.41 (1.04-39.10)
Transplantation time (year)	7 (5-32)

*Parametric values are presented as mean±standard deviation and non-parametric values as median (minimum-maximum). p<0.05 was accepted as significant. HT: hypertension; CAD: coronary artery disease; DM: diabetes mellitus; Hb: hemoglobin; GFR: glomerular filtration rate; HDL: high density lipoprotein; LDL: low density lipoprotein; CRP: C-reactive protein

nificant difference between smoking and GFR, the development of post-transplant HT, DM, CAD (p>0.05 for all values). There was no alcohol consumption in the donors included in the study.

Of the total participants, 67% were women. No significant difference was found between gender and GFR (p=0.713).

There were 11 (17%) donors with a BMI ≥30 kg/m^2, and the number of those with GFR <60 mL/min was 5 (7.9%). There was no relationship between BMI and GFR (p=0.629).

Eight donors were hypertensive (12.6%), and ten (15.8%) were hypertensive in the post-transplant follow-up. The remaining 45 (71.4%) donors were normotensive. When we evaluated the

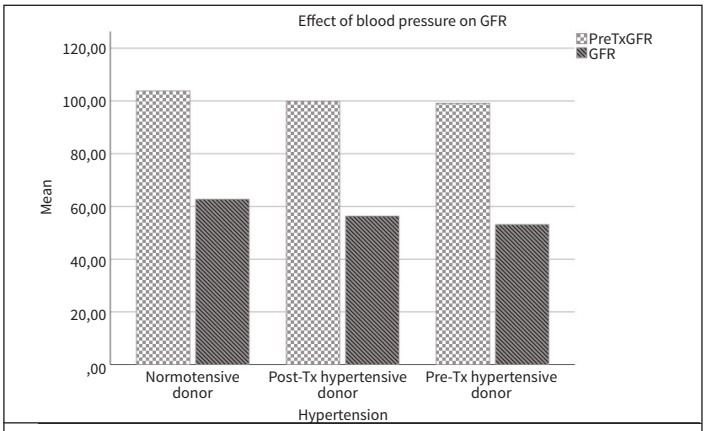

Figure 1. The effect of blood pressure on glomerular filtration according to donor groups.
GFR: glomerular filtration rate; pre-Tx GFR: glomerular filtration rate before transplantation; post-Tx hypertensive donor: donor diagnosed with hypertension after transplant; pre-Tx hypertensive donor: donor diagnosed with hypertension before transplantation.

blood pressure groups in terms of GFR, the hypertensive group (GFR: 53.12±12.08 mL/min) before transplant was found to have a significant decrease in GFR compared with the normotensive (GFR: 62.68±9.70 mL/min) group (p=0.021). There was no statistical difference between other HT groups (p>0.05 for all values). The change of donors according to GFR values before and after the transplant is shown in Figure 1.

One donor was diagnosed with CAD, DM, and HT after transplant and HbA1C was 9%, GFR 37 mL/min, and MAU 336 mg/day. One donor was diagnosed with CAD and HT, and GFR was 48 mL/min and MAU was 70.38 mg/day. Both had a BMI <30 kg/m^2, and both were male. One donor was just diabetic. This woman donor had an HbA1C of 6.0%, GFR 78 mL/min, MAU 14.35 mg/day, and BMI 28 kg/m^2. Those diagnosed with diabetes were not related to their recipients.

In our correlation evaluation with age, GFR was inversely proportional (r =-0.514, p<0.01), and UA was directly proportional (r=0.362, p<0.01). Correlation result of GFR and UA was inversely proportional (r=-0.364, p<0.01). No relation was found between other serum and urine parameters and GFR, HT, CAD, and DM (p>0.05 for all values).

When we did multivariate regression analysis of age, UA, and blood pressure groups for GFR, the only independent variable that appeared was age (p<0.001).

DISCUSSION

The primary concern for donors after live transplantation is the consequence of increased workload (hyperfiltration, increased intra-glomerular pressure) per nephron after a 50% reduction in kidney mass. This concern began when Hostetter et al. (7) reported that glomerular hypertension, albuminuria, focal segmental glomerulosclerosis, and eventually ESKD developed as a result of partial renal ablation after nephrectomy.

In his meta-analysis published in 2006, Boudville et al. (8) stated that donor blood pressure might increase by 5 mm Hg in 5-10 years after transplantation. The DONOR Network working group noted an increase in proteinuria (9). The study of Oslo University Hospital, on the other hand, drew attention to the fact that ESKD was higher in donors compared with the control group and also to the role of genetic factors (10). Of all the kidney transplants in Turkey, 78.9% are from live donors, and 41% of these are mothers (11). It is not desirable that the rate of live transplants is so much higher in comparison with the rate of cadaveric transplants. However, it is known that the results are better for the recipient of a live transplant compared with the results of the transplants from a cadaver. Despite the decreased kidney function values in older live donors, the transplant results are similar to those of young cadaveric kidney transplants (12). Almost all the donors in our center have a kinship relationship with the recipients. This means that they share a common genetic heritage, the same environmental factors, and quality of life. Therefore, post-transplant follow-up of the donor, especially long-term follow-up, becomes important. The United Organ Sharing Network (UNOS) has been reporting the 6th and 12th month results for the post-transplant donor since 1999 and extended its follow-up to 24th month since 2007. In an article by Mandelbrot et al. (13), the donor's lack of compliance with follow-up and insurances not refunded were shown to be at the top of the obstacles to UNOS data.

Although there is no problem in repayment in our country, difficulties are observed in the compliance of the donors after the first six months. In our study, the low number of patients is due to the same reason. The importance of long-term follow-up is particularly important for factors that will increase the risk of CKD and CAD, such as decreased GFR, MAU, and HT (14). Although the existence of risks is accepted in this regard, there are studies suggesting that it is not different from the general population. In a three-year prospective controlled study published by Kasiske et al. (15) in 2015, it was stated that serum parameters and blood pressure values of donors were similar to those of the control group, except for UA and phosphate values, while GFR increased in donors and decreased in the control group. The first of the two studies on the risk of developing ESKD and comparison with the healthy non-donor population in kidney donors over 15 years belongs to Norway, and the rate was 0.44% (0.5%-0.06%) (10). On the other hand, in the second study, which was in USA, result was 0.27% (0.31%-0.04%)/100 patient year follow-up (16). However, the dominant opinion is that these studies do not provide information regarding the risk of ESKD and donor basal characteristics (17). The low-risk subgroup results of seven general population cohorts for assessing lifetime and 15-year risk for ESKD in healthy renal donors in the USA, with a method developed by the "CKD process consortium," which is part of the KDIGO 2017 living kidney donor follow-up assessment guide, have been found to be similar to living kidney donors. (18). The model used in the study (http://www.transplantmodels.com/esrdrisk/) investigates age, gender, type-2 DM, albumin/creatinine ratio, total cholesterol level, low density cholesterol level, race, GFR, systolic blood pressure, antihypertensive use, BMI, smoking, and history of kidney stones. The first limitation that is pointed out is that although Grams drew attention to the importance of genetic heritage in his study, the model did not consider those with relatives diagnosed with ESKD (19). Second, instead of the measured GFR, the estimated GFR calculation could lead to misleading results (20). Third, in two large studies, it was stated that the risk of ESKD after transplantation in kidney donors was higher than that of non-donors, and it was stated that the risk of ESKD was similar in kidney donors and non-donors with an online calculation model that was developed (21).

Unclear concerns about elderly donors include whether the transplant results are acceptable for the recipient, perioperative death of the donor, impaired kidney function, and increased CVD risk factors (2, 12, 22, 23) because age is the major risk factor for ESKD (19). However, in the 5.5-year follow-up study of Velosa, in which 140 donors under the age of 35 years and above the age of 55 years were compared, GFR values after donor nephrectomy were found as 68±8 mL/min and 65±8 mL/min (24). In a similar result, in a study with 539 donors who were under the age of 60 years and over between 1994 and 2006, there was no significant difference in the maximum decrease in GFR between the two groups found, and in older patients, GFR was <60 mL/min and it was statistically significant (25). In our study, age and UA were directly proportional and GFR and age and UA were inversely proportional, which is similar to the results of non-donor CKD patients.

In the evaluation of the donors who were normotensive, hypertensive before nephrectomy, and hypertensive after nephrectomy in terms of GFR, there was a significant decrease in GFR in the hypertensive before transplant group compared with that of the normotensive group ($p<0.05$). There was no difference between the post-transplant HT and the normotensive groups ($p>0.05$). In the review of Hourmant et al. (12), it was stated that the diagnosis of HT after transplantation was not an important factor in the decrease of donor GFR in the long term. With this result, the follow-up and pre-transplant training of donors diagnosed with HT before the transplant becomes important (Figure 1).

Limitations of this study are:

- The number of live kidney donors in the study remained low. As in the USA data, which we mentioned at the beginning of the article, there are problems in our country also in terms of donors in terms of compliance with outpatient follow-up. However, our study results have resulted in compliance with large studies.
- The majority of live kidney donor transplants in our center were related to the recipients. In non-related transplants, the donor is the partner of the recipient and the number is very few. In other studies, it is stated that the risk in trans-

plantations associated with relatives in the process of living kidney donors to ESKD is higher than that in those not associated with relatives. No information was provided in our study on this subject.

- It is stated that BMI is one of the determining factors in the development of CKD. In our study, no significant result could be achieved because there was no significant difference in BMI among the donors. In the study comparing obese donors with non-obese and general population, Tavakol et al. (26) stated that there was no decrease in renal functions, hypertension, and other cardiovascular events in the long term. Obesity is a serious problem in our country. It brings accompanying diseases and prevents them from being suitable donors for transplantation. Our patients who had DM or CAD in the post-transplant period in our study also had a BMI of <30 kg/m^2.
- It is stated that the male gender is another factor affecting the development of CKD. According to Muzaale et al. (16), the risk of ESKD is higher in males than in females, in the elderly than in the young, in the black race than in Caucasians, and in related transplants (where the donor is related to the recipient) than in non-related transplants. In the guide, it is criticized as "donor GFR values before transplantation are unknown," based on this study (3). There are studies claiming that estrogen protects women in terms of kidney function. Specifically, they indicate that it causes increased endothelial nitrite oxide production, inhibition of angiotensin-II production, inhibition of mesengial cell and extracellular matrix increase (27, 28). However, it is stated that these results are prominent in premenopausal period. The average age of women in our study during transplantation was 47.10±8.99 years. This may explain why there was no gender difference in terms of GFR.

In our study, in a socio-economically and socio-culturally homogeneous group, donors with at least a five-year follow-up were evaluated in terms of all risk criteria, although the number of participants was low. In our study, the age of the donor and UA level were found to be related to GFR. A significant difference was found between the group with pre-transplant hypertension and the normotensive group in terms of GFR. In multivariate analysis, when we evaluated age, UA and hypertension in terms of GFR, we found that age alone was an independent risk factor. Long-term results of donor health in studies performed to date are not clear. As we perform live transplants mostly with donors related to the recipients, larger scale studies are still needed to understand donor safety by considering the genetic factors and the effects of decreased kidney mass.

CONCLUSION

In our study, only age was found to be an independent risk factor. Although there are studies about various factors affecting long-term results in donors, the results may be different among countries and even among transplant centers. In studies with non-donor control groups, the results also vary. Despite the single-center results, we believe that this study contributes to the literature in terms of notification of the results from Turkey.

Ethics Committee Approval: Ethics committee approval was received for this study from the the Clinical Research Ethics Committee of University of Health Sciences Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital (Approval Date: August 06, 2018; Approval Number: 53/10)

Informed Consent: Informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - K.G.A.; Design - K.G.A., M.D.A.; Supervision - M.D.A.; Data Collection and/or Processing - K.G.A.; Analysis and/or Interpretation - K.G.A., M.D.A.; Literature Search - K.G.A.; Writing - K.G.A., M.D.A.; Critical Reviews - K.G.A., M.D.A.

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