A 4-year Follow-up of Living Unrelated Donors of Kidney Allograft in Iran

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Introduction. Shortage of deceased donor kidneys has resulted in an increased rate of kidney transplantation from living unrelated donors (LURDs). However, there are concerns about short-term and long-term morbidity of the donors. This study reports the clinical and biochemical factors in a follow-up program of Iranian LURDs, one of the largest reported series of kidney donors.

Materials and Methods. Of 7500 individuals who underwent living donor nephrectomies between 2005 and 2008, a total of 1549 participated in this study. They were followed for 18 to 48 months after the kidney donation. The average time for the first study visit was 316.72 days after donation.

Results. The mean age of donors was 30.43 ± 6.16 years old. Men consisted 82.5% of the group. Systolic hypertension was detected in 0.2% and diastolic hypertension in 1% of the LURDs; however, anemia prevalence was as high as 47.2%. Hyperuricemia was found in 21.2% of the LURDs, while proteinuria was seen in 13.7%. Glomerular filtration rate was greater than 90 mL/min in 38.2% of the donors, 60 mL/min to 90 mL/min in 54.5%, and less than 60 mL/min in 7.3%. A GFR less than 45 mL/min was seen in 0.1% of the donors.

Conclusions. Data suggested that the LURDs in Iran have an appropriate health condition comparable to other donors in other parts of the world. Considering the high prevalence of hyperuricemia in our population and its importance as a risk factor for kidney failure, monitoring serum uric acid in follow-up programs is suggested.

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INTRODUCTION

Kidney transplantation is considered the treatment of choice for most patients with end-stage renal disease (ESRD).[1] Shortage of deceased donor kidneys despite increasing need for kidney transplantation, favorable short-term and long-term patient and graft survival, and the possibility of preemptive transplantation have resulted in an increased rate of kidney transplantation from living unrelated donor (LURD).[2,3] However, there are some concerns about short-term and long-term morbidity of the donors. Mortality and serious postoperative complications have been reported to be 0.03% and 1.4% to 2%, respectively.[4,5]

Serum creatinine level and risk of ESRD does not seem to be increased in donors compared to the general nondonor population.[6,7] Although hypertension and proteinuria may develop in some

donors, donation could not be accounted for it definitely. On the other hand, several investigators have reported that the rate of proteinuria and hypertension is not higher in kidney donors.[8,9] In recent years, hyperuricemia has been described as an important risk factor for progressive kidney dysfunction by several authors.[10,11] Nevertheless, prevalence of hyperuricemia in kidney donors is not evaluated sufficiently. To our knowledge, only one study by Yazawa and colleagues assessed the prevalence of hyperuricemia in donors and reported it to be 27%.[12]

In Iran, a controlled LURD transplantation program started in 1988. Although the Iranian model of kidney transplantation has proved to be efficient in recipient side, there are limited data in donor side of the program.[13-15] We had previously reported psychosocial and financial status of Iranian donors.[16] Here, we present the results of clinical and biochemical follow-up of 1549 Iranian LURDs, which comprise one of the largest reported series of kidney donors. Moreover, we assessed the prevalence of hyperuricemia after kidney donation in this group of patients.

MATERIALS AND METHODS

Between 2005 and 2008, a total of 7500 living donor nephrectomies were performed in different transplantation centers of Iran. To be eligible for kidney donation, all potential donors had to be free from any significant health problem such as diabetes mellitus, hypertension, malignancies, chronic infections (tuberculosis, human immunodeficiency virus, hepatitis B and C, etc), and proteinuria and they had to carry a low anesthesia risk and a glomerular filtration rate (GFR) greater than 90 mL/min/1.73 m^2 of body surface area prior to kidney donation.[17] In the screening phase of the study, all donors were contacted by phone and asked to come to the Medical Center for Special Diseases for a free-of-charge evaluation. A total of 1549 LURDs accepted our invitation and were enrolled into the study.

After a written consent was obtained from the participants, they were evaluated by comprehensive physical examination as well as laboratory tests. They were followed for 18 to 48 months after donation. Follow-up data were recorded by a general practitioner. The main evaluated parameters included body mass index, blood pressure, hemoglobin, serum uric acid, serum lipid profile (including low-density lipoprotein cholesterol), fasting plasma glucose, blood urea nitrogen, serum creatinine, and urine albumin-creatinine ratio. The estimated GFR was calculated using the Cockcroft-Gault formula. Systolic hypertension was defined as systolic blood pressure higher than 140 mm Hg; diastolic hypertension, as diastolic blood pressure higher than 90 mm Hg; anemia, as a hemoglobin level less than 13 g/dL in men and 11 g/dL in women; impaired fasting plasma glucose, as a fasting glucose level between 100 mg/dL and 125 mg/dL; hyperuricemia, as a uric acid level higher than 7.5 mg/dL in men and 6.5 mg/dL in women; and hyperlipidemia, as a low-density lipoprotein cholesterol higher than 130 mg/dL. Microalbuminuria was defined as a urine albumin-creatinine ratio of above 30 mg/g in an untimed urine sample.

Data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, Ill, USA). Values for quantitative data were described as mean ± standard deviation, and the prevalence rate of abnormal conditions were reported as percentage.

RESULTS

Of 7500 donors who had nephrectomy between 2005 and 2008, a total of 1549 LURDs participated in this study. The mean age of the donors was 30.43 ± 6.16 years old. Men consisted 82.5% of the donors. The average time for the first study visit was 316.72 days after the donation, and 91% of the participants had at least 3 visits during the study. Table 1 shows the mean of the evaluated parameters, and Table 2 shows the prevalence of abnormal findings at any of the visits. Hyperuricemia was asymptomatic in all but 1 donor. The estimated

Table 1. Mean Values of the Evaluated Parameters

Parameter	Value
Body mass index, kg/m^2	23.54 ± 4.42
Systolic blood pressure, mm Hg	107.00 ± 12.22
Diastolic blood pressure, mm Hg	75.3 ± 7.73
Hemoglobin (male, female), g/dL	13.6 ± 1.5 (13.9, 12.0)
Glomerular filtration rate, mL/min	87.7 ± 24.6
Albumin-creatinine ratio, mg/g	6.19 ± 9.14
Fasting plasma glucose, mg/dL	92.83 ± 12.81
Uric acid (male, female), mg/dL	5.86 ± 1.30 (5.98, 5.31)
Low-density lipoprotein cholesterol, mg/dL	98.12 ± 32.20

Table 2. Prevalence of Abnormal Findings

Finding	Prevalence, %
Systolic hypertension	0.2
Diastolic hypertension	1.0
Anemia (male, female)	47.2 (45.5, 54.6)
Impaired fasting plasma glucose	19.1
Hyperuricemia (male, female)	21.2 (22.2, 13.3)
Body mass index < 18.5 kg/m^2	10.0
Body mass index > 30 kg/m^2	9.0
Hyperlipidemia	20.3
Proteinuria	13.7

GFR was greater than 90 mL/min in 38.2% of the donors, 60 mL/min to 90 mL/min in 54.5%, and less than 60 mL/min in 7.3%. A GFR less than 45 mL/min was seen in 0.1% of the donors.

DISCUSSION

In most developing countries, lack of suitable legislation and infrastructure precluded growth of deceased donor program. To avoid long waiting list of deceased donor kidney transplant, living donor transplantation seems to be a suitable solution. While living donor transplantation offers advantages to the recipients such as better patient and graft survival, there have been some concerns about short-term and long-term consequences of kidney donation for the donors.[2,3] One of the main concerns is related to the kidney function changes and potential related consequences. Earliest data on the natural history of living with a single kidney was related to patients with congenital single kidney and patients with nontransplant uninephrectomies. Baudoin and colleagues reported the longest follow-up of patients after uninephrectomy.[18] They followed up patients who underwent uninephrectomy before the age of 16 years for up to 52 years. They concluded that kidney function was generally well maintained. However, lower kidney function, higher blood pressure, and higher urinary protein excretion were seen after 25 years of follow-up.[18] Some other authors also reported mild proteinuria, increased blood pressure, and occasional case reports of kidney failure after uninephrectomy.[19,20]

Several studies have evaluated long-term renal consequences of kidney donation. Most of them revealed that GFR was approximately 70% of the GFR in age-matched population, while hypertension prevalence did not increase, but urinary protein excretion increased. However, none of the studies reported a progressive deterioration of kidney function beyond the age-related changes after donation.[10,21,22] Ramcharan and Matas reported a study with 20- to 37-year follow-up of kidney donors, one of the longest reported follow-ups.[21] They showed that the average serum creatinine level was not deteriorated, there was little proteinuria, and hypertension incidence was similar to the age-matched general population. On the other hand, kidney failure and ESRD was developed in a few donors.[21] In a study published in 2013 by Mjøen and colleagues, the authors showed that the risk of ESRD was higher in the donors than healthy population but all of the donors who developed ESRD were related to their recipients.[23] Recently, Muzaale and colleagues showed that the 15-year cumulative incidence of ESRD was higher in living kidney donors than the control group. Although, the mean GFR of donors at donation time was 101 mL/min/1.73 m^2, 22.1% of the donors had a GFR less than 80 mL/min/1.73 m^2 at the same time.[24]

In our study, the mean body mass index, systolic and diastolic blood pressure, hemoglobin level, and serum levels of uric acid, glucose, and low-density lipoprotein cholesterol were in the normal range. The mean GFR was 87.66 ± 24.06 mL/min, which was less than the normal range but above 70% of normal. Proteinuria was detected in 13.7% of the participants. Although prevalence of proteinuria was higher than the general population, it was in the range of previously reported values after donor nephrectomy.[10,22,25] The prevalence of anemia was higher than the general population, but the prevalence of hyperuricemia, impaired fasting plasma glucose, and hypertension were not different.[26-29]

Hyperuricemia has long been known to be associated with kidney dysfunction, but it was considered as a marker of dysfunction and not a risk factor for it.[30] However, several authors have described the causative role of hyperuricemia in progressive kidney function deterioration in recent years.[31] Kang and colleagues examined the effect of hyperuricemia on kidney disease progression in rats after 5/6 remnant kidney surgery. They reported that hyperuricemia resulted in increased systemic blood pressure, proteinuria, kidney dysfunction, and progressive renal scarring.[32] Several mechanisms have been suggested for this

association including endothelial dysfunction, vascular smooth muscle proliferation, activation of inflammatory pathways, monocyte chemoattractant protein-1 secretion in renal tubular cells, insulin resistance, and impaired vascular nitric oxide production.[31] Chang and colleagues described hyperuricemia as an independent risk factor for chronic kidney disease, increasing the risk for CKD by 3.6 folds.[11] In another study by Iseki and colleagues, 48 177 participants were screened for hyperuricemia and kidney dysfunction. The authors reported that hyperuricemia correlated with a higher incidence of ESRD.[9]

Although several studies have evaluated kidney donors after a long follow-up period, unfortunately, hyperuricemia has not been sufficiently evaluated in donor studies. To our knowledge, only one study by Yazawa and colleagues evaluated hyperuricemia prevalence in 63 donors and reported it to be 27.8%.[12] In our study, hyperuricemia was observed in 21.2% of donors. Hyperuricemia prevalence in donors does not seem to be higher than that in the general population. However, considering its importance as a risk factor for ESRD, its prevalence should be one of the main factors in kidney donors' follow-up program.

Animal studies on CKD suggest that anemia could contribute to the deterioration of kidney function mainly through hypoxia of the tubular cells that leads to tubulointerstitial damage and worsening of the kidney function.[33,34] Additionally, erythrocytes represent a major antioxidant component of blood and that oxidative stress appears to contribute to glomerulosclerosis and tubulointerstitial damage.[35] In humans, it has been shown that anemia is an independent risk factor for progression of CKD.[36,37] In addition, in a few randomized controlled studies have suggested that anemia correction could slow the progression of CKD.[38,39] Although anemia (hemoglobin < 11 g/dL) in the Iranian population is reported as high as 28%,[40] anemia was even more common in our LURDs (45.5% in men and 54.6% in women). This high prevalence is alarming and demands a more comprehensive investigation on the other factors (nutritional, genetic, and socioeconomic factors). Currently, we are gathering more data to address this issue in the near future.

This study encountered some limitations. First, we did not have access to baseline pre-donation medical records and laboratory tests. Second, we did not compare donors' data with a control group. Third, although all of the LURDs who had donated a kidney between 2005 and 2008 were invited to take part in the survey, only 1549 were willing to participate in this study. The cause of which could have been the low socioeconomic status and unawareness of donors about importance of medical follow-up at least annually. We had many missing or wrong addresses, probably due to temporary rental residency of the donors and this may have been one of the causes of our missing data. It also could mean that those donors who were not satisfied from their general health went to clinic and those who had a sense of wellbeing did not. Fourth, the LURDs were followed up for a short period of time.

CONCLUSIONS

Our study indicates that some of the abnormal findings such as anemia could have been due to preexisting underlying causes. Precise physical examination and paraclinical evaluation of donors should be emphasized. We suggest establishment of a network to gather donors' medical data and evaluate their long-term outcome. We are going to continue this study to follow a larger number of donors for a longer duration.

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CONFLICT OF INTEREST

None declared.

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