Pretransplant uric acid levels may be predictive for prognosis of renal transplant donors

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CLINICAL STUDY

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ABSTRACT
Background The living kidney donor counseling prior to the operation may be helpful to learn how to properly care for the remaining single kidney for the rest of their lives. Worsening kidney function is associated with elevated serum uric acid (UA) levels. In this study, we compared the baseline laboratory findings of renal transplant donors with their follow-up laboratory values. **Methods** The study consisted of 173 adult donors including 91 females and 82 males with a mean age of 46.82 ± 11.31 years. The follow-up clinical and laboratory examinations were performed on the third day at the end of the first and the sixth months of the surgery. According to donor's creatinine levels we constituted two groups: high creatinine and normal creatinine. **Results** Patients within the high creatinine group had significantly higher mean serum UA levels when compared with the normal creatinine group. In multivariate analysis, among the other effective variables, UA level alone was found to be the most effective parameter predicting the post-transplant creatinine levels ($p = 0.004$, odds ratio: 12.4, 95% CI: 2.3–68.3) at sixth month post-transplantation. In the ROC analysis for the effects of UA, the following cutoff values were found: >6 mg/dL in men (sensitivity 81.3%, specificity 76.9%, positive predictive value 89.7%, negative predictive value 62.5%, accuracy 80%) and ≥ 5 mg/dL in women (sensitivity 72.2, specificity 74.4%, positive predictive value 89.7%, negative predictive value 62.5%, accuracy: 73.7%). **Conclusion** Pretransplant serum UA levels can give important clues regarding the renal functions of the donors during the postoperative period.

Introduction

Due to the reduction in the deceased donor pool, living kidney donor use increases gradually during the recent years.[1] However, the living kidney donor pool fails to cover the requirement due to various reasons. This shortage in the living kidney donor pool mandates that the donor selection criteria be pushed to its limits.[2] For example, people approaching the upper age limit or lower glomerular filtration limit as well as overweight persons are sometimes selected for the donation process. Also, mildly hypertensive or glucose intolerant donors are considered to be fit. Applying the living kidney donor selection criteria within limits helps to minimize the risk for complications.[3] The risks and benefits both for the donor and recipient should be rigorously evaluated, and the risks should not exceed the benefits for either of them.[4] The follow-up controls of the donors after the transplantation procedure are not as frequent as it is for the recipients. Although donors are evaluated prior to the donation, they may be prone to renal insufficiency, hypertension, cardiovascular

diseases, or diabetes postoperatively. Donors lose roughly 50% of their nephrons following the donation procedure. In studies on donors, increased creatinine values begin to subside at the end of the first week at the earliest, and in some cases it may take several months to reach normal values.[5] Donor counseling prior to the operation may be helpful to learn how to properly care for the remaining single kidney for the rest of their lives.

Uric acid (UA) is a product of purine metabolism and is filtered through glomeruli and then reabsorbed from the proximal tubules. This results in 70% excretion from the kidneys and the remaining 30% is excreted through the gastrointestinal tract.[6] Worsening kidney function is associated with elevated serum UA levels due to the impairment of UA transport through nephrons.[7] Elevated UA levels may also be a sign for the deterioration of glomerular filtration rate (GFR) and the emergence of a kidney disease.[8] Renal parenchymal lesions may be related with higher levels of UA.[9] UA may be associated with kidney damage through direct or

indirect pathways. Endothelial dysfunction and elevated renin–angiotensin–aldosterone activity associated with higher UA levels may be directly related with the kidney damage found in hyperuricemia.[10]

Hyperuricemia is also thought to be related with kidney impairment through indirect pathways. Microalbuminuria in Type II diabetes, untreated hypertension, and pre-hypertension are presumed to be related with serum UA levels.[11,12] Renal functional impairment in non-proteinuric Type I diabetics is thought to be related with high-normal serum UA levels.[13] As a result, serum UA levels may be a predictor for renal dysfunction. The predictor value of serum UA levels in renal transplant donors is uncertain. In this study, we compared the baseline laboratory findings of renal transplant donors with their follow-up laboratory values.

Methods

This study included living renal transplantation donors during the years 2011–2015 in Baskent University's two different centers for renal transplantation. The study consisted of 173 adult donors including 91 females and 82 males with a mean age of 46.82 ± 11.31 years. Donor characteristics such as age, gender, past medical history, use of any medications, physical examination findings, and follow-up information were retrieved from the medical database of the healthcare centers. All of the subjects have undergone cardiological, respiratory, gastroenterological, dental, and psychiatric consultations. Blood urea nitrogen (BUN), creatinine, electrolytes, calcium (Ca), phosphorus (P), UA, high-sensitive C-reactive protein (hs-CRP) levels were determined by either the C8000 system (Abbott, USA) or Cobas e-411 (Roche, Germany) autoanalyzer. Urinary protein and microalbumin levels were determined, and creatinine clearance rates were calculated in all donors on a 24-h urinary specimen prior to the donation surgery. The follow-up clinical and laboratory examinations were performed on the third day at the end of the first and the sixth months of the surgery. The exclusion criteria for the donors consisted of the following: age <18 years, body mass index (BMI) >35, any use of medications for hypertension or diabetes, presence of any kidney disease, malignant or ongoing infectious diseases, cardiovascular diseases, gout, any psychiatric disorders, or elevated UA levels.

This study was conducted according to the Helsinki declaration and the study protocol was approved by the local institute's Committee on Human Research (our local ethics body). All of the subjects gave their informed consents.

Statistical analysis

Statistical analyses were carried out using SPSS (SPSS Inc. Version13.0, Chicago, IL, USA). The results were presented as means ± standard deviation for continuous variables and frequency and percent values for categorical variables. Mean values among groups were compared by either Student's T test when the distribution was normal or Mann–Whitney U test if otherwise. A logistic regression was used to identify the independent predictors of the sixth month increase in creatinine. Inclusion of variables was assessed using a forward method. The receiver operating characteristic (ROC) curve and the area under ROC (AUROC) curve analyses were used to assess the utility of parameters in the levels of UA. p-Values less than 0.05 were considered statistically significant.

Results

The demographic and laboratory values for the subjects are depicted in Table 1. An increase of 30% or more in creatinine values in any subject or a creatinine value of >1.4 in males and >1.3 in females were considered to be elevated at the end of the sixth month after surgery. These criteria classified 71.1% of male and 32.1% of female donors and an overall 49.5% of all of the donors to be in the high creatinine group. The characteristics for donors either with high or normal creatinine groups are presented in Table 2. Patients within the high creatinine group were predominantly male, had significantly higher levels of pretransplant BUN, creatinine clearance rate, and mean serum UA levels when compared with the normal creatinine group. In multivariate analysis, among the other effective variables such as age, pretransplant creatinine, BUN, creatinine clearance rate of the living

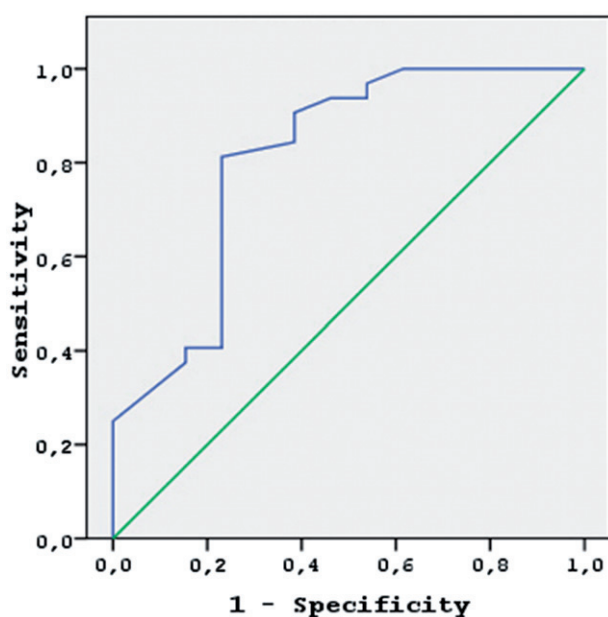Table 1. The demographic and laboratory values for the donors.

N	173
Male/female	82/91
Age (years)	46.82 ± 11.31
BMI (kg/m2)	28.56 ± 4.8
BUN (mg/dL)	12.78 ± 2.72
Creatinine clearance (mL/s)	132.85 ± 25.66
Sodium (mmol/L)	138.26 ± 2.22
Potassium (mmol/L)	4.17 ± 0.29
Calcium (mg/dL)	9.33 ± 0.62
Phosphorus (mg/dL)	3.71 ± 0.65
Magnesium (mg/dL)	2.10 ± 0.28
Uric acid (mg/dL)	5.24 ± 1.25
Third day creatinine (mg/dL)	1.12 ± 0.26
First month creatinine (mg/dL)	1.10 ± 0.24
Sixth month creatinine (mg/dL)	1.10 ± 0.25
hs-CRP (mg/L)	4.56 ± 4.16
24-h proteinuria (mg/24-h)	218.28 ± 85.60
24-h microalbuminuria (mg/24-h)	21.42 ± 24.69

Notes: BMI: body mass index, BUN: blood urea nitrogen, hs-CRP: high-sensitive C-reactive protein; Age, BMI and all laboratory values: (mean ± SD).

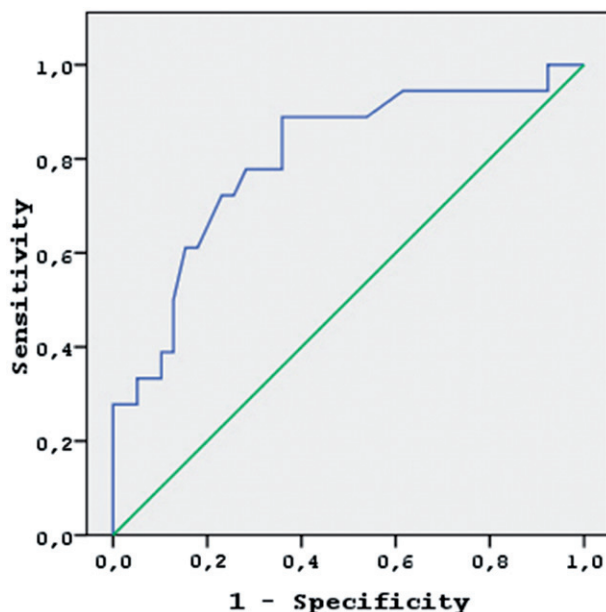Table 2. The characteristics for donors either with high or normal creatinine groups.

	Normal creatinine sixth month group	High creatinine sixth month group	p values
n	51	50	
Age (years)	46.84 ± 11.28	49.48 ± 10.06	ns
Female/Male	38/13	18/32	<0.0001
BUN (mg/dL)	12.29 ± 2.72	13.85 ± 2.51	0.041
BMI (kg/m^2)	28.7 ± 4.8	27.55 ± 3.35	ns
Creatinine clearance (mL/s)	125.52 ± 25.04	145.05 ± 23.49	0.004
Sodium (mmol/L)	138.32 ± 2.04	138.20 ± 2.64	ns
Potassium (mmol/L)	4.15 ± 0.33	4.22 ± 0.24	ns
Calcium (mg/dL)	9.23 ± 0.72	9.54 ± 0.28	ns
Phosphorus (mg/dL)	3.80 ± 0.64	3.48 ± 0.65	ns
Uric acid (mg/dL)	4.46 ± 1.02	6.52 ± 0.70	<0.0001
hs-CRP (mg/L)	4.11 ± 4.08	5.64 ± 4.36	ns
24-h proteinuria (mg/24-h)	208.82 ± 88.95	237.55 ± 81.81	ns
24-h microalbuminuria (mg/24-h)	16.61 ± 8.60	30.68 ± 39.01	ns

Notes: ns: non-significant, BUN: blood urea nitrogen, hs-CRP: high-sensitive C-reactive protein; Age, BMI and all laboratory values: (mean ± SD).

Figure 2. The ROC analysis for the effects of UA, cutoff values ≥5 mg/dL in women.

Figure 1. The ROC analysis for the effects of UA, cutoff values >6 mg/dL in men.

donor, UA level alone was found to be the most effective parameter predicting the post-transplant creatinine levels (p = 0.004, odds ratio: 12.4, 95% CI: 2.3–68.3) at sixth month post-transplantation.

In the ROC analysis for the effects of UA, the following cutoff values were found: >6 mg/dL in men (Figure 1) (sensitivity 81.3%, specificity 76.9%, positive predictive value 89.7%, negative predictive value 62.5%, accuracy 80%) and ≥5 mg/dL in women (Figure 2) (sensitivity 72.2, specificity 74.4%, positive predictive value 89.7%, negative predictive value 62.5%, accuracy: 73.7%).

Discussion

According to our renal function impairment criteria, donors having UA levels higher than 6 mg/dL in males and 5 mg/dL in females prior to surgery pose a significantly higher risk for postoperative kidney function impairment. In donors whose creatinine values still persist at high levels at the end of the sixth month may develop chronic kidney disease (CKD) sometime later. We have not encountered any studies that investigate the predictive value of the pretransplant UA levels on the post-transplant kidney function in living donors. The studies that evaluate the predictive value of UA levels on renal function impairment mostly investigate the values of the recipients. As there are a couple of confounding factors that affect the UA levels in these studies such as cyclosporine-induced hyperuricemia, they are of limited value. In a study performed on kidney transplantation recipients by Haririan et al., higher serum UA levels were found to be associated with higher risk for graft loss and a decrease in estimated GFR.[14] However, Akalin et al. reported that death, graft failure, new cardiovascular events, and chronic graft nephropathy were more frequent in hyperuricemic recipients.[15] Bandukwala et al. demonstrated the association of hyperuricemia with the decrease in renal allograft function in their study of 405 stable renal transplant recipients.[16] Renal graft outcomes were found to be poorer in hyperuricemic recipients in general.

Studies on the relationship between UA levels and renal function report equivocal results. In studies performed on healthy individuals, UA levels were found

to be a useful predictor during the follow-up of renal functions. Increased UA levels were found to be predictive for incipient kidney disease and end-stage renal disease in people with normal renal function as well as the progression in individuals with kidney disease.[17,18] While Ishani et al., in their study on male subjects, report a relation between UA levels[19] and end stage kidney disease, an independent association was only observed for women in another study from Japan.[20] Zhang et al. studied a community-based Chinese population with eGFR >60 mL/min/1.73 m^2 and found UA levels to be independently associated with the likelihood for the decline in renal function.[21] Although, the association was not significant in the modification of diet in renal disease (MDRD) study of Madero et al.[22] Previous studies revealed inconsistent results, and researches among the non-hypertensive and non-diabetic population are limited. As research regarding the predictiveness of UA levels and kidney damage on the non-hypertensive and non-diabetic population is scarce in the literature, the present study has a value in itself. The present study underlines that UA levels which may be of importance during the living donor exclusion process. As the donor loses almost 50% of its nephrons instantly following the surgery, the benefits of donation must outweigh the risks associated with the procedure. The search regarding the risk factors and the clinical course regarding the development of kidney dysfunction following kidney donation is still far from being complete.[23] Living donor assessment prior to kidney donation aims at choosing the most suitable donor with a minimum risk of complication.[24] Because we are currently pushing the donor selection criteria to its limits (e.g., accepting donors with a GFR at lower limits, overweight donors, donors with glucose intolerance, elderly donors, and mildly hypertensive individuals on monotherapy) to overcome the shortage of the living donor pool, we presume that pretransplant UA values may be useful for the follow-up of the donors after surgical intervention. The literature discusses whether the increase in UA is a result or a reason for kidney function impairment. Not all of the hypertensive or diabetic individuals universally have elevated levels of UA. For instance, in the adult population, the prevalence of prehypertension and hypertension is approximately 60%, whereas prevalence of hyperuricemia (defined as UA >6.0 mg/dL in women and UA >7.0 mg/dL in men) is approximately 17%.[25] In such populations, UA may have an enhancing role for end-organ impairment through direct or indirect pathways. The nephrotoxic effect of elevated UA levels is supported in animal experiments and cellular biological studies. Higher UA levels leading to glomerular hypertension, elevated renal vascular resistance, reduced renal blood flow, activation of renin–angiotensin system (RAS), arteriolosclerosis, glomerular hypertrophy, glomerulosclerosis, and interstitial disease have been shown in various animal experiments. In these studies, the mentioned effects were suggested to be induced through oxidative stress and endothelial dysfunction caused by higher levels of UA.[26,27] Nitric oxide generated in vitro in endothelial cells was found to be directly impaired by UA.[10] Our findings of UA levels within normal range (<7.2 mg/dL in males and <6 mg/dL in females) in the present study are of significance. In the cardiovascular health study (CHS) of Choncol et al., a strong correlation was observed between the baseline kidney function and UA levels.[28] Interestingly, although the presence of a strong cross-sectional association between baseline UA levels and baseline kidney function was found along with an annual decrease of ≥3 mL/min 1.73 m^2 in the patients ≥65 year of age with UA levels >5.9 mg/dL in the longitudinal analysis, Choncol et al. failed to disclose any significant relationship between UA levels and incident CKD defined by eGFR <60 mL/min per 1.73 m^2 in the final examination of their study results. In non-proteinuric Type I diabetic patients with normal to high levels of UA, an early decline in GFRs was reported.[13] Among these studies, Ficociello et al. reported a 40% increase in the odds of developing early GFR loss for every 1 mg/dL increase in serum UA level.[29] The presence of a relation between the UA levels and the baseline kidney function was suggested in other studies.[17] In a study by Gerhardt et al. including 350 kidney transplant recipients with functioning grafts one year after the procedure, UA levels greater than 8.1 mg/dL in men and 6.1 mg/dL in women were found to be associated with worsening graft survival in the following five years when compared with normouricemic graft recipients (five-year rate 68.8% vs. 83.3%, respectively).[30] Studies on individuals with higher levels of UA show that these people are more prone to obesity, hypertension, diabetes, and cardiovascular events when compared with normouricemic individuals.[31] These diseases and entities are among the factors that may affect the renal function of the living donors either directly or indirectly later on during their lives. These diseases are significant risk factors for living donors following nephron loss. In living donors with elevated UA levels, precautions about the mentioned diseases and entities may provide significant health benefits during their lives following nephron loss. There are studies that report the beneficial effects of UA-lowering dietary precautions and medications in the progress of CKD. Sturm et al. followed 177 non-diabetic CKD patients (stage I–V) for seven years looking for an association between UA levels and CKD progression and observed that UA was not predictive for

CKD progression. However, when they have excluded the patients using UA-lowering drugs, the analyses revealed a faster progression of CKD with high levels of UA.[32] Mild or moderate renal dysfunction is present in 20–60% of patients with gout.[33] Before the availability of UA lowering agents, as many as 10–25% of patients with gout developed end-stage renal disease.[34] In living kidney donors, UA levels that approach their upper limits but are within the normal range seem to be useful to predict the postoperative elevation in the creatinine levels in the present study. This observation leads us to recommend UA-lowering drugs and precautions to be effective in living donors, in whom UA levels approach their upper limits but are within their normal range prior to the operation. This may lessen the load and hence preserve the function of the remaining kidney in the living donors following the transplantation.

Limited sample size and the shorter duration of follow-up are the limitations of the present study. Therefore, the results of this study need to be supported by further clinical trials performed on a larger sample of living donors with elevated levels of UA prior to donation procedure and with a follow-up period longer than six months.

Conclusion

Pretransplant serum UA levels can give important clues regarding the renal functions of the donors during the postoperative period.

Disclosure statement

The author reports no conflicts of interest.

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