Introduction

Kidney transplantation is the choice of treatment for end-stage renal disease (ESRD). Limited cadaveric transplantation is insufficient to meet the demand and living donor kidney transplantation has been performed since the 1950s and the success rate has increased in the following years.1 Kidney recipients are followed by transplant clinicians, but information about the renal outcomes of donors has recently been published.2,3

Nephrectomy causes renal mass reduction. Improvements in surgical techniques have decreased postoperative complications, but the future effects of nephron loss are uncertain.

Effect of unilateral nephrectomy on urinary angiotensinogen levels in living kidney donors: 1 year follow-up study

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Abstract

Background: Urinary angiotensinogen (uAGT) has recently been proposed as a marker of kidney injury and activated intrarenal renin–angiotensin system. We investigated the effects of living donor nephrectomy on uAGT levels, blood pressure, estimated glomerular filtration rate, proteinuria and compensatory hypertrophy in the remaining kidney of living kidney donors.

Methods: Twenty living kidney donors were included in the study and followed for 1 year. uAGT levels were measured with enzyme-linked immunosorbent assay preoperatively and postoperatively at the 15th day, 1, 6 and 12 months.

Results: Four donors were excluded from the study due to lack of data. The mean baseline estimated glomerular filtration rate was 98 ± 15 ml/min/1.73 m². Serum creatinine, uAGT/creatinine, uAGT/protein levels were higher and estimated glomerular filtration rate was lower than baseline values at all time periods. Urinary protein/creatinine levels increased after donor nephrectomy, but after 6 months they returned to baseline values. Renal volume increased after nephrectomy, but these changes did not show any correlation with uAGT/creatinine, uAGT/protein, estimated glomerular filtration rate or systolic/diastolic blood pressures. uAGT/creatinine at 6 months and urinary protein/creatinine ratio at 12 months showed a positive correlation (P=0.008, r=0.639).

Conclusion: After donor nephrectomy, increasing uAGT levels can be the result of activation of the intrarenal renin–angiotensin system affecting the compensatory changes in the remaining kidney. The long-term effects of increased uAGT levels on the remaining kidney should be examined more closely in future studies.

Keywords

Angiotensinogen, intrarenal renin–angiotensin system, kidney transplantation, living kidney donor, nephrectomy

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Many compensatory changes occur after nephrectomy, including increased renal blood flow, effective renal plasma flow, and glomerular filtration rate (GFR) and decreased afferent and efferent arteriolar pressures. These haemodynamic changes result in increased glomerular pressure, which may cause glomerulosclerosis. A low risk of the development of ESRD in donors suggests that different protective mechanisms are involved in the long term.\(^2,3\)

Angiotensin II (Ang II) is an important component of the renin–angiotensin system (RAS), and is responsible for preserving the fluid balance and vascular tone of the body by showing its effect mainly on the afferent arteriole. Nephrectomy changes the response of the kidney to Ang II as an increase in renal resistance, and causes an increase in glomerular pressure without causing blood pressure changes as a result of the shift of the main effect from the afferent arteriole to the efferent arteriole. Whether these changes are due to systemic or intrarenal RAS effects is unknown.\(^5\)

Urinary angiotensinogen (uAGT) is synthesised in proximal tubule cells and then excreted to the tubular lumen. After cleavage by renin, angiotensin I occurs and through the angiotensin-converting enzyme, Ang II develops. Increased intrarenal Ang II causes malignant hypertension and renal damage in animal studies.\(^6\) In cell culture studies, Ang II was responsible for the proliferation of glomerular cells, type I collagen increase in mesangial cells and hypertrophy of tubular cells. So Ang II has many effects on growth and fibrogenesis in the kidney.\(^7\)

uAGT is a marker of intrarenal RAS, but there is still a debate as to whether it may be a marker or a result of renal dysfunction. Previous studies showed that uAGT increases in diabetic nephropathy, autosomal dominant polycystic kidney disease, IgA nephropathy, chronic kidney disease and kidney transplant recipients.\(^8\)\(^–\)\(^12\)

In this study we aimed to investigate the effects of living donor nephrectomy on uAGT levels, blood pressure, GFR, proteinuria and compensatory hypertrophy of the remnant kidney in living kidney donors during a 1-year follow-up.

**Materials and methods**

This was a prospective cohort study performed after approval by Ankara University School of Medicine ethics committee for clinical studies in accordance with Helsinki Declaration guidelines, and written informed consent was obtained from all participants (19 July 2013; no.: 46004091/302-4). The Turkish Society of Hypertension and Renal Diseases partially funded the cost of the study.

Living kidney donor candidates were evaluated between July 2013 and May 2014 and 20 donors were included in the study. Demographic features (age, gender, body mass index, body surface area (BSA)) were recorded. Physical examination (office blood pressure) and biochemical parameters (blood urea nitrogen, creatinine (Cre), uric acid, sodium, potassium, urine protein/creatinine ratio (UPCR)) were obtained preoperatively and postoperatively on the 15th day, 1, 6 and 12 months. GFR was estimated with the CKD-EPI formula (GFR = 141 \times \min (Scr/κ, 1)\alpha \times \max(Scr/κ, 1) – 1.209 \times 0.993 \text{age} \times 0.108 [\text{if female}] \times 1.159 [\text{if black}]; \kappa = 0.7 \text{ for women and 0.9 for men}, \alpha = -0.329 \text{ for women and -0.411 for men, min indicates the minimum of Scr/ or 1, and max indicates the maximum of Scr/κ or 1}).\(^13\)

All donors were analysed for kidney volume by ultrasonography before surgery and at months 6 and 12 to show the compensatory hypertrophy in the remnant kidney. Ultrasonography was performed with the Toshiba Applio (Tokyo, Japan) by using a 2–4 MHz convex transducer by one expert radiologist. Donors were scanned from a lateral or posterolateral view for optimal visualisation of the kidney. The maximum length of the kidney in the longitudinal plane was measured. The width and thickness were measured in two orthogonal directions in the plane perpendicular to the longitudinal axis of the kidney at the level of the renal hilum. The renal volume was calculated by multiplying these three measurements with 0.523. The unit of measurement was the centimetre (cm).\(^14\) Renal volumes are corrected for BSA.\(^15\)

Samples were collected preoperatively and postoperatively at the 15th day, 1, 6 and 12 months and refrigerated at −80°C. uAGT measurements were made with a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Human Total Angiotensinogen Assay Kit; IBL, Japan) after all samples were collected. Urine samples were stored the night before the work day at +4°C. ELISA measurements was based on the method recommended by the manufacturer. The urine samples were diluted 10-fold with enzyme immunoassay buffer. After preparation of the samples, the antibody solution was added to the precoated plate. Following the instructions in the manual, the chromogen and stop solution was added, respectively, and finally the plate was read on the plate reader to obtain the standard curve, and the results were calculated. The tests were performed in Ankara University School of Medicine, Ibn-Sina Hospital, Research Laboratory of the Department of Nephrology. The results of uAGT were obtained as ng/ml. uAGT levels were normalised with urinary creatinine and urinary protein.

**Statistical analysis**

Statistical analysis was performed using the statistical package for social science 16.0 (SPSS Inc., Chicago, IL, USA). Demographic and clinical data are expressed as mean ± SD, mean ± SE percentage, or, if the data showed no normal distribution, as medians and ranges. Temporal changes in individual parameters were analysed using the two-tailed Wilcoxon matched-pairs test, repeated measures analysis of variance followed by Bonferroni’s post-test, or Friedman’s
test followed by Dunn’s post-test as appropriate. Spearman and Pearson correlation tests were used to assess associations between variables. Mixed effects models were used to evaluate the associations between study parameters over time also after kidney donation. Significance was defined at the 0.05 level.

**Results**

Twenty healthy donors were included in the study. Four donors were excluded from the study due to lack of data. After exclusions, 16 patients were included in the study. The mean age of the donors was 28 ± 9 years. Three donors were men and 13 donors were women. Five of the donors were parents, eight donors were spouses, two donors were relatives and one donor was a sibling. With the exception of one donor, all donors had left nephrectomy. The baseline characteristics of living kidney donors are presented in Table 1. Briefly, preoperative mean office systolic blood pressure (SBP) was 112 ± 13 mmHg and diastolic blood pressure (DBP) was 73 ± 8 mmHg. Mean body mass index was 29 ± 3 kg/m² and BSA was 1.79 ± 0.14 m². Fasting plasma glucose was 87 ± 9 mg/dl. Urinary protein was 70 ± 26 mg/day and creatinine clearance was 128 ± 34 ml/min/1.73 m² (Table 1).

| Parameter                                      | Result     |
|------------------------------------------------|------------|
| Age (mean ± SD, years)                         | 48±9       |
| Gender (female/male, n)                        | 13/3       |
| Relation with kidney recipients                |            |
| - Mother                                       | 4          |
| - Father                                       | 1          |
| - Spouse                                       | 8          |
| - Relative                                     | 2          |
| - Sibling                                      | 1          |
| BMI (mean ± SD, kg/m²)                         | 29±3       |
| Systolic blood pressure (mean ± SD, mmHg)      | 112±13     |
| Diastolic blood pressure (mean ± SD, mmHg)     | 73±8       |
| 24-Hour proteinuria (mean ± SD, mg/day)        | 70±26      |
| eGFR (mean ± SD, ml/min/1.73 m²)               | 98±15      |
| Creatinine clearance (mean ± SD, ml/min/1.73 m²)| 128±34     |
| Nephrectomy side (left/right, n)               | 15/1       |

BMI: body mass index; eGFR: estimated glomerular filtration rate.

Office SBP and DBP did not show a significant change throughout the study. At the 15th day, SBP was minimally elevated, but there was no statistical significance and the SBP level was never elevated above the normal limits. Office DBP showed an undulating course and returned to baseline levels after 1 year. There was no difference from baseline DBP ($P>0.05$).

uAGT/creatinine was increased about fourfold immediately after nephrectomy ($P<0.01$). The increase continued until month 6 ($P<0.01$) and then showed a slightly decrease at month 12, but was still fivefold higher than baseline ($P<0.05$).

uAGT/protein was higher than baseline values and showed a similar trend to uAGT/creatinine. It was highest at month 6 ($P<0.001$) and showed a mild decrease at year 1 ($P<0.01$).

Baseline kidney volume was 122 cm³/m² and after nephrectomy kidney volume was increased 29 cm³/m² (23%) at month 6 and 47 cm³/m² (39%) at year 1 ($P<0.001$). Markers of kidney function such as creatinine or eGFR had no relationship with AGT excretion. Neither uAGT/creatinine nor uAGT/protein showed a correlation with other study parameters ($P>0.05$). The only statistically significant correlation was found between uAGT/creatinine at month 6 and UPCR at year 1 ($r=0.639$, $P=0.008$). Kidney volume changes and also both SBP and DBP had no correlation with AGT excretion.

Mixed effects models were used to evaluate the associations, if any, between changes in uAGT/creatinine and other study parameters over time also after kidney donation. In living kidney donors, increased uAGT/creatinine levels did not demonstrate any association with the change seen in all parameters assessed in this study during 1-year follow-up.

**Discussion**

This study showed that uAGT excretion increases after nephrectomy in healthy living donors. Although it tends to decrease after 6 months, it remains high at year 1. Proteinuria increases after nephrectomy, but returns to baseline values at the first year.

eGFR decreased 31% after nephrectomy in our study and this result is consistent with previous studies. After 11 years’ follow-up eGFR loss was 30% and no patient developed ESRD. Mean age was similar with our study. Another study with 6 months’ follow-up showed similar GFR loss in donors. ESRD risk seems lower in kidney donors, but some studies report increased ESRD risk especially in African American donors. Kidney donors show similar characteristics after nephrectomy. At 1 month postoperatively renal function stabilises and no significant change develops at 1 year follow-up. Long-term follow-up results show that unless additional risk factors such as diabetes, obesity and proteinuria develop, there is no increase in
Table 2. Changes to study parameters after nephrectomy compared to predonation levels (n=16).

| Parameter                        | Preoperative | Postoperative 15th day | Postoperative 1st month | Postoperative 6th month | Postoperative 1st year | P value |
|---------------------------------|--------------|-------------------------|-------------------------|-------------------------|-------------------------|---------|
| Cre (mg/dl) (mean ± SD)         | 0.73 ± 0.14  | 1.09 ± 0.25***          | 1.09 ± 0.26***          | 1.01 ± 0.2***           | 1.06 ± 0.2***           | **P<0.001|
| eGFR (ml/min/1.73 m²) (mean ± SD)| 98 ± 15      | 68 ± 18***              | 67 ± 20***              | 72 ± 17***              | 68 ± 16***              | ***P<0.001|
| Uric acid (mg/dl) (mean ± SD)   | 4.5 ± 1.1    | 4.2 ± 1.2**             | 5.0 ± 1.3***            | 4.9 ± 1.2***            | 5 ± 1.3***              | **P<0.01 |
| UPCR (g/g) (mean ± SD)          | 0.06 ± 0.01  | 0.09 ± 0.04**           | 0.08 ± 0.04*            | 0.09 ± 0.08#            | 0.06 ± 0.02#            | *P<0.05 |
| Office SBP (mmHg) (mean ± SD)   | 112 ± 13     | 119 ± 11#               | 113 ± 7#                | 114 ± 17#               | 110 ± 9#                | #P>0.05 |
| Office DBP (mmHg) (mean ± SD)   | 73 ± 8       | 77 ± 9#                 | 78 ± 6#                 | 76 ± 9#                 | 72 ± 6#                 | #P>0.05 |
| uAGT/cre (µg/g) (median ± SE)   | 4.75 ± 0.70  | 17.4 ± 4.9***           | 28.8 ± 6.58**           | 36.1 ± 8.3**            | 23.9 ± 7.7*             | **P<0.01 |
| uAGT/pro (µg/g) (median ± SE)   | 77 ± 13      | 187 ± 38**              | 312 ± 47***             | 450 ± 65***             | 300 ± 62**              | ***P<0.001|
| cRV (cm³/m²) (mean ± SD)        | 122 ± 22     | 151 ± 31***             | 169 ± 29***             | ***P<0.001              |                         |         |

Cre: creatinine; Pro: protein; eGFR: estimated glomerular filtration rate; UPCR: urinary protein/creatinine ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; uAGT: urinary angiotensinogen, cRV: corrected renal volume (renal volume/body surface area).

* / ** / *** P values are given by comparing the parameter to the baseline value.

ESRD risk in the kidney donor population. A meta-analysis also confirmed that kidney donors have the same risk for developing ESRD as age-matched controls at long-term follow-up.19

ESRD is an important and minatory endpoint after kidney donation, but clinicians have still not defined the cardiac effects of reduced GFR in otherwise healthy people. A controlled study showed an increase in left ventricular mass and a decrease in aortic distensibility in donors after nephrectomy. Therefore, in the long term low GFR due to nephrectomy may be a cardiovascular risk factor for kidney donors.20

In our study, we observed that uric acid levels decreased in the early postnephrectomy period. After the first month, it showed an increase and remained high during the study period compared to baseline values, but no donor developed overt hyperuricemia. This can be explained by hyperfiltration after nephrectomy and low eGFR may responsible for the increase in uric acid levels at follow-up. Controlled studies demonstrate that kidney donors have higher uric acid levels than controls.21 A causal relationship between hyperuricemia and chronic kidney disease is still not clear; our study suggests that the kidney responds with hyperfiltration to an abrupt fall in eGFR (nephrectomy) and donors did not develop elevation of uric acid at this time, but thereafter with the continuous low eGFR levels uric acid levels remained stable and higher than baseline levels.

Many studies on proteinuria after nephrectomy have been reported. A controlled study of living kidney donors demonstrated that the urinary albumin/creatinine ratio and total protein excretion rate were similar.21 Proteinuria remains below 1 g/day in most donors in the long term.2 A 40-year follow-up study showed that only 6.2% of donors developed proteinuria and the risk factors were male gender and higher body mass index.3

The compensatory increase in renal volume after nephrectomy ranged from 22% to 30% and our results were similar. Long-term follow-up studies showed that hypertrophy developed less in the elderly and body mass was associated with kidney volume and eGFR.22,23

In rats, Ang II infusion after nephrectomy causes an increase in renal vascular reactivity. Joly et al. demonstrated that vasodilator prostaglandins decreased the constrictor effect of Ang II, but after nephrectomy this effect was diminished.24 In humans, the response of the remaining kidney to Ang II was also changed after nephrectomy. The expected changes such as increased GFR and renal blood flow occurred and Ang II response was influenced by the baseline reactivity of renal vessels. Lower GFR, lower glomerular pressure and increased afferent arteriole resistance was associated with a greater renal response to Ang II infusion.3 These effects may be considered as a systemic Ang II model, but the effect of the intrarenal RAS in these responses has not yet been elucidated. There are as yet no studies in humans about the effect of nephrectomy on Ang II. uAGT is a marker of the intrarenal RAS and is produced from the S3 segment of the proximal tubule then released to the tubular lumen and excreted with urine. Ang II, derived from the proximal tubule AGT, results in hypertension as a consequence of increased tubular sodium and water absorption.25 Gociman et al. showed increased water intake and diuresis, immunostaining of AGT at proximal tubule sections, a 30% increase in remnant kidney weight and increased uAGT/kidney weight excretion in mice after nephrectomy.26 While the vast majority of the glomerular ultrafiltrate is absorbed in the proximal tubule, increased expression of AGT in the proximal tubule may play an important role in ensuring circulating volumetric balance. After unilateral nephrectomy, elevation of AGT expression...
without systemic RAS activation may trigger GFR uptake before compensatory hypertrophy developed.

Zhang et al. found that uAGT was increased in patients with chronic kidney disease (CKD). As the eGFR fall increases, uAGT excretion and type IV collagen excretion was increased.27 The eGFR results of our donors are compatible with stage II CKD. Animal studies showed that Ang II infused mice exhibit increased proinflammatory cytokine expression and also increased tubulointerstitial fibrosis.28 In our study the positive correlation between month 6 uAGT/creatinine and year 1 urinary protein/creatinine may be an early sign of renal damage. An increase in uAGT – the precursor of intrarenal Ang II – may be the leading finding of future renal fibrosis.

The uAGT/protein level did not show a correlation with other study parameters, but increased at the follow-up when compared to baseline values and remained high over the whole study. The study by Eriguchi et al.29 showed AGT immunostaining in injured podocytes of rats and intraglomerular AGT signals in patients with focal segmental glomerulosclerosis. In the human study patients with focal segmental sclerosis showed higher levels of uAGT/protein than patients with minimal change disease.29 uAGT/protein may be a marker for podocyte damage and affect the uAGT level. When the effect of nephrectomy on glomerular haemodynamics is examined, Lenihan et al. showed that increased renal plasma flow, hyperperfusion and hypertrophy of the remaining glomeruli cause adaptive hyperfiltration without causing glomerular hypertension.30 So there is no expected glomerular damage, and the increase in AGT is not attributable to the glomerulus. Increased uAGT may be the reason for hypertrophy of the remaining kidney.

Our study has several limitations. First, this is a preliminary study, and a limited number of living donors were examined after donor nephrectomy only for 1 year. Thus the results obtained should be confirmed using a larger cohort in the future with long-term follow-up. Second, glomerular haemodynamics and compensatory changes in the remaining kidney were not evaluated in detail. Although it is well known that the physiological function of the local RAS in the kidney includes the regulation of blood pressure, glomerular filtration, and reabsorption at the tubules, the underlying mechanisms of compensatory changes after nephrectomy are still not well defined. Despite the fact that uAGT has been proposed as a good marker of intraglomerular Ang II activation, the results obtained should be confirmed using a larger number of living donors.

The increase of uAGT after nephrectomy in donors may be a result of hyperfiltration and compensatory hypertrophy or may be a sign of early renal injury with a consequence of declining GFR. Ang II plays an important role in the development of compensatory changes in the remaining kidney after unilateral nephrectomy, but it is still unclear whether systemic or intrarenal RAS activation is more important. There may be other pathways such as prostaglandins or paracrine/autocrine effects of Ang II. Increasing the number of donors and prolongation of the follow-up period may lead to the elucidation of the parameters associated with the increase in uAGT after nephrectomy and a better assessment of the risk associated with nephrectomy in renal donors.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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