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Original Article

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The Effect of Large Simple Renal Cysts on Serum Renalase/Epinephrine Ratio and Angiotensinogen Levels

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Abstract

Objective: Large solitary renal cysts (SRC) may result in renal ischemia. Renalase, a protective enzyme against ischemic renal injury, has an effective role in controlling blood pressure (BP). Therefore, we aimed to investigate the relationships among pre- and postoperative serum angiotensinogen, epinephrine, renalase/epinephrine ratio, and BP in patients who underwent laparoscopic cyst decortication.

Materials and Methods: We included 20 patients with large SRC and 16 healthy individuals in this prospective study. Cysts were diagnosed by ultrasonography and characterized using computed tomography. Blood and urine samples were collected during pre- and postoperative periods. In addition, 12-hour ambulatory BP values were recorded. Serum angiotensinogen, renalase, and epinephrine levels were measured by the enzyme-linked immunosorbent assay method.

Results: There was no statistically significant difference in angiotensinogen and renalase levels between patient and control groups (p=0.205, p=0.163, respectively), but preoperative renalase/epinephrine ratio was significantly higher in patients (p=0.006) than in the control group. In addition, renalase/epinephrine ratio was significantly lower in the postoperative period (p=0.018). Univariate and multivariate logistic regression analyses demonstrated that a higher renalase/epinephrine ratio was associated with the presence of SRC (p=0.028, p=0.016, respectively).

Conclusion: A high renalase/epinephrine ratio may be associated with the presence of large SRC. We think that renalase may be a biomarker in the management of SRC and decision making in surgical procedures. Association of renalase with large SRC should be explored in future studies.

Keywords: Angiotensinogen, blood pressure, epinephrine, renalase, simple renal cyst

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INTRODUCTION

Solitary renal cysts (SRC) are one of the most common type of renal cyst diseases. In the general population, the prevalence of SRC varies from 20% to 50%, and the incidence increases with aging. Most of the patients are diagnosed incidentally and other patients present with pain, and hematuria and hypertension (HT) can be observed if the cyst is too large (1). Laparoscopic cyst decortication (LCD) is an effective and reliable treatment option in symptomatic patients. The indications of LCD include pain, hematuria, HT, and urinary system obstruction. Chronic pulmonary obstructive diseases, obesity, and cardiac failure are the main contraindications. Like all surgeries, bleeding, thromboembolism, and conversion to open surgery are the complications (2).

Angiotensinogen is the only precursor of all angiotensin peptides in the renin-angiotensin-aldosterone system (RAAS) and is converted to angiotensin-1 by renin as the first step of this system. It has recently been mentioned that the angiotensinogen gene may also have an effect on the RAAS activation in SRC and on HT (3). RAAS may

be activated due to localized renal ischemia that may occur because of chronic parenchymal compression of the large cyst (4). However, the exact mechanism of SRC-related HT is still unknown.

Renalase, discovered as a flavoprotein, is expressed strongly in the proximal tubule of the kidney. It plays an important role in controlling blood pressure (BP) and cardiac functions by catabolizing catecholamines like epinephrine and dopamine precursors (5). Experimental studies have also shown that renalase has anti-inflammatory, anti-oxidant, anti-apoptotic, and protective effects against ischemic renal injury. These properties are considered to be independent from the catecholamine metabolisms (6). Moreover, the results of recent studies suggest that renalase may be protective against ischemic damage caused by large SRC. Therefore, we aimed to investigate the associations among pre- and postoperative serum angiotensinogen, epinephrine, renalase levels, renalase/epinephrine ratio, and BP in patients with SRC by comparing them with healthy controls.

MATERIALS AND METHODS

Study Design and Population

This prospective study was approved by the Ethics Committee of Hitit University (Approval Date: January 06, 2017; Approval Number: 2016-50) and conducted in accordance with Declaration of Helsinki. All participants provided written informed consent to participate in the study.

We included patients with symptomatic SRC (Group 1) who presented with flank pain to our clinic and age-matched healthy controls (Group 2). All participants were evaluated in nephrology and urology clinics, and detailed physical examinations were performed and medical histories were recorded. The cysts were localized and characterized by the use of ultrasonography and contrast-enhanced computed tomography with a renal-mass protocol. We calculated the volume of a cyst using the following equation: Volume=(l×w×d)×0.523; l, w, and d are the geometric length, width, and depth of the cyst, respectively (7).

Blood samples required for biochemical parameters (blood urea nitrogen, creatinine, glucose, sodium, potassium, calcium, phosphorus, uric acid, albumin, C-reactive protein), complete blood count, angiotensinogen, renalase, and epinephrine values were obtained 1 week before and 1 month after the LCD.

Main Points

- It was shown that high renalase/epinephrine ratio may be related to the presence of large SRC.
- This may be due to the effect of renalase on ischemic renal damage independent of catecholamine metabolism.
- We think that renalase may be a biomarker in the management of large renal cysts and decision-making in surgical procedures.

Blood samples were taken before and after the operation, and 24-hour urine samples were taken for measurement of protein excretion. At the same time, 12-hour (daytime) ambulatory BP measurements were recorded, and average values were determined. Patients were said to have HT if they had systolic BP ≥135 mm Hg, diastolic BP ≥85 mm Hg (8), or if they used antihypertensive drugs. All patients were confirmed to have the disappearance of cyst volume by computed tomography 1 month after LCD.

Patients with uncontrolled HT and diabetes mellitus (DM), congestive heart failure, chronic liver and/or kidney failure, malignancy history, active infection, renal artery stenosis, autosomal dominant polycystic kidneys, small asymptomatic simple cysts (<5 cm), cyst number ≥2 or complicated cysts, those who had undergone open or laparoscopic surgery on the same kidney, cysts with a radiologic diagnosis other than Bosniak type I and II, cysts associated with the collecting system, and those who were using any kind of medication that could influence the RAAS activation (such as RAAS blockers) were excluded from the study.

Biochemical Analysis

All blood samples were obtained in the morning after 12 hours of fasting. The biochemical parameters were measured using Beckman Coulter AU 5800, and complete blood count analysis was performed by MindrayBC-6800 hematology analyzer. Estimated glomerular filtration rate values were determined by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (9). Samples collected for angiotensinogen, renalase, and epinephrine measurements were centrifuged at 2,500 rpm, for 20 min and stored at -80°C until the day of measurement. Concentrations of angiotensinogen (Cat. No: E-EL-H0300, Elapscience Biotechnology Co. Ltd), renalase, and epinephrine (Cat. No: YHB2566Hu, Shanghai Yehua Biotechnology Co. Ltd and Cat. No: YHB1118Hu, Shanghai Yehua Biotechnology Co. Ltd, respectively) were measured by the enzyme-linked immunosorbent assay method using commercially available kits, in accordance with the manufacturers' instructions. Intra-assay coefficient of variations for angiotensinogen, renalase, and epinephrine assays were <10%, and inter-assay coefficient of variations for these three biomarkers were <12%. The sensitivities for angiotensinogen, renalase, and epinephrine assays were 0.94 ng/mL, 0.51 ng/mL, and 2.49 ng/L, respectively. Assay ranges of angiotensinogen, renalase, and epinephrine were 1.56-100 ng/mL, 1-400 ng/mL, and 5-1.000 ng/L, respectively.

Laparoscopic Cyst Decortication Procedure

Laparoscopic renal cyst decortication was performed with transperitoneal and retroperitoneal techniques by the same surgeons. The operations were performed in the lateral decubitus position under general anesthesia. Three ports were inserted (11 mm for camera and 5 mm trocars for others). The Gerota's fascia was opened to reach the kidney, and the cyst wall was

recognized. The cyst was dissected from adjacent fat tissues, and the fluid was aspirated. The cyst wall was cut with scissors, using monopolar and bipolar devices.

Statistical Analysis

All statistical analyses were performed using the IBM Statistical Package for the Social Sciences software for Windows version 23.0 (IBM SPSS Corp.; Armonk, NY, USA). Kolmogorov-Smirnoff analysis was used to test for the Gaussian distribution. The data were expressed as mean±standard deviation and median (25^{th}-75^{th} interquartile range) for Gaussian-distributed variables and variables that were not Gaussian distributed, respectively. Comparisons between groups were undertaken using the Student's t-test or Mann-Whitney U test, as appropriate. Wilcoxon signed-rank test was used for the comparison of parameters in paired samples. Categorical variables were compared using the χ^2 test. Spearman correlation analysis was used to analyze associations. The diagnostic accuracy of the biochemical variables was assessed by calculating the areas under the receiver operating characteristic (ROC) curves, sensitivity, and specificity. In addition, the independent effect of each variable was assessed using univariate logistic regression analysis, and then significant parameters were assessed using multivariate logistic regression analysis. All of the reported p values were 2-tailed, and those less than 0.05 were considered to be statistically significant.

RESULTS

Twenty patients (male: 12; mean age: 59±11 years) and 16 healthy controls (male: 8; mean age: 57±5 years) were included in this study. The characteristics of the patients, including their demographic, somatometric, medical history, comorbid diseases, kidney side, cyst location, maximum diameter of the cyst, and volume of cyst, are given in Table 1.

Table 1. Baseline characteristics of patients

Variables	Patients (n=20)
Gender; male, n (%)	12 (60)
Age, years	59±11
Hypertension, n (%)	10 (50)
DM, n (%)	3 (15)
Current smoker, n (%)	4 (20)
Systolic BP, mm Hg	118±15
Diastolic BP, mm Hg	78±12
BMI, kg/m^2	29.6±5.4
Antihypertensive treatment	
Calcium channel blocker, n (%)	7 (35)
Thiazide-like diuretic, n (%)	3 (15)
Properties of cysts	
Laterality; right, n (%)	11 (55)
Maximum diameter of cyst, mm	79±23
Volume of cyst, mm^3	215±161
Localization of cysts, n (%)	
Upper pole	7 (35)
Middle pole	10 (50)
Lower pole	2 (10)
Parapelvic	1 (5)
Surgical procedures	
Transperitoneal/retroperitoneal, n (%)	15 (75)/5 (25)

Epinephrine levels were significantly lower in the patient group than in the control group (p=0.042), but the renalase/epinephrine ratio was significantly higher (p=0.006). However, angiotensinogen and renalase levels were not significantly different between groups (p=0.205, p=0.163, respectively). Comparison of the demographic and laboratory variables of the groups is shown in Table 2.

There were no significant differences in pre- and postoperative angiotensinogen and renalase levels of patients (p=0.088, p=0.831, respectively). Postoperative epinephrine levels were found to be higher without the statistical significance (p=0.055), but there was a statistically significant difference in the renalase/epinephrine ratio (p=0.018) after the LCD (Figure 1). In addition, postoperative mean systolic/diastolic BP, mean arterial pressure, and pulse pressure were not significantly different (Table 3).

Statistically significant positive correlations were detected between renalase and epinephrine values in all participants (r=0.933, p<0.001), in the patient group (pre- and postoperative) (r=0.962, p<0.001 and r=0.988, p<0.001, respectively) and the control group (r=0.971, p<0.001). There was no statistically significant correlation between angiotensinogen and renalase/epinephrine ratio either in the total study population or in patient group pre- and postoperatively (p=0.595, p=0.646, p=0.072, respectively).

ROC curve analysis was used to select optimum cutoff thresholds with the greatest discriminative power to identify patients with SRC. Renalase/epinephrine ratio gave the largest area under the ROC curve for the presence of SRC (0.778 [0.619-0.938], p=0.007) (Figure 2). The cutoff point of 332 for renalase/epinephrine ratio had a specificity of 72% and sensitivity of 74%.

Univariate and multivariate logistic regression analyses were performed to determine the independent factors associated with the presence of SRC. In univariate logistic regression analysis, body mass index (BMI) (p=0.050), glucose (p=0.037),

Table 2. Comparative variables of the patients and control groups

Variables	Patients (n=20)	Controls (n=16)	p
Age, years	59±11	57±5	0.388
Gender; male, n (%)	12 (60)	8 (50)	0.549
Body mass index, kg/m^2	29.3±5.4	23.9±3.1	0.028
DM, n (%)	3 (15)	0 (0)	-
Hypertension, n (%)	11 (55)	0 (0)	-
Smoking, n (%)	4 (20)	1 (6.2)	0.236
Systolic BP, mm Hg	117 (110-132)	121 (113-130)	0.646
Diastolic BP, mm Hg	78 (72-85)	80 (76-80)	0.932
Blood urea nitrogen, mg/dL	13.4±3.8	15.2±4.7	0.238
Creatinine, mg/dL	0.77±0.2	0.72±0.14	0.414
CKD-EPI, mL/dk/1.73 m^2	97±18	100±9	0.475
Hemoglobin, g/dL	14.9±1.3	14.6±1.3	0.401
Glucose, mg/dL	105±19	98±10	0.023
C-reactive protein, mg/dL	3.3 (3.2-3.8)	3.2 (3.1-4.3)	0.369
Proteinuria, mg/day	100 (90-154)	75 (70-96)	0.026
Renalase, ng/mL	40 (24-52)	47 (41-85)	0.163
Epinephrine, ng/mL	0.117 (0.071-0.145)	0.151 (0.124-0.322)	0.042
Renalase/epinephrine	378±87	314±42	0.006
Angiotensinogen, ng/mL	9.3 (2.7-16.7)	5.9 (2.6-9.9)	0.205

Categorical data are presented as frequencies and percentages; continuous variables are presented as mean±standard deviations or median (25th-75th interquartile range), as appropriate.
CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

Table 3. Comparison of pre- and postoperative variables of patients (n=20)

Variables	Preoperative	Postoperative	p
Systolic BP, mm Hg	118±15	121±14	0.761
Diastolic BP, mm Hg	77±11	81±11	0.108
Pulse pressure, mm Hg	43±4	45±11	0.648
Mean arterial pressure, mm Hg	96±12	102±12	0.060
Blood urea nitrogen, mg/dL	13.5±3.8	13.7±4.1	0.778
Creatinine, mg/dL	0.77±0.2	0.73±0.2	0.031
CKD-EPI, mL/dk/1.73 m^2	97±18	100±17	0.077
Hemoglobin, g/dL	14.9±1.3	14.5±1.3	0.400
C-reactive protein, mg/dL	3.3 (3.2-3.8)	3.3 (3.2-5.3)	0.679
Proteinuria, mg/day	131±78	138±87	0.756
Angiotensinogen, ng/mL	9.3 (2.7-16.7)	7.0 (2.6-12.3)	0.088
Renalase, ng/mL	40 (24-52)	42 (20-69)	0.831
Epinephrine, ng/mL	0.118 (0.071-0.145)	0.124 (0.07-0.24)	0.055
Renalase/Epinephrine	378±87	316±56	0.018

Continuous variables are presented as mean±standard deviations or median (25th-75th interquartile range) as appropriate.
CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

Table 4. Univariate and multivariate logistic regression analysis of variables associated with the presence of simple renal cyst

Variables	Univariate analysis			Multivariate analysis		
	OR (95% CI)	Wald	p	OR (95% CI)	Wald	p
BMI	1.201 (0.998-1.445)	3.775	0.050	1.279 (1.019-1.606)	4.495	0.034
A	1.042 (0.975-1.113)	1.479	0.224			
R	0.993 (0.974-1.013)	0.452	0.501			
E	0.001 (0.000-6.943)	2.413	0.120			
R/E	1.022 (1.002-1.043)	4.841	0.028	1.029 (1.005-1.054)	5.761	0.016

A: angiotensinogen; BMI: body mass index; E: epinephrine; LCD: laparoscopic cyst decortication; R: renalase

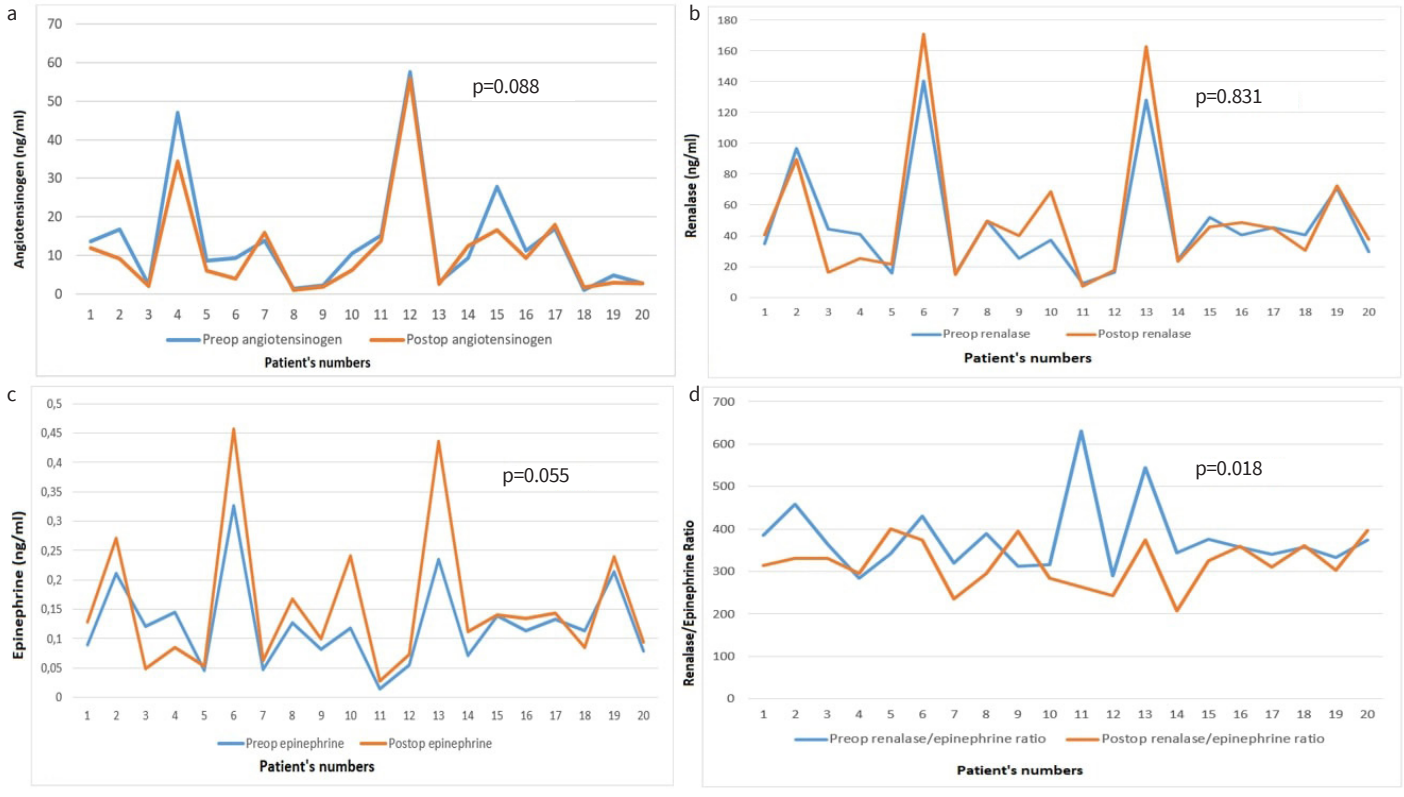

Figure 1. a-d. Preoperative and postoperative individual values of patients: a) angiotensinogen; b) renalase; c) epinephrine d) renalase/epinephrine ratio.

potassium (p=0.040), uric acid (p=0.050), and renalase/epinephrine ratio (p=0.028) were associated with the presence of SRC. However, multivariate logistic regression analysis of factors statistically significant in the univariate logistic regression analysis showed that BMI (p=0.034) and renalase/epinephrine ratio (p=0.016) were significantly associated with the presence of SRC (Table 4).

DISCUSSION

This is the first study explaining the association between the presence of large SRC and high renalase/epinephrine ratio. The renalase, an amine oxidase, is released to systemic circulation from renal tubule cells and is effective on the metabolism of catecholamines (5, 10). Some experimental studies have shown that renalase decreased the epinephrine levels (10). It has been shown that serum renalase levels decreased in rats exposed to subtotal nephrectomy (11) and increased with elevated BP after the catecholamine infusion (12). It was suggested that the reduction of renalase synthesis from renal tubules in patients with chronic renal disease leads to plasma renalase deficiency and increased circulating catecholamines (13). In patients with primary HT (14) and type 2 DM (15), positive correlation of renalase with catecholamine level and BP was also demonstrated. These findings suggest that serum renalase and catecholamine levels may affect each other. In previous studies, it was shown that renalase has the most affinity to epinephrine among cathechol-

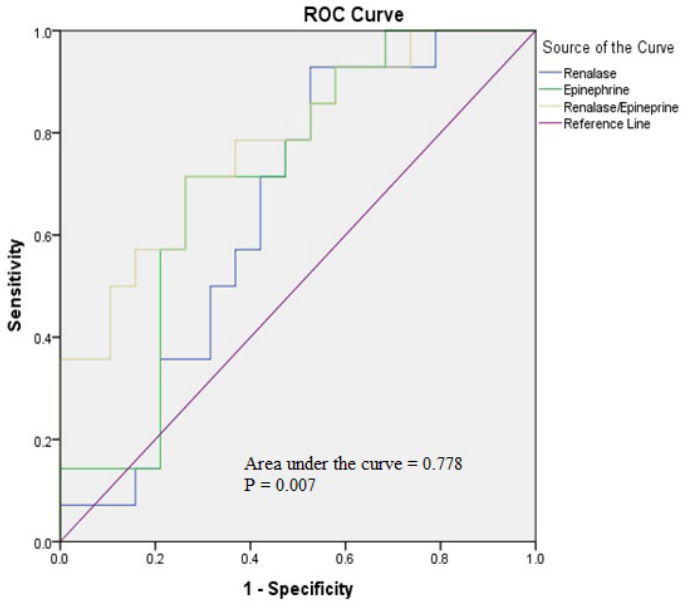

Figure 2. ROC curve analysis of renalase/epinephrine ratio to identify patients with large simple renal cyst.

amines (5, 10). Therefore, we also used renalase/epinephrine ratio when serum renalase level was evaluated. Similar to the literature, there was a positive correlation between serum renalase and epinephrine levels in the current study. In our study, we have also shown that there may be a positive correlation between large SRC and serum renalase/epinephrine ratio independent from BP. These findings show that the use of renalase with epinephrine would be more accurate, rather than using only renalase. A recent cross-sectional study reported that renalase levels were lower in patients with normotensive solitary SRC without comorbid disease than in healthy controls (16). These different results can be explained by differences in the study design, population, and identification methods used. In addition, currently, there are no explanatory data on the cause and pathophysiologic results of low renalase level in normotensive patients without comorbidities.

Previous studies have shown a relationship between HT and SRC (17, 18). In the study by Suher et al. (19), the prevalence of both HT and obesity was found to be higher in patients with SRC. The presence of HT history in 50% of the patients who participated in our study also supports the association between HT and SRC. In addition, our study also shows that there may be a relationship between increased BMI and SRC, although there is not enough evidence in the literature.

In SRC-associated HT, local ischemia caused by parenchymal compression may cause renin release from epithelial cells lining a cyst wall, and the surrounding connective tissue cells activate the RAAS (20). The RAAS is pivotal to the regulation of BP through the actions of angiotensin II. Angiotensinogen is a member of the serine protease inhibitor family and is the only precursor of angiotensin II, which is a biologically active hormone, and other angiotensin peptides (21). Angiotensinogen, produced mainly by hepatocytes and released to systemic circulation, is converted to angiotensin I by renin and then to angiotensin II by the angiotensin-converting enzyme (22). There is growing evidence that the regulation and function of angiotensinogen, considered a passive substructure of RAAS, is more complex than is known. Experimental rat studies in the recent years have shown that increased plasma angiotensinogen may have an independent role in HT pathogenesis (23), and hepatic angiotensinogen inhibition may be associated with low BP (24). In a study conducted in the Indian population, it was reported that angiotensinogen gene variants and their haploids may play a role in HT development (25). Furthermore, it was suggested that the angiotensinogen genotype may affect RAAS in relation to the SRC-formation process and HT in the Iranian population (3). In our study, we could not find any association between serum angiotensinogen and BP levels, and there were also no statistically significant differences for serum angiotensinogen and BP levels after LCD. The absence of changes in serum angiotensinogen levels and BP suggests that there is no ischemic damage and/or increased RAAS activation despite the presence of large SRC. It should be noted that genetic variability may have an effect on systemic angiotensinogen levels. Another explanation for the stability in angiotensinogen level may be related to the possible protective effect of renalase against the formation of ischemic damage, causing renin release.

Recent experimental studies have suggested that renalase has a renoprotective effect with anti-apoptotic, anti-inflammatory, and anti-oxidative effects in ischemic acute renal injury (6, 26) and contrast-induced nephropathy (27). This effect of the renalase may be mediated by catecholamine metabolism but may also occur by intracellular signal cascade activation independent of catecholamine metabolism (6). *In vitro* and *in vivo* tumor necrosis factor alpha activation or hypoxia-induced factor 1 alpha-mediated renalase expression can cause renoprotective (26) and cardioprotective effects (28). The results of these studies strongly suggest the cytoprotective effect of renalase. After LCD, we found a significant decrease in renalase/epinephrine ratio, which was very close to the ratio in healthy controls. This finding suggests that renal hypoxia caused by renal cysts increases the renalase level.

The studies published in recent years about the relationship between renalase and HT are interesting. Some studies showed that higher renalase levels were related with high BP (14, 15). In addition, associations between the renalase gene polymorphism and the higher prevalence rate of HT were found in some studies (29). The effect of renalase on HT is still not clear, but some researchers think that renalase has an antihypertensive effect on catecholamine metabolism (14, 15). In our study, prevalence of HT and high renalase/epinephrine ratio support the association between renalase and HT in this population, although there is no significant difference in BP between the patient group and normotensive control group. Moreover, there

was no significant difference in BP after LCD when compared with baseline values. According to the findings of previous studies and our study, the relationship between BP and low renalase level after LCD should be evaluated in large patient populations.

Limitations

There are some limitations in the current study. This study includes a small number of patients from one center. The duration of the renal cysts diagnosis is unknown and some of the patients with renal cysts had no diagnosis of HT. In addition, the validation of the renalase/epinephrine ratio has not been done with output products such as metanephrine or other, more relevant enzymes, such as monoamine oxidase.

CONCLUSION

The renoprotective effect of renalase against ischemic renal damage is known. In our study, it was shown that high renalase/epinephrine ratio may be related to the presence of large SRC. The presence of large SRC and an LCD operation have no effect on angiotensinogen level. This may be due to the effect of renalase on ischemic renal damage, independent of catecholamine metabolism. We think that renalase may be a biomarker in the management of large renal cysts and decision making in surgical procedures.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Hitit University (Approval Date: January 06, 2017; Approval Number: 2016-50).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.E.; Design - B.E.; Supervision - B.E.; Resources - B.E., S.Ç., H.K.; Materials - B.E., H.K., S.Ç., M.S., Ö.Y.; Data Collection and/or Processing - B.E., S.Ç., İ.D., M.S., H.K.; Analysis and/or Interpretation - B.E., S.Ç., İ.D., O.Y.; Literature Search - B.E., S.Ç., Ö.Y., M.S.; Writing - B.E., H.K.; Critical Review - B.E., İ.D., S.Ç., Ö.Y., H.K.

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