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Original Article

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Role of Local Renin Angiotensin System Activation on Blood Pressure and Residual Renal Function in Peritoneal Dialysis Patients

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Abstract

Objective: Several studies have shown that local renin–angiotensin system (RAS) activity in the kidneys may play a role in the pathogenesis of hypertension and kidney damage in patients with chronic kidney disease. In this study, we aimed to investigate the effect of local RAS activity on hypertension and residual renal function (RRF) in patients undergoing peritoneal dialysis (PD).

Materials and Methods: Fifty patients with residual urine undergoing PD were included in the study. They were divided into the hypertensive (n=30) and non-hypertensive (n=20) groups. The urine angiotensinogen-to-creatinine ratio, which is an indicator of local RAS activity, was compared between the two groups. Factors affecting this ratio were also investigated.

Results: There was no significant difference in the mean urine angiotensinogen-to-creatinine ratios between the two groups. A correlation analysis revealed that the urine angiotensinogen-to-creatinine ratio had a significant negative correlation with RRF determined by 24-hour creatinine excretion (r=−0.391, p=0.005). There was a positive correlation between the urine angiotensinogen-to-creatinine ratio with proteinuria (r=0.289, p=0.04) and negative correlation with serum albumin (r=−0.280, p=0.049). However, we could not find any association between the urine angiotensinogen-to-creatinine ratio and blood pressure values.

Conclusion: Local RAS activation in the kidney reflected by urinary angiotensinogen is associated with RRF and proteinuria in patients undergoing PD; however, high blood pressure was not correlated with urinary angiotensinogen levels.

Keywords: Hypertension, local RAS, peritoneal dialysis, residual renal function, urinary angiotensinogen

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INTRODUCTION

Hypertension is an important cause of cardiovascular morbidity and mortality in patients undergoing peritoneal dialysis (PD) treatment (1). Prevalence of hypertension is reported to range between 30% and 90% in this population (2-4). Although hypervolemia due to loss of residual renal function (RRF) is considered as the main factor underlying hypertension (5), the pathogenesis of hypertension is complex and multi-factorial. The role of renin-angiotensin system (RAS) activity is also a well-known factor in the pathogenesis of hypertension (6). Angiotensinogen is the substrate for renin, which is the rate-limiting enzyme of RAS. Plasma angiotensinogen is produced by the liver, but it cannot be filtered through the glomerular basement membrane because of a high molecular weight, and thus it cannot be detected in urine (7). Angiotensinogen is also synthesized locally by proximal tubular cells and secreted into the tubular lumen in the kidney (8). Therefore, angiotensinogen levels measured in urine reflect the activity of local RAS in the kidneys. Several studies have shown that local RAS activity in the kidneys may play a role in the pathogenesis of hypertension and kidney damage in patients with chronic kidney disease (9-11). However, there is no previous report regarding the relation between local renal RAS activity, blood pressure,

and RRF in patients undergoing PD treatment. In this study, we aimed to investigate the relation between local renal RAS activity reflected by urinary angiotensinogen levels, blood pressure, and RRF in patients undergoing PD.

MATERIALS AND METHODS

Study Population

Adult patients with end-stage renal disease who were undergoing PD treatment for longer than 6 months and who had daily residual urine volume of more than 100 mL were included in this study. Exclusion criteria were current use of RAS blocker drugs, active malignancy, and active infection. Patients were on either continuous ambulatory PD or continuous cyclic PD, with a targeted weekly total of Kt/V>1.7. None of patients were hypervolemic, based on the clinical assessment and evaluation of the cardiothoracic ratio. This study was conducted in accordance with the Declaration of Helsinki and approved by the Local Ethics Committee of Hacettepe University Medical Faculty. All patients were fully informed, and all gave written consents to participate in the study.

Demographic characteristics, etiologies of renal failure, comorbidities, durations of PD, types of PD, weekly Kt/V's, and daily urine volumes of the patients were obtained from hospital records. The ultrafiltration volume was calculated as the mean value of daily ultrafiltration volumes of the last 1 month.

Hemoglobin, blood urea nitrogen, creatinine, electrolytes, albumin, protein, C-reactive protein, lipid parameters, parathyroid hormone, and 24-hour urinary protein excretion were obtained from all patients.

The RRF was predicted by the following creatinine clearance formula: 24 hour creatinine excretion/ (1440xserum creatinine). Creatinine clearance was corrected for the body surface area. Office blood pressures were used in the analysis, and measurements were performed according to the American Heart Association recommendations (12). Patients were divided into the hypertensive and non-hypertensive groups and included into the hypertensive group if they had a previous diagnosis of hypertension and were currently treated with at least one antihypertensive drug.

Urine Angiotensinogen Measurements

We collected 10 mL urine samples from all patients. Within 30 minutes of collection, the samples were centrifuged at 1000 rpm for 20 minutes and stored at -80°C for maximum 3 months before analyses. Measurements were performed by an angiotensinogen enzyme-linked immunosorbent assay kit (Uscn Life Science Inc. Wuhan, China). The angiotensinogen-to-creatinine ratio was used in the analyses to eliminate the confounding effect of urine volume on angiotensin concentration, as previously described (13). Urine creatinine values were determined by spectrophotometric assay. The urine angiotensinogen-to-creatinine ratio is compared between patients with and without hypertension.

Statistical Analysis

The Statistical Package for Social Sciences version 17 (SPSS Inc., Chicago, IL, USA) was used for all analyses. The Kolmogorov-Smirnov test was used to determine distribution characteristics, and the Levene test was used to determine the homogeneity of variances. Continuous variables were compared with the independent samples t-test or Mann-Whitney U test, where appropriate. Categorical variables were compared with the chi-square test. The Pearson correlation coefficient was used for continuous variables with normal distribution, and the Spearman correlation coefficient was used for continuous variables that were not normally distributed. A $p<0.05$ was considered to be statistically significant.

RESULTS

Fifty patients undergoing PD (31 male, 19 female) were included in the study. The mean age of the patients was 49.1±13.0 years, and the mean duration of PD was 36.2±19.9 months. The patients

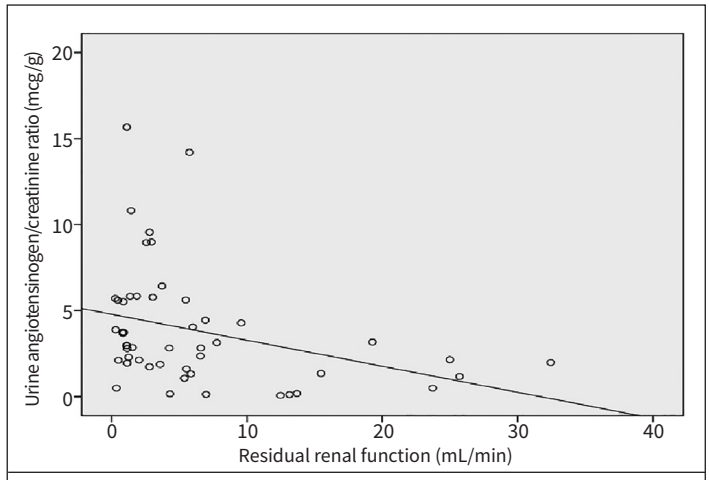

Figure 1. Correlation analysis between urine angiotensinogen-to-creatinine ratio and residual renal function determined by 24-hour creatinine excretion (r=−0.397, p=0.004)

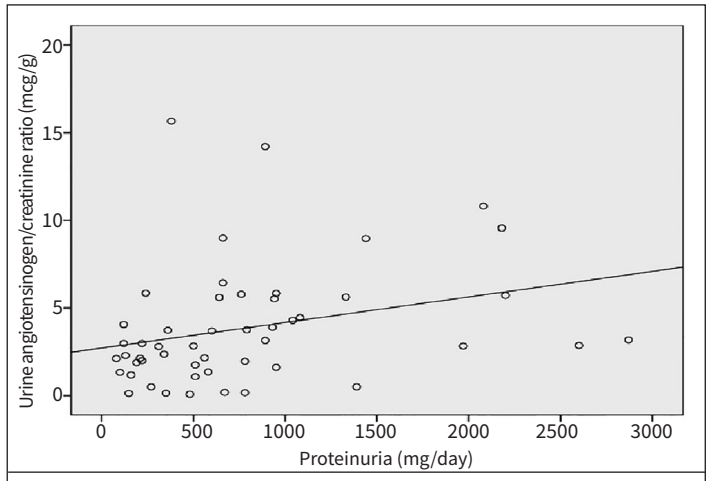

Figure 2. Correlation analysis between urine angiotensinogen-to-creatinine ratio and proteinuria (r=0.289, p=0.04)

Table 1. Demographic and clinical characteristics of patients with and without hypertension

	Patients With Hypertension (n=30)	Patients Without Hypertension (n=20)	p
Age (years)	52.1±12.6	44.7±12.6	0.049
Gender (male/female)	20 (66.7%)/10 (33.3%)	11 (55.0%)/9 (45.0%)	
Body mass index (kg/m^2)	26.5±5.2	26.6±6.0	>0.05
Mean systolic blood pressure (mmHg)	126.8±10.0	122.8±11.3	>0.05
Mean diastolic blood pressure (mmHg)	79.3±6.5	78.3±6.1	>0.05
Residual urine (mL/day)	808.3±537.7	660.0±586.8	>0.05
Residual renal function (mL/min)	8.1±0.9	4.7±0.7	0.035
Peritoneal dialysis modality			
CAPD	17	11	>0.05
APD	13	9	
Duration of peritoneal dialysis (months)	37.0±21.4	35.1±17.7	>0.05
Weekly Kt/V	3.14±1.27	2.49±0.72	0.044
Ultrafiltration volume (mL)	1260.0±311.7	1097.5±327.1	>0.05
Primary kidney disease (n)			>0.05
Hypertension			
Diabetes mellitus Glomerulonephritis	10	8	
Polycystic kidney disease	9	4	
Nephrolithiasis	2	3	
Unknown	3	1	
Pyelonephritis			
Amyloidosis	2	1	
Polyarteritis nodosa	2	1	
Neurogenic bladder	1	-	
	-	1	
	1	-	
	-	1	
Number of antihypertensive drugs (n,%)			
One	18 (60.0%)	-	
Two	10 (33.3%)	-	
Three	2 (6.7%)	-	
Types of antihypertensive drugs (n,%)			
Calcium channel blocker	24 (80.0%)	-	
Beta blocker	17 (56.7%)	-	
Alpha blocker	3 (10.0%)	-	

were divided into two groups, as hypertensive and non-hypertensive. There were 30 hypertensive and 20 normotensive patients. Blood pressures were well controlled in all patients with hypertension. Demographic and clinical characteristics of patients with and without hypertension are shown in Table 1, and laboratory values are shown in Table 2. Patients with and without hypertension had similar demographic and clinical characteristics and laboratory values, except for age and weekly Kt/V, which were slightly higher in the hypertensive group (p=0.049 and p=0.044, respectively). Patients with hypertension also had significantly better preserved RRF when compared to patients without hypertension (8.1±0.9 mL/min vs. 4.7±0.7 mL/min, respectively, p=0.035).

Patients with hypertension were compared to patients without hypertension with regard to urinary angiotensinogen excretion.

Table 2. Laboratory values of patients with and without hypertension

	Patients With Hypertension (n=30)	Patients Without Hypertension (n=20)	p
Creatinine (mg/dL)	8.21±3.01	9.73±2.15	0.042
Potassium (mEq/L)	4.49±0.74	4.27±0.82	>0.05
Sodium (mEq/L)	136.67±3.96	137.30±3.80	>0.05
Blood urea nitrogen (mEq/L)	58.74±18.99	55.59±16.17	>0.05
Calcium (mg/dL)	8.44±0.64	8.89±1.05	>0.05
Phosphorus (mg/dL)	5.02±1.32	5.25±1.48	>0.05
Albumin (g/dL)	3.48±0.46	3.67±0.47	>0.05
Protein (g/dL)	6.64±0.77	6.86±0.71	>0.05
Hemoglobin (g/dL)	11.28±1.68	11.51±1.02	>0.05
CRP (mg/dL)	1.91±3.54	1.72±2.21	>0.05
Cholesterol (mg/dL)	187.16±45.58	194.53±51.74	>0.05
LDL cholesterol (mg/dL)	117.48±27.33	118.42±41.67	>0.05
HDL cholesterol (mg/dL)	40.69±10.47	40.37±11.31	>0.05
Triglyceride (mg/dL)	194.21±105.54	214.26±119.82	>0.05
PTH (pg/mL)	528.65±413.55	709.79±449.55	>0.05
ALP (U/L)	136.76±61.40	120.95±51.58	>0.05
ALT (U/L)	16.31±11.32	14.32±7.80	>0.05

CRP: C-reactive protein; LDL: low-density lipoprotein; HDL: high-density lipoprotein; PTH: parathormone; ALP: alkaline phosphatase; ALT: alanine transaminase

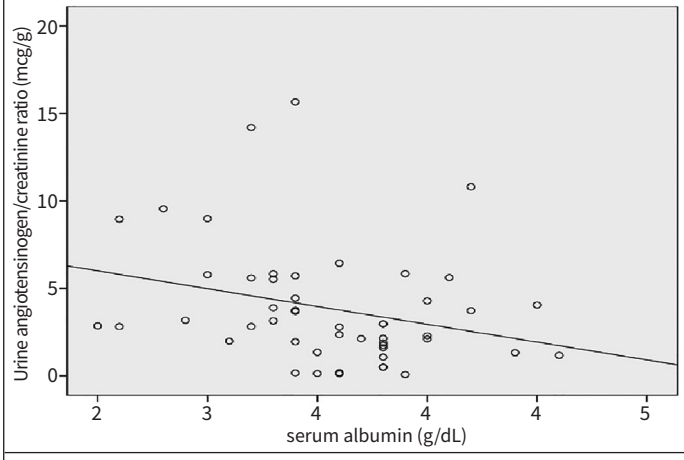

Figure 3. Correlation analysis between urine angiotensinogen-to-creatinine ratio and serum albumin levels (r=−0.280, p=0.049)

The mean urine angiotensinogen/creatinine ratio was 3.51±2.90 µg/g in patients with hypertension and 4.37±4.10 µg/g in patients without hypertension. There was no statistically significant difference between the two groups (p>0.05). Blood pressure values, daily residual urine volumes, and ultrafiltration volumes were also not different between the two groups.

The correlation analysis showed that the urine angiotensinogen-to-creatinine ratio had a significant negative correlation with RRF determined by 24-hour creatinine excretion (r=−0.391, p=0.005) (Figure 1). There was a positive correlation of the urine angiotensinogen-to-creatinine ratio with proteinuria (r=0.289, p=0.04) (Figure 2) and negative correlation with serum albumin levels (r=−0.280, p=0.049) (Figure 3). However, we could not find any association between the urine angiotensinogen-to-creatinine ratio and neither systolic nor diastolic blood pressure values. The urine angiotensinogen-to-creatinine ratio was negatively correlated with weekly Kt/V (r= −0.328, p=0.02). It was not correlated with other laboratory values, including sodium, potassium, blood urea nitrogen, calcium, phosphorus, total protein, hemoglobin, C-reactive protein, total cholesterol, triglyceride, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, parathyroid hormone, or demographic parameters including age, duration of PD, and body mass index.

DISCUSSION

This study showed that local RAS activation in the kidney reflected by urinary angiotensinogen was associated with RRF and proteinuria in patients undergoing PD; however, high blood pressure was not correlated with urinary angiotensinogen levels.

RAS plays important roles in maintaining sodium and extracellular fluid balance, and it also regulates blood pressure. Beside hypertension, RAS hyperactivity has also been correlated with elevated glomerular pressure that results in proteinuria, glomerular injury (14), and renal fibrosis (15). Even though local RAS, to the best of our knowledge, has not been investigated previously in dialysis patients, clinical studies showed that local RAS activation in the kidney may play a role in the development of hypertension and kidney damage in patients with chronic kidney disease (CKD) (16-21). Similarly to previous studies, this study that included patients undergoing PD showed that kidney damage reflected by RRF and proteinuria are related to local RAS activation represented by urinary angiotensinogen levels.

In PD, the RRF is associated with morbidity and mortality (22). High RRF provides better control of malnutrition, hypertension, left ventricular hypertrophy, overhydration, inflammation, and infection (5, 23-27). A large body of evidence shows that the RAS activation is critical in chronic irreversible renal injury leading to glomerulosclerosis and tubulointerstitial fibrosis. The RAS-mediated injury progresses further even after the initiation of PD and is likely to contribute to the RRF decline (28). Similarly, our results also demonstrated that local RAS activity is negatively correlated with RRF in patients undergoing PD. The results may partially explain the potential underlying principle for the benefit of RAS inhibition in the preservation of RRF in these patients (29-31).

RAS is the key player in the development and progression of CKD by promoting fibrosis or through its action on glomerular hemodynamics and enhancing proteinuria. Recent clinical studies performed on patients with CKD (17, 20), amyloidosis (32), and diabetes (33, 34) revealed that urinary angiotensinogen levels were positively correlated with urinary protein excretion. Although some authors suggest that the association between urinary angiotensinogen excretion and proteinuria is simply due to tubular damage and hence more shedding into urine, the origin of urinary angiotensinogen excretion was proved to be intrarenal in other studies (35). Pharmacological inhibition of the RAS decreases proteinuria in patients with glomerulonephritis and CKD. Local RAS inhibition in the kidney may be one of the underlying mechanisms of the antiproteinuric effect of RAS blockers. RAS blockers were shown to decrease local RAS activation in patients with glomerulonephritis (36) and CKD (37). The urine angiotensinogen-to-creatinine ratios before treatment with RAS blockers are also a good predictor of the antiproteinuric effect of these drugs in patients with non-diabetic CKD (38) and diabetic patients (39), as patients with high ratios show a more dramatic antiproteinuric response. In compliance with these findings, this study also showed that local RAS activation is associated with proteinuria in patients undergoing PD.

In experimental studies, it was shown that local RAS activity plays an important role in the pathogenesis of hypertension (40-42). However, the clinical results of studies in patients with CKD and primary hypertension were inconsistent. In a population sample enrolled in the Bogalusa Heart study, a significant association between urinary angiotensinogen excretion and systolic blood pressure and diastolic pressure was observed (43). In another study, no independent association between urinary angiotensinogen excretion and blood pressure in the multiple regression analysis was observed in patients with CKD, despite a significant association in single correlation for systolic and diastolic blood pressures (16). Similarly, we could not find any association between urinary angiotensinogen levels and blood pressure measurements in patients undergoing PD. Additionally, there was no difference in urinary angiotensinogen levels between hypertensive and normotensive patients.

These findings may be due to several reasons. All patients included in the study were using antihypertensives, and there was no difference in the blood pressure values between patients with and without hypertension. Hypertensive patients undergoing PD have a significantly higher volume status. A high extracellular volume may suppress the local RAS activation in this population.

There are substantial differences among the assays used to measure urine angiotensinogen. Therefore, currently it is not possible to define the exact reference ranges for urine angiotensinogen in hypertensive or normotensive subjects with normal or impaired renal function.

This study should be interpreted within the context of its limitations. One of the major limitations was a small sample size. In addition, the study was cross sectional, and therefore it could not draw any causal conclusions on the relation between urinary angiotensinogen excretion and blood pressure. However, the patients enrolled in this study were consecutive patients instead of a random population sample, and to the best of our knowledge, this is the first study that evaluated urinary angiotensinogen and blood pressure relation in patients undergoing PD. Despite the small sample size, statistically significant correlations were observed between local RAS activity, proteinuria, and RRF. Finally, we did not measure other components of the intrarenal RAS, such as urinary renin. Therefore, the comparison between these components for diagnostic accuracy could not be performed.

CONCLUSION

Urinary angiotensinogen excretion is higher with a greater loss of RRF, and it is associated with proteinuria in patients undergoing PD. These results suggest that local RAS activation in the kidney represented by urinary angiotensinogen excretion might be a mediator of kidney damage in patients undergoing PD. However, this study could not show any relation between hypertension and urinary angiotensinogen excretion; further large sample size studies are needed to evaluate causal relation between local RAS activation and blood pressure elevation in patients undergoing PD.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Hacettepe University School of Medicine.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept and Design - T.Y., B.A.; Supervision - B.A.; Resources - T.Y., A.A., R.Y., M.D.; Materials - T.Y., A.A., R.Y.; Data Collection and/or Processing - T.Y., A.A., E.T., M.A., M.D.; Analysis and/or Interpretation - T.Y., B.A.; Literature Search - T.Y., M.A., Y.E.; Writing Manuscript - T.Y., R.Y.; Critical Review - M.A., Y.E., B.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

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