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Original Article

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Is There a Role of ADAMTS-1 in Cyst Development in Autosomal Dominant Polycystic Kidney Disease?

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Abstract

Objective: Autosomal dominant polycystic kidney disease (ADPKD) is the most commonly inherited kidney disease. It is characterized by the development of multiple bilateral cysts that cause enlargement of the kidney. The underlying mechanisms related with renal cyst development in ADPKD have been tried to be explained by cellular hyperproliferation, epithelial fluid secretion, and extracellular matrix remodeling. All cystic disorders have some extracellular matrix abnormalities, but data about this step are limited in the literature. We investigated blood and urine levels of A Disintegrin and Metalloproteinase with Thrombospondin motifs 1 (ADAMTS-1) in patients with ADPKD to evaluate the possible role of ADAMTS-1 in cyst development.

Materials and Methods: A case-control study was conducted in a training and research hospital. A total of 58 patients with ADPKD and 29 healthy volunteers were recruited. Serum and urine ADAMTS-1 levels were determined using a human enzyme-linked immunoassay in all subjects.

Results: The serum ADAMTS-1 concentrations were lower in the ADPKD group than in the controls, but the difference was not statistically significant (p=0.653). The urine ADAMTS-1 levels were also not statistically different between the groups (p=0.921).

Conclusion: This is the first study to investigate the role of ADAMTS in kidney disease in humans. In contrast to animal studies, the role of ADAMTS-1 in the extracellular matrix remodeling phase of cyst development is not apparent. Further detailed studies are needed on the possible role of other ADAMTS family members in the remodeling of the extracellular matrix in ADPKD.

Keywords: A Disintegrin and Metalloproteinase with Thrombospondin motifs 1, cyst development, autosomal dominant polycystic kidney disease

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INTRODUCTION

Kidney cysts that originate from the tubules can be seen in different genetic and non-genetic disorders. Autosomal dominant polycystic kidney disease (ADPKD), the most common inherited kidney disease, is characterized by the development of multiple bilateral cysts that cause enlargement of the kidney (1, 2). The estimated prevalence of ADPKD is 3-4 cases per 10,000 in the general population, and eventually half of all affected patients will have end-stage renal disease (ESRD) by the age of 60 years (1, 3, 4). The PKD1 and PKD2 gene products are polycystin-1 (PC1) and polycystin-2 (PC2) and the mutations in these genes lead to ADPKD, 85% and 15% of the cases, respectively (5). The underlying mechanisms related with renal cyst development in ADPKD have been tried to be explained by cellular hyperproliferation, epithelial fluid secretion, and extracellular matrix remodeling (6). The role of PKD1 and PKD2 mutations in cellular hyperproliferation are well known, and there are informative studies in the literature about this step (1, 3). Ghata et al. (6) provided a detailed account of the epithelial fluid secretion phase of cyst development in ADPKD. All cystic disorders have some extracellular matrix abnormalities, but data about this step are limited in the literature (1, 6).

A Disintegrin and Metalloproteinase with Thrombospondin motifs (ADAMTS) are extracellular zinc metalloendo-

peptidases that have diverse roles in tissue morphogenesis and pathophysiologic remodeling, inflammation, and vascular biology (7). A unique member of this family is ADAMTS-1, which belongs to aggrecanase and proteoglycanase clades, and cleave extracellular proteins, including aggrecan, versican, brevican, and neurocan (8, 9), and this clade also has angioinhibitory properties (10). Two animal studies showed that ADAMTS-1 was essential for the development and function of mouse kidneys (11, 12). Mittaz et al. (13) also reported that all ADAMTS-1 null mice displayed a kidney defect, characterized by shrinkage of both the cortex and medulla, and an enlarged calyceal space.

The important extra renal manifestations of ADPKD were cerebral aneurysms and thoraco-abdominal aortic dissections (3, 14, 15). Also, abnormal levels of ADAMTS-1 were reported in thoracal and abdominal aortic aneurysms (16, 17). Ren et al. (16) reported that protein and mRNA expressions of ADAMTS-1 and ADAMTS-4 were higher in thoracic aortic aneurysm than in controls. However, Vorkapic et al. (17) reported that expression of several ADAMTS family members, particularly ADAMTS-1, was down-regulated at the mRNA level in aneurysms compared with control aorta. Arning et al. (18) reported the increased risk of intracranial aneurysm (ICA) development in patients with ADAMTS gene variants; carriers of ADAMTS 2 gene variants had the highest risk for ICA according to their study results. They also reported that some single nucleotide polymorphisms (SNPs) in the ADAMTS 12 and ADAMTS 13 genes (ADAMTS12 variant rs1364044 and ADAMTS13 variants rs739469 and rs4962153) were associated with a protective effect against ICA; whereas, 2 different ADAMTS 13 variants (rs2301612, rs2285489) brought an important risk for ICA development. Studies related with ADAMTS might be illuminating for the extracellular matrix remodeling phase of cyst development. Herein, we investigated the blood and urine levels of ADAMTS-1 in patients with ADPKD to evaluate the possible role of ADAMTS-1 in cyst development.

MATERIALS AND METHODS

This is a single-center, case-control study with 58 patients with ADPKD and 29 healthy control subjects. Patients who were diagnosed as having ADPKD through ultrasonography and family history were recruited to the study. All patients were followed up at our hospital, in the Department of Nephrology. Patients who had stage 1-5 chronic kidney disease according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (19) and with at least one year's follow-up were included in the study. Patients with diabetes mellitus, malignancy, active inflammation, and cardiovascular disease were excluded. Ethics Committee of KTO Karatay University (Approval Date: June 18, 2018; Approval Number: 41901325-050.99) approved the study protocol and all patients gave written informed consent.

Main Points

- A Disintegrin and Metalloproteinase with Thrombospondin motifs (ADAMTS) are extracellular zinc metalloendopeptidases that have diverse roles in tissue morphogenesis and pathophysiologic remodeling, inflammation, and vascular biology.
- Animal studies showed that ADAMTS-1 was essential for the development and function of mouse kidneys. ADAMTS-1 null mice displayed a kidney defect, characterized by shrinkage of both the cortex and medulla, and an enlarged calyceal space.
- In the light of animal studies, we hypotized that ADAMTS-1 might have a role in the development of ADPKD. This is the first study that investigate the possible role of ADAMTS-1 in ADPKD patients.

Physical examinations, anthropometric measurements, and biochemical screening were performed on all patients and healthy controls. All demographic and laboratory results were taken from the patients' records at that visit. The serum and urine samples for ADAMTS-1 were taken during a routine follow-up visit at the outpatient clinics. Blood was collected from the median cubital vein of the patients into serum separation tubes. The tubes were centrifuged at 1,500 g for 10 min. The serum samples were immediately placed in a freezer at -80°C and stored until the day of the ADAMTS-1 study. ADAMTS-1 levels were analyzed using a commercially available human enzyme-linked immunosorbent assay kit (Cloud-Clone Corp.; Wuhan, Hubei, China) with an Awarnes Chromete 4300 Microplate Reader and Awarnes Statfax 2600 Microplate Strip Washer. The range of values detected by this assay was 1.56-100 ng/mL. Intra- and inter-assay coefficient of variations were 10% and 12%, respectively. The principle of this kit was sandwich enzyme-linked immunosorbent assay-basedin vitro quantitative measurement using capture antibodies and biotinylated detection antibodies for capture and detection purposes, respectively. The optical density was measured spectrophotometrically at a wavelength of 450±2 nm. The minimal limit of detection is 0.56 ng/mL. C-reactive protein (CRP) measurements were performed using nephelometry with afully automated Siemens BNII analyzer (Siemens Inc.). The reference range of CRP was 0-5 mg/L.

Statistical Analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences software version 22 (IBM Corp.; Armonk, NY, USA). Continuous variables are given as mean± standard deviation, if the distribution of data was normal, and as median (minimum-maximum), if the distribution was not normal. In the comparison of differences between independent groups, the significance test of the difference between the 2 means (independent samples t-test) was used when the parametric test assumptions were met. The Mann-Whitney U test was used to compare differences between independent groups when the parametric test assumptions were not provided. Categorical variables were tested by the chi-square test. For differences, $p<0.05$ was considered statistically significant.

RESULTS

The study included 58 patients with ADPKD (34 females, 24 males) and 29 healthy controls (18 females, 11 males). The

Table 1. The features of the patients with ADPKD

	ADPKD (n=58)
The mean age at diagnosis (years)	37.8±16.3
The median follow-up time (years)	12 (interquartile range:14)
Family history (%)	49 (84.5)
Hypertension (%)	38 (65.5)
Intracranial aneurysm (%)	1 (1.7)
Abdominal aortic aneurysm (%)	3 (5.2)
Valvular abnormalities (%)	7 (12.5)
Liver cyst (%)	31 (53.4)
The mean diameter of the largest cysts in kidney (cm)	5.7±1.8
The mean length of kidney (cm)	15.5±2.7
Frequent urinary tract infection (%)	6 (10.3%)
Hematuria (%)	5 (8.6%)
Flank pain (%)	27 (46.5%)

Table 2. The demographic data and laboratory values in patients and controls

	ADPKD (n=58)	Control (n=29)	p
Age (years)	52.5±14.3	47.2±13.7	0.101
Female/male (%)	34 (59%)/24 (41%)	18 (62)/11 (38%)	0.819
BMI (kg/m^2)	28.4±5.2	26.5±3.8	0.760
Smoking (%)	9 (15.5%)	5 (17.2%)	0.283
Hypertension (%)	38 (65%)	3 (10%)	<0.001
Hemoglobin (g/dL)	13.6±1.9	13.7±1.9	0.807
Leukocyte (×10^3/μL)	7.7±2.2	7.5±2.5	0.757
Platelet (×10^3/μL)	263.6±71.2	278.1±77.4	0.389
Total cholesterol (mg/dL)	196.4±35.1	203.7±33.0	0.383
Triglyceride (mg/dL)	112.5 (66.5)	103 (53.25)	0.059
LDL-C (mg/dL)	122.4±29.3	132±25.2	0.138
HDL-C (mg/dL)	45.4±10.7	48.8±10.9	0.302
Ferritin (μg/L)	77 (107.5)	17.5 (74.15)	0.283
ALT (U/L)	15 (8.25)	17 (11.5)	0.594
AST (U/L)	21 (8.5)	20 (9.0)	0.860

BMI: body mass index; BUN: blood urea nitrogen; LDL: low-density lipoprotein; HDL: high-density lipoprotein; ALT: alanine aminotransferase; AST: aspartate aminotransferase

mean ages of the patients and controls were 52.5±14.3 years and 47.2±13.7 years, respectively. There were no statistically significant differences in terms of age, sex, body mass index (BMI), and cigarette smoking (p>0.05). The median follow-up time of ADPKD was 12 years (interquartilerange: 14). Hypertension was more common in patientswith ADPKD than in the controls (p<0.05); all of the hypertensive patients using at least one antihypertensive drug and blood pressures were within normal limits. Three patients had abdominal aortic aneurysms and only one patient had an ICA among the patients with ADPKD. Thirty-one (53.4%) patients with ADPKD had liver cysts. The characteristics of the patients with ADPKD are summarized in Table 1.

Table 3. The laboratory values in patients and controls

	ADPKD (n=58)	Control (n=29)	p
BUN (mg/dL)	41.5 (29.50)	27 (12.50)	<0.001
Creatinine (mg/dL)	1.1 (0.91)	0.84 (0.33)	<0.001
eGFR (mL/min/1.73 m^2)	60.4±28.6	87.4±21.1	<0.001
Serum ADAMTS1 (ng/mL)	0.46 (0.48)	0.51 (0.30)	0.653
Urine ADAMTS1 (ng/mL)	0.72 (0.38)	0.71 (0.36)	0.921
CRP (mg/L)	3.40 (6.98)	3.06 (3.08)	0.798
24 hour urine protein (mg/dL)	104.6 (300.7)	74.1 (46.23)	0.149
Sodium (mEq/L)	139±2.7	139.2±1.85	0.976
Potassium (mEq/L)	4.5±0.5	4.3±0.3	0.174
Calcium (mg/dL)	9.3±0.6	9.2±0.4	0.272
Phosphorus (mg/dL)	3.38±0.7	3.2±0.6	0.235
PTH (pg/mL)	115 (157.65)	69.25 (35.53)	0.008
Uric acid (mg/dL)	6.2±1.86	4.7±1.32	<0.001
Albumin (g/dL)	4.1±0.4	4.2±0.3	0.182

BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; ADAMTS: A Disintegrin and Metalloproteinase with Thrombospondin motifs; CRP: C-reactive protein; PTH: parathormone

As expected, the patients with ADPKD had higher creatinine, blood urea nitrogen (BUN), parathormone, and lower estimated glomerular filtration rate (eGFR) values. Twenty-four-hour urine protein results were not statistically different (p=0.149). The CRP levels were similar in the 2 groups (p=0.798). The demographic data and laboratory values are summarized in Table 2 and Table 3.

Serum ADAMTS-1 levels were lower in the ADPKD group than in the controls, but the difference was not statistically significant (p=0.653). Urine ADAMTS-1 levels were similar in both group (p=0.921). The serum ADAMTS-1 levels of patients with ADPKD with and without liver cysts was not statistically different (p=0.591). The urine ADAMTS-1 results in patients with ADPKD with and without liver cysts were also similar (p=473). There was no statistically significant difference either in serum or

urine ADAMTS-1 levels between patients with ADPKD with liver cyst and controls (p=0.976; p=0.767, respectively).

DISCUSSION

Cyst formation and progression has 3 principal mechanisms: cell proliferation, fluid secretion into cysts, and remodeling of the extracellular matrix surrounding expanding cysts. The abnormalities in expression of collagen I and IV, integrins, beta-catenin metalloproteinase activators, and inhibitors might be important during remodeling of the extracellular matrix of renal cysts (6). Since it was described in 1997, the ADAMTS family has drawn considerable attention and has associated with many physiological and pathologic conditions (20).

Three animal studies reported that ADAMTS-1 had importance in renal cyst development (12, 13, 21). Although animal studies make important contributions to understanding the pathophysiology of disease, the situation in animals may not always coincide with that of humans. After these 3 valuable studies, we thought that patients with ADPKD might have abnormal ADAMTS-1 levels compared with controls. This is the first study to investigate the role of ADAMTS-1 in human kidney disease. The present study revealed that patients with ADPKD had lower serum levels of ADAMTS-1 than controls, but the difference was not statistically significant. Also, the urine levels of ADAMTS -1 were similar to those of healthy controls.

A histopathologic investigation of ADAMTS-1 could not be conducted because there is no renal biopsy indication for ADPKD. The low number of patients included might be another weakness of our study. These two handicaps may be the reason for our study results being different from the animal study results. If we had more patients, we might have investigated ADAMTS-1 levels according to chronic kidney disease stages (21) or the Mayo Clinic imaging classification of ADPKD (22).

ICAs might be seen in 6%-12% of patients with ADPKD (23, 24). Arning et al. (18) reported that there was a relationship between ICA and 3 members of the ADAMTS family. Although they did not study ADAMTS-1, knowing that ADAMTS has a role in the development of aneurysms suggests that ADAMTS may have a role in the development of renal cysts. Aortic aneurysms are estimated to occur in 1%to 10% of patients with ADPKD (25). Ren et al. (16) showed that patients with thoracic aortic aneurysms and dissections had elevated tissue levels of ADAMTS-1 and ADAMTS-4. Versican, which is a large extracellular matrix proteoglycan, is degraded more than in thoracic aortic aneurysms, as a consequence of the increased expression of ADAMTS proteins. A disorganized extracellular matrix may cause aneurysms and dissections. Ren et al.'s (16) study also suggests that a member of ADAMTS family may have a role in the development of renal cysts. In our study, it would be misleading to comment on ADAMTS-1 levels because of the small number of patients with ICA or thoracic aortic aneurysm.

CONCLUSION

A disorganized extracellular matrix is important for the development of ADPKD, and ADAMTS proteins are essential for the regulation of the extracellular matrix. This is the first study to investigate the possible role of ADAMTS proteins in cystic renal disease in humans. We showed that ADAMTS-1 has no role in the development of renal cysts in ADPKD. However, other ADAMTS family members may have a role in the pathophysiology of renal cystic diseases. Further detailed studies are needed on the possible role of ADAMTS family members in remodeling of the extracellular matrix in ADPKD.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of KTO Karatay University (Approval Date: June 18, 2018; Approval Number: 41901325-050.99).

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

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Conflict of interest: The authors have no conflict of interest to declare.

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