Annals of Medical Research
DOI: 10.5455/annalsmedres.2019.06.332 2019;26(10):2437-43

Original Article

The association of urotensin II with arterial stiffness and atherosclerosis in patients with autosomal dominant polycystic kidney disease

Melahat Coban[1], Suleyman Dolu[2], Yildiz Kilar Sozer[3], Bekir Erol[3], Emre Asilturk[4], Hamit Yasar Ellidag[5]

[1]Antalya Training and Research Hospital, Department of Nephrology, Antalya, Turkey
[2]Antalya Training and Research Hospital, Department of Internal Medicine, Antalya, Turkey
[3]Antalya Training and Research Hospital, Department of Radiology, Antalya, Turkey
[4]Antalya Training and Research Hospital, Department of Cardiology, Antalya, Turkey
[5]Antalya Training and Research Hospital, Department of Biochemistry, Antalya, Turkey

Abstract

Aim: Cardiovascular events are associated with increased mortality in patients with autosomal dominant polycystic kidney disease (ADPKD). Urotensin II (UT II) is the most potent vasoconstrictor peptide. The aim of the study was to investigate the relationship between UT II and arterial stiffness (AS) and atherosclerosis in ADPKD patients.

Material and Methods: This cross-sectional study was conducted on 55 ADPKD patients with a mean age of 50 ± 14.4years. The presence of AS was determined with brachial-ankle pulse wave velocity (baPWV) and the presence of atherosclerosis was determined with carotid artery intima-media thickness (CA-IMT). Plasma UT II levels were determined by enzyme-linked immunosorbent assay.

Results: Mean $\log_{10}$ UT II was 0.92±0.16 ng/mL. Mean baPWV and CA-IMT were 7.65±1.5 m/sec and 0.63±0.13 mm, respectively. Log_{10} UT II ($p=0.009$), baPWV ($p < 0.001$) and CA-IMT ($p=0.001$) were high in patients compared to healthy individuals. There was an independent relationship between $\log_{10}$ UT II and creatinine ($p=0.044$) and spot urine protein-creatinine ratio (UPCR) ($p=0.026$) in multiple regression analysis. There was no relationship between $\log_{10}$ UT II and baPWV and CA-IMT.

Conclusion: High plasma UT II levels were observed in ADPKD patients compared to healthy individuals. There was a relationship between UT II and kidney dysfunction and proteinuria. There was no relationship between UT II and AS and atherosclerosis.

Keywords: Autosomal dominant polycystic kidney disease; arterial stiffness; atherosclerosis; urotensin II.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by multiple cyst formations in organs of the body. Although development of cysts and parenchymal destruction begins decades ago, reduction in kidney functions and end-stage renal disease (ESRD) development is seen after 4th decade in individuals with the PKD1 gene (85%), and after the 7th decade in those with the PKD2 gene (15%). In ADPKD patients, cardiovascular (CV) events are the most common cause of mortality and morbidity.

Presence of atherosclerosis can be assessed ultrasonographically with carotid artery intima-media thickness (CA-IMT), and it is a non-invasive and simple method. Increased CA-IMT may be regarded as an indicator for increased risk of CV events. Kocaman et al. proposed that CA-IMT was increased in ADPKD patients compared to healthy individuals, and that atherosclerosis development started from the early stages of the disease (1). Wang et al. showed that increased CA-IMT values were observed in adult ADPKD patients, and that atherosclerosis development was a CV complication developing at an advanced age (2).

In patients with chronic kidney disease (CKD), arterial stiffness (AS) development is one of the most common CV complication, and is a predictor of increased CV mortality

Received: 18.06.2019 **Accepted:** 07.08.2019 **Available online:** 24.10.2019
Corresponding Author: Antalya Training and Research Hospital, Department of Nephrology, Antalya, Turkey
E-mail: melahatcoban@hotmail.com

and morbidity. Townsend et al. proposed that advanced age, genetic factors, endothelial dysfunction, local or systemic infection were risk factors for AS development in patients with CKD (3). Borresen et al. found increased AS development in normotensive ADPKD patients with normal creatinine levels compared to healthy individuals (4). Kocyigit et al. reported that AS development in ADPKD patients started before elevation of creatinine levels and blood pressure, starting from the early stages of the disease (5).

Urotensin II (UT II) is the most potent known (ranges should be expanded) vasoconstrictor peptide. It is synthesized in endothelial cells of arteries mainly in the distal and collector tubules in kidneys, other than kidneys, in central and peripheral nervous system, gastrointestinal system, and the adrenal gland. In their study on animals, Richards et al. reported that the effect of UT II on peripheral vessels varies according to the injected dose of UT II dose and type and status of vascular bed (6). Wilkinson et al. suggested that high levels of serum UT II in humans had no effect on blood vessels (7).

Tsoukas et al. reported that there is a relationship between elevated plasma UT II levels and increased CV events (8). Song et al. suggested that UT II promotes proliferation and collagen synthesis in adventitial fibroblast cells (9). Satıroglu et al. reported that UT II was synthesized from infiltrating macrophages in atherosclerotic lesions, smooth muscle cells and endothelial cells, and caused the development of atherosclerosis (10). Totsune et al. reported an inverse relationship between elevated plasma UT II levels and atherosclerosis in ESRD patients on dialysis (11). Mallamaci et al. reported an inverse relationship between UT and CV risk markers, sympathetic and natriuretic activity, and reported that high plasma UT II levels had vasculoprotective effect in ESRD patients on dialysis (12).

Matsushita reported that low levels of plasma UT II were observed in patients with hypertensive CKD due to the increased fractional excretion of UT II from the kidney (13). In contrast, Mori et al. reported high levels of plasma UT II in patients with CKD (14). Ravani et al. reported that serum levels of UT II increased from the early stages of renal failure in CKD patients (15). Tsoukas et al. reported that patients with CKD had elevated plasma UT II levels due to reduced renal clearance or increased renal production (8).

There is a limited number of studies that investigate the prevalence of atherosclerosis and AS development and the associated factors in patients with ADPKD. Additionally, there are few studies which examine the association between plasma UT II and AS and atherosclerosis in patients with heart failure and healthy population (16), the number of studies in ADPKD patients is low and the results are still contradictory today. Therefore, the aim of our study was to investigate the association of plasma UT II with AS assessed with brachial-ankle pulse wave velocity (baPWV), and with atherosclerosis assessed with CA-IMT in ADPKD patients.

MATERIALS and METHODS

Patient selection

This cross-sectional study was conducted between January 2018 and March 2019 with patients followed in nephrology outpatient clinic of Antalya Training and Research Hospital due to the diagnosis of autosomal dominant polycystic kidney disease (ADPKD). There were 22 male (40%) and 33 female (60%) patients with a mean age of 50 ± 14.4 years. The patient group was compared with the control group comprised of 40 healthy volunteers with no comorbidity or medication use. The diagnosis of ADPKD was made based on family history, imaging studies, Ravine criteria (17). Study inclusion criteria were: age >18 years (the range should be narrowed); diagnosis of ADPKD based on family history, clinical and radiological findings; no previous history of pacemaker, coronary artery disease or cardiac interventions. The study exclusion criteria were: patient's refusal to participate in the study, diagnosis of ADPKD ruled out based on family history and imaging studies, active infection or malignancy, peripheral vascular disease, previous history of cardiac intervention (coronary angiography, valvular replacement, cardiac pacemaker), or history of heart disease detected echocardiographically (atrial fibrillation, left ventricular systolic dysfunction (left ventricular ejection fraction < 45%). Purpose of the study was explained to all participants and written consent was obtained from all those who accepted. Written approval was obtained from Antalya Training and Research Hospital Ethics Committee for the execution of the study.

Laboratory measurements and data collection

Venous blood samples were taken from study group after 8-12 hours of overnight fasting, centrifuged for 10 minutes at 4°C, and the supernatants were stored at -80°C. Serum creatinine, hs-CRP (high-sensitive C reactive protein), total cholesterol (T-C), triglyceride, high density lipoprotein cholesterol (HDL-C), levels were analyzed spectrophotometrically using Beckman coulter commercial kits and Beckman coulter AU5800 (Beckman coulter Instrumentation, San Diego, CA, USA) autoanalyser. Low density lipoprotein cholesterol (LDL-C) level was determined with Friedewald formula (18). Plasma urotensin II (UT II) (Elabscience, Shanghai, China) level was measured with enzyme-linked immunosorbent assay (ELISA). The inter- and intra-assay coefficients of variations were < 10%; detection range was 0.31-20 ng/mL and assay sensitivity was 0.19 ng/mL for UT II.

The demographic characteristics (sex, age, body mass index), comorbid diseases, and antihypertensive drugs were recorded for the entire study group. Renal function was determined with estimated glomerular filtration rate (eGFR), serum creatinine, and spot urine protein/creatinine rate (UPCR). The UPCR value was determined from the second urine after the first urine in the morning is removed. eGFR value was determined with Modification of Diet in Renal Disease (MDRD) (19) criteria. On the basis of

the eGFR, patients were divided into subgroups according to the stage of CKD. Blood pressure measurements were performed with both arms by the same nurse after 15 minutes of rest, and the averages of the measurements were taken. The presence of hypertension (HT) was determined with antihypertensive medication use and previous history of hypertensive disease or systolic blood pressure (SBP) ≥ 140 mmHg and diastolic blood pressure (DBP) ≥ 90 mmHg. The presence of hyperlipidemia was determined with having fasting serum T-C ≥ 200 mg/dL, LDL-C ≥ 130 mg/dL or triglyceride ≥ 200 mg/dL or a history of antihyperlipidemic drug use.

Carotid artery intima-media thickness

Right and left common carotid arteries (CCA) were visualized with high resolution B-Mode ultrasonography (USG) device (Siemens, CA, USA), using 5-10 mHz linear probe. Measurements were performed in supine position while patient's neck was angled approximately 20° to the contralateral side. The measurements were performed at 3 points: right and left CCA, bifurcation, and the first 2 cm segment of the internal carotid artery. Carotid artery intima-media thickness (CA-IMT) measurements were performed by evaluating the posterior wall. CA-IMT was determined by longitudinal examination of the distance defined between vascular lumen echogenicity and media/adventitia echogenicity. Each measurement was repeated three times, and the average of left and right measurements were taken (20).

Brachial-ankle pulse wave velocity

For assessment of arterial stiffness (AS), the brachial ankle pulse wave velocity (baPWV) value was calculated with ankle-brachial index (ABI)-form device (D-52222, Stolberg, Germany). Using the method described by Yokoyama et al., blood pressure in both arms and legs were calculated automatically and synchronously (21). Using waves obtained from brachial and tibial arteries, start and end interval transition times (TT) of brachial and ankle waveforms were calculated. Transmission distance between brachial and ankle was determined according to body weight. The distance between suprasternal notch-brachium (LB) was calculated using the formula: 0.2195 × height of the patient (in cm) − 2.0734; and the distance between suprasternal notch- ankle (LA) was calculated using the formula: 0.8129 × height of the patient (in cm) +12.328. BaPWV value was calculated with the formula: (LA-LB)/TT.

Statistical Analysis

Continuous data were expressed as mean ± standard deviation, where as categorical data were expressed as percentage (%). In comparison of patient characteristics with healthy control group and in comparison of patient characteristics with mean $\log_{10}$ UT II levels; Mann-Whitney U test was used for non-normally distributed quantitative variables, Student's t-test was used for normally distributed quantitative variables. Spearman and Pearson correlation tests were used to determine the factors associated with $\log_{10}$ UT II. Multiple linear regression analysis controlled for age and sex was used to determine independent factors associated with $\log_{10}$ UT II. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

Fifty-five (22 (40%) male/33(60%) female) patients with a mean age of 50 ± 14.4 years were included in the study. Mean SBP was 126.91 ± 13.67 mmHg and DBP was 84.76 ± 10.39 mmHg. Antihypertensive drugs used were angiotensin converting enzyme inhibitor (n = 11), angiotensin II receptor blocker (n =13), Ca channel blocker (n = 19), beta blocker (n = 22) and alpha blocker (n = 2) and others (n = 1). According to the CKD stages, 30 (54.5%) of the patients were stage 3, 18 (32.7%) were stage 4 and 7 (12.8%) were predialysis stage 5. Mean creatinine was 3.1 ± 0.5 mg/dL and mean UPCR was 826.29 ± 392.9 mg/dL. Mean albumin 4.22 ± 0.25 g/dL and mean hs-CRP was 2.67 ± 2.87 mg/L. Mean log10 UT II was 0.92 ± 0.16 ng/mL. Mean baPWV was 7.65 ± 1.5 m/sec and mean CA-IMT was 0.63 ± 0.13 mm. Patients were compared with 40 (23 (57.5%) male/17 (42.5%) female) healthy subjects with a mean age of 49 ± 7.2 years. Log10 UT II ($p = 0.009$), creatinine, UPCR, baPWV (all $p < 0.001$) and CA-IMT ($p = 0.001$) were significantly higher in patients compared to healthy individuals. There was no significant difference in albumin, hs-CRP, T-C, HDL-C, LDL-C and triglyceride between the two groups (Table 1).Relationship between

UT II and atherosclerosis and arterial stiffness

Significant correlation was found between $\log_{10}$ UT II and creatinine (r=0.259, p=0.047) and UPCR (r=0.352, p=.008). There was no significant correlation between $\log_{10}$ UT II and baPWV (r = 0.233, p = 0.102) and CA-IMT (r=-0.002, p=0.990).

Mean $\log_{10}$ UT II level was determined as 0.84 ng/mL. Creatinine ($p = 0.025$) and UPCR ($p = 0.018$) were significantly higher in patients with $\log_{10}$ UT II > 0.84 compared to patients with $\log_{10}$ UT II ≤ 0.84. There was no significant difference between the two groups regarding of baPWV and CA-IMT ($p > 0.05$) (Table 2).

Multiple linear regression analysis adjusted for age and gender showed a significant independent association between $\log_{10}$ UT II and creatinine ($p = 0.044$) and UPCR ($p = 0.026$). There was no significant relationship between $\log_{10}$ UT II and baPWV and CA-IMT ($p > 0.05$) (Table 3).

DISCUSSION

To our knowledge, this is the first study to investigate the relationship between plasma UT II and atherosclerotic peripheral vascular complications in ADPKD patients. We found high plasma UT II levels in ADPKD patients compared to healthy individuals. Patients with ADPKD may exhibit greater amounts of UT II synthesis because of increased number of cysts. Similar to the results of our study, Garoufi et al. reported that higher plasma UT II levels were observed in predialysis CKD patients compared to

Table 1. Clinical, demographic characteristics and laboratory values of patient and healthy control group

	Patient (n = 55) Mean ± S.D./n (%)	Healthy control group (n = 40) Mean ± S.D./n (%)	p-value
Age (years)	50 ± 14.4	49 ± 7.2	
Male/Female	22 (40%)/33(60%)	23 (57.5%)/ 17 (42.5%)	
Hypertension	39 (70.9%)		
SBP (mmHg)/DBP (mmHg)	126.91 ± 13.67/84.76 ± 10.39	119.13 ± 11.85/78.56 ± 9.91	
Use of antihypertensive drugs			
ACE inh/ARB	11 (20%)/13 (23.6%)		
Ca channel blocker	19 (34.5%)		
Alpha blocker	2 (3.6%)		
Beta blocker	11 (20%)		
Others	1 (1.8%)		
CKD			
Stage 1-2	30 (54.5%)		
Stage 3-4	18 (32.7%)		
Predialysis stage 5	7 (12.8%)		
Creatinine (mg/dL)	1.59 ± 0.97	0.83 ± 0.1	**< 0.001**
UPCR (mg/dL)	326.29 ± 392.9	46.89 ± 57.03	**< 0.001**
Albumin (g/dL)	4.39 ± 0.25	4.36 ± 0.28	0.476
hs-CRP (mg/L)	2.39 ± 2.24	2.67 ± 2.87	0.888
T-C (mg/dL)	192.64 ± 38.2	189.82 ± 43.72	0.732
LDL-C (mg/dL)	113.89 ± 34.77	116.22 ± 34.8	0.740
Triglyceride (mg/dL)	135.18 ± 54.74	139.76 ± 95.45	0.274
HDL-C (mg/dL)	55.4 ± 17.92	48.24 ± 14.23	0.270
Log_{10} UT II (ng/mL)	0.92 ± 0.16	0.84 ± 0.14	**0.009**
baPWV (m/sec)	7.65 ± 1.5	6.62 ± 0.9	**< 0.001**
CA-IMT (mm)	0.63 ± 0.13	0.55 ± 0.08	**0.001**
≥ 0.9 mm	2 (3.6%)	0 (0)	

Data are presented as n (%), mean ± standard deviation. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE inh, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; UPCR, spot urine protein-creatinine ratio; hs-CRP, high-sensitive C reactive protein; T-C, total-cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; UT II, urotensin II; baPWV, brachial-ankle pulse wave velocity; CA-IMT, carotid artery intima-media thickness

Table 2. Comparison of patient characteristics compared to mean log_{10} UT II levels

	Log_{10} UT II ≤ 0.84 ng/mL (n = 26)	Log_{10} UT II > 0.84 ng/mL (n = 29)	p-value
Creatinine (mg/dL)	1 (0.69-2.96)	1.82 (0.7-4.19)	**0.025**
UPCR (mg/dL)	120 (4-1000)	200 (3-1380)	**0.018**
Albumin (g/dL)	4.4 ± 0.24	4.38 ± 0.26	0.760
hs-CRP (mg/L)	1.2 (0.21-9.08)	2.38 (0.16-6.6)	0.196
T-C (mg/dL)	191.77 ± 34.77	193.41 ± 41.64	0.875
LDL-C (mg/dL)	112 ± 32.87	115.59 ± 36.89	0.706
Triglyceride (mg/dL)	134.81 ± 51.12	135.52 ± 58.7	0.962
HDL-C (mg/dL)	51.5 (38-69)	54 (35-136)	0.926
baPWV (m/sec)	7.54 ± 1.5	7.76 ± 1.47	0.584
CA-IMT (mm)	0.6 (0.5-0.8)	0.6 (0.5-1.1)	0.277

Data are presented as mean ± standard deviation and median (min-max). Student's t test, Mann-Whitney U test

Table 3. Factors associated with log_{10} UT II in multivariate analysis			
	βeta	Standard error	p-value
Creatinine (mg/dL)	0.310	0.022	**0.044**
UPCR (mg/dL)	0.348	0.001	**0.026**
Albumin (g/dL)	0.036	0.098	0.837
hs-CRP (mg/L)	0.070	0.011	0.698
T-C (mg/dL)	-0.601	0.001	0.068
LDL-C (mg/dL)	0.552	0.001	0.093
Triglyceride (mg/dL)	0.259	0.001	0.103
HDL-C (mg/dL)	0.420	0.002	0.063
baPWV (m/sec)	0.514	0.035	0.158
CA-IMT (mm)	0.050	0.192	0.769
Multiple lineer regression analysis (R = 0.439; R2 = 0.193; p = 0.157)			

healthy individuals (22). Böhm et al. reported that two-fold higher plasma UT II levels were observed in CKD patients compared to healthy individuals (23). Totsune et al. reported that two-fold higher plasma UT II levels were observed in ESRD patients on dialysis compared to healthy individuals (11).

Zoccali et al. suggested that the effect of UT II on renal function varies in relation to the underlying disease (24). Zhang et al. reported a marked increase in eGFR values when continuous infusion of UT II was administered at low doses to the renal arteries of mice (25). Song et al. reported a considerable reduction in eGFR values when low and single doses of UT II infusion were given to the systemic circulation of mice and UT II antagonist reversed this effect (26). Abdel-Razik et al., in their study conducted with mice, reported that the renal effects of UT II were dose-dependent and that a significant reduction in eGFR values was observed with high-dose UT II (27). Tian et al., in their study conducted with patients with diabetic nephropathy, reported that high plasma UT II levels caused renal fibrosis and impairment of renal function due to vasoconstrictive effect (28). In our study, monitoring a significant relationship between UT II and creatinine suggests that plasma UT II levels increased as renal failure progressed in ADPKD patients. The reason for the differences between the studies may be related to the fact that the renal effects of UT II vary in relation to dose of applied UT II, type and area of application.

Totsune et al. reported that there was no relationship between UT II and proteinuria in patients with diabetic nephropathy (11). Mosenkis et al. reported an inverse relationship between UT II and proteinuria in CKD patients (29). Balat et al., in their study conducted with children, reported that plasma UT II levels decreased due to urinary excretion of UT II as a result of the high tubular protein load during glomerulonephritis relapse period, an inverse relationship was observed between UT II and proteinuria. They reported that UT II levels increased in the remission period of glomerulonephritis, but there was no relationship between UT II and proteinuria (30). In our study, it was observed that there was a positive correlation between plasma UT II levels and creatinine and proteinuria in ADPKD patients. As it is suggested in another study by Balat et al. (31), the synthesis of UT II may be increasing in fibrotic and sclerotic tissues developed in ADPKD patients with advanced renal failure. Increased plasma UT II levels may lead to renal fibrosis by increasing collagen synthesis from fibroblasts as described by Zhang et al. (32) or may lead to a considerable increase in creatinine levels by a constrictor effect on afferent arteriole or by a dilator effect on efferent arteriole as indicated in a study by Song et al. (9).

Although it is known that UT II is potent vasoconstrictor and affects cardiac functions, the results of studies on the effect of peripheral vessels vary. Hassan et al. reported an increase in UT II synthesis from endothelial cells and lymphocytes in the atherosclerotic region and the relationship between increased levels of UT II and atherosclerosis development (33). Suguro et al. reported that elevated plasma UT II levels were associated with increased arterial intima-media thickness and plaque formation in hypertensive patients (34). Bousette et al. reported that the association between UT II and the development of atherosclerosis was due to vascular vasoactivities or mitogenic effects in smooth muscle cells (35). Zoccali et al. reported that UT II was inversely related to CV events and that is due to its remodeling effect on endothelial functions, high plasma UT II levels showed vasculoprotective effect in CKD patients (36). In Stefoni et al.'s study of ESRD patients entering dialysis, high levels of plasma UT II was reported to have an inverse relationship with atherosclerosis development (37).

In our study, we observed increased atherosclerosis and AS in ADPKD patients compared to healthy individuals. No significant differences were observed in atherosclerosis and AS development between high and low levels of UT II, and no relationship was observed between UT II and atherosclerosis and AS. Hillier et al. reported that UT II does not cause any hemodynamic effects in different size and different vessel beds in patients with peripheral

vascular disease (38). Affolter et al. reported no known systemic hemodynamic effects of UT II, despite a 100-fold increase in serum levels, and no relationship between UT II and atherosclerosis and AS (39). Another study showed that despite the 30-fold increase in serum levels, UT II given through the brachial artery had no effect on the regulation of arterial and venous tone and systemic circulation. It has been suggested that this may be due to a lack of receptor density, high fullness of receptors, or poor binding to signal transduction mechanisms in this region (7). The major source of circulating UT II is renal tubules. In ADPKD patients, more quantities but molecular effect defective UT II synthesis may be performed from the damaged renal tubules due to the effect of multiple renal cysts, or resistance to its effect due to high occupancy rate at the receptors may occur due to high serum levels. Another reason is, similar to that reported in the previous study (40), UT II receptors are only found in coronary vessels and cardiac myocytes and in ADPKD patients, receptor synthesis may not appear on peripheral vessels. Therefore, there may be no significant relationship between UT II and atherosclerotic peripheral vascular complications in ADPKD patients.

Watanabe et al. reported that there was an association between increased UT II synthesis from atherosclerotic lesions in hypertensive patients and inflammatory cytokines released from inflammatory cells (41). Bousette et al. reported that there is a relationship between UT II and inflammatory cells and inflammation markers in atherosclerotic lesions (35). In contrast to these studies, Mallamaci et al. reported that there was an inverse relationship between UT II and inflammation markers in ESRD patients on dialysis (12). In another study, it was reported that UT II was inversely related to the vasculoprotective and antiatherogenic marker transforming growth factor beta-1 and with albumin and fibrinogen, which are indicators of inflammation (42). Daughertry et al. reported that inflammatory cells play an important role in the pathogenesis of atherosclerosis and AS (43). In our study, no relationship between UT II with atherosclerosis and AS was identified. In addition, there was no association between UT II with the known risk factors of atherosclerosis and AS; albumin, hs-CRP, which are markers of inflammation, and hyperlipidemia. The results suggest that UT II does not play a role in the pathogenesis of atherosclerotic peripheral vascular complications in ADPKD patients.

There are some limitations of our study affecting the results. First, the study was conducted in a single center and with a small number of patients. Second, since the study was cross-sectional, the long-term effects of the relationship between plasma UT II levels and AS and atherosclerosis in ADPKD patients were not examined. Third, the presence of AS was determined by the baPWV device, and the carotid-femoral pulse wave velocity device with a higher sensitivity was not used. Fourth, the presence of atherosclerosis was determined by B-Mode USG, instead of gold standard intravascular USG. Fifth, endothelial activation (intercellular adhesion molecule-1, asymmetric dimethylarginine) and other serum inflammatory markers (interleukin, fibrinogen), which are risk factors in the development of atherosclerosis and AS, were not studied. Sixth, the urine UT II and sodium levels of the patients were not examined in order to investigate the effect on hypervolemia. Seventh, plasma UT II levels were determined by ELISA, radioimmunassay (44) method, which is considered to be more valuable when biologically active UT II was determined, was not used.

CONCLUSIONS

In conlusion, it was observed that patients with ADPKD had elevated plasma UT II levels and increased AS and atherosclerosis development compared to healthy individuals, in our study. It was observed that there was a positive relationship between plasma UT II levels and creatinine and proteinuria. High plasma UT II levels can be used as a marker of adverse renal events in patients with ADPKD. It was observed that there was no relationship between plasma UT II and atherosclerosis and AS in patients with ADPKD (delete the second sentence). It was observed that there was no association between UT II with hyperlipidemia and inflammation, which are involved in the pathogenesis of atherosclerosis and AS development. There is no relationship between plasma UT II and atherosclerotic peripheral vascular events in patients with ADPKD. However, due to the differences between the results of studies conducted on this subject, there is a need for further multicentered randomized controlled trials conducted with more patients, in which the relationship between plasma UT II levels and peripheral vascular complications are examined in ADPKD patients.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: The study was approved by the ethics committee of Antalya Training and Research Hospital.

Melahat Coban ORCID: 0000-0001-5761-7675
Suleyman Dolu ORCID: 0000-0002-7496-9493
Yıldız Kılar Sozer ORCID: 0000-0001-6406-7309
Bekir Erol ORCID: 0000-0002-9444-3405
Emre Asılturk ORCID: 0000-0005-6874-9934
Hamit Yasar Ellidag ORCID: 0000-0002-7511-2547

REFERENCES

1. Kocaman O, Oflaz H, Yekeler E, et al. Endothelial dysfunction and increased carotid intima-media thickness in patients with autosomal dominant polycystic kidney disease. Am J Kidney Dis 2004;43:854-60.
2. Wang D, Iversen J, Wilcox CS, et al. Endothelial dysfunction and reduced nitric oxide in resistance arteries in autosomal-dominant polycystic kidney disease. Kidney Int 2003;64:1381–8.
3. Townsend RR, Wimmer NJ, Chirinos JA, et al. Aortic PWV in chronic kidney disease. A CRIC ancillary study. Am J Hypertens 2010;23:282–9.
4. Borresen ML, Wang D, Strandgaard S. Pulse wave reflection

is amplified in normotensive patients with autosomal-dominant polycystic kidney disease and normal renal function. Am J Nephrol 2007;27:240-6.
5. Kocyigit I, Kaya MG, Orscelik O, et al. Early arterial stiffness and inflammatory bio-markers in normotensive polycystic kidney disease patients. Am J Nephrol 2012;36:11-8.
6. Richards AM, Charles C. Urotensin II in the cardiovascular system. Peptides 2004;25:1795-802.
7. Wilkinson IB, Affolter JT, de Haas SL, et al. High plasma concentrations of human urotensin II do not alter local or systemic hemodynamics in man. Cardiovasc Res 2002;53:341-7.
8. Tsoukas P, Kane E, Giaid A. Potential clinical implications of the urotensin II receptor antagonists. Front Pharmacol 2011;2:38.
9. Song N, Ding W, Chu S, et al. Urotensin II stimulates vascular endothelial growth factor secretion from adventitial fibroblasts in synergy with angiotensin II. Circ J 2012;76:1267-73.
10. Satıroglu O, Durakoglugil ME, Cetin M, et al. The role of urotensin II and atherosclerotic risk factors in patients with slow coronary flow. Interv Med Appl Sci 2016;8:158–63.
11. Totsune K, Takahashi K, Arihara Z, et al. Role of urotensin II in patients on dialysis. Lancet 2001;358:810-1.9.
12. Mallamaci F, Cutrupi S, Pizzini P, et al. Urotensin II in end-stage renal disease: an inverse correlate of sympathetic function and cardiac natriuretic peptides. J Nephrol 2005;18:727–32.
13. Matsushita M, Shichiri M, Imai T, et al. Co-expression of urotensin II and its receptor (GPR14) in human cardiovascular and renal tissues. J Hypertens 2001;19:2185–90.
14. Mori N, Hirose T, Nakayama T, et al. Increased expression of urotensin II-related peptide and its receptor in kidney with hypertension or renal failure. Peptides 2009;30:400-8.
15. Ravani P, Tripepi G, Pecchini P, et al. Urotensin II is an inverse predictor of death and fatal cardiovascular events in chronic kidney disease. Kidney Int 2008;73:95-101.
16. Ashton N. Renal and vascular actions of urotensin II. Kidney Int 2006;70:624-9.
17. Ravine D, Gibson RN, Walker RG, et al. Evaluation of ultrasonographic diagnostic criteria for autosomal dominant polycystic kidney disease 1. Lancet 1994;343:824-7.
18. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.
19. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-70.
20. Homma S, Hirose N, Ishida H, et al. Carotid plaque and intima-media thickness assessed by B-mode ultrasonography in subjects ranging from young adults to centenarians. Stroke 2001;32:830-5.
21. Yokoyama H, Shoji T, Kimoto E, et al. Pulse wave velocity in lower-limb arteries among diabetic patients with peripheral arterial disease. J Atheroscler Thromb 2003;10:253-8.
22. Garoufi A, Drapanioti S, Marmarinos A, et al. Plasma Urotensin II levels in children and adolescents with chronic kidney disease: a single-centre study. BMC Nephrol 2017;18:113.
23. Böhm F, Pernow J. Urotensin II evokes potent vasoconstriction in humans in vivo. Br J Pharmacol 2002;135:25-7.
24. Zoccali C, Mallamaci F. Urotensin II: a cardiovascular and renal update. Current Opinion in Nephrology and Hypertension 2008;17:199-204.
25. Zhang AY, Chen YF, Zhang DX, et al. Urotensin II is a nitric oxide-dependent vasodilator and natriuretic peptide in the rat kidney. Am J Physiol 2003;285:792–8.
26. Song W, Abdel-Razik AE, Lu W, et al. Urotensin II and renal function in the rat. Kidney Int 2006;69:1360-8.
27 Abdel-Razik AE, Forty EJ, Balment RJ, et al. Renal haemodynamic and tubular actions of urotensin II in the rat. J Endocrinol 2008;198:617–24.
28. Tian L, Li C, Qi J, et al. Diabetes-induced upregulation of urotensin II and its receptor plays an important role in TGF-beta1-mediated renal fibrosis and dysfunction. Am J Physiol Endocrinol Metab 2008;295:E1234-42.
29. Mosenkis A, Kallem RR, Danoff TM, et al. Renal impairment, hypertension and plasma urotensin II. Nephrol Dial Transplant 2011;26:609-14.
30. Balat A, Pakir IH, Gok F, et al. Urotensin-II levels in children with minimal change nephrotic syndrome. Pediatr Nephrol 2005;20:42-5.
31. Balat A, Karakok M, Yılmaz K, et al. Urotensin-II immunoreactivity in children with chronic glomerulonephritis. Renal Failure 2007;29:573–8.
32. Zhang YG, Li J, Li YG, et al. Urotensin II induces phenotypic differentiation, migration, and collagen synthesis of adventitial fibroblasts from rat aorta. J Hypertens 2008;26:1119–26.
33. Hassan GS, Douglas SA, Ohlstein EH, et al. Expression of urotensin-II in human coronary atherosclerosis. Peptides 2005;26:2464-72.
34. Suguro T, Watanebe T, Ban Y, et al. Increased human urotensin II levels are correlated with carotid atherosclerosis in essential hypertension. Am J Hypertens 2007;20:211–7.
35. Bousette N, Patel L, Douglas SA, et al. Increased expression of urotensin II and its cognate receptor GPR14 in atherosclerotic lesions of the human aorta. Atherosclerosis 2004;176:117-23.
36. Zoccali C, Mallamaci F, Tripepi G, et al. Urotensin II is an inverse predictor of incident cardiovascular events in end-stage renal disease. Kidney Int 2006;69:1253-8.
37. Stefoni S, Cianciolo G, Donati G, et al. Low TGF-beta1 serum levels are a risk factor for atherosclerosis disease in ESRD patients. Kidney Int 2002;61:324-35.
38. Hillier C, Berry C, Petrie MC, et al. Effects of urotensin II in human arteries and veins of varying caliber. Circulation 2001;103:1378-81.
39. Affolter JT, Newby DE, Wilkinson IB, et al. No effect on central or peripheral blood pressure of systemic urotensin II infusion in humans. Br J Clin Pharmacol 2002;54:617-21.
40. Maguire JJ, Davenport AP. Is urotensin-II the new endothelin? Br J Pharmacol 2002;137:579–588.
41. Watanabe T, Kanome T, Miyazaki A. Relationship between hypertension and atherosclerosis: from a viewpoint of the most potent vasoconstrictor human urotensin II. Curr Hypertens Rev 2006;2:237–46.
42. Mallamaci F, Cutrupi S, Pizzini P, et al. Urotensin II and biomarkers of endothelial activation and atherosclerosis in end-stage renal disease. Am J Hypertens 2006;19:505-10.
43. Daugherty A, Rateri DL. T lymphocytes in atherosclerosis: the yin-yang of Th1 and th2 influence on lesion formation. Circ Res 2002;90:1039–40.
44. Aiyar N, Guida B, Ao Z, et al. Differential levels of "urotensin-II-like" activity determined by radio-receptor and radioimmuno-assays. Peptides 2004;25:1339-47.