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Association of OSR-1 With Vascular Dysfunction and Hypertension in Polycystic Kidney Disease

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Abstract: Autosomal-dominant polycystic kidney disease (ADPKD) is associated with oxidative stress and hypertension development before renal function decline and cardiovascular disease development. Oxidative stress-responsive kinase-1 (OSR-1) participates in the signaling regulating Na^+ transport during oxidative stress and also plays a role in the regulation of cell volume and blood pressure. Therefore, we aimed to investigate the potential role of OSR-1 in ADPKD patients. Eighty ADPKD patients, 80 healthy controls, and 80 non-ADPKD patients with hypertension were enrolled in this cross-sectional study. Twenty-four-hour ambulatory blood pressure monitoring was conducted in all participants. Blood samples were taken after 12-h fasting for the measurement of biochemical parameters and OSR-1 gene expression. Vascular dysfunction was assessed using ischemia-induced forearm flow-mediated vasodilation (FMD). Briefly, of the 80 ADPKD patients, 41(51%) were male, and 53(66%) of them were hypertensive. The mean age of the 80 controls was 35.3 ± 12.6 years, and 37(46%) of them were male. The mean age of the 80 non-ADPKD patients with hypertension was 44.6 ± 11.9 years, and 38(47.5) of them were male. There were significant differences in serum *OSR-1* gene expression between the ADPKD patients and the control subjects. Serum *OSR-1* gene expression was also significantly increased in hypertensive ADPKD patients in comparison with both normotensive ADPKD counterparts and non-ADPKD hypertensive subjects. Serum *OSR-1* gene expression was increased in patients with ADPKD than healthy subjects. Low estimated glomerular filtration rate (eGFR), *OSR-1* gene expression, total kidney volume (TKV), and high-density lipoprotein (HDL) were also independently associated with hypertension in ADPKD patients. **Key Words:** Endothelial dysfunction, Gene expression, Hypertension, Oxidative stress, Polycystic kidney disease.

Autosomal-dominant polycystic kidney disease (ADPKD) is the most common hereditary reason of chronic kidney disease, and hypertension occurs in the early stage of the disease without evidence of renal function decline (1,2). Moreover, hypertension is associated with both rapid progression to end-stage renal disease (ESRD) and increased cardiovascular events in the ADPKD population (3,4). Although the precise mechanism of hypertension has not been clarified yet, many factors including activation of the systemic renin angiotensin system (RAS) due to cyst compression, intrarenal RAS activation, fluid retention, subsequently impaired sodium handling, inflammation, endothelial dysfunction, and hyperuricemia have been reported to cause hypertension in ADPKD (5–9).

Endothelial dysfunction, which is an early determinant of vascular injury and cardiovascular disease (5), is present in early-stage ADPKD patients as endothelium-dependent relaxation is impaired, and endothelial nitric oxide synthase activity is decreased (6,7). Endothelial dysfunction and hypertension have been demonstrated in ADPKD patients in our previous studies (8,10,11).

Hypertension is a major cardiovascular risk factor. Vascular damage due to oxidative stress plays a pivotal role in the pathophysiology of hypertension.

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Physiologically, reactive oxygen species regulate vascular function through redox-sensitive signaling pathways. In hypertension, oxidative stress promotes endothelial dysfunction, vascular remodeling, and inflammation, leading to vascular damage (12,13).

The oxidative stress-responsive kinase-1 (OSR-1) participates in the signaling regulating the transport of electrolytes as Na^+, K^+, and Cl^- through cell membranes during oxidative stress. Thus, it has been speculated that OSR-1 contributes to the regulation of cell volume, transepithelial transport, and renal salt excretion (14–16). Presumably due to its impact on renal tubular salt transport, OSR-1 participates in the regulation of extracellular volume and blood pressure (17). It has been recently shown that OSR-1 is linked to some forms of hypertension such as pseudohyperaldosteronism type II (18).

Hypertension pathogenesis has not been completely clarified in ADPKD; it has been speculated that endothelial dysfunction and oxidative stress may contribute to hypertension development. However, data about the potential role of OSR-1 in patients with ADPKD are lacking, and thus, we aimed to investigate the relation between OSR-1 and hypertension in these populations.

MATERIALS AND METHODS

Study population

ADPKD patients, registered by the Erciyes University School of Medicine in the Turkish Society of Nephrology Polycystic Kidney Disease Working Group Registry, were evaluated for this study between December 2016 and March 2017. The study was approved by the local ethics committee. A diagnosis of ADPKD was established on clinical grounds and family history and confirmed using the ultrasonographic criteria described by Pei et al. (19). ADPKD patients who had well-known reduced glomerular filtration rate (GFR < 30 mL/min) and cardiovascular disorders were excluded from the study. A total of 127 ADPKD patients were enrolled in the study. These patients were reevaluated in terms of systemic inflammation, urinary tract stones, and infection. Urinary infection was defined as an infection only if confirmed by one or more positive urinary cultures. Of the patients, 24 were excluded due to acute infections, and 23 patients were excluded due to unwillingness to participate in the study. Stages of CKD were determined using the estimated glomerular filtration rate (eGFR), calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (20). A total of 80 ADPKD patients were included in the final analysis. We recruited 80 healthy subjects into the control group, matched to the ADPKD patients for age and gender, from our outpatient department whose primary reason for referral did not include diabetes or cardiovascular or renal disease. We also recruited 80 non-ADPKD hypertensive patients to the study. All of the participants were included after signing written informed consent forms. Finally, 80 ADPKD patients with and without hypertension, 80 non-ADPKD hypertensive patients, and 80 healthy subjects were eligible for the study.

Informed consent was obtained from all individual participants included in the study.

Biochemical measurements

Blood samples were taken from the vein of the antecubital fossa, with subjects in a seated position and following a 20-min rest after 12 h of fasting. Glucose, creatinine, and lipid profile were determined using standard methods.

OSR-1 mRNA expression studies by quantitative real-time PCR

The total RNA, extracted and purified from whole blood using Trizol Reagent (Thermo Fisher Scientific, Waltham, MA, USA), was prepared by an in vitro transcription. The concentration of purified RNA was diluted with RNase-free water (Qiagen, Hilden, Germany) and stored at −80°C until use. Total RNA was reverse transcribed to complementary DNA (cDNA) using a Transcriptor High Fidelity cDNA synthesis Kit (Roche, Basel, Switzerland). Reactions for reverse transcription proceeded according to manufacturer's protocol: cDNA was amplified for 10 min at 29°C, for 60 min at 48°C, and for 5 min at 85°C. The cDNA was quantified using real time quantitative PCR. All quantitative PCR (qPCR) experiments were performed using a Light Cycler 480 Instrument II (Roche) for the *OSR-1 gene.* OSR-1 For Real Time Catalog Assay (Roche) was used in order to determine qPCR results. All applications were performed using the Light Cycler 480 Probes Master Mix (Roche). The thermal cycling conditions included an initial denaturation step at 95°C for 10 min, followed by 45 cycles at 95°C for 15 s and 60°C for 30 s, and 72°C for a minute. The last cooling step had one cycle of 30 s at 40°C. All samples were performed in duplicate, and the values were normalized to (β-actin). The relatively quantitative expression of OSR-1 was calculated by the method of $\mathbf{2^{-\Delta\Delta Ct}}$.

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Ambulatory blood pressure measurements

The 24-h blood pressure monitoring was performed using a Del Mar Medical Ressurometer Model P6 (Del Mar Reynolds, Irvine, CA, USA), and the results were assessed using the manufacturer's computer software. Ambulatory measurements were conducted once every 15 min from 7 am until 11 pm and once every 30 min from 11 pm until 7 am. Evaluation was performed taking the mean values of day and night blood pressures into account. Hypertension was considered to be present if the average systolic pressure was ≥130 mmHg and/or average diastolic pressure was ≥80 mmHg all day or if the individual was taking antihypertensive medication.

Endothelial function test

Measurements were made by a single observer using an ATL 5000 ultrasound system (Advanced Technology Laboratories Inc., Bothell, WA, USA) with a 12-Mhz probe. The subjects remained at rest in the supine position for at least 15 min before the examination started. Each subject's right arm was comfortably immobilized in the extended position to allow consistent recording of the brachial artery 2–4 cm above the antecubital fossa. Three adjacent measurements of end-diastolic brachial artery diameter were made from single 2D frames. All ultrasound images were recorded on Super Video Home System (S-VHS) videotape for subsequent blinded analysis. The maximum flow-mediated vasodilation (FMD) diameters were calculated as the average of the three consecutive maximum diameter measurements after hyperemia and nitroglycerin, respectively. The FMD was then calculated as the percentage change in diameter compared with baseline resting diameters.

Magnetic resonance imaging protocol

Magnetic resonance imaging (MRI) was performed with a 1.5-T system (MAGNETOM Aera; Siemens, Erlangen, Germany). The following MRI sequences were obtained: breath-hold T1-weighted ultra-fast gradient echo (VIBE) without fat saturation (coronal plane, FOV: 350 mm, slice thickness: 3 mm, TR: 3.95 ms, TE:1.88 ms, averages**:** 1, bandwidth: 540 Hz/px, flip angle: 5, voxel size: 0.9 × 0.9 × 3 mm), T2-weighted turbo spin echo without fat saturation (coronal plane, FOV: 300 mm, slice thickness: 5 mm, TR: 2340 ms, TE: 105 ms, averages: 2, bandwidth: 221 Hz/px, voxel size: 0.8 × 0.8 × 5 mm), and T2-weighted ultra-fast spin echo (HASTE) with fat saturation (coronal plane, FOV: 350 mm, slice thickness: 3 mm, TR: 1200 ms, TE: 94 ms, averages: 1, bandwidth:710 Hz/px, voxel size: 1.1 × 1.1 × 3 mm). An 18-channel phased array body coil was used as a coil. Gadolinium contrast was not applied to patients due to the possible risk of developing nephrogenic systemic fibrosis.

Kidney volume assessment

MRI images were transferred to a postprocessing workstation (VitreaWorkstation, Version 4.1.51, Toshiba Medical Systems, Minnesota, USA). For each kidney, the number of slices of kidneys that can be seen and their mid-slices were examined. Then, kidney volumes were calculated using the mid-slice technique that was defined by Bae et al. (21). For this purpose, a line was drawn around the kidney on mid-slice for each kidney on breath-hold T1-weighted ultrafast gradient echo MRI sequences. Mid-slice area, the number of slices of kidneys that can be seen, slice thickness, and a constant that was found by Bae et al. were used for kidney volume assessment by multiplying with each other.

Statistical analysis

Histogram and q-q plots were examined; Shapiro–Wilk's test was applied to test the data normality. Levene's test was used to assess variance homogeneity. To compare the differences between groups, Pearson's χ^2 analysis was used for categorical variables, and independent-samples *t*-test or Mann–Whitney *U* tests were used for continuous variables. One-way analysis of variance and the Tukey post-hoc test for multiple comparisons were used to compare healthy control subjects and patient groups. The Spearman's test was used for correlation analysis. Covariance analyses were used to conduct adjusted analysis. Univariate and multiple logistic regression analysis were applied to identify the risk factors of hypertension in ADPKD patients. Significant variables at $P < 0.25$ were considered in the multiple model, and the forward elimination method was used with a likelihood ratio statistic to detect the independent risk factors. Odds ratios were calculated with 95% confidence intervals. Analyses were conducted using R 3.2.0 (www.r-project.org). A *P* value less than 5% was considered statistically significant.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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RESULTS

Characteristics of ADPKD patients with and without hypertension and healthy controls

The demographic, clinical, and laboratory characteristics of the study's ADPKD patients, hypertensive non-ADPKD patients, and controls are shown in Table 1. Compared with healthy controls, ADPKD patients had higher blood pressure levels ($P < 0.001$) and *OSR-1* gene expression levels ($P < 0.001$) and lower eGFR levels ($P < 0.001$). Compared with non-ADPKD hypertensive subjects, all ADPKD patients had lower blood pressure levels ($P < 0.001$) and lower eGFR levels ($P < 0.001$).

ADPKD patients divided into two groups according to presence of hypertension are presented in Table 2. Compared with ADPKD patients without hypertension, ADPKD patients with hypertension were older (38.0 ± 11; 45.0 ± 15, $P = 0.045$), had higher serum uric acid levels (5.39 ± 1.83; 6.94 ± 1.91 $P = 0.001$), triglyceride levels (115.0 [92.0–158.0]; 137.0 [107.0–199.0], $P = 0.038$), total kidney volume (878 [585–1123], 1280 [976–1572], $P < 0.001$), and *OSR-1* gene expression levels (0.6 [0.1–2.4]; 1.9 [0.1–10.8], $P = 0.037$) (Fig. 1a,b) and lower HDL cholesterol (48.1 [38.0–57.0]; 40.0 [32.5–46.5], $P = 0.004$), FMD (7.9 [6.6–8.2]; 6.9 [6.0–7.5], $P = 0.015$), eGFR (98.0 [84.0–107.0]; 49.7 [27.3–75.5], $P < 0.001$), and hemoglobin levels (14.42 ± 1.71; 13.55 ± 1.80, $P = 0.047$). Compared with non-ADPKD patients with hypertension, hypertensive ADPKD patients had higher *OSR-1* gene expression levels (1.9 [0.1–10.8]; 1.1 [0.1–7.9], $P = 0.037$) and lower eGFR (49.7 [27.3–75.5]; 88.0 [76.4–95.5], $P < 0.001$) and FMD (6.9 [6.0–7.5]; 7.3 [6.2–7.7], $P = 0.015$). Other parameters were similar among the groups.

Univariate and multiple regression analysis in determination of hypertension

As shown in Table 3, we constructed age-adjusted univariate and multiple regression analysis models to assess the relative independence of hypertension presence. Multiple regression analysis showed that OSR-1 (OR [95%CI]: 1.04 [1.01–1.10]), eGFR (OR [95%CI]: 0.96 [0.94–0.98]), TKV (OR [95%CI]**:** 1.56 [1.32–1.82]), and HDL cholesterol (OR [95%CI]**:** 0.93 [0.87–0.99]) are independent determinants of hypertension in ADPKD patients. In addition, there is a strong correlation between OSR-1 and FMD in patients with ADPKD (R: −0.600, $P < 0.001$) (Fig. 2).

DISCUSSION

This study demonstrates several interesting and novel findings regarding *OSR-1* gene expression and their relation with hypertension in ADPKD population. First, OSR-1 expression levels are significantly increased in ADPKD patients compared to healthy subjects. Second, hypertensive ADPKD patients had significantly higher OSR-1 expressions than both normotensive ones and non-ADPKD hypertensive patients. Moreover, we demonstrated that hypertensive ADPKD patients had low levels of FMD and HDL levels in comparison with normotensive patients. Finally, we showed, for the first time, that *OSR-1* gene expression independently predicted hypertension in ADPKD population.

Hypertension occurs in early stages in the ADPKD population, it often leads to cardiovascular complications, and progression of renal dysfunciton (2). The evidence of early vascular changes and endothelial dysfunction in normotensive ADPKD patients side tracked authors to investigate

TABLE 1. *Demographic and clinical features of patients with autosomal-dominant polycystic kidney disease and healthy controls*

Variable	Groups			*P value*
	Control ($n = 80$)	ADPKD patients ($n = 80$)	Non-ADPKD patients with HT ($n = 80$)	
Gender				
Female	43	39	42	0.227
Male	37	41	38	
Age (years)	41.3 ± 12.6	43.8 ± 13.1	44.6 ± 11.9	0.173
eGFR[†] (mL/min/1.73 m^2)	98.1 ± 17.3	$76.0 \pm 31.5^{‡,§}$	$88.0 \pm 17.6^{‡}$	**<0.001**
BMI (kg/m^2)	23.9 ± 3.5	25.6 ± 4.1	24.7 ± 3.9	0.120
Average 24-h systolic BP, (mmHg)	109.5 ± 6.2	$127.0 \pm 9.4^{‡,§}$	$138.0 \pm 10.4^{‡}$	**<0.001**
Average 24-h diastolic BP, (mmHg)	70.9 ± 4.7	$86.9 \pm 6.5^{‡,§}$	$92.6 \pm 7.8^{‡}$	**<0.001**
OSR-1	0.4 (0.1–3.1)	1.3 (0.1–10.8)[‡]	1.1 (0.1–7.9)[‡]	**<0.001**
Hemoglobin (g/dL)	13.9 ± 2.2	13.3 ± 1.6	13.7 ± 1.8	0.751

[†]$P = \chi^2$ value. [‡]$P < 0.05$ vs. healthy controls. [§]$P < 0.05$ vs. non-ADPKD patients with hypertension.

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TABLE 2. *Comparison of ADPKD patients with and without hypertension in terms of demographical and biochemical parameters*[†]

Variables	ADPKD without hypertension (n = 53)	ADPKD with hypertension (n = 27)	Non-ADPKD with hypertension (n = 80)	P value
Gender				
Male	12 (44.4)	28 (52.8)[‡]	38 (47.5)	0.478
Female	15 (55.6)	25 (47.2)	42 (52.5)	
Age (years)	38.0 ± 11	45.0 ± 15[‡]	44.6 ± 11.9[‡]	**0.045**
Uric acid (mg/dL)	5.39 ± 1.83[§]	6.94 ± 1.91[‡]	6.4 ± 2.2	**0.001**
Calcium (mg/dL)	9.35 ± 0.54	9.32 ± 0.56	9.1 ± 0.7	0.835
Phosphorus (mg/dL)	3.41 ± 0.50	3.40 ± 0.63	3.5 ± 0.9	0.969
Albumin (g/dL)	4.0(3.8–4.3)	4.0 (3.8–4.2)	4.2 (3.9–4.1)	0.585
Triglycerides (mg/dL)	115.0 (92.0–158.0)[§]	137.0 (107.0–199.0)[‡]	135.0 (109.0–195.0)	**0.038**
Total cholesterol (mg/dL)	190.0 (159.0–214.0)	194.0 (177.5–218.0)	196.0 (179.0–220.0)	0.658
HDL cholesterol (mg/dL)	48.1 (38.0–57.0)[§]	40.0 (32.5–46.5)[‡]	38.0 (31.0–44.0)	**0.004**
LDL cholesterol (mg/dL)	116.6 (85.9–137.8)	118.2 (84.8–136.7)	121.4 (90.2–148-4)	0.779
Proteinuria (g/day)	0.2 (0.1–0.3)	0.2 (0.1–0.7)	0.17 (0.1–0.5)	0.269
CRP(mg/L)	3.66 (3.1–5.2)	4.1 (3.7–5.9)	3.4 (2.2–4.7)	0.150
OSR-1	0.6 (0.1–2.4)[§]	1.9 (0.1–10.8)[‡,§]	1.1 (0.1–7.9)	**0.037**
FMD (%)	7.9 (6.6–8.2)[§]	6.9 (6.0–7.5)[‡,§]	7.3 (6.2–7.7)	**0.015**
eGFR (mL/min/1.73 m^2)	98.0 (84.0–107.0)[§]	49.7 (30.3–77.5)[‡,§]	88.0 (76.4–95.5)	**<0.001**
TKV (mL)	878 (585–1123)	1280 (976–1572)	—	**<0.001**
Hemoglobin (g/dL)	14.42 ± 1.71	13.55 ± 1.80[‡]	13.7 ± 1.8	**0.047**

[†]Values are expressed as n (%), mean ± SD, or median (first to third quartiles), $P = \chi^2$ value. [‡]$P < 0.05$ vs. ADPKD without hypertension. [§]$P < 0.05$ vs. non-ADPKD patients with hypertension. HDL, high-density lipoprotein; LDL, low-density lipoprotein; TKV, total kidney volume.

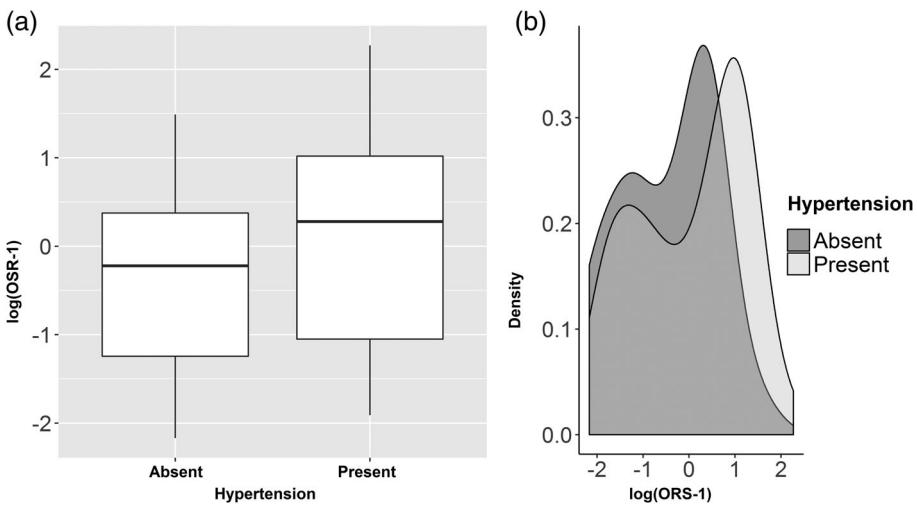


FIG. 1. (a) Box plot displaying the distribution of log(OSR-1) in ADPKD patients with and without hypertension (OSR1 levels: hypertension absent group: 0.6 (0.1–2.4), hypertension present group: (1.9 [0.1–10.8]; P = 0.037). (b) Density plot displaying the distribution of log(OSR-1) in ADPKD patients with and without hypertension (OSR1 levels: hypertension absent group: 0.6 (0.1–2.4), hypertension present group: (1.9 [0.1–10.8]; P = 0.037).

hypertension pathogenesis (5,10–12). Several studies have shown that that both systemic and intrarenal RAS activation, hyperuricemia, inflammation, and increased oxidative stress contribute to the early development of hypertension in the ADPKD population (8–10,12). Wang et al. showed that endothelium-dependent relaxation is impaired and endothelial nitric oxide synthase activity is diminished in normotensive ADPKD patients before the deterioration of kidney function (22). In keeping with this study, we and other researchers also showed that endothelial dysfunction due to the impaired release of nitric oxide has been observed in these patients (7,8,10,23). On the other hand, Menon et al. showed increased oxidative stress, which is monitored by plasma 8-epi-prostaglandin F 2α (8-epi-PGF2α) and superoxide dismutase (SOD) in both normotensive and hypertensive ADPKD patients (24). Depending on this result, it has been concluded that oxidative stress was evident in

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TABLE 3. *Univariate and multiple logistic regression analysis indicating the risk factors of hypertension in ADPKD patients.*

Variables	Univariate regression		Multiple regression OR (95% CI)	*P* value
	Crude OR (95% CI)	Adjusted† OR (95% CI)		
Gender				
Female	1.00	1.00	—	
Male	0.71 (0.28–1.81)	0.52 (0.19–1.45)	—	
Age (years)	1.05 (1.01–1.09)	—	—	
OSR-1	1.10 (1.00–1.21)	1.08 (1.01–1.19)	1.04 (1.01–1.10)	**0.032**
FMD (%)	0.65 (0.45–0.95)	0.62 (0.41–0.93)	—	
eGFR (mL/min/1.73 m^2)	0.96 (0.94–0.98)	0.95 (0.93–0.98)	0.96 (0.94–0.98)	**0.041**
TKV (mL)	1.68 (1.29–1.91)	1.61 (1.32–1.88)	1.56 (1.32–1.82)	**0.013**
Glucose (mg/dL)	1.01 (0.99–1.04)	1.01 (0.98–1.03)	—	
BUN (mg/dL)	1.09 (1.03–1.15)	1.08 (1.01–1.15)	—	
Creatinine (mg/dL)	5.39 (1.91–15.15)	4.50 (1.55–13.12)	—	
Uric acid (mg/dL)	1.53 (1.17–2.00)	1.42 (1.06–1.89)	—	
Sodium (mmol/L)	0.94 (0.77–1.16)	0.95 (0.76–1.18)	—	
Potassium, (mmol/L)	2.71 (1.00–7.33)	2.09 (0.71–6.10)	—	
Calcium (mg/dL)	0.91 (0.39–2.13)	0.89 (0.36–2.19)	—	
Phosphorus (mg/dL)	0.98 (0.45–2.18)	1.05 (0.45–2.42)	—	
Albumin (g/dL)	0.96 (0.37–2.50)	1.44 (0.53–3.91)	—	
Triglycerides (mg/dL)	1.01 (1.00–1.02)	1.01 (0.99–1.01)	—	
Total cholesterol (mg/dL)	1.00 (0.99–1.01)	1.00 (0.99–1.00)	—	
HDL cholesterol (mg/dL)	0.92 (0.87–0.97)	0.92 (0.87–0.97)	0.93 (0.87–0.99)	**0.039**
LDL cholesterol (mg/dL)	1.00 (0.99–1.01)	1.00 (0.99–1.00)	—	
Hemoglobin(g/dL)	0.75 (0.57–1.00)	0.77 (0.57–1.03)	—	
Proteinuria (g/day)	0.92 (0.60–1.42)	0.81 (0.51–1.27)	—	

†Adjusted for age. CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio.

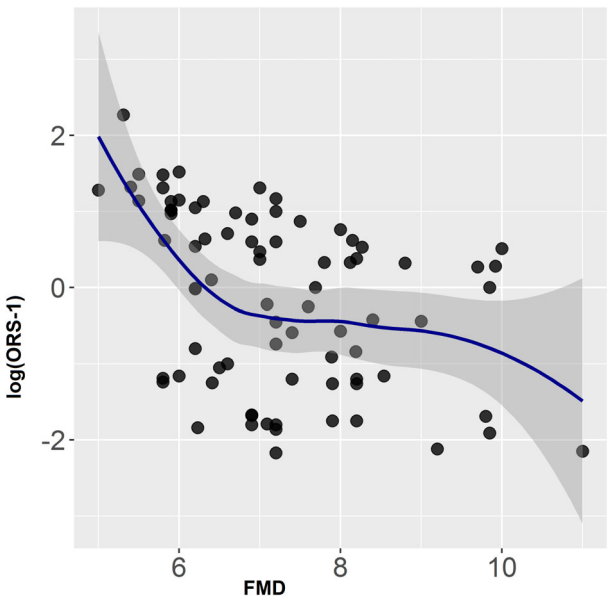


FIG. 2. Scatter plot displaying the relationship between FMD and log (OSR-1) (r: −0.600, $P < 0.001$). [Color figure can be viewed at wileyonlinelibrary.com]

early-stage ADPKD patients. The origin of the increased oxidative stress and the association between oxidative stress and clinical outcomes are still obscure in that population. *OSR-1* is a gene that was recently recognized in the occurrence of increased oxidative stress in many conditions; thus, we aimed to investigate this gene and its association with the clinical course of ADPKD patients.

The OSR-1 is engaged in the regulation of epithelial transport under oxidative stress. OSR-1 upregulates the NaCl (NCC) and Na^+,K^+,$2Cl^-$ (NKCC2) cotransporters and thus impacts blood pressure (15,25,26). OSR-1 contributes to cell volume regulation by stimulating cellular ion uptake (27,28). OSR-1 is under the control of with-no-K (Lys) (WNK) kinases (14), which are similarly involved in the regulation of renal tubular ion transport and blood pressure (14,29,30). Mutations of genes encoding WNK kinases may lead to Gordon's syndrome, a monogenic disease characterized by hypertension and hyperkalemia (31,32). OSR-1 participates in the regulation of further epithelial transport processes, such as Na^+-based transport systems (15,16).

In this regard, there were many animal and in vivo studies to explore the potential role of OSR-1 in blood pressure regulation. However, nothing is known about the relation of OSR-1 with hypertension and of oxidative stress in ADPKD population. Pathare et al. showed that OSR-1 is expressed in proximal renal tubules and participates in the regulation of FGF 23 release and renal tubular phosphate transport in mice models (33). In addition, it

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has been reported that the PI3K/Akt signaling pathway activates the WNK-OSR-1/SPAK-NCC phosphorylation cascade in hyperinsulinemic db/db mice. This mechanism may play a role in the pathogenesis of salt-sensitive hypertension in human hyperinsulinemic conditions such as the metabolic syndrome (34). Shih-Hua Lin et al. studied the role of OSR-1 in mice models and reported that impaired phosphorylation of Na^+–K^+–$2Cl^-$ cotransporter by OSR-1 deficiency was associated with hypotension. They found that OSR-1 plays a dual role in arterial tonicity and renal Na^+ reabsorption, primarily through NKCC1 and NKCC2, respectively. They also suggested that the development of OSR-1 inhibitors may be a promising direction for antihypertensive therapy in the future (35).

CONCLUSION

This study demonstrated that *OSR-1* gene expression was found to be higher in the autosomal dominant polycystic kidney disease population than healthy subjects, and *OSR-1* gene expression is significantly increased in hypertensive ADPKD patients in comparison with normotensive ones. Moreover, *OSR-1* gene expression independently predicted hypertension in ADPKD patients. This study may provide an important background role of *OSR-1* gene expression on the development of hypertension in ADPKD patients.

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Conflict of Interest: None.

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