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Serum vasohibin-1 and suppression of tumorigenicity-2 levels in children with predialysis chronic kidney disease

Nuran ÇETİN[1,*], Nadide Melike SAV[2]

[1]Department of Pediatric Nephrology, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey
[2]Department of Pediatric Nephrology, Düzce Atatürk State Hospital, Düzce, Turkey

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Background/aim: Chronic kidney disease (CKD), which is one of the most important health problems worldwide, could be considered as an immune inflammatory disease. A prognostic biomarker may be helpful in determining the progression of CKD in children. We aimed to investigate the serum vasohibin-1 and soluble suppression of tumorigenicity-2 (sST2) levels as potential biomarkers in children with predialysis CKD.

Materials and methods: Forty-seven children with stage 2–4 CKD and 20 healthy controls were included in this cross-sectional study. Glomerular filtration rate (GFR) and urinary excretion of protein were measured in 24-h urine samples. Serum vasohibin-1 levels and sST2 were measured. The results were expressed as pg/mL and ng/mL, respectively.

Results: Serum vasohibin-1 levels were similar between the patients and the control group ($P > 0.05$), but serum vasohibin-1 levels were higher in patients with proteinuria than in nonproteinuric patients (2574.5 ± 701.60 vs. 1822.4 ± 300.32 pg/mL, $P = 0.001$). A positive correlation was found between serum vasohibin-1 levels and 24-h urine protein values in patients ($P = 0.036$). Serum sST2 levels were higher in patients than the control group ($P = 0.013$). The patients with hypertension had higher sST2 levels than normotensive patients ($P = 0.015$). Serum vasohibin-1 and sST2 levels were not correlated with age, GFR, albumin, hemoglobin, or PTH levels.

Conclusion: Serum vasohibin-1 and sST2 levels were not associated with decline in renal function. Elevated serum vasohibin levels may be a compensatory response to proteinuria in patients with predialysis CKD. The measurement of serum sST2 levels might contribute to early detection of hypertension in patients.

Key words: Angiogenesis, vasohibin-1, soluble suppression of tumorigenicity-2, predialysis chronic kidney disease, children

1. Introduction

Chronic kidney disease (CKD) is becoming a public health problem worldwide. Children with CKD have high morbidity and mortality (1). Systemic hypertension, proteinuria, and tubulointerstitial fibrosis play critical roles in CKD progression (2). Recent studies have suggested that CKD is an immune inflammatory disease, and inflammatory biomarkers may be predictors of deteriorated renal function (3,4). Renal inflammation has an important role in the initiation and progression of CKD. Multiple inflammatory signaling molecules, such as monocyte chemoattractant protein-1, nuclear factor κB, and transforming growth factor β, contribute to renal fibrosis (5).

Suppression of tumorigenicity-2 (ST2) is one of the members of the interleukin (IL)-1 receptor family and it has two isoforms (transmembrane and soluble forms). It has been suggested that soluble ST2 (sST2) might protect against inflammation by preventing the ST2/IL-33 signaling pathway (6). Soluble ST2 interrupts the stimulation of IL-33-mediated Th2-type immune response (7). Thus, sST2 plays an important role in the regulation of the Th1/Th2-associated immune response and modulation of the inflammatory response (8). Moreover, sST2 has antiinflammatory properties owing to the negative regulation of Toll-like receptor (TLR)-2 and TLR-4 (9). In addition, serum sST2 level may serve as a biomarker in several inflammatory diseases (10). The IL-33 signaling pathway could contribute to the development of renal fibrosis in a mouse model of ischemia/reperfusion injury. It has been shown that administrating sST2 could decrease the development of renal fibrosis by reducing inflammatory cell infiltration (11).

Angiogenesis, defined as the formation of new blood vessels, plays a role in physiological events and in some disorders, such as tumor growth, rheumatoid arthritis,

* Correspondence: nurancetin17@hotmail.com

and neointimal formation (12). The angiogenesis stimulators and inhibitors regulate the formation of new blood vessels. The regulators of angiogenesis contribute to kidney development (13). Vasohibin-1, an endogenous angiogenesis inhibitor, is expressed in the vascular endothelium. Other angiogenesis inhibitors, such as angiostatin and endostatin, lead to endothelial cell death. However, vasohibin-1 has both antiangiogenetic and endothelial cell protective effects (14). Vasohibin-1 exhibited therapeutic effects in experimental models of atherosclerosis and diabetic nephropathy (15). A recent study suggested that an imbalance in the angiogenesis regulators may influence CKD progression (16).

In this study, we aimed to investigate the serum vasohibin-1 and sST2 levels in children with predialysis CKD. Considering previous reports, we hypothesized that serum vasohibin-1 and sST2 levels may be potential biomarkers of CKD progression. In order to test this hypothesis, we evaluated the relationship between these potential biomarkers and the clinical or laboratory characteristics of children with CKD. To our knowledge, this is the first study to investigate the clinical significance of serum vasohibin-1 and sST2 levels in children with predialysis CKD.

2. Materials and methods

2.1. Study group

Forty-seven children with stage 2–4 CKD who were followed in our Pediatric Nephrology Outpatient Clinic between September 2010 and March 2017 were included in this cross-sectional study. The underlying diseases in the study group were as follows: renal hypoplasia/dysplasia, 27.7% (n = 13); reflux nephropathy, 23.4% (n = 11); obstructive uropathy, 12.8% (n = 6); neurogenic bladder, 10.6% (n = 5); bilateral multicystic dysplastic kidney, 6.4% (n = 3); hemolytic uremic syndrome, 6.4% (n = 3); renovascular anomalies, 4.3% (n = 2); autosomal dominant polycystic kidney disease, 4.3% (n = 2); and undetermined aetiology, 4.3% (n = 2). CKD was defined as the presence of kidney damage or a decrease in the glomerular filtration rate (GFR < 60 mL min^{-1} 1.73 m^{-2}) lasting for at least 3 months. The Kidney Disease: Improving Global Outcomes (KDIGO 2012) guideline was used to determine the CKD stage (17). Clinical history, demographic data, and physical examination findings were recorded. Patients with active infection, obesity, nephrotic range of proteinuria, congenital heart disease, or vascular disease were excluded from the study. Patients who received corticosteroid therapy at the beginning of the study were also excluded.

Nineteen of the 47 patients were taking antihypertensive medication [17 angiotensin converting enzyme inhibitor (ACEI) and 2 amlodipine] at the time of the study. Patients with anemia or secondary hyperparathyroidism were treated with erythropoietin or calcitriol as per the KDIGO guideline (18,19). In addition, 6 patients were taking a drug to decrease their uric acid level.

Twenty healthy sex- and age-matched controls were included in this study. The detailed physical examination results and blood pressure values of the control group were normal. None of the controls exhibited malnutrition, developmental delay, or obesity. Moreover, there was no evidence of active infection or history of drug use within the past month. The parents of the patients and controls gave their informed consent for study participation.

This study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki (Protocol Number: 80558721/G-66; date of approval by the ethics committee: 03.13.2017).

2.2. Laboratory data

Peripheral venous blood samples were obtained in the morning after an overnight fast. Serum hemoglobin, C-reactive protein (CRP), creatinine (Cr), blood urea nitrogen (BUN), albumin, uric acid, phosphorus, and parathyroid hormone (PTH) levels were determined using blood specimens of the patients and controls. All patients were toilet-trained. Thus, the GFR and urinary protein levels were measured in 24-h urine samples collected in urine containers. Renal clearance of endogenous creatinine (CrCs) was calculated using the formula CrCs = UCr × V × 1.73/sCr × t × body surface area (BSA) (UCr = urine creatinine excretion, V = volume of urine over a given time period, t = period of urine collection [24 h or 1440 min]). Proteinuria was defined as urinary protein excretion of >4 mg/m^2 per hour (20). Office blood pressure values were measured by manual auscultation using a mercury sphygmomanometer by trained personnel.

The tubes of venous blood samples were centrifuged at 2000 × *g* (10 min) to remove the plasma and serum. Supernatants were then frozen at –80 °C until further use. Serum vasohibin-1 levels and sST2 were measured using a commercial enzyme-linked immunosorbent assay kit (ELISA) (Sunred, D2E201125231/201704 and eBioscience, BMS2048/144719020, respectively). As a heterogeneous assay, ELISA separates some components of the analytical reaction mixture by adsorbing certain components onto a solid phase that is physically immobilized. Absorbance readings of microplates and calculations were performed using VICTOR X3 (PerkinElmer, Waltham, MA, USA). The results are expressed in terms of pg/mL and ng/mL, respectively.

2.3. Ambulatory blood pressure monitoring

Ambulatory blood pressure (BP) monitoring (ABPM) was performed over 24 h using the Scanlight II/III long-term blood pressure monitoring system. Blood pressure was measured every 20 min during daytime (0800–2200

hours) and every 30 min during nighttime (2200–0800 hours). Hypertension was defined as an average systolic BP (SBP) and/or diastolic BP (DBP) above the 95th percentile according to sex, age, and height (21). Nondipping status was defined as lower than 10% reduction in nocturnal average systolic and/or diastolic BP.

2.4. Statistical analyses

Statistical analyses were performed using SPSS 11.0 (SPSS Inc., Chicago, IL, USA). Values are expressed as mean ± standard deviation (SD) for continuous variables and as median and interquartile range (IQR) for qualitative variables. The Shapiro–Wilk test was used to determine the normality of data. Means were compared using independent sample t-tests for normally distributed data. The comparison of nonnormally distributed data was performed using the Mann–Whitney U test. Correlations between variables were evaluated using Pearson's or Spearman's test, as appropriate. $P < 0.05$ was considered statistically significant. Qualitative variables were compared using the chi-square test.

3. Results

Forty-seven patients and 20 healthy children were included in this study. The mean age of the patients was 11.5 ± 4.78 years (range: 4–17 years). Demographic data and hemoglobin, CRP, creatinine, BUN, albumin, uric acid, phosphorus, and PTH levels of the patient and control groups are shown in Table 1. There were no differences between the groups in terms of age and sex. Serum albumin levels were lower in the patients than in controls. Albumin levels were negatively correlated with PTH. Serum albumin and hemoglobin were positively correlated with GFR. Hemoglobin and serum phosphate levels of the two groups were similar (Table 1).

Serum sST2 levels were higher in the CKD patients than in controls ($P = 0.013$). The serum sST2 levels were not significantly correlated with age, GFR, creatinine, or 24-h urine protein ($P = 0.446$, $P = 0.143$, $P = 0.828$, $P = 0.143$, respectively). Serum vasohibin-1 levels of the patients and controls were similar ($P = 0.242$, Table 1). A positive correlation was found between the serum vasohibin-1 levels and 24-h urine protein values ($P = 0.036$). Serum vasohibin-1 levels were higher in patients with proteinuria than in nonproteinuric patients (2574.5 ± 701.60 vs. 1822.4 ± 300.32 pg/mL, $P = 0.001$). However, there was no correlation between the serum vasohibin-1 levels and age, GFR, albumin, hemoglobin, or PTH levels ($P = 0.901$, $P = 0.714$, $P = 0.551$, $P = 0.662$, $P = 0.332$, respectively). Serum sST2 and vasohibin-1 levels of the female and male subjects were comparable ($P = 0.365$). In addition, the serum sST2

Table 1. The laboratory data of the patients and control group.

	Patients (n = 47)	Control group (n = 20)	P
Age (years)	11.6 ± 4.71	11.7 ± 3.25	0.925
Female (n, %)	12 (25.5)	10 (50)	0.353
Body mass index (kg/m^2)	17.7 ± 2.81	18.2 ± 3.64	0.703
Hemoglobin (g/dL)	11.8 ± 2.27	12.8 ± 0.75	0.069
C-reactive protein (mg/dL)	0.34 (0.32–0.72)	0.32 (0.31–0.34)	0.009
Creatinine (mg/dL)	2.3 ± 1.56	0.5 ± 0.07	0.000
Albumin (g/dL)	4.2 ± 0.66	4.7 ± 0.44	0.009
Uric acid (mg/dL)	5.2 ± 0.90	3.9 ± 0.93	0.000
Phosphorus (mg/dL)	4.4 ± 0.80	4.4 ± 0.62	0.77
Bicarbonate (mmol/L)	21.6 ± 3.49	-	-
25-OH vitamin D (ng/mL)	21.6 ± 9.26	-	-
PTH (pg/mL)	99.7 (68.64–203.55)	43 (34–54)	0.000
Vasohibin-1 (pg/mL)	2168.5 ± 630.80	2636.5 ± 1083.86	0.24
Soluble ST2 (ng/mL)	6.4 ± 1.25	5.5 ± 1.24	0.013
Glomerular filtration rate (mL min^{-1} 1.73 m^{-2})	37.5 (25.52–63.52)	150 (128–177.07)	0.00
24-h urine protein (mg m^{-2} h^{-1})	19 (4–30)	-	-

Values are expressed as mean ± SD or median (interquartile range). PTH: Parathyroid hormone, ST2: suppression of tumorigenicity-2. $P < 0.05$ was considered significant.

and vasohibin-1 levels were compared between different age groups (range 4–11 years [n = 21] and range 12–18 years [n = 26]). Serum sST2 and vasohibin-1 levels of the two age groups did not differ significantly (P = 0.078, P = 0.418, respectively). The patients had higher CRP levels than the controls (P = 0.009, Table 1). However, we did not observe significant correlations between the CRP levels and serum sST2 or vasohibin-1 levels (P = 0.138, P = 0.956, respectively). Office SBP and DBP were not significantly correlated with the serum vasohibin-1 levels (P = 0.827, P = 0.224, respectively).

The office and ABPM measurements of the patients are shown in Table 2. Nineteen (40.4%) patients had hypertension. The average nighttime DBP as well as the average office systolic and diastolic BP values were significantly higher in patients than in the healthy controls (P = 0.003, P = 0.001, P = 0.000, respectively, Table 2). Serum sST2 levels were higher in patients with hypertension (P = 0.015, Table 3). However, there was no correlation between the serum sST2 levels and ABPM values as well as office BP measurements (data not shown, P > 0.05).

The laboratory data of patients with stage 2, 3, and 4 CKD are shown in Table 4. Serum albumin levels and hemoglobin concentrations were significantly lower in the advanced CKD stages. The patients with advanced stages of CKD had significantly higher serum PTH levels. However, there were no statistically significant differences in the serum vasohibin-1 and sST2 levels between the three stages of CKD (P > 0.05).

4. Discussion

In this study, we investigated the serum vasohibin-1 and sST2 levels in children with predialysis CKD. Our study results showed that children with predialysis CKD had significantly higher serum sST2 levels than healthy controls, although the sST2 levels were not correlated with serum creatinine or GFR. Furthermore, sST2 levels were higher in patients with hypertension. Serum vasohibin-1 levels were higher in patients with proteinuria. There was a positive correlation between serum vasohibin-1 levels and urine protein values.

Albumin, the major plasma protein, is produced only in the liver. Serum albumin levels are reduced in liver disease, malnutrition, and kidney diseases with urinary loss of protein. Hypoalbuminemia is one of the most common findings of CKD (22,23). Systemic inflammation contributes to the decrease in serum albumin levels in CKD (24). In our study, the serum albumin levels were lower in patients than in controls. Moreover, there were significant differences among the CKD stages. The lower serum albumin levels might be a result of the combined effects of inflammation and inadequate protein and caloric intake in CKD patients. However, we did not evaluate nutritional status in our study. Thus, further detailed studies are required to confirm the relationship between serum albumin levels and inflammatory or nutritional status.

The IL-33/ST2 axis plays an important role in chronic inflammatory disorders. sST2 inhibits the recruitment of bone marrow-derived fibroblasts, and suppresses the infiltration of inflammatory cells in the kidney by inhibiting IL-33 (12). Increased serum sST2 levels have been observed in immune disorders, such as systemic lupus erythematosus, rheumatoid arthritis, and sepsis (25–27). The literature contains conflicting reports on the relationship between sST2 levels and renal function. Mok

Table 2. Values of ambulatory blood pressure monitoring of the patients.

	Patients (n = 47)	Control group (n = 20)	P
DBP (mmHg)	76.2 ± 10.99	62.4 ± 7.14	0.000
SBP (mmHg)	116.8 ± 11.24	106.1 ± 8.26	0.001
Daytime SBP (mmHg)	112.8 ± 13.44	108 ± 5.28	0.113
Daytime DBP (mmHg)	71.4 ± 14.25	64.9 ± 5.09	0.250
Nighttime SBP (mmHg)	102.8 ± 17.01	99 ± 5.19	0.069
Nighttime DBP (mmHg)	66.4 ± 16.06	54.7 ± 3.74	0.003
Daytime SBP load (%)	15.4 (0–31.75)	0 (0–0)	0.000
Daytime DBP load (%)	10 (0–52.5)	0 (0–0)	0.000
Nighttime SBP load (%)	5.5 (0–46.25)	0 (0–6)	0.046
Nighttime DBP load (%)	0 (0–56.5)	0 (0–5)	0.065

Data are shown as mean ± SD or median (interquartile range). SBP: Systolic blood pressure, DBP: diastolic blood pressure. P < 0.05 was considered significant.

Tale 3. Laboratory data of patients with and without hypertension.

	Hypertension (+) (n = 19)	Hypertension (-) (n = 28)	P
Hemoglobin (g/dL)	11.6 ± 2.47	12 ± 2.10	0.610
C-reactive protein (mg/dL)	0.36 (0.34–0.73)	0.34 (0.34–0.54)	0.277
Albumin (g/dL)	4 ± 0.80	4.4 ± 0.52	0.141
Phosphorus (mg/dL)	4.3 ± 0.90	4.4 ± 0.74	0.750
Uric acid (mg/dL)	5.4 ± 0.65	4.9 ± 1.11	0.150
PTH (pg/mL)	170.1 (68.1–204)	88.6 (66.7–141)	0.420
Vasohibin-1 (pg/mL)	1833.5 (1781.7–2609.2)	2014.6 (1685.1–511.3)	0.861
sST2 (ng/mL)	7.03 ± 0.76	5.86 ± 1.33	0.015
GFR (mL min^{-1} 1.73 m^{-2})	37.9 ± 19.5	54.7 ± 24.28	0.071
24-h urine protein (mg m^{-2} h^{-1})	25 (4–35)	11.5 (3.85–26.5)	0.318

Data are shown as mean ± SD or median (interquartile range). PTH: Parathyroid hormone, SST2: soluble suppression of tumorigenicity-2, GFR: glomerular filtration rate. $P < 0.05$ was considered significant.

et al. (27) reported that sST2 levels were higher in patients with systemic lupus erythematosus and were positively correlated with disease activity and severity. However, increased serum sST2 level was not a good predictor of active lupus nephritis. Bao et al. (28) showed that patients aged >18 years with nondialysis CKD had higher sST2 levels. There was a significant correlation between serum sST2 level and disease severity. Dieplinger et al. showed that serum sST2 levels were similar in patients with renal failure and in healthy individuals (29). ST2 is an important biomarker reflecting mechanical stress in cardiovascular disease. The ST2/IL-33 axis may play a role in the development of hypertension owing to its effects on the immune system and inflammation. ST2 expression is increased by cardiomyocytes in response to mechanical stretch (30). Coglianese et al. (31) reported that sST2 was associated with BP values. Bartunek et al. (32) showed a strong relationship between sST2 and diastolic load in healthy subjects. They reported that ST2 was produced in the myocardium and the endothelial cells. Harrison et al. (33) suggested that sST2 was helpful in the early detection of SBP changes in the population. To our knowledge, this is the first study to show elevated levels of serum sST2 in children with predialysis CKD. In our study, the serum ST2 levels were not significantly correlated with serum creatinine and estimated GFR in patients. The decreased renal function alone cannot explain the increased sST2 levels in our CKD patients. However, children with hypertension had significantly higher sST2 levels. The elevated mechanical stretch by hypertension may have led to the increased sST2 levels. Thus, our results may suggest that serum sST2 is a preferable biomarker for hypertension in children with predialysis CKD. The diagnostic value of the serum sST2 level for hypertension may be related to its independence from renal function.

The renoprotective effects of ACEI treatment have been known for a long time. ACEI treatment delays the progression of CKD by regulating BP and controlling the glomerular hydraulic pressure with the ultrafiltration of proteins (34,35). In addition, the negative effects on the production of proinflammatory cytokines, immune cells infiltration, and extracellular matrix expansion of ACEI treatment contribute to renoprotection (36). Although serum sST2 levels were higher in patients with hypertension, we could not demonstrate a significant correlation between the serum sST2 levels and ABPM values in this study. Seventeen patients were receiving ACEI treatment at the time of the study. The lack of correlation between the sST2 levels and ABPM values or renal function might be related to the ACEI treatment owing to the above-mentioned mechanisms.

In recent years, it has been reported that disorders in angiogenesis contributed to CKD progression (37). Vasohibin-1, an endogenous angiogenesis inhibitor, plays an important role in the maintenance of endothelial cells. Several studies have reported that vasohibin-1 plays a protective role against CKD progression. Saito et al. (38) showed a therapeutic efficacy of vasohibin-1 by the inhibition of chemokine and a direct protective effect on glomerular podocytes in diabetic nephropathy. Hinamoto et al. (39) reported the expression of vasohibin-1 in the glomeruli and interstitial inflammatory cells in CKD patients. Another study showed that vasohibin-1 had a protective role against renal inflammation and fibrosis

Table 4. Laboratory data of patients with stage 2, 3, and 4 chronic kidney disease.

	Stage 4 CKD (n = 16)	Stage 3 CKD (n = 19)	Stage 2 CKD (n = 12)	P
Hemoglobin (g/dL)	9.8 ± 1.25	11.7 ± 1.68	13.5 ± 1.93	P1 = 0.017 P2 = 0.017 P3 = 0.000
C-reactive protein (mg/dL)	0.53 (0.34–1.57)	0.34 (0.34–0.36)	0.34 (0.34–0.72)	P1 = 0.234 P2 = 0.463 P3 = 0.574
Albumin (g/dL)	3.7 ± 0.73	4.3± 0.43	4.7 ± 0.45	P1 = 0.042 P2 = 0.040 P3 = 0.003
Phosphorus (mg/dL)	4.8 ± 0.93	4.3 ± 0.74	4.1 ± 0.58	P1 = 0.213 P2 = 0.466 P3 = 0.057
Creatinine (mg/dL)	4 ± 1.34	1.8 ± 1.25	1.2 ± 0.31	P1 = 0.002 P2 = 0.165 P3 = 0.000
PTH (pg/mL)	334.8 ± 162	94.8 ± 47.2	79.1 ± 24.21	P1 = 0.000 P2 = 0.000 P3 = 0.000
Vasohibin-1 (pg/mL)	2114 ± 494.82	2306.5 ± 744.05	2241.5 ± 781.18	P1 = 0.540 P2 = 0.540 P3 = 0.920
Soluble ST2 (ng/mL)	6.49 ± 1.56	6.5 ± 0.99	5.6 ± 1.39	P1 = 0.721 P2 = 0.982 P3 = 0.284
GFR (mL min^{-1} 1.73 m^{-2})	20.9 ± 4.52	41.8 ± 9.18	73.5 ± 9.74	P1 = 0.000 P2 = 0.000 P3 = 0.000
24-h protein (mg m^{-2} h^{-1})	25.5 (7.75–35.75)	12 (3.62–24.25)	4 (3.25–23.5)	P1 = 0.101 P2 = 0.696 P3 = 0.074

Data are shown as mean ± SD or median (interquartile range). CKD: Chronic kidney disease, PTH: parathyroid hormone, ST2: suppression of tumorigenicity-2, GFR: glomerular filtration rate. $P < 0.05$ was considered significant. P1: Between stage 4 and 3 of CKD, P2: between stage 3 and 2 of CKD, P3: between stage 4 and 2 of CKD.

in unilateral ureteral obstruction (40). Nasu et al. (15) demonstrated that vasohibin-1 led to antifibrotic and antiinflammatory changes in the glomerular endothelial and mesangial cells. They reported that serum vasohibin-1 was negatively correlated with age and systolic or diastolic BP in patients with renal disorders. Another trial reported an association between elevated urinary and plasma levels of vasohibin-1 and progressive decline of renal function. The patients with elevated serum vasohibin-1 levels had significantly higher GFR compared to the group with lower serum vasohibin-1 levels (41). To our knowledge, there are no studies of plasma vasohibin-1 levels in children with CKD. In this study, serum vasohibin-1 levels were similar between the patients and controls. Moreover, serum vasohibin-1 levels were not significantly correlated with renal function. However, there was a statistically significant correlation between serum vasohibin-1 levels and urine protein values. This finding suggests that serum vasohibin may be related to the compensatory response to proteinuria in patients with predialysis CKD. However, we only measured the serum vasohibin-1 levels. Urine vasohibin-1 level may be a better indicator of renal expression than the serum concentration. The determination of the origin of circulating vasohibin-1 may be more helpful in understanding the mechanisms of action on the kidneys in CKD patients. If patients with

stage 1 and 5 CKD had been included in this study, further detailed results might have been obtained with respect to the relationship between serum vasohibin-1 levels and renal function.

It has been reported that active vitamin D and its analogues exert a renoprotective role by the inhibition of the intrarenal renin-angiotensin system (RAS) as well as antiinflammatory and antifibrotic effects on the kidney tissue. Vitamin D supplementation reduces albuminuria in CKD (42, 43). Some patients included in this cross-sectional study were receiving ACEI or active vitamin D treatments. Antiinflammatory and antifibrotic properties of treatment with ACEI or vitamin D may be a possible factor explaining the lack of correlation between renal function and serum vasohibin-1 with sST2 levels.

There are certain limitations of our study. Our study is a cross-sectional study with a small sample size. We did not measure the urine levels of vasohibin-1 and sST2. Therefore, we could not determine the relationship between urine and serum levels.

In conclusion, our results showed that serum vasohibin-1 and sST2 levels were not associated with the decline in renal function in patients with predialysis CKD. The measurement of serum sST2 levels might contribute to the early detection of hypertension in patients. Vasohibin-1 appears to play a role in the pathogenesis of proteinuria that leads to CKD progression. Larger prospective studies are needed to confirm the clinical relevance of serum vasohibin-1 and sST2 levels in children with predialysis CKD.

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