Original Article

The serum sclerostin level is positively associated with the aortic augmentation index in patients on peritoneal dialysis

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Abstract

Objective: Sclerostin is a canonical Wingless (Wnt)/β-catenin signaling pathway inhibitor and had been associated with high arterial stiffness in patients with chronic kidney disease. The aortic augmentation index (AIx), a noninvasive method of assessing central hemodynamics/wave reflections, has been widely used as a clinical index of arterial stiffness. The aim of this study was to evaluate the relationship between fasting serum sclerostin levels and AIx values in peritoneal dialysis (PD) patients. **Materials and Methods:** Fasting blood samples were obtained from 75 PD patients. The aortic AIx value was measured using a validated tonometry system (SphygmoCor, AtCor Medical, Sydney, New South Wales, Australia). Serum sclerostin and dickkopf-1 (DKK1) levels were quantified using commercial enzyme-linked immunosorbent assay kits. **Results:** Women PD patients had higher aortic AIx values than men ($P = 0.039$), while lower aortic AIx values were found in PD patients who used statins ($P = 0.004$). Univariate linear analysis of the aortic AIx values in PD patients showed that systolic blood pressure ($P = 0.001$), diastolic blood pressure ($P = 0.018$), and serum sclerostin levels ($P = 0.001$) were positively correlated, while height ($P = 0.018$), body weight ($P = 0.001$), body mass index ($P = 0.043$), and weekly total creatinine clearance ($P = 0.015$) were negatively correlated with aortic AIx values in PD patients. Multivariate linear regression analysis of the factors significantly associated with the aortic AIx values showed that serum sclerostin levels (adjusted $R^2 = 0.057$, $P = 0.011$) and systolic blood pressure (adjusted $R^2 = 0.125$, $P = 0.004$) were positively associated, while body weight (adjusted $R^2 = 0.113$, $P = 0.002$) was inversely associated with aortic AIx values in PD patients. **Conclusion:** In this study, the serum sclerostin level, but not DKK1, was positively associated with aortic AIx values in PD patients.

Keywords: *Aortic augmentation index, Dickkopf-1, Peritoneal dialysis, Sclerostin*

Introduction

Cardiovascular disease remains the leading cause of mortality in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) [1,2]. Cardiovascular risk factors in CKD include underlying diseases (such as hypertension, diabetes, and dyslipidemia), toxins, anemia, and an increased load of calcium and likely reflect the presence of traditional risk factors [2]. CKD with coexisting cardiovascular disease also has worse outcomes than those without it [3,4]. Long-term variability in blood pressure is associated with cardiovascular and mortality outcomes [5]. The aortic augmentation index (AIx) is the difference between the early and late pressure peaks divided by the pulse pressure, reflecting the increase in the afterload for the heart to eject blood [6,7]. Aortic AIx values have been shown to reflect arterial stiffness and cardiovascular disease [8], and therefore, measures of aortic AIx values may estimate cardiovascular risks in ESRD patients [9,10].

The prevalence of vascular calcification is very high in CKD patients, with calcium deposition in vascular layers [11]. The canonical Wingless (Wnt) pathway is responsible for calcium regulation and plays a role in the pathogenesis of vascular calcification [12]. Sclerostin and dickkopf-1 (DKK1) are Wnt pathway signaling antagonists [13,14]. This study sought to investigate the association between sclerostin and DKK1 levels and aortic AIx values in peritoneal dialysis (PD) patients.

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MATERIALS AND METHODS

Patients

PD patients who underwent regular PD for more than 3 months were recruited from Hualien and Dalin Tzu Chi Hospitals from June 2015 to October 2016. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Protection of Human Subjects Institutional Review Board of Tzu Chi University and Hospital (IRB103-136-A). All patients provided informed consents before participating in this study. Patients were excluded if they had an acute infection, malignancy, acute myocardial infarction, pulmonary edema, or heart failure at the time of blood sampling or if they refused to sign the informed consent. Finally, 75 patients were enrolled in the study for data collection and analysis. Among the patients, 55 received continuous ambulatory PD (Dianeal, Baxter Health Care, Taiwan), with 3–5 dialysate exchanges per day while the other 20 PD patients underwent 3–5 dialysate exchanges each night with an automated device (automated PD). PD patients collected dialysate for 24 h at home, and a serum creatinine value was obtained the following morning to calculate the dialysate (peritoneal) creatinine clearance (Clcr). Urine, if present, was also simultaneously collected to determine the residual renal Clcr. The total of the weekly residual renal Clcr and weekly dialysate Clcr was the weekly total Clcr, which was used in this analysis. The weekly fractional clearance index for urea (weekly Kt/V), weekly peritoneal fractional clearance index for urea (peritoneal Kt/V), weekly renal fractional clearance index for urea (renal Kt/V), weekly total Clcr, weekly dialysate (peritoneal) Clcr, weekly renal Clcr, and residual renal Clcr were provided from the medical records.

Anthropometric analysis

All anthropometric factors were measured during the morning, after overnight fasting, without dialysate in the abdominal cavity. Body weight was measured in light clothing and without shoes to the nearest 0.5 kg; height was measured to the nearest 0.5 cm. Body mass index (BMI) was calculated as the weight (kg) divided by the height squared (m^2) [15,16].

Biochemical investigations

Fasting blood samples of approximately 5 mL were taken in the morning, before PD dialysate exchange, and were immediately centrifuged at 3000 ×*g* for 10 min. Serum levels of albumin, blood urea nitrogen, creatinine, fasting glucose, total cholesterol, triglycerides (TGs), total calcium, and phosphorus were measured using an autoanalyzer (Siemens Advia 1800, Siemens Healthcare GmbH, Henkestr, Germany). Serum sclerostin and DKK1 levels (Biomedica immunoassays, Vienna, Austria) and intact parathyroid hormone (iPTH) (Diagnostic Systems Laboratories, Webster, Texas, USA) concentrations were quantified using commercially enzyme-linked immunosorbent assays [17].

Pulse wave analysis and aortic augmentation index assessment

Patients were positioned supine and allowed to rest for at least 10 min before the test in the morning without dialysate in the abdominal cavity. Pulse wave analysis was performed using applanation tonometry on the right radial artery and analyzed by SphygmoCor software (SphygmoCor system, AtCor Medical, Sydney, New South Wales, Australia) [18]. SphygmoCor software was applied for the pulse wave analyses by the calculation of a number of major indices including the aortic AIx. The aortic AIx is a measure of the degree to which the peak of a measured pressure wave is over and above the peak of the incident pressure wave due to the addition of the reflected pressure wave. The aortic AIx was expressed as the augmentation pressure (aortic systolic pressure minus the inflection pressure) divided by the pulse pressure, expressed as a percentage and corrected to a heart rate of 75 bpm using a regression to the population heart rate dependency of the AIx by the SphygmoCor software [7].

Statistical analysis

Data were tested for normal distribution using the Kolmogorov–Smirnov test. Data were expressed as means ± standard deviation for normally distributed data and comparisons between patients were performed using Student's independent *t*-test (two-tailed). Data were expressed as medians and interquartile ranges for nonnormally distributed patterns. The serum glucose, TG, iPTH, residual renal Clcr, weekly renal Kt/V, and weekly renal Clcr datasets showed skewed nonnormal distributions and therefore were recalculated by transformation to the base 10 logarithm; after transformation, the log-glucose, log-TG log-iPTH, residual renal Clcr, weekly renal Kt/V, and weekly renal Clcr were then normally distributed. Univariate linear regression analysis was first applied to the clinical variables that correlated with the aortic AIx values in PD patients. The variables that were significantly associated with the aortic AIx were then evaluated for independence by multivariate forward stepwise regression analysis. All data were analyzed using SPSS for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

RESULTS

The anthropometric and biochemical data of all PD participants are shown in Table 1. The mean age of the 75 PD patients was 56.6 years and they had received PD for 51.3 months. The mean aortic AIx value was 24.8% and the mean serum sclerostin and DKK1 levels were 4234.2 pmol/L and 326.1 pmol/L, respectively.

The associations between comorbidity, PD model, and drugs used and the aortic AIx values are shown in Table 2. The prevalence of diabetes and hypertension was 45.3% ($n = 34$) and 88.0% ($n = 66$), respectively. Forty-two (56.0%) of these patients were women and they had higher aortic AIx values than the men PD patients ($P = 0.039$). No significant differences were observed in the aortic AIx based on diabetes, hypertension, PD model, or usage of angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, β-blockers, calcium-channel blockers, and fibrates except for statins. The 20 (26.7%) PD patients who used statins had significantly lower aortic AIx values than those who did not ($P = 0.004$).

Univariate linear regression analysis of the aortic AIx values for the 75 PD patients is shown in Table 3. Systolic blood pressure ($r = 0.370$, $P = 0.001$), diastolic blood pressure ($r = 0.272$,

Table 1: Clinical and analytical characteristics of 75 peripheral dialysis patients

Items	Parameter		Parameter	
Anthropometric data	Age (years)	56.63±14.95	Height (cm)	160.36±8.32
	Body weight (kg)	64.01±14.45	Body mass index (kg/m^2)	24.96±4.37
	Augmentation index (%)	24.79±11.24	PD vintage (months)	51.29±41.94
	SBP (mmHg)	143.80±23.98	DBP (mmHg)	84.93±13.03
Biochemical data	Albumin (g/dL)	3.72±0.37	Total cholesterol (mg/dL)	168.69±39.166
	Triglycerides (mg/dL)	150.00 (96.00-231.00)	Fasting glucose (mg/dL)	106.00 (96.00-130.00)
	BUN (mg/dL)	58.71±18.61	Creatinine (mg/dL)	10.91±3.08
	Total Calcium (mg/dL)	9.09±0.78	Phosphorus (mg/dL)	5.22±1.45
	iPTH (pg/mL)	238.50 (120.20-510.00)	Sclerostin (pg/mL)	4234.20±1874.87
	Dickkopf-1 (pg/mL)	326.11±215.82	Residual renal Clcr (mL/min)	1.72 (0–5.50)
	Weekly Kt/V	2.10±0.41	Weekly peritoneal Kt/V	1.78±0.44
	Weekly renal Kt/V	0.10 (0-0.65)	Weekly total Clcr (L/week)	59.68±23.89
	Weekly renal Clcr (L/week)	6.64 (0-22.89)	Weekly peritoneal Clcr (L/week)	42.73±15.84

Values for continuous variables given as means±SD and variables not normally distributed given as medians and interquartile range. PD: Peritoneal dialysis, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BUN: Blood urea nitrogen, iPTH: Intact parathyroid hormone, Clcr: Creatinine clearance, Kt/V: Fractional clearance index for urea, SD: Standard deviation

Table 2: Clinical characteristics and aortic augmentation index levels of the 75 peripheral dialysis patients

Characteristic	n (%)	Augmentation index	P
Gender			
Male	33 (44.0)	21.76±12.07	0.039*
Female	42 (56.0)	27.17±10.25	
Diabetes			
No	41 (54.7)	26.56±10.66	0.138
Yes	34 (45.3)	22.65±11.90	
Hypertension			
No	9 (12.0)	20.56±10.08	0.235
Yes	66 (88.0)	25.36±11.44	
PD model			
CAPD	55 (73.3)	24.16±10.72	0.434
APD	20 (26.7)	26.50±13.02	
Smoking			
No	65 (86.7)	25.23±11.20	0.391
Yes	10 (13.3)	21.90±12.43	
ACE inhibitor use			
No	71 (94.7)	24.85±11.24	0.852
Yes	4 (5.3)	23.75±14.77	
ARB use			
No	43 (57.3)	25.37±12.36	0.607
Yes	32 (42.7)	24.00±9.92	
β-blocker use			
No	48 (64.0)	26.13±11.80	0.174
Yes	27 (36.0)	22.41±10.24	
CCB use			
No	39 (52.0)	24.69±12.90	0.941
Yes	36 (48.0)	24.89±9.54	
Statin use			
No	55 (73.3)	27.04±11.04	0.004*
Yes	20 (26.7)	18.60±9.97	
Fibrate use			
No	72 (96.0)	24.64±11.37	0.584
Yes	3 (4.0)	28.33±11.93	

*$P<0.05$ was considered statistically significant after Student's independent t-test. Data are expressed as means±SD. PD: Peritoneal dialysis, CAPD: Continuous ambulatory peritoneal dialysis, APD: Automated peritoneal dialysis, ACE: Angiotensin-converting enzyme, ARB: Angiotensin-receptor blocker, CCB: Calcium-channel blocker, SD: Standard deviation

$P = 0.018$), and serum sclerostin levels ($r = 0.363$, $P = 0.001$) were positively correlated, while height ($r = -0.272$, $P = 0.018$), body weight ($r = -0.370$, $P = 0.001$), BMI ($r = -0.235$, $P = 0.043$), and weekly total Clcr ($r = -0.279$, $P = 0.015$) were negatively correlated with the aortic AIx values in PD patients.

The variables that were significantly associated with the aortic AIx values (gender, statin use, height, body weight, BMI, systolic blood pressure, diastolic blood pressure, weekly total Clcr, and sclerostin) were analyzed by forward stepwise linear regression. Serum sclerostin (β =0.263, adjusted R^2 = 0.057, $P = 0.011$), systolic blood pressure (β =0.294, adjusted R^2 = 0.125, $P = 0.004$), and body height (β = −0.323, adjusted R^2 = 0.113, $P = 0.002$) were independent factors that were associated with the aortic AIx in PD patients [Table 4].

DISCUSSION

The results showed that systolic blood pressure and serum sclerostin levels were positively correlated, while body weight was negatively correlated with the aortic AIx values in PD patients. The DKK1 level was not found to be correlated with aortic AIx values in PD patients.

Many studies have reported that women have higher systolic pressure augmentation than males of the same age and that may help explain the greater degree of age-related increase in left ventricular mass and symptomatic heart failure in women than men [19-21]. A meta-analysis of clinical trials reported that statin therapy reduced aortic AIx values [22]. In our study, women had higher aortic AIx values than men, while lower aortic AIx values were found in PD patients taking statins.

Short height is an important risk factor for elevated radial AIx values in patients with never-treated hypertension [20]. Changes in aortic AIx values were highly associated with changes in height from the ages of 8–14 years [21]. The aortic AIx value was inversely associated with BMI in a cross-sectional study of 393 consecutive patients with suspected stable coronary artery disease who underwent coronary angiography [23]. The aortic AIx value was associated with low body

Table 3: Correlation of aortic augmentation index levels and clinical variables by univariate linear regression analysis among the 75 peripheral dialysis patients

Variable	R	P
Age (years)	0.056	0.633
Peritoneal dialysis vintage (months)	0.152	0.193
Height (cm)	−0.272	0.018*
Body weight (kg)	−0.370	0.001*
Body mass index (kg/m²)	−0.235	0.043*
SBP (mmHg)	0.370	0.001*
Diastolic blood pressure (mmHg)	0.272	0.018*
Albumin (g/dL)	−0.112	0.341
Total cholesterol (mg/dL)	−0.073	0.533
Log-triglycerides (mg/dL)	−0.051	0.665
Log-glucose (mg/dL)	−0.110	0.348
Blood urea nitrogen (mg/dL)	−0.005	0.967
Creatinine (mg/dL)	−0.065	0.580
Total calcium (mg/dL)	0.015	0.899
Phosphorus (mg/dL)	−0.037	0.752
Log-Intact parathyroid hormone (pg/mL)	−0.094	0.424
Sclerostin (pg/mL)	0.363	0.001*
Dickkopf-1 (pg/mL)	−0.140	0.231
Log-residual renal Clcr (mL/min)	−0.059	0.617
Weekly Kt/V	0.084	0.474
Weekly peritoneal Kt/V	0.205	0.077
Log-Weekly renal Kt/V	−0.107	0.362
Weekly total Clcr (L/week)	−0.279	0.015*
Weekly peritoneal Clcr (L/week)	−0.030	0.800
Log-weekly renal Clcr (L/week)	−0.087	0.458

*Data for triglycerides, glucose, intact parathyroid hormone, residual renal Clcr, weekly renal Kt/V, and weekly renal Clcr levels showed skewed distributions, and therefore were log-transformed before analysis. *$P<0.05$ is considered statistically significant in univariate linear analyses. Clcr: Creatinine clearance, Kt/V: Fractional clearance index for urea, SBP: Systolic blood pressure

Table 4: Multivariate stepwise linear regression analysis of factors significantly associated with the aortic AIx values in univariate analysis and correlation to aortic augmentation index levels among 75 peripheral dialysis patients

Items	β	Adjusted R^2	Adjusted R^2 change	P
SBP (mmHg)	0.294	0.125	0.125	0.004*
Body weight (kg)	−0.323	0.238	0.113	0.002*
Sclerostin (pg/mL)	0.263	0.295	0.057	0.011*

*$P<0.05$ is considered statistically significant in multivariate stepwise linear regression analysis. SBP: Systolic blood pressure

weight in patients younger than 60 years in a cross-sectional study from the Copenhagen City Heart Study [24]. Aortic stiffness raises the systolic blood pressure, placing a systolic burden on the heart, while the accompanying reduced diastolic blood pressure may limit the required increase in coronary blood flow [25]. The aortic AIx value was positively associated with systolic blood pressure and diastolic blood pressure in 3432 patients from the Copenhagen City Heart Study [24]. Our results noted that systolic and diastolic blood pressure was positively correlated whereas height, body weight, and BMI were negatively correlated with the aortic AIx values in PD patients. After adjusting the significant variables by forward

stepwise linear regression, systolic blood pressure and body height were also associated with the aortic AIx values in these patients. Decline of residual renal function was positively associated with mortality in PD patients [26]. One study noted that residual renal function, but not the results on a peritoneal function test, was associated with peripheral arterial stiffness as determined by brachial-ankle pulse wave velocity in PD patients [27]. Another study also noted that residual renal function was associated with aortic arterial stiffness determined using carotid-femoral pulse wave velocity in PD patients [28]. However, our results noted that weekly total Clcr, but not residual renal function, was negatively associated with aortic AIx values in our PD patients. Further studies are required to elucidate the relationship between residual renal function, the results of peritoneal function tests, and aortic AIx values in PD patients.

Sclerostin is a 190-amino-acid glycoprotein secreted mostly by osteocytes. It decreases bone formation by inhibiting the Wnt pathway [13,14]. Recent studies have indicated that sclerostin plays a role in vascular calcification in CKD [29] and ESRD patients [30]. Sclerostin had been associated with high arterial stiffness in stage 2–5D CKD patients [31] and peripheral arterial stiffness in kidney transplantation patients [17]. A higher aortic AIx value was associated with abdominal aortic calcification in 2920 patients from the Framingham Heart Study Third Generation and Offspring Cohort [32]. In our study, the serum sclerostin level was significantly positively associated with aortic AIx values in PD patients, while the serum DKK1 level was not. After adjusting a variety of factors in forward stepwise linear regression, the serum sclerostin level was also positively associated with aortic AIx values in our PD patients.

Our study has some limitations. First, it had a cross-sectional design, and thus long-term prospective studies are needed to confirm our findings. Second, the study enrolled a limited number of participants and there was no case-matched control group, which could have resulted in selection bias. Antihypertensive drugs such as angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and calcium-channel blockers may reduce aortic AI values [33]. However, our results did not find significant differences in the aortic AIx values in patients using angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, β-blockers, or calcium-channel blockers. Yamada *et al*. noted that the serum sclerostin level was significantly associated with the iPTH level in PD patients [34]. Our study noted that the serum sclerostin level was not associated with the serum log-iPTH level ($r = 0.017$, $P = 0.883$) and the serum iPTH level was not associated with aortic AIx values in PD patients. Further studies are therefore required to elucidate the relationship between aortic AIx values and drugs or Wnt/β-catenin signaling pathway inhibitors in PD patients.

CONCLUSION

The present study showed that the serum sclerostin level was independently associated with aortic AIx values, whereas the serum DKK1 was not, in our PD patients. Furthermore, systolic blood pressure was positively correlated whereas body weight was negatively correlated with aortic AIx values in PD patients.

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Conflicts of interest

There are no conflicts of interest.

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