Tzu Chi Medical Journal 2025; 37 (2): 204-210

Original Article

Serum osteopontin level is independently associated with arterial stiffness in patients on hemodialysis

*Po-Yu Huang[a,b†], Bang-Gee Hsu[c,d†], Chih-Hsien Wang[c,d], Jen-Pi Tsai[a,d]**

[a]Division of Nephrology, Department of Internal Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi, Taiwan, [b]Institute of Medical Sciences, Tzu Chi University, Hualien, Taiwan, [c]Division of Nephrology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan, [d]School of Medicine, Tzu Chi University, Hualien, Taiwan

[†]Both authors contributed equally to this work.

Submission : 04-Mar-2024
Revision : 01-Apr-2024
Acceptance : 19-Apr-2024
Web Publication : 03-Jul-2024

Abstract

Objectives: Carotid–femoral pulse wave velocity (cfPWV) is an approach primarily adopted to define arterial stiffness (AS), which is one of the major contributors to unfavorable cardiovascular outcomes. Osteopontin (OPN), in addition to regulation of bone homeostasis, is an inflammatory mediator of atherosclerosis. We performed a research which estimated the correlation between blood OPN levels and AS in participants on maintenance hemodialysis (MHD). **Materials and Methods:** One hundred and twenty-six patients who received long-term MHD were included in the cross-sectional study. cfPWV values were calculated based on the carotid and femoral pulsation waveforms. Patients with cfPWV >10 m/s were categorized into the AS group. We utilized a commercially available enzyme-linked immunosorbent assay to check serum concentrations of OPN. **Results:** Study patients belonging to AS were found to be older, had significantly higher prevalence of underlying diabetes mellitus (DM) and hypertension, had higher systolic blood pressure, and had higher serum total calcium and OPN levels. After adjusting for these variables, multivariate logistic regression analysis disclosed that OPN levels, older age, DM, and total serum calcium levels were independently correlated with AS in patients on MHD. Multivariate analysis based on forward stepwise linear regression also showed that the logarithmically transformed OPN level was an independent correlate of cfPWV in these participants. **Conclusion:** Serum OPN concentrations had a positive correlation with cfPWV and were therefore related to AS in patients on MHD.

Keywords: *Arterial stiffness, Carotid–femoral pulse wave velocity, Hemodialysis, Osteopontin*

Introduction

Cardiovascular (CV) diseases are highly prevalent among patients with kidney failure and account for nearly half of all deaths in individuals undergoing hemodialysis treatment [1]. Arterial stiffness (AS) precedes the onset of adverse CV events and, more importantly, has a predictive role in CV mortality and all-cause mortality, particularly among patients with end-stage kidney disease (ESKD) [2-4]. An interplay of aberrant activation of the renin-angiotensin system, vascular smooth muscle cell (VSMC) migration, inflammatory milieu, oxidative stress, increased collagen deposition relative to the amount of elastin, diminished insulin sensitivity, mechanical factors, and genetic and epigenetic modifications contributes to the vascular stiffening [5,6]. Carotid–femoral pulse wave velocity (cfPWV) is primarily used for the noninvasive measurement of AS [7,8]. As reported by a systematic review and meta-analysis, cfPWV is an invaluable estimate of CV morbidities and related deaths [9].

Access this article online

Quick Response Code:

Website: www.tcmjmed.com

DOI: 10.4103/tcmj.tcmj_60_24

Osteopontin (OPN), an N-linked glycosylated protein, has a variety of physiologic and pathophysiologic roles, including regulation of bone mineralization, modulation of ectopic calcification, and pathological mineralization of the vasculature as well as in inflammation, insulin resistance, cancer, and tissue healing and remodeling [10,11]. OPN expression is upregulated at sites of acute and chronic inflammation and serves as a chemotactic factor and a proinflammatory cytokine that influences multiple immune cell types [10,12]. OPN is also a pro-atherosclerotic cytokine that causes neointimal hyperplasia, impairs the contractile function of VSMCs, induces oxidative stress, and increases

***Address for correspondence:** Dr. Jen-Pi Tsai, Division of Nephrology, Department of Internal Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, 2, Min-Sheng Road, Dalin Town, Chiayi, Taiwan.
E-mail: tsaininimd1491@gmail.com

How to cite this article: Huang PY, Hsu BG, Wang CH, Tsai JP. Serum osteopontin level is independently associated with arterial stiffness in patients on hemodialysis. Tzu Chi Med J 2025;37(2):204-10.

the vulnerability to atherosclerotic plaque instability [13,14]. In addition, OPN is associated with endothelial dysfunction, which is likely mediated by stimulation of arginase activity along with impaired nitric oxide bioavailability [15]. On the contrary, OPN acts as an inhibitor of vascular, valvular, and renal calcification, and increased OPN concentration is observed in calcified plaques [13,16]. In *OPN* gene knockout mice, high phosphate feeding led to vascular calcification [17]. The proposed mechanism of OPN-mediated regulation of ectopic calcification is that OPN binds to bioapatite and acts as a recognition site for macrophages and giant cells; therefore, carbonic anhydrase II is locally upregulated. The resultant increase in proton efflux acidifies the local environment and induces bioapatite dissolution [18].

Clinically, OPN is implicated in various CV diseases, including ischemic heart disease, cardiac dysfunction, dilated cardiomyopathy, and atherosclerotic disorders [19]. Circulating OPN levels are higher in adult and pediatric populations on maintenance hemodialysis (MHD) [20,21]. In fact, serum OPN concentrations become elevated in different stages of chronic renal insufficiency [22]. OPN molecule has also been reported to exist in the areas of peritoneal calcifications among patients receiving prolonged continuous ambulatory peritoneal dialysis [23]. Prior research has established the positive link between serum OPN levels and AS in individuals with hypertension (HTN), rheumatoid arthritis, and coronary artery disease (CAD) [24-26]. An independent association of log-OPN with cfPWV was also found in geriatric populations [27].

To sum up, AS participates in the medication of CV complications among patients suffering from kidney failure, and OPN contributes to cardiac dysfunction and vasculopathy. To the best of our knowledge, data exploring the correlation between OPN concentration and vascular stiffening in MHD populations are sparse. As a consequence, the purpose of the clinical study was to discover the association of serum OPN level with AS in patients undergoing long-term MHD.

Materials and methods

Research design and sample

This cross-sectional study underwent inspection and approval by the Research Ethics Committee, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (IRB103-136-B) on March 15, 2017. This study was conducted in accordance with the Declaration of Helsinki. From March to July in 2015, we took on judgment sampling methods to enroll 126 participants with ESKD in a single medical center in Hualian, Taiwan. A written form of informed consent was provided to each patient. Inclusion criteria were beyond 20 years of age and regular MHD (thrice weekly, using the standard concentration of bicarbonate for the dialysis solution) for 3 months or longer. During each dialysis therapy, all the dialyzers used for each participant were identical (FX class high-flux dialyzer, Fresenius Medical Care, Bad Homburg, Germany). Participants were considered to be eliminated from the clinical study providing that they had active infectious diseases, malignancy, previous amputation of upper or lower limbs, cerebrovascular accidents, peripheral arterial diseases, pulmonary congestion or edema, bed-ridden status around the period of blood draw process, and the inability to complete the informed consent.

After the participants were sitting in quiescence for 10 min, we checked the systolic blood pressures (SBPs) and diastolic blood pressures (DBPs) for three times using a mercury sphygmomanometer and choosing appropriately sized cuffs. Conditions including ongoing usage of antihypertensives for 2 weeks, a SBP exceeding or equal to 140 mm Hg, and/or a DBP exceeding or equal to 90 mm Hg fulfilled the definition of HTN. Maintenance antidiabetic therapy and/or a fasting glucose of ≥126 mg/dL made a diagnosis of diabetes mellitus (DM). For chronic medication use including classes of antihypertensives and lipid-lowering drugs, we reviewed the data from medical charts.

Anthropometric analysis

Body weights were checked prior to and directly after a dialysis session when patients wore only light clothing and stockings, with the value rounding off to the closest half-kilogram. Height was measured with patients standing erect and then quantified to the closest half-centimeter. We measured patients' waist circumferences by finding out the smallest value (finally rounded to the nearest half-centimeter when recorded) between the lower border of ribs and intercristal line. The body mass index was calculated as weight divided by height squared (kg/m^2). All the data were obtained by one trained operator.

Biochemical determinations

A specimen of 5 mL blood was drawn from each patient at the time of hemodialysis initiation when they were fasting for 8 h or longer. The fractional clearance index for urea (Kt/V) and urea reduction ratio were measured at the initiation as well as the immediately after the completion of the dialysis session using single-pool urea kinetic modeling mathematics. The specimens then underwent centrifugation at 3000 ×*g* for approximately 10 min. After the centrifugation, we separated the serum for storage at 4°C. Within 1 h after the collection of samples, the serum was tested for concentrations of total cholesterol, triglyceride (TG), glucose, blood urea nitrogen, creatinine, C-reactive protein (CRP), total calcium, and phosphate with an autoanalyzer (Siemens Advia 1800, Siemens Healthcare GmbH, Henkestr, Germany) [28-30]. Serum OPN (Thermo Fisher Scientific Inc., Wal-tham, MA, USA) and intact parathyroid hormone (iPTH) levels (Abcam, Cambridge, MA, USA) were estimated via enzyme-linked immuno-sorbent assays [28-30].

Aortic stiffness by carotid–femoral pulse wave velocity measurements

Estimation of cfPWV to was carried out using pressure applanation tonometric methods (SphygmoCor system, AtCor Medical, NSW, Australia) [28-30]. The study participants stayed in recumbency in a noiseless and air-conditioned room after a minimum of 10-minute rest. Recordings were in accordance with electrocardiography (ECG) with the reference time at R wave. Pulse wave monitoring was performed and continuously recorded over both the femoral and carotid pulsations. The carotid–femoral distance was determined by

the subtraction method, which was the difference between the distance from the carotid pulsation location to the suprasternal notch and that from the suprasternal notch to the femoral pulsation. The software then managed the pulse wave results and ECG data, so as to finalize the results of the average differential time between the R wave peaks on ECG and pulse waves of 10 consecutive heart beats. The distance divided by the mean differential time produced the results of cfPWV. Quality control contained in the software were utilized to track data uniformity. In agreement with the European Society of Hypertension and the European Society of Cardiology guidelines, AS was indicated by a cfPWV of higher than 10 m/s [31].

Statistical analysis

The continuous variables underwent the Kolmogorov–Smirnov test to determine the normality. Variables following normal distribution patterns were expressed as mean ± standard deviation, and comparisons between the two patient groups were performed with Student's independent *t*-test (two-tailed). Data without normality were represented as medians and interquartile ranges. Categorical variables were compared between the groups using the Chi-square test. Since the MHD duration, TG, glucose, iPTH, and OPN did not follow normal distribution patterns, these variables underwent base 10 logarithmic transformations. To examine the association with cfPWV, variables that were tested for independence from the results of linear correlation analysis were further assessed in multivariate stepwise regression analysis. To examine the possible predictors of AS, multivariate logistic regression analysis was adopted. The receiver operating characteristic (ROC) curve along with the area under the curve (AUC) helped to identify the optimal cutoff value of OPN for the differentiation between AS and non-AS in participants on MHD. It was considered to reach the statistical significance when a $P < 0.05$. Data analyses were processed through SPSS software for Windows (version 19.0; SPSS Inc., Chicago, IL, USA).

Results

The clinical features of the 126 individuals on MHD are shown in Table 1. Underlying chronic medical illnesses included DM (n = 56; 44.4%) and HTN (n = 61; 48.4%). Fifty-three patients on MHD (42.1%) were categorized into the AS group. The patients with AS had significantly increased

Table 1: The baseline characteristics of the chronically hemodialyzed patients with arterial stiffness (defined as carotid–femoral pulse wave velocity >10.0 m/s) and of those in the nonarterial stiffness group (carotid–femoral pulse wave velocity ≤10.0 m/s)

Characteristics	All patients (*n*=126)	Group without AS (*n*=73)	AS group (*n*=53)	*P*
Age (years)	63.06±13.21	60.93±13.97	67.28±11.22	0.007*
HD duration (months)	59.40 (23.40–123.84)	73.92 (23.10–134.76)	55.68 (23.52–95.88)	0.204
Height (cm)	159.71±8.18	159.36±8.60	160.19±7.63	0.575
Body weight (kg)	63.27±14.89	62.74±15.51	64.00±14.10	0.642
BMI (kg/m^2)	24.67±4.93	24.55±5.20	24.83±4.56	0.758
Carotid–femoral PWV (m/s)	10.16±3.40	7.87±1.41	13.30±2.77	<0.001*
SBP (mmHg)	143.56±27.30	139.41±27.24	149.28±26.58	0.045*
DBP (mmHg)	77.45±15.73	77.81±15.63	76.96±15.99	0.767
TCH (mg/dL)	145.97±34.09	147.05±38.13	144.47±27.87	0.676
TG (mg/dL)	112.00 (85.50–182.00)	106.00 (82.50–192.50)	121.00 (89.50–174.50)	0.413
Glucose (mg/dL)	131.00 (109.75–169.00)	129.00 (103.00–159.00)	135.00 (112.50–179.00)	0.106
Blood urea nitrogen (mg/dL)	61.41±15.43	60.25±14.67	63.02±16.42	0.321
Creatinine (mg/dL)	9.44±2.14	9.46±2.11	9.42±2.20	0.928
Total calcium (mg/dL)	9.02±0.79	8.90±0.75	9.19±0.82	0.044*
Phosphorus (mg/dL)	4.77±1.32	4.79±1.36	4.75±1.29	0.856
CRP (mg/dL)	0.295 (0.08–0.95)	0.32 (0.0875–0.95)	0.26 (0.08–0.95)	0.835
Intact parathyroid hormone (pg/mL)	209.35 (76.85–484.86)	258.50 (109.05–485.35)	157.60 (51.50–480.50)	0.173
OPN (pg/mL)	16.74 (11.96–22.43)	13.79 (10.98–19.99)	19.86 (13.77–41.33)	<0.001*
Urea reduction rate	0.73±0.04	0.73±0.04	0.73±0.04	0.879
Kt/V (Gotch)	1.33±0.16	1.34±0.17	1.33±0.15	0.798
Female, *n* (%)	60 (47.6)	38 (52.1)	22 (41.5)	0.242
DM, *n* (%)	56 (44.4)	23 (31.5)	33 (62.3)	0.001*
HTN, *n* (%)	61 (48.4)	29 (39.7)	32 (60.4)	0.022*
Angiotensin receptor blocker, *n* (%)	33 (26.2)	19 (26.0)	14 (26.4)	0.961
β-blocker, *n* (%)	36 (28.6)	20 (27.4)	16 (30.2)	0.732
Calcium channel blocker, *n* (%)	47 (37.3)	29 (39.7)	18 (34.0)	0.509
Statin, *n* (%)	20 (15.9)	10 (13.7)	10 (18.9)	0.433
Fibrate, *n* (%)	15 (11.9)	9 (12.3)	6 (11.3)	0.863

*P<0.05 was considered statistically significant, The results of the continuous variables are shown as means±SD and were compared between groups with Student's *t*-test, variables not fulfilling normality are shown as medians and IQRs and further compared with the Mann–Whitney *U*-test, values expressed as numbers (%) are analyzed by the Chi-square test. PWV: Pulse wave velocity, Kt/V: Fractional clearance index for urea, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, CRP: C-reactive protein, DM: Diabetes mellitus, HTN: Hypertension, TCH: Total cholesterol, TG: Triglyceride, SD: Standard deviation, IQRs: Interquartile ranges, AS: Arterial stiffness, OPN: Osteopontin, HD: Hemodialysis

odds of having DM (P = 0.001) and HTN (P = 0.022), higher SBP (P = 0.045), higher serum total calcium (P = 0.044) and OPN (P < 0.001) levels, and were more likely to be older (P = 0.007) when compared with the group without AS. These two groups did not differ significantly in sex or in the use of antihypertensives (including angiotensin receptor blockers, β-blockers, and calcium channel blockers) or lipid-lowering agents (including statins and fibrates).

After adjustment of the factors that showed significant differences between the two groups (DM, HTN, age, SBP, total calcium, and OPN level) with multivariate logistic regression analysis, the results disclosed that OPN level (odds ratio [OR], 1.095; 95% confidence interval [CI], 1.041–1.152; P < 0.001), age (OR, 1.068; 95% CI, 1.026–1.112; P = 0.001), DM (OR, 6.564; 95% CI, 2.293–18.792; P < 0.001), and total serum calcium level (OR, 2.503; 95% CI, 1.114–3.784; P = 0.021) were independently associated AS in individuals on MHD [Table 2].

Based on the results of the ROC curve analysis, the optimal cutoff of serum OPN concentration to distinguish AS from non-AS was 23.63 ng/mL with a sensitivity of 41.51% (95% CI, 28.1%–55.9%), a specificity of 90.41% (95% CI, 81.2%–96.1%), and an AUC of 0.708 (95% CI, 0.621–0.786; P < 0.001) [Figure 1].

The results of simple linear correlation and multivariate linear analyses of the parameters associated with the cfPWV values in patients on MHD are shown in Table 3. DM (r = 0.324; P < 0.001) and logarithmically transformed OPN level (log-OPN, r = 0.281; P = 0.001) were positively associated with cfPWV in accordance with the simple linear correlation analysis in patients on MHD. Multivariate forward stepwise linear regression analysis also showed that DM (β = 0.302; P < 0.001) and log-OPN level (β = 0.255; P = 0.002) were independently associated with cfPWV values in patients on MHD.

Discussion

The results demonstrate an important finding that OPN levels as well as the existence of underlying DM are independent correlates of cfPWV in patients on MHD. Furthermore, age and total serum calcium levels independently predict the presence of AS in patients on MHD.

Although the literature shows that serum OPN levels are positively linked to cfPWV and that increased OPN expression is observed in the endothelium, VSMCs, and foamy macrophages in atherosclerotic plaques [10,32], the mechanisms underlying OPN-induced atherosclerosis are not completely understood. One possible explanation is that OPN binds to the αVβ3 integrin on the surface of VSMCs, which promotes cell proliferation and migration. Besides, inflammation is central to the pathophysiology of atherosclerosis, and OPN may induce vascular inflammation and contribute to atherosclerosis and related vasculopathy [10,33,34]. OPN, which is upregulated during macrophage differentiation, plays a critical role in the migration, survival, phagocytic ability, and cytokine production of macrophages [12]. Among populations with chronic kidney disease, serum OPN concentrations were found to be closely related to the glomerular filtration rate (GFR) as well as certain biomarkers such as serum homocysteine and symmetric dimethylarginine levels [22,35]. Symmetric dimethylarginine reflects the extent of oxidative stress and acts an endogenous regulator of nitric oxide synthesis, both of which are associated with endothelial dysfunction and a propensity to atherogenesis. Serum nitric oxide levels were also noted to be inversely correlated with GFR [22].

Serum OPN levels were noted to be strongly correlated with carotid artery intima-media thickness in patients with early kidney disease [22]. The log-OPN levels in serum were significantly greater among patients with 3-vessel CAD than in those without CAD; after the adjustment of confounding factors, including severity and common risk factors of CAD, multivariate linear regression analysis revealed that the correlation between log-OPN and cfPWV was marginally significant [36]. Among patients with essential HTN, plasma OPN levels were positively correlated with the mean intima-media thickness and demonstrated a negative relationship with the ratio of mean diastolic and systolic flow velocities of the common carotid artery, which was used to

Table 2: Multivariate logistic regression analysis of the parameters associated with arterial stiffness among 126 patients on maintenance hemodialysis

Variables	OR	95% CI	*P*
OPN (pg/mL)	1.095	1.041–1.152	<0.001*
Age (year)	1.068	1.026–1.112	0.001*
Total calcium (mg/dL)	2.503	1.114–3.784	0.021*
DM (present)	6.564	2.293–18.792	<0.001*
SBP (mmHg)	0.999	0.979–1.019	0.897
HTN (present)	2.084	0.767–5.661	0.150

*P<0.05 was considered statistically significant. Data were analyzed using multivariate logistic regression analysis (adopted factors: DM, HTN, age, SBP, total calcium, and OPN). The Cox and Snell R^2 and Nagelkerke R^2 were 0.340 and 0.457, respectively. CI: Confidence interval, OR: Odds ratio, DM: Diabetes mellitus, HTN: Hypertension, SBP: Systolic blood pressure, OPN: Osteopontin

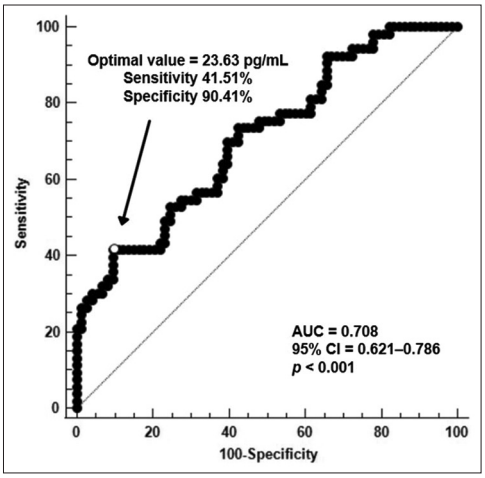

Figure 1: The area under the receiver operating characteristic curve displays the diagnostic accuracy of serum osteopontin level in the prediction of arterial stiffness among patients on hemodialysis

Table 3: Correlation between carotid–femoral pulse wave velocity and clinical parameters among 126 patients on hemodialysis

Variables	Carotid–femoral PWV (m/s)				
	Simple linear correlation		Multivariable linear regression		
	r	*P*	Beta	Adjusted R^2 change	*P*
Female	−0.130	0.146	-	-	-
DM	0.324	<0.001*	0.302	0.098	<0.001*
HTN	0.099	0.271	-	-	-
Age (years)	0.127	0.156	-	-	-
Log-HD duration (months)	−0.097	0.281	-	-	-
Height (cm)	0.113	0.206	-	-	-
Body weight (kg)	0.084	0.349	-	-	-
BMI (kg/m^2)	0.041	0.647	-	-	-
SBP (mmHg)	0.166	0.063	-	-	-
DBP (mmHg)	−0.015	0.869	-	-	-
TCH (mg/dL)	−0.028	0.756	-	-	-
Log-TG (mg/dL)	0.096	0.283	-	-	-
Log-glucose (mg/dL)	0.141	0.116	-	-	-
Blood urea nitrogen (mg/dL)	0.145	0.104	-	-	-
Creatinine (mg/dL)	0.049	0.587	-	-	-
Total calcium (mg/dL)	0.126	0.160	-	-	-
Phosphorus (mg/dL)	0.019	0.833	-	-	-
Log-iPTH (pg/mL)	−0.158	0.077	-	-	-
Log-OPN (pg/mL)	0.281	0.001*	0.255	0.058	0.002*
Urea reduction rate	0.015	0.868	-	-	-
Kt/V (Gotch)	0.007	0.936	-	-	-

*P<0.05 was considered statistically significant. The variables including HD duration, TG, glucose, iPTH, and OPN levels showed a skewed distribution and therefore were log-transformed before the analysis. Data were analyzed using the simple linear correlation or multivariate stepwise linear regression analysis (adopted factors: DM and OPN). PWV: Pulse wave velocity, HD: Hemodialysis, iPTH: Intact parathyroid hormone, Kt/V: Fractional clearance index for urea, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, DM: Diabetes mellitus, HTN: Hypertension, TCH: Total cholesterol, TG: Triglyceride, OPN: Osteopontin

estimate peripheral vascular resistance. Furthermore, plasma aldosterone levels were positively correlated with OPN levels, and aldosterone was shown to be an independent determinant of OPN levels [33]. However, in one study, despite the markedly elevated OPN levels in patients on MHD, neither the OPN nor the osteoprotegerin level was correlated with vascular stiffness parameters, as measured by cfPWV. In this study, the serum levels of osteocalcin, a matrix protein secreted primarily by osteoblasts, were associated with AS [37].

Diabetes and advancing age are also significantly associated with AS, as noted in our results. The association between AS and hyperglycemia as well as aging had been well established; the pathogenic link and previous evidence were further discussed in detail in our previous publication [38].

Total serum calcium was also shown to be an independent correlate of AS. Among the general population, serum calcium levels are positively correlated with risk of nonfatal and fatal CV disease, myocardial infarction, and stroke [39]. Dysregulated calcium and phosphate homeostasis as well as increased medial and intimal calcification occur in kidney failure [40]. In patients on HD, positive calcium balance may be attributable to the use of dialysis fluids with higher calcium concentrations and the administration calcium-containing oral phosphate binders [41]. In our study, though, the serum phosphorus or iPTH levels did not markedly differ between the AS and non-AS groups.

The present investigation did not show a significantly elevated level of CRP in the chronically hemodialyzed patients with AS. This was in contrast to the results from previous publications. A study recruiting relatively healthy adults showed that blood high-sensitivity CRP levels were inversely correlated with the elasticity of large arteries [42]. Another cross-sectional study concluded that among hypertensive patients, high-sensitivity CRP independently predicted the increased cfPWV and augmentation index, both of which were indicators of AS [43]. As mentioned above, inflammation is central to the pathogenesis of stiffening of large arteries, particularly in patients on maintenance dialysis [44]. However, based on the current investigation, we did not find the blood CRP as a correlate of AS.

This study has some limitations. First, the overall patient number was small. Second, we recruited primarily middle-aged to older patients, and therefore, the results of this study may not apply to all age groups. Third, the study's cross-sectional design increases the difficulty in defining the causal relationship between OPN and arterial stiffening. The cross-sectional design with a relatively short study period also subjects to prevalence-incidence bias. As a result, a prospective cohort study may help us better understand the utility of changes in serum OPN concentrations on clinical outcome prediction. Fourth, for DM as the variable included in the multivariate logistic regression analysis [Table 2], there was a wide range of 95% CI for the OR, which resulted in sparse data bias and inflation of OR [45]. Fifth, we did not measure certain lipid profiles acting as CV risk variables, namely low-density and high-density lipoprotein cholesterols.

Sixth, we did not explore the clinical or biological correlates of OPN in the study; thus, the exact pathways of OPN in affecting CV outcomes might not be known at the present time. Eventually, we did not concomitantly quantify the concentrations of other bone-specific biomarkers such as osteocalcin or osteoprotegerin. Incorporation of a series of novel biomarkers for CV complications to optimize the predictive value of AS and related adverse CV sequelae in patients on MHD is a critical area of future research.

Conclusions

We can conclude from this study that in patients on MHD, circulating OPN concentrations are positively correlated with AS which is measured via cfPWV.

Acknowledgments

We would like to thank the participants joining in the study.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Financial support and sponsorship

This study was funded by a grant from Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan, grant number TCRD107-28 and TCMF-CP 110-02.

Conflicts of interest

Dr. Bang-Gee Hsu, an editorial board member at *Tzu Chi Medical Journal*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

References

1. Bello AK, Okpechi IG, Osman MA, Cho Y, Htay H, Jha V, et al. Epidemiology of haemodialysis outcomes. Nat Rev Nephrol 2022;18:378-95.
2. Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM. Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end-stage renal disease. Hypertension 1998;32:570-4.
3. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001;37:1236-41.
4. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: A systematic review and meta-analysis. J Am Coll Cardiol 2010;55:1318-27.
5. Lacolley P, Regnault V, Laurent S. Mechanisms of arterial stiffening: From mechanotransduction to epigenetics. Arterioscler Thromb Vasc Biol 2020;40:1055-62.
6. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. Arterioscler Thromb Vasc Biol 2005;25:932-43.
7. Park JB, Sharman JE, Li Y, Munakata M, Shirai K, Chen CH, et al. Expert consensus on the clinical use of pulse wave velocity in Asia. Pulse (Basel) 2022;10:1-18.
8. Wilkinson IB, Mäki Petäjä KM, Mitchell GF. Uses of arterial stiffness in clinical practice. Arterioscler Thromb Vasc Biol 2020;40:1063-7.
9. Zhong Q, Hu MJ, Cui YJ, Liang L, Zhou MM, Yang YW, et al. Carotid-femoral pulse wave velocity in the prediction of cardiovascular events and mortality: An updated systematic review and meta-analysis. Angiology 2018;69:617-29.
10. Icer MA, Gezmen Karadag M. The multiple functions and mechanisms of osteopontin. Clin Biochem 2018;59:17-24.
11. Scatena M, Liaw L, Giachelli CM. Osteopontin: A multifunctional molecule regulating chronic inflammation and vascular disease. Arterioscler Thromb Vasc Biol 2007;27:2302-9.
12. Lund SA, Giachelli CM, Scatena M. The role of osteopontin in inflammatory processes. J Cell Commun Signal 2009;3:311-22.
13. Lok ZS, Lyle AN. Osteopontin in vascular disease. Arterioscler Thromb Vasc Biol 2019;39:613-22.
14. Wolak T. Osteopontin – A multi-modal marker and mediator in atherosclerotic vascular disease. Atherosclerosis 2014;236:327-37.
15. Moschetta D, Di Minno MN, Porro B, Perrucci GL, Valerio V, Alfieri V, et al. Relationship between plasma osteopontin and arginine pathway metabolites in patients with overt coronary artery disease. Front Physiol 2020;11:982.
16. Lee SJ, Lee IK, Jeon JH. Vascular calcification-new insights into its mechanism. Int J Mol Sci 2020;21:2685.
17. Paloian NJ, Leaf EM, Giachelli CM. Osteopontin protects against high phosphate-induced nephrocalcinosis and vascular calcification. Kidney Int 2016;89:1027-36.
18. Steitz SA, Speer MY, McKee MD, Liaw L, Almeida M, Yang H, et al. Osteopontin inhibits mineral deposition and promotes regression of ectopic calcification. Am J Pathol 2002;161:2035-46.
19. Shirakawa K, Sano M. Osteopontin in cardiovascular diseases. Biomolecules 2021;11:1047.
20. Druck A, Patel D, Bansal V, Hoppensteadt D, Fareed J. Osteopontin levels in patients with chronic kidney disease stage 5 on hemodialysis directly correlate with intact parathyroid hormone and alkaline phosphatase. Clin Appl Thromb Hemost 2019;25:1076029619896621.
21. Mohamed R, Tawfeek E, Abdel Salam M, Ghoraba NM, Maghraby H. The relationship between circulating levels of osteopontin with carotid intima-media thickness in children on regular hemodialysis. Open J Nephrol 2021;11:467-76.
22. Chaitanya V, Devi NH, Suchitra MM, Rao PV, Lakshmi BV, Kumar VS. Osteopontin, cardiovascular risk factors and carotid intima-media thickness in chronic kidney disease. Indian J Nephrol 2018;28:358-64.
23. Nakazato Y, Yamaji Y, Oshima N, Hayashi M, Saruta T. Calcification and osteopontin localization in the peritoneum of patients on long-term continuous ambulatory peritoneal dialysis therapy. Nephrol Dial Transplant 2002;17:1293-303.
24. Bazzichi L, Ghiadoni L, Rossi A, Bernardini M, Lanza M, De Feo F, et al. Osteopontin is associated with increased arterial stiffness in rheumatoid arthritis. Mol Med 2009;15:402-6.
25. Chang YC, Tsai JP, Wang JH, Hsu BG. A retrospective cohort study of the association between serum osteopontin levels and aortic stiffness in hypertensive patients. Int J Environ Res Public Health 2022;19:477.
26. Maniatis K, Siasos G, Oikonomou E, Vavuranakis M, Zaromytidou M, Mourouzis K, et al. Osteoprotegerin and osteopontin serum levels are associated with vascular function and inflammation in coronary artery disease patients. Curr Vasc Pharmacol 2020;18:523-30.
27. Lee CJ, Wang JH, Chen YC, Chen ML, Yang CF, Hsu BG. Serum osteopontin level correlates with carotid-femoral pulse wave velocity in geriatric persons. Biomed Res Int 2014;2014:570698.
28. Hou JS, Wang CH, Lai YH, Kuo CH, Lin YL, Hsu BG, et al. Serum malondialdehyde-modified low-density lipoprotein is a risk factor for central arterial stiffness in maintenance hemodialysis patients. Nutrients 2020;12:2160.
29. Lai YH, Wang CH, Kuo CH, Lin YL, Tsai JP, Hsu BG. Serum P-cresyl sulfate is a predictor of central arterial stiffness in patients on maintenance hemodialysis. Toxins (Basel) 2019;12:10.
30. Wu CF, Hou JS, Wang CH, Lin YL, Lai YH, Kuo CH, et al. Serum

sclerostin but not DKK-1 correlated with central arterial stiffness in end stage renal disease patients. Int J Environ Res Public Health 2020;17:1230.

31. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021-104.
32. O'Brien ER, Garvin MR, Stewart DK, Hinohara T, Simpson JB, Schwartz SM, et al. Osteopontin is synthesized by macrophage, smooth muscle, and endothelial cells in primary and restenotic human coronary atherosclerotic plaques. Arterioscler Thromb 1994;14:1648-56.
33. Kurata M, Okura T, Watanabe S, Fukuoka T, Higaki J. Osteopontin and carotid atherosclerosis in patients with essential hypertension. Clin Sci (Lond) 2006;111:319-24.
34. Rangaswami H, Bulbule A, Kundu GC. Osteopontin: Role in cell signaling and cancer progression. Trends Cell Biol 2006;16:79-87.
35. Lorenzen J, Krämer R, Kliem V, Bode Boeger SM, Veldink H, Haller H, et al. Circulating levels of osteopontin are closely related to glomerular filtration rate and cardiovascular risk markers in patients with chronic kidney disease. Eur J Clin Invest 2010;40:294-300.
36. Tousoulis D, Siasos G, Maniatis K, Oikonomou E, Kioufis S, Zaromitidou M, et al. Serum osteoprotegerin and osteopontin levels are associated with arterial stiffness and the presence and severity of coronary artery disease. Int J Cardiol 2013;167:1924-8.
37. Csiky B, Sági B, Peti A, Lakatos O, Prémusz V, Sulyok E. The impact of osteocalcin, osteoprotegerin and osteopontin on arterial stiffness in chronic renal failure patients on hemodialysis. Kidney Blood Press Res 2017;42:1312-21.
38. Huang PY, Huang CS, Lin YL, Chen YH, Hung SC, Tsai JP, et al. Positive association of serum galectin-3 with the development of aortic stiffness of patients on peritoneal dialysis. J Clin Med 2023;12:3519.
39. Rohrmann S, Garmo H, Malmström H, Hammar N, Jungner I, Walldius G, et al. Association between serum calcium concentration and risk of incident and fatal cardiovascular disease in the prospective AMORIS study. Atherosclerosis 2016;251:85-93.
40. Chen Y, Zhao X, Wu H. Arterial stiffness: A focus on vascular calcification and its link to bone mineralization. Arterioscler Thromb Vasc Biol 2020;40:1078-93.
41. Kirmizis D, Basile C. Calcium balance in hemodialysis: More uncertainty than certainty. Semin Dial 2020;33:103-8.
42. Yasmin, McEniery CM, Wallace S, Mackenzie IS, Cockcroft JR, Wilkinson IB. C-reactive protein is associated with arterial stiffness in apparently healthy individuals. Arterioscler Thromb Vasc Biol 2004;24:969-74.
43. Mahmud A, Feely J. Arterial stiffness is related to systemic inflammation in essential hypertension. Hypertension 2005;46:1118-22.
44. Inserra F, Forcada P, Castellaro A, Castellaro C. Chronic kidney disease and arterial stiffness: A two-way path. Front Med (Lausanne) 2021;8:765924.
45. Tzeng IS. To handle the inflation of odds ratios in a retrospective study with a profile penalized log-likelihood approach. J Clin Lab Anal 2021;35:e23849.