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# Aortic Arch Calcification and Bone-Associated Molecules in Peritoneal Dialysis Patients

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**Keywords**
Peritoneal dialysis · Aortic arch calcification · Fibroblast growth factor-23 · Osteoprotegerin

**Abstract**
***Background/Aims:*** Aortic arch calcification (AoAC) is a fatal complication in dialysis. AoAC progression-related molecules in continuous ambulatory peritoneal dialysis (CAPD) remain unclear. ***Methods:*** AoAC was estimated using plain chest radiography scoring (AoACS) in 30 CAPD patients (age 49.3 ± 13.4 years). AoAC progression was defined as increased AoACS on follow-up chest X-ray at the end of the study (progressors). Fibroblast growth factor-23 and osteoprotegerin (OPG) were measured. ***Results***: Median follow-up was 38.5 months. Progressors were older, had shorter PD vintage, higher body mass index, and higher serum OPG levels (255.6 ± 109.2 pg/mL) than nonprogressors (183.4 ± 68.2 pg/mL; $p = 0.0400$). Progressors also showed higher pulse pressure (62.4 ± 20.0 mm Hg) and pulse wave velocity (1,909.9 ± 310.6 cm/s) than nonprogressors (48.5 ± 13.6 mm Hg; $p = 0.0030$ and 1,390.1 ± 252.8 cm/s; $p = 0.0005$, respectively). ***Conclusion***: AoAC progression was associated with increased aortic stiffness. OPG may be associated with AoAC progression in CAPD.


## Introduction

Cardiovascular disease (CVD) is the major cause of death in patients with end-stage renal disease (ESRD) in Japan [1]. Because the high prevalence of CVD cannot be fully accounted for by the traditional risk factors, such as advanced age, hypertension, diabetes, smoking, and dyslipidemia, uremia-related factors have been implicated in the pathogenesis of CVD in hemodialysis (HD) patients [2]. Vascular calcification (VC) in the coronary arteries and the aorta has been recognized as an important risk factor for CVD in HD patients [3]. Recently, accumulating evidence has revealed that disturbances in calcium-phosphate metabolism play a pivotal role in CVD, partly via the development of VC [4].

A previous study has demonstrated the association between the presence and extent of VC and outcome in the dialysis population [5]. VC has been identified as a critical surrogate marker to predict CVD in dialysis patients [6]. The extent of VC can be quantified with computed tomography (CT). However, even though CT is a well-validated, noninvasive, imaging technique that is considered the gold standard for quantifying VC, it cannot be routinely performed due to the relatively high cost of testing and the exposure to a high dose of radiation. Plain radi-

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ography is a convenient and inexpensive alternative tool for VC detection.

In the general population, aortic arch calcification (AoAC) identified on chest radiography has been shown to correlate with cardiovascular mortality [7]. We have recently reported on the utility of assessing the grade of AoAC, as determined by a simple chest X-ray [8, 9]. AoAC grade was significantly associated with a clustering of traditional risk factors. However, it is still not known whether AoAC progression in CAPD patients is associated with bone-associated markers, such as fibroblast growth factor-23 and osteoprotegerin (OPG). As such, the aim of this study was to determine the relationship between AoAC progression and bone-associated molecules in CAPD patients.

## Patients and Methods

*Study Population*

This retrospective observational study enrolled 30 CAPD patients from the Department of Blood Purification, Tokyo Women's Medical University Hospital. The study was carried out from January 2010 to the end of December 2010. Exclusion criteria were dialysis vintage of less than 6 months after the start of PD therapy and likelihood of discontinuing PD therapy within 6 months. All subjects provided written informed consent before participation in the study. The study protocol was approved by the Ethics Committee of Tokyo Women's Medical University. Baseline demographic, clinical, and biochemical data were collected along with assessments of comorbidities at the time of enrollment.

*Assessment of AoAC*

We performed a retrospective review of the 30 CAPD patients. Two radiologists (one specializing in chest radiography) independently reviewed all chest radiographs obtained from the patients. Radiographs were assessed for the presence of AoAC using a specific scale as previously described [8]. The scale that was divided into 16 circumferences was attached to the aortic arch on chest radiography and then the number of sectors with calcification was divided by 16. AoAC score (AoACS) was then expressed as a percentage. This value was used as the indicator of AoAC. Our previous study confirmed that AoACS was highly correlated with AoAC volume evaluated by MSCT ($r = 0.635$, $p < 0.001$) [8]. Progression of AoAC was defined as an increase in AoACS on follow-up chest X-ray at the end of the study relative to that at baseline (progressors). No progression of AoAC was categorized as nonprogressors.

*Clinical Data Assessment*

Demographic and clinical data, including age, sex, body mass index (BMI), etiology of ESRD, and comorbidities, were collected at baseline. Use of medications, including antihypertensive agents, lipid-lowering agents, and calcium (Ca)-based or non-Ca-based phosphate (P) binders, was recorded. Blood pressure (BP) was recorded at 3 regular intervals, after the subject had rested in the supine position for at least 10 min and the average value of the 3 measurements was adopted. Pulse pressure (PP) was calculated using the formula, PP = systolic BP – diastolic BP. Diabetes was defined using World Health Organization criteria.

At the time of enrollment, serum levels of albumin, creatinine, Ca, P, Ca x P products, HbA1c, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and C-reactive protein were measured using routine laboratory methods. Serum calcium levels were adjusted using the formula (calcium + [4-albumin]). Serum intact parathyroid hormone was measured once at the time of chest radiology using an Allegro Intact parathyroid hormone immunoradiometric assay (IRMA; Nichol's Institute, San Juan Capistrano, CA, USA). Serum fibroblast growth factor-23 and OPG levels were measured using a sandwich enzyme-linked immunosorbent assay as previously described [10, 11].

Pulse wave velocity (PWV), intima-media thickness, and cardiac functions were assessed as previously described [12].

*Statistical Analysis*

Continuous variables are expressed as mean ± SD and categorical variables as percentages. Differences between the groups were analyzed using ANOVA and Kruskal-Wallis tests for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Pairwise comparisons were performed with independent sample *t* tests for normally distributed variables and Mann-Whitney U tests for skewed variables. To evaluate the change in AoACS, Wilcoxon's test was used. All analyses were performed using JMP for Windows version 11 (SAS Institute, Cary, NC, USA). A $p$ value of less than 0.05 was considered statistically significant.

## Results

Mean age of the 30 CAPD patients was 49.3 ± 13.4 years, and 18 patients (60%) were male. Mean dialysis vintage was 38.5 ± 31.4 months. Etiology of ESRD was glomerulonephritis in 23 patients (76.7%), hypertensive nephrosclerosis in 4 patients, diabetes in 3 patients, and graft failure after kidney transplantation in 1 patient. Three patients were treated with a combination of CAPD and HD. Two patients had a history of congestive heart failure. Median follow-up period was 38.5 months. Table 1 shows the comparison of demographic characteristics between progressors and nonprogressors at the time of enrollment. Compared with the nonprogressors, progressors were older and had shorter PD vintage and higher BMI values. There were no significant differences in prescriptions between progressors and nonprogressors.

As shown in Table 2, in terms of differences in the biochemical profiles between progressors and nonprogressors, progressors showed a lower serum Ca concentration (8.9 ± 0.6 vs. 9.6 ± 0.7 mg/dL, respectively; $p = 0.0195$), higher HbA1c (5.2 ± 0.7 vs. 4.6 ± 0.6%; $p = 0.0498$), and

**Table 1.** Demographic characteristics of the study population

| | Progressors ($n$ = 11) | Nonprogressors ($n$ = 14) | $p$ value |
|---|---|---|---|
| PD vintage, months, mean ± SD | 17.2±413.0 | 54.9±33.4 | 0.0003 |
| Age, years, mean ± SD | 55.1±12.4 | 44.8±11.2 | 0.0020 |
| Male, *n* (%) | 6 (54.5) | 12 (85.7) | ns |
| Body weight, kg, mean ± SD | 60.5±17.4 | 56.1±9.8 | ns |
| BMI, kg/m$^2$, mean ± SD | 23.6±4.0 | 20.5±2.44 | 0.0340 |
| Diabetes, *n* (%) | 2 (18.2) | 0 (0.0) | ns |
| Nephrosclerosis, *n* (%) | 4 (36.3) | 2 (14.3) | ns |
| Posttransplantation, *n* (%) | 1 (9.0) | 1 (7.1) | ns |
| HD hybrid, *n* (%) | 1 (9.0) | 2 (14.3) | ns |
| History of heart failure, *n* (%) | 1 (9.0) | 1 (7.1) | ns |
| New CVD events, *n* (%) | 3 (27.3) | 2 (14.3) | ns |
| Vitamin D, *n* (%) | 8 (72.7) | 11 (78.6) | ns |
| $CaCO_3$, *n* (%) | 8 (72.7) | 10 (71.4) | ns |
| Sevelamer, *n* (%) | 2 (18.2) | 8 (57.4) | ns |
| Antihypertensives, *n* (%) | 11 (100.0) | 12 (85.7) | ns |
| Statins, *n* (%) | 4 (36.4) | 5 (35.7) | ns |

ns, not significant; PD, peritoneal dialysis; BMI, body mass index; HD hemodialysis, CVD, cardiovascular disease.

**Table 2.** Biochemical characteristics of the study population

| | All ($n$ = 30), mean ± SD | Progressors ($n$ = 11), mean ± SD | Nonprogressors ($n$ = 14), mean ± SD | $p$ value |
|---|---|---|---|---|
| Albumin, g/dL | 3.5±0.4 | 3.5±0.4 | 3.6±0.4 | 0.2616 |
| Creatinine, mg/dL | 12.2±4.0 | 10.8±4.1 | 12.7±3.9 | 0.3328 |
| Hemoglobin, g/dL | 10.7±12.8 | 11.0±1.2 | 10.6±1.3 | 0.9542 |
| Ca, mg/dL | 9.1±0.7 | 8.9±0.6 | 9.6±0.7 | 0.0195 |
| P, mg/dL | 5.9±1.2 | 5.8±1.3 | 6.0±1.2 | 0.7588 |
| Ca × P, mg/dL$^2$ | 53.5±11.7 | 51.6±11.2 | 57.3±12.2 | 0.2167 |
| iPTH, pg/mL | 257.9±327.6 | 255.8±342.1 | 262.5±280.0 | 0.9618 |
| Blood sugar, mg/dL | 100.6±19.2 | 106.8±24.1 | 97.4±17.5 | 0.0590 |
| HbA1c, % | 4.9±0.6 | 5.2±0.7 | 4.6±0.4 | 0.0498 |
| TC, mg/dL | 173.8±46.4 | 159.1±65.2 | 179.8±36.9 | 0.7421 |
| HDL-C, mg/dL | 49.8±216.9 | 52.8±18.5 | 45.3±13.5 | 0.0782 |
| LDL-C, mg/dL | 109.6±30.4 | 127.3±30.8 | 106.0±23.3 | 0.7438 |
| TG, mg/dL | 138.5±69.1 | 135.3±58.7 | 150.7±75.2 | 0.8108 |
| HCO3, mEq/L | 22.4±3.2 | 23.2±1.2 | 22.1±0.9 | 0.5477 |
| CRP, mg/dL | 0.4±0.6 | 0.5±0.8 | 0.3±0.5 | 0.2448 |
| OPG, pg/mL | | 255.6±109.2 | 183.4±68.2 | 0.0400 |
| FGF-23, pg/mL | | 51,329.8±4 3,025.2 | 68,985.5±84,056.0 | 0.2800 |

iPTH, intact parathyroid hormone; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; CRP, C-reactive protein; OPG, osteoprotegerin; FGF-23, fibroblast growth factor-23; Ca, calcium; P, phosphate.

**Table 3.** Cardiovascular profiles of study population

| | Progressors ($n$ = 11), mean ± SD | Nonprogressors ($n$ = 14), mean ± SD | $p$ value |
|---|---|---|---|
| Systolic BP, mm Hg | 152.0±25.3 | 129.6±23.6 | 0.0170 |
| Diastolic BP, mm Hg | 95.6±10.1 | 79.5±15.0 | 0.0020 |
| Pulse pressure, mm Hg | 62.4±20.0 | 48.5±13.6 | 0.0400 |
| Pulse rate, beats/min | 75.8±7.8 | 67.4±11.2 | 0.0030 |
| CTR, % | 49.9±6.18 | 45.1±6.1 | 0.0340 |
| BNP, pg/mL | 156.2±132.2 | 141.9±227.0 | 0.4400 |
| LVM, g | 229.3±105.5 | 173.4±78.9 | 0.0500 |
| LVMI, g/m$^2$ | 127.5±46.5 | 123.7±62.9 | 0.4400 |
| LVDd, mm | 4.7±0.5 | 4.8±0.6 | 0.6100 |
| LVDs, mm | 3.1±0.6 | 3.3±0.5 | 0.1700 |
| FS, % | 0.3±0.08 | 0.3±0.05 | 0.0900 |
| PWV, cm/s | 1,909.9±310.6 | 1,390.1±252.8 | 0.0005 |
| IMT, mm | 1.94±0.7 | 1.61±0.8 | 0.2000 |
| ABI | 1.19±0.13 | 1.15±0.06 | 0.1700 |

BP, blood pressure; CTR, cardiothoracic ratio; BNP, brain natriuretic peptide; LVM, left ventricular mass; LVMI, LVM index; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; FS, fractional shortening; PWV, pulse wave velocity; IMT, intimal thickness; ABI, ankle-brachial index.

**Table 4.** PD markers of study population

| | Progression (+) ($n$ = 11), mean ± SD | Progression (–) ($n$ = 14), mean ± SD | $p$ value |
|---|---|---|---|
| Urine volume, mL/day | 808.5±716.3 | 381.5±653.6 | 0.0600 |
| Fluid removal, mL/day | 469.2±655.0 | 808.3±433.2 | 0.0700 |
| Dialysis dose, mL/day | 5,276.9±702.5 | 6,950.0±2,603.5 | 0.0370 |
| D/P Cr | 0.68±0.13 | 0.51±0.13 | 0.0430 |
| Weekly Kt/V | 1.70±0.45 | 1.85±0.30 | 0.2100 |
| Absorbed calories, kcal/day | 168.0±89.3 | 219.4±80.1 | ns |
| Protein loss, g/day | 5.60±4.5 | 4.48±1.39 | ns |
| NaCl excretion, g/day | 8.25±3.1 | 7.58±3.9 | ns |
| Ca excretion, mg/day | –22.1±42.4 | –8.74±12.9 | ns |
| P excretion, mg/day | 393.2±147.0 | 358.9±99.6 | ns |
| High sugar dialysate, $n$ (%) | 3 (27.2) | 6 (42.9) | ns |
| Hypocalcemic dialysate, $n$ (%) | 4 (36.3) | 4 (28.6) | ns |
| Icodextrin $n$ (%) | 4 (36.3) | 4 (28.6) | ns |

ns, not significant; D/P Cr, dialysate/plasma creatinine ratio.

higher serum OPG levels (255.6 ± 109.2vs. 183.4 ± 68.2 pg/mL; $p$ = 0.0400).

Table 3 shows a comparison of the cardiovascular profiles between progressors and nonprogressors. Progressors had higher PP than nonprogressors (62.4 ± 20.0 vs. 48.5 ± 13.6 mm Hg; $p$ = 0.0030) and greater cardio-thoracic ratio (CTR) values (49.9 ± 6.18 vs. 45.1 ± 6.1%; $p$ = 0.0340). There were no significant differences in echocardiographic parameters between the 2 groups. However, progressors had higher PWV than nonprogressors (1,909.9 ± 310.6 vs. 1,390.1 ± 252.8 cm/s; $p$ = 0.0005).

Table 4 shows the comparison of PD markers between progressors and nonprogressors. Progressors had lower dialysis dose than nonprogressors (5,276.9 ± 702.5 vs. 6,950.0 ± 2,603.5 mL/day; $p$ = 0.0370) and greater CTR values (49.9 ± 6.18 vs. 45.1 ± 6.1%; $p$ = 0.0430).

To investigate the reliability of AoACS evaluated by plain chest radiology, 2 radiologists independently evaluated chest radiographs during the study period. This was performed under double-blinded conditions. The coefficient of intra-observer variation was 2.2 and 2.0%. Any differences between their interpretations were resolved by consensus reading of a committee of 3 additional investigators who were also double-blinded to the study protocol.

## Discussion

AoAC was common and progressive in CAPD patients in this study. Compared with nonprogressors, progressors were older and had a shorter duration of PD therapy and higher BMI. They also had lower serum Ca levels and higher HbA1c values and serum OPG levels, as well as higher PP, PWV, and CTR values. Finally, progressors had lower dialysis dose than nonprogressors.

VC has been associated with numerous traditional cardiovascular risk factors, including advanced age, hypertension, diabetes, and dyslipidemia, as well as with nontraditional cardiovascular risk factors, including hyperphosphatemia, hyperparathyroidism, and excessive calcium intake [13]. The hemodynamic consequences of VC include loss of arterial elasticity, increased PWV, left ventricular hypertrophy, decreased coronary artery perfusion, and myocardial ischemia [13].

Older age, shorter duration of PD therapy, and higher BMI were associated with AoAC progression in the present study. Arterial media calcification has previously been shown to be an independent risk factor for mortality in HD patients [14]. Martino et al. [15] showed for the first time the predictive value of abdominal AoACs for outcomes in Italian PD patients. In a recent report from Korea [16], 184 dialysis patients (32% PD) were enrolled. Patients were divided into 2 groups based on the presence or absence of AoAC progression, and clinical and biochemical parameters were compared. Half of the patients had progressive AoAC. Age >65 years, dialysis duration, diabetes, and the presence of AoAC at baseline were related to AoAC progression. Recently, Makela et al. [17] have shown that AoACS is a strong independent predictor of cardiovascular events, and patients without calcifications had a more favorable outcome than those with calcifications [18].

OPG is a decoy receptor for the receptor activator of nuclear factor κB ligand, is a key regulator of bone metabolism, and has an effect on the vascular system [19]. The discovery that OPG-deficient mice (OPG –/– mice) develop severe osteoporosis and arterial calcification suggests that OPG is the molecule linking the vascular and skeletal systems [20]. Previous studies suggest that OPG is an arterial calcification inhibitor and is released by endothelial cells as a protective mechanism to ensure their survival in certain pathological conditions, such as diabetes mellitus, chronic kidney disease, and other metabolic disorders [21–24]. Higher OPG levels have been independently associated with cardiovascular events in PD patients [25] and have been positively correlated with the area of the aorta affected by VC, as assessed by CT [26]. It is therefore possible that OPG is a novel biomarker of CVD in PD patients [27].

In the present study, AoAC progression was associated with an increase in PP, CTR, and PWV in CAPD patients. The hemodynamic consequences of VC include loss of arterial elasticity, increase in PWV, development of left ventricular hypertrophy, decrease in coronary artery perfusion, and myocardial ischemia [28] in association with higher serum levels of OPG [29] in PD patients. Moreover, progressors had higher CTR values than nonprogressors in the present study. The greater frequency of arterial hypertension in PD patients may be due to the hydration status, considering that these patients are more susceptible to extracellular volume expansion than HD patients [30].

Zhang et al. [30] performed a meta-analysis to investigate the association between the presence of AoAC and cardiovascular or all-cause mortality risk in maintenance dialysis patients. A total of 8 studies with 3,256 dialysis patients were identified. Compared with patients without AoAC, the presence of AoAC was associated with greater cardiovascular or all-cause mortality risk. Regular follow-up for AoAC might be helpful in the stratification of mortality risk in dialysis patients.

There are some limitations in this study. AoAC assessed by chest X-ray may underestimate the true extent of Ca deposition in the aortic wall. Second, our small number of PD patients comprised older adults with a trend toward acceleration of VC. Thus, predictive values of AoAC progression cannot be extrapolated to younger PD patients. Third, the present study did not adjust covariates in a consistent manner, and this lack of adjustment may have led to a slight overestimation of the values. Very few studies were included in the meta-analysis of PD and therefore more well-designed prospective studies are needed to confirm our findings.

## Conclusion

This study found that in addition to older age, progressors among CAPD patients showed an increase in PP and PWV, higher CTR values, and elevated serum OPG levels. Hemodynamic changes and OPG may be associated with VC progression in these patients.


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## Prior Publication

This is an original work, and it has not been published in whole or in part elsewhere and is not under consideration by any other journal.

## References


1 Masakane I, Taniguchi M, Nakai S, Tsuchida K, Goto S, Wada A, Ogata S, Hasegawa T, Hamano T, Hanafusa N, Hoshino J, Minakuchi J, Nakamoto H; Japanese Society for Dialysis Therapy Renal Data Registry Committee: Annual dialysis data report 2015, JSDT renal data registry. Ren Replace Ther 2018;4:19.

2 Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM: Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 2004; 15:2208–2218.

3 Cannata-Andia JB, Rodriguez-Garcia M, Carrillo-Lopez N, Naves-Diaz M, Diaz-López B: Vascular calcifications: pathogenesis, management, and impact on clinical outcomes. J Am Soc Nephrol 2006;17(12 suppl 3):S267–S273.

4 Shanahan CM, Crouthamel MH, Kapustin A, Giachelli CM: Arterial calcification in chronic kidney disease: key roles for calcium and phosphate. Circ Res 2011;109:697–711.

5 Noordzij M, Cranenburg EM, Engelsman LF, Hermans MM, Boeschoten EW, Brandenburg VM, Bos WJ, Kooman JP, Dekker FW, Ketteler M, Schurgers LJ, Krediet RT, Korevaar JC; NECOSAD Study Group: Progression of aortic calcification is associated with disorders of mineral metabolism and mortality in chronic dialysis patients. Nephrol Dial Transplant 2011;26:1662–1669.

6 Rubin MF, Rosas SE, Chirinos JA, Townsend RR: Surrogate markers of cardiovascular disease in CKD: what's under the hood? Am J Kidney Dis 2011;57:488–497.

7 Iribarren C, Sidney S, Sternfeld B, Browner WS: Calcification of the aortic arch: risk factors and association with coronary heart disease, stroke, and peripheral vascular disease. JAMA 2000;283:2810–2815.

8 Ogawa T, Ishida H, Matsuda N, Fujiu A, Matsuda A, Ito K, Ando Y, Nitta K: Simple evaluation of aortic arch calcification by chest radiography in hemodialysis patients. Hemodial Int 2009;13:301–306.

9 Inoue T, Ogawa T, Ishida H, Ando Y, Nitta K: Aortic arch calcification evaluated on chest X-ray is a strong independent predictor of cardiovascular events in chronic hemodialysis patients. Heart Vessels 2012;27:135–142.

10 Sugimoto H, Ogawa T, Iwabuchi Y, Otsuka K, Nitta K: Relationship between serum fibroblast growth factor-23 level and mortality in chronic hemodialysis patients. Int Urol Nephrol 2014;46:99–106.

11 Nitta K, Akiba T, Uchida K, Kawashima A, Yumura W, Kabaya T, Nihei H: The progression of vascular calcification and serum osteoprotegerin levels in patients on long-term hemodialysis. Am J Kidney Dis 2003;42:303–309.

12 Akamatsu M, Ogawa T, Fujiu A, Matsuda N, Nitta K: Clinical assessment of atherosclerotic parameters and cardiac function in chronic hemodialysis patients. Clin Exp Nephrol 2009;13:651–658.

13 Nitta K, Ogawa T: Vascular calcification in end-stage renal disease patients. Contrib Nephrol 2015;185:156–167.

14 Verbeke F, Van Biesen W, Honkanen E, Wikstrom B, Jensen PB, Krzesinski JM, Rasmussen M, Vanholder R, Rensma PL; CORD Study Investigators: Prognostic value of aortic stiffness and calcification for cardiovascular events and mortality in dialysis patients: outcome of the calcification outcome in renal disease (CORD) study. Clin J Am Soc Nephrol 2011;6153–159.

15 Martino F, Di Loreto P, Giacomini D, Kaushik M, Rodighiero MP, Crepaldi C, Ronco C: Abdominal aortic calcification is an independent predictor of cardiovascular events in peritoneal dialysis patients. Ther Apher Dial 2013; 17:448–453.

16 Kim HG, Song SW, Kim TY, Kim YO: Risk factors for progression of aortic arch calcification in patients on maintenance hemodialysis and peritoneal dialysis. Hemodial Int 2011; 15:460–467.

17 Mäkelä S, Asola M, Hadimeri H, Heaf J, Heiro M, Kauppila L, Ljungman S, Ots-Rosenberg M, Povlsen JV, Rogland B, Roessel P, Uhlinova J, Vainiotalo M, Svensson MK, Huhtala H, Saha H: Abdominal aortic calcifications predict survival in peritoneal dialysis patients. Perit Dial Int 2018; 38:366–373.

18 Rochette L, Meloux A, Rigal E, Zeller M, Cottin Y, Vergely C: The role of osteoprotegerin in the crosstalk between vessels and bone: Its potential utility as a marker of cardiometabolic disease. Pharmacol Ther 2018;182:115–132.

19 Bucay N, Sarosi I, Dunstan CR, Morony S, Tarpley J, Capparelli C, Scully S, Tan HL, Xu W, Lacey DL, Boyle WJ, Simonet WS: Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. Genes Dev 1998;12:1260–1268.

20 Onyia JE, Miles RR, Yang X, Halladay DL, Hale J, Glasebrook A, McClure D, Seno G, Churgay L, Chandrasekhar S, Martin TJ: In vivo demonstration that human parathyroid hormone 1–38 inhibits the expression of osteoprotegerin in bone with the kinetics of an immediate early gene. J Bone Miner Res 2000; 15:863–871.

21 Kim SM, Lee J, Ryu OH, Lee KW, Kim HY, Seo JA, Kim SG, Kim NH, Baik SH, Choi DS, Choi KM: Serum osteoprotegerin levels are associated with inflammation and pulse wave velocity. Clin Endocrinol 2005;63:594–598.
22 Mikami S, Hamano T, Fujii N, Nagasawa Y, Isaka Y, Moriyama T, Matsuhisa M, Ito T, Imai E, Hori M: Serum osteoprotegerin as a screening tool for coronary artery calcification score in diabetic pre-dialysis patients. Hypertens Res 2008;31:1163–1170.
23 Morena M, Jaussent I, Dupuy AM, Bargnoux AS, Kuster N, Chenine L, Leray-Moragues H, Klouche K, Vernhet H, Canaud B, Cristol JP: Osteoprotegerin and sclerostin in chronic kidney disease prior to dialysis: potential partners in vascular calcification. Nephrol Dial Transplant 2015;30:1345–1356.
24 Koo HM, Do HM, Kim EJ, Lee MJ, Shin DH, Kim SJ, Oh HJ, Yoo DE, Kim JK, Park JT, Han SH, Kang SW, Choi KH, Yoo TH: Elevated osteoprotegerin is associated with inflammation, malnutrition and new onset cardiovascular events in peritoneal dialysis patients. Atherosclerosis 2011;219:925–930.
25 Huang JW, Lien YC, Yang CY, Liu KL, Wu CF, Yen CJ, Wu CK, Lee JK, Ho SR, Wu HY, Chiang CK, Cheng HT, Shyu RS, Hung KY: Osteoprotegerin, inflammation and dyslipidemia are associated with abdominal aortic calcification in non-diabetic patients on peritoneal dialysis. Nutr Metab Cardiovasc 2014;24:236–242.
26 Avila M, Mora C, Prado MDC, Zavala M, Paniagua R; Mexican Collaborative Group: Osteoprotegerin is the strongest predictor for progression of arterial calcification in peritoneal dialysis patients. Am J Nephrol 2017;46:39–46.
27 Jung JY, Hwang YH, Lee SW, Lee H, Kim DK, Kim S, Oh YG, Yang J, Joo KW, Ahn C, Oh KH: Factors associated with aortic stiffness and its change over time in peritoneal dialysis patients. Nephrol Dial Transplant 2010;25:4041–4048.
28 Krzanowski M, Janda K, Dumnicka P, Dubiel M, Stompor M, Kusnierz-Cabala B, Grodzicki T, Sulowicz W: Relationship between aortic pulse wave velocity, selected proinflammatory cytokines, and vascular calcification parameters in peritoneal dialysis patients. J Hypertens 2014;32:142–148.
29 Lai S, Molfino A, Russo GE, Testorio M, Galani A, Innico G, Frassetti N, Pistolesi V, Morabito S, Rossi Fanelli F: Cardiac, inflammatory and metabolic parameters: hemodialysis versus peritoneal dialysis. Cardiorenal Med 2015;5:20–30.
30 Zhang A, Wang S, Li H, Yang J, Wu H: Aortic arch calcification and risk of cardiovascular or all-cause and mortality in dialysis patients: a meta-analysis. Sci Rep 2016;6:35375.