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RESEARCH ARTICLE

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Serum osteoprotegerin level in hemodialysis patients using low-flux reused dialyzer in relation to atherosclerosis

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Abstract

Aims: To assess the relation of high serum OPG level and carotid atherosclerosis in maintenance hemodialysis (MHD) patients using low-flux reused dialyzer.

Materials and Methods: We examined 209 MHD patients with and without carotid atherosclerosis (83 patients and 126 patients) to establish the relation between OPG and atherosclerosis.

Results: The proportion of carotid atherosclerosis was 39.7%. The median serum OPG level was 45.3 pmol/L. Serum OPG had a good predicting value for atherosclerosis in MHD patients using low-flux reused dialyzer (AUC = 0.934, $p < 0.001$, cutoff value = 43.35 pmol/L, Se = 81.3%, Sp = 90.9%).

Conclusions: In this study, serum OPG had a good predicting value for atherosclerosis in MHD patients using low-flux reused dialyzer.

KEYWORDS
atherosclerosis, hemodialysis, serum osteoprotegerin

1 | INTRODUCTION

Osteoprotegerin (OPG) is a glycoprotein belonging to the TNF-α receptor superfamily, which consists of 401 amino acids with a molecular weight of 60 kDa.[1] In addition, substances such as the receptor activators of nuclear factor kappa-B ligand (RANKL) and TNF-related apoptosis-inducing ligand (TRAIL) are also members of this family.[1-3] OPG can inhibit bone metastasis of tumors by inhibiting bone resorption, prevents bone loss in adjuvant arthritis without effect on inflammation, and may provide a pharmacological tool for osteoporotic and erosive bone disorders.[1] OPG is expressed in vivo by endothelial cells (ECs), dendritic cells, vascular smooth muscle cells (VSMCs), and osteoblasts and has been detected by immunohistochemistry in aortic and coronary atherosclerotic plaques within or in the proximity of VSMCs.[4,5] OPG is released from blood cells such as neutrophils and stems cells under basal conditions by ECs upon stimulation with inflammatory cytokines, hormones, and various circulating compounds.[6,7]

Recently, higher serum levels of OPG associated with atherosclerosis and vascular calcification have consistently been reported in many chronic diseases.[8-11] Atherosclerosis, inflammation, and vascular calcification characterize chronic kidney disease.[12,13] The relationship between elevated serum OPG and atherosclerosis and vascular calcification in maintenance hemodialysis patients was

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reported in many previous studies.[14-16] Primarily, circulating OPG is known to be an independent predictor of all-cause mortality in CKD patients,[17] as well as an independent marker of central arterial stiffness, subclinical atherosclerosis, and cardiac function in maintenance hemodialysis patients.[15,16] However, there are few studies on OPG concentrations and atherosclerosis in patients using low-flux membranes and membranes' reuse. Therefore, we performed this study to determine the relationship of serum OPG concentrations with atherosclerosis in maintenance hemodialysis patients using low-flux dialyzer reuse.

2 | PATIENTS AND METHODS

2.1 | Patients

From 578 patients at two hemodialysis centers, we selected 209 patients with eligibility criteria. Patients who were currently using low-flux reused dialyzer, older than 18 years old, with hemodialysis >3 months were included in our study. The exclusion criteria included acute condition (illness, infection) and malignancy. All selected patients were treated with stable and regular hemodialysis using a low-flux reused dialyzer three times weekly. Each dialysis session prolonged about 3.5–4.5 h to get the target of Kt/V ≥ 1.2. We calculated Kt/V base on the formula of Daugirdas.[18]

According to the Vietnamese Ministry of Health guidelines, we reused dialyzer six times in each patient. After the end of the dialysis session, the dialyzer was cleaned with RO water for 30 min, then soaked and disinfected with a 0.7% peracetic acid solution and stored in a dedicated refrigerator at a temperature of 2–8 degrees Celsius. Before use in patients, the dialyzer is rinsed with RO water for 30 min and confirmed to be free of peracetic acid in the dialysis solution with the peracetic acid 2000 test strip.

We defined anemia as hemoglobin <130g/L in males or <120 g/L in females.[19] Diabetes was detected and diagnosed based on the criteria of the American Diabetes Association.[20] Hypertension was diagnosed when the patient has at least twice the blood pressure >140/90 mm Hg or the blood pressure is under drug control.

We divided all patients into two groups base on the appearance of atherosclerosis: Group 1 (n = 83): patients with atherosclerosis; Group 2 (n = 126): patients without atherosclerosis.

2.2 | Biochemical assays and other measurements

We take the patient's peripheral blood before the 2nd dialysis session of the week to measure some hematological and biochemical indicators. The ELISA system measured serum OPG during admission (Using USA Human OPG ELISA Kit, MyBioSource).

We also performed carotid artery Doppler ultrasound to measure intima-media thickness (IMT) and evaluate subclinical atherosclerosis. The standard value of IMT was below 0.9 mm based on the European Guidelines' criteria for the management of Hypertension in 2013.[21]

2.3 | Statistical analysis

We processed and analyzed data by the Statistical Package for Social Science (SPSS) version 20.0. We used Student's t test to compare two mean value of continuous normal distribution data and Mann-Whitney U test to compare two median value of non-normal distribution data. We used the chi-square test to compare two groups of categorical data. We performed the receiver operating characteristic (ROC) curves model to determine the predicting value of OPG for the appearance of atherosclerosis. Multivariable logistic regression analysis was performed to identify the predictors of subclinical atherosclerosis. A p-value <0.05 was considered significant.

3 | RESULTS

Our results in Table 1 showed that the mean age of patients was 46.36 years old, of which 54.1% of them were male. The proportion of diabetes and anemia was 12.0% and 91.9%, respectively. The median duration of hemodialysis was 52 months. There was 39.7% of patients having carotid atherosclerosis (83/209 patients).

As the results in Table 2, in Group 1, the ratio of hypertension; diabetes was higher, duration of hemodialysis was longer, and serum median phosphorus, PTH, and OPG levels were significantly higher than those Group 2 ($p < 0.05$).

The multivariate logistic regression analysis in Table 3 showed that diabetes, serum phosphorus, PTH, and OPG levels were independent factors related to atherosclerosis ($p < 0.05$).

Based on the ROC curve model in Figure 1, there were some factors that predicted atherosclerosis, in which serum OPG level had the strongest value (AUC = 0.934, cutoff value = 43.35 pmol/L, Se = 81.3%, Sp = 90.9%, $p < 0.001$).

4 | DISCUSSION

4.1 | Prevalence atherosclerosis and serum OPG concentration

Atherosclerosis is common in chronic kidney disease (CKD) patients and maintenance hemodialysis patients. We met 39.7% of patients with carotid atherosclerosis plaques. Our result was similar to that of other authors. Zhao B. et al.[22] found 74.3% of patients with carotid atherosclerotic plaques in a study enrolled by 140 CKD patients (44.3% diabetes). Yu L. et al.[23] conducted a study with 330 MHD patients with an average age was 63.43 years old, median hemodialysis duration was 69 months, 16.4% diabetes, and the presence of atherosclerosis was 57.3% (189 cases). In peritoneal dialysis (PD) patients, Lee M.J. et al.[24] announced 36.3% of patients had carotid

TABLE 1 Clinical characteristics and laboratory parameters of study patients (n = 209)

Clinical characteristics and laboratory parameters	Mean ± SD/ Median/ n, %
Ages (Year)	46.36 ± 15.71
Gender	
Male	113 (54.1)
Female	96 (45.9)
Diabetes (n, %)	25 (12)
Hemodialysis time (Month)	
Median	52 (30.5–94.5)
Min	3
Max	230
Hypertension	173 (82.8)
Carotid Atherosclerosis	83 (39.7)
BMI (kg/cm^2)	
<18.5	54 (25.8)
18.5–22.9	104 (49.8)
23-< 25	30 (14.4)
≥25	21 (10)
Average	20.89 ± 3.37
Hemoglobin (g/L)	99.67 ± 16.95
Anemia	192 (91.9)
Urea (mmol/L)	25.47 ± 7.1
Creatinine (μmol/L)	650.62 (537.03–860.2)
Albumin (g/L)	38.38 ± 6.84
Calcium (mmol/L)	2.1 ± 0.38
Phosphorus (mg/dL)	1.45 (1.14–1.93)
PTH (pg/mL)	143.5 (50.92–295)
Lipid disorder	
Yes	144 (69.2)
No	64 (30.8)
Increase acid uric	
Yes	62 (29.7)
No	147 (70.3)
OPG (pmol/L)	45.3 (37.8–66.64)

Abbreviations: BMI, body mass index; OPG, osteoprotegerin; PTH, parathyroid hormone.

TABLE 2 Compare of clinical characteristics and laboratory parameters of patients with and without atherosclerosis

Characteristics	With carotid atherosclerosis (n = 83)	Without carotid atherosclerosis (n = 126)	p
Ages (Year)	48.85 ± 14.03	44.72 ± 16.58	0.063
Gender			
Male	37 (44.6)	76 (60.3)	*0.025*
Female	46 (55.4)	50 (39.7)	
Diabetes	22 (26.5)	3 (2.4)	*<0.001*
Hemodialysis time (Month)			
Median	88 (50–136)	38.5 (22–65.5)	*<0.001*
Min	5	3	
Max	230	156	
Hypertension	74 (89.2)	99 (78.6)	*0.047*
BMI (kg/cm^2)			
< 18.5	21 (25.3)	33 (26.2)	0.658
18.5–22.9	40 (48.2)	64 (50.8)	
23-< 25	11 (13.3)	19 (15.1)	
≥25	11 (13.3)	10 (7.9)	
Mean	21.26 ± 3.52	20.66 ± 3.05	0.204
Hemoglobin (g/L)	100.22 ± 16.45	99.31 ± 17.33	0.705
Anemia	78 (94)	114 (90.5)	0.365
Urea (mmol/L)	26.00 ± 6.42	25.12 ± 7.53	0.381
Creatinine (μmol/L)	617.91 (527.74–735.48)	724.43 (546.75–969.55)	*0.003*
Albumin (g/L)	38.26 ± 5.81	38.45 ± 7.46	0.847
Calcium (mmol/L)	2.06 ± 0.42	2.12 ± 0.35	0.241
Phosphorus (mg/dL)	1.61 (1.25–1.97)	1.37 (1.11–1.86)	0.031
PTH (pg/mL)	252.5 (126.75–391)	61.2 (30.55–186.47)	*<0.001*
Lipid disorder			
Yes	61 (74.4)	83 (65.9)	0.193
No	21 (25.6)	43 (34.1)	
Increase acid uric			
Yes	20 (24.1)	42 (33.3)	0.153
No	63 (75.9)	84 (66.7)	
OPG (pmol/L)	56.3 (45.3–78.5)	41.2 (33.35–55.54)	*<0.001*

Abbreviations: BMI, body mass index; PTH, parathyroid hormone; OPG, osteoprotegerin.

The difference is statistically significant with $p < 0.05$.

atherosclerosis in a study that used 88 patients with an average age was 53.8 years old, 25% diabetes, and the median duration of PD was 34 months.

In our study, the median serum OPG level was 45.3 pmol/L (Table 1). OPG concentration was reported to be higher than usual in CKD patients.[25] Elevated OPG levels correlate with an increased incidence of atherosclerosis and vascular calcification[26] because OPG participates in mineral metabolism through osteoclastogenesis inhibition, osteoclast activation, and osteoclast-like formation.[27] The role of OPG is a regulator in bone turnover. They are secreted by some tissues' cells, especially in osteoblasts, and act as vascular calcification inhibitors. In CKD patients, increased secretion of OPG is related to osteoporosis, bone formation. When the level of OPG increases in the blood, since the secretion of OPG increases, it will

inhibit the calcification of blood vessels, but this is only reverse regulation in CKD patients. This issue explains that CKD patients often have calcified blood vessels and increase the level of OPG.

4.2 | The relation between atherosclerosis and some patients' characteristics

Our study showed that in atherosclerosis patients, the proportion of hypertension and diabetes were higher, hemodialysis duration was longer, serum median phosphorus, PTH, and OPG concentration were higher significantly than those without atherosclerosis group, $p < 0.05$; <0.001 (Table 2). Diabetes, serum phosphorus, PTH, and OPG levels were independently related to atherosclerotic plaques, $p < 0.05$ (Table 3). Atherosclerosis is the process of regulating several critical biological mechanisms that occur in the endothelium, including inflammatory responses, immunity, and angiogenesis.[28] Endothelial dysfunction, pre-atherosclerosis, has an increasing incidence and degree of renal failure severity.[29] Endothelial dysfunction in CKD patients results from impaired endothelial repair and regeneration as well as multifactorial endothelial damage.[30] This issue explains why atherosclerosis is common in patients with CKD. Several mechanisms can explain the relation between OPG and atherosclerosis. Inflammation and endothelial dysfunction may indicate hyperuremia in hemodialysis patients. Inflammation plays a crucial role in the production of OPG and the progression and complications of atherosclerosis. Moreover, endothelial dysfunction, linked to inflammation, is an early pathological event in atherosclerosis.[31]

TABLE 3 Multivariate logistic regression analysis between atherosclerosis and some clinical variables in the study patients

Variable	OR	95% CI	*p*
Age	1.036	0.996–1.077	0.08
Diabetes	9.067	1.064–77.284	*0.044*
Hemodialysis time	1.010	0.985–1.035	0.442
Creatinine	0.995	0.989–1.001	0.099
Phosphorus	4.920	1.268–19.09	*0.021*
PTH	1.008	1.002–1.013	*0.009*
OPG	1.360	1.195–1.547	*<0.001*

Abbreviations: OPG, osteoprotegerin; PTH, parathyroid hormone.
The difference is statistically significant with $p < 0.05$

4.3 | Factors predict atherosclerosis

Atherosclerosis often results in cardiovascular events (CVD), the most severe complication and a significant cause of mortality in patients on MHD.[23] We found some factors, which could predict atherosclerosis in MHD patients, such as duration of hemodialysis, serum PTH, and OPG levels. Our result confirmed the duration of hemodialysis; the level of serum PTH had predictive values to atherosclerosis. The serum OPG had a higher predictive value than hemodialysis duration and serum PTH (Figure 1). The result confirmed an association of high serum OPG level (> 43.35 pmol/L) with atherosclerosis in maintenance hemodialysis patients, who used low-flux membrane and reuse of dialyzer.

The results of our study once again confirm the close association between circulating elevated OPG concentration and atherosclerosis in MHD patients. Of note, plasma OPG has been demonstrated to

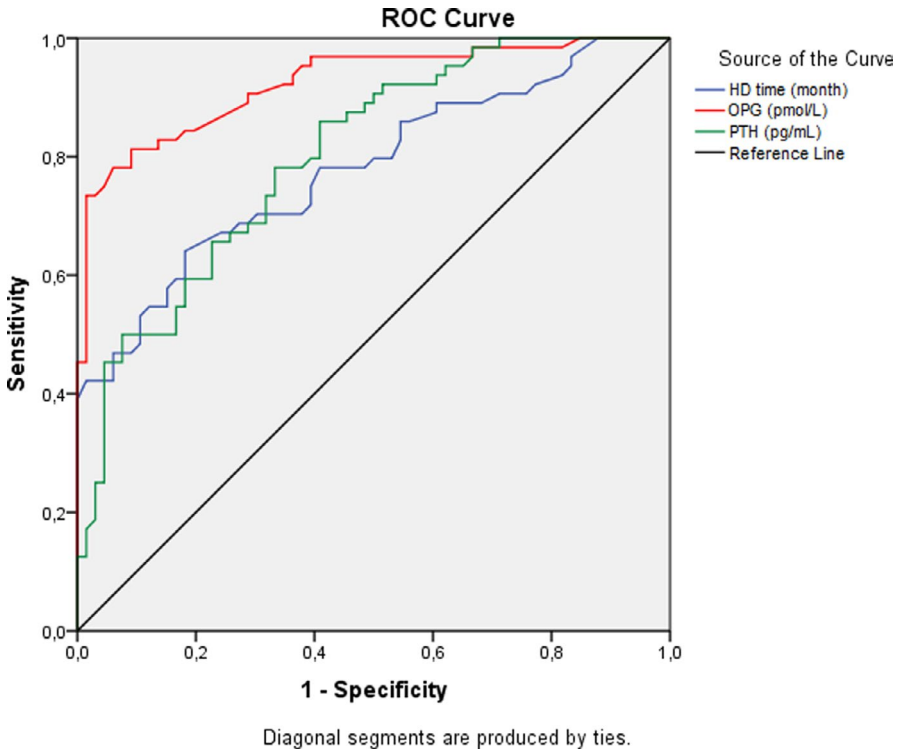

FIGURE 1 Receiver operating characteristics (ROC) curves of hemodialysis time, OPG, and PTH for prediction of atherosclerosis

be an independent risk factor for the 10-year incidence of CVD and vascular mortality.[32] OPG has also been shown to enhance the matrix content in plaques[33] and be involved in endothelial function.[34] With these insights, clinicians can use circulating OPG levels as a laboratory indicator to inform the development of new therapies to reduce the incidence and severity of atherosclerosis, vascular calcification, and artery stiffness, and finally reduce the rate of cardiovascular events, improving the quality of life for MHD patients.

Our study has strong points: It was performed on a large enough sample of patients, surveyed OPG concentrations, and assessed subclinical atherosclerotic, as well as providing a cutoff point of OPG concentration predicts subclinical atherosclerosis. However, the research still has some limitations: Firstly, we have only designed a cross-sectional study, not a longitudinal study; secondly, our study did not evaluate other risk factors for atherosclerosis such as old age and high-sensitivity C-reactive protein (hs-CRP) in MHD patients using low-flux reused dialyzer.

5 | CONCLUSION

In conclusion, the prevalence of carotid atherosclerosis was 39.7%, and high serum OPG concentration was a good predictor of atherosclerosis in MHD patients who used low-flux membrane and reusing the dialyzer.

6 | SUMMARY POINTS

- Among hemodialysis patients using low-flux dialyzer reuse, the prevalence of carotid atherosclerosis was 39.7%.
- The ratio of hypertension, the ratio of diabetes was higher, the duration of hemodialysis was longer, and serum median phosphorus, PTH, and OPG concentration were significantly higher in patients with atherosclerosis than those without atherosclerosis.
- High serum OPG concentration was a good predictor of atherosclerosis in maintenance hemodialysis patients who used low-flux membrane and dialyzer reuse.

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Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial, or otherwise.

AUTHOR CONTRIBUTION

Tung Do Van, Tuan Nguyen Minh, and Mao Can Van involved in research idea and study design. Quyen Dao Bui Quy, Toan Nguyen Duy, and Lan Le Thi Huong involved in data acquisition. Toan Pham Quoc and Hoang Nguyen Cong involved in data analysis/interpretation. Kien Nguyen Trung and Huong Bui Thi Thu involved in statistical analysis. Tien Tran Viet, Quyet Do, and Thang Le Viet involved in supervision or mentorship.

DATA AVAILABILITY STATEMENT

Authors are able to provide additional relevant original data underpinning their research, if requested by the editor or reviewers.

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