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Osteoprotegerin as a Marker of Cardiovascular Events in Patients with Chronic Kidney Disease

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ABSTRACT

Background: Cardiovascular disease (CVD) represents the primary cause of death among individuals with End-stage renal disease (ESRD). Osteoprotegerin (OPG), a key modulator of bone metabolism that inhibits osteoclast differentiation and activation, has been implicated in vascular calcification. Elevated serum OPG concentrations have been accompanied with aortic calcification and elevated mortality risk in ESRD individuals.

Objectives: This study aimed to evaluate the utility of serum OPG as an indicator for CVD in ESRD patients.

Methods: In this cross-sectional study, 86 ESRD participants (44 males, 42 females) underwent comprehensive clinical evaluation, laboratory tests encompassing complete blood count (CBC), serum creatinine, liver enzymes, and imaging (Doppler ultrasound to measure carotid IMT and Echocardiography). Serum OPG concentrations were assayed.

Results: Serum OPG was liable to be a predictor of left ventricular hypertrophy (LVH) and increased LV cavity size. An OPG cutoff value >14 ng/mL predicted LVH with 62.5% sensitivity and 100% specificity. Similarly, a cutoff >12 ng/mL predicted increased LV cavity size with 100% sensitivity and 62.5% specificity.

Conclusion: Elevated serum OPG concentrations were related to elevated cardiovascular risk in ESRD participants and may serve as a valuable biomarker for early recognition of LV structural abnormalities. Large multicentric studies are warranted to validate this conclusion.

Keywords: Osteoprotegerin, Marker, Cardiovascular, Chronic Kidney Disease.

INTRODUCTION

Chronic kidney disease (CKD) constitutes a significant global issue challenge. End-stage renal disease (ESRD), the advanced phase of CKD, is accompanied with markedly elevated morbidity and mortality risks. CKD describes ongoing structural or functional kidney dysfunction present for a duration exceeding three months. Early detection of CKD remains difficult as initial stages are frequently asymptomatic [(1)].

Cardiovascular disease (CVD) predisposes for approximately 30% of deaths globally, particularly in CKD patients [(2)]. The presence of albuminuria is associated with an elevated risk of cardiovascular disease and progressive kidney disease [(3)]. Despite the high incidence of CVD, classical risk factors do not completely clarify the elevated mortality rates [(4)]. Consequently, the need for up-to-date biomarker risk factors has become critically important. Indicators of inflammation, oxidative stress, and cardiovascular calcification have been widely investigated [(5-7)]. The leading role of OPG as an indicator of cardiovascular risk in both general and CKD populations has gained significant importance for CVD diagnosis [(8)].

OPG is a circulatory glycoprotein that functions as a decoy receptor for cytokines, antagonizing the receptor activator for nuclear factor κB ligand (RANKL) and tumour necrosis factor-associated apoptosis-inducing ligand [(9)]. OPG has been classified as a principal regulator of bone remodeling through its capacity to antagonize RANKL and suppress bone resorption. Moreover, OPG is involved in both the immune and cardiovascular systems. Elevated OPG concentrations have been related to vascular calcification, a prevalent complication in CKD and a significant risk factor for CVD. OPG may inhibit vascular smooth muscle cell apoptosis and promote a more osteogenic phenotype in these cells, leading to increased calcification. In vivo in animal subjects, OPG deficiency has been linked to severe vascular calcification, suggesting its protective role against this process [(10)]. OPG contributes to immune system activity and can modulate inflammation, which is critical in the pathogenesis of CVD. It engages with tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), influencing apoptosis and inflammatory pathways in vascular tissues. This modulation may predispose to atherosclerosis and other vascular diseases [(10, 11)].

High serum concentrations of OPG directly correlated with various biomarkers of vascular damage, including vascular stiffness, endothelial dysfunction, and coronary artery disease (CAD). This association suggests that OPG may serve as a marker for vascular health and a predictor of adverse cardiovascular events. Given its involvement in both bone metabolism and vascular pathology, OPG has been recognized as an important biomarker for CVD diagnosis. Its concentrations can reflect the extent of vascular damage and the probability of cardiovascular complications, particularly among populations at elevated risk, including individuals with CKD [(11)]. OPG concentrations are directly related to biomarkers of vascular damage, including vascular stiffness, endothelial dysfunction, coronary calcification, CAD,

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and heart failure in both those without CVD and individuals with CKD [12].

Given the disproportionately high burden of CVD in ESRD patients often inadequately explained by traditional risk factors, there is a critical need for reliable biomarkers that enable earlier detection and risk stratification. OPG has been implicated in vascular calcification and myocardial remodeling, suggesting its potential role as a non-invasive predictor of cardiovascular complications. By evaluating its correlation with echocardiographic parameters such as left ventricular hypertrophy (LVH) and increased cavity size. Therefore, this research aimed to establish the prospective function of OPG used as a signifier for prognosis. The identification of OPG as a surrogate marker may improve cardiovascular risk assessment, guide early intervention strategies, and ultimately contribute to reduce morbidity and mortality in this vulnerable patient cohort.

PATIENTS AND METHODS

Design and population: This cross-sectional study included 86 ESRD participants undergoing haemodialysis at the Nephrology Unit of University Hospital from September 2023 to September 2024.

Exclusion criteria: ESRD participants who had been with dialysis vintage less than six months, those < 18 years, participants with known CVD, and patients with HIV, hepatitis B/C infections, patients with malignancy, those with other chronic inflammatory diseases and those who refused consent.

Methods: All cases underwent a baseline laboratory assessment, including fresh blood sampling (CBC, liver functions test, renal functions test, iron profile (serum iron, transferrin saturation and serum ferritin were done), serum parathyroid hormone and assessment of dialysis efficiency by bun reduction ratio and Kt/v also were done.

CVD assessment was done by Echocardiography and by Doppler ultrasound with assessment of carotid intimal medial thickness.

Carotid ultrasound: Was done by a lecturer of radiology participating in our research. Intima-media thickness (IMT) serves as a non-invasive sonographic indicator of the extent of atheromatous vascular disease affecting end organs. The combined thickness of the intimal and medial layers of blood vessels undergoes alterations in response to various pathological conditions and can be accurately and reliably measured using B-mode ultrasound imaging of the common carotid arteries (CCA) [13, 14].

Various protocols exist for the assessment of CCA-IMT. When measuring IMT, areas containing atheromatous plaques should be excluded to ensure accuracy. The measurement was performed between the double echogenic stripe representing the blood-intima interface (far wall) and the media-adventitia junction (near wall) respectively [15]: The participant should be placed supine with the head rotated away from the side being examined.

Sagittal imaging of the CCA should be employed, with a minimum of five measurements taken on each side to calculate an average IMT. Measurements are to be performed on the posterior wall of both the right and left CCA, approximately 1 cm proximal to the carotid bifurcation. Echocardiography was done to all cases by a lecturer of cardiology to find any signs of cardiovascular affection in all ESRD patients, the used echocardiography machine was Philips echocardiography (Figure 1).

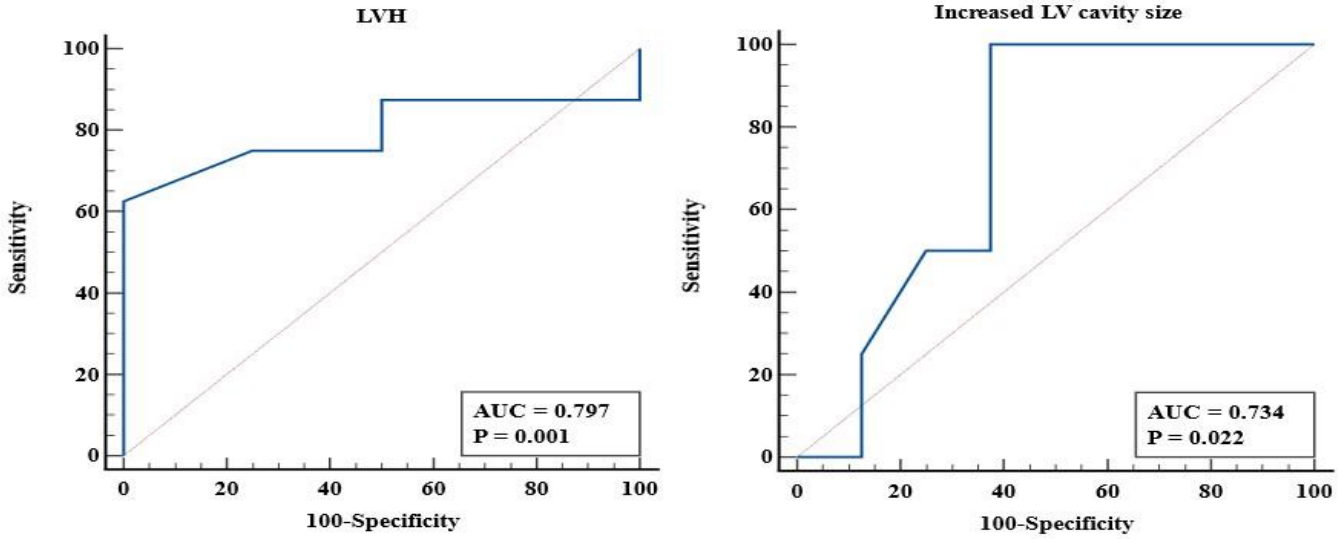

Figure (1): Sagittal B mode image of right common carotid artery with measurement of intima media thickness at the posterior arterial wall.

Sample collection and laboratory assessment: Five millilitres of venous blood aliquots were withdrawn from participant's pre- and post-hemodialysis using sterile venepuncture under complete aseptic conditions without venous stasis. Each sample was divided into two tubes: 4 mL of fresh blood was drawn into plain tubes, left for 15 minutes for coagulation, and then centrifugation at 3000 rpm for 10 minutes. Separated serum was kept under controlled conditions at -20 ºC for routine laboratory investigations and for the assay of human OPG. To conduct a complete blood count, approximately 1 mL of blood was drawn into an EDTA tube, and the test was executed using an XT-1800i Haematology Analyzer (SYSMEX, Kobe, Japan). The following routine laboratory investigations were performed: Serum creatinine, serum urea, sodium, calcium, potassium, phosphorus, serum albumin, AST, ALT, serum iron, and ferritin using a Beckman AU480 Chemistry Analyzer (Beckman Instruments Inc., Carlsbad, California, USA). Parathyroid hormone concentrations were measured using Vidas 2120 (BioMerieux, France).

Serum human OPG Assay: The detection of serum OPG concentrations was performed via the Human OPG ELISA Kit supplied by Bioassay Technology Laboratory Co, Ltd, China, with catalogue number E1558Hu, in accordance with the manufacturer's guidelines.

Ethical approval: Ethical approval was granted by The Medical Ethical Standards of the Institution. Informed consents from all patients were obtained following The Local Ethical Committee of the Faculty of Medicine, Menoufia University, Egypt, which approved the investigation protocol and procedures according to relevant guidelines. Ethical approval number MTM4-2 in August 2023. The Declaration of Helsinki was strictly adhered.

Statistical analysis

It was executed via version 28.0 (SPSS Inc., Chicago, IL, USA). The distribution pattern of the variables was analysed via the Kolmogorov–Smirnov test. Normally distributed numerical variables were presented as mean ± standard deviation, while non-normally distributed variables were shown as median (interquartile range). Discrete data were given as number (percentage). OPG concentrations were compared between patients with different echocardiographic or clinical outcomes using Student's t-test or Mann–Whitney U test as appropriate. According to the distribution pattern of the variable, correlations were performed via either Pearson's correlation test or Spearman's rank test. The optimum cut-off concentrations of OPG values for predicting LVH or increased LV cavity size were determined via the receiver operating characteristic (ROC) curve analysis. A two-sided P value ≤ 0.05 was deemed significant.

RESULTS

A total of 86 cases (44 males, 42 females) satisfied the inclusion criteria and consented to take part in the research. The participants' median age was 43.5 years (range: 25–60), with 44 (51.2%) were males and 42 (48.8%) females. Regarding the clinical history, 16 (18.6%) participants had a history of diabetes mellitus (DM), and 63 (73.3%) had a history of hypertension (HTN). During dialysis, 15 (17.4%) participants reported a history of intradialytic HTN, and 33 (38.4%) reported intradialytic hypotension. Of the 86 participants, 25 (29.1%) had residual renal function (RRF). The median urine output per day was 50 mL (range: 50–75), and the median intradialytic weight gain was 3 kg (range: 2–4 kg). Regarding echocardiographic data, 8 (9.3%) participants had an increase in left ventricular (LV) cavity size, 18 (20.9%) had diastolic dysfunction, and 16(18.6%) had LVH. For ultrasound data, the median right IMT was 0.07 mm (range: 0.06–0.085), and the median left IMT was 0.075 mm (range: 0.06–0.09). Regarding the link among OPG and cardiovascular risk, there was a marked inverse linkage among OPG and Rt (r =-0.325, p =0.003) and Lt (r =-0.320, p =0.004) intimal medial thickness. Also, OPG was notably elevated in participants with increased LV cavity size (p =0.007) and LVH (p =0.019) relative to those without (Tables 1 and 2).

Table (1): Correlation between OPG and cardiovascular risk (intimal medial thickness)

Parameter	Correlation Coefficient (r)	p-value
Rt intimal medial thickness	-0.325	**0.003***
Lt intimal medial thickness	-0.320	**0.004***

Data is presented as r (p value), OPG: Osteoprotegerin, Rt: Right, Lt: Left, *Statistically significant as p value <0.05.

Table (2): Association between OPG and echo findings

Parameter	OPG Biomarker Level (ng/mL)	Statistical Test	p-value
Increase in LV cavity size			
Yes	14.5 (14 – 15.15)	U = 94	**0.007***
No	11.75 (7.65 – 14.75)		
Diastolic dysfunction			
Yes	14 (11.5 – 15)	U = 60	0.721
No	14 (4 – 15)		
LVH			
Yes	14.75 (12.75 – 15.1	U = 102	**0.019***
No	11.65 (7.65 – 13)		

Data is presented as median (IQR) or n (%), **OPG:** Osteoprotegerin, **LV:** Left ventricle, **LVH:** Left ventricular hypertrophy, ***:** Statistically significant as p value <0.05.

Regarding the association between OPG and clinical data, OPG was significantly lower in with a history of DM (p =0.002) or patients who suffered with intradialytic hypotension (p =0.003) relative to those without. There was no marked difference in OPG level among participants according to sex, HTN, intradialytic HTN, or RRF (**Table 3).**

Table (3): Association between OPG and clinical data

Parameter	OPG Biomarker Level (ng/mL)	Statistical Test	p-value
Sex			
Male	12.9 (10.65 – 14.5)	U = 1055	0.257
Female	13.5 (11.5 – 15.2)		
DM			
Yes	10.9 (4.2 – 13.25)	U = 288	**0.002***
No	13.5 (11.5 – 15)		
HTN			
Yes	13.5 (11.3 – 14.5)	U = 715	0.926
No	13.3 (11.6 – 15)		
Intradialytic hypertension			
Yes	14.5 (7.85 – 16)	U = 576	0.188
No	13.5 (11.15 – 14.75)		
Intradialytic hypotension			
Yes	11.5 (10.8 – 13.8)	U = 1010	**0.003***
No	14.5 (11.7 – 15.2)		
RRF			
Yes	14 (11 – 15)	U = 698	0.703
No	13.5 (11.5 – 15)		

Data is presented as median (IQR) or n (%), **OPG:** Osteoprotegerin, **DM:** Diabetes mellites, **HTN:** Hypertension, **RRF:** Residual renal function, ***:** Statistically significant as p value <0.05.

There was a marked inverse linkage among OPG and age (r =-0.346, p =0.002) and ferritin (r =-0.482, p <0.001) and there was a marked linear linkage among OPG and urine output per day (r =0.431, p =0.04), K (r =0.291, p =0.014), and Kt/v (r =0.333, p =0.044) (Table 4).

Table (4): Correlation between OPG and other parameters (age, dialysis data, and laboratory data)

Parameter	Correlation Coefficient (r)	p-value
Age (years)	-0.346	**0.002***
Duration of dialysis (year)	0.058	0.617
Urine output per day (ml/day)	0.431	**0.04***
Intradialytic weight gain (kg)	-0.109	0.386
Hb	-0.105	0.387
Hct	-0.021	0.862
Plat	0.067	0.582
WBCs	0.092	0.451
AST	0.045	0.713
ALT	-0.164	0.175
Albumin	0.273	0.153
BUN pre dialysis	-0.037	0.762
BUN post dialysis	0.010	0.935
Serum creatinine	0.051	0.677
K	0.291	**0.014***
Ca	0.215	0.074
Po	-0.059	0.630
Na4	-0.034	0.781
Iron	0.043	0.791
Ferritin	-0.482	**<0.001***
PTH	-0.132	0.360
Kt/V	0.333	**0.044***

Data is presented as r (p value), **OPG:** Osteoprotegerin, **Hb:** Hemoglobin, **Hct:** Hematocrit, **Plat:** Platelets, **WBCs:** White blood cells, **AST:** Aspartate transaminase, **ALT:** Alanine transaminase, **BUN:** Blood urea nitrogen, **K:** Potassium, **Ca:** Calcium, **Po:** Phosphorus, **PTH:** Parathormone, ***:** Statistically significant as p value <0.05.

OPG is a notable predictor of LVH and increased LV cavity size with an AUC of 0.797 and 0.734 and p value of 0.001 and 0.022 respectively. OPG at a cut-off value of >14 ng/mL, it can predict LVH with a sensitivity of 62.5% and specificity of 100% and at a cut-off value of >12 ng/mL, it can predict increased LV cavity size with a sensitivity of 100% and specificity of 62.5% (Figure 2).

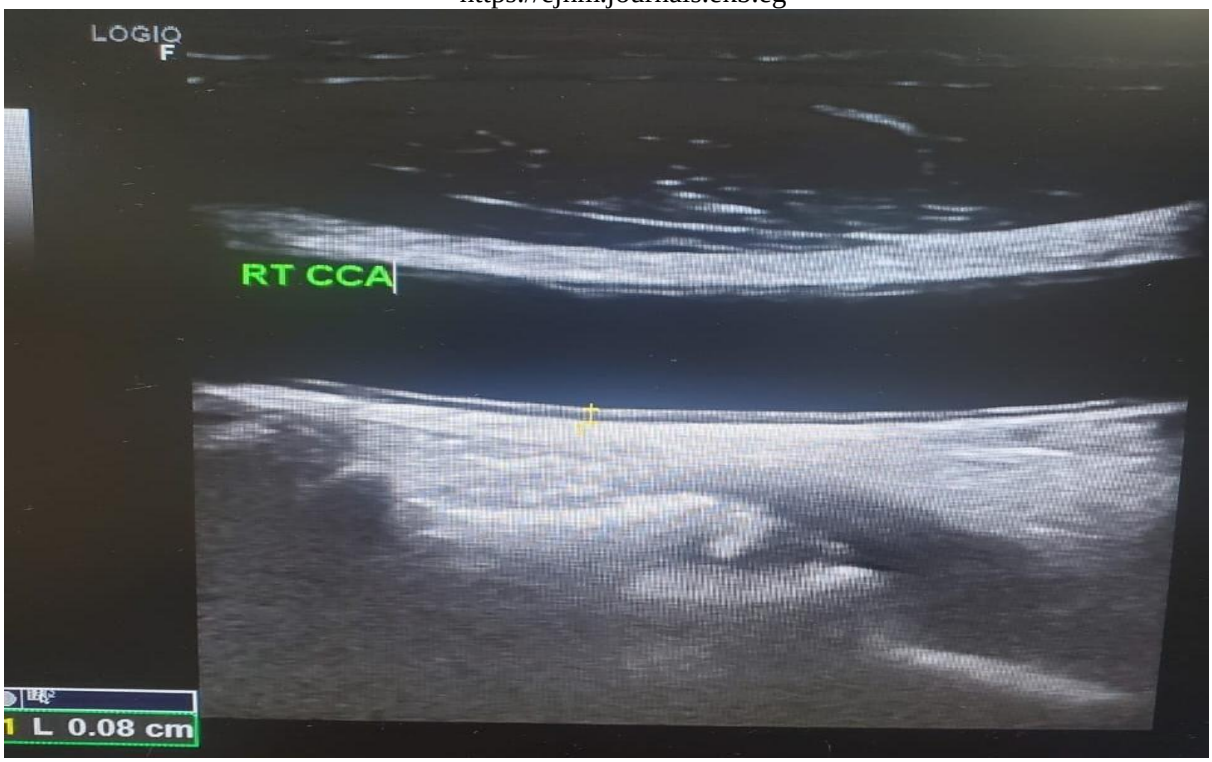

Figure (2): ROC curve analysis of the ability of OPG biomarker to predict LVH and increased LV cavity size in patients with chronic kidney diseases.

DISCUSSION

Cardiovascular adverse events are the major etiology of mortality in individuals with CKD, particularly those on haemodialysis, who face a 10- to 30-fold elevated likelihood of cardiovascular mortality related to the general population [16]. OPG, a secretory glycoprotein of the TNF receptor superfamily, plays a crucial role in bone metabolism and regulation [11, 17]. By inhibiting osteoclastogenesis through attaching to RANKL, OPG prevents RANKL from interplaying with its receptor, RANK [18]. In CKD patients, OPG concentrations are markedly elevated in relation to the general public and are linked to unfavorable cardiovascular events [19-22].

Our study documented that OPG was a robust indicator of LVH and increased LV cavity size, with AUC values of 0.797 and 0.734 respectively ($p = 0.001$ and $p = 0.022$). Specifically, an OPG cut-off value of >14 ng/mL predicted LVH with a sensitivity of 62.5% and specificity of 100%, while >12 ng/mL predicted increased LV cavity size with a sensitivity of 100% and specificity of 62.5%.

These findings align with those of previous studies, as those by **Morena *et al.*** [23] and **Matsubara *et al.*** [24], which reported greater mortality rates in ESRD individuals with elevated OPG concentrations. **Alderson *et al.*** [8] found that OPG concentrations were linked to elevated mortality probability in ESRD patients. **Kuźniewski *et al.*** [25] suggested that OPG and TRAIL might serve as biomarkers for cardiovascular mortality in stage 5 CKD individuals, indicating that OPG concentrations can predict both all-cause and cardiovascular mortality. More recently, **Huang *et al.*** [26] confirmed the link among OPG concentrations and cardiovascular mortality in CKD patients, although they noted limitations in their studies, such as the inclusion of only ESRD patients and insufficient adjustments for confounding variables.

Taken together, these studies postulate that increased OPG concentrations are predictive of an elevated probability of overall and cardiovascular mortality among participants with CKD. Despite its established link to vascular calcification, the exact pathway through which OPG influences mortality still elusive. Recent theories propose that OPG could serve as an indicator for atherosclerotic disease and myocardial ischemia [27-31]. Our finding supports the hypothesis that increased OPG concentrations may lead to myocardial impairment.

Regarding cardiac function, the association between OPG and ventricular performance warrants further investigation. Former investigations present conflicting findings: For example, **Lindberg *et al.*** [32] reported an association among OPG concentrations and reduced ejection fraction in individuals following acute ischemic events. While, **Shetelig *et al.*** [33] found no such association in patients with coronary disease. **Sigrist *et al.*** [34] indicated that elevated OPG concentrations were independently linked to elevated mortality risk in ESRD patients, regardless of CRP concentrations. Recently, **Wieczorek-Surdacka *et al.*** [35] documented a link among higher OPG concentrations and worse renal and cardiovascular outcomes in CKD individuals with stable CAD, including an autonomous correlation among elevated OPG concentrations and a lower hArg/ADMA ratio.

In postmenopausal women with DM, higher OPG concentrations have been related to elevated cardiovascular mortality [36]. Conversely, our study documented that serum OPG concentrations were reduced in individuals with DM ($p = 0.002$). This inconsistency may warrant further investigation.

An age-related rise in OPG concentrations has been observed [37]. Yet, our research revealed a marked inverse linkage among OPG and age ($r = -0.346$, $p = 0.002$). Additionally, we found marked negative correlations among OPG and right ($r = -0.325$, $p = 0.003$) and left ($r = -0.320$, $p = 0.004$) intimal medial thickness. Interestingly, our study documented a statistically marked inverse linkage among serum OPG concentrations and carotid IMT, a finding that contrasts with several reports in the literature that suggest a positive association. This discrepancy may reflect variations in study populations, stages of vascular disease, or underlying inflammatory and metabolic profiles. It is possible that in our ESRD cohort, OPG acts in a counter-regulatory manner in earlier stages of vascular remodeling, or that factors such as malnutrition-inflammation complex syndrome (MICS), altered bone mineral metabolism, or dialysis-related influences that modulate this relationship differently. Further longitudinal and mechanistic investigations are recommended to explore the role of OPG in vascular pathology among ESRD patients. OPG concentrations were also markedly elevated in participants with increased LV cavity size ($p = 0.007$) and LVH ($p = 0.019$) relative to those without these conditions.

LIMITATIONS

Our study included its non-interventional nature, which precludes causal conclusions, a small sample size that limited multivariate analysis, and the collection of a single centre study within a restricted time frame. Additionally, we did not measure other relevant biomarkers related to OPG, as RANKL and TRAIL, or assess vascular calcification using coronary artery calcium scores.

CONCLUSION

Serum OPG concentrations are markedly associated with echocardiographic indicators of cardiovascular remodeling including LVH and cavity dilation, in ESRD patients. OPG may act as a non-invasive biomarker for early identification of subclinical cardiovascular changes. Further prospective studies are required to confirm its predictive utility and assess its role in risk-guided interventions. Additional studies should explore the relationship among OPG concentrations and other biomarkers of cardiovascular mortality, as well as to investigate whether interventions to lower circulating OPG concentrations in CKD individuals could mitigate the elevated cardiovascular mortality documented in this population.

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