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Osteoprotegerin and uremic osteoporosis in chronic hemodialysis patients

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Abstract
Introduction Osteoprotegerin (OPG) is a powerful inhibitor of osteoclast activity, and it plays an important role in bone metabolism. In hemodialysis (HD) patients, the relationship between OPG and bone mineral density (BMD) is important, but remains unclear yet. The study objective was to assess the OPG role related to uremic osteoporosis in HD patients.
Methods This cross-sectional study has been realized on a cohort of 63 chronic HD patients. Inclusion criteria: elderly prevalent HD patients with an age over 55 years old. Exclusion criteria: previous bone disease or previous renal transplant; neoplasia; parathyroidectomy, hormone replacement therapy. The data regarding demographical and clinical characteristics, including treatments for mineral and cardiovascular complications, were recorded. Serum OPG and mineral markers levels were measured. BMD was assessed by calcaneus quantitative ultrasound; it measured broadband ultrasound attenuation, speed of sound (SOS) and stiffness index (STI).
Results The high OPG levels were associated with higher bone mineral density (OPG–SOS $P = 0.003$; $R = 0.37$; OPG–STI $P = 0.03$; $R = 0.28$). Malnutrition, anemia and advanced age correlated with bone demineralization. Males had higher bone density parameters than females. In patients treated with vitamin D ($P = 0.005$), the BMD was increased comparing to patients without these treatments.
Conclusions OPG levels had directly correlated with bone mineral density parameters. Our study further confirms the critical role of OPG in the pathogenesis of uremic osteoporosis in ESRD. Whether the increased circulant OPG protect against bone loss in patients undergoing HD remains to be established.

Keywords Osteoprotegerin · Osteoporosis · Hemodialysis

Introduction

Bone damage in patients with chronic kidney disease (CKD), in the spectrum of chronic kidney disease–mineral and bone disorders (CKD–MBD), represents a daily challenge for nephrologists. The impact of CKD on bone health may be immediate regarding biological equilibrium or delayed as fractures and vascular calcifications. Renal osteodystrophy (ROD) occurs in patients with advanced CKD, including osteitis fibrosa cystica, adynamic bone disease, osteomalacia and mixed uremic osteodystrophy [1]. At the present time, diagnosis of bone disease in CKD is based on clinical signs, laboratory findings and bone radiographs. Histomorphometry remains the gold standard to evaluate bone health, but it is rarely performed in clinical practice.

Patients with CKD may have also osteoporosis, either before or after developing kidney disease. Osteoporosis is a common disease in elderly general population that is characterized by low bone mass with microarchitectural disruption and skeletal fragility, resulting in an increased risk of fracture. In the general adult population, the clinical

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diagnosis of osteoporosis is made in one of two ways: the presence of a low trauma fracture independent of the prevailing bone mineral density (BMD), or in the absence of a preexisting fracture, a certain level of BMD defined in standard deviation score terms, the T-score. Osteoporosis means T-score below −2.5 SD, and osteopenia is T-score between −1 and −2.5 SD [2]. The criteria of osteoporosis refer only to postmenopausal elderly women and are based on measurement of BMD by dual energy X-ray absorptiometry (DXA) examination [3]. In 2008, a World Health Organization (WHO) task force introduced a Fracture Risk Assessment Tool (FRAX), which estimates the 10-year probability of osteoporotic fractures, which does not include any adjustment of risk according to glomerular filtration rate [4]. In the setting of CKD, the diagnosis of osteoporosis is not stated precisely.

Independent of the bone damage type, BMD measurement is important for mortality risk assessment and risk of fractures prediction [5]. Although its predictive value in dialysis is not yet confirmed, many authors recommend DXA to identify fracture risk in end-stage renal disease (ESRD) patients [6]. The technique has certain limits [7], and it is not used in current clinical practice [1].

The target for secondary osteoporosis diagnosis is to identify cases with low bone strength [8]. Bone strength is characterized by BMD, but also by the quality of the bone. The quality of the bone cannot be assessed only using DXA. In addition to the BMD, quantitative ultrasound osteodensitometry (QUS) provides information on the bone elasticity and structure, being complementary investigations. QUS had been accepted as a good predictor of osteoporotic fracture risk [9]. In addition to predicting fracture risk, other studies have found that QUS is at least as good, and possibly better than clinical risk factors for predicting women at risk for osteoporosis [10]. The power to predict the global and hip risk of fractures on fragile bone, especially in elderly women, is equally strong in QUS and DXA [11]; it can be used in conjunction with clinical risk factors to identify patients at high risk of osteoporotic fractures which require initiation of specific therapy [12]. QUS is an acceptable, cheap, non-radiative and easy-to-use method for assessing bone health. In addition, in dialysis patients who are difficult to mobilize, QUS can be realized in the dialysis center, quality that should not be neglected.

Osteoprotegerin (OPG) is a powerful inhibitor of osteoclast activity, and it plays an important role in bone metabolism. It is widely recognized that biomarkers are of main importance in detecting the complications of chronic kidney disease from early stages [13]. In experimental studies, deficit in OPG led to osteoporosis and the excess of OPG resulted in osteopetrosis [14]. Also, OPG administration can produce osteoporosis regression [14]. Some clinical studies demonstrated that increased OPG serum levels are associated with low BMD [15]. Genetically engineered recombinant OPG and anti-RANKL antibodies are a current indication for osteoporosis in elderly patients [16, 17]. Further studies are absolutely and urgently needed in order to determine the effects of OPG on bones in hemodialysis (HD) patients, because OPG-RANKL system could become an essential therapeutic target. Correlations between OPG and BMD have attracted the interest of many researchers both in the general population and in renal patients. In dialysis patients, study results were contradictory, detecting either positive or negative association or even a lack of association between serum OPG levels and BMD. In HD patients, the relationship between OPG and BMD is important, but remains unclear yet.

The study goal was to assess the osteoprotegerin role related to uremic osteoporosis in HD patients and to identify factors which favor the osseous demineralization in elderly HD patients. This research is aimed to bring new elements in understanding the pathogenic mechanisms that favor CKD–MBD in relation to OPG and to evaluate the OPG influence on chronic HD patients' morbidity. The study objectives are: to evaluate the relationship between OPG and bone mineral density in elderly HD patients; to establish the link between biochemical markers of CKD–MBD and bone demineralization from ROD in elderly HD patients; to establish the link between demographic characteristics, nutrition parameters and current treatments and bone demineralization in elderly HD patients.

Methods

This cross-sectional, analytical study has been realized on a cohort of ESRD patients, randomly selected. All were on conventional HD therapy in Nefromed Dialysis Center Cluj-Napoca. *Inclusion criteria*: elderly prevalent HD patients with an age over 55 years old, who also agreed to participate to this research. *Exclusion criteria*: previous bone disease or previous renal transplant; neoplasia; parathyroidectomy, women on hormone replacement therapy. Among all 131 patients on conventional HD therapy in Nefromed Dialysis Center Cluj-Napoca, 63 met the eligibility criteria.

All patients were receiving conventional 4–5 h HD, three times weekly, with synthetic (polysulphone) dialyzers, bicarbonate dialysate and heparin as standard anticoagulants. Dialysis was prescript in order to achieve adequacy ($spKt/V \geq 1.2$).

The following data were recorded: age, gender, presence of diabetes, HD vintage, dialysate calcium, HD prescription and treatments for mineral metabolism complications.

Body mass index (BMI = weight/height^2) was calculated. Serum levels of calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), intact parathyroid hormone (iPTH—Roche second-generation assay), urea, creatinine, albumin, cholesterol, triglycerides, C-reactive protein (CRP) and OPG (human-OPG ELISA, Biomedica, Wien, Austria) were measured. Biochemical evaluation was performed in a central laboratory. Blood samples were drawn prior to the HD session in the same week of the QUS study. Hemodialysis (HD) adequacy was evaluated using the clearance of urea (spKt/V = 2.4X (1 − urea post-HD/urea pre-HD) − 0.276).

Bone mineral density was assessed by calcaneus (heel) quantitative ultrasound. QUS device was OsteoMed PEGASUS Prestige. QUS measures the transmission of ultrasound through accessible limb bones or the reflectance of the ultrasound waves from the bone surface. Pegasus apparatus was used and the following parameters were determined: broadband ultrasound attenuation (BUA) (dB/MHz), speed of sounds (SOS) (m/s), T-score, Z-score and stiffness index (STI). SOS is a measure of BMD and bone elasticity, BUA measures BMD and bone structure, STI is a composite parameter resulting from SOS and BUA.

Statistics

Mean ± standard deviation expressed continuous variables when normal distribution and the median (inter-quartile range) had expressed them when the distribution was not normal. Qualitative variables were expressed as frequencies. The Kolmogorov–Smirnov test was employed for the continuous variables to compare the observed cumulative distribution function with the normal distribution. The statistical comparison was performed using *t* test for variables with normal distribution or the Mann–Whitney rank sum test for the others. Chi-square or Fisher exact test were used to test the relationship between qualitative variables. Parametric (Pearson) and nonparametric (Spearman) correlations were determined to test the relationship between QUS testing and other parameters. Independent variables associated with bone demineralization were identified using linear regression, stepwise method. Statistically, significance was considered when P value was < 0.05. All statistical analyses were performed using SPSS 16.0 statistics packages.

Ethical issues

All patients signed an informed consent prior to the study entry. The study protocol conformed to the ethical guidelines. IRB/Ethics Committee approval has been obtained (IRB approval number 178/2014).

Results

Mean age was 68.74 ± 7.92 years old; mean HD vintage was 47.53 ± 48.30 months. All patients were caucasians. In the studied cohort, there were 29 females (46%), 19 diabetes patients (30.15%) and 9 were smokers (14.28%). Fifty-two patients were treated with calcium salts (82.53%); 22 patients were treated with vitamin D (calcitriol) (34.92%); and 15 patients were treated with sevelamer (23.8%) (Table 1). None received calcimimetics or lanthanum. Twenty-nine patients (46%) had 1.25% dialysate calcium and patients (54%) had 1.5% dialysate calcium. Distribution according to T-score was as follows: 40 patients had the T-score ≤ −2.5 (63.5%); 14 patients had the T-score > −2.5 and ≤ −1(22.2%); and 9 patients had the T-score > −1(14.3%).

The following correlations were obtained applying linear regression: OPG–SOS ($P = 0.003$, R = 0.37); OPG–STI ($P = 0.03$, $R = 0.28$); OPG–BUA ($P = 0.37$); and OPG–T-score ($P = 0.85$) (Figs. 1, 2). OPG correlated also with age ($P = 0.03$, $R = 0.27$), BMI ($P = 0.04$, $R = -0.26$), URR ($P = 0.02$, $R = 0.29$) and iPTH ($P = 0.01$, $R = -0.35$).

In linear regression, stepwise method, all quantitative variables were entered into the equation; only BMI ($P = 0.01$; $b = 0.33$ 95%CI = 0.14–0.52) remained a predictor for BUA. Only Hb ($P < 0.01$, $b = 10.26$; 95%CI = 5.65–14.88) and Ca salts ($P < 0.01$, $b = 21.69$; 95%CI = 10.27–33.12) remained predictors for SOS.

The statistically significant correlations between BMD and other parameters are reproduced in Table 2. Serum albumin, iPTH, ALP and CRP were not correlated with indices of QUS measurement.

Comparing BMD parameters according to gender, BUA was significantly increased in males versus females ($P = 0.048$).

The group of patients was divided into two subgroups, according to the treatment. Those who received treatment with vitamin D derivates had significantly increased BUA and STI versus those without vitamin D ($P = 0.005$, respectively, $P = 0.01$). Higher Ca in dialysate was associated with higher SOS ($P = 0.03$). Treatments with calcium salts or sevelamer did not influence bone mineral density.

Discussion

In our studied HD patients, QUS was able to detect bone demineralization. Osteoporosis and osteopenia are medical terms validated for the general population; they are somewhat not characteristic for secondary bone demineralization, as in ESRD [18]. There is uncertainty related to the applicability of the established WHO classification of BMD

Table 1 Characteristics of the studied cohort

Characteristics	Media ± DS/median (25th–75th percentile)	Minim	Maxim
Age (years)	68.74 ± 7.93	56	89
HD vintage (months)	33 (14−60)	2	272
BMI (kg/m^2)	28.37 ± 5.82	17.93	43.82
OPG (pmol/ml)	5.9 (4.20–8.20)	2	19.6
Ca (mg/dl)	8.37 ± 0.48	7.36	9.96
P (mg/dl)	5.09 ± 1.63	1.87	8.83
CaxP (mg^2/dl^2)	42.90 ± 14.61	16	75
iPTH (pg/ml)	219.50 (104.27–420.87)	28	1297
ALP (U/l)	66 (54–84.5)	41	378
URR	73.21 ± 9.82	53.7	100
Kt/V	1.48 ± 0.23	1	2.1
Bicarbonate (U/l)	17.46 ± 3.45	9.1	25.3
Hb (g/dl)	11.61 ± 1.22	8.8	15.2
Cholesterol (mg/dl)	164.5 (140.5–202.5)	58	362
Trygliceride (mg/dl)	133.5 (95.75–189.25)	40	556
Creatinine (mg/dl)	7.96 (6.76–9.4)	2.52	13.7
Albumin (g/dl)	4.10 (3.96–4.32)	3.38	4.81
CRP (mg/dl)	1.15 (0.49–2.70)	0.04	15.44
BUA (dB/MHz)	51.71 (49.42–55.87)	46.11	65.02
SOS (m/s)	1592.36 ± 24.69	1546	1594.1
T-score	−3.04 (−3.42 to −2.3)	−3.77	−0.36
Z-score	−1.60 ± 0.74	−2.64	0.54
STI	98.23 ± 7.87	82.4	114.8

SD standard deviation, *HD* hemodialysis, *OPG* osteoprotegerin, *BMI* body mass index, *Ca* calcium, *P* phosphorus, *iPTH* intact parathyroide hormone, *ALP* alkaline phosphatase, *URR* urea reduction ratio, *Kt/V* clearance of urea, *CRP* C-reactive protein, *BUA* broadband ultrasound attenuation, *SOS* speed of sound, *STI* stiffness index

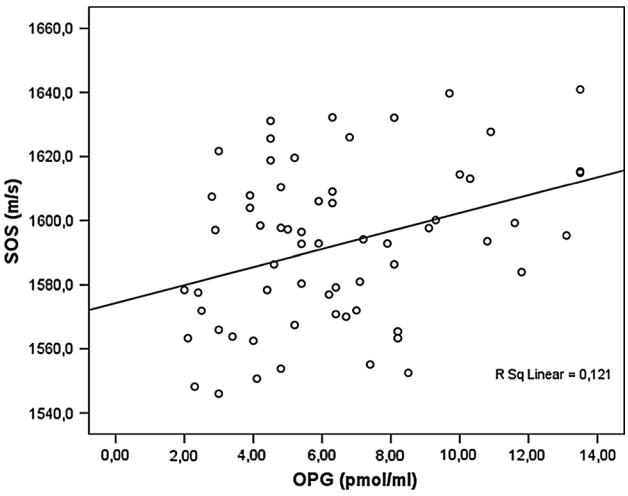

Fig. 1 Correlation between OPG and SOS ($P = 0.003$; $R = 0.348$)

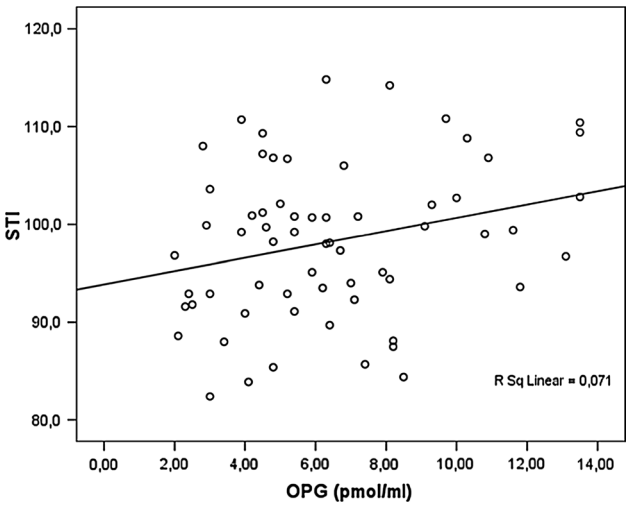

Fig. 2 Correlation between OPG and STI ($P = 0.03$; $R = 0.27$)

according to T-score DXA thresholds. McCloskey's meta-analysis confirmed that quantitative ultrasound is a valuable tool, because it is an independent predictor of fracture for men and women particularly at low QUS values [19].

Similar to other studies [20, 21] our study demonstrated that bone demineralization is prevalent in elderly HD patients. Some studies revealed an acceptable concordance

Table 2 Correlations between BMD and other parameters

	BUA (dB/MHz)	SOS (m/s)	T-score	Z-score	STI
Age (years)	**$P = 0.02$; $R = -0.30$**	**$P = 0.03$; $R = -0.28$**	**$P = 0.04$; $R = -0.26$**	$P = 0.44$; $R = -0.10$	**$P = 0.005$; $R = -0.35$**
HD vintage (months)	$P = 0.14$; $R = -0.19$	**$P = 0.08$; $R = 0.22$**	**$P = 0.02$; $R = -0.28$**	**$P = 0.006$; $R = -0.34$**	$P = 0.36$; $R = 0.12$
BMI (kg/m^2)	**$P = 0.001$; $R = 0.41$**	$P = 0.84$; $R = -0.03$	**$P < 0.001$; $R = 0.52$**	**$P < 0.001$; $R = 0.53$**	$P = 0.64$; $R = 0.06$
Cholesterol (mg/dl)	**$P = 0.05$; $R = 0.27$**	$P = 0.08$; $R = 0.24$	**$P = 0.008$; $R = 0.36$**	**$P = 0.004$; $R = 0.39$**	**$P = 0.03$; $R = 0.29$**
Tryglycerides (mg/dl)	$P = 0.07$; $R = 0.25$	$P = 0.56$; $R = -0.32$	**$P = 0.02$; $R = 0.32$**	**$P = 0.02$; $R = 0.31$**	$P = 0.92$; $R = -0.01$
Creatinine (mg/dl)	**$P = 0.03$; $R = 0.28$**	$P = 0.65$; $R = 0.06$	$P = 0.20$; $R = 0.16$	$P = 0.86$; $R = 0.02$	$P = 0.27$; $R = 0.14$
Hb (g/dl)	$P = 0.09$; $R = 0.22$	$P = 0.001$; $R = 0.42$	$P = 0.23$; $R = 0.15$	$P = 0.76$; $R = 0.04$	**$P = 0<0.001$; $R = 0.47$**
URR	**$P = 0.03$; $R = -0.27$**	$P = 0.54$; $R = 0.08$	$P = 0.37$; $R = -0.11$	$P = 0.10$; $R = -0.21$	$P = 0.47$; $R = -0.09$
CRP (mg/dl)	$P = 0.06$; $R = 0.20$	$P = 0.07$; $R = -0.19$	$P = 0.11$; $R = 0.21$	$P = 0.21$; $R = 0.16$	$P = 0.14$; $R = -0.19$
Ca (mg/dl)	$P = 0.57$; $R = 0.07$	**$P = 0.003$; $R = 0.36$**	$P = 0.75$; $R = 0.04$	$P = 0.60$; $R = 0.07$	**$P = 0.005$; $R = 0.35$**
P (mg/dl)	**$P = 0.03$; $R = 0.28$**	$P = 0.10$; $R = 0.21$	**$P = 0.01$; $R = 0.33$**	**$P = 0.05$; $R = 0.25$**	**$p = 0.04$; $R = 0.26$**
Bicarbonate (mmol/l)	$P = 0.46$; $R = 0.10$	$P = 0.63$; $R = 0.06$	$P = 0.19$; $R = 0.17$	$P = 0.14$; $R = 0.19$	$P = 0.40$; $R = 0.11$

Bold values indicate significant correlations

SD standard deviation, *HD* hemodialysis, *OPG* osteoprotegerin, *BMI* body mass index, *Ca* calcium, *P* phosphorus, *URR* urea reduction ratio, *CRP* C-reactive protein, *BUA* broadband ultrasound attenuation, *SOS* speed of sound, *STI* stiffness index

between QUS and DXA in chronic HD patients [22]. However, even in the general population, QUS and DXA compliance is not high enough; the explanation is that they measure different parameters and different skeletal areas [23]. In the general population, QUS plays an important role in assessing bone health [24]. A prospective 10-year follow-up study established that QUS and DXA have the same fraction risk prediction power [25]. The utility of the former was proved in HD patients also, predicting the risk of fractures [26–28].

In our group of HD patients, OPG levels were high comparing with reference values. This result is concordant with Demir's recent study [29]. It has been reported that circulating OPG is increased in experimental animals fed with high-fat diet [30], but in our study OPG was inversely correlated with BMI.

The higher OPG levels were correlated directly with SOS and STI, reflecting an increased bone mineralization. Thus, OPG might act to prevent bone loss in HD patients. In healthy persons, it was shown that OPG serum levels are positively correlated with bone metabolism markers and are negatively correlated with BMD. In chronic HD patients, Nakashima et al. [31] had demonstrated that BMD is positively correlated with OPG and negatively correlated with HD vintage and iPTH levels. Avila et al. [32] had showed there is no association between osteopenia and OPG in women on dialysis. The precise role of OPG in ROD pathogenesis remains unknown, and further studies are needed to elucidate it. OPG/sRANKL system is an independent determinant of bone volume and turnover [20]. A study on postmenopausal osteoporosis HD women observed that serum OPG levels are higher in HD patients with osteoporosis compared to same age women not on HD; it also demonstrated that increased OPG is associated with low BMD in postmenopausal HD patients [33]. It had suggested that it is a consequence of imbalances in kinetics of bones that occurs in CKD. Our study results are in contrast with the data available for the healthy population, but are consistent with the findings of Nakashima [31], which also showed a positive correlation between OPG and BMD. It is well established that elevated serum OPG levels are associated with vascular damage and increased risk of cardiovascular events [34] including in HD patients [35]. Also, vascular calcification and renal osteodystrophy have a pathogenetic link in HD patients [36]. Nascimento et al. [37] reported in a 3-year follow-up study that increased OPG levels were independently associated with increased risk of death in HD patients.

As the post hoc analysis of the FREEDOM trial showed us, at the present time, we have available a new therapeutic tool [38]. Denosumab was effective in reducing fracture risk, improving bone mineral density and was not associated with an increase in adverse events, including changes in estimated glomerular filtration rate, among women with impaired kidney function [38–40]. Currently there are no clinical studies to prove the benefits of antiosteoporotic treatment in reducing the fracture risk in patients selected by QUS measurements. However, the International Society of Clinical Densitometry Official Position is that pharmacological treatment can be initiated in case the fracture probability is sufficiently high even central DXA cannot be done. In this case, fracture probability should be assessed by heel QUS using device-specific thresholds and in conjunction with clinical risk factors [23, 41].

In our study, iPTH was not associated with bone demineralization in HD patients. The relationship between BMD and iPTH is not constant in trials, but it was shown that BMI has a positive influence on BMD [20, 42].

Nutrition (BMI, cholesterol, tryglycerides, creatinine and Hb) was an important determinant of BMD in our study. Some studies have shown that older age, low weight, low albumin and increased ALP are important risk factors for low BMD [33]. Moreover, it has been reported that circulating OPG is increased in experimental animals fed with high-fat diet [30].

In the present study, there was a significant difference between the QUS-measured parameters according to the gender of patients, consistent with the literature indicating that demineralization in women would be more important in patients with ESRD; increased HD vintage was associated with lower Z-score, consistent with other studies [43].

Bone mineralization was better in patients receiving treatment with high calcium dialysate or vitamin D; it was not influenced by the treatment with sevelamer. These results correspond to data available for the general population; the patients deficient in vitamin D with or without associated hypocalcemia develop bone complications. These data can be explained by a potential deficit of Ca and vitamin D, whose correction is beneficial for the bone.

Limitations of the study consist in a relatively reduced number of patients, which restrain us to generalize the results. Its cross-sectional nature does not permit causative associations. QUS examination validity in HD patients is not certain, as it has not been yet compared with the gold standard.

Some challenges remain in the modern management of secondary osteoporosis: development of better diagnostic tools for the quality of bone, the evaluation of fracture risk and the most appropriate selection of patients for therapy [44–46].

Conclusions

Elevated OPG correlated directly with ultrasonographic parameters of good bone mineralization, suggesting that OPG may protect bone against bone loss in HD patients. Advanced age, absence of treatment with vitamin D and malnutrition correlated with bone demineralization. These results justify the statement that OPG is an important piece in CKD–MBD, but its exact role in HD patients remains to be established in future research.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

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