Original Report: Patient-Oriented, Translational Research

American Journal of Nephrology

Am J Nephrol 2009;29:257–263
DOI: 10.1159/000157629

Received: March 27, 2008
Accepted: July 16, 2008
Published online: September 19, 2008

Elevated Osteoprotegerin Levels Predict Cardiovascular Events in New Hemodialysis Patients

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Key Words
Osteoprotegerin · Cardiovascular events · Vascular calcification · Aortic calcification index · Hemodialysis patients

Abstract
Background: Patients on hemodialysis (HD) frequently experience cardiovascular events associated with vascular calcification. We investigated the involvement of osteoprotegerin (OPG), an inhibitor of vascular calcification, in the incidence of cardiovascular events and mortality among new HD patients. ***Methods:*** We conducted a prospective cohort study of the association of serum OPG levels with morbidity and mortality in subjects who became new HD patients between June 2000 and May 2006. ***Results:*** A total of 99 patients (age 58.9 ± 14.6 years, 65 male, 34 female) were prospectively followed up for 41.5 ± 20.2 months. During this period, 27 patients developed cardiovascular events and 12 died of causes related to cardiovascular disease. When divided into 2 groups according to OPG levels, the high OPG group showed a higher prevalence of cardiovascular morbidity and mortality compared with the low OPG group. Cox's proportional hazards analysis associated the new onset of cardiovascular events with the high OPG group (HR 2.88, 95% CI 1.09–7.62, p = 0.033). Furthermore, the high OPG group at the start of HD was significantly associated with older age, male gender and a high aortic calcification index. ***Conclusions:*** Elevated levels of serum OPG in new HD patients may predict subsequent cardiovascular events.

Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients receiving maintenance hemodialysis (HD) [1]. In the general population, the presence and extent of vascular calcification (VC) is highly correlated with cardiovascular events and mortality [2, 3]. Extensive arterial calcification is typical of HD patients, even at a young age [4, 5]. However, the relationships between the extent of VC at the start of HD treatment and the incidence of CVD morbidity and mortality have not been clarified.

Vascular calcification is thought to be influenced by inhibitory factors [6, 7], as are elevated calcium and/or phosphate levels, and secondary hyperparathyroidism or hypothyroidism [8–11]. Among these inhibitors, osteoprotegerin (OPG), known as osteoclastogenesis inhibi-

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tory factor, is a cytokine and a member of the tumor necrosis factor receptor superfamily. It is a basic glycoprotein comprising 401 amino acid residues arranged into 7 structural domains. It is found as either a 60-kDa monomer or a 120-kDa dimer linked by disulfide bonds. OPG inhibits the differentiation of macrophages into osteoclasts and also regulates the resorption of bone in vitro and in vivo [12]. Involvement of OPG in VC has been confirmed by the discovery of its mRNA in calcified arteries but not in normal ones [13]. During the last few years, OPG has been shown to be implicated in human atherosclerosis and VC. A high serum OPG level is reportedly associated with severe coronary atherosclerosis [14], and both fatal stroke and overall vascular mortality [15]. In addition, OPG is thought to be an independent predictor for VC in patients with diabetes mellitus (DM) [16] or those on long-term HD [17].

Increased OPG levels or the degree of VC were recently shown to be associated with all-cause and cardiovascular mortality in maintenance dialysis patients [18, 19]. To clarify if the measurement of OPG at the start of maintenance HD therapy is useful for clinical follow-up of HD patients, in the present study we investigated the relationships between OPG levels and VC, cardiovascular events and all-cause mortality.

Subjects and Methods

Subjects and Data Collection

Consecutive new HD patients who initiated maintenance dialysis therapy and attended our dialysis centers for longer than 3 months between June 2000 and May 2006 were enrolled in the study. Three times a week, all patients received 4 h of hemodialysis with bicarbonate dialysate containing 3.0 mEq/l of calcium. Among these 361 patients, 99 who agreed to provide blood samples for analysis and to receive abdominal computed tomography examination were included in this prospective cohort study. Patients were followed-up until May 2007 or death, if it occurred earlier than May 2007. The medical and clinical records were searched for history and CVD events (ischemic heart diseases including acute myocardial infarction, unstable angina and angina pectoris, chronic heart failure, dissecting aortic aneurysm, cerebral infarction and cerebral hemorrhage). In the present study, cardiovascular events also included sudden death in addition to CVD events.

Ischemic heart disease was diagnosed when the patient had typical symptoms, abnormal electrocardiogram, echocardiogram and/or coronary artery stenosis confirmed by catheterization. Cerebrovascular disease was confirmed both by typical symptoms with physical findings and by computed tomography scans or magnetic resonance imaging.

The study was approved by the ethics committee of the institute and all patients gave informed consent before participation in the study.

Biochemical Assays and Other Measurements

Blood samples were collected from all patients in the morning before the first HD session of the week. Serum intact parathyroid hormone and OPG concentrations were measured using electrochemiluminescence immunoassay (Roche Diagnostics) and enzyme-linked immunosorbent assay (Immundiagnostik AG), respectively. As previously reported [20], abdominal aortic calcification index (ACI) was determined using abdominal computed tomography images, which was scanned at admission for introduction to dialysis therapy.

Clinical status was evaluated by means of routine clinical examination before the regular HD session. Systolic and diastolic blood pressures and pulse rate were measured in the supine position and mean values for 1 week were used for the analysis.

Statistical Analysis

Statistical analyses were carried out using the SPSS software version 11 (SPSS Inc., Chicago, Ill., USA). Data are expressed as means ± SD. Differences between groups were evaluated by unpaired Student's t test for continuous variables after confirmation of normal distributions for all variables, and the χ^2 test for dichotomized variables. Differences among groups were determined by analysis of variance (one-way ANOVA). Survival curves were estimated by means of the Kaplan-Meier method and evaluated using the log-rank test. Prognostic variables for survival were examined first by using the univariate Cox proportional hazards model, and variables with $p < 0.15$ were forced into multivariate Cox proportional hazards models. The logistic analysis was used to assess the impact of multiple covariates for a categorical variable. The results of multivariate analyses are expressed as a hazard ratio (HR) with 95% confidence intervals (CI) and a p value. $p < 0.05$ was considered statistically significant.

Results

Patients' Characteristics

This study cohort comprised 65 males and 34 females. Their ages ranged from 20 to 86 years (mean age 58.9 ± 14.6 years). The primary causes of renal failure were diabetic nephropathy (n = 41), chronic glomerulonephritis (n = 29), nephrosclerosis (n = 7), and other (n = 22). The mean value of body mass index (BMI) was 22.9 ± 3.8. The mean of OPG concentration in serum was 137 ± 68 pg/ml (range 27–323 pg/ml). ACI ranged from 1 to 98% (mean ACI 30.5 ± 24.3%). Forty (40.4%) patients were smokers. Thirty-two (32.3%) patients received angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers, 22 (22.2%) patients received antiplatelet agents and 21 (21.2%) patients received $CaCO_3$ and/or activated vitamin D_3.

Table 1. Comparison of baseline characteristics and outcome between low and high OPG groups

	Low OPG (n = 50) (85.4 ± 22.3 pg/ml)	High OPG (n = 49) (189.8 ± 57.1 pg/ml)	p
Age, year	52.1 ± 13.6	65.8 ± 12.1	<0.001
Sex (female/male)	22/28	12/37	0.057
DM	17 (34)	24 (49)	0.156
Smoking	19 (38)	21 (43)	0.685
BMI	23.5 ± 3.8	22.4 ± 3.8	0.156
$CaCO_3$/vitamin D_3	8 (16)	13 (27)	0.227
ACEI/ARB	19 (38)	13 (27)	0.342
ACI, %	21.0 ± 18.6	40.2 ± 25.8	<0.001
Systolic blood pressure, mm Hg	160 ± 30	157 ± 24	0.664
Diastolic blood pressure, mm Hg	87.4 ± 20.1	79.8 ± 15.7	0.04
Albumin, mg/dl	3.4 ± 0.6	3.2 ± 0.6	0.119
Total cholesterol, mg/dl	190 ± 56	182 ± 62	0.524
Corrected calcium, mg/dl	8.6 ± 0.8	8.7 ± 1.0	0.345
Phosphate, mg/dl	5.5 ± 2.0	4.6 ± 1.4	0.013
Alkaline phosphatase, IU/l	327 ± 275	295 ± 124	0.453
Intact PTH, pg/ml	225 ± 142	210 ± 152	0.601
CRP, mg/dl	0.7 ± 1.0	0.5 ± 0.7	0.317
Past cardiovascular events	13 (26)	14 (29)	0.774
New cardiovascular events	6 (12)	21 (43)	0.001
Death	5 (10)	16 (33)	0.007
Cardiovascular death	2 (4)	10 (20)	0.015

Data are means ± SD or numbers with percentages in parentheses. ACEI = Angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; PTH = parathyroid hormone; CRP = C-reactive protein.

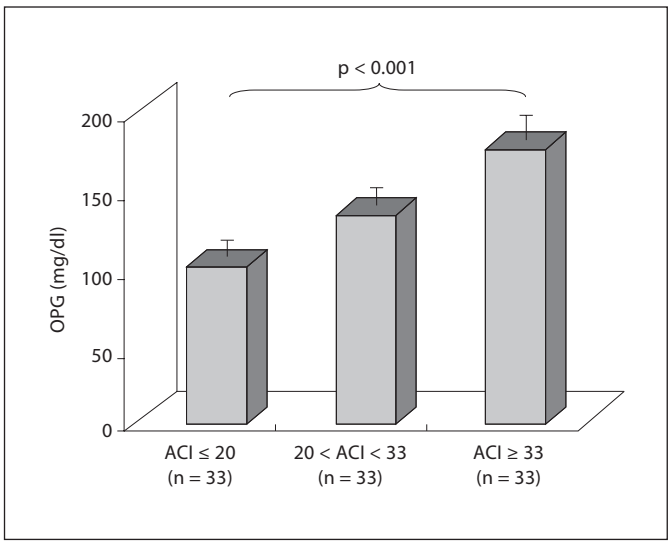


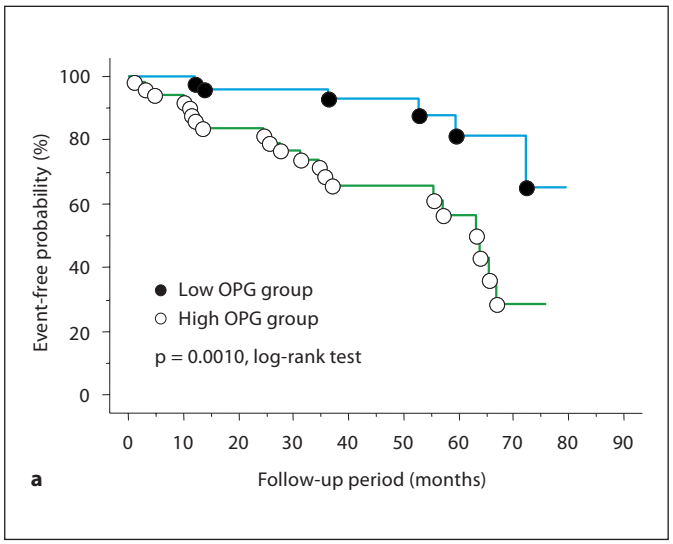
Fig. 1. Association between serum OPG and ACI in new HD patients. The patients were divided into 3 groups according to their ACI: ≤20% (1–20%), >20% and <33%, and ≥33% (33–98%). Higher serum OPG levels are significantly associated with more severe ACI ($p < 0.001$, one-way ANOVA). Data are expressed as mean ± SEM.

Cardiovascular Events and Outcome

Twenty-seven patients had a history of cardiovascular events before the start of maintenance HD therapy. Of these 27, only 2 patients experienced more than 1 cardiovascular event. Ischemic heart diseases included acute myocardial infarction (n = 2), unstable angina (n = 2) and angina pectoris (n = 5). Two patients underwent coronary artery bypass grafting. Chronic heart failure, cerebral infarction, cerebral bleeding and dissecting aortic aneurysm were found in 2, 10, 6, and 2 patients, respectively. During the follow-up periods (41.5 ± 20.2 months), 27 patients had cardiovascular events, which included ischemic heart diseases (n = 7), chronic heart failure (n = 2), dissecting aortic aneurysm (n = 3), cerebral infarction (n = 6), cerebral bleeding (n = 3) and sudden death (n = 6) as the first cardiovascular event. At the end of follow-up, 21 total deaths were recorded. The causes of cardiovascular deaths were ischemic heart disease (n = 2), chronic heart failure (n = 2), cerebral hemorrhage (n = 2) and sudden death (n = 6). Non-cardiovascular deaths consisted of sepsis (n = 2), malnutrition (n = 2) and malignancy (n = 5).

Comparison between the Patients with Low and High OPG Concentrations in Serum

Patients were divided into 2 groups according to the serum OPG level. The low OPG group (n = 50) had OPG levels below the median level for all patients, the high OPG group (n = 50) had OPG levels above the median. A comparison of the baseline characteristics of the patients in the 2 groups is shown in table 1. Patients in the high OPG group were significantly older than those in the low OPG group. ACI and both all-cause and cardiovascular mortality were significantly higher in the high OPG group than the low OPG group. Similarly, the number of patients with cardiovascular events after the start of maintenance HD therapy was significantly greater in the high OPG group than the low OPG group. Moreover, when the degrees of ACI were classified into tertiles, higher serum OPG levels were associated with more severe ACI (fig. 1).



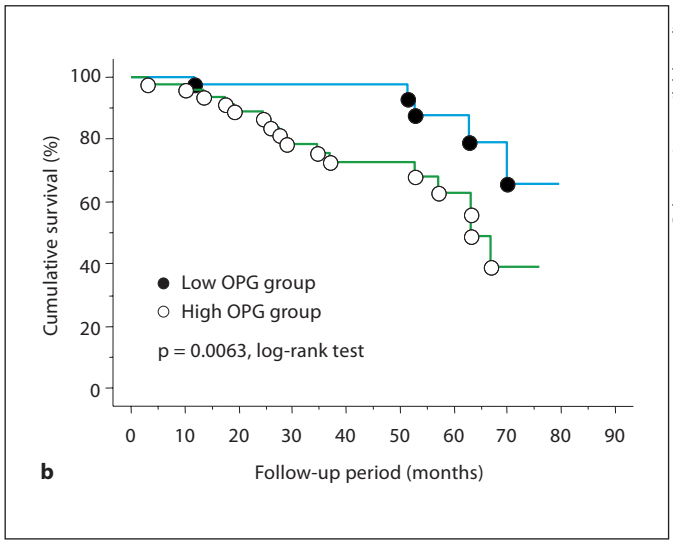


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Fig. 2. Kaplan-Meier analysis of cardiovasular events (**a**) and all-cause mortality (**b**) of 99 new HD patients. Patients with high OPG levels showed significantly greater morbidity from cardiovascular events and mortality from all causes than those with low OPG levels (p = 0.001 and p = 0.006, respectively, log-rank test).

Table 2. Multivariate Cox proportional hazards analysis

	Cardiovascular events			All-cause mortality		
	HR	95% CI	p	HR	95% CI	p
Age (/1 year)	–	–	–	1.07	1.03–1.12	0.002
Albumin (/1 g/dl)	–	–	–	0.36	0.17–0.75	0.006
ACI (high vs. low)	13.3	3.07–58.1	0.001	3.67	1.18–11.5	0.025
OPG (high vs. low)	2.88	1.09–7.62	0.033	–	–	–
Past cardiovascular events (presence vs. absence)	2.47	1.10–5.52	0.028	–	–	–

Kaplan-Meier Analysis

Kaplan-Meier analyses were performed to determine the univariate association between the level of OPG in serum and outcomes of the cohort. Compared with the low OPG group, the high OPG group showed a higher prevalence of cardiovascular events and all-cause mortality (fig. 2).

Univariate and Multivariate Analyses with Cox Proportional Hazard Model

In univariate analysis for cardiovascular events, the most important associated factors were found to be age (HR 1.05, p = 0.004), serum albumin level (HR 0.50, p = 0.024), ACI (high vs. low, HR 18.0, p = 0.001), serum OPG (high vs. low, HR 4.23, p = 0.002), and past cardiovascular events (presence vs. absence, HR 2.61, p = 0.015). Intermediate associated factors were DM (presence vs. absence, HR 1.75, p = 0.149), corrected calcium (HR 1.49, p = 0.087), and increased CRP (≥0.3 mg/dl; presence vs. absence, HR 1.87, p = 0.114). On the other hand, sex, smoking, BMI, medications, blood pressure, total cholesterol, phosphate, alkaline phosphatase and intact parathyroid hormone were not significantly associated with cardiovascular events. In multivariate analysis, ACI, serum OPG and past cardiovascular events were the most statistically important prognostic factors to predict new cardiovascular events (table 2).

Table 3. Logistic analysis of factors associated with OPG level

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Age	1.086	1.045–1.128	<0.001	1.051	1.005–1.100	0.030
Sex (male vs. female)	2.943	1.231–7.035	0.015	3.034	1.028–8.948	0.044
DM	1.864	0.829–4.189	0.132	1.867	0.615–5.666	0.270
Smoking	1.224	0.548–2.734	0.696			
BMI	0.925	0.830–1.031	0.159			
$CaCO_3$/vitamin D_3	1.896	0.707–5.086	0.497			
ACEI/ARB	0.589	0.257–1.383	0.548			
ACI (high vs. low)	5.833	2.454–13.87	<0.001	4.994	1.690–14.76	0.004
Systolic blood pressure	0.997	0.982–1.012	0.661			
Diastolic blood pressure	0.976	0.952–1.000	0.047	0.989	0.961–1.019	0.476
Albumin	0.584	0.296–1.154	0.122	1.137	0.465–2.783	0.778
Total cholesterol	0.998	0.991–1.005	0.521			
Corrected calcium	1.237	0.797–1.919	0.343			
Phosphate	0.737	0.572–0.948	0.018	0.755	0.527–1.081	0.125
Alkaline phosphatase	0.999	0.997–1.001	0.470			
Intact PTH	0.999	0.997–1.002	0.597			
Increased CRP	0.957	0.432–2.110	0.912			
Past cardiovascular events	1.138	0.470–0.774	0.774			

ACEI = Angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; PTH = parathyroid hormone; increased CRP = C-reactive protein ≥ 0.3 mg/dl.

In the univariate analysis for all-cause mortality in new HD patients, there were many significant, associated factors: age, BMI, diastolic blood pressure, serum albumin, corrected serum calcium and phosphate, increased C-reactive protein (presence vs. absence), ACI (high vs. low) and OPG (high vs. low). In the multivariate analysis, age, serum albumin and ACI were the most statistically important prognostic factors to predict death (table 2).

Logistic Analysis of Factors Associated with OPG Level

Using the logistic analysis method, we examined the factors contributing to OPG levels in new HD patients. We selected the following factors with a correlation coefficient of less than 0.15 with respect to OPG levels: age, sex (female or male), DM (presence or absence), diastolic blood pressure, serum albumin, serum phosphate and ACI (high vs. low) (table 3). Multivariate regression analysis showed that the high OPG group at the start of HD was significantly associated with older age (HR 1.05, 95% CI 1.01–1.10, p = 0.030), male sex (HR 3.03, 95% CI 1.03–8.95, p = 0.044) and high ACI (HR 4.99, 95% CI 1.69–14.76, p = 0.004).

Discussion

Our results showed that elevated levels of OPG predicted subsequent cardiovascular events, independently of the levels of ACI or past cardiovascular events, in new HD patients. Also, high serum OPG at the start of HD was independently associated with older age, male sex and high ACI. However, no association was observed between serum OPG levels and bone mineral markers or CRP levels, or between high serum OPG and mortality in these HD patients.

Cardiovascular mortality, which might be related to VC, is the leading cause of death in patients treated by dialysis, with mortality rates of 10–30 times higher than the general population despite stratification for sex, race and presence of DM [1, 21]. Nearly all studies have shown that once coronary artery calcification is present in dialysis patients, it rapidly progresses [4, 22, 23]. In the present study, one third of the patients had cardiovascular events in a period of 41.5 ± 20.2 months after the start of HD therapy, and half of the deceased patients died of cardiovascular-related causes. Many risk factors of VC have been found, such as high serum levels of calcium, phosphate, Ca × P, and parathyroid hormone (mineral metabolism fac-

tors), in addition to age and duration of dialysis [8–11]. Abnormal bone turnover in chronic renal failure is considered to be one of the pathogenic links to VC, but the present study did not reveal an association between these mineral metabolism factors and cardiovascular events or mortality. Recently, several calcification inhibitors were reported to have a role in metastatic calcification [6, 7, 12]. Among these factors, OPG is also implicated in human atherosclerosis and vascular mortality [14–19]. As for maintenance dialysis patients, likewise, elevated OPG levels were reported to be independently associated with aortic calcification [17, 23, 24] and cardiovascular mortality [18, 19]. Extensive arterial calcification is typical of HD patients, even at a young age [4, 5]. Furthermore, VC is common and progressive in patients with chronic kidney disease [25, 26], which is a major and serious risk factor for CVD [27]. In this study, serum OPG level was found to be increased in accordance with the severity of ACI in new HD patients (fig. 1). These findings suggest that there may be a prior relationship between OPG and VC before the induction of HD therapy.

Although previous reports revealed that the severity of ACI is associated with subsequent cardiovascular-related mortality [4, 19], there are few reports showing the relationships between the degree of ACI at the start of HD treatment and the incidence of CVD morbidity and/or mortality. Spiegel et al. [28] reported that 60% and 70% of patients new to hemodialysis had evidence of coronary artery and aortic calcification, respectively. The present study showed that subsequent cardiovascular events in new HD patients may be predicted by measuring plasma OPG independently of ACI, as shown by multivariate analysis. This result means that OPG does not merely increase as a compensatory mechanism for VC. In agreement with previous studies [16, 29], age and sex also influenced OPG levels in the present study. Morena et al. [18] showed that high serum OPG level is a vascular risk factor, in particular in dialysis patients who have high C-reactive protein levels. In addition, OPG is known to participate in the vascular cytokine network [30]. These studies suggest that inflammation has an additive detrimental effect on the link between high levels of OPG and cardiovascular events and mortality; however, our study could not show that OPG and CRP are directly correlated. Furthermore, the present study did not show an association between OPG levels and all-cause and cardiovascular mortality. The reason may be related to the small number of patients (n = 12), although more than half of the deceased patients died of cardiovascular-related causes. In any case, regular determination of this marker may be useful as part of the clinical follow-up of new dialysis patients.

Other factors, such as sex and metabolic factors, are possibly associated with elevated serum OPG levels and cardiovascular events, as previously reported [29, 31, 32]. Male sex and DM were predominant in the high OPG group compared with the low OPG group in this study, but these were not significant factors for predicting subsequent cardiovascular events. The reason may be the small number of patients in this study.

In contrast to OPG-knockout mice which develop arterial calcification [12], the present study showed that increased serum OPG levels were associated with the severity of VC (ACI) and new cardiovascular events. A number of studies [14–16, 29] have suggested that the increased OPG levels represent a compensatory defense mechanism for VC, while Moe et al. [33] proposed that elevated OPG levels may reflect an ongoing attempt by arteries to remodel, behaving like osteoblasts. In addition, Coen et al. [34] showed that elevation of serum OPG level was related to low turnover bone, which does not allow bone to take up a mineral load, thereby leading to VC. On the other hand, Haas et al. [35] showed that elevated OPG in dialysis patients was associated with high turnover bone disease. In the present study, as in previous studies [33, 36], increased serum OPG levels were not correlated with mineral metabolism factors and/or bone turnover markers. It is possible that medications might affect the levels of these parameters (including OPG), but the present study was not designed to determine the effect of the medications on these parameters in such a small number of patients. Thus, this paradoxical finding may be due to the complex interaction of OPG with other factors. Further studies are warranted to clarify the role of OPG in VC and cardiovascular events.

In conclusion, high serum OPG level was a predictor of cardiovascular events in new HD patients and was associated with severity of VC, as were age and sex. Further analyses with data on a large number of patients, as part of a longitudinal study, are necessary to determine the clinical relevance of this observation.

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