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Osteoprotegerin and mortality in hemodialysis patients with cardiovascular disease

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Key words

osteoprotegerin
– chronic kidney disease
– dialysis – cardiovascular disease – all-cause mortality

Abstract. **Background:** Patients treated with hemodialysis (HD) have an increased mortality, mainly caused by cardiovascular disease (CVD). Osteoprotegerin (OPG) is a glycoprotein involved in the regulation of the vascular calcification process. Previous studies have demonstrated that OPG is a prognostic marker of mortality. The aim of this study was to investigate if OPG was a prognostic marker of all-cause mortality in high-risk patients with end-stage renal disease and CVD. **Methods:** We prospectively followed 206 HD patients with CVD. OPG was measured at baseline and the patients were followed for 2 years or until reaching the primary endpoint, i.e., all-cause mortality. **Results:** All-cause mortality during follow-up was 44% (90/206). High OPG was associated with increased mortality, using the first tertile as reference, with an unadjusted HR of 1.70 (CI 1.00 – 2.88) for the second tertile and HR of 1.63 (CI 0.96 – 2.78) for the third tertile. In a multivariate Cox-regression analysis age, CRP and OPG in both the second and third tertile were significantly associated with increased mortality. In the unadjusted survival analysis, a test for trend of OPG yielded a p-value of 0.08; in the adjusted analyses, the p-value for trend was 0.03. **Conclusions:** In a high-risk population of hemodialysis patients with previously documented cardiovascular disease, a high level of OPG was an independent risk marker of all-cause mortality.

Introduction

In patients treated with hemodialysis (HD) the leading cause of mortality is cardiovascular disease (CVD), with a mortality rate of more than 10% during the first year of HD [1]. This may in part be caused by a higher

prevalence of risk factors for CVD in patients treated with chronic HD than in the general population [2, 3]. Additional risk factors for CVD specific for the uremic state, such as anemia, inflammation and secondary hyperparathyroidism, are also common in HD patients [4, 5, 6]. The pathophysiology of the aggressive arteriosclerotic processes causing CVD remain only partly understood [7]. Recent studies have focused on the underlying mechanisms of the uremic mineral bone disorder and its association with CVD [8].

Osteoprotegerin (OPG) is a glycoprotein and member of the tumor necrosis factor (TNF) superfamily [9]. OPG is expressed by endothelial cells, vascular smooth muscle cells and osteoblasts and acts as a decoy receptor for receptor activator NF- κ B ligand (RANKL) [10, 11] and TNF-related apoptosis-inducing ligand (TRAIL) [12].

Human studies have demonstrated that elevated OPG is related to the severity and progression of coronary and aortic calcification [13, 14]. Elevated OPG is also associated with mortality in the general population [15, 16] and in several other high risk subpopulations [17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27].

In the vascular system OPG up-regulation causes a TNF- α sensitization of the endothelial cells in which monocytes migrate into the vascular intima [28]. This is one of the mediating processes in the development of arteriosclerotic disease [29]. However, studies also indicate that OPG has a role as a “survival factor” of endothelial cells that is mediated by inhibition of TRAIL. TRAIL is expressed by endothelial cells and vascular smooth muscle cells and may contribute to

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apoptosis of vascular smooth muscle cells leading to plaque instability [30].

Plasma levels of OPG are higher in patients with end-stage renal disease (ESRD) compared with sex and age matched controls [31]. In addition, in patients with chronic kidney disease (CKD) Stage 4, patients treated with HD, and renal transplant patients, OPG is also a predictor of mortality [32, 33, 34, 35, 36, 37, 38, 39].

The aim of this prospective cohort study was to examine whether OPG would add additional prognostic information in a high-risk population of ESRD patients with CVD undergoing HD.

Materials and methods

Study design

This present study was a sub-study of a randomized, double-blind intervention trial in HD patients with established CVD, comparing the effect of marine n-3 polyunsaturated fatty acids to placebo as secondary prevention of CV events and all-cause mortality [40].

Inclusion criteria were treatment with HD for at least 6 months and CVD. CVD were defined as previously documented myocardial infarction (MI), angina pectoris, angiographically proven coronary artery disease (CAD), stroke, transient ischemic attack (TCI), or peripheral vascular disease (PAD). Exclusion criteria were malignant disease, anticipated poor compliance or participation in other clinical trials.

Patients were recruited from 11 Danish dialysis departments. Of 717 potential participants, 233 met the inclusion criteria. 27 patients refused to participate and finally 206 patients were included in the study.

Follow-up was 2 years or until reaching the predefined end-point, all-cause mortality.

Blood sampling and laboratory analysis

Blood was drawn before a usual dialysis session and before intervention in the primary trial. Serum was stored at -80°C until analysis. Plasma levels of OPG were quantified by commercially available monoclonal antibod-

ies (DY085E from R&D Systems, Abingdon, UK) as previously described [41], however, modifying the assay to a Time-Resolved Immuno Fluorimetry Assay (TRIFMA). At concentrations of 1,000 ng/l the intra- and inter-assay variations were below 5% and 9%, respectively. The limit of detection was 15 ng/l.

Hemodialysis efficiency was quantified by Kt/V (in 75% of the population) or urea reduction ratio (URR) (in 25% of the population).

Statistical analyses

Data of normally distributed variables are reported as mean standard deviation (\pm SD), and median (range) for non-normally distributed variables. Levels of OPG were divided into tertiles for statistical analysis.

Unpaired Student's t-test was used for comparisons between normally distributed variables and Mann-Whitney's test was used for non-normally distributed variables. The χ^2 -test was used to compare non-continuous data. Mortality was displayed as Kaplan-Meier plot (Log-rank test) 1 minus cumulative survival according to OPG tertiles. Cox proportional-hazards regression model were used to estimate the unadjusted and adjusted hazard ratios with 95% confidence interval (CI) for univariate and multivariate predictors of mortality. Analysis of primary endpoints, were adjusted for baseline characteristic (sex, age, blood pressure, diabetes mellitus, calcium-phosphate product, albumin, fibrinogen, C-reactive protein (CRP), and adiponectin levels in plasma and treatment with marine n-3 polyunsaturated fatty acids/placebo). Tests for trend were calculated by entering OPG as a continuous variable in the relevant Cox regression model and reporting the associated Wald p-value. A two-tailed p-value < 0.05 was considered statistically significant. All statistical analyses were performed using the commercially available STATA version 9.1.

Results

Baseline characteristics of the 206 HD patients divided in OPG tertiles are sum-

Table 1. Baseline characteristics according to osteoprotegerin (OPG) tertiles.

Baseline	Total	Tertiles		
		1	2	3
Number	206	69	69	68
OPG (ng/l), range	1.346 – 31.320	1.346 – 4.120	4.120 – 6.042	6.042 – 31.320
OPG (ng/l), mean	5.517 ± 3.182	3.314 ± 607	5.127 ± 590	8.151 ± 4.250
Characteristic				
Sex, male	133 (65%)	51 (74%)	39 (57%)	43 (63%)
Age (years)	67 ± 12	66 ± 11	66 ± 12	68 ± 12
Body mass index (kg/m ²)	24.3 ± 4.3	24.7 ± 4.6	24.3 ± 4.3	23.9 ± 3.8
Diabetes	50 (24%)	15 (22%)	19 (28%)	16 (24%)
Blood pressure (mmHg)				
systolic	151 ± 28	146 ± 27	148 ± 28	158 ± 29
diastolic	77 ± 15	75 ± 15	75 ± 16	80 ± 13
Cardiovascular disease				
Angina pectoris	75 (36%)	20 (29%)	23 (33%)	32 (47%)
Myocardial infarction	66 (32%)	19 (28%)	24 (35%)	23 (34%)
PCI/CABG	55 (27%)	19 (28%)	21 (30%)	15 (22%)
TIA/Stroke	85 (41%)	36 (52%)	22 (32%)	27 (40%)
Peripheral vascular disease	71 (34%)	19 (28%)	31 (45%)	21 (31%)
Hemodialysis				
Time on dialysis (months)	44 ± 41	42 ± 46	43 ± 38	47 ± 37
Dialysis efficiency (Kt/v)	1.41 ± 0.30	1.41 ± 0.30	1.43 ± 0.37	1.38 ± 0.22
Dialysis efficiency (URR)	73.7 ± 5.0	73.0 ± 5.7	74.0 ± 5.7	73.9 ± 4.2
Laboratory parameters				
Hemoglobin (mmol/l)	7.3 ± 0.8	7.2 ± 0.8	7.3 ± 0.7	7.4 ± 0.8
Albumin (g/l)	36.1 ± 4.2	35.9 ± 3.3	36.8 ± 3.7	35.6 ± 5.4
Adiponectin (mg/l)	19.7 ± 12.3	16.0 ± 10.6	19.9 ± 11.1	23.3 ± 13.9
Fibrinogen (µmol/l)	13.9 ± 4.0	13.6 ± 4.4	14.1 ± 4.1	13.9 ± 3.5
CRP (mg/l)	14.0 ± 21.0	17.0 ± 31.4	14.9 ± 14.4	10.1 ± 10.6
Ca ²⁺ × P product (mmol ² /l ²)	4.3 ± 1.0	4.1 ± 1.1	4.4 ± 1.1	4.4 ± 0.9

Table 2. Primary endpoint and hazard ratios according to osteoprotegerin (OPG) tertiles. Data adjusted for baseline characteristics: sex, age, blood pressure, diabetes, calcium-phosphate product, albumin, fibrinogen, CRP, adiponectin and treatment with n-3 polyunsaturated fatty acids/placebo.

Endpoint outcome	Tertiles		
	1	2	3
Mortality (all-cause)	23 (33%)	34 (49%)	33 (49%)
Unadjusted			
Hazard ratio (CI)	1	1.70 (1.00 – 2.89)	1.63 (0.96 – 2.78)
p-value	N/A	0.049	0.072
Adjusted			
Hazard ratio (CI)	1	1.98 (1.12 – 3.49)	1.94 (1.05 – 3.56)
p-value	N/A	0.018	0.033

marized in Table 1. Mean follow-up time to the primary endpoint was 301 days in this study. All-cause mortality during the 2 years follow-up was 44% (90/206) equivalent to a mortality rate at 29.4 per 100 person years.

Levels of OPG were divided into tertiles, first: 1,346 – 4,120 ng/l, second: 4,120 – 6,042 ng/l, third: 6,042 – 31,320 ng/l. High OPG was associated with increased mortality, using the first tertile as reference, with an unadjusted hazard ratio (HR) of 1.70 (CI 1.00

– 2.89, p-value < 0.05) for the 2nd tertile and 1.63 (CI 0.96 – 2.78, p-value = 0.07) for the 3rd tertile. When adjusted for sex, age, blood pressure, diabetes, calcium-phosphate product, albumin, fibrinogen, CRP and adiponectin and treatment with marine n-3 polyunsaturated fatty acids/placebo the adjusted OPG HR was 1.98 (CI 1.13 – 3.49, p-value = 0.02) for the 2nd tertile and 1.94 (CI 1.05 – 3.56, p-value = 0.03) for the 3rd tertile. Unadjusted and adjusted HRs are summarized in Table 2.

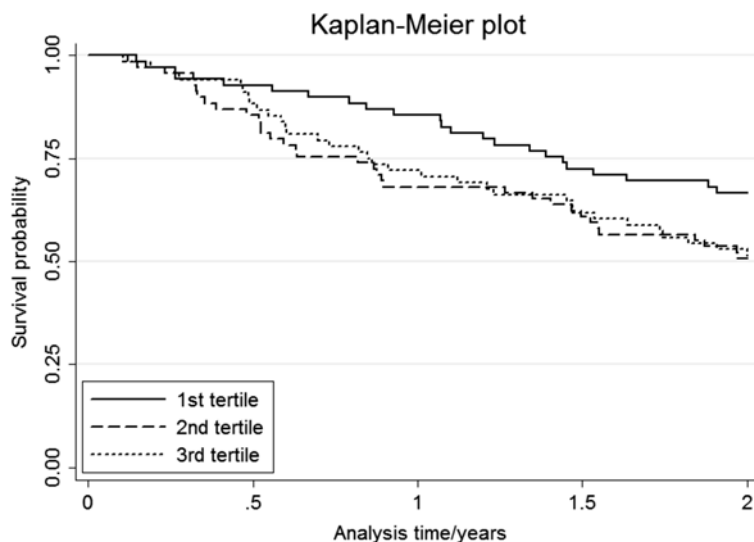


Figure 1. Kaplan-Meier plot showing survival probability according to osteoprotegerin (OPG) tertiles.

In multivariate Cox-regression analysis age (p-value < 0.001), CRP (p-value < 0.05), OPG in the 2nd (p-value = 0.02) and 3rd tertile (p-value = 0.03) were significantly associated with increased mortality. Figure 1 shows a Kaplan Meier plot for survival according to OPG-tertiles.

In the unadjusted survival analysis, a test for trend of OPG yielded a p-value of 0.08; in the adjusted survival analyses, the p-value for trend was 0.03.

Discussion

This study is, to the best of our knowledge, the first to evaluate OPG as a risk factor in a selected cohort of patients with the combination of both ESRD and CVD. The results revealed an association between OPG and all-cause mortality in these high risk ESRD patients, when adjusting for other risk factors.

The mortality rate of 29.4 per 100 person years was high compared to the general Danish HD population (23 per 100 person years). This confirms that this study population comprised a high risk chronic HD population due to the previous documented CVD.

OPG and chronic kidney disease

Plasma levels of OPG are higher in patients with CKD Stage 2 – 5 compared with

sex and age matched controls [31]. Furthermore, it is known that a decline in renal function results in increased OPG levels [49]. In addition, ESRD patients treated with HD and peritoneal dialysis have higher OPG levels than CKD Stage 4 – 5 patients not undergoing dialysis [37]. One study has shown that OPG decrease following renal transplantation [49].

OPG is associated with markers of inflammation, endothelial dysfunction, oxidative stress and CVD in patients with ESRD commencing treatment with HD [39]. Furthermore, OPG is associated with vascular calcification in coronary arteries in patients with CKD Stage 2 – 5 [33, 49, 49] as well as in the aorta for patients with ESRD [36, 37]. Both progression of vascular calcification [49, 49] and CV events are related to high level of OPG in patients with CKD [34, 36, 49].

As might be expected in this study population, high concentrations of OPG were observed compared to other studies where identical monoclonal antibodies were used [15, 22, 23, 33, 49].

OPG and mortality

Two larger population-based cohort studies, the Framingham Study with 3,250 participants and the Tromsø Study with 6,265 participants, have demonstrated that elevated OPG is positively associated to both vascular, nonvascular, and all-cause mortality in the general population [15, 16].

Elevated OPG levels predict negative outcome in patients with CVD. This has been demonstrated in patients with stable CAD and in patients with acute coronary syndrome (ACS) [18, 20, 23]. In addition, OPG predict a poor outcome in both patients with symptomatic aortic stenosis and stroke [17, 25, 26].

Despite the generally elevated levels of OPG in patients with CKD, OPG remain a predictor of all-cause mortality in this population. Previous studies of patients with both CKD Stage 4 and 5 have demonstrated that OPG is associated with all-cause mortality. Compared to our study, these patients were younger, had a lower prevalence of CVD and lower mortality rates [33, 37].

Two separate cohorts of ESRD patients have previously been evaluated close to the start of renal replacement therapy. Thus, Nishiura et al. [36] included 99 patients with a mean age of 59 years where 27% had a medical history of CVD [36]. Matsubara et al. [39] studied 265 patients with a lower mean age of 53 years but a higher prevalence of CVD of 35%. OPG levels were related to all cause-mortality in both studies despite relatively low mortality rates.

Two previous studies in patients treated with chronic HD have examined the association between OPG and all-cause mortality. Nakashima et al. [36] followed a cohort of 151 normoalbuminemic HD patients for 6 years. In this study, 33% of the patients had a clinical history of CVD. The mortality rate was 4.4 per 100 patient years which is relatively low compared to previously reported mortality rates in Japanese ESRD patients [35]. However, OPG was still related to all-cause mortality.

In contrast to the previous studies mentioned, Morena et al. [34] found the lowest mortality in the middle tertile of OPG in a cohort of 185 HD patients. Nevertheless, only high levels of OPG were significantly associated with both CV mortality and all-cause mortality. This study included patients with a high age (mean of 67 years) and a high prevalence of CVD at baseline. During 2 years of follow-up 50 patients died, which is high compared to other studies, but lower than the mortality rate in our study.

Strengths and limitations

The strength of this study is that it includes a well characterized patient population with ESRD and CVD. The study is limited by the relatively small number of patients but the high primary event rate during follow-up may compensate for this. The choice of all-cause mortality as primary endpoint reduces the risk of misclassification.

Conclusion

In a high-risk population of hemodialysis patients with previously documented CVD a

high level of OPG was an independent risk marker of all-cause mortality.

Disclosures

The authors have no disclosures.

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