Elevated serum osteoprotegerin levels are associated with inflammation, malnutrition, and new onset cardiovascular events in peritoneal dialysis patients

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ABSTRACT

Elevated serum osteoprotegerin levels are associated with inflammation, malnutrition, and new onset cardiovascular events in peritoneal dialysis patients

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Backgrounds : Osteoprotegerin (OPG) is known to regulate bone mineral metabolism and to be also associated with inflammation, cardiovascular disease (CVD), and mortality. Malnutrition–inflammation-atherosclerosis (MIA) syndrome is commonly found and closely linked to mortality in patients with renal failure. The aim of this study was to investigate the associations between OPG and MIA syndrome in prevalent peritoneal dialysis (PD) patients.

Methods : Prevalent PD patients for more than 6 months were followed from March 2005 to May 2010. At baseline, OPG, hs-CRP, albumin, and % lean body mass (LBM) by creatinine kinetics were checked, and subjective global assessment (SGA) was performed. New-onset cardiovascular events and patient's mortality were evaluated during the study period. Based on the median level of OPG, patients were classified as lower OPG (LO) group (n = 88) and higher OPG (HO) group (n = 88).

Results : A total of 176 patients (age 52.0 ± 11.8 years, male 50.6%, duration of PD 105.3 ± 67.2 months) were recruited and followed. In HO group, age, hs-CRP levels, and Charlson's comorbidity indices were higher, while serum albumin levels, %LBM, and SGA score were significantly lower than LO group. OPG levels were positively correlated with inflammatory markers, whereas negatively correlated with nutritional status. Cardiovascular events occurred in 51 patients during the study period. Univariate cox regression analysis revealed OPG to be a risk factor for newly developed CVD [per an increase by 1 in log OPG, Hazard ratio (HR): 2.34; 95% Confidence interval (CI): 1.35~4.04; p = 0.002], which remained significant after adjustment for age, sex, diabetes, and duration of PD. (HR: 2.00; 95% CI: 1.13~3.89; p = 0.02). However when hs-CRP levels and %LBM were included

for further adjustment, the significance of OPG disappeared (HR: 1.92; 95% CI: 0.96~3.63; p = 0.06, HR: 1.79; 95% CI: 0.92~3.53; p = 0.09 respectively). A total of 28 patients died. Mortality rate was higher in HO group than in LO group (n = 20, 22.7% versus n = 8, 9.1%), but there was no statistical significance (p = 0.06).

Conclusion: Serum OPG levels were significantly correlated with markers of systemic inflammation and malnutrition. Also, OPG worked as a significant predictor of newly developed CVD in PD patients. These findings suggest OPG might be a prognostic indicator of MIA syndrome in prevalent PD patients.

Key words : *osteoprotegerin, inflammation, malnutrition, cardiovascular disease, peritoneal dialysis*

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I. INTRODUCTION

Atherosclerotic cardiovascular disease (CVD) is highly prevalent and more common in patients with end stage renal disease (ESRD) compared with the general population. Moreover, CVD is the leading cause of death in ESRD patients.[1] Non-traditional risk factors as well as traditional risk factors such as diabetes, hypertension, smoking, and dyslipidemia are attributable to high prevalence of CVD and mortality for dialysis patients.[2] Chronic inflammation and malnutrition as non-traditional risk factors play an important role in the development of CVD in ESRD patients.[3]

Chronic inflammation, as evidenced by elevated proinflammatory cytokines such as interleukin-6 (IL-6), soluble intercellular adhesion molecule-1 (ICAM-1), and C-reactive protein (CRP), is a well known risk factor for atherosclerosis and has been shown to predict cardiovascular mortality in ESRD patients.[4,5] Moreover, chronic inflammation is closely associated with malnutrition and weight loss as it increases protein-energy wasting in this population.[6]

Osteoprotegerin (OPG) is a decoy receptor for receptor activator of nuclear factor κB ligand (RANKL), which disturbs interaction between RANKL and RANK (receptor activator of nuclear factor κB) on the surface of osteoclast precursors and inhibits differentiation or activation of osteoclasts.[7] This protective molecule for bone resorption is now viewed from a different angle as a mediator of inflammation or biomarker for vascular pathology showing a close association with the development of cardiovascular complications.[8,9] There are increasing data that elevated OPG levels are significantly associated with atherosclerosis and endothelial dysfunction in the general

population[10]. Elevated OPG levels are also associated with cardiovascular events in non-dialysis chronic kidney disease (CKD) and incidental hemodialysis patients[11,12]. In addition, an observational study showed that serum concentrations of OPG are elevated in mal-nourished patients with CKD stage 5.[13]

Therefore, the aim of this study was to investigate the associations between OPG and inflammation and malnutrition in patients maintained on peritoneal dialysis (PD). In addition, we examined a prognostic value of OPG on cardiovascular events and mortality in prevalent PD patients.

II. MATERIALS AND METHODS

1. Patient population

This observational study included 176 prevalent ESRD patients on PD who had been followed-up at Yonsei University Health System in Seoul, Korea. We recruited patients who were older than 20 years of age, had maintained PD for more than 6 months, had no overt infections during the last 3 months prior to the start of this study, and had no medical history of malignancy or other chronic inflammatory diseases (e.g., rheumatoid arthritis or systemic lupus erythematosus).

A senior nursing clinician obtained the demographic data through an interview. The body mass index (BMI) was calculated as the weight (kg) divided by height squared (m^2). To simulate the actual dialysis condition, all patients had a full abdomen at the time of sampling. Blood samples for laboratory measurements were drawn from the antecubital vein at 2-hour after the first PD exchange with 1.5% dextrose dialysate after overnight fasting. The preceding overnight dwell was regulated with 1.5% dextrose dialysate to standardize the glucose load. Comorbid conditions of study subjects were assessed by the Charlson's Comorbidity Index (CCI)[14]. All participants gave their informed consent before entering the study.

2. Laboratory measurements

Plasma and serum were separated from blood within 30 minutes and stored at -70°C until analysis. OPG (Roche Diagnostics, Manheim, Germany) was measured by enzyme linked immunosorbent assay (ELISA), and hs-CRP levels were determined using a BN II analyzer (Dade Behring, Newark, DE, USA) by the latex-enhanced immunoephelometric method. The homeostasis model assessment (HOMA) index which indicates the degree of insulin sensitivity, was calculated by the following formula:

HOMA index = fasting plasma insulin (mU/L) × glucose (mmol/L) / 22.5

3. *Peritoneal equilibration test, assessment of dialysis adequacy, lean body mass by creatinine kinetics and subjective global assessment*

Standard peritoneal equilibrium test (PET) using 4.25% glucose dialysate was performed and patients were classified into one of the four peritoneal transporter group (high, high average, low average, and low) according to the value of dialysate-to-plasma creatinine ratio at 4 hours (D/Pcr4) defined by Twardowski et al.[15]

In addition, urea kinetic studies were performed from a 24-hour collection of dialysate and urine at baseline. Dialysis adequacy was determined by measuring total weekly urea clearance (Kt/Vurea) using standard methods. Lean body mass (LBM) was estimated using creatinine kinetics (CK), and percent lean body mass (%LBM) was calculated as LBM normalized to dry weight.[16] Residual renal function (RRF) was determined as an average of urea and creatinine clearance from a 24-hour urine collection.

Simultaneously, we performed the subjective global assessment (SGA) of the nutritional status of the subjects using a seven-point scale. Patients with the SGA score lower than 5 were defined as malnourished.[17]

4. *Follow-up and endpoints*

Patients were followed from March 2005 until death, transfer to an alternative dialysis method, or

May 2010. Patients who underwent kidney transplantation were censored at the time of kidney transplantation. Primary endpoints were newly developed cardiovascular events defined as coronary artery disease (coronary artery bypass surgery, percutaneous intervention, or acute myocardial infarction), sudden death, congestive heart failure, peripheral artery obstructive disease (revascularization or amputation), and cerebrovascular accident.

5. *Statistical analysis*

Data are expressed as means ± standard deviation (SD) or median for continuous variables and the number and percentage for categorical variables. Based on the median level of OPG, patients were classified as lower OPG group (LO group, OPG < 1,254 pg/mL) and higher OPG group (HO group, OPG ≥ 1,254 pg/mL). The two groups were compared by Student t-test for continuous variables and chi-square test for categorical variables. Pearson's correlation coefficients were calculated to examine the association between OPG and other variables. Comparisons for cardiovascular events and patient survival were performed by Kaplan-Meier analysis, and multivariate Cox regression analysis was performed to determine risk factors for cardiovascular events. We conducted receiver operating characteristic (ROC) analysis to compare the predictive accuracy of OPG, hs-CRP, and %LBM in the development of cardiovascular events, and the area under the curve (AUC) was calculated. *P*-values less than 0.05 were considered significant. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) for Windows, version 18.0 (Chicago, IL, USA).

III. RESULTS

1. *Baseline characteristics of subjects*

Baseline demographic and laboratory characteristics of the patients are detailed in Table 1. The mean age was 52.0 ± 11.8 years and 50.6% (n = 89) were male. The mean duration of peritoneal dialysis was 105.3 ± 67.2 months, and 21.0% of the patients (n = 37) had diabetes. LO and HO groups showed

no significant differences in gender, presence of diabetes, duration of peritoneal dialysis, Ca x P products, dialysis adequacy, proportion of high transporters on PET, and D/Pcr4. However, patients with high OPG levels were significantly older (57.7 ± 10.4 versus 46.3 ± 10.3 years, $p < 0.001$). Serum hs-CRP levels (4.6 ± 7.7 versus 2.5 ± 4.8 mg/L, $p = 0.02$) and Charlson's comorbidity indices (3.7 ± 1.7 versus 2.7 ± 1.0 points, $p < 0.001$) were also significantly higher in HO group compared to LO group, whereas serum albumin levels (3.4 ± 0.4 versus 3.6 ± 0.4 g/dL, $p = 0.002$) and %LBM (68.8 ± 11.9 versus 74.6 ± 10.6%, $p = 0.001$) were lower in HO group. In addition, the proportion of malnourished patients (SGA score ≤ 5) was significantly higher in HO group compared to LO group (44.6% versus 25.0%, $p = 0.02$).

Table 1. Baseline characteristics of the subjects based on the median level of OPG

	All (n = 176)	Lower OPG (n = 88)	Higher OPG (n = 88)	*p-value*
Age (years)	52.0 ± 11.8	46.3 ± 10.3	57.7 ± 10.4	< 0.001*
Sex (Male : Female)	89 : 87	42 : 46	47 : 41	0.55
Diabetes mellitus	37 (21.0%)	13 (14.8%)	24 (27.3%)	0.06
Duration of peritoneal dialysis (months)	105.3 ± 67.2	99.0 ± 64.5	111.6 ± 69.6	0.21
OPG (pg/mL)	1276.6 ± 669.7	757.2 ± 272.6	1795.9 ± 531.1	< 0.001*
Hemoglobin (g/dL)	10.3 ± 1.4	10.5 ± 1.4	10.1 ± 1.3	0.07
Calcium (mg/dL)	9.2 ± 0.9	9.2 ± 0.9	9.1 ± 0.9	0.53
Phosphorus (mg/dL)	4.9 ± 1.2	5.0 ± 1.0	4.8 ± 1.3	0.25
Ca x P product	44.9 ± 11.6	45.9 ± 9.8	44.0 ± 13.1	0.26
Parathyroid hormone (pg/mL)	243.3 ± 244.6	213.8 ± 186.6	272.7 ± 287.8	0.11
Albumin (g/dL)	3.5 ± 0.4	3.6 ± 0.4	3.4 ± 0.4	0.002†
Total-cholesterol (mg/dL)	182.5 ± 40.4	186.5 ± 39.2	178.6 ± 41.5	0.20
LDL-cholesterol (mg/dL)	106.1 ± 36.2	108.4 ± 35.8	103.7 ± 36.7	0.40
Triglyceride (mg/dL)	148.1 ± 105.4	146.5 ± 100.9	149.7 ± 110.3	0.84
HDL-cholesterol (mg/L)	45.1 ± 21.9	45.9 ± 13.2	44.3 ± 28.1	0.62
Hs-CRP (mg/L)	3.6 ± 6.5	2.5 ± 4.8	4.6 ± 7.7	0.02‡
HOMA index	4.4 ± 3.9	3.8 ± 2.6	4.9 ± 4.8	0.06
Kt/V urea	1.98 ± 0.37	1.95 ± 0.38	1.99 ± 0.36	0.43
Residual GFR (mL/min/1.73 m^2)	1.00 ± 1.95	1.13 ± 1.93	0.88 ± 1.98	0.40
D/P creatinine at 4 hr	0.75 ± 0.12	0.76 ± 0.13	0.74 ± 0.12	0.35

Peritoneal equilibration test				0.13
High	19 (10.2%)	6 (6.8%)	13 (13.6%)	
Non-High	157 (89.6%)	82 (93.1%)	75 (86%)	
%Lean body mass (%)	71.7 ± 11.6	74.6 ± 10.6	68.8 ± 11.9	0.001†
Malnourished (SGA ≤ 5)	61 (34.6%)	22 (25.0%)	39 (44.6%)	0.02‡
Charlson's comorbidity index	3.2 ± 1.5	2.7 ± 1.0	3.7 ± 1.7	< 0.001*

* < 0.001 ; † < 0.01 ; ‡ < 0.05

Data are expressed as mean ± standard deviation or number of patients (percent).

OPG, osteoprotegerin; Ca, calcium; P, phosphorous; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Hs-CRP, high sensitivity C-reactive protein; HOMA, homeostasis model assessment; GFR, glomerular filtration rate; D/P, dialysate-to-plasma; SGA, subjective global assessment.

2. Correlation analysis between serum osteoprotegerin levels and other parameters

Table 2 shows the association of demographic, biochemical, and dialytic parameters with serum OPG levels. There were significant positive correlations between OPG levels and old age (r = 0.359, $p < 0.001$), presence of diabetes (r = 0.186, $p = 0.02$), serum hs-CRP levels (r = 0.272, $p = 0.007$), and Charlson's comorbidity index (r = 0.319, $p < 0.001$). In addition, OPG levels inversely correlated with serum albumin levels (r = -0.362, $p < 0.001$), %LBM (r = -0.299, $p = 0.001$), and SGA score (r = -0.217, $p = 0.004$). Though OPG levels tend to increase in high transporters, no correlation was found with D/Pcr4. There were no significant association between serum OPG levels and HOMA index, RRF.

Table 2. Pearson's correlation coefficients of OPG with clinical parameters

Variables	correlation coefficient	*p-value*
Age (years)	0.359	< 0.001*
Sex (Male)	-0.123	0.10
Diabetes mellitus	0.186	0.02‡
Duration of peritoneal dialysis (months)	0.104	0.17
Hemoglobin (g/dL)	-0.130	0.09
Calcium (mg/dL)	-0.049	0.52
Phosphorus (mg/dL)	0.181	0.08
Ca X P product	0.179	0.09
Parathyroid hormone (pg/mL)	0.068	0.37
Albumin (g/dL)	-0.362	< 0.001*
Total-cholesterol (mg/dL)	-0.005	0.27
LDL-cholesterol (mg/dL)	-0.031	0.68
Triglyceride (mg/dL)	-0.005	0.94
HDL-cholesterol (mg/L)	0.041	0.59
Hs-CRP (mg/L)	0.272	0.007†
HOMA index	0.093	0.24
D/P creatinine at 4 hr	0.016	0.84
Peritoneal equilibration test (High)	0.232	0.002†
Kt/V urea	0.024	0.75
Residual GFR (mL/min/1.73 m^2)	-0.079	0.30
%Lean body mass (%)	-0.299	0.001†
SGA	-0.217	0.004†
Charlson's comorbidity index	0.319	< 0.001*

* < 0.001 ; † < 0.01 ; ‡ < 0.05

OPG, osteoprotegerin; Ca, calcium; P, phosphorous; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hs-CRP, high sensitivity C-reactive protein; HOMA, homeostasis model assessment; GFR, glomerular filtration rate; D/P, dialysate to plasma; SGA, subjective global assessment.

3. Risk analysis for cardiovascular events

During the study period, cardiovascular events occurred in 51 patients: coronary artery disease, including acute myocardial infarction, in 19, congestive heart failure in 9, peripheral artery obstructive disease in 6, cerebrovascular accident in 11, and sudden death in 6. The rate of newly developed cardiovascular events was significantly higher in HO group (n = 36, 40.9%) than in LO group (n = 15, 17%, $p < 0.01$). Kaplan-Meier plots showed that time to cardiovascular events was significantly longer in LO group compared to HO group (Figure 1).

Results of univariate and multivariate Cox proportional hazards analysis models of OPG are displayed in Table 3. Univariate Cox regression analysis revealed that higher OPG level [per an increase by 1 in log OPG, Hazard ratio (HR): 2.34; 95% Confidence interval (CI): 1.35~4.04; $p = 0.002$] was a significant risk factor for cardiovascular events. Adjustments made in successive models revealed that higher OPG level (HR: 2.0; 95% CI: 1.13~3.89; $p = 0.02$) remained robust as a significant predictor of cardiovascular events when adjustments were made for age, sex, diabetes, duration of PD, LDL-cholesterol, and RRF. Meanwhile, when %LBM and hs-CRP levels were included for further adjustment, the significance of OPG as a risk factor of cardiovascular events disappeared (HR: 1.92; 95% CI: 0.96~3.63; $p = 0.06$, and HR: 1.79; 95% CI: 0.92~3.53; $p = 0.09$).

The receiver operating characteristic (ROC) curves using variables (OPG, hs-CRP, and %LBM) are plotted in Figure 2. The areas under the curve (AUCs) of OPG, hs-CRP, and %LBM for the development of cardiovascular events were 0.683, 0.659, and 0.682, respectively ($p < 0.01$ for all).

4. Patient survival

During the follow-up period, 28 patients died. The most common cause of death was cardiovascular disease (46.4%) followed by infection (39.3%) and malignancy (10.7%). Mortality rate in HO group was higher than in LO group (n = 20, 22.7% vs. n = 8, 9.1%), but there was no statistical significance ($p = 0.06$, Figure 1).

Table 3. Hazard ratios and 95% confidence intervals for cardiovascular events according to the serum levels of OPG (Cox Proportional Hazards Analysis)

	Log OPG		
	HR (per 1 increase in log OPG)	95% CI	*p-value*
[1]Model 1	2.34	1.35-4.04	0.002
[2]Model 2	2.0	1.13-3.89	0.02
[3]Model 3	1.92	0.96-3.63	0.06
[4]Model 4	1.79	0.92-3.53	0.09

[1]Model 1: Unadjusted relative risk; [2]Model 2: Adjusted for age, sex, duration of peritoneal dialysis, diabetes, LDL-cholesterol, and residual renal function; [3]Model 3: Adjusted for Model 2 plus %lean body mass; [4]Model 4: Adjusted for Model 2 plus log hs-CRP.

OPG, osteoprotegerin; LDL, low-density lipoprotein; hs-CRP, high sensitivity C-reactive protein; HR, hazard ratio; CI, confidence interval

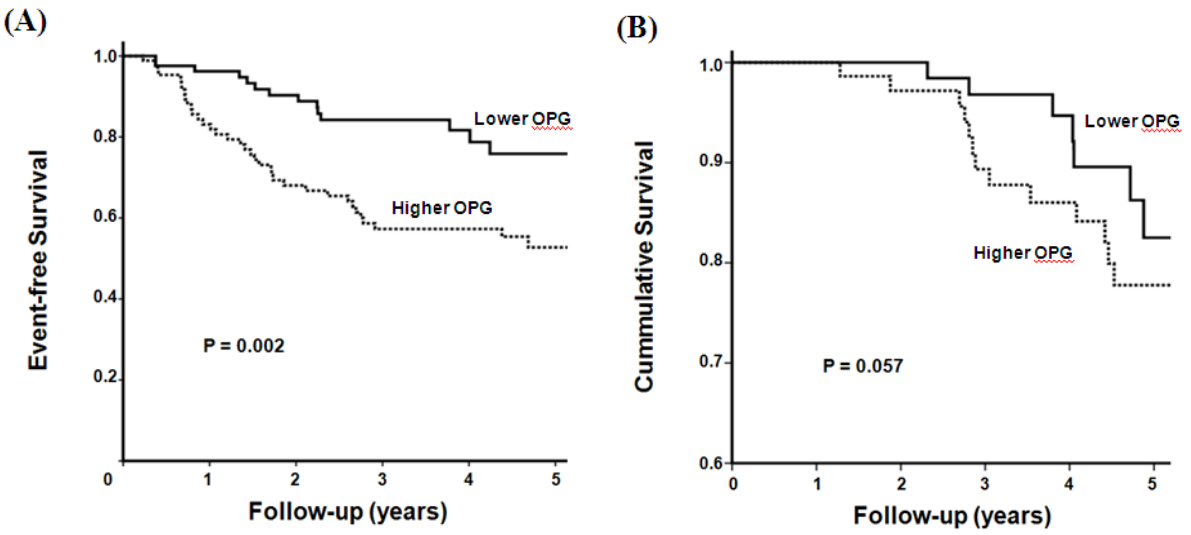

Figure 1. Kaplan-Meier survival analysis for cardiovascular event-free survival (A) and patient's survival (B) based on osteoprotegerin (OPG) levels. Patients with higher OPG level showed significantly higher cardiovascular events than patients with lower OPG level ($p < 0.01$). Mortality rate in higher OPG group was higher than in lower OPG group (n = 20, 22.7% vs. n = 8, 9.1%), but there was no significance ($p = 0.06$).

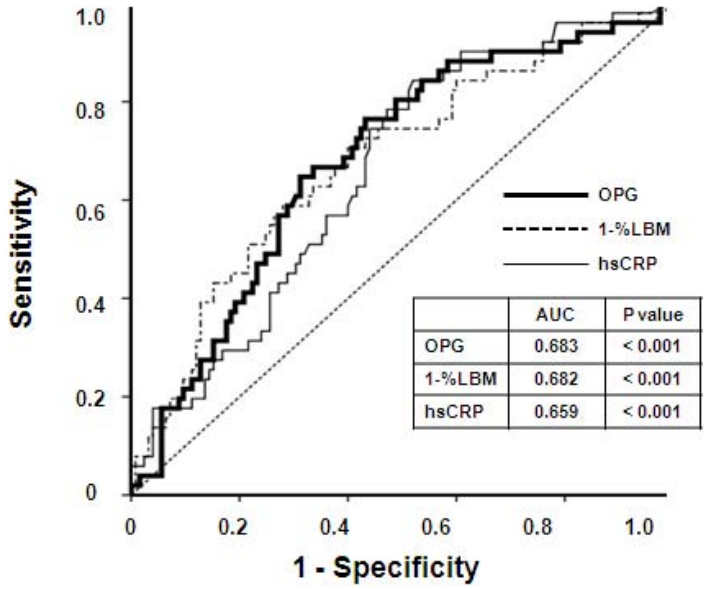

Figure 2. ROC curves using variables (OPG, hs-CRP, and %LBM). The AUCs of OPG, hs-CRP, and % LBM were 0.683, 0.659, and 0.682, respectively ($p < 0.001$).

IV. DISCUSSION

In this observational study, we found that serum OPG levels are closely correlated with inflammatory and nutritional status in continuous ambulatory peritoneal dialysis (CAPD) patients. Furthermore, this study showed that elevated OPG levels are significantly associated with newly developed cardiovascular events in prevalent CAPD patients.

OPG is a member of tumor necrosis factor (TNF) receptor superfamily which acts as a decoy receptor for RANKL. RANKL interacts with RANK on osteoclast precursor and induces activation/differentiation of osteoclast, which in turn causes bone resorption. OPG plays a role as a reversible inhibitor in this process.[8,9] In addition, it is known to be produced by various cells, including vascular smooth muscle cells (VSMCs) and endothelial cells and have a functional role in the vascular pathology.[18,19] Although OPG seems to have a protective effect for vascular calcification or atherosclerotic process in vitro and experimental models[20-22], many recent studies reported that OPG levels are elevated in patients with various atherosclerotic diseases such as coronary and peripheral artery disease, ventricular dysfunction, and cerebrovascular accident in both non-dialysis CKD and ESRD patients on dialysis[23-26]. These vascular pathologies in combination with elevated OPG levels are more prominent in patients with poor renal function.[13] In addition, the extent and progression of vascular calcification increase in accordance with OPG levels in patients on hemodialysis.[27] These findings implicate that OPG might be increased by an incomplete compensatory mechanism for vascular calcification and is a biomarker predictive of atherosclerosis in CKD patients.

Moreover, numerous studies also reported that OPG levels are well correlated with CRP, an acute reactant protein in active atherosclerotic process, and this finding suggests the possible role of OPG as an active mediator of vascular pathology via inflammation.[28] Several mechanisms have been suggested for the role of OPG in enhanced systemic inflammation. OPG induces migration/endothelial aggregation of inflammatory cells and hinders TNF-related apoptosis-inducing ligand (TRAIL) from binding to its receptor, inhibiting apoptosis of infiltrating inflammatory cells.[29]

In addition, RANKL/OPG systems are essential for lymph node organogensis and lymphocyte development. OPG ligand also activates T cells (induce T cell memory function, prime cytotoxic T cells, influence Th1/Th2 cell fate decision and cytokine production) by interacting with dendritic cells.[30] As such, OPG modulates the immune system and induces proinflammatory cytokine production in VSMCs and macrophages.[31] Moreover, OPG production is regulated and increased by proinflammatory cytokines such as IL-1, IL-6, TNF-α, and platelet derived growth factor (PDGF) in VSMCs and endothelial cells.[19,32,33] The close interplay between OPG and inflammation has been validated in various diseases. OPG levels are commonly elevated in patients with typical chronic inflammatory diseases such as rheumatoid arthritis, and OPG levels are upregulated by circulating TNF-α which can be normalized by anti-TNF-α therapy.[34] In addition, most studies performed with dialysis population showed that OPG and inflammatory cytokines, including CRP and IL-6, are closely associated with each other.[13,19]

Malnutrition-inflammation complex syndrome is commonly found and is closely linked to the acceleration of atherosclerotic cardiovascular disease in ESRD patients.[6,35] Chronic infection, dialysis membrane, and uremia per se predispose patients with CKD or ESRD to proinflammatory status. Proinflammatory cytokines in turn cause malnutrition by increasing protein hydrolysis, directly affecting the gastrointestinal system, or indirectly decreasing appetite.[3] As mentioned above, accumulating data has shown that high OPG levels are closely related with inflammation and atherosclerosis. Matsubara et al. also demonstrated a relationship of high OPG levels with inflammation and malnutrition,[13] which are significant risk factors in atherosclerotic cardiovascular disease in advanced CKD patients. We also observed significantly higher hs-CRP levels and higher incidence of malnutrition in PD patients with elevated OPG levels. Moreover, the significance of OPG in predicting newly developed cardiovascular events disappeared after adjusting for hs-CRP and %LBM, respectively. These findings indicate that higher OPG levels and malnutrition-inflammation are interrelated and do not impose separate risks for cardiovascular disease. An observational study by Morena et al. also showed that serum OPG levels were associated with mortality in ESRD population, demonstrating that OPG is a significant risk factor in patients with

high CRP levels, but not in patients with normal CRP levels.[36] Furthermore, another recent study also revealed that OPG levels are not related with CRP levels in normo-albuminemic HD patients.[37] Based on the previous and present results, OPG seems to be closely associated with atherosclerotic change in dialysis patients, which might be possibly mediated by inflammation and malnutrition.

In this study, the overall mortality rate tended to be higher in patients with elevated OPG levels, without significance. Twenty-eight patients died, and only 13 were due to cardiovascular disease. This figure is quite low, which might indicate a lack of statistical power. This is partly because our study subjects were relatively stable and young PD patients. A longer follow up with a larger sample size is needed to evaluate the prognostic value of OPG for mortality in PD patients.

Although concomitant medications were not investigated in the present study, no association was observed between OPG levels and bone mineral metabolism markers, including Ca, P, Ca x P, and PTH as shown in previous reports.[36,38] Wittersheim et al. tried to reveal the associations between bone status and serum OPG concentrations in ESRD patients. Although OPG levels were elevated in HD and PD patients, there was no association between circulating OPG concentrations and bone mineral metabolism, including bone densitometry and markers of bone turnover rate and bone resorption rate.[39] Our results also failed to show the relationship of OPG levels with bone mineral markers. These findings suggest that OPG is not merely a marker of bone mineral metabolism, but a more complex marker for inflammation, malnutrition, and vascular calcification in CAPD patients.

Several shortcomings should be discussed in this study. First, we included relatively small number of patients from a single center. Therefore, further larger scaled studies are needed to confirm our findings. In addition, since the present study is an observational study rather than interventional study and single measurements of the OPG at baseline were used for analysis, the causal relationship between high OPG levels and cardiovascular prognosis has not been clarified. Last, as we did not perform the imaging analysis for vascular calcification such as coronary CT, quantitative comparison between vascular calcification and OPG levels could not be conducted. Although we did not investigate vascular calcification in subjects, elevation of serum OPG levels in PD patients has been observed and found to be associated with vascular calcification and arterial stiffness.[37,40] Vascular

calcification and consequent endothelial dysfunction might also be attributable to the development of cardiovascular events in this population.

V. CONCLUSION

In conclusion, we demonstrated that serum OPG level is a meaningful predictor of cardiovascular events in CAPD patients. It is also significantly correlated with markers of systemic inflammation and malnutrition. These findings suggest that OPG could be helpful to assess the cardiovascular risk in PD patients.

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ABSTRACT(IN KOREAN)

복막 투석 환자에서 심혈관 질환의 예측인자로서 osteoprotegerin의 의의

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구향모

목적: Osteoprotegerin (OPG)은 골대사를 조절하는 것으로 알려져 있는 물질로, 최근 만성 염증, 심혈관 질환의 발생 및 사망률과 밀접한 관련성이 있음이 밝혀지면서 주목을 받고있다. 영양실조-염증-동맥경화 증후군 (malnutrition-inflammation-atherosclerosis, MIA syndrome)은 신부전 환자에서 흔히 관찰되며 불량한 예후와 연관되어 있다. 저자들은 본 연구에서 복막투석중인 말기 신부전 환자를 대상으로 OPG와 MIA 증후군을 구성하는 요소들 사이의 연관관계 및 OPG에 따른 심혈관 질환의 발생과 환자의 사망률과의 연관성에 대해 알아보고자 하였다.

방법: 연세대학교 의과대학 병원에서 6 개월 이상 복막투석을 유지하였던 환자를 대상으로 2005 년 3 월부터 2010 년 5 월까지 관찰 연구를 진행하였다. 연구 시작 시점에 OPG, 고감도 C-반응단백, 알부민 등을 측정하였으며, 크레아티닌 약동학을 이용하여 제지방 체중 (% lean body mass)을 계산하였고, 설문을 통하여 SGA (subjective global assessment)를 측정하였다. 상기 기간동안 심부전, 허혈성 심질환 등의 심혈관계 합병증 발생 여부와 환자의 사망여부를 조사하였다. 환자들은 OPG의 중앙값을 기준으로 증가군 (Higher OPG, HO)과 정상군 (Lower OPG, LO)으로 분류되었다.

결과: 총 176 명의 환자가 연구에 포함되었다. 대상 환자의 평균 연령은 52.0±11.8 세, 남성은 50.6% 이었고, 총 복막투석 기간은 105.3±67.2 개월 이었다. HO 군과 LO 군 사이에 성별, 투석 기간, 당뇨병의 유무, 칼슘과 인의 곱 수치, 인슐린 저항성 (homeostasis model assessment, HOMA), 투석의 효율성, 잔여신기능 등은 차이가

없었으나, HO 군에서 평균 연령이 더 높았고, 고감도 C-반응단백과 Charlson comorbidity index 가 의미있게 높았으며 알부민과 제지방 체중, SGA 값은 낮았다. OPG 와 다른 변수들간의 상관분석 결과 염증을 나타내는 지표들과는 양의 상관관계를, 영양 상태를 나타내는 지표들과는 음의 상관관계를 보여주었다. 심혈관계 합병증은 51 명의 환자에서 새로이 발생하였는데 HO 군에서의 발생빈도 (36/88, 40.9%)가 LO 군 (15/88, 17%)에 비해 의미있게 높았다 ($p < 0.01$). 단변량 콕스 분석상 OPG 는 심혈관계 합병증 발생의 주요한 위험인자였으며 [Hazard ratio (HR): 2.34; 95% confidence interval (CI): 1.13~3.89; p = 0.002], 성별, 나이, 당뇨, 투석 기간등의 변수로 보정 후에도 OPG 는 여전히 심혈관계 합병증 발생을 예측하는 독립적인 변수로 작용하였다 (HR: 2.00; 95% CI: 1.13~3.89; p = 0.02). 그러나 고감도 C-반응단백과 제지방 체중을 통제 변수에 포함시킨 분석에서는 통계학적 의의가 사라졌는데 (각각 HR: 2.00; 95% CI: 0.96~3.63; p = 0.06, HR: 1.79; 95% CI: 0.92~3.53; p = 0.09) 이는 OPG 가 염증 반응 및 영양 결핍을 야기함으로써 심혈관계 합병증 발생에 영향을 미쳤을 가능성을 시사한다.

결론: 본 연구는 OPG 가 염증 및 영양 결핍 상태를 나타내는 변수들과 밀접하게 연관되어 있으며, 복막투석 중인 말기 신부전 환자에서 심혈관계 합병증 발생의 독립적인 예측 인자로 작용함을 보여주었다. 이러한 사실은 영양실조-염증-동맥경화 증후군을 매개하는 인자로서 OPG 의 역할을 제시하고 있다.

핵심되는 말 : osteoprotegerin, 염증, 영양 결핍, 심혈관 질환, 복막 투석