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Serum Osteoprotegerin Concentration and Bone Mineral Density in Hemodialysis Patients with Diabetes Mellitus

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In diabetic patients with poor glycemic control, a reduction in bone mineral density (BMD) has been reported. Since osteoprotegerin (OPG) has an inhibitory effect on osteoclast differentiation and bone resorption, OPG might be involved in the pathogenesis of renal osteodystrophy (ROD) in diabetic patients receiving hemodialysis (HD). The aim of the present study was to examine the role of OPG in the bone metabolism of HD patients with noninsulin-dependent diabetes mellitus (NIDDM). Serum OPG levels were measured in 62 patients (32 diabetic and 30 non-diabetic) with a mean age of 57.1 ± 1.3 years using a sandwich enzyme immunoassay. Computed X-ray densitometry was used to measure BMD. Bone biochemical markers, such as intact parathyroid hormone (iPTH), osteocalcin and bone alkaline phosphatase, were determined simultaneously. Serum OPG levels were significantly increased in HD patients, compared with age-matched healthy volunteers (240.9 ± 13.1 vs 66.6 ± 6.2 pg/ml). No significant difference in serum OPG levels was observed in subgroups classified according to their serum iPTH levels. In addition, no significant correlation was observed between serum OPG levels and serum levels of bone metabolic markers or BMD in all HD patients. However, serum OPG levels were positively correlated with serum iPTH levels ($r = 0.587$, $p < 0.01$) in HD patients with NIDDM. Moreover, a negative correlation was observed between serum OPG levels and BMD ($r = -0.333$, $p < 0.05$) in these patients. OPG may act as a counter-regulatory factor to prevent further bone loss in HD patients with NIDDM. The determination of serum OPG levels in combination with iPTH can be used as a marker for the noninvasive diagnosis of ROD in these patients.

Key words: osteoprotegerin, hemodialysis, bone mineral density, diabetes mellitus, parathyroid hormone

Introduction

Recently, the number of patients with diabetic nephropathy who require hemodialysis (HD) has been rapidly increasing. In addition, more than one third of all patients on maintenance HD therapy have diabetes mellitus (DM)[1]. Renal osteodystrophy (ROD) is a major complication in HD patients, but the clinical features of metabolic bone disease in diabetic patients undergoing HD remains to be clarified. ROD in diabetic patients might differ from that in nondiabetics receiving HD. Previous reports have shown a reduced incidence of secondary hyperparathyroidism in diabetic patients receiving HD[2)~4)]. Mori et al[5] reported that the incidence of bone loss was lower in diabetic patients than in nondiabetics receiving HD, possibly due to low levels of serum parathyroid hormone (PTH). Moreover, secondary hyperparathyroidism in diabetic patients develops slower than in nondiabetics undergoing HD[6]. Since osteoblast function was influenced by age, sex, and blood levels of insulin and glucose[7)8)], the evaluation of bone metabolism in HD patients with DM was thought to be complicated.

Osteoprotegerin (OPG) is a decoy receptor that blocks the interaction of nuclear factor-κB (RANK) with its ligand (RANKL), thereby inhibiting osteoclast differentiation and activity[9]. OPG and the OPG ligand (OPGL) constitue a complex mediatory sys-

tem involved in the regulation of the resorption process in bone, which is probably responsible for the homeostatic mechanism of bone turnover. Recent experimental evidence has suggested that changes in this system may form the basis of some metabolic bone diseases, like osteoporosis and osteopetrosis[9)10)]. Recent studies have shown that PTH acts by enhancing the production of the osteoclastogenic factor OPGL and by inhibiting the synthesis of the soluble receptor OPG, which blocks the biological effect of OPGL[11)~13)].

The present study evaluated the serum levels of OPG in HD patients with or without DM, and examined the relationship between serum OPG levels and several biochemical markers or bone mineral density (BMD) in these patients.

Subjects and Methods

Subjects and study design

Sixty-two maintenance HD patients (44 males and 18 females) in the Minami Senju Hospital were enrolled in the present study. The mean age of the patients was 57.1 ± 1.3 years, and the mean duration of HD therapy was 6.5 ± 0.7 years. The underlying diseases were noninsulin-dependent DM (NIDDM) in 32 patients and chronic glomerulonephritis (CGN) without DM in 30 patients. We excluded patients with a history of a parathyroidectomy or clinically evident aluminum accumulation. The control group consisted of 20 healthy volunteers, 35-68 years of age (mean 55.8 ± 3.5). Informed consent was obtained prior to enrollment in the study.

HD was performed three times weekly (4 h/day) using hollow-fiber dialyzers, such as cellulose triacetate (FB, Nipro, Osaka, Japan) and polysulfone (PS, Fresenius, Germany). The calcium concentration of the dialysate was 3.0 mmol/*l*; this concentration was not changed during the observation period. The blood flow rate was 200 ml/min, and the dialysate flow rate was 500 ml/min. Calcium carbonate ($CaCO_3$) was used as a phosphate binder, and vitamin D was administered in the form of either alfacalcidol or calcitriol. The $CaCO_3$ was administrated in 93.8% in DM group and in 96.7% in CGN group. Vitamin D was administrated to 40.6% of patients in the DM group and to 30.0% of patients in the CGN group. The body weight, blood pressure, and serum concentrations of urea nitrogen, creatinine, albumin, calcium (Ca) and inorganic phosphorus (Pi) were measured before HD. All serum samples obtained from patients that did not have an infectious agent were stored at −20 ℃.

Evaluation of bone mineral density (BMD)

The BMD of the second metacarpal was measured in both hands using a computed X-ray densitometer (CXD; Teijin Diagnostics, Tokyo, Japan)[14)]. The CXD method measures the bone density at the middle of the second metacarpal using a radiograph of the hand relative to a standardized aluminum step wedge (20 steps, 1 mm/step). The computer algorithm compares the bone radiodensity with the gradations of the aluminum step wedge, calculating the bone thickness as an aluminum equivalent (mm Al) with the same X-ray absorption. This CXD method for measuring BMD has been validated in a number of ways, both by assessing its reproducibility and by comparing its results with those of dual-energy X-ray absorptiometry at the same and at other sites. The precision error for measuring BMD using the CXD method is 0.2-1.2%[14)].

Measurement of biochemical markers

Serum OPG was measured using a sandwich enzyme immunoassay purchased from Immunodiagnostik (Bensheim, Germany). This immunoassay uses two highly specific antibodies against human OPG. The detection antibody was a biotin-labelled polyclonal antiserum OPG antibody derived from a goat immunized with recombinant human OPG. The intra- and inter-assay variation coefficients (CVs) were 8 and 12%, respectively. Normal values for a large number of normal subjects of different ages, obtained using the same assay method, have been recently reported[15)].

The serum intact PTH (iPTH) concentration was measured by radioimmunoassay (RIA; Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Patients were classified into the following three groups according to their serum iPTH levels: a low PTH group (iPTH <100 pg/ml), a median PTH group (100-450 pg/ml), and a high PTH group (iPTH >450 pg/ml). These groups were defined

based on the criteria presented by Torres et al[16] and Qi et al[17]. The concentration of intact osteocalcin (iOC) in the serum was measured using an established enzyme immunoassay with antibodies to the N- and C-terminal regions of human osteocalcin (Teijin Diagnostics, Tokyo, Japan). The intra- and inter-assay CVs were 4.6 and 6.3%, respectively. The reference range of serum iOC levels is 2.2 to 5.4 ng/ml. An enzyme immunoassay was used to measure bone alkaline phosphatase (BAP; SRL Co, Tokyo, Japan). The intra- and inter-assay CVs were 4.2 and 7.2%, respectively. The normal mean BAP values are 13.0-33.9 U/*l* in males and 9.6-35.4 U/*l* in females. The corrected Ca level was calculated according to the following formula: corrected Ca = serum Ca + (4-serum albumin).

Statistical analysis

All values are presented as mean ± SEM. An analysis of variance (ANOVA) followed by Scheffe's multiple-range test were used to analyze the individual parameters of the different groups. Pearson's correlation test was used to examine the relationship between the serum levels of OPG and BAP, iOC, iPTH and BMD. Differences in sex, age, duration of dialysis, and etiology of renal disease were compared using the χ^2 test. A p value less than 0.05 was considered to be statistically significant.

Results

We compared the serum OPG levels in all HD patients and age-matched healthy volunteers. As shown in Fig. 1, the mean serum OPG level in HD patients (240.9 ± 13.1 pg/ml) was significantly greater than that in age-matched control subjects (66.6 ± 6.2 pg/ml). The clinical and laboratory parameters of the three PTH groups are shown in Table 1. No significant differences in age, sex, and duration of dialysis were observed among the three PTH groups (low PTH; 42.3 ± 4.9 pg/ml, median PTH; 217.9 ± 16.0 pg/ml, high PTH; 596.0 ± 91.0 pg/ml). Nakashima et al[18] reported that serum iPTH levels less than 65 pg/ml in hemodialysis patients with adynamic bone disease (ABD) is associated with radial BMD. Diabetic patients accounted for 63.6% of the patients in the low PTH groups; this percentage was significantly higher than those in the other PTH groups. In dialysis patients due to CGN, no significant correlation was detected in the relationship between serum OPG levels and serum iPTH levels ($r = 0.212$, $p = 0.125$) or BMD ($r = 0.145$, $p = 0.203$). When the dialysis patients with DM (n = 32) were divided into three groups according to serum iPTH levels, serum OPG levels tended to increase in association with serum iPTH levels (low PTH; 197.0 ± 17.4 pg/ml, median PTH; 292.8 ± 36.8 pg/ml, high PTH; 396.0 ± 80.2 pg/ml). Serum levels of BAP and iOC were significantly lower in the low PTH group than in the other PTH groups. No significant differences in serum OPG levels were observed among the three PTH groups.

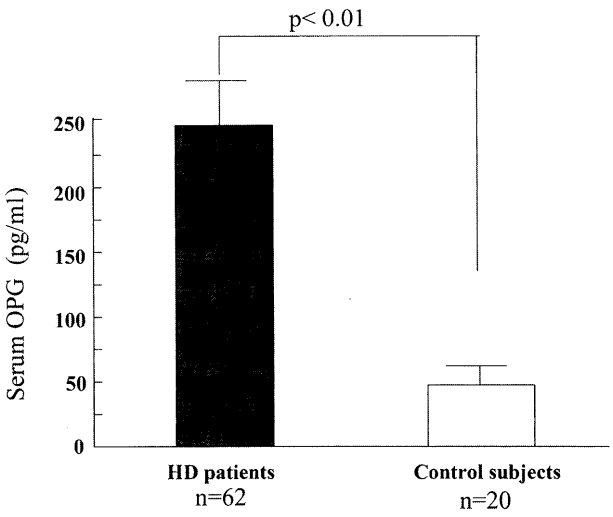

Fig. 1 Serum osteoprotegerin (OPG) levels in control subjects (n = 20) and in all hemodialysis (HD) patients (n = 62)

Clinical and laboratory parameters were compared in subgroups according to the etiology of renal disease. As shown in Table 2, no significant differences in sex, age, duration of dialysis, and serum levels of corrected Ca, Pi, BAP, or OPG were observed between the groups. The serum iPTH level in the DM group (116.0 ± 22.3 pg/ml) was significantly lower than that (190.6 ± 37.7 pg/ml) in the CGN group ($p = 0.004$). The serum iOC level was significantly lower in the DM group (32.5 ± 5.8 ng/ml) than in the CGN group (98.1 ± 22.1 ng/ml) ($p = 0.001$). A positive correlation was observed between the serum levels of iPTH and OPG in HD patients with DM (Fig. 2), but a significant correlation

Table 1 Clinical findings of hemodialysis patient groups classified according to serum levels of intact PTH

	All patients	Low PTH	Median PTH	High PTH
Male/Female	44/18	22/11	19/4	2/3
Age (years)	57.1 ± 1.3	55.8 ± 1.8	58.1 ± 2.0	56.8 ± 6.5
Duration of HD (years)	6.5 ± 0.7	5.4 ± 0.8	7.0 ± 1.3	11.2 ± 1.6
Diabetes (%)	51.6	63.6	34.8	40.0
Corrected Ca (mg/dl)	9.8 ± 0.1	9.7 ± 0.2	9.4 ± 0.2	10.1 ± 0.2
Pi (mg/dl)	5.4 ± 0.1	5.3 ± 0.2	5.5 ± 0.2	6.3 ± 0.4
BAP (U/*l*)	24.3 ± 1.9	19.5 ± 1.5	27.0 ± 3.2	44.8 ± 11.3
iOC (ng/ml)	64.2 ± 11.8	24.1 ± 3.6	80.5 ± 8.0	262.4 ± 105.0
OPG (pg/ml)	233.0 ± 12.6	233.5 ± 15.4	223.7 ± 22.8	297.8 ± 65.1

Pi: phosphorus, BAP: bone alkaline phosphatase, iOC: intact osteocalcin, OPG: osteoprotegerin.

Table 2 Clinical and laboratory parameters in hemodialysis patient groups classified according to the etiology of renal disease

	CGN (n=30)	DM (n=32)	p
Male/Female	21/9	23/9	NS
Age (years)	55.6 ± 1.8	58.5 ± 1.9	NS
Duration of HD (years)	6.5 ± 1.0	6.4 ± 0.9	NS
Corrected Ca (mg/dl)	10.0 ± 0.1	9.7 ± 0.2	NS
Pi (mg/dl)	5.5 ± 0.2	5.3 ± 0.2	NS
BAP (U/*l*)	24.0 ± 2.4	24.6 ± 2.9	NS
iOC (ng/ml)	98.1 ± 22.1	32.5 ± 5.8	0.001
iPTH (pg/ml)	190.6 ± 37.7	116.0 ± 22.3	0.004
OPG (pg/ml)	221.3 ± 18.4	243.9 ± 17.5	NS

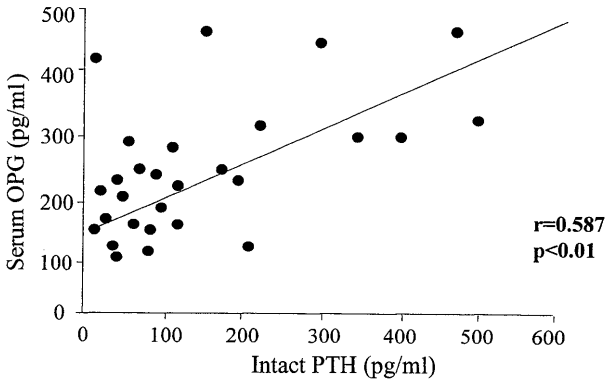

Fig. 2 Correlation between serum levels of osteoprotegerin (OPG) and intact parathyroid hormone (iPTH) in hemodialysis patients with noninsulin-dependent diabetes mellitus (n=32)

was not observed in the overall HD patient group.

In all patients, the mean BMD value was 2.46 ± 0.06 mmAl, ranging from 1.43 to 3.25 mmAl. No significant difference in BMD was observed in sex. All women studied were postmenopausal, suggesting that metabolic factors, such as Ca, Pi, iPTH, and prescribed doses of $CaCO_3$ and active vitamin D, act on the BMD more than sexual hormones in dialysis patients. The serum OPG levels (218.3 ± 15.3 pg/ml) in patients with higher BMD group (>2.5 mmAl) were significantly lower than those (280.3 ± 18.7 pg/ml) in patients with lower BMD group (<2.5 mmAl) ($p=0.0389$). No significant difference in BMD was observed between the DM group (2.51 ± 0.08 mmAl) and the CGN group (2.41 ± 0.08 mmAl). Accordingly, we examined the correlation between biological bone markers and BMD in the DM group. A negative correlation was observed between the age and the BMD ($r=0.587$, $p<0.01$). No significant correlation was found between BMD and clinical parameters, such as the duration of dialysis and serum levels of corrected Ca, Pi and HbA_{1c}. Figure 3 depicts the relationship between BMD and serum OPG levels in the DM group. Serum OPG levels were negatively correlated with BMD (-0.333, $p<0.05$). Many factors, PTH in particular, simultaneously modify bone metabolism, which would mask

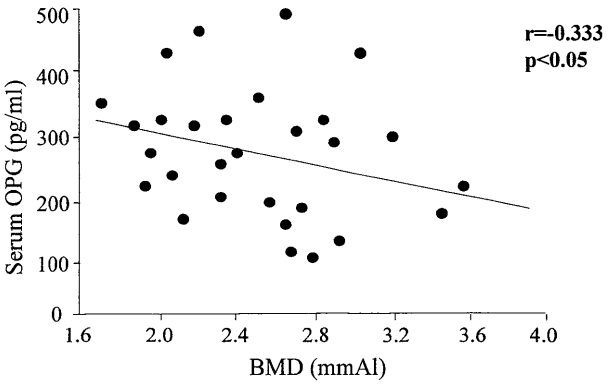

Fig. 3 Relationship between serum osteoprotegerin (OPG) levels and bone mineral density (BMD) in hemodialysis patients with noninsulin-dependent diabetes mellitus (n = 32)

Table 3 Correlation between serum OPG levels and clinical or biochemical markers in hemodialysis patients with diabetes mellitus

	r	p
Age (years)	0.401	0.039
Duration of HD (years)	0.004	0.982
Corrected Ca (mg/dl)	0.296	0.099
Pi (mg/dl)	0.111	0.543
BAP (U/*l*)	0.083	0.655
iOC (ng/ml)	0.464	0.007
iPTH (pg/ml)	0.587	0.005

the action of OPG in uremic patients. The aim of the present study was to elucidate the factors that affect the circulating OPG levels. Table 3 summarizes the correlations between serum OPG levels and clinical or biochemical parameters in HD patients with NIDDM.

Discussion

The spectrum of ROD in HD patients has changed, and much attention has recently been directed toward ABD[19)~21)]. Although the precise mechanism of ABD is not fully understood, hypoparathyroidism is considered to be one of the causative factors[22)23)]. DM is thought to be responsible for apparent absolute or relative hypoparathyroidism[24)]. In the present study, diabetic patients accounted for 63.6% of the patients in the low PTH group, a significantly higher percentage than those observed in the other PTH groups. Therefore, we focused on bone metabolism in HD patients with NIDDM.

The present study clearly demonstrates that circulating OPG is significantly higher in HD patients than in healthy volunteers, but that the serum OPG levels in subgroups divided according to their serum iPTH levels are not significantly different. The serum OPG level in HD patients with NIDDM is negatively correlated with BMD, while no significant correlation was observed in overall HD patients. Therefore, the reduction in bone turnover in HD patients with NIDDM is probably not due to excessive OPG production, and OPG may be involved in bone turnover independently of iPTH in these patients.

OPG has recently been identified as a novel cytokine, that acts on bone tissues to increase bone mineral density and volume by decreasing the number of active osteoclasts in vitro[9)]. The cells producing OPG in dialysis patients remain unknown. Factor regulating the OPG levels in dialysis patients remain unclear. At least decreased renal clearance seems unlikely to be the main reason[25)]. At overexpression of OPG in transgenic mice resulted in osteopetrosis[9)], while OPG-deficient mice developed severe osteoporosis[10)]. These experimental data suggest a counter-regulatory function of OPG that prevents further bone loss.

Yano et al[26)] reported that circulating OPG increased with age and was significantly elevated in postmenopausal women with osteoporosis. This finding has led to the speculation that circulating OPG levels are regulated by age-related factors and that the increase in their serum concentration may be a compensatory response against enhanced osteoclastic bone resorption. Szulc et al[27)] reported a negative correlation between serum OPG levels and serum PTH levels, but no correlation with BMD. Serum PTH levels and the gene expression of OPG in bone cells have also been reported to be inversely correlated in postmenopausal women[28)]. These clinical findings support the hypothesis of a counter-regulatory function of OPG for preventing bone loss.

Kazama et al[29)] recently showed that serum OPG levels were elevated in uremic patients, independent of serum iPTH, and suggested that circulating

OPG was an independent factor affecting bone metabolism in uremic patients. Moreover, several studies have recently reported and discussed serum OPG levels in HD patients. Haas et al[30] showed that a combination of OPG and iPTH can be used as a marker for the noninvasive diagnosis of ROD in HD patients. Coen et al[31] demonstrated that serum OPG levels are lower in ABD patients than in patients with predominant hyperparathyroidism, and significant negative correlations were found between serum OPG and iPTH levels. The authors concluded that the determination of serum OPG levels could be useful in the diagnosis of low turnover bone disease in HD patients.

In summary, serum OPG levels were significantly higher in HD patients than in healthy volunteers, and circulating OPG may be involved in the development of ROD in HD patients with NIDDM, acting as a counter-regulatory factor to prevent further bone loss. The determination of serum OPG levels might be helpful in evaluating bone metabolism in these patients.

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糖尿病を合併した血液透析患者における血清 osteoprotegerin 濃度と骨密度の関連性

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血糖コントロールが不良の糖尿病患者においては，骨密度の低下が認められることが報告されている．Osteoprotegerin (OPG) は骨芽細胞の分化や骨吸収を修飾する因子として注目されているため，糖尿病を合併する透析患者の腎性骨症の病態に関与している可能性がある．本研究の目的は，インスリン非依存性の糖尿病を合併する血液透析患者において，骨代謝マーカーとしての血清 OPG 濃度測定の意義に関して検討することである．対象は62例の維持透析患者（糖尿病合併は32例）で，平均年齢は57.1±1.3歳である．血清 OPG 濃度は市販の ELISA キットで測定し，第2中手骨の骨密度は CXD (computed X-ray densitometry) 法で計測した．骨代謝マーカーとして，副甲状腺ホルモン（iPTH），オステオカルシン（iOC）および骨型アルカリフォスファターゼ（BAP）も同時に測定した．透析患者の血清 OPG 濃度（240.9±13.1 pg/ml）は，健常者（66.6±6.2 pg/ml）に比して有意に増加していた．iPTH 濃度により3群に分けた場合，各群間における血清 OPG 濃度には有意な差異を認めなかった．全症例における検討では，血清 OPG 濃度は骨代謝マーカーおよび骨密度との間に有意な相関はなかった．しかし，糖尿病合併例では，血清 OPG 濃度は iPTH 濃度との間に正の相関（$r=0.587$，$p<0.01$）を，骨密度との間には負の相関（$r=-0.333$，$p<0.05$）を認めた．これらの結果から，糖尿病を合併する透析患者においては，低回転骨を併発している場合，血清 OPG 濃度が増加することで骨密度の低下を抑制している可能性があり，血清 iPTH 濃度とともに血清 OPG 濃度の測定は，腎性骨症の病態を把握するのに有用であると考えられた．