Serum osteoprotegrin level is lower in peritoneal dialysis patients than in hemodialysis ones

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Abstract

Purpose: Osteoprotegrin (OPG) and OPG-ligand are involved in bone turnover induced by parathyroid hormone (PTH) in renal osteodystrophy. We determined serum OPG level in dialysis patients and checked its correlations with other parameters of bone turnover.

Material and methods: Serum level of OPG, PTH, phosphates (Pi), calcium, total alkaline phosphatase (AP) and pH was determined in 29 peritoneal dialysis (PD) patients and 41 hemodialysis (HD) ones.

Results: OPG level was lower in PD than HD patients (4.0, 2.1-13.4 pmol/L vs 7.9, 0.9-16.5 pmol/L; $p = 0.000$) and in both groups it was higher than in controls (2.2, 1.0-3.9 pmol/L; $p = 0.000$). PD patients had also lower AP (78.0, 34.0-583.0 U/L vs 116.0, 59.0-577.0 U/L; $p = 0.000$) and Pi (1.4 ± 0.4 mmol/L vs 3.4 ± 2.6 mmol/L; $p = 0.000$) than HD patients, but higher calcium level (2.4 ± 0.2 mmol/L vs 2.2 ± 0.3 mmol/L; $p = 0.002$) and pH (7.412 ± 0.051 vs 7.326 ± 0.043; $p = 0.000$). The only correlation displayed in PD patients for OPG was negative one with pH ($r = -0.417$, $p = 0.038$) and in HD patients – positive with Pi ($r = 0.548$, $p = 0.000$). OPG level was elevated in 38 HD (92,7%) and in 15 PD (51,7%) patients. There was correlation between serum OPG and AP ($r = -0.615$, $p = 0.033$) and calcium ($r = 0.575$, $p = 0.040$) in group characterised by normal OPG value. There were no significant correlations in group with elevated OPG level.

Conclusions: Lower serum OPG level in PD patients may be connected with lower activity of osteoclasts and less compensating production of OPG in this group of patients. Lower serum OPG level may contribute to higher serum calcium level in PD patients.

Kay words: osteoprotegrin, parathormone, peritoneal dialysis, hemodialysis.

Introduction

The precise mechanism of different kinds of renal osteodystrophy (ROD) is still not fully understood and ROD is still one of the major complications of chronic renal failure, and is associated with increasing morbidity over time. Recently, it was suggested that osteoprotegrin/osteoptotegrin-ligand (OPG/OPG-L) system is involved in pathogenesis of ROD [1,2].

OPG is a member of the tumor necrosis factor (TNF) – receptor superfamily. Its gene is located on chromosome 8q23-24 [3], and OPG mRNA has wide tissue distribution, that is not restricted to bone or immune tissues [3-5]. OPG is synthesized as a 401 amino acids peptide for the human, of which the signal peptide is cleaved, thus generating the mature peptide (380 amino acids) [3,4]. In contrast to all other TNF-receptor superfamily members, OPG lacks transmembrane and cytoplasmic domeins and is secreted as soluble protein [3-5]. Synthesis of OPG in osteoblastic lineage cells is increased by the cytokines such as interleukin (IL)-1α, IL-1β, TNF-α, TNF-β, 1α,25-$(OH)_2D_3$, bone morphogenetic protein 2 [6] and by antiresorptive agents estrogen [7] and transforming growth factor-β (TGF-β) [8]. Protein level is however decreased by glucocorticoids [9], prostaglandin E_2 (PGE_2) [10] and by the pure estrogen receptor antagonist ICI 182,780 [7]. OPG acts as a soluble secreted receptor for OPG-L that prevents it from binding to an activating osteoclast differentiation and activation

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Figure 1. **Serum osteoprotegrin (OPG) level in dialysed patients and controls**

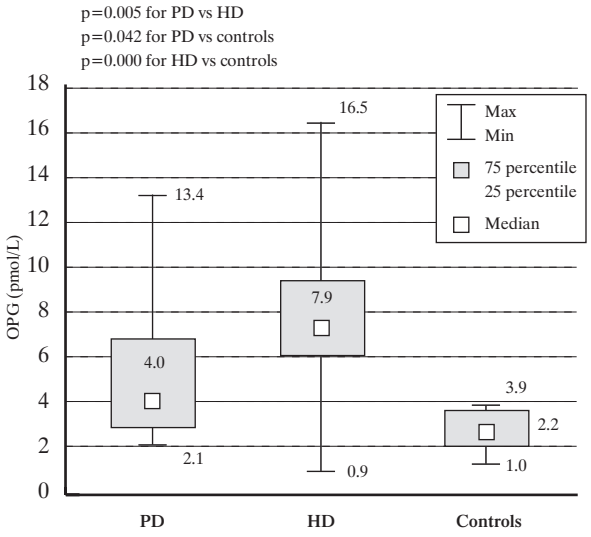
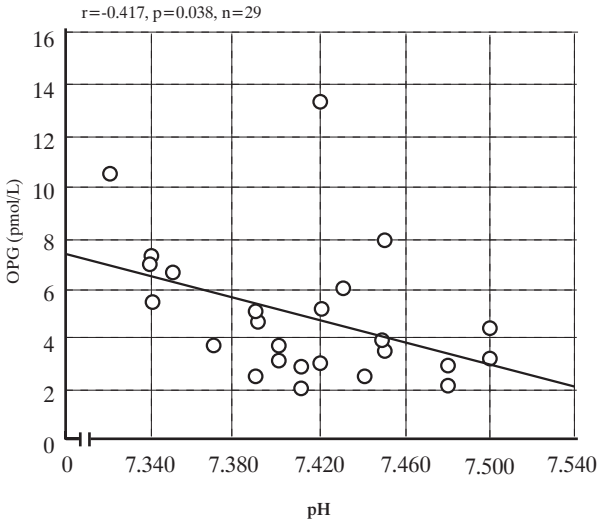


Figure 2. **A correlation between osteoprotegrin (OPG) serum concentration and blood pH in PD patients**



receptor (ODAR) on the osteoclast surface. Thus, the biological effects of OPG on bone cells are the opposite of that of OPG-L, including inhibition of terminal stages of osteoclast differentiation [4,5,11], suppression of the activation of mature osteoclasts [5,12], and induction of apoptosis [13]. OPG also inhibits osteoclastic pit formation of mature osteoclasts [5,12] and antagonizes the induction of bone resorption by $1\alpha,25\text{-}(OH)_2D_3$, PGE_2, parathormone (PTH), IL-1α (5,14), as well as OPG-L [14].

In this study we checked serum OPG concentration in peritoneal dialysis (PD) and hemodialysis (HD) patients and correlated it with routinely measured parameters of bone metabolism.

Material and methods

The study was performed in 29 PD patients (age 55.1 ± 14.5 years, PD duration 11.4; 0.1-57.4 months) and 41 HD ones (age 63.0 ± 10.6 years, HD duration 24.1; 1.1-186.3 months). The causes of end stage renal disease in PD patients were the following: diabetic nephropathy (9 patients), chronic glomerulonephritis (6 patients), tubulointerstitial nephropathy (6 patients), polycystic kidney disease (3 patients), hypertensive nephropathy (2 patients), unknown (3 patients). In HD patients, end stage renal disease was caused by diabetic nephropathy (10 patients), tubulointerstitial nephropathy (9 patients), chronic glomerulonephritis (8 patients), polycystic kidney disease (6 patients), obstructive nephropathy (3 patients), ischaemic nephropathy (1 patients), unknown reasons (4 patients). Difference between HD and PD patients in terms of age and dialysis duration did not achieve statistical significance. The control group (CG) included 13 healthy volunteers.

Serum OPG concentration was measured by enzyme immunoassay (Biomedica, Vienna, Austria) using specific biotinylated OPG detection antibody. In the first step they combine to detected substance and respectively to the precoauted capture anti-OPG antibody and form a sandwich. In the last step OPG is quantitated by an enzyme catalyzed color change detectable on standard ELISA reader. The amount of color developed is directly proportional to the amount of measured substance.

Serum concentration of intact PTH and cyclase activating PTH/cyclase inactive PTH (CAP/CIP) ratio were measured by immunoradiometric assay (DuoPTH, BioRepair, Sinsheim, Germany). Other parameters such as phosphates (Pi), total calcium, total alkaline phosphatase (AP) activity and blood pH were simultaneously measured by routinely used methods.

All results are expressed as mean ± SD or median and range, when appropriate. ANOVA for nonparametric data was used to elucidate differences between HD, PD and CG. Either Student's t-test for paired data or Mann-Whitney U test was used to checked differences between PD and HD patients. Spearman's and Pearson's coefficients were respectively used to describe correlations between non-normal and normal distributed variables. P less than 0.05 was considered as statistically significant.

Results

Serum OPG level was significantly lower in PD than HD patients and in both groups it was higher than in CG (*Fig. 1*). PD patients had also lower AP (78.0, 34.0-583.0 U/L vs 116.0, 59.0-577.0 U/L; p = 0.000) and Pi (1.4 ± 0.4 mmol/L vs 3.4 ± 2.6 mmol/L; p = 0.000) concentrations than HD patients, but higher serum calcium level (2.4 ± 0.2 mmol/L vs 2.2 ± 0.3 mmol/L; p = 0.002) and pH (7.412 ± 0.051 vs 7.326 ± 0.043; p = 0.000). The only correlation displayed in PD patients for OPG was negative correlation with pH (*Fig. 2*) and in HD patients – positive with Pi (*Fig. 3*). Serum OPG level was elevated above normal value in 38 HD (92,7%) and in 15 PD (51,7%) patients. There was significant correlation between serum OPG level and AP (*Fig. 4*) and serum calcium (*Fig. 5*)

Figure 3. **A correlation between serum concentration of osteoprotegrin (OPG) and inorganic phosphates (Pi) in HD patients**

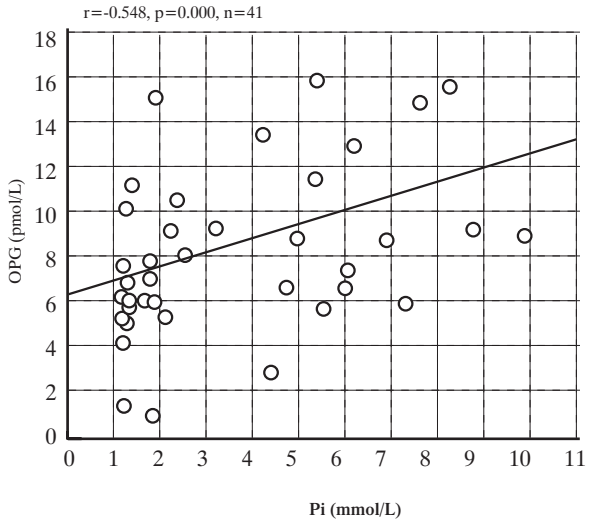


Figure 4. **A correlation between serum osteoprotegrin (OPG) concentration and total alkaline phosphatase (AP) activity in serum of PD patients showing normal serum OPG level**

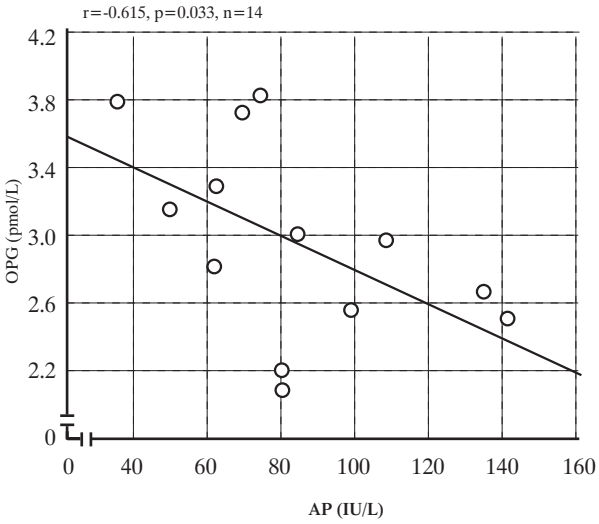
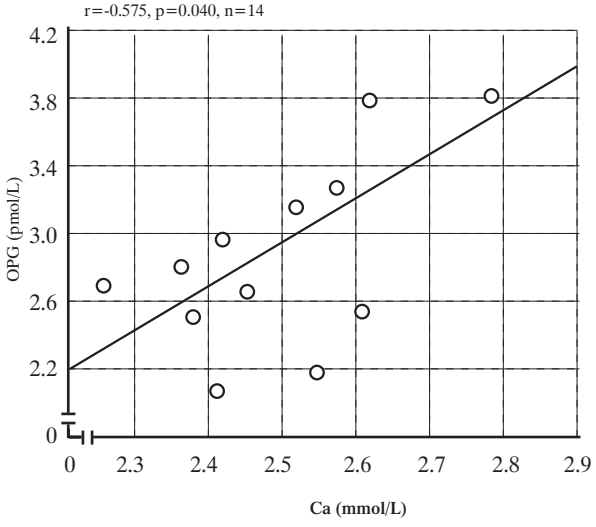


Figure 5. **A correlation between serum concentration of osteoprotegrin (OPG) and total calcium (Ca) in PD patients showing normal serum OPG level**



in group characterised by normal OPG value. There were no significant correlations in group with elevated OPG level.

We did not disclose any significant differences between PD (2.0, 0.9-4.7), HD (1,7, 0.8-4.2) and CG (1.6, 0.9-3.6) in terms of CAP/CIP ratio and it did not correlate significantly with any of examined parameters in PD and HD patients.

Discussion

Our results confirm prior reports on elevated serum OPG in HD patients [1,2]. In our study also PD patients had significantly higher serum OPG concentration than controls, but they had lower level of this cytokine than HD patients. The issue if elevated level of serum OPG is connected with adynamic bone disease (ABD) or high bone turnover disease is not clear [1,2]. We lean towards hypothesis that lower serum OPG level is connected with lower activity of osteoclasts, what appeared in ABD [2], and with less compensating production of OPG. Coen et al. [2] found inverse correlation of serum OPG level with histomorphometric parameters of bone resorption. Such situation may take place in PD patients, who are more predisposed to ABD [15].

Negative correlations between serum OPG level and pH or AP showed in PD patients and positive correlation of OPG with Pi in HD ones seems to confirm relationship between lower activity of osteoclasts and lower serum OPG concentration [2]. Futhermore, lower serum OPG level may contribute to higher serum calcium level in PD patients, because OPG causes a decrease in serum calcium concentration [16].

We did not display correlation between CAP/CIP ratio and level of OPG in serum in any of separated group, however Coen et al. [2] revealed inverse correlation of serum intact PTH and CAP with OPG but only in patients with hyperparathyroidism or mixed osteodystrophy.

In summary, differences in serum OPG concentration showed between dialyzed groups and CG, may indicate that ROD is more advanced in HD patients than PD ones. Lower serum OPG level in PD group is probably connected with lower activity of osteoclasts and less compensating production of OPG. In the about 50% of PD patients osteoclasts function is also disturbed (elevated OPG level). Correlations of OPG with calcium and Pi describe their influence on osteoclasts activity; correlation with pH confirms considerable influence of pH on bone metabolism.

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