PART FOUR

Metabolism and Nutrition

Advances in Peritoneal Dialysis, Vol. 23, 2007

Serum Level of Intact Parathyroid Hormone and Other Markers of Bone Metabolism in Dialyzed Patients

Alicja E. Grzegorzewska, Monika Młot–Michalska

In the present study, we evaluated and compared serum markers of bone turnover in dialyzed patients with serum intact parathyroid hormone (iPTH) < 100 pg/mL (LBT group, n = *9), 100 – 150 pg/mL (MIX group,* n = *6), and iPTH > 150 pg/mL (non-LBT group,* n = *15). Laboratory parameters included iPTH; cyclase activating parathyroid hormone (CAP); osteoprotegerin (OPG); OPG ligand (OPGL); inorganic phosphates; total Ca, urea, and creatinine; alkaline phosphatase activity; and blood pH. Cyclase inactive parathyroid hormone (CIP) was calculated by subtraction of CAP from iPTH.*

When results were adjusted for sex, age, dialysis modality, and dialysis duration, only CAP and CIP were significantly different between the groups. For the LBT, MIX, and non-LBT groups respectively, mean serum values for CAP were 20.3 pg/mL (range: 6.53 – 50.7 pg/mL), 79.3 pg/mL (range: 53.4 – 99.0 pg/mL), and 343.3 pg/mL (range: 102.1 – 887.9 pg/mL) and for CIP they were 7.74 pg/mL (range: 2.41 – 48.4 pg/mL), 50.2 pg/mL (range: 29.5 – 68.0 pg/mL), and 129.0 pg/mL (range: 62.4 – 399.0 pg/mL).

In a selection of dialyzed patients, serum CAP and CIP concentrations—but not CAP/CIP ratio, OPG, OPGL, and OPGL/OPG ratio—can, like iPTH values, be used to categorize those suspected of having adynamic bone.

Key words
Parathyroid hormone, osteoprotegerin, osteoprotegerin ligand

From: Chair and Department of Nephrology, Transplantology and Internal Diseases, Karol Marcinkowski University of Medical Sciences, Poznań, Poland.

Introduction

The scientific literature contains various definitions of low, normal, and high intact parathyroid hormone (iPTH) levels in dialyzed patients, indicating difficulty in selecting a precise iPTH cutoff level for "normal" uremic bone. According to the Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Bone Metabolism and Disease (1), patients with chronic kidney disease can be grouped by iPTH level into an adynamic low bone turnover group [LBT (iPTH < 100 mg/mL)] and a normal or high bone turnover group (iPTH > 100 pg/mL). However, some adult patients with iPTH in the range 100 – 150 pg/mL also possibly have adynamic LBT (Cantor T. What to look for in assessing the value of an existing or new PTH test. Presented at the 24th Annual Conference on Peritoneal Dialysis; February 9 – 11, 2004; San Antonio, TX).

African Americans with adynamic LBT may show the same average iPTH as do Caucasians with high bone turnover (Amerling R. What is the third generation PTH assay and how do third generation assays differ? Presented at the 24th Annual Conference on Peritoneal Dialysis; February 9 – 11, 2004; San Antonio, TX). In children, LBT was recently defined by serum iPTH < 150 pg/mL and total Ca > 10 mg/dL (2). Thus, the cutoff concentration for serum iPTH of 100 pg/mL has limitations as an indicator separating different types of bone metabolism in dialyzed patients.

Recently, other parameters related to bone turnover have been introduced as diagnostic tools in uremic osteodystrophy. Among them are serum levels of cyclase activating parathyroid hormone (CAP), osteoprotegerin (OPG), and osteoprotegerin ligand (OPGL). Our earlier study showed that a serum cyclase inactive parathyroid hormone (CIP)

concentration < 25 pg/mL can be used like iPTH < 100 pg/mL to categorize LBT patients in a dialysis population, but that, after adjustment of results for sex, age, dialysis duration, and dialysis modality, serum concentrations of CAP, OPG, and OPGL are not different in patients with serum iPTH concentrations above or below 100 pg/mL (3). Lack of an intermediate group between the lower and higher iPTH groups may influence the aforementioned results.

In the present study, we evaluated and compared selected serum markers of bone turnover in 3 groups of dialyzed patients: iPTH < 100 pg/mL (LBT group), iPTH 100 – 150 pg/mL (MIX group), and iPTH > 150 pg/mL (non-LBT group).

Patients and methods

Studies were carried out in 30 dialyzed patients. The LBT group consisted of 9 patients [4 women, 5 men; mean age: 61.3 ± 12.6 years; 5 on hemodialysis (HD), 4 on peritoneal dialysis (PD); median dialysis duration: 7.15 months (range: 1.35 – 67.3 months)]; the MIX group, of 6 patients [3 women, 3 men; mean age: 59.3 ± 10.4 years; 4 on HD, 2 on PD; median dialysis duration: 17.3 months (range: 4.74 – 124.4 months)]; and the non-LBT group, of 15 patients [7 women, 8 men; mean age: 59.5 ± 13.1 years; 12 on HD, 3 on PD; median dialysis duration: 26.8 months (range: 3.55 – 186.3 months)]. We observed no significant differences in the distribution of sex, age, dialysis modality, or dialysis duration between the groups.

Measured laboratory parameters included serum concentrations of iPTH; CAP; OPG; soluble OPGL; inorganic phosphates; total Ca, urea, and creatinine; serum total alkaline phosphatase activity; and blood pH. Calculated parameters included serum CIP (serum iPTH minus serum CAP), CAP/CIP ratio, and OPGL/OPG ratio. Serum levels of iPTH and CAP were determined by immunoradiometric assay (DuoPTH: BioRepair, Sinsheim, Germany). Levels of OPG and OPGL were evaluated by enzymatic immunoassay (Biomedica, Vienna, Austria). Other laboratory markers were determined using standard methods.

Results are expressed as mean and one standard deviation, or as median and range. The results were compared after adjustment for sex, age, dialysis modality, and dialysis duration using analysis of covariance methodology. A p value below 0.05 was considered statistically significant.

Results

The mean iPTH values in the three groups as selected by iPTH concentration were 39.0 ± 30.7 pg/mL (LBT group), 126.0 ± 21.2 pg/mL (MIX group), and 500 ± 298 pg/mL (non-LBT group). After adjustment for sex, age, dialysis modality, and dialysis duration, CAP (Figure 1) and CIP (Figure 2) were seen to be significantly different between the groups. Nevertheless, the CAP results overlapped between groups. In the MIX group, 33% of patients (n = 2) showed CAP values similar to those observed in the LBT group, and 17% of patients (n = 1) showed CAP values similar to those in the non-LBT group. No CIP results in the LBT and non-LBT groups overlapped.

The CAP/CIP ratio did not differ between the groups: LBT, 2.09 ± 1.46; MIX, 1.63 ± 0.63; non-LBT, 2.32 ± 0.87. Serum levels of OPG and OPGL; OPGL/OPG ratio; serum concentrations of total Ca, inorganic phosphates, urea, and creatinine; and blood pH were not significantly different between the study groups (Table I).

Discussion

Three groups of dialyzed patients were analyzed in the present study. The group with serum iPTH levels below 100 pg/mL was assumed to have LBT, and dialyzed patients showing iPTH levels over 150 pg/mL possibly included people with normal or high bone turnover. Patients having serum iPTH levels in the range 100 – 150 pg/mL may have had either LBT or

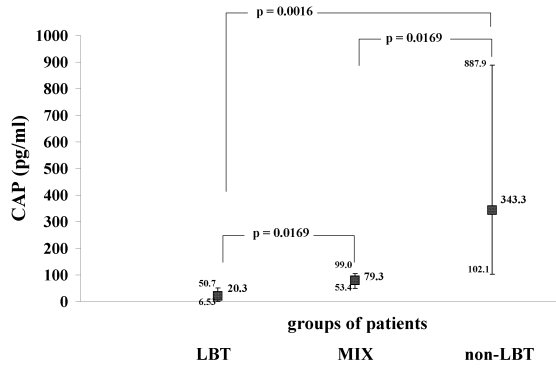

FIGURE 1 Serum cyclase activating parathyroid (CAP) hormone level in patients grouped by level of serum intact parathyroid hormone (iPTH): <100 pg/mL [low bone turnover (LBT) group], 100 – 150 pg/mL (MIX group), and >100 pg/mL (non-LBT group).

high bone turnover (Cantor T. What to look for in assessing the value of an existing or new PTH test. Presented at the 24th Annual Conference on Peritoneal Dialysis; February 9 – 11, 2004; San Antonio, TX). No evidence is available to support a serum iPTH value that, in clinical practice, sufficiently distinguishes patients with normal or high bone turnover from those with LBT.

In a previous study, we grouped dialyzed patients by iPTH serum concentrations below or above 100 pg/mL (3). Those two groups were additionally different only in serum CIP concentration. Serum CIP (7–84 PTH) appears to operate through the C-terminal PTH receptor. It has hypocalcemic properties and is able to lower bone turnover by inhibiting osteoclast formation, with a resulting overall inhibition of bone resorption (Cantor T. The clinical application of cyclase activating PTH assay and the inhibitor ratio. Presented at the 23rd Annual Conference on Peritoneal Dialysis; March 2 – 4, 2003; Seattle, WA).

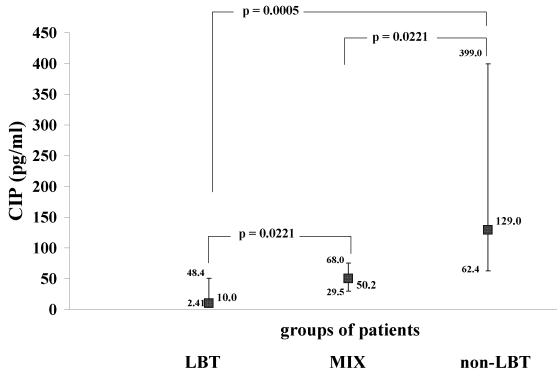

FIGURE 2 Serum cyclase inactive parathyroid (CIP) hormone level in patients grouped by level of serum intact parathyroid hormone (iPTH) : <100 pg/mL [low bone turnover (LBT) group], 100 – 150 pg/mL (MIX group), and >100 pg/mL (non-LBT group).

Groups of patients with the lowest and the highest iPTH levels usually show significant differences in serum markers of bone metabolism other than iPTH (4,5). The intermediate group may not exhibit values of bone markers different from those in the group with the lowest iPTH.

When we separated patients with a serum iPTH concentration of 100 – 150 pg/mL from those having a serum iPTH concentration above 100 pg/mL, significant differences in CAP concentration could also be observed between the groups. Serum CAP, which consists of 84 amino acids, operates through the PTH/PTH-related peptide receptor. It exerts a hypercalcemic effect and increases bone turnover (Cantor T. The clinical application of cyclase activating PTH assay and the inhibitor ratio. Presented at the 23rd Annual Conference on Peritoneal Dialysis; March 2 – 4, 2003; Seattle, WA).

Second-generation iPTH assays measure the sum of CAP and CIP. This estimation of iPTH, if considered to be "active" PTH, which increases bone turnover, yields a PTH activity about 30% – 50% above the actual level because of the detection of CIP in addition to CAP (6; Amerling R. What is the third generation PTH assay and how do third generation assays differ? Presented at the 24th Annual Conference on Peritoneal Dialysis; February 9 – 11, 2004; San Antonio, TX). Advanced-assay third-generation

TABLE I Results of selected parameters examined in dialyzed patients grouped by serum level of parathyroid hormone

Parameter	*LBT group*	*MIX group*	*Non-LBT group*
Serum OPG (pmol/L)	7.97±4.84	8.11±4.65	6.87±2.79
Serum OPGL (pmol/L)	1.73 (0.00–5.27)	2.13 (0.00–3.33)	0.87 (0.00–10.00)
OPGL/OPG ratio	0.16 (0.00–1.60)	0.24 (0.00–0.75)	0.10 (0.00–1.45)
Serum total AP (U/L)	84±26	129±90	221±179
Serum total Ca (mmol/L)	2.48±0.22	2.33±0.14	2.28±0.25
Serum inorganic phosphates (mmol/L)	1.67±0.47	1.78±0.48	1.75±0.62
Serum urea (mmol/L)	17.1±6.7	18.2±6.1	20.2±5.3
Serum creatinine (μmol/L)	680±208	659±108	800±226
Blood pH	7.39±0.05	7.41±0.13	7.35±0.07

LBT = low bone turnover group; MIX = mixed bone metabolism group; OPG = osteoprotegerin; OPGL = osteoprotegerin ligand; AP = alkaline phosphatase.

methodology measures biologically active CAP (Amerling R. What is the third generation PTH assay and how do third generation assays differ? Presented at the 24th Annual Conference on Peritoneal Dialysis; February 9 – 11, 2004; San Antonio, TX). Theoretically, then, separate detection of CAP should therefore be more useful in predicting bone turnover in dialyzed patients. However, in children treated with PD, first- and second-generation immunometric PTH assays had similar predictive value for bone metabolism (7).

The CAP/CIP ratio was recently suggested to be useful in assessing bone turnover in dialysis patients. It was shown to predict bone turnover with a histologically determined 93% predictability. A CAP/CIP ratio below unity indicated adynamic LBT in dialysis patients in 87.5% of cases. The more difficult task was to determine the CAP/CIP ratio characteristic of high bone turnover, because even among patients with a CAP/CIP ratio of 2.0 or higher, 60% of patients had normal bone turnover. For clinical practice, a value of 1.4 was suggested as an appropriate cutoff: dialysis patients with LBT should have a CAP/CIP ratio below 1.4, and patients with normal or high BT should have a CAP/CIP ratio above 1.4 (Cantor T. What to look for in assessing the value of an existing or new PTH test. Presented at the 24th Annual Conference on Peritoneal Dialysis; February 9 – 11, 2004; San Antonio, TX).

In our study, the mean values of the CAP/CIP ratio were not statistically significant in patients grouped by serum iPTH level. Our results indicate that, not only the CAP/CIP ratio, but also serum levels of OPG and OPGL and the OPGL/OPG ratio, lack the predictive meaning of iPTH level in grouping patients. According to Mesquita *et al.* (8), circulating OPG and OPGL also do not predict bone turnover (at least in PD patients), because they do not correlate with serum levels of carboxy-terminal extension peptide of type I procollagen or of betacellulin, or with bone mineral density measured at spine, hip, and radius. In studies by Albalate *et al.* (5), high turnover was defined by iPTH > 450 pg/mL and bone alkaline phosphatase > 20 μg/L, and LBT was assumed in patients with iPTH < 150 pg/mL and bone alkaline phosphatase < 15 μg/L. Patients grouped in this manner also showed significant differences in CAP, CIP, iPTH/OPG ratio, and tartrate-resistant acid phosphatase.

Conclusions

The data presented here indicate that serum CAP and CIP concentrations—but not CAP/CIP ratio, OPG, OPGL, or OPGL/OPG ratio—have a predictive value similar to that of iPTH in classifying dialyzed patients suspected of having adynamic bone.

References

1 National Kidney Foundation. K/DOQI Clinical Practice Guideline for Bone Metabolism and Disease in Chronic Kidney Disease. Am J Kidney Dis 2003;42(Suppl 3):S1–201.
2 Avila–Diaz M, Matos M, Garcia–Lopez E, *et al.* Serum markers of low-turnover bone disease in Mexican children with chronic kidney disease undergoing dialysis. Perit Dial Int 2006;26:78–84.
3 Grzegorzewska AE, Młot–Michalska M. Serum markers of bone turnover in dialyzed patients grouped by level of intact parathyroid hormone. Adv Perit Dial 2006;22:203–6.
4 Bunio A, Steciwko A, Masztalerz–Migas A, *et al.* Markers of bone metabolism and its usefulness in assessment of bone turnover in hemodialysis patients in relation to PTH concentration (Polish). Nefrol Dial Pol 2006;10:7–11.
5 Albalate M, de la Piedra C, Fernandez C, *et al.* Association between phosphate removal and markers of bone turnover in haemodialysis patients. Nephrol Dial Transplant 2006;21:1626–32.
6 Lehmann G, Stein G, Huller M, Schemer R, Ramakrishnan K, Goodman WG. Specific measurement of PTH (1–84) in various forms of renal osteodystrophy (ROD) as assessed by bone histomorphometry. Kidney Int 2005;68:1206–14.
7 Salusky IB, Goodman WG, Kuizon BD, *et al.* Similar predictive value of bone turnover using first- and second-generation immunometric PTH assays in pediatric patients treated with peritoneal dialysis. Kidney Int 2003;63:1801–8.
8 Mesquita M, Wittersheim E, Demulder A, Dratwa M, Bergmann P. Bone cytokines and renal osteodystrophy in peritoneal dialysis patients. Adv Perit Dial 2005;21:181–4.

Corresponding author:
Alicja E. Grzegorzewska, MD PhD, Chair and Department of Nephrology, Transplantology and Internal Diseases, Karol Marcinkowski University of Medical Sciences, Al. Przybyszewskiego 49, Poznań 60-355 Poland.
E-mail:
alicja_grzegorzewska@yahoo.com