We evaluated serum markers of bone turnover (BT) in patients suspected to have low bone turnover (LBT) given their serum level of intact parathyroid hormone (iPTH). Studies were carried out in 30 dialyzed patients.

In 9 patients, iPTH was below 100 pg/mL (LBT group), and in 21, it was above 100 pg/mL (non-LBT group). Other measured laboratory parameters included serum concentrations of cyclase inactivating parathyroid hormone (CAP), osteoprotegerin (OPG), OPG ligand (OPGL), inorganic phosphates, total calcium, creatinine, urea, serum alkaline phosphatase (ALP) activity, and blood pH. The LBT group showed significantly lower levels of iPTH (39.0 ± 30.7 pg/mL), CAP (23.2 ± 16.9 pg/mL), cyclase inactive parathyroid hormone (CIP: 15.8 ± 15.0 pg/mL), and total ALP (83.9 ± 26.2 IU/L) than did the non-LBT group (393 ± 304 pg/mL, 268 ± 216 pg/mL, 126 ± 96 pg/mL, and 202 ± 167 IU/L respectively). We observed no significant differences between the groups in the other examined parameters. When results were adjusted for sex, age, and dialysis modality and duration, differences remained significant only for iPTH and CIP.

Our data indicate that a serum CIP concentration below 25 pg/mL has a significance similar to that of an iPTH concentration below 100 pg/mL in determining which dialyzed patients likely have LBT.

Key words
Parathyroid hormone, osteoprotegerin, osteoprotegerin ligand

Introduction
In clinical practice, a serum level of intact parathyroid hormone (iPTH) below 100 pg/mL is used as a noninvasive marker of adynamic bone [low bone turnover (LBT)] in dialyzed patients (1). 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).

The parathyroid glands secreted CAP (which consists of 84 amino acids) and cyclase inactive parathyroid hormone (CIP, in which amino acids 1–6 are cleaved). Cyclase activating parathyroid hormone operates through the PTH/PTH-related peptide receptor; it exerts a hypercalcemic effect and increases bone turnover. Cyclase inactive parathyroid hormone 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 [T. Cantor, 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, U.S.A. Audio available online at: www.hdcn.com/symp/03adc/03adc_2.htm (password required); accessed July 24, 2006].

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, therefore yields a PTH activity about 30% above the actual level because of the detection of CIP in addition to CAP. Advanced-assay third-generation methodology measures biologically active CAP [R. Amerling, What is the 3rd generation PTH assay and how do 3rd generation assays differ? Presented at the 24th Annual Conference on Peritoneal Dialysis; February 9–11, 2004; San Antonio, TX, U.S.A. Audio available online at: www.hdcn.com/symp/04adc/04adc_5.htm (password required); accessed July 24, 2006]. Separate detection of CAP
should therefore be theoretically more useful in predicting bone turnover in dialyzed patients.

Whether elevated serum OPG is connected with low or high bone turnover in dialyzed patients (2–4) is unclear. The inverse correlation of serum OPG levels with histomorphometric parameters of bone resorption suggests that higher levels of serum OPG may be related to lower bone turnover (3). Many authors found a positive correlation between serum OPG concentration and age in healthy humans of both sexes (5–7). A study by Ueland et al. (8) showed an age-related increase in OPG in cortical bone that was significantly correlated with femoral neck and lumbar spine bone mineral density in postmenopausal women. A positive correlation between age and OPG was also detected in trabecular bone. Our earlier studies also showed that older dialyzed patients had higher serum OPG levels than did younger ones (9).

On the other hand, our uremic patients treated with hemodialysis (HD) experience higher bone turnover than do healthy volunteers, as indicated by higher serum levels of iPTH and CAP. However, increased serum CIP was also observed, and the CAP:CIP ratio remained relatively constant, independent of uremic or healthy status and dialysis modality. Serum levels of OPG showed the same pattern of changes as iPTH, CAP, and CIP, and correlated positively with all three parameters (10–12).

Serum levels of OPGL and the OPGL:OPG ratio were significantly higher in controls and in peritoneal dialysis (PD) patients than in HD patients, but when dialyzed patients were grouped by age, with adjustments for sex, dialysis modality, and dialysis duration, differences in serum OPGL and the OPGL:OPG ratio became nonsignificant (9–11). Other authors (5,13) also did not describe a correlation between OPGL and age, but Liu et al. (6) showed a negative correlation. Pulsatelli et al. (14) observed significantly reduced OPGL levels in a group of healthy subjects aged between 81 and 90 years as compared with levels in younger age groups. We found no data in the scientific literature that showed differences in serum OPGL level or in the OPGL:OPG ratio in patients grouped according to iPTH level.

In the present study, we evaluated the aforementioned serum markers of bone turnover in dialyzed patients suspected of having LBT because of a serum level of iPTH below 100 pg/mL. We also compared levels of those markers to levels in dialyzed patients not suspected of LBT because of their serum iPTH level.

Patients and methods
Our study was carried out in 30 dialyzed patients. In 9 of them (4 women, 5 men), iPTH was below 100 pg/mL (LBT group), and in 21 of them (10 women, 11 men), iPTH was above 100 pg/mL (non-LBT group). No significant differences were found in the distribution of dialysis modality within the groups (5 patients on HD vs. 4 on PD in the LBT group; 16 patients on HD vs. 5 on PD in the non-LBT group) or in dialysis duration between the groups (LBT group: median, 7.15 months; range, 1.35 – 67.34 months; non-LBT group: median, 24.64 months; range, 3.55 – 186.32 months). Patients suspected and not suspected of having LBT did not differ in their serum concentrations of urea (17.1 ± 6.7 mmol/L vs. 19.6 ± 5.4 mmol/L) or creatinine (680 ± 208 µmol/L vs. 765 ± 220 µmol/L), or in blood pH (7.39 ± 0.05 vs. 7.36 ± 0.08).

Measured laboratory parameters included serum concentrations of iPTH, CAP, OPG, soluble OPGL, inorganic phosphates, total calcium, and serum total alkaline phosphatase (ALP) activity. Calculated parameters included serum CIP level (serum iPTH level – serum CAP level), CAP:CIP ratio, and OPGL:OPG ratio. Serum levels of iPTH and CAP were determined by immunoradiometric assay (DuoPTH: BioRepair, Sinsheim, Germany), and 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 1 standard deviation, or as median and range. The Mann-Whitney test was used for statistical comparisons. Additionally, all results were compared using the ANCOVA methodology with adjustments for sex, age, and dialysis modality and duration.

Results
Dialyzed patients grouped by serum iPTH had significantly different serum iPTH concentrations (LBT group: 39.0 ± 30.7 pg/mL; non-LBT group: 393 ± 304 pg/mL). Additionally, the LBT group showed a significantly lower CAP level (23.2 ± 16.9 pg/mL), CIP level (15.8 ± 15.0 pg/mL), and total ALP level (83.9 ± 26.2 IU/L) than did the non-LBT group (268 ± 216 pg/mL, 126 ± 96 pg/mL, and 202 ± 167 IU/L).
respectively). When results were adjusted for sex, age, and dialysis modality and duration, differences remained significant only for iPTH (Figure 1) and CIP (Figure 2). The LBT patients, selected for iPTH levels below 100 pg/mL, demonstrated serum levels of CIP below 25 pg/mL in 89% of cases. Values of the CAP:CIP ratio were not different in LBT and non-LBT patients (2.09 ± 1.46 vs. 2.12 ± 0.86). The adjustments for sex, age, and dialysis modality and duration did not influence the statistical analysis.

Serum levels of OPG, OPGL, total calcium, inorganic phosphates, and OPGL:OPG ratio were not significantly different in the study groups, whether the analysis was performed without or with adjustments (Table I).

Discussion
We analyzed two groups of dialyzed patients in our study. The group with a serum iPTH level below 100 pg/mL was assumed to have LBT; dialyzed patients showing a serum iPTH level over 100 pg/mL were assumed to have normal or high turnover bone, although LBT cannot be excluded, especially in patients whose serum iPTH level was in the 100 – 150 pg/mL range (1). 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.

Our findings show that suspected LBT is associated with lower serum levels of CAP and CIP and lower serum ALP activity. However, serum CAP and ALP are also affected by the combined influence of age, sex, and dialysis modality and duration. These latter effects are not exerted on serum CIP. We suggest generally that, in cases of LBT, CIP generation is diminished through a mechanism of inhibition of osteoclast formation to prevent further lowering of bone turnover (T. Cantor, 2003. Op cit.).

In both study groups, the mean CAP:CIP ratios were above 2.0. The optimal range for this ratio is suggested to be 1.5 – 1.8 (1; T. Cantor, 2003. Op cit.), but Tokumoto (15) found a CAP:CIP ratio of 2.21 in uremic patients with normal bone turnover as validated by bone histology.

Our finding of similar CAP:CIP ratios in patients with iPTH levels either below and above 100 pg/mL was a surprise. The CAP:CIP ratio was recently suggested to be useful in assessing bone turnover in dialysis patients. It was demonstrated to predict bone turnover with a histologically determined 93% predictability. A
CAP:CIP ratio below 1 indicated a dynamic LBT in dialysis patients in 87.5% of cases (16). The more difficult task was to determine the CAP:CIP ratio characteristic of high turnover bone, because even among patients with a CAP:CIP ratio of 2.0 or higher, 60% of patients had normal bone turnover [T. Cantor, 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, U.S.A. Audio available online at: www.hdcn.com/symp/04adc/04adc_5.htm (password required); accessed July 24, 2006]. For clinical practice, a value of 1.4 was suggested as an appropriate cut-off: dialysis patients with LBT should have a CAP:CIP ratio below 1.4, and patients with normal or high turnover bone should have a CAP:CIP ratio above 1.4.

Our results indicate that the CAP:CIP and OPGL:OPG ratios and serum levels of OPG and OPGL lack a meaning similar to that of iPTH in grouping patients with renal osteodystrophy. Mesquita et al. (4) also found that circulating OPG and OPGL 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, betacellulin, or bone density measured at spine, hip, and radius.

Conclusions

Our data indicate that a serum CIP concentration below 25 pg/mL has a significance similar to that of an iPTH concentration below 100 pg/mL in determining which dialyzed patients likely have LBT.

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