Parathyroid Hormone-Related Bone Loss in End-Stage Renal Disease: Where to Measure?

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ABSTRACT
Introduction: Low bone mass and elevated parathyroid hormone (PTH) serum levels are frequently found in patients with end-stage renal disease (ESRD). Our aim was to correlate serum PTH with bone mineral density (BMD) T- and Z-score measured by dual-energy X-ray absorptiometry (DXA) at different sites in patients with ESRD treated by hemodialysis (HD) or peritoneal dialysis (PD).

Material and Methods: We assessed 31 consecutive patients with ESRD (23 sub HD, 8 sub PD). Serum parathyroid

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Renal osteodystrophy is almost universally found in patients with end-stage renal disease (ESRD). Although bone biopsy is the gold standard for assessment of bone status it is infrequently used.

Guidelines (KDIGO, 2009) recommend the use of dual-energy X-ray absorptiometry (DXA), as a method for measuring bone quantity, in all dialysis patients who either have had fractures or have risk factors for osteoporosis but state against routine use of DXA for bone mineral density (BMD) measurement. This is because low BMD measured by DXA was consistently associated with an increased risk of low trauma fractures in general population but in patients with ESRD studies produced conflicting results (Inaba et al., 2005; Jamal et al., 2002; Kaji et al., 2002; Urena et al., 2003; Yamaguchi et al., 1996). There are many causes of this heterogeneity including secondary hyperparathyroidism, presence of low bone turnover disease, osteomalacia, site of BMD measurement or fracture assessment (clinical vs. radiological).

In primary hyperparathyroidism high serum parathyroid hormone (PTH) levels are associated low BMD (Sitges-Serra et al., 2010), particularly at cortical sites (Duan et al., 1999). In dialysis patients a correlation between serum intact PTH (i-PTH) levels and DXA-measured BMD is not universally accepted. It has been demonstrated in most (Dolgos et al., 2008; Grzegorzewska and Mlot-Michalska, 2010; Huang et al., 2009; Urena et al., 2003) but not all (Zayour et al., 2004) hemodialysis (HD) patients and refuted in peritoneal dialysis (PD) (Ersoy et al., 2006). Most studies correlating i-PTH serum levels with BMD in dialysis patients used lumbar spine (Dolgos et al., 2008; Grzegorzewska and Mlot-Michalska, 2010; Huang et al., 2009; Urena et al., 2003; Zayour et al., 2004) and femoral sites (Dolgos et al., 2008; Huang et al., 2009; Urena et al., 2003; Zayour et al., 2004) and only a few used one-third radius (Yamaguchi et al., 1996; Zayour et al., 2004). A meta-analysis showed that BMD measured at radial sites is a better predictor of any type of fracture than BMD measured at lumbar of femoral sites (Jamal et al., 2007). Also, these different studies used absolute BMD, T-score or Z-score for reporting DXA-measured BMD.

Our aim was to correlate i-PTH serum levels with DXA-measured BMD in different bone sites in ESRD patients.

PATIENTS AND METHODS

Patients

We consecutively assessed 31 patients with ESRD referred to our clinic for evaluation of parathyroid function between 2012 and 2015. Eight patients were treated with PD and 23 with HD. The etiology of ESRD was chronic glomerulonephritis (8 cases), autosomal dominant polycystic kidney disease (4 cases), tubulointerstitial nephritis (3 cases), hypertensive nephrosclerosis (2 cases), focal segmental glomerulosclerosis (1 case), uric acid nephropathy (1 case), acute glomerulonephritis (1 case), chronic pyelonephritis (1 case), Alport syndrome (1 case), reflux nephropathy (2 cases), nephrolithiasis (2 cases), diabetic nephropathy (1 case) and unknown (4 cases). Patients treated with 1,25 dihydroxyvitamin D, vitamin D derivates (paricalcitol) or calcimimetics were excluded from the study. Patients’ characteristics can be found in Table 1.

Methods

Serum parathyroid hormone (COBAS Elecsys® PTH (1-84) [Roche Diagnostics, Mannheim, Germany]), measuring range 1.20 – 5000 pg/mL, and 25OH vitamin D (COBAS Elecsys® Vitamin D total [Roche Diagnostics, Mannheim, Germany]), measuring range 5.00 – 60 ng/mL, were measured on Cobas e601 in all patients. In HD patients all biochemical measurements were done in the day between dialysis sessions.

BMD was assessed in all patients at following sites: femoral neck, total proximal femur, 1/3 radius,
ultradistal (UD) radius and total radius. Radial BMD was assessed in the forearm without arteriovenous fistula. DXA was performed by the same operator on the same Prodigy Lunar scanner (Lunar Corporation, Madison, WI). The densitometer was calibrated everyday using a standard phantom specimen. BMD results were obtained in absolute values (g/cm²), T-score and in Z-score.

Statistics
Correlations were assessed using Pearson correlation coefficient. For between groups of serum i-PTH tertiles comparisons we used one-way ANOVA. For each regression model the independent predictors were PTH, 25OHD, years on dialysis, dialysis type and BMI. The dependent variable is the corresponding BMD T- or Z-score. All statistics were calculated using MedCalc software, version 8.0.0.1 (MedCalc Software bvba, Ostend, Belgium).

RESULTS
Correlation coefficients between i-PTH serum levels and BMD T- or Z-scores for different bone sites are shown in Table 2. PTH did not correlate with either BMD T- or Z-score in femoral sites. A significant correlation was found with both BMD T- and Z-scores at cortical bone sites: one-third radius and total radius. The best correlation is shown in Fig. 1.

Fig. 2 shows BMD T- and Z-scores stratified by PTH tertiles. T- and Z-scores were significantly lower at one-third radius and total radius than at femoral neck or total femur in the second and third tertiles. UD radius showed no consistent effect.

The multiple regression models results are presented in Table 3. Total proximal femur and UD radius T- and Z-scores did not correlate with any of the proposed variables. Total femur Z-score correlated weakly with years on dialysis (r= -0.453, p=0.046). The regression models for 1/3 radius and total radius Z-score were statistically significant with a coefficient of determination of 0.485 and 0.403 respectively.

There were no significant differences for BMD T- or Z-score at any measurement site between pre- (7 cases) and postmenopausal (14 cases) women.

DISCUSSION
Our aim was to correlate i-PTH serum levels with DXA-measured BMD in different bone site in ESRD.
patients. The study included both PD and HD treated patients.

We showed that PTH is an important predictor of BMD T and Z-scores at cortical bone measurement sites. BMD T- and Z-scores at the one-third and total radius significantly correlated with serum i-PTH in the whole group and also in the HD subgroup. The strongest correlation was that with one-third radius BMD Z-score with a correlation coefficient of -0.655 in HD patients. In the PD subgroup the only significant correlation was between PTH and BMD Z-score at the one-third radius level, probably due to the small number of patients. PTH was the only significant independent predictor for BMD T- and Z-score in multiple regression models.

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<th>Table 3. Multiple regression models for each BMD measurement site</th>
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<td><strong>Coefficient of determination</strong></td>
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For each regression model the independent predictors were PTH, 25(OH)D, years on dialysis, dialysis type and BMI. The dependent variable is the corresponding BMD T- or Z-score.

25(OH)D, 25-hydroxy vitamin D; BMD, bone mineral density; BMI, body mass index; PTH, parathyroid hormone; UD, ultradistal.

**Figure 1.** Correlation (solid line) and 95% confidence interval (dashed lines) between serum i-PTH and one-third radius BMD Z-score ($r=-0.641$, $p<0.001$) in patients with hemodialysis (filled circles) and peritoneal dialysis (empty circles).

**Figure 2.** One-third radius BMD Z-score (A) or T-score (B) according to serum i-PTH tertiles. $p<0.01$ for trend at one-third and total radius for both Z-score and T-score (ANOVA). Both BMD T- and Z-scores were significantly lower ($p<0.01$) at one-third radius and total radius than at femoral neck or total femur in the second and third PTH tertiles.
The association with low trauma fractures (Inaba et al., 2005; Jamal et al., 2002; Kaji et al., 2002; Urena et al., 2003; Yamaguchi et al., 1996). Our study provides evidence that BMD measurement integrates the chronic PTH effects on bone and could reinforce PTH serial measurements. One-third radius BMD Z-score could become a useful tool in monitoring and treatment decision in renal secondary hyperparathyroidism.

The main limitation of our study is the small number of patients (31 subjects), particularly those on PD (8 subjects). It is probable that, by increasing the number of patients, the correlations between serum PTH and BMD T- or Z-scores would become significant also in PD patients. However, our study enrolled only patients not treated with calcitriol, vitamin D derivates or calcimimetics which allowed us to correlate serum PTH with BMD on a wide range of values, even at very high PTH levels.

In conclusion our study found a significant correlation between serum PTH level and DXA-measured BMD in ESRD patients. From all the common BMD measurement sites our data support the use of Z-score at one-third radius as it captures best the bone loss due to renal secondary hyperparathyroidism.

Conflict of interest

None to declare.

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