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Original Paper

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

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REZUMAT

Pierderea de masă osoasă asociată parathormonului la pacienții cu boală renală în stadiul final: unde să măsurăm?

Introducere: Pacienții cu boală renală în stadiul final (BRSF) prezintă adesea masă osoasă scăzută și nivele crescute ale parathormonului (PTH). Obiectivul nostru a fost să corelăm PTH-ul seric cu scorul T și Z al densității minerale osoase (DMO) măsurate prin absorbțiometrie dual cu raze X (DXA) la diferite situsuri osoase la pacienții cu BRSF sub hemodializă (HD) sau dializă peritoneală (DP).
Materiale și metode: Am evaluat 31 de pacienți consecutivi cu BRSF (23 sub HD, 8 sub DP). La toți pacienții am determinat PTH-ul și 25OH vitamina D serică. DMO a fost evaluată prin DXA la următoarele situsuri: colul femural, femurul proximal total și radiusul 1/3, ultradistal și total. DMO radială a fost determinată la antebrațul fără fistulă arteriovenoasă. Scorurile T și Z au fost asigurate de producător. Variabilele clinice utilizate au fost indicele de masă corporală (IMC), anii de dializă și tipul dializei. Au fost excluși pacienții tratați cu derivate de 1,25 dihidroxivitamina D (paricalcitol) sau calcimimetice.
Rezultate: PTH-ul seric s-a corelat semnificativ cu scorurile T și Z ale DMO la nivelul radiusului 1/3 (r=-0.503 și -0.641) și total (r=-0.396 și respectiv -0.558). DMO la nivelul radiusului 1/3 și total a fost semnificativ mai redusă comparativ cu situsurile femurale odată cu creșterea nivelului PTH-ului. La niciun situs tipul dializei, anii de dializă, 25OH vitamina D și IMC nu s-au corelat cu DMO.
Concluzii: Am găsit o corelație semnificativă între PTH-ul seric și DMO măsurată prin DXA la pacienții cu BRSF. Dintre toate situsurile de măsurare a DMO datele noaste recomandă utilizarea scorului Z la nivelul radiusului 1/3.

Cuvinte cheie: parathormon, densitate minerală osoasă, boală renală în stadiul final, dializă

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 on HD and 8 on PD). Serum parathyroid

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hormone and 25OH vitamin D were measured in all patients. BMD was assessed by DXA at following sites: femoral neck, total proximal femur, one-third, ultradistal and total radius. Radial BMD was assessed in the forearm without arteriovenous fistula. BMD T- and Z-score were provided by the manufacturer. The clinical variables used in the study were body mass index (BMI), years of dialysis and dialysis type. Patients treated with 1,25 dihydroxyvitamin D, vitamin D derivates (paricalcitol) or calcimimentics were excluded.

Results: Serum PTH correlated significantly with BMD T- and Z-scores at the 1/3 (r=-503 and -0.641 respectively) and total (r=-396 and -0.558 respectively) radius levels. BMD at one-third and total radius was sgnificantly lower than at femoral sites with increasing PTH levels. Dialysis type, years of dialysis, 25OH vitamin D and BMI did not correlated with BMD at any site.

Conclusions: We found a significant correlation between PTH serum levels 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.

Key words: parathyroid hormone, bone mineral density, end-stage renal disease, dialysis

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 hyperparathiroidism 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 universaly accepted. It has been demonstrated in most (Dolgos et al., 2008; Grzegorzewska and Młot-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 Młot-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 neprhopathy (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 calcimimentics 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 sesions.

BMD was assessed in all patients at following sites: femoral neck, total proximal femur, 1/3 radius,

Table 1. Patients' characteristics

	HD (n = 23)	PD (n = 8)	All (n = 31)
Age (years)	55 (43, 58.5)	59.5 (44, 66.5)	55 (42, 60.7)
Sex (F:M)	15:8	6:2	21:10
Years on dialysis	5 (1.5, 7)	5 (2.75, 6)	5 (2, 6.7)
BMI (kg/m^2)	23.6 (21.9, 29.8)	24.8 (22.1, 28.1)	23.8 (21.7, 28.3)
PTH (pg/mL)	1177 (289, 1814)	1056 (573, 1571)	1177 (403, 1717)
25OH vitamin D (ng/mL)	13 (8, 19)	5.2 (3.6, 6.1)	8.3 (5.5, 16.1)

Data are prsented as median (25, 75 percentile) except for sex (number).
BMI, body mass index; HD, hemodialysis; PD, peritoneal dialysis; PTH, parathyroid hormone.

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/cm^2), 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 coeffcient 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

Table 2. Correlation coefficients between serum PTH level and T- and Z-scores at different bone sites

	HD (n = 23)	PD (n = 8)	All (n = 31)
Femoral neck			
T-score	-0.092	0.22	-0.044
Z-score	-0.370	-0.156	-0.337
Total femur			
T-score	-0.034	0.151	-0.005
Z-score	-0.042	-0.08	-0.202
One-third radius			
T-score	-0.552*	-0.266	-0.503*
Z-score	-0.655*	-0.628*	-0.641*
Ultradistal radius			
T-score	-0.129	0.195	-0.060
Z-score	-0.289	-0.052	-0.238
Total radius			
T-score	-0.482*	-0.026	-0.396*
Z-score	-0.603*	-0.379	-0.558*

p<0.05; HD, hemodialysis; PD, peritoneal dialysis

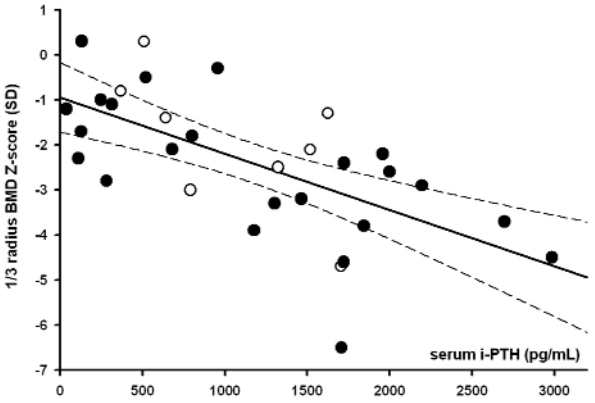

Figure 1. Correlation (solid line) and 95% confidence interval (dashed lines) between serum i-PTH and one-third radius BMD Z-score (r=-0.641, p<0.001) in patients with hemodialysis (filled circles) and peritoneal dialysis (empty circles).

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.

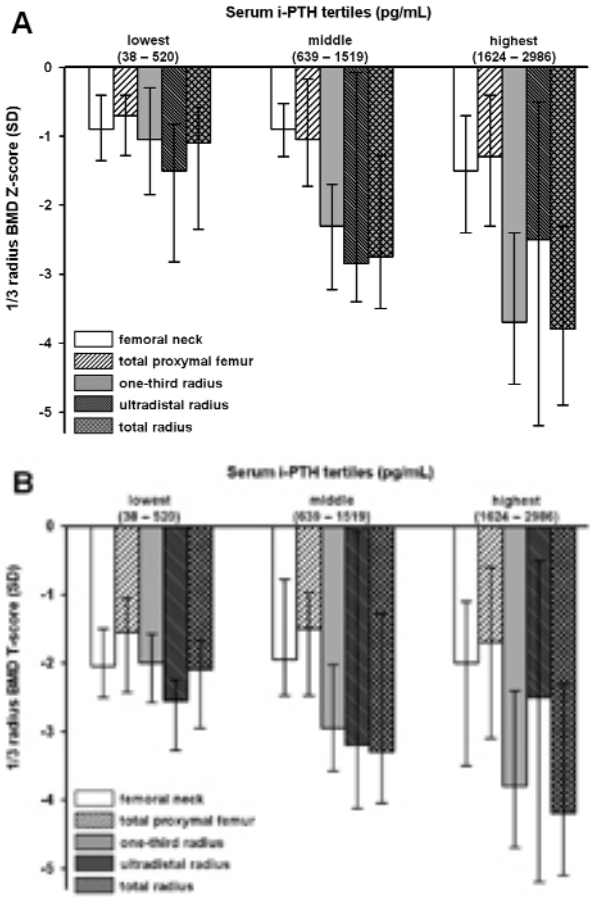

Figure 2. One-third radius BMD Z-score (A) or T-score (B) according to serum i-PTH tertiles. p<0.01 for trend at one-third and total radius for both Z-score and T-score (ANOVA). Both BMD T- and Z-scores were significantly lower (p<0.01) at one-third radius and total radius than at femoral neck or total femur in the second and third PTH tertiles.

Table 3. Multiple regression models for each BMD measurement site

	Coefficient of determination	P value	Independent predictors
Femoral neck			
T-score	0.115	0.66	none
Z-score	0.230	0.22	none
Total proximal femur			
T-score	0.216	0.26	none
Z-score	0.248	0.18	Years on dialysys
1/3 radius			
T-score	0.319	0.07	PTH
Z-score	0.485	0.004	PTH
UD radius			
T-score	0.131	0.59	none
Z-score	0.206	0.29	none
Total radius			
T-score	0.247	0.18	PTH
Z-score	0.403	0.01	PTH

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

Most publishes studies (Dolgos et al., 2008; Grzegorzewska and Młot-Michalska, 2010; Huang et al., 2009; Urena et al., 2003) found a significant correlation between serum PTH and DXA-measured BMD in HD patients. It is interesting that these studies used lumbar spine and proxymal femur for DXA BMD measurement although in primary hyperparathyroidism a low BMD is found particularly at one-third radius (Duan et al., 1999). The correlation coefficient ranged between 0.14 (Huang et al., 2009) and 0.3 (Urena et al., 2003) at femoral neck and 0.25 (Huang et al., 2009) and 0.33 (Urena et al., 2003) in lumbar spine. In our study the correlation coefficient was 0.33 at the femoral neck confirming other studies results. We did not use lumbar spine BMD because of the wide range of patients' age (between 20 and 75 years of age) and corresponding vertebral osteoarthritis. Also, the aortic calcifications precludes a precise DXA measurement of BMD in ESRD patients.

Of the studies that used one-third radius BMD some found a correlation with serum PTH only in men (Yamaguchi et al., 1996) while other did not (Zayour et al., 2004). Compared with these published studies (Yamaguchi et al., 1996; Zayour et al., 2004) our population showed severe secondary hyperparathyroidism with half of the patients having a serum PTH over 1000 ng/mL and this could explain the strenght of the correlation between serum PTH and DXA-measured BMD Z-score, -0.641 in our study vs. -0.382 in the study of Yamagouchi (Yamaguchi et al., 1996).

The magnitude of the effect (PTH explains 0.41 of one-third radius Z-score variation) is surprising given the heterogeneity of our patients concerning the years on dialysis (ranged from 0.2 to 16 with a median of 5 years).

We also showed that BMD 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 PTH tertiles. The difference ranged between 1.09 (CI 95% 0.07 – 2.10) SD for T-score between one-third radius and femoral neck in the second tertile and 2.04 (CI 95% 0.59 – 3.48) SD for Z-score between total radius and total proxymal femur in the third tertile. Only in the first tertile the PTH serum level was within the recommended range (KDIGO, 2009) for ESRD while the patients in the second and particularly the third tertile showed severe hyperparathyroidism. As one-third radius contains only cortical bone this explains the significant differences over sites of mixed trabecular-cortical bone with increasing PTH serum levels.

Currently there are no indications for using DXA-measured BMD as a treatment criteria in ESRD (KDIGO, 2009) due to conflicting results concerning 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 calctriol, 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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REFERENCES

1. Dolgos S, Hartmann A, Bψnsnes S, Ueland T, Isaksen GA, Godang K, Pfeffer P, Bollerslev J. Determinants of bone mass in end-stage renal failure patients at the time of kidney transplantation. Clin Transplant 2008; 22: 462–468. doi:10.1111/j.1399-0012.2008.00810.x
2. Duan Y, De Luca V, Seeman E. Parathyroid hormone deficiency and excess: similar effects on trabecular bone but differing effects on cortical bone. J Clin Endocrinol Metab 1999; 84: 718–722. doi:10.1210/jcem.84.2.5498
3. Ersoy FF, Passadakis SP, Tam P, Memmos ED, Katopodis PK, Ozener C, Akηiηek F, Camsari T, Ateş K, Ataman R, Vlachojannis JG, Dombros AN, Utaş C,Akpolat T, Bozfakioğlu S, Wu G, Karayaylali I, Arinsoy T, Stathakis PC, Yavuz M, Tsakiris JD, Dimitriades CA, Yilmaz ME, Gόltekin M, Karayalηin B, Yardimsever M, Oreopoulos DG. Bone mineral density and its correlation with clinical and laboratory factors in chronic peritoneal dialysis patients. J Bone Mineral Metab 2006; 24: 79–86. doi:10.1007/s00774-005-0650-3
4. Grzegorzewska AE, Młot-Michalska M. Predictors of bone mineral density in dialyzed and non-dialyzed patients with chronic kidney disease. Adv Perit Dial 2010; 26: 116–124.
5. Huang GS, Chu TS, Lou MF, Hwang SL, Yang RS. Factors

associated with low bone mass in the hemodialysis patients--a cross-sectional correlation study. BMC Musculoskel Dis 2009; 10: 60. doi:10.1186/1471-2474-10-60
6. Inaba M, Okuno S, Kumeda Y, Yamakawa T, Ishimura E, Nishizawa Y. Increased incidence of vertebral fracture in older female hemodialyzed patients with type 2 diabetes mellitus. Calcif Tissue Int 2005; 76: 256–260. doi:10.1007/s00223-004-0094-0
7. Jamal SA, Chase C, Goh YI, Richardson R, Hawker GA. Bone density and heel ultrasound testing do not identify patients with dialysis-dependent renal failure who have had fractures. Am J Kidney Dis 2002; 39: 843–849. doi:10.1053/ajkd.2002.32006
8. Jamal SA, Hayden JA, Beyene J. Low bone mineral density and fractures in long-term hemodialysis patients: a meta-analysis. Am J Kidney Dis 2007; 49: 674–681. doi:10.1053/j.ajkd.2007.02.264
9. Kaji H, Suzuki M, Yano S, Sugimoto T, Chihara K, Hattori S, Sekita K. Risk factors for hip fracture in hemodialysis patients. Am J Nephrol 2002; 22: 325–331. doi: 10.1159/000065222
10. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int 2009; 76: S1–S130. doi:10.1038/ki.2009.188
11. Sitges-Serra A, Garcva L, Prieto R, Peęa MJ, Noguıs X, Sancho JJ. Effect of parathyroidectomy for primary hyperparathyroidism on bone mineral density in postmenopausal women. Br J Surg 2010; 97: 1013–1019. doi:10.1002/bjs.7044
12. Urena P, Bernard-Poenaru O, Ostertag A, Baudoin C, Cohen-Solal M, Cantor T, de Vernejoul MC. Bone mineral density, biochemical markers and skeletal fractures in haemodialysis patients. Nephrol Dial Transplant 2003; 18: 2325–2331. doi:10.1093/ndt/gfg403
13. Yamaguchi T, Kanno E, Tsubota J, Shiomi T, Nakai M, Hattori S. Retrospective study on the usefulness of radius and lumbar bone density in the separation of hemodialysis patients with fractures from those without fractures. Bone 1996; 19: 549–555. doi:10.1016/S8756-3282(96)00246-3
14. Zayour D, Daouk M, Medawar W, Salamoun M, El-Hajj Fuleihan G. Predictors of bone mineral density in patients on hemodialysis. Transplant Proc 2004; 36: 1297–1301. doi:10.1016/j.transproceed.2004.05.069