Predictors of Bone Mineral Density in Patients on Hemodialysis

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ABSTRACT

Renal osteodystrophy is a universal complication of uremia. Renal failure patients are at risk for low bone mineral density (BMD) and fractures. Parathyroid hormone (PTH) plays a pivotal role in the pathophysiology of uremic bone disease. Histomorphometric studies suggest that the maintenance of PTH levels between two and four times the upper limit of normal is associated with the lowest prevalence of two common forms of osteodystrophy: osteitis fibrosa cystica and adynamic bone disease. The purpose of this study was to investigate whether the above recommendation for PTH levels in dialysis patients corresponds to a more optimal BMD with a special emphasis on diabetic versus nondiabetic subjects. Twenty-eight patients with chronic renal failure on hemodialysis underwent measurement of PTH levels, as well as BMD at the lumbar spine, hip, and forearm. They were divided into three groups based on the mean PTH level over the 5 years prior to having BMD measured. Osteoporosis was diagnosed in 55% of men and 87% of women on dialysis. Predictors of BMD were gender, duration on hemodialysis, and diabetes. Our study supports the histomorphometry-based studies suggesting that the maintenance of intact PTH levels two to four times the upper limit of normal may be associated with better skeletal health in uremic patients on hemodialysis, and that the diabetic subgroup is at particular risk for low BMD.

CHRONIC RENAL FAILURE is almost universally associated with impaired mineral and bone metabolism.[1–3] Originally high turnover bone disease was the most prevalent. However, the relative frequency of different entities in the spectrum of renal osteodystrophy has recently undergone a change with an increased prevalence of adynamic bone disease.[3–5] Diabetes mellitus is believed to be one of the factors contributing to an increased frequency of adynamic bone disease.[4–7] The effect of diabetes on renal osteodystrophy and its relation to bone mineral density (BMD) have not been fully elucidated, but it has been suggested that uremic diabetic patients are at higher fracture risk posttransplantation than nondiabetics.[8]

Although circulating intact PTH levels correlate with the severity of hyperparathyroidism, only moderately elevated[5,9,10] levels do not accurately predict the type of renal osteodystrophy. However, it is generally accepted that PTH levels below 100 pg/mL are associated with an increased incidence of adynamic bone disease, whereas levels above 450 pg/mL point to osteitis fibrosa cystica or mixed uremic osteodystrophy.[9,10] Interestingly, both types of metabolic bone disorders at opposite ends of the spectrum of uremic osteodystrophy are associated with increased fracture risk. Because of the relative state of skeletal resistance to PTH in renal failure, the recommendation has been to maintain a PTH level two to four times the upper limit of normal.[9–12] It has also been suggested that PTH levels below 200 pg/mL are associated with an increased risk of fracture.[13] BMD is one of the best predictors of fracture.[14,15] It is well known that BMD is reduced in patients with chronic renal failure[6,16,17] and that uremic patients are at a higher risk of fractures.[13,16] However, to our knowledge, few studies have systematically evaluated BMD in the various types of renal osteodystrophy categorized by PTH levels or systematically compared BMD in uremic diabetic compared to nondiabetic patients.[18,19] The aims of our study therefore were to: assess whether recommendations to keep PTH levels two to

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four times the upper limit of normal correspond to optimal BMD in patients on hemodialysis and to compare BMD in uremic diabetic versus nondiabetic patients on hemodialysis.

MATERIAL AND METHODS

This cross-sectional study was performed in the renal dialysis unit of our tertiary referral medical center in year 2000. Twenty-eight patients were included in the current analyses. The patients received two to three dialysis sessions per week, each treatment lasting 4 hours, for several years, to target the urea reduction rate to more than 65%. As recorded by the dialysis records, the 1-year survival rate in the study group was 21.4%, which is comparable to an equivalent population in the United States.[20] The total calcium concentration in the dialysate was 7 mg/dL. Clinical information including age, gender, weight, and body mass index (weight kg/height m^2) and diabetes diagnosis was obtained from the dialysis unit records. Of 28 patients, 25 were on $CaCO_3$ supplements; 20 of 28 were on vitamin D with 17 being on one alphacalcidiol (calcitriol is not available in our country). Calcium carbonate was used as a phosphate binder. No aluminum-based derivatives were used. Only one man was on testosterone replacement, and no women were taking hormone replacement therapy.

Serum calcium, phosphorous, and alkaline phosphatase were measured three to four times per year for each patient. Serum iPTH was determined in the dialysis unit twice/year for each patient and plasma aluminum was measured once, in the year of BMD measurement. The average for each of the biochemical variables was derived from variables obtained over 5 years prior to performing the BMD measurements. Serum iPTH was measured with ELSA-PTH immunoradiometric assay (Cis Bio International, Gif-Sur-Yvette, France). Serum alkaline phosphatase was measured by a colorimetric method using the Hitachi 912 analyzer in the chemistry laboratory (Hitachi, Roche Diagnostics, Germany).

BMD of the lumbar spine, total hip, femoral neck, trochanter, and forearm were measured using Lunar DPX-L densitometer (Lunar, Madison, Wis, USA). Osteoporosis was defined as a BMD T score at any site less than −2.5, and osteopenia was defined as a BMD T score between −1 and −2.5.[21] Results were expressed as mean values (± SD). Comparison of continuous variables was performed using a two-tailed student *t* test, with comparisons between the three subgroups by ANOVA. Comparison of categorical variables was performed using chi-square analyses.

RESULTS

Patient Characteristics

Twenty-eight patients, 20 men and 8 women, were enrolled in the study at a mean age of 61 ± 15 years (median age 63 years, range = 21 to 81 years); six of eight women were postmenopausal. The mean serum calcium, phosphorous, plasma aluminum level, alkaline phosphatase, and PTH levels are shown in Table 1. Women were slightly more obese than men, had been on dialysis for the same number of years, had significantly higher aluminum levels, and as expected had a significantly lower BMD at the total hip and forearm and a higher prevalence of osteoporosis (Table 1).

Osteoporosis at any one of the three skeletal sites in any given patient was present in 64% of the study group overall, whereas osteopenia was observed in 29% of patients and only 7% displayed a normal BMD at all three sites. The overall study group showed a significant inverse relationship between the number of years on dialysis and BMD at skeletal sites enriched in cortical bone, such as the forearm and total hip ($R = -0.58$ and $R = -0.47$; $P = .004$ and .03, respectively). There was no significant relationship between age and BMD in our study group.

Table 1. Characteristics of Study Group Overall and by Gender

Variable	All subjects (n = 28)	Men (n = 20)	Women (n = 8)
Age (years)	61 (15)	61 (16)	61 (13)
BMI (kg/m^2)	26 (5)	26 (4)	27 (7)
Hematocrit (%)	30.4 (4.2)	30 (5)	31 (2)
Albumin (g/L)	36.2 (3.2)	35.7 (3.2)	37.5 (3.3)
Mean PTH (pg/mL)	200 (191)	192 (172)	221 (244)
Alkaline phosphatase (U/L)	107 (92)	111 (108)	97 (18.5)
Calcium (mg/dL)	9.5 (0.8)	9.4 (0.9)	9.8 (0.6)
Phosphorous (mg/dL)	6.2 (2.9)	5.6 (1.5)	7.6 (4.7)
Aluminum (μg/L)	35 (8)	31.7 (4.7)	41.7 (10.3)*
No. dialysis sessions/week	2.7 (0.5)	2.6 (0.5)	2.9 (0.4)
Years on dialysis	5.9 (6.8)	5.9 (7)	5.8 (7)
Lumbar spine BMD (g/cm^2)	1.09 (0.2)	1.13 (0.18)	0.99 (0.3)
1/3 radius BMD (g/cm^2)	0.59 (0.1)	0.63 (0.13)	0.50 (0.08)*
Total hip BMD (g/cm^2)	0.83 (0.2)	0.87 (0.16)	0.72 (0.2)*
No. (%) osteoporotic at any site	18 (64)	11 (55)	7 (87)

*$P < .05$, statistically significant.

BMD by Category of Osteodystrophy Defined by PTH Levels

Patients were divided into three groups based on studies correlating bone histomophometry findings with intact PTH levels with the recommendations having been to aim at keeping PTH levels between two to four times the upper limit of normal.[10–12] As shown in Table 2, subjects in all three groups had comparable mean ages and numbers of years on dialysis, although the group with low PTH levels, <120 pg/mL, tended to have the highest proportion of diabetic patients. In general BMD at cortical sites, proximal radius, and total hip tended to be least reduced in the group with intermediate intact PTH levels, that is between 120 and 250 pg/mL.

BMD in Diabetic Versus Nondiabetic Patients

There were 10 diabetic and 18 nondiabetic patients. The mean age, BMI, and number of dialysis sessions per week were comparable between the two groups. PTH levels were significantly lower in diabetic patients (Table 3), who tended to have a lower BMD at the spine and total hip as compared to nondiabetic subjects, despite their similar age and shorter duration on dialysis (Fig 1A). Furthermore, subgroup analysis by gender revealed a lower BMD in diabetic women but not diabetic men at the lumbar spine, total hip, and femoral neck as compared to nondiabetic subjects, a finding that achieved significance for the lumbar spine (Fig 1B). The majority (70%) of the diabetic patients were osteoporotic at all skeletal sites; 30% were osteopenic, whereas none had a normal BMD at all three sites. Con-

Table 2. Characteristics of Patients as Categorized by Intact PTH Levels

Variable	PTH (pg/mL)		
	<120	120–250	>250
Number of patients	13	8	7
Diabetic	8*	2*	0*
History of fracture	4	1	1
Age (years)	58 (15)	70 (11)	58 (18)
BMI (kg/m^2)	25 (3)	29 (7)	25 (4)
Hematocrit (%)	30.4 (4.6)	31.8 (3.8)	29 (3.9)
Albumin (g/L)	36.1 (3.4)	36.5 (3.6)	36 (3.1)
No. dialysis sessions/week	3 (0.4)	2.5 (0.5)	2.6 (0.5)
Years on dialysis	4 (4)	6 (7)	8.9 (8.9)
Mean PTH (pg/mL)	64 (35)*	193 (29)*	462 (200)*
Alkaline phosphatase (U/L)	119 (135)	89 (21)	103 (14)
Serum calcium (mg/dL)	9.7 (0.6)	9.2 (1.2)	9.5 (0.8)
Serum phosphorous (mg/dL)	6.6 (4)	5.5 (1.6)	6.3 (1.4)
Aluminum (μg/L)	33 (9)	37 (7)	35 (11)
Lumbar spine BMD (g/cm^2)	1.04 (0.3)	1.15 (0.12)	1.13 (0.15)
Total hip BMD (g/cm^2)	0.83 (0.2)	0.85 (0.16)	0.80 (0.17)
1/3 radius BMD (g/cm^2)	0.59 (0.13)	0.63 (0.12)	0.53 (0.14)
% osteoporotic	62	62	71

*$P < .05$, statistically significant.

versely, 61% of nondiabetic patients were osteoporotic, 28% were osteopenic, and 11% had a normal BMD at all three sites.

DISCUSSION

In our study, a significant proportion (64%) of patients on chronic hemodialysis should osteoporosis by BMD criteria, an incidence much higher than that expected for persons of similar age (<15%).[22] Long duration dialysis and diabetic diagnosis were associated with higher risk for a low BMD. Several studies have previously found BMD to be decreased in dialysis patients.[17,18,23,24] Indeed, the subgroup of patients with the highest tertile for PTH levels showed the highest lumbar spine BMD. Whereas our results confirmed previous studies demonstrating a significant relationship between time on dialysis and cortical site, BMD,[16,25,26] other investigators have demonstrated that the deleterious effect of uremia on bone health starts well before dialysis and worsens with the severity of renal failure.[6,17] Ideally, the effect on BMD of dialysis time should be assessed in longitudinal studies. However, we are unaware of any. To date, 10/28 patients who participated in the study in year 2000 died and 4/28 underwent a kidney transplant, thus explaining the difficulty of longitudinal studies.

Table 3. Characteristics of Patients: Diabetic vs Nondiabetic Subjects

Variable	Diabetic (n = 10)	Nondiabetic (n = 18)
Age (years)	62 (12)	61 (17)
BMI (kg/m^2)	27 (6)	26 (4)
Hematocrit (%)	30.2 (5)	30.6 (3.8)
Albumin (g/L)	35.3 (3.4)	36.7 (3.2)
% fracture	30	17
No. dialysis sessions/week	2.8 (0.4)	2.6 (0.5)
Years on dialysis	3.0 (1.7)	7.6 (8)
Mean PTH (pg/mL)	79 (53)	278 (170)*
Alkaline phosphatase (U/L)	82 (16)	118 (132)
Serum calcium (mg/dL)	9.9 (0.6)	9.3 (0.9)*
Serum phosphorous (mg/dL)	7.1 (4.4)	5.7 (1.4)
Aluminum (μg/L)	35.7 (9.7)	34.4 (7.6)
Lumbar spine BMD (g/cm^2)	1.05 (0.26)	1.12 (0.18)
1/3 radius BMD (g/cm^2)	0.61 (0.13)	0.58 (0.13)
Total hip BMD (g/cm^2)	0.81 (0.21)	0.84 (0.17)
% osteoporotic	70	61

*$P < .05$.

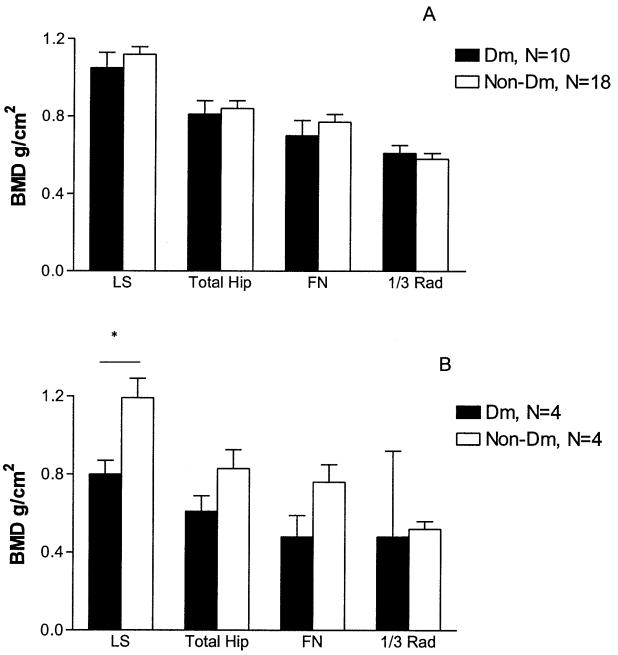

Fig 1. Bone mineral density (BMD) at the lumbar spine (LS), total hip, femoral neck (FN), and 1/3 radius (1/3 Rad) in 10 diabetic men and women (Dm, closed bars) and 18 nondiabetic men and women (Non-Dm, open bars) patients on hemodialysis (**A**) and in similar subgroups in female patients only (**B**). Number expressed as mean values ± SEMs. *$P = .018$ for difference between two groups.

BMD is the single most powerful predictor of osteoporotic fractures.[14,15] Patients on chronic hemodialysis are at an increased risk of fractures both at the lumbar spine and hip.[13,16] In a study that recruited 187 patients on hemodialysis, 21% had one or more vertebral fractures. A decreased BMD by one standard deviation doubled the odds ratio for vertebral fracture. Lumbosacral BMD was also correlated with fracture.[16] Dialysis patients showed a standardized hip fracture ratio 17.4 times greater than the general population.[13]

Furthermore, hip fractures in dialysis patients occurred at a younger age and caused higher mortality than is observed in the general population.[16] We did not observe any difference in fracture rates between diabetic and non-

diabetic subjects or in patients with PTH levels between 120 and 250 pg/mL, possibly due to our relatively small sample size. Moreover, fracture was not a primary endpoint in our study.

In a study evaluating 81 patients on dialysis, serum PTH values below 120 pg/mL were highly predictive of low turnover bone disease, values above 450 pg/mL 100% specific for high turnover bone disease, and those between 120 and 250 pg/mL with normal bone histology, findings that have been confirmed in several other studies.[10–12] The PTH values reported herein represented the mean of an average of seven determinations per patient over 5 years, a strength of our observations. Patients with a mean level between 120 and 250 pg/mL showed a trend toward the most optimal BMD, paralleling observations that with these PTH levels show the most normal bone histology[10–12] with a lower risk of either vertebral or hip fractures.[13,16] The lack of a significance between BMD values in the subgroups was probably due to our small sample size. We believe that our findings provide additional data supporting the use of target PTH levels at two to four times the upper limit of normal as a strategy to preserve skeletal health in hemodialysis patients.

In our study, diabetic hemodialysis patients showed lower BMD than nondiabetics, as well as a higher prevalence of osteoporosis as defined by densitometric criteria. Although the lower BMD in diabetics achieved statistical significance only in women at the spine, the magnitude of the decrements noted in all patients and at all skeletal sites would be expected to result in a 30% to 50% increase in fracture risk.[27] Furthermore, recent data suggest that despite relatively normal BMD diabetic women are at higher risk for fractures than non diabetics, which further underscores the relevance of our findings.[28] To our knowledge, the only previously published study comparing BMD in hemodialyzed patients with versus without diabetes demonstrated a trend similar to ours.[19] We also demonstrated that diabetic patients had significantly lower PTH values than nondiabetics, an observation that may partially explain their lower BMD. Our relatively small sample size did not allow us to dissect the respective effect of diabetes versus low PTH on BMD in uremic patients. This shortcoming limits the general applicability of our results in the overall dialysis population. However, our results are in accord with data that demonstrate a higher incidence in diabetic subjects[4–6] of nonaluminum, low turnover bone disease accompanied by impaired bone formation and resorption, otherwise known as adynamic bone disease, and with the reported greater incidence of fractures in diabetic posttransplant patients.[8] We do not believe that our low PTH results are secondary to increased sun exposure, as we and others have previously reported hypovitaminosis D in several age groups in our population.[29–31] Since patients with diabetes mellitus and renal failure are at higher risk for low BMD and fracture, one may be tempted to prescribe antiresorptive therapy, a strategy that may be potentially harmful to them, as to any subgroup of patients with adynamic bone disease.[32] Indeed, in vivo and in vitro data demonstrate that decreased bone remodeling results in loss of skeletal integrity.[32]

In conclusion, predictors of BMD among patients on hemodialysis include gender, duration of dialysis, presence of diabetes, and possibly low (<120 pg/mL) or high (>250 pg/mL) PTH levels. Special attention should be given to uremic diabetic patients and to those with low PTH levels in view of their lower BMD and therefore potentially greater risk for fractures.

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