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Research paper

Parathyroid hormone response to severe vitamin D deficiency is associated with femoral neck bone mineral density: an observational study of 405 women with hip-fracture

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ABSTRACT

OBJECTIVE: Hip-fracture patients with vitamin D deficiency can have either secondary hyperparathyroidism or normal levels of parathyroid hormone (PTH). We hypothesized that bone mineral density (BMD) could be lower in patients with high PTH levels than in those with normal levels of PTH, irrespectively of the severity of vitamin D depletion. DESIGN: In this cross-sectional study, we examined 405 women who had serum 25-hydroxyvitamin D below 12ng/ml 20.0 ± 5.9 (mean ± SD) days after a hip-fracture. PTH was assessed by a chemiluminescent immunometric assay and BMD by dual-energy x-ray absorptiometry at the unfractured femoral neck. RESULTS: BMD was significantly lower in the 148 women with secondary hyperparathyroidism than in the 257 with normal PTH levels: the mean T-score (SD) was -2.88 (0.93) and -2.65 (0.83), respectively, in the two groups (mean difference 0.23; 95% CI 0.05 - 0.41; P = 0.010). The association between PTH status and BMD persisted after adjustment for age, body mass index, phosphate, albumin-adjusted total calcium, 25-hydroxyvitamin D, estimated glomerular filtration rate, and magnesium (P=0.01). The presence of secondary hyperparathyroidism was significantly associated with a femoral neck T-score lower than -2.5. The adjusted odds ratio was 1.81 (95% CI 1.11 - 2.95; P=0.017). CONCLUSIONS: Our results show that PTH levels in the presence of severe vitamin D deficiency were significantly associated with femoral BMD in women with hip-fracture. Prevention and treatment of vitamin D deficiency may be particularly relevant in women who develop secondary hyperparathyroidism.

Key words: Hip-fracture, Parathyroid hormone, Secondary hyperparathyroidism, Vitamin D

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INTRODUCTION

The beneficial effects of vitamin D on bone tissue have long been known and have been attributed to the role of its active metabolites in the intestinal absorption of calcium and in the process of bone

mineralization.[1] Recently, numerous extra-skeletal effects of vitamin D have been shown, including actions on neuromuscular and cognitive functions which can reduce the risk of falling.[2,3] Overall, vitamin D is thought to exert favorable effects on both bone fragility and fall risk, i.e., the two major risk factors for osteoporotic fractures in older people. As a consequence, the administration of vitamin D is recommended worldwide to reduce the risk of fractures.[4] However, substantial proportions of older people are still affected by vitamin D deficiency[5,6] and very low serum levels of 25-hydroxyvitamin D are common at the time of hospitalization for a fracture of the hip,[7-10] with no apparent improvements in the last decade.[11]

Parathyroid hormone (PTH) excess can contribute to bone loss[12] and possibly to fall risk [13] in patients with vitamin D depletion because the latter is an established cause of secondary hyperparathyroidism.[14,15] However, PTH elevation is not always found in vitamin D depletion: several patients with severe vitamin D deficiency do not have PTH excess, as first shown by Sahota et al.[16] and confirmed by several recent reports.[17-20] At present, the reasons why vitamin D depletion leads to either secondary hyperparathyroidism or normal PTH levels in individual subjects are not clear.[16-20] In any case, the PTH response to vitamin D depletion may result in different levels of bone loss.[16]

Our aim was to study the relationship between PTH values and bone mineral density (BMD) in hip-fracture women with vitamin D depletion. We hypothesized that women with secondary hyperparathyroidism could have lower BMD levels than those with normal PTH levels.

METHODS

Patients and setting

We retrospectively evaluated 730 Caucasian women with a hip-fracture, admitted consecutively to our Physical Medicine and Rehabilitation division. Our hospital is in Torino, Italy, a city with about one million inhabitants and the 730 women came from several orthopedic wards in various hospitals. All the women were referred for acute inpatient rehabilitation by the consultant physiatrists of the orthopedic wards. The criteria agreed on for selecting women with hip-fractures to undergo acute inpatient rehabilitation were as follows: (1) health conditions allowing a total of three hours of physical therapy and/or occupational therapy daily; (2) weight-bearing to tolerance on the fractured hip; and (3) a potential high increase in ability to function in activities of daily living as a result of an intensive rehabilitation regimen. A total of 31 of the 730 women we evaluated were excluded from our study because their hip-fracture was caused by either major trauma or cancer affecting bone. The remaining 699 women had sustained fractures that either were spontaneous or resulted from minimal trauma (trauma equal to or less than a fall from a standing position). Nine of these 699 women were excluded from our study because of either albumin-adjusted serum levels of calcium exceeding 11mg/dl or low estimated glomerular filtration rate (GFR <15ml/min). Twelve women were excluded because they could not undergo dual-energy x-ray absorptiometry (DXA) assessment due to either refusal or presence of an arthroplasty at the non-fractured hip. Eight patients were excluded because of missing data. Among the remaining 670 women we focused on the 405 with serum levels of 25-hydroxyvitamin D below 12ng/ml. Institutional Review Board approval was obtained for the study protocol.

Outcome Measures

A blood sample was collected during the first three days of hospitalization, 20.0 ± 5.9 days (mean ± SD) after fracture occurrence, in the morning after an overnight fast. In each subject we evaluated 25-hydroxyvitamin D by an immunoenzymatic assay (coefficient of variation intrassay <8%; interassay <10%) (IDS Inc., Fountain Hills, AZ, USA), PTH by two-site chemiluminescent enzyme-labelled immunometric assay (coefficient of variation intraassay 5.7%, interassay 8.8%) (DPC Inc., Los Angeles, CA, USA), total calcium (by a photometric color test), phosphate, albumin, magnesium, and creatinine. GFR was estimated by the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation.

In all 405 women we assessed BMD at the non-fractured femoral neck by DXA (Hologic Discovery bone densitometer, USA) on the same day as the blood sample collection. The results were recorded as

T-scores (the reference population was derived from the third National Health and Nutrition Examination Survey). The coefficient of variation within subjects calculated from two repeated measurements with repositioning was 1%. Body weight and height were measured in each subject and body mass index (BMI) was calculated as weight/height^2.

None of the patients included in the study had begun specific treatment with drugs for osteoporosis after fracture occurrence before the DXA and laboratory assessment.

Data Analyses

The 405 women were divided into two groups according to their PTH levels: secondary hyperparathyroidism was diagnosed with high PTH levels (>75pg/ml), whereas levels ≤75pg/ml where defined as normal. Comparisons between the two groups of women were performed by a Student *T* test for the continuous variables, which were normally distributed based on a Shapiro-Wilk test (i.e., age, BMI, and BMD) and on a Mann-Whitney *U* test for the continuous variables which were non-normally distributed (i.e., PTH, phosphate, albumin-adjusted total calcium, 25-hydroxyvitamin D, estimated GFR, and magnesium). Additionally, femoral BMD expressed as a T-score was included in a standard linear multiple regression model as the dependent variable. The regression model included the following eight independent variables: presence of either secondary hyperparathyroidism or normal PTH levels, age, BMI, phosphate, albumin-adjusted total calcium, 25-hydroxyvitamin D, estimated GFR, and magnesium. The residuals were normally distributed in the regression model. Homoscedasticity was verified by plotting the residuals against the predicted values: the variance of the residuals looked homogeneous across levels of the predicted values. Collinearity diagnostics showed that the percent of variance in each predictor that could not be accounted for by the other predictors was always greater than 90% (no redundant predictors were found).

A binary logistic regression test was used to adjust the association between PTH category (either elevated or normal) and a femoral neck T-score lower than -2.5 for the seven potential confounders listed above.

The statistical package used was SPSS, version 14. The significance threshold was set at 0.05.

RESULTS

One hundred forty-eight of the 405 women (37%) had secondary hyperparathyroidism (PTH serum levels exceeding 75pg/ml), whereas the remaining 257 (63%) had normal PTH levels despite severe vitamin D deficiency. Table 1 shows the descriptive characteristics of the two groups of women and the between-group comparisons. Mean BMD levels were significantly lower in the women with secondary hyperparathyroidism than in those with normal PTH

Table 1. Comparisons between the women with functional hypoparathyroidism and those with secondary hyperparathyroidism

Variable	Functional hypoparathyroidism (N=257)	Secondary hyperparathyroidism (N=148)	P
Age (years), mean (SD)	78.7 (8.1)	82.4 (6.7)	<0.001
Body Mass Index (kg/m^2), mean (SD)	22.9 (4.1)	23.6 (4.2)	0.131
PTH (pg/ml)	47 (34-61)	107 (85-139)	<0.001
Phosphate (mg/dl)	3.7 (3.3-4.1)	3.4 (3.1-3.8)	<0.001
Albumin-adjusted calcium (mg/dl)	9.0 (8.2-9.5)	8.9 (7.8-9.5)	0.114
25-hydroxyvitamin D (ng/ml)	6.8 (3.8-9.0)	7.0 (4.0-8.9)	0.778
Estimated GFR (ml/min)	74.5 (63.8-87.8)	71.1 (56.0-84.3)	<0.001
Magnesium (mg/dl)	2.0 (1.9-2.1)	2.0 (2.0-2.1)	0.415
BMD (T-score), mean (SD)	-2.65 (0.83)	-2.88 (0.93)	0.010
BMD (g/cm^2), mean (SD)	0.55 (0.09)	0.52 (0.10)	0.010

Data are shown as median and interquartile range where not otherwise stated.

levels: the mean T-score (SD) was -2.88 (0.93) and -2.65 (0.83), respectively, in the two groups (mean difference 0.23; 95%CI 0.05 - 0.41; P = 0.010). The results of linear multiple regression for BMD measured at the femoral neck are shown in Table 2: three of the eight independent variables included in the standard regression model (i.e. PTH status, BMI, and age) were significantly associated with the dependent variable (femoral BMD expressed as a T-score). In particular, the presence of secondary hyperparathyroidism was negatively associated with BMD (p=0.001).A low BMD value (femoral neck T-score lower than -2.5) was found in 157 of the 257 women with normal PTH levels (i.e., 61%), whereas it was observed in 103 of the 148 women with secondary hyperparathyroidism (i.e., 70%). After multiple adjustments, the presence of secondary hyperparathyroidism was significantly associated with a femoral neck T-score lower than -2.5. The adjusted odds ratio was 1.81 (95% CI 1.11 - 2.95; P=0.017), as shown in Table 3.

DISCUSSION

Data show that PTH response to severe vitamin D deficiency was significantly associated with BMD assessed at the femoral neck after a hip-fracture:

Table 2. Linear multiple regression analysis model

Independent variables	B (95% CI)	Beta	P
(Constant)	-2.81 (-4.52; -1.10)		0.001
PTH status (either secondary hyperparathyroidism or functional hypoparathyroidism)	-0.28 (-0.46; -0.11)	-0.16	0.001
Age (years)	-0.01 (-0.02; 0)	-0.10	0.043
Body Mass Index (kg/m^2)	0.08 (0.06; 1.0)	0.36	<0.001
Phosphate (mg/dl)	-0.02 (-0.16; 0.11)	-0.01	0.774
Albumin-adjusted calcium (mg/dl)	-0.05 (-0.13; 0.03)	-0.06	0.216
25-hydroxyvitamin D (ng/ml)	0.01 (-0.02; 0.04)	0.03	0.442
Estimated GFR (ml/min)	-0.003 (-0.01; 0.00)	-0.08	0.079
Magnesium (mg/dl)	0.001 (-0.01; 0.01)	0.01	0.895

The dependent variable was femoral bone mineral density expressed as a T-score. The independent variables were those listed in the Table. For each independent variable, unstandardized B coefficients with 95% confidence intervals, standardized Beta coefficients, and P values are shown. Secondary hyperparathyroidism was conventionally attributed a value of 1 (functional hypoparathyroidism was conventionally attributed a value of 0). $R^2 = 0.18$; $F = 11.0$; $p<0.001$.

Table 3. Binary logistic regression analysis model

	Odds Ratio and 95% CI	P
PTH status (either secondary hyperparathyroidism or functional hypoparathyroidism)	1.81 (1.11 - 2.95)	0.017
Age	1.02 (0.99 - 1.05)	0.143
Body Mass Index	0.86 (0.81 - 0.91)	<0.001
Phosphate (mg/dl)	1.12 (0.77 - 1.64)	0.547
Albumin-adjusted calcium (mg/dl)	1.15 (0.92 - 1.44)	0.212
25-hydroxyvitamin D	0.98 (0.91 - 1.05)	0.583
Estimated GFR	1.01 (0.99 - 1.02)	0.093
Magnesium	0.99 (0.97 - 1.02)	0.595

The dependent variable was the presence of a low T-score (T-score < -2.5 at femoral neck assessment of bone mineral density) that was conventionally attributed a value of 1 (a T-score higher than -2.5 was conventionally attributed a value of 0). The independent variables included in the regression model are listed in the Table. Secondary hyperparathyroidism was conventionally attributed a value of 1 (functional hypoparathyroidism was conventionally attributed a value of 0). The full model was statistically significant ($\chi^2 = 45.7$; df=8; P<0.001).

the women with secondary hyperparathyroidism had lower levels of BMD than those with normal PTH levels. Two previous reports have addressed the same issue, with conflicting results.[16,18] Both the above studies investigated hip-fracture women with vitamin D depletion. Sahota et al. showed that hip BMD was lower in the women with PTH excess than in those with normal PTH levels, in agreement with our report.[16] Conversely, Amaozugan et al. did not find any significant associations between PTH status and hip BMD.[18] The reasons for this discrepancy are not obvious. One possible explanation may be the presence of confounding factors. Indeed, several variables may play a confounding role by affecting PTH levels, BMD, or both.[12,14,17,21] One strength of our study consists in the multiple adjustments we undertook: we took into account the role of age, BMI, phosphate, calcium, 25-hydroxyvitamin D, estimated GFR, and magnesium, whereas in the two previous studies no adjustments were performed.[16,18] One more strength of our study is sample size: we investigated 405 women, whereas Sahota et al. and Amazougan et al. studied 122 and 133 women, respectively.[16,18]

The link we show between secondary hyperparathyroidsm and reduced BMD is not surprising since a sustained elevation of PTH levels is known to exert catabolic effects on bone resulting in bone fragility.[12,14] The clinical significance of our results rests on the excess of bone loss found in hip-fracture women with vitamin D depletion who developed secondary hyperaparathyroidism versus those who did not. Besides bone loss, other adverse consequences have been associated with PTH excess in hip-fracture patients, who are frail subjects[7,8,22] with a high risk of recurrent falls[23] and fractures,[4,24] several comorbidities,[22] and reduced life expectancy.[25] The unfavorable outcomes associated with PTH excess include prolonged length of stay in hospital,[26] reduced recovery in ability to function in activities of daily living,[27] increased risk of being discharged to institutional care,[26] myocardial injury,[26,28] and even all-cause mortality.[26,28,29] The negative prognostic role of secondary hyperparathyroidism after hip-fracture is consistent with data in other groups of patients affected by various diseases, and even in the general aged population.[30,31] Notably, PTH excess may worsen sarcopenia,[32] which is highly prevalent in hip-fracture patients.[33]

Vitamin D deficiency was highly prevalent in our sample of hip-fracture inpatients, in agreement with the wider literature.[7-11,16,18-21,26] We confirm that a substantial proportion of hip-fracture patients with severe vitamin D deficiency do not have secondary PTH elevation,[16-20] though we did not elucidate the mechanisms underlying different PTH responses to vitamin D deficiency in different subjects. Magnesium depletion may play a pivotal role because it is associated with blunted PTH secretion,[34,35] besides resistance to PTH action.[36] We adjusted our data for serum magnesium levels, but they do not accurately reflect intracellular magnesium concentrations, which may be the actual determinants of PTH response.[35,37] Sahota et al, hypothesized other potential explanations to justify the blunted PTH response in individual subjects with vitamin D deficiency.[38] Dysfunction of the parathyroid glands may be a potential cause and may include abnormalities of the parathyroid calcium sensing receptor, abnormalities of the serum 1,25-dihydroxyvitamin D receptor, or rarer causes such as abnormal expression of growth repressing genes within the gland, although these plausible hypotheses need to be supported by data. One more possible explanation for the inconsistent relationship between vitamin D deficiency and PTH excess could be the assessment of total and not free calcifediol concentration. In fact, similar concentrations of total 25-hydroxyvitamin D may result in different levels of free bioactive calcifediol, which in turn result in different PTH levels in the presence of different levels of binding proteins.[39,40] Notably, following a hip-fracture major changes in vitamin D-binding protein are expected because of both protein-depletion due to malnutrition[41] and selective consumption due to the involvement of vitamin D-binding protein in the repair of injuried tissues.[42]

Our study has limitations. We evaluated one sample of Caucasian women who were surgically operated on and who were referred for inpatient rehabilitation. As a consequence, our results are not generalizable to the overall population of hip-fracture patients. In particular, the PTH response to vitamin D deficiency is different between men and women.[20] Further studies should clarify the relationship between PTH levels and BMD in vitamin D depleted men. We did not collect data on some factors that could alter PTH

levels, including dietary calcium intake and use of diuretics or corticosteroids. Seasonal variations in 25-hydroxyvitamin D levels were not investigated. Blood samples for laboratory assessment were collected around three weeks after fracture occurrence, thus a role of hospitalization in worsening the deficiency of vitamin D and modulating PTH response cannot be excluded. We assessed vitamin D status by measuring 25-hydroxyvitamin D levels. Although this is universally considered the best approach to assess an individual's vitamin D status, caveats, confounders, and controversies exist regarding this measurement.[43] Finally, the cross-sectional design does not prove causal inference.

In conclusion, our results show that PTH response to vitamin D deficiency was significantly associated with femoral BMD in hip-fracture women. Prevention and treatment of vitamin D deficiency may be particularly relevant in those women who develop secondary hyperparathyroidism. Data from intervention trials with vitamin D supplements should be analyzed taking into account basal PTH levels which may affect the clinical benefits due to vitamin D supplementation.

CONFLICT OF INTEREST

On behalf of all authors, the corresponding author states that there is no conflict of interest.

The study was not funded. The authors have no conflicts of interest.

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