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ORIGINAL ARTICLE

Parathyroid-hormone variance is only marginally explained by a panel of determinants: a cross-sectional study of 909 hip-fracture patients

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Abstract Several factors affect the levels of parathyroid hormone (PTH) in hip-fracture patients. We hypothesized that a panel of easily assessable determinants could account for both a substantial proportion of PTH variance and the occurrence of secondary hyperparathyroidism. We evaluated 909 of 981 hip-fracture inpatients admitted consecutively to our Rehabilitation division. In each patient we assessed PTH, 25-hydroxyvitamin D, albumin-adjusted total calcium, phosphate, magnesium, and creatinine on a fasting blood sample 21.3 ± 6.1 (mean ± SD) days after fracture occurrence. Glomerular filtration rate (GFR) was estimated by the 4-variable Modification of Diet in Renal Disease Study equation. Functional level was assessed using the Barthel index. On multivariate analysis, six factors (phosphate, albumin-adjusted total calcium, estimated GFR (eGFR), 25-hydroxyvitamin D, age, and magnesium) were significantly associated with PTH levels. Overall, the panel of variables accounted for 23.7 % of PTH variance. Among the 909 patients, 304 (33.4 %) had PTH levels exceeding the normal range. Six factors (phosphate, albumin-adjusted total calcium, eGFR, 25-hydroxyvitamin D, age, and Barthel index scores) were significantly associated with the category of PTH level (either normal or elevated). The model correctly classified 70.4 % of cases. For the optimal cut-off point, sensitivity was 80 % and specificity was 61 %. Data shows that six factors were significantly associated with PTH levels in hip-fracture inpatients. However, the six factors accounted for only 23.7 % of PTH variance and the presence or absence of secondary hyperparathyroidism was correctly categorized in a modest proportion of cases. We conclude that more knowledge is needed on the factors affecting PTH levels after hip fracture.

Keywords Hip fracture · Parathyroid hormone · Secondary hyperparathyroidism · Vitamin D

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Introduction

Parathyroid hormone (PTH) affects the skeleton in a complex way [1] which may lead to anabolic or catabolic effects depending on whether the exposure to PTH is intermittent as during treatment with exogenous PTH in osteoporosis [2, 3] or continuous as in primary and secondary hyperparathyroidism (HPT) [4, 5]. Among aged people, a secondary increase in PTH levels is common and has been attributed to several factors, including vitamin D deficiency, impaired renal function, inadequate calcium intake, and estrogen depletion [5].

Hip fractures represent the most severe consequence of bone fragility, because they result in 10–20 % excess mortality within 1 year [6] and approximately 20 % of hip-fracture survivors require long-term nursing home care, whereas only 40 % fully regain their pre-injury level of independence [7]. On the whole, the burden of hip fractures can be estimated as disability-adjusted life years lost and represent a challenge for the healthcare systems in several countries throughout the world [8].

Hip-fracture patients are aged, severely deficient in vitamin D, poorly nourished, and affected by relevant

comorbidity including impaired renal function with progressive multisystem decline, loss of physiologic reserve and increased vulnerability to disease and death [9, 10]. In these patients, secondary HPT is commonly observed [11–15] and has been implicated in the genesis of low bone mineral density [16], hip fracture itself [5, 17], and even unfavorable outcomes following hip fracture occurrence [14, 15, 18]. Unfortunately, the overall capability of a panel of determinants to account for both PTH variance and occurrence of secondary HPT is scarcely known. Our aim was to investigate the factors affecting PTH levels in a large sample of inpatients following a fracture of the hip. We hypothesized that a panel of easily assessable determinants could account for both a substantial proportion of PTH variance and the occurrence of secondary HPT.

Materials and methods

Patients

We retrospectively evaluated 981 white people with hip fracture admitted consecutively to our Physical Medicine and Rehabilitation division. We focused on white patients because few non-white, elderly people live in our country. Our hospital is in a city with about one million inhabitants and the patients came from several orthopedic wards. All the patients were referred for acute inpatient rehabilitation by the consultant physiatrists of the orthopedic wards. A total of 52 of the 981 subjects were excluded from the study, because their hip fracture was caused by either major trauma or cancer affecting the bone. The remaining 929 people suffered from fractures that either were spontaneous or caused by minimal trauma (trauma equal to or less than a fall from a standing position). A total of 11 of the 929 people were excluded from the study because of either albumin-adjusted serum levels of calcium >11 mg/dl or very low estimated glomerular filtration rate (eGFR <15 ml/min). Nine patients were excluded because of missing data. The final study sample included 909 people. IRB approval was obtained for the study protocol.

Outcome measures

A blood sample was collected during the first 3 days of hospitalization, 21.3 ± 6.1 days (mean ± SD) after fracture occurrence, in the morning after an overnight fasting. In each subject, we evaluated PTH by two-site chemiluminescent enzyme-labelled immunometric assay (coefficient of variation intraassay 5.7 %, interassay 8.8 %) (DPC Inc., Los Angeles, CA, USA), 25-hydroxyvitamin D by an immunoenzymatic assay (coefficient of variation intrassay <8 %; interassay <10 %) (IDS Inc., Fountain Hills, AZ, 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 [19].

Body weight and height were measured in each subject, and body mass index (BMI) was calculated as weight/height^2. To assess the degree of functional recovery, skilled physiatrists performed the Barthel Index (original version, unchanged) [20]. The functional index assesses basic activities of daily living; its score ranges from 0 (total dependence) to 100 (total independence). Presence of cognitive impairment (Mini Mental State Examination <24/30), and neurologic impairment (impairment found at clinical examination due to neurologic diseases, i.e., Parkinson's disease, stroke with hemiplegia, paraparesis, monoparesis, tetraparesis or cerebellar syndrome) were recorded for each subject. Hip fracture type was categorized as either cervical or trochanteric in each subject, on the basis of radiographic and surgical findings.

Data analysis

At a preliminary step we investigated the association between each potential determinant and PTH levels. For continuous variables (i.e., 25-hydroxyvitamin D, albumin-adjusted calcium, phosphate, magnesium, eGFR, albumin, age, BMI, time between fracture occurrence and blood sample collection) and for the ordinal variable (Barthel index scores) we performed a bivariate correlation test. We performed Spearman rank correlation test, because PTH was non-normally distributed using Shapiro–Wilk test. For the dichotomous variables (i.e., sex, cognitive impairment, neurologic impairment, and fracture type), we investigated differences between groups in PTH levels by using the Mann–Whitney test.

For 9 of the potential determinants (i.e., 25-hydroxyvitamin D, albumin-adjusted calcium, phosphate, magnesium, eGFR, albumin, age, Barthel index scores, and sex) we found a significant bivariate correlation with PTH levels (for the dichotomous variable a significant between-group difference).

We included the 9 potential determinants as independent variables in a linear multiple regression model. The dependent variable in the regression model was the PTH level. Because the dependent variable was non-normally distributed, area transformation was performed, using the formula $(r - 1/2)/w$, where w is the number of observations and r is the rank, as previously described [21, 22]. Following area transformation of the dependent variable, 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 >85 % (no redundant predictors were found).

A further analysis was performed after categorization of the PTH levels into two groups—≤75 pg/ml (within the normal range) or >75 (exceeding the normal range). We included the 9 potential determinants of PTH levels in a binary logistic regression model (the independent variable was dichotomous, having either normal or high levels of PTH). Because laboratory reference values are largely based on studies in vitamin D-deficient populations, the threshold for normal PTH levels has been criticized. Therefore, it has been proposed that the upper limit of PTH reference values should be decreased. To take into account this criticism, we performed a further categorization of the patients into two classes, using the upper limit of the lowest quartile of PTH (39 pg/ml) to discriminate the patients as previously described by Bjorkman et al. [23]. The logistic regression analysis was repeated with the new criterion for patient categorization. Receiver operating characteristic (ROC) curve analysis was performed to assess the ability of the panel of determinants included in binary logistic regression models to discriminate subjects with either normal or elevated levels of PTH. The Youden index was used to find optimal cut-off points.

The statistical package used was SPSS, version 14, (SPSS, Inc., Chicago, IL, USA).

Results

Median PTH level in the 909 people was 58.0 pg/ml (interquartile range from 39−88 pg/ml). Descriptive statistics for the 909 people are shown in Table 1. Results from linear multiple regression are shown in Table 2; six factors (i.e., phosphate, albumin-adjusted total calcium, eGFR, 25-hydroxyvitamin D, age, and magnesium) were significantly associated with PTH levels. Overall, the panel of determinants predicted 23.7 % of the variance in PTH levels.

Among the 909 people, 304 (33.4 %) had PTH levels exceeding the normal range (whereas 605 had PTH levels within the normal range). Table 3 shows data from binary logistic regression; six factors were significantly associated with the category of PTH level. The prediction equation was:

$$\text{Log}\ (p/1-p) = 4.42 - 0.88a - 0.37b - 0.02c - 0.02d + 0.03e - 0.001f$$

where p is the probability of having HPT, a = phosphate (mg/dl), b = albumin adjusted total calcium (mg/dl),

Table 1 Characteristics of the study sample ($N = 909$) shown as median and interquartile range when not otherwise stated

Age (years)	81.0 (76.0−85.5)
Phosphate (mg/dl)	3.6 (3.3−4.0)
Albumin-adjusted total calcium (mg/dl)	8.8 (7.8−9.4)
25-Hydroxyvitamin D (ng/ml)	9.6 (6.0−16.4)
Estimated GFR (ml/min)	73.5 (61.6−86.9)
Magnesium (mg/dl)	2.0 (1.9−2.1)
Albumin (g/dl)	3.1 (2.8−3.4)
Body mass index (kg/m^2)	22.7 (20.0−25.6)
Barthel index score	45 (30−55)
Cognitive impairment (%)	27 %
Neurologic impairment (%)	17 %
Sex (women/men, %)	87/13
Hip fracture type (cervical/trochanteric, %)	46/54

Table 2 Multiple regression analysis model

Variables	Partial correlation	p
Phosphate	−0.285	<0.001
Albumin-adjusted total calcium	−0.265	<0.001
25-Hydroxyvitamin D	−0.202	<0.001
Estimated GFR	−0.188	<0.001
Age	0.079	0.018
Magnesium	0.067	0.044
Barthel index score	−0.060	0.071
Sex	0.049	0.142
Albumin	−0.024	0.472

The dependent variable was PTH serum level in 909 patients (after normalization by area transformation). The independent variables were those listed in the Table. $R^2 = 0.237$; $F = 46.8$; $p < 0.001$

Table 3 Binary logistic regression analysis

	B (SE)	Odds ratio and 95 % CI	p
Phosphate	−0.88 (0.15)	0.42 (0.31−0.56)	<0.001
Albumin-adjusted total calcium	−0.37 (0.09)	0.69 (0.58−0.82)	<0.001
25-Hydroxyvitamin D	−0.02 (0.01)	0.98 (0.96−0.99)	<0.001
Estimated GFR	−0.02 (0.004)	0.98 (0.97−0.99)	<0.001
Age	0.03 (0.01)	1.03 (1.00−1.05)	0.028
Magnesium	0.06 (0.03)	1.06 (0.99−1.14)	0.077
Barthel index score	−0.001 (0.00)	0.99 (0.99−1.00)	0.032
Sex	−0.30 (0.23)	0.74 (0.47−1.15)	0.181
Albumin	0.01 (0.20)	1.01 (0.68−1.51)	0.953

The dependent variable was the PTH level categorized as ≤75 (that was conventionally attributed a value of 0) or >75 (that was conventionally attributed a value of 1). The independent variables included in the regression model are listed in the Table. The full model was statistically significant ($\chi^2 = 163.4$; $df = 9$; $p < 0.001$)

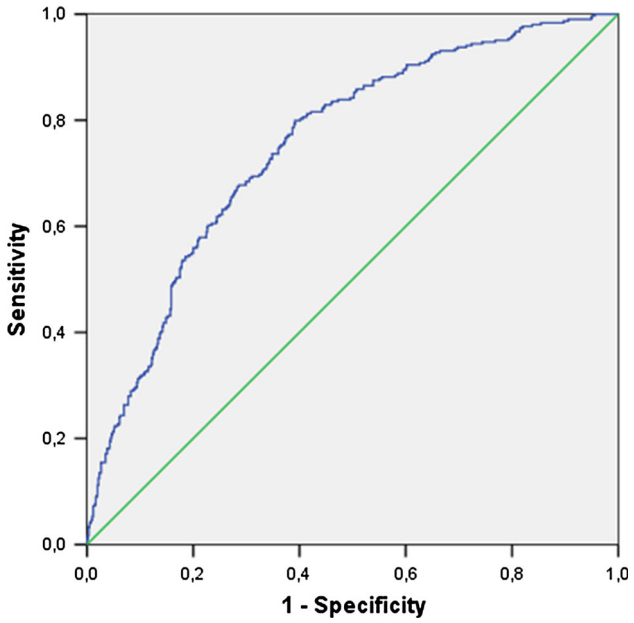

Fig. 1 Receiver operating characteristic (ROC) curve analysis. We assessed the ability of the panel of determinants shown in Table 3 to discriminate subjects with PTH levels either >75 pg/ml or ≤75 pg/ml. The area under the *curve* was 0.75 (SE 0.02; 95 % CI 0.72−0.78)

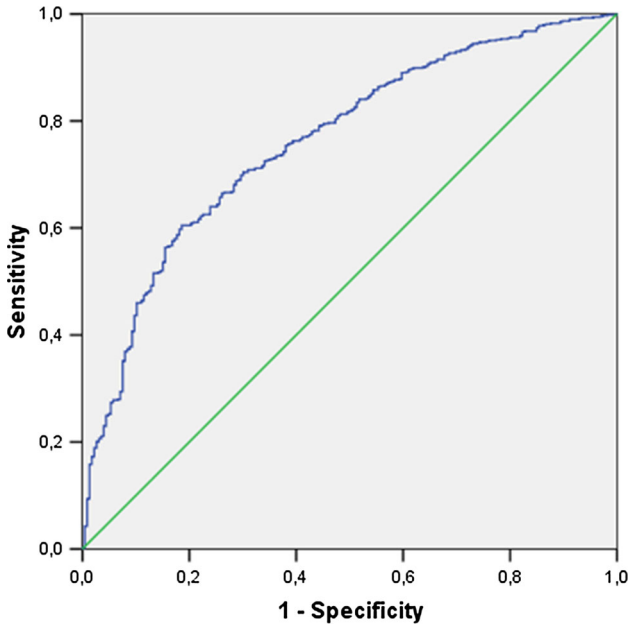

Fig. 2 Receiver operating characteristic (ROC) curve analysis. We assessed the ability of the panel of determinants shown in Table 4 to discriminate subjects with PTH levels either >39 pg/ml or ≤39 pg/ml. The area under the *curve* was 0.76 (SE 0.02; 95 % CI 0.73−0.80)

Table 4 Binary logistic regression analysis

	B (SE)	Odds ratio and 95 % CI	*p*
Phosphate	−1.00 (0.17)	0.37 (0.26−0.51)	<0.001
Albumin-adjusted total calcium	−0.49 (0.11)	0.61 (0.50−0.75)	<0.001
25-Hydroxyvitamin D	−0.02 (0.01)	0.98 (0.96−0.99)	<0.001
Estimated GFR	−0.015 (0.004)	0.98 (0.98−0.99)	<0.001
Age	0.01 (0.01)	1.01 (0.99−1.03)	0.365
Magnesium	0.05 (0.03)	1.05 (0.98−1.13)	0.143
Barthel index score	0.00 (0.00)	1.00 (1.00−1.00)	0.153
Sex	−0.28 (0.27)	0.76 (0.44−1.29)	0.311
Albumin	−0.14 (0.21)	0.87 (0.57−1.30)	0.492

The dependent variable was the PTH level categorized according to the upper limit of the lowest quartile as ≤39 (that was conventionally attributed a value of 0) or >39 (that was conventionally attributed a value of 1). The independent variables included in the regression model are listed in the Table. The full model was statistically significant ($\chi^2 = 146.0$; $df = 9$; $p < 0.001$)

c = 25-hydroxyvitamin D (ng/ml), d = eGFR (ml/min), e = age (years), and f = Barthel index score.

The model correctly classified 70.4 % of cases. ROC curve analysis to assess the ability of the panel of determinants included in the logistic regression model to discriminate subjects with either normal or elevated levels of PTH is shown in Fig. 1. For the optimal cut-off point sensitivity was 80 % and specificity was 61 % (at a predicted probability $p = 0.29$).

Table 4 shows data from binary logistic regression when the threshold for defining high PTH levels was shifted to the upper value of the lowest quartile (39 pg/ml). Four factors were significantly associated with the category of PTH level. The prediction equation was:

$$\text{Log}\ (p/1-p) = 9.55 - a - 0.49b - 0.02c - 0.015d$$

where p is the probability of having HPT, a = phosphate (mg/dl), b = albumin adjusted total calcium (mg/dl), c = 25-hydroxyvitamin D (ng/ml), d = eGFR (ml/min). The model correctly classified 77.4 % of cases. ROC curve analysis is shown in Fig. 2. For the optimal cut-off point sensitivity was 60 % and specificity was 82 % (at a predicted probability $p = 0.79$).

Discussion

Data shows that secondary HPT was common among hip-fracture patients; the prevalence of 33.4 % is quite similar to the one reported by LeBoff et al. [12] and Fisher et al. [15], whereas in other previous studies it ranged from 17 % [11] to approximately 50 % [13, 14]. We show that six factors were independently associated with PTH levels at multivariate analysis. However, our main result was that on the whole the six factors accounted for only 23.7 % of PTH variance and the presence or absence of secondary HPT was correctly categorized in a modest proportion of cases. Consistently with the wider literature, the vast majority of

the patients included in this study had low levels of 25-hydroxyvitamin D [13, 14, 21, 24], i.e., a known cause of secondary HPT [5, 25]. However, about two in three of our patients did not have secondary HPT. The high frequency of normal PTH levels among hip-fracture patients with severe vitamin D deficiency has been firstly shown by Sahota et al. [26]. They found that only 50 % of women with 25-hydroxyvitamin D <12 ng/ml had secondary HPT whereas the remaining 50 % had inappropriate normal PTH levels they defined as 'functional hypoparathyroidism'. The authors found similar results in the previous literature regarding both young and old people [26, 27], and concluded that functional hypoparathyroidism was a common condition, although previously unrecognized. Recent reports further confirmed the high prevalence of functional hypoparathyroidism in hip-fracture patients [23, 28, 29], in agreement with our finding.

Convincing explanations for low PTH levels in vitamin D depletion are still lacking. Bjorkman hypothesized that reduced mobility may be the cause of blunted PTH response in many subjects due to increased bone resorption from the unloaded skeleton resulting in a non-PTH mediated release of calcium [23]. However, PTH levels strongly varied among the patients studied by Bjorkman, despite the fact they were all bedridden. In our study, the level of functional recovery assessed by the Barthel index was not significantly associated with PTH and only marginally contributed to categorize PTH excess. Overall, reduced mobility seems not to be the key factor to justify the unexplained PTH variance. Besides mobility level, serum calcium is affected by several factors and is known as a major determinant of PTH [5]. We showed that albumin-adjusted total calcium was actually associated with PTH values, but it accounted for a small proportion of PTH variance. In chronic kidney disease, mineral metabolism disturbances start early and PTH elevation together with a decrease in both serum 1,25-dihydroxyvitamin D and urine phosphate excretion is an initial alteration [30–32]. As chronic renal failure progresses, the increase in serum phosphate and finally a decrease in serum calcium play a relevant role in the further increase of PTH levels [30–32]. In agreement with these findings, we actually showed that both eGFR and serum phosphate were significantly associated with PTH levels. Aging itself may be associated with an increased PTH secretion [33, 34], and may modulate PTH response in vitamin D deficiency. We actually showed that age was an independent predictor of PTH levels, but, again, its role was modest. Magnesium depletion is associated with blunted PTH secretion [35], besides resistance to PTH action [36]. We actually showed a significant although weak relationship between circulating magnesium and PTH. Intracellular magnesium may be a stronger predictor of PTH, because enzymes which mediate PTH synthesis and its cellular response (adenylate cyclase and phospholipase C) are known to be highly magnesium dependent [37]. Unfortunately, serum magnesium does not accurately reflect intracellular magnesium concentrations [38], several patients with normal circulating magnesium are magnesium depleted [39], and magnesium deficiency (shown by a magnesium loading test) was shown as an important factor contributing to blunted PTH response to vitamin D deficiency in osteoporotic patients [39]. Clearly, further studies are necessary to investigate the role of magnesium, which may be crucial. Sahota et al. [40] hypothesized other potential explanations to justify the blunted PTH response in vitamin D depletion. 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 [41], but these plausible hypotheses need support by data. An alternative explanation of the difficulties in predicting PTH excess may rest on inappropriate thresholds used to define 'normal' PTH levels, because thresholds were established by studies in vitamin D-deficient populations. Lowering the threshold to define 'high' PTH level to the upper limit of the lowest quartile [23] actually increased the accuracy of our model (from 70−77 %), but a substantial proportion of patients were still not correctly categorized.

Our study has limitations. The cross-sectional nature impairs the causal relationship. We evaluated a sample of white people, who were surgically operated on, and were referred for inpatient rehabilitation. As a consequence, our results are not generalizable to the overall population of hip-fracture patients. It is plausible that a part of the unexplained variance in PTH levels may depend on factors we did not investigate, including dietary calcium intake [5] and use of loop diuretics [42] or corticosteroids. We cannot exclude that hip fracture itself plays a confounding role by affecting bone and mineral metabolism, although we found no significant relationships between fracture type or time between fracture occurrence and blood sample collection and PTH levels. We had no control groups, so we cannot investigate differences in PTH determinants between hip fracture patients and other people. Despite limitations, our results show that six predictive factors were independently associated with PTH levels, but a large proportion of the variance in PTH was not accounted for. The full elucidation of the factors affecting PTH level is a crucial issue and should be further addressed to optimize the strategies for prevention and treatment of secondary HPT in hip-fracture patients. This is expected to result in preventing bone loss and fragility fractures [16, 17, 43–45] which are common in hip-fracture survivors [7, 8]. Furthermore, correcting secondary HPT may improve post-fracture recovery,

complications and mortality [14, 15, 18], although these effects were hypothesized on the basis of observational studies which do not prove cause and effect relationships [46] and need confirmation by intervention trials.

Conflict of interest All authors have no conflicts of interest.

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