J Endocrinol Invest (2015) 38:1129–1135
DOI 10.1007/s40618-015-0320-9

ORIGINAL ARTICLE

Parathyroid hormone response to two levels of vitamin D deficiency is associated with high risk of medical problems during hospitalization in patients with hip fracture

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Received: 2 February 2015 / Accepted: 21 May 2015 / Published online: 6 June 2015

Abstract
Background Vitamin D and the parathyroid hormone (PTH) response play an important role in hip fracture patients. This study was carried out to determine the factors associated with the PTH response to different levels of vitamin D deficiency during hospitalization.
Methods This was a cross-sectional study of patients over 64 years of age admitted with an acute fragility hip fracture between March 1st 2009 and November 30th 2012. Demographic, clinical, functional, and cognitive function were evaluated at admission and during hospitalization. Levels of 25-hydroxyvitamin D (25-OHD) and PTH were analyzed. Two 25-OHD cut-off points were considered, <12 ng/ml and 12–20 ng/ml. Multivariate logistic regression analysis was used.
Results Mean age of the 607 patients included was 84.7 years (SD 7.10), and 81.9 % were women. The mean 25-OHD level in the total sample was 13.2 (SD 11.1) ng/ml. Levels of 25-OHD <12 ng/ml were present in 347 patients (57.2 %), of whom 158 (45.5 %) had secondary hyperparathyroidism (SHPT) (PTH >65 pg/ml). 25-OHD levels of 12–20 ng/ml were present in 168 (27.7 %) patients, of whom 47 (28 %) had SHPT. Following logistic regression, SHPT was associated in both groups (25-OHD <12 and 12–20 ng/ml) with a greater number of medical problems during hospitalization. In the 25-OHD group <12 ng/ml, SHPT was also associated with poorer glomerular filtration rates.
Conclusion The PTH response to vitamin D deficiency in hip fracture patients may be a marker for patients with higher risk of developing multiple medical problems, both when considering severe (<12 ng/ml) and moderate (12–20 ng/ml) vitamin D deficiency.

Keywords Elderly · Hip fracture · Vitamin D · Secondary hyperparathyroidism · Outcomes

Introduction

Vitamin D deficiency is highly prevalent in older adults in general, and in patients with hip fracture in particular. The prevalence of this deficiency varies, with some studies reporting levels under 12 ng/ml in 38–68 % of hip fracture patients [1], and another study finding levels of <20 ng/ml in up to 62 % of these patients [2]. Alterations in vitamin D functions have been associated with values of <12 ng/ml in some studies, and with values of 12–20 ng/ml in others, although the optimal level for some vitamin D functions is around 40 ng/ml [3], depending on the health outcome in question [4].

Parathyroid hormone (PTH) is negatively correlated with vitamin D; the lower the vitamin D level, the higher the PTH [5]. Secondary hyperparathyroidism (SHPT) in the elderly is attributed to various factors, including vitamin D deficiency and impaired renal function. This type of hyperparathyroidism involves increased bone turnover,

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with increased bone loss mainly at the cortical level, which is the mechanism by which the hip is affected.

But not all patients with hip fracture and vitamin D deficiency develop SHPT [6]. Sahota et al. [1] in 2001 studied patients with a severe deficiency of vitamin D (<12 ng/ml) and found that half of them did not have elevated PTH, a condition that was called "functional hypoparathyroidism". Subsequently, in 2006, Sakuma et al. [2] showed that SHPT developed in 20–40 % of patients with a milder level of vitamin D deficiency (<20 ng/ml) [7]. It is not known why the same level of vitamin D is associated with SHPT in some patients but not in others. Some factors act independently of those known to elevate PTH, such as renal function, advanced age and mobility problems in the elderly [8].

Whatever the mechanism is, the increase in PTH in response to vitamin D deficiency is not beneficial for patients. Several studies have shown that the elevation of serum PTH in patients with hip fracture is independently associated with poor outcomes and falls [9–11]. In healthy older adults, it has been associated with loss of muscle mass and strength [12]. The increase in PTH as a response to vitamin D deficiency may be one of the markers that explain the different clinical and functional course in hip fracture, within the heterogeneity presented by these patients [13]. Conversely, in patients with vitamin D deficiency who lack a compensatory mechanism to produce increased PTH, this lack of elevation of PTH may play a protective role. If this association is confirmed, measurement of serum PTH could be useful in clinical practice to detect patients with a higher probability of poor outcome.

The objective of this study was to determine the factors associated with the PTH response to two levels of vitamin D deficiency (severe, <12 ng/ml and moderate, 12–20 ng/ml) in patients with hip fracture, and to evaluate whether the response at either of the two levels is associated with poor outcomes.

Materials and methods

Subjects

The study was carried out in a 1300-bed university hospital, in Madrid (Spain). This was a cross-sectional study of patients over 64 years of age admitted for a proximal femur fracture of probable osteoporotic etiology from March 1st 2009 to November 30th 2012. Patients were admitted directly from the emergency department to an acute orthogeriatric unit, with responsibility shared between the orthopedics and geriatrics departments [14]. All patients were Caucasic.

The inclusion criteria were: (1) having sustained a fall from their own standing height resulting in hip fracture; (2) absence of a terminal disease (advanced cancer); (3) no hypercalcemia; (4) no history of primary hyperparathyroidism; (5) estimated glomerular filtration rate higher than 29 ml/min; (6) consent for study inclusion.

Demographic (age, sex, previous living situation) and clinical data (type of fracture, previous medical conditions, Charlson Index [15], and surgical risk according to the American Society of Anesthesiologists (ASA) [16] classification were collected at hospital admission. Functional level before hospitalization and at discharge was assessed by applying the Barthel index [17]. Cognitive function was evaluated by applying Pfeiffer's questionnaire [18] and the Red Cross Mental Impairment Scale [19], which allows assessment of the patient's current and previous cognitive status.

As variables of the process of care during hospitalization, we measured the number of medical problems (all the active clinical diagnoses of problems requiring treatment during hospitalization), the length of hospital stay and the discharge destination. All study patients, or their relatives, if they had cognitive impairment, consented to the use of their data for research.

Biological parameters

A blood sample was collected during the first 5 days of hospitalization. We assessed serum vitamin D levels (25-OHD), PTH, total calcium, phosphate, proteins, albumin, creatinine and alkaline phosphatase. Serum 25-OHD was measured using a direct competitive chemiluminescence immunoassay in a LIAISON® System (DiaSorin, Stillwater, MN). The adult reference range was 30–100 ng/ml, analytical sensitivity was 4 ng/mL and the intra- and inter-assay coefficient of variation (CV) was 3.3 and 6.9 %, respectively. Serum intact PTH was measured using a two-site chemiluminescent enzyme-labeled immunometric assay in an IMMULITE® 2500 System (Siemens, Tarrytown, NY). The adult reference range was 12–65 pg/ml (1.3–6.8 pmol/l), analytical sensitivity was 3.0 pg/mL (0.3 pmol/l) and the intra- and inter-assay CV was 4.3 and 6.3 %, respectively. Renal glomerular filtration rate (GFR) was estimated by the 4-variable Modification of Diet in Renal Disease (MDRD) study equation [20].

Statistical analysis

We analyzed the PTH response to two levels of vitamin D deficiency: <12 ng/ml and 12–20 ng/ml.

The dependent variable was PTH, classified as either functional hypoparathyroidism (PTH ≤65 pg/ml) or SPTH (>65 pg/ml).

Two-sample non-parametric comparison was performed using the Mann–Whitney test for continuous variables and

the Chi- square test (or Fisher's exact test) for categorical variables.

The multivariate logistic regression analysis was performed using a forward stepwise model for the dependent variable SPTH in response to the two levels of vitamin D deficiency, with 25-OHD <12 ng/ml or 12–20 ng/ml. The variables that were significantly associated with SPTH and those with $p < 0.10$ were entered into the model.

The models were tested by the area under the ROC curve. The data were analyzed using the statistical program SPSS/PC 20.

Results

Of the 677 patients admitted during the study period, 70 were excluded: 56 had GFR estimated by MDRD of less than 30 ml/min, 8 had terminal cancer, in four cases, the blood sample was lost, and 2 had primary hyperparathyroidism. A total of 607 patients were included in the study; their mean age was 84.7 years (SD 7.10) and 81.9 % were women. The mean 25-OHD level was 13.2 (SD 11.1). In 347 patients (57.2 %), 25-OHD levels were <12 ng/ml and in 168 (27.7 %), they were 12–20 ng/ml. The mean time from admission to blood sample extraction was 3.3 days (SD 1.6).

A total of 158 patients (45.5 %) with 25-OHD levels <12 ng/ml had SHPT versus 47 (28 %) of those with levels of 12–20 ng/ml (Fig. 1). The Pearson correlation coefficient between 25-OHD and PTH was $r = -0.228$ ($p < 0.001$).

Tables 1 and 2 show the characteristics of patients with 25-OHD <12 ng/ml and with 12–20 ng/ml, respectively, with regard to PTH response.

Among patients with severe vitamin D deficiency (25-OHD levels <12 ng/ml), those patients with SHPT, as compared to those with normal levels of PTH ("functional hypoparathyroidism"), were older, more often men, more frequently living in a nursing home, had a higher Charlson Index and greater surgical risk (ASA III-IV), showed a lower GFR estimated by MDRD, more frequently needed diuretic therapy, and had a lower vitamin D level. These patients had a larger number of medical problems and were more likely to die during hospitalization.

Among patients with moderate vitamin D deficiency (25-OHD levels 12–20 ng/ml), those with SHPT were older and showed a lower GFR estimated by MDRD. The same as in the group with severe deficiency, a larger number of medical problems was detected in these patients during hospitalization but, in contrast, they had poorer functional (Barthel index) and cognitive status (Pfeiffer's Questionnaire) at discharge.

In both the group of patients with severe (<12 ng/ml) and moderate (12–20 ng/ml) vitamin D deficiency, no differences were found in previous functional or cognitive status, or in the analytical parameters measured (plasma levels of calcium, albumin and phosphate).

The multivariate logistic regression analysis was performed. The variables that were significantly associated with SPTH and those with $p < 0.10$ were entered into the model. In the case of severe vitamin D deficiency age, sex, previous living situation, Charlson Index, furosemide treatment, surgical risk according to the ASA, serum vitamin D levels, GRF estimated by MDRD, Alkaline phosphatase, number of medical problems during hospitalization, and in-hospital mortality were entered. In the case of moderate vitamin D deficiency age, GRF estimated by MDRD, number of medical problems during hospitalization, Barthel index and Pfeiffer score were entered.

Table 3 shows the factors associated with SHPT in the two levels of Vitamin D deficiency (25-OHD <12 and 12–20 ng/ml). In both cases, SHPT was associated with an increased number of medical problems during hospitalization. In the group with 25-OHD <12 ng/ml, SHPT was also associated with poorer GFR and lower vitamin D level.

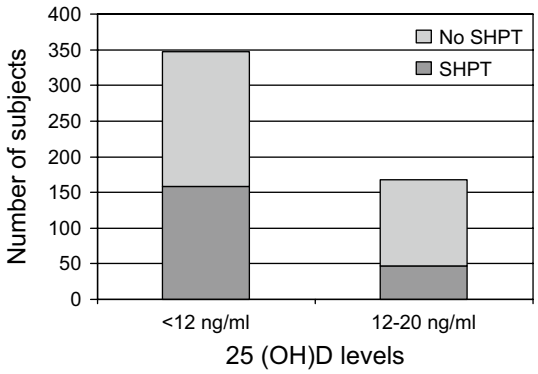

Fig. 1 Frequency of secondary hyperparathyroidism (SHPT) (PTH >65 pg/ml) in function of the levels of 25 (OH)D deficiency in 607 patients with acute hip fracture

Discussion

This study confirms once again that elderly patients admitted with hip fracture have a high prevalence of 25-OHD deficiency. Using a cut-off of 25-OHD <12 ng/ml, vitamin D deficiency was present in 57.2 % of our patients, while the corresponding prevalence with a cut-off of 20 ng/ml was 84.9 %.

SHPT was also frequent. Almost half of the patients with vitamin D deficiency <12 ng/ml had SHPT (45.5 %), and over a quarter of those with vitamin D deficiency of 12–20 ng/ml (28 %). These SHPT levels are similar to those reported by some authors [1], whereas others have found a lower prevalence [2, 6].

Table 1 Comparison of characteristics of patients with hip fracture and Vitamin D deficiency <12 ng/ml ($N = 347$) according to their parathyroid hormone response (PTH ≤65 pg/ml and >65 pg/ml)

Variables	PTH ≤ 65 pg/ml 189 (54.5 %)	PTH > 65 pg/ml 158 (45.5 %)
Baseline		
Age (years) $\bar{x}$ (SD)	84.6 (6.7)	86 (7.5)*
Women *n* (%)	160 (84.7)	122 (77.2)*
Living in nursing home *n* (%)	49 (25.9)	53 (33.5)*
Charlson index $\bar{x}$ (SD)	1.1 (1.0)	1.4 (1.3)**
Calcium and vitamin D treatment *n* (%)	9 (4.8)	6 (3.8)
Corticosteroid treatment *n* (%)	3 (1.6)	4 (2.5)
Furosemide treatment *n* (%)	32 (16.9)	45 (28.5)***
Barthel index $\bar{x}$ (SD)	72.6 (27.3)	73.2 (24.7)
RCM mental scale, $\bar{x}$ (SD)	1.1 (1.3)	1.1 (1.2)
Admission		
Admission October–March *n* (%)	98 (51.9)	84 (53.2)
Pfeiffer score $\bar{x}$ (SD)	4.4 (3.3)	4.4 (3.2)
Subcapital fracture *n* (%)	78 (41.3)	71 (44.9)
ASA III-IV *n* (%)	115 (60.8)	110 (69.6)*
25-OHD (ng/ml) $\bar{x}$ (SD)	7.2 (2.1)	6.3 (2.5)***
Calcium (mg/dl) $\bar{x}$ (SD)	8.7 (0.4)	8.7 (0.6)
Albumin (g/dl) $\bar{x}$ (SD)	3.0 (0.3)	3.1 (0.3)
Phosphate (mg/dl) $\bar{x}$ (SD)	3.0 (0.3)	3.3 (0.8)
eGFR (ml/m) $\bar{x}$ (SD)	63.1 (20.6)	53.1 (17.0)***
Alkaline phosphatase (UI/L) $\bar{x}$ (SD)	89.6 (48.5.9)	93.2 (45.6)*
Discharge		
Number of medical problems during hospitalization $\bar{x}$ (SD)	9.1 (2.4)	10.4 (2.7)***
Barthel Index $\bar{x}$ (SD)	33.0 (19.2)	32.6 (20.9)
Pfeiffer score $\bar{x}$ (SD)	4.4 (3.3)	4.1 (3.3)
Days before surgery$\bar{x}$ (SD)	3.4 (2.2)	3.2 (2.1)
Length of stay $\bar{x}$ (SD)	10.6 (4.9)	10.8 (4.5)
In-hospital mortality *n* (%)	2 (1.1)	6 (3.8)*

RCM Red Cross Mental Impairment Scale, *eGFR* Glomerular Filtration Rate estimated by 4-variable Modification of Diet in Renal Disease, *25-OHD* 25-hydroxyvitamin D

* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

In our study, SHPT was independently associated with an increased number of medical problems during hospitalization. Although the difference is small, this fact was shown at both levels of vitamin D deficiency, indicating greater clinical complexity in patients with SHPT. In the bivariate analysis, in the case of patients with severe vitamin D deficiency, we found a higher mortality in those who had SHPT, although this variable did not remain independently associated after the regression analysis. In other studies, a PTH response has also been associated with indirect data of greater patient complexity during hospitalization for hip fracture, such as increased in-hospital mortality, prolonged stay, more referrals to institutional care [9] and worse functional recovery after the fracture [10]. Increased PTH has also been proposed as a mortality predictor in frail aged inpatients [21]. SHPT in response to vitamin D deficiency also occurs at younger ages. Non response to PTH, known as "functional hypoparathyroidism," has a bone-protective effect [1, 22], although not all the authors confirm this fact [23].

In the patient group with more severe vitamin D deficiency (<12 ng/ml), SHPT was also found to be independently associated with lower levels of vitamin D and worse renal function estimated by MDRD, but this association was not found in patients with higher vitamin D levels (12–20 ng/ml).

In the overall sample, the correlation between 25-OHD and PTH levels was low ($r = -0.22$), similar to what other authors have reported. However, there are studies showing that the response to PTH and thus the frequency of SHPT is lower when vitamin D levels are higher, and that levels over 40 ng/mL protect against development of SHPT [24].

It has also been seen that better levels of estimated renal function may be protective, avoiding the development

Table 2 Comparison of characteristics of patients with hip fracture and vitamin D deficiency 12–20 ng/ml ($N = 168$) according to their parathyroid hormone response (PTH ≤ 65 pg/ml and > 65 pg/ml)

Variables	PTH ≤ 65 pg/ml 121 (72 %)	PTH > 65 pg/ml 47 (28 %)
Baseline		
Age (years) $\bar{x}$ (SD)	83.4 (7.0)	85.6 (6.5)*
Women *n* (%)	98 (81)	39 (83)
Living in nursing home *n* (%)	21 (17.4)	10 (21.3)
Charlson Index $\bar{x}$ (SD)	1.2 (1.3)	1.2 (1.1)
Calcium and vitamin D treatment *n* (%)	27 (22.3)	8 (17)
Corticosteroid treatment *n* (%)	4 (3.3)	1 (2.1)
Furosemide treatment *n* (%)	18 (14.9)	12 (25.5)
Barthel index $\bar{x}$ (SD)	80.0 (25.3)	79.3 (21.7)
RCM mental scale, $\bar{x}$ (SD)	0.9 (1.2)	1.0 (1.1)
Admission		
Admission October–March *n* (%)	57 (47.1)	18 (38.3)
Pfeiffer score $\bar{x}$ (SD)	3.5 (3.4)	4.4 (3.3)
Subcapital fracture *n* (%)	47 (38.8)	21 (44.7)
ASA III-IV *n* (%)	70 (57.9)	33 (70.2)
25-OHD (ng/ml) $\bar{x}$ (SD)	15.6 (2.6)	15.5 (2.5)
Calcium (mg/dl) $\bar{x}$ (SD)	8.7 (0.4)	8.6 (0.7)
Albumin (g/dl) $\bar{x}$ (SD)	3.1 (0.3)	3.0 (0.3)
Phosphate (mg/dl) $\bar{x}$ (SD)	3.2 (0.6)	3.3 (0.6)
eGFR (ml/m) $\bar{x}$ (SD)	60.2 (18.5)	49.9 (18.1)***
Alkaline phosphatase (UI/L) $\bar{x}$ (SD)	84.4 (36.6)	86.5 (41.6)
Discharge		
Number of medical problems during hospitalization $\bar{x}$ (SD)	8.9 (2.6)	10.5 (2.3)***
Barthel index $\bar{x}$ (SD)	39.2 (18.9)	31.7 (19.4)**
Pfeiffer score $\bar{x}$ (SD)	3.1 (3.3)	4.1 (3.1)**
Days before surgery $\bar{x}$ (SD)	3.3 (2.0)	2.9 (1.6)
Length of stay $\bar{x}$ (SD)	10.2 (3.1)	11.0 (4.2)
In-hospital mortality *n* (%)	2 (1.7)	2 (4.3)

RCM Red Cross Mental Impairment Scale, *eGFR* Glomerular Filtration Rate estimated by 4-variable Modification of Diet in Renal Disease, *25-OHD* 25-hydroxyvitamin D

*$p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Table 3 Factors associated with secondary hyperparathyroidism (PTH >65 pg/ml) in patients with hip fracture according to the level of vitamin D deficiency <12 ng/ml ($N = 347$) or 12–20 ng/ml ($N = 168$) in logistic regression analysis

25-Hydroxyvitamin D < 12 ng/ml	B	SE B	P	OR	OR 95 % CI
Number of medical problems during hospitalization	0.162	0.047	0.001	1.175	1.073–1.288
Vitamin D level	−0.159	0.051	0.002	0.853	0.772–0.942
Estimated GFR (MDRD)	−0.034	0.007	0.000	0.967	0.954–0.981
Area under ROC curve = 0.707 (95 % CI 0.653–0.761)					
25-Hydroxyvitamin D 12–20 ng/ml					
Number of medical problems during hospitalization	0.254	0.081	0.002	1.289	1.101–1.510
Area under ROC curve = 0.686 (95 % CI 0.596–0.776)					

GFR Glomerular Filtration Rate, *MDRD* 4-variable Modification of Diet in Renal Disease

of SHPT. These results have been reported previously by various authors [6, 25]. In general, as estimated GFR goes down, PTH increases [8]. As a result of the multivariate analysis, we found that low GFR is indeed associated with SHPT, but only when vitamin D deficiency is severe and not when it is mild.

Like other studies, we found no association between PTH response and level of serum calcium or alkaline phosphatase [22, 26].

Other authors have found an association of PTH with type of fracture [1] and sex [7, 25], age and number of lost functions in the capacity to perform basic activities of daily living [27], although we did not find such an association after adjusting for the rest of the variables analyzed.

A limitation of this study is that the PTH response in patients with hip fracture may have been overestimated. We measured 25-OHD and PTH, on average, 3.3 days (SD 1.6) after admission through the emergency department. The possible importance of sampling times has been analyzed by others. Some authors consider that measurement immediately after the fracture may overestimate the prevalence of SHPT [28], and that PTH levels are reduced within a week after the hip fracture [29]. Others do not find that PTH is elevated with respect to its subsequent evolution if measured in the period immediately following hip fracture [30].

Another possible study limitation is the lack of data on the patients' dietary calcium intake or magnesium status. In the case of calcium, although no data on intake were collected, there were no differences in plasma levels of calcium or albumin in patients with and without SHPT for either of the two levels of vitamin D deficiency. The possible influence of magnesium deficiency in the PTH response was not measured.

In conclusion, we found that the PTH response in elderly patients with hip fracture is associated with an increased number of active medical problems during hospitalization in patients with 25-OHD deficiency, both in cases of severe (<12 ng/mL) and moderate (12–20 ng/ml) vitamin D deficiency. SHPT in these patients is thus an indicator of greater clinical complexity during hospitalization.

If these findings are demonstrated in other patient series—while nonetheless recognizing the heterogeneity of elderly adults admitted for hip fracture—consideration should be given to including the PTH response to vitamin D deficiency as a marker of greater complexity in these patients during their hospitalization.

Acknowledgements This study was conducted in part with the support provided to emerging research groups IdiPaz-2012 of the Research Institute of the La Paz University Hospital (IdiPAZ). Project no. HULP PI-1334. The authors thank Dr. Jose Manuel Iturzaeta of the Clinical Analysis Service for assistance in processing and determining the analyses of vitamin D and PTH.

Conflict of interest All the authors declare that they do not have conflict of interest.

Ethical approval All procedures performed in studies involving human participants and/or animals were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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