PARATHYROID HORMONE RESPONSE TO SEVERE VITAMIN D DEFICIENCY
IS SEX ASSOCIATED: AN OBSERVATIONAL STUDY OF 571 HIP FRACTURE INPATIENTS

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Abstract: Objectives: To investigate the association between sex and parathyroid hormone response to severe vitamin D deficiency after hip fracture. Design: Cross-sectional study. Setting: Rehabilitation hospital in Italy. Participants: 571 consecutive inpatients with hip fracture and severe vitamin D deficiency (serum 25-hydroxyvitamin D < 12ng/ml), without hypercalcemia or estimated glomerular filtration rate (GFR) < 15ml/min. Measurements: In each patient we assessed PTH (by two-site chemiluminescent enzyme-labelled immunometric assay), 25-hydroxyvitamin D (by immunoenzymatic assay), albumin-adjusted total calcium, phosphate, magnesium, and creatinine 21.3 ± 6.1 (mean ± SD) days after fracture occurrence. Functional level was assessed using the Barthel index. PTH response to vitamin D deficiency was classified as either secondary hyperparathyroidism (serum PTH >75pg/ml) or functional hypoparathyroidism, i.e., inappropriate normal levels of PTH (≤75pg/ml). Results: Among the 571 patients, 336 (59%) had functional hypoparathyroidism, whereas 235 (41%) had secondary hyperparathyroidism. PTH status was significantly different between sexes (p=0.003): we found functional hypoparathyroidism in 61% of women and 43% of men (secondary hyperparathyroidism in 39% of women and 57% of men). The significance of the between-sex difference was maintained after adjustment for age, estimated GFR, phosphate, albumin-adjusted total calcium, albumin, Barthel index scores, 25-hydroxyvitamin D, and hip fracture type (either cervical or trochanteric). The adjusted odds ratio was 1.85 (95%CI from 1.09 to 3.13; p=0.023). Conclusions: Data shows that PTH response to vitamin D deficiency was sex-associated following a fracture of the hip. The higher prevalence of secondary hyperparathyroidism may play a role in the known prognostic disadvantage found in hip-fracture men.

Key words: Hip fracture, parathyroid hormone, secondary hyperparathyroidism, vitamin D.

Introduction

A secondary increase in parathyroid hormone (PTH) is often found in aged people and has been attributed to several factors, including vitamin D deficiency, impaired renal function, inadequate calcium intake, and estrogen depletion (1). Unsurprisingly, secondary hyperparathyroidism is highly prevalent among hip-fracture patients (2-6) who are aged, deficient in vitamin D, poorly nourished, and affected by relevant comorbidity including impaired renal function with progressive multisystem decline and loss of physiologic reserve (7-9). However, PTH elevation is not always found in vitamin D depletion: several hip-fracture patients with severe vitamin D deficiency do not have PTH excess, as firstly shown by Sahota et al. (10) and confirmed by several recent reports (11-13). The condition of having inappropriately normal levels of PTH has been named “functional hypoparathyroidism” (10). At now, it is not clear the reasons why vitamin D depletion leads to either secondary hyperparathyroidism or functional hypoparathyroidism in individual subjects (10-13).

Hip fractures represent the most severe consequence of bone fragility, because they result in a 8% to 36% excess mortality within one year (14) and approximately 20% of hip fracture survivors require long-term nursing home care, whereas only 40% fully regain their pre-injury level of independence (15). On the whole, the burden of hip fractures can be estimated as disability-adjusted life-years lost and represents a challenge for the healthcare systems in a lot of countries throughout the world (16).

A sustained elevation of PTH levels exerts catabolic effects on bone and has been implicated in the genesis of bone fragility and hip fractures (1, 17, 18). Furthermore, PTH excess may lead to an unfavorable outcome following hip fracture occurrence (5, 6, 19). Several other factors are associated with adverse prognosis. Among them, male sex plays a relevant role because it has been consistently associated with high risk of complications, high mortality rates, and increased risk of institutionalization (14, 20-22). However, no studies investigated the association between sex and prevalence of secondary hyperparathyroidism in vitamin D depleted patients with a fragility fracture of the hip. We hypothesized that functional hypoparathyroidism (and its inverse condition secondary hyperparathyroidism) may be sex associated in hip fracture patients.

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 various 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 exceeding 11mg/dl or low estimated glomerular filtration rate (GFR <15ml/min). Nine patients were excluded because of missing data. The 909 remaining patients included 788 women (87%) and 121 men. Among these 909, we focused on the 571 patients (492 women = 86% and 79 men) with serum levels of 25-hydroxyvitamin D below 12ng/ml. Nine of the 571 patients (two men and seven women) had an estimated GFR between 15 ml/min and 30 ml/min. They were included in the final sample. However, we repeated statistical analyses after excluding them from the study, because a relevant decrease in 1,25-dihydroxyvitamin D synthesis in these patients may be a pivotal factor in affecting the relationship between 25-hydroxyvitamin D and PTH. Institution Revision Board approval was obtained for the study protocol.

**Outcome Measures**

A blood sample was collected during the first three 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 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 intrassay 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 (23).

Body weight and height were measured in each subject, and body mass index (BMI) was calculated as weight/height². To assess the degree of functional recovery, skilled physiatrists performed the Barthel Index (original version, unchanged) (24). The functional index assesses basic activities of daily living; its score ranges from 0 (total dependence) to 100 (total independence). Each fracture was classified as either cervical or trochanteric on the basis of radiological and surgical findings.

**Data Analysis**

Preliminary comparisons between men and women were performed by a Mann-Whitney U test for both the continuous variables (i.e., age, PTH, 25-hydroxyvitamin D, albumin, albumin-adjusted total calcium, phosphate, GFR estimate, and magnesium) that were all non-normally distributed at a Shapiro-Wilk test and for the ordinal variable (Barthel index score). The relationship between sex and either normal (≤ 75pg/ml) or high PTH levels (>75pg/ml), and between sex and hip fracture type were investigated by a χ² test for independence with Yates continuity correction. A binary logistic regression test was used to adjust the association between sex and PTH category (either normal or elevated) for the potential confounders listed in Table 1. At a preliminary step, we investigated for each of the ten potential confounders the univariate relationship with both sex and PTH category. For eight of the ten variables (i.e., age, phosphate, albumin-adjusted calcium, 25-hydroxyvitamin D, estimated GFR, albumin, Barthel index score, and hip fracture type) a Mann-Whitney U test (for hip fracture type a χ² test for independence with Yates continuity correction) showed a p value below 0.2 for either the between-sex or the between-PTH-category comparisons or for both of them. We included the eight variables together with sex in the binary logistic regression model as independent variables (the dependent variable was PTH category, classified as either normal or elevated).

All statistical analyses were repeated after excluding from the study sample the nine patients (two men and seven women) whose estimated GFR was between 15 and 30 ml/min. The statistical package used was SPSS, version 14.

**Results**

Preliminary comparisons between the 492 women and the 79 men with severe vitamin D-deficiency are shown in Table 1. Two-hundred thirty-five of the 571 patients (41%) had secondary hyperparathyroidism (PTH serum levels exceeding 75pg/ml), whereas the remaining 336 (59%) had functional hypoparathyroidism (normal PTH levels despite severe vitamin D deficiency). PTH status was significantly different between sexes (p=0.003): we found functional hypoparathyroidism in 61% of women and 43% of men (secondary hyperparathyroidism in 39% of women and 57% of men), as shown in Table 2. The significance of the between-sex difference was maintained after adjustment for age, estimated GFR, phosphate, albumin-adjusted total calcium, albumin, Barthel index scores, 25-hydroxyvitamin D, and hip fracture type. The adjusted odds ratio was 1.85 (95%CI from 1.09 to 3.13; p=0.023).

Excluding from analyses the nine patients with an estimated GFR between 15 and 30 ml/min did not materially change the results (data not shown).

**Discussion**

Data shows that PTH response to severe vitamin D deficiency was sex-associated in hip-fracture patients: vitamin D-deficient women had a higher prevalence of functional hypoparathyroidism (and a lower prevalence of secondary