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Hypovitaminosis D in Internal Medicine Inpatients

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Abstract. Some studies have suggested that hypovitaminosis D may be a consequence of protein-calorie malnutrition. This study assessed both the relationship between vitamin D status, malnutrition, calcium and phosphorus metabolism indices and the importance attached by internists to these alterations. There were 239 patients admitted to an internal medicine division who underwent examinations to assess nutritional state, liver and renal function, and bone metabolism. At the end of the study, the clinical data included in the discharge letter, the treatment prescribed, and the diagnosis assigned to patients on their hospital discharge form were collected. Hypovitaminosis D was found in 72% and hypoalbuminemia in 34.3% of patients. Subjects with hypovitaminosis were generally older and had lower albumin levels than those with mild or no hypovitaminosis. 25-Hydroxyvitamin D was inversely related with parathyroid hormone and directly related with albumin. Alterations of calcium and phosphorus metabolism were present in 55.6% and recorded by the division's physicians for only 13.53% of patients, of whom 72.37% were not specifically treated. There is a direct correlation between 25-hydroxyvitamin D and albumin levels. The high incidence and the metabolic consequence of hypovitaminosis D and of protein-calorie malnutrition is significantly underestimated and undertreated by physicians.

Key words: Albumin — Inpatient — Malnutrition — Parathyroid hormone — Vitamin D

Vitamin D deficiency is a known cause of an alteration of calcium and phosphorus metabolism leading to secondary increase in parathyroid secretory activity, bone loss, and hence increased risk of fractures [1]. It may equally augment the risk of falling and consequent fractures through the establishment of myopathy and altered proprioception [2, 3].

Recent studies have also shown that vitamin D is a differentiating agent in various types of cells and can alter their proliferation. These findings have led to investigation of its effects in the treatment of cancer and in modulation of the immune system and central nervous system (CNS). The epidemiological data point to a very close correlation between exposure to sunlight, and hence the production of vitamin D, and the incidence of breast, prostate, and colon cancers [3–5]. Data of this kind can be drawn from Afro-American studies of low exposure to ultraviolet B (UVB) rays and the higher incidence of tumor incidence and mortality in periods of the year during which exposure to sunlight is reduced [6]. Very interesting data on the the low serum 25-hydroxyvitamin D level as an important risk factor for the incidence of prostate and colorectal carcinomas were reported by brilliant large studies [7, 8]. Various aspects of vitamin D indicate that it could also be involved in susceptibility to inflammatory bowel disease [9, 10] and diabetes [11, 12]. Its direct action on the CNS is suggested by the local expression of its receptors [13, 14], while other data from a murine stroke model suggest that it protects the CNS against aging [15] and cell death [16]. A high prevalence of hypovitaminosis D in nonhospitalized elderly subjects, persons dwelling in communities, and patients admitted to hospital for acute disorders has also been observed [17–24].

Vitamin D is produced in sufficient quantities through correct exposure of the skin to UVB rays. The ability to do so, however, diminishes with age [17]. A relation between a varied and balanced diet and 25-hydroxyvitamin D levels has been suggested, and its deficiency may be associated with protein and caloric malnutrition [25, 26]. Malnutrition is observed in 20–50% of elderly subjects on admission to hospital, and a person's nutritional state is greatly influenced by chronic diseases and a period of hospitalization [27]. This study assessed the relationship between vitamin D status, protein malnutrition, and calcium and phosphorus metabolism indices in internal medicine inpatients and the importance attached by internists to malnutrition and altered calcium and phosphorus metabolism when patients are discharged.

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Table 1. Reasons for admission of enrolled patients

Admission diseases	Cases (*n*)
Pneumonia	41
Chronic obstructive pulmonary disease	40
Pulmonary edema and respiratory insufficiency	35
Shock and cardiac insufficiency	38
Cerebrovascular diseases	21
Pulmonary cancer	11
Metabolic diseases	9
Diabetes mellitus	7
Angina pectoris	7
Dementia	7
Pulmonary embolism	6
Others	17

Materials and Methods

Patients

An examination was made of the clinical characteristics of 277 patients (140 female, 137 male) consecutively admitted to an internal medicine division for acute disorders or the recrudescence of chronic disorders from August to November 2003. Thirty-eight were discarded because their anamnesis included a diagnosis of disorders or the administration of drugs with a possible influence on bone metabolism; reasons for admission are shown in Table 1.

The 239 patients enrolled in the study underwent routine examinations to assess their nutritional state (serum albumin) [24], liver and renal function, and calcium and phosphorus metabolism in the morning after an overnight fast within 24 hours of admission.

Methods

Our routine laboratory methods were used to measure serum calcium, phosphorus, and albumin; creatinine; parathyroid hormone (PTH); bone alkaline phosphatase (BAP); and 25-hydroxyvitamin D. With the exception of 25-hydroxyvitamin D and BAP, the results were immediately available for use in diagnosis and treatment. 25-Hydroxyvitamin D was measured at the end of the study with an immunoenzymatic assay (DRG Diagnostics, Harburg, Germany) in a battery of tests on sera frozen at −20°C. The interassay variation coefficient was 7.5%. Serum calcium values were adjusted for albumin levels if albumin was <4 g/dL by means of the following formula:

$$\text{Corrected calcium} = \text{serum calcium mg/dL} + 0.7 \times (4 - \text{albumin g/dL})$$

The laboratory reference intervals were serum calcium, 8.5−12 mg/dL; serum phosphorus, 2.8−5 mg/dL; PTH, 12−72 pg/mL; urinary calcium, 50−300 mg/24 hours: BAP, 14−42 IU/L; albumin, 3.2−6.7 g/dL; creatinine, 0.5−1.5 mg/dL.

Definition of Hypovitaminosis

The following stratification was taken from the literature [19]: hydroxyvitamin D levels <20 nM/L, 20−37 nM/L, >37 nM/L.

Definition of Malnutrition

Since there were no cases of hepatic insufficiency, malnutrition was defined as serum albumin <3 g/dL.

Hospital Discharge Forms

At the end of the study, the clinical data included in the discharge letter, the treatment prescribed, and the code references assigned to patients on their hospital discharge form (HDF) were collected.

Statistics

Stepwise one-way analysis of variance (ANOVA) was employed to assess the significance of the distribution of the parameter values between the two sexes. Significant differences between 25-hydroxyvitamin D classes were identified with ANOVA for the continuous variables and the chi-squared test after correction for the Yates continuity to analyze the gender distribution in the three classes. Values found significantly different in this analysis were used to build a linear regression model. The SPSS 14.0 for Windows package (SPSS, Chicago, IL) was used, with $P < 0.05$ as the significance cut-off.

Results

Blood Chemistry

Hypovitaminosis D was found in 72% of the patients: <20 nM/mL in 40.2% (50 M, 46 F) and 20−37 nM/mL in 31.8% (31 M, 45 F). 25-hydroxyvitamin D levels were >37 nM/mL in the other 28% (25 M, 42 F). The gender distribution in these three classes was not significant.

Hypoalbuminemia (serum albumin <3.0 g/dL) was present in 34.3% of the population. Women displayed significantly lower 25-hydroxyvitamin D and higher BAP levels. There were no significant sex differences in albumin levels and bone turnover indices (Table 2).

Examination of the distribution of age and of the analyte values measured (Table 3) showed that age, serum albumin, and PTH were significantly different in the three 25-hydroxyvitamin D classes.

The linear regression model showed that 25-hydroxyvitamin D was inversely related with PTH and directly related with albumin (Table 4). 25-Hydroxyvitamin D levels were 30% predicted by these two variables. PTH as a dependent variable was inversely related with serum calcium and 25-hydroxyvitamin D status and directly related with age (Table 4). These two variables accounted for about 30% of the PTH variations.

The HDFs

Alterations of calcium and phosphorus metabolism were present in 133 patients (55.6%): 8.8% presented a corrected serum calcium value <8.6 mg/dL and the other 98.2% presented secondary increase in parathyroid secretory activity with normal serum calcium levels. These alterations, however, were mentioned on the HDFs of only six patients (3.3%). Treatment with calcium and vitamin D was prescribed for 36/133 patients (27.1%) and with calcium, vitamin D, and biphosphonates for seven patients (0.53%). The remaining 72.37% were not specifically treated. Protein-calorie malnutri-

Table 2. One way ANOVA results (mean ± standard deviation) for age, 25-hydroxyvitamin D, markers of calcium and phosphorus metabolism, albumin, and creatinine as distributed according to sex

	Female (n = 133)	Male (n = 106)	P
Age (years)	77.34 ± 11.69	75.33 ± 11.16	NS
Calcium (mg/dL)	9.35 ± 0.64	9.32 ± 0.71	NS
Phosphorus (mg/dL)	3.5 ± 0.76	3.4 ± 0.86	NS
PTH (pg/mL)	93.52 ± 56.12	83.35 ± 56.67	NS
25−Hydroxyvitamin D (nM/L)	29.34 ± 23.54	36.74 ± 30.5	0.03
BAP (IU/L)	29.02 ± 26.01	23.86 ± 15.36	0.04
Calciuria 24/hours (mg)	80.22 ± 65.8	77.92 ± 60.37	NS
Albumin (g/dL)	3.05 ± 0.51	3.14 ± 0.52	NS
Creatinine (mg/dL)	1.08 ± 0.43	1.31 ± 0.62	0.0005

Table 3. One way ANOVA results (mean ± standard deviation) for age, markers of calcium and phosphorus metabolism, albumin, and creatinine as distributed according to classes of 25-hydroxyvitamin D: < 20, 20−37, or > 37 nM/dL

	< 20 nM/dL	20−37 nM/dL	> 37 nM/dL	P
Age (years)	77.8 ± 10.99	76.24 ± 11.68	72.92 ± 12.46	0.03
Calcium (mg/dL)	9.32 ± 0.79	9.33 ± 0.69	9.36 ± 0.55	NS
Phosphorus (mg/dL)	3.39 ± 1.01	3.49 ± 0.7	3.62 ± 0.63	NS
PTH (pg/mL)	103.75 ± 61.92	80.63 ± 47.67	69.96 ± 47.53	0.000
BAP (IU/L)	26.25 ± 20.8	25.96 ± 16.6	26.3 ± 18.36	NS
Calciuria 24/hours (mg)	69.77 ± 66.2	77.15 ± 58.96	88.35 ± 82.26	NS
Albumin (g/dL)	2.94 ± 0.58	3.17 ± 0.41	3.28 ± 0.43	0.000
Creatinine (mg/dL)	1.24 ± 0.64	1.09 ± 0.45	1.24 ± 0.49	NS

Table 4. Stepwise linear regression models for 25-hydroxyvitamin D and PTH levels as dependent variables

	Standardized ß	Standardized t	P
25-Hydroxyvitamin D (R^2 = 0.30)			
PTH	0.21	−3.26	0.001
Albumin	0.17	2.69	0.007
PTH (R^2 = 0.39)			
Age	0.26	3.760	0.0002
Calcium	−0.17	−2.53	0.01
25-Hydroxyvitamin D	−0.17	−2.48	0.01

tion was not diagnosed in any of the patients with hypoalbuminemia.

Discussion

In epidemiological terms, collection of samples for 25-hydroxyvitamin D in a short time period of evaluation rules out a significant influence of seasonal variations [28] on our discovery of a 72% prevalence of 25-hydroxyvitamin D levels < 37 nM/mL in outpatients admitted to an internal medicine division for acute disorders or the recrudescence of chronic disorders. Our data provide further evidence of the physiopathological mechanism whereby hypovitaminosis D, by reducing serum calcium levels, increases those of PTH, which is inversely correlated with 25-hydroxyvitamin D levels. The latter, too, have been correlated with nutritional status. An inverse relation between body mass index and 25-hydroxyvitamin D levels provoked by storage of fat-soluble vitamin D in adipose tissue or a subject's lifestyle has been suggested, together with a difference in the relation between vitamin D and lipids as opposed to proteins due to the existence of a direct correlation between vitamin D and albumin [29, 30]. Protein-calorie malnutrition may thus be supposed to play an important part in the determination of 25-hydroxyvitamin D levels and hence calcium and phosphorus metabolism, while reduced dietary intake can be postulated as the prime cause of hypovitaminosis D. In contrast with the findings of Premaor et al. [30], our PTH levels were not directly influenced by albuminemia. Age, on the other hand, while significantly different in the three hypovitaminosis classes, was not directly linked to 25-hydrox-

yvitamin D levels despite the data that correlate vitamin D status with age. In our opinion, this is because the influence of age is engulfed in the predictive variants PTH and serum albumin. Recent data correlate 25-hydroxyvitamin D levels with the variety of the diet. Elia and Stratton [25] underscore the importance of fruit and vegetables in the maintenance of a sufficient vitamin level, while Dunnigan et al. [26] postulate a direct correlation between the quantity of meat in the diet and 25-hydroxyvitamin D.

Examination of the discharge letters and HDFs of our patients indicated that the internal medicine division's physician was not sufficiently aware of the question of secondary increase in parathyroid secretory activity as a consequence of hypovitaminosis D since the presence of a calcium-phosphorus alteration was mentioned in a small percentage of cases and no specific treatment was prescribed for many patients. It is clear, therefore, that practitioners tend to underestimate the problem despite the fact that it has long been known that vitamin D deficiency is very common, especially in the elderly, and is the cause of changes in bone metabolism that eventually lead to osteomalacia and fractures and despite the many reports of the involvement of vitamin D in the CNS, in regulation of the immune system, and in protection against chronic crippling diseases [31, 32]. There was also a significant underestimation of protein-calorie malnutrition. Here again it is known that malnutrition is a determinant factor of many chronic disorders, including bone loss [27].

Stress must thus be laid on the need for general practitioners to adopt a correct approach to changes in calcium-phosphorus metabolism and especially secondary increase in parathyroid secretory activity as a consequence of hypovitaminosis D in elderly patients, particularly when they are admitted to hospital for acute disorders or the recrudescence of chronic disorders, even if they were not previously in an institution. Furthermore, greater attention must be devoted to the question of chronic malnutrition in the elderly and its important implications for both their bone metabolism and their general health.

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