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Hyperparathyroidism Secondary to Hypovitaminosis D in Hypoalbuminemic Is Less Intense than in Normoalbuminemic Patients

A Prevalence Study in Medical Inpatients in Southern Brazil

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Hypovitaminosis D has been reported in tropical countries, but this hormone has seldom been studied in Brazil. Our purpose was to study the prevalence of hypovitaminosis D in patients hospitalized in internal medicine wards in Southern Brazil. Possible associated factors were studied. We studied 81 adult patients in early spring. Mean serum 25(OH)D was12 ± 8.57 ng/mL; hypovitaminosis D was severe (<10 ng/mL) in 27 (33.3%) patients, and moderate (≥10 ng/mL and <20 ng/mL) in 36 (44.5%) patients. Clinical evaluation did not yield any data associated with hypovitaminosis D. Serum 25(OH)D levels of up to 20 ng/mL were associated with decreased mean serum total calcium (p = 0.001), ionized calcium (p = 0.01), and phosphorus (p = 0.044) levels, and increased mean serum PTH level (p = 0.001). In a multiple regression model, serum PTH level was independently affected by serum total calcium (p = 0.01), phosphorus (p = 0.009), and albumin (p = 0.009) levels. Hypovitaminosis D patients had lower mean serum albumin levels (p = 0.004), and serum 25(OH)D levels were directly correlated to serum albumin levels (p < 0.0001). Albumin influenced independently PTH response to hypovitaminosis D; normoalbuminemic hypovitaminosis D patients had higher mean serum PTH than hypoalbuminemic patients. Conclusion: Hypovitaminosis D prevalence was very high in medical inpatients in Southern Brazil, in early spring. Nevertheless, secondary hyperparathyroidism was less intense in hypoalbuminemic hypovitaminosis D patients suggesting that in these patients free serum 25(OH)D was closer to normal.

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Introduction

Vitamin D was discovered at the beginning of last century and its deficiency is associated to rickets in children and osteomalacia in adults. Clinical disease progresses slowly and, very often, is asymptomatic, with secondary hyperparathyroidism *(1–3)*, bone mass loss *(1,4)*, and higher risk of fractures *(5,6)*.

Measurement of total 25(OH)vitamin D [25(OH)D] concentration is considered to be the best method to diagnose hypovitaminosis D. Serum concentrations below 20 ng/mL have been associated with increase in parathyroid hormone (PTH) and bone loss *(7)*.

Serum 25(OH)D, both in young adults and in the elderly, varies according to the geographical region and is dependent on latitude *(8)*. It is higher near the Equator and in areas of dry weather *(9)*. However, 25(OH)D deficiency has also been reported in low latitude areas *(9,10)*. Hypovitaminosis D has already been described in Latin America *(11,12)*. Few studies so far have been conducted to determine its prevalence in Brazil *(13,14)*. In Rio Grande do Sul, a state in Southern Brazil, there is a higher risk of 25(OH)D deficiency because of the latitude and high humidity.

Hypovitaminosis D prevalence is increased in older individuals with chronic diseases, such as dementia *(8,15,16)*, gastrointestinal tract diseases *(17,18)*, renal failure *(19)*, rheumatoid arthritis *(20)*, congestive heart failure *(21)*, and during the post-menopausal period *(22)*. It has also been found in patients who were administered anticonvulsive drugs and other medications *(23,24)*, in institutionalized patients *(25,26)*, and in inpatients in general hospitals *(27,28)*.

The general purpose of our study was to evaluate the prevalence of 25(OH)D deficiency in patients hospitalized in internal medicine wards of Hospital de Clínicas de Porto Alegre, Brazil, in early spring. Specific goals were to identify factors associated with 25(OH)D deficiency and to

Table 1
Characteristics of the 81 Study Patients[a]

Variable	
Mean age (years)	59.8 ± 17.2
Sex	
Male	44 (54.3)
Female	37 (45.7)
Phototype	
I–II	47 (58.7)
III–IV	33 (41.4)
V–VI	0
BMI (kg/m^2)	26.21 ± 6.4
Current smoking	29 (35.8)
Alcohol abuse	17 (21)
Vitamin D supplementation	3 (3.7)
Walked more than 3 h/wk	31 (38.6)
Sunlight exposure*	62 (76.6)
Length of disease (days)	10 (3–30)
Cause of hospitalization	
Respiratory infection	20 (24.7)
Vascular disease	13 (16.0)
Cancer	7 (8.6)
Urinary tract infection	5 (6.2)
Congestive heart failure	4 (4.9)
Tuberculosis	3 (3.7)
Others	29 (35.8)

[a]Data expressed in mean ± SD; *n*(%); median (25/75). *More than 3 h/wk.

Table 2
Clinical Characteristics of Patients With and Without Hypovitaminosis D (*n* = 81)[a]

25(OH)vitamin D	<20 ng/mL	≥20 ng/mL
Mean age (years)	60.9 ± 17	55.9 ± 17.8
Sex		
Male	32	5
Female	31	13
Phototype		
I–II	34	13
III–IV	28	5
V–VI	0	0
BMI (kg/m^2)	26.4 ± 6.8	25.6 ± 4.9
Current smoking	21/63	8/18
Alcohol abuse	11/63	6/18
Vitamin D supplementation	2/63	1/18
Walked more than 3 h/wk	23/63	8/18
Sunlight exposure more than 3 h/wk	51/63	11/18
Immobilization (d)	10/63	1/18
Length of disease (d)	8 (2/30)	15 (7/30)
Use of anticonvulsives	2/63	2/18
Use of diuretics	26/63	6/18

[a]Data expressed in mean ± SD; number of patients/total number of patients; median (25/75 percentile). There was no statistically significant difference in the data above.

evaluate the correlation between vitamin D, PTH, calcium, and albumin.

Results

In October 2000, 150 patients were hospitalized in the internal medicine wards of Hospital de Clínicas de Porto Alegre, and 81 agreed to participate in this study. Characteristics of these patients are described in Table 1 and were not significantly different from those of patients that were not evaluated. Forty-four (54.3%) patients were male, 37 (45.7%) were older than 65 yr, and 47 (58.8%) were light skinned. Most patients had been hospitalized due to respiratory infection, cancer, cerebral vascular accident, and peripheral vascular disease. Mean serum 25(OH)D concentration was 12 ± 8.57 ng/mL.

Hypovitaminosis D was severe in 27 patients (33.3%), and moderate in 36 (44.5%). No clinical data were associated with hypovitaminosis D. Exposure to sunlight was not associated with hypovitaminosis either (Table 2).

Hypovitaminosis D patients had lower mean serum level of total calcium, ionized calcium, phosphorus, and albumin. Their mean serum PTH level was about 30 pg/mL higher than mean serum PTH level of patients with adequate vitamin D concentrations, as shown in Fig. 1. There were no significant differences in mean serum creatinine, magnesium, and alkaline phosphatase level, or in mean urinary calcium and phosphorus level.

Serum 25(OH)D levels were positively correlated with serum total and ionized calcium, phosphorus, and albumin levels, and negatively correlated with serum PTH levels, as shown in Fig. 2. Multiple linear regression revealed that PTH response to vitamin D was constant when adjusted to serum magnesium level, exposure to sunlight, and amount of physical exercise. PTH response to 25(OH)D was independently affected by calcium, phosphorus, and albumin. PTH response to calcium was constant even after adjustment to albumin. Albumin affected the model independently of calcium (Table 3).

Eight patients had serum PTH levels below 10 pg/mL; serum 25(OH)D concentrations were higher than 40 ng/mL for three of them, and higher than 20 ng/mL for two. Of the three patients with hypovitaminosis D and low serum PTH levels, one had bone metastasis [25(OH)D = 9.6 ng/mL, albumin = 3.4 g/dL, ionized calcium = 5.0 mg/dL], one was taking thiazide diuretics [25(OH)D = 11.6 ng/mL, albumin = 2.5 g/dL, total calcium = 8.0 mg/dL], and the other had diabetes [25(OH)D = 5.4 ng/mL, albumin = 3.5 g/dL, ionized calcium = 4.6 mg/dL].

Of the patients with hypovitaminosis D, 23 (37%) had secondary hyperparathyroidism (PTH ≥ 47.8 pg/mL). Characteristic clinical signs were not observed in these patients.

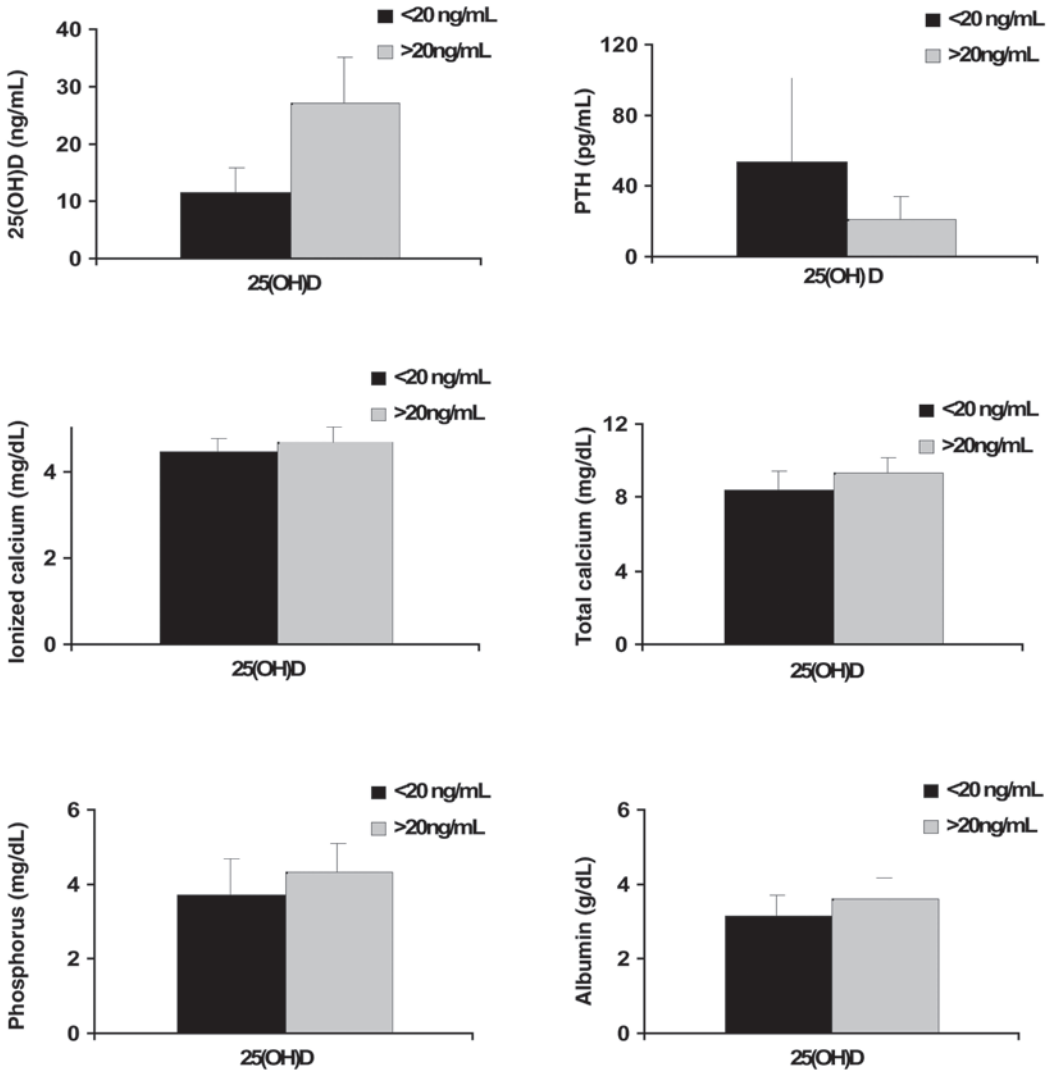

Fig. 1. Parathyroid hormone (PTH), ionized calcium, total calcium, phosphorus, and albumin in hypovitaminosis D [25(OH)D < 20 ng/mL, *n* = 61] and non-hypovitaminosis D patients [25(OH)D ≥ 20 ng/mL, *n* = 18]. Data are mean ± SD.

Serum albumin level was significantly lower, there were no significant differences in mean serum ionized calcium, total calcium, phosphorus, creatinine, magnesium, alkaline phosphatase, and 25(OH)Vitamin D levels, or in mean urinary calcium and phosphorus levels, as shown in Fig. 3.

In the group of patients with hypovitaminosis D, patients with normal serum albumin levels (≥3.5 g/dL) had mean serum PTH level higher than patients with hypoalbuminemia. Results for this group of patients revealed a direct correlation between 25(OH)D and albumin ($r = 0.356$, $p = 0.005$), and between albumin and PTH ($r = 0.269$, $p = 0.036$).

Discussion

Until recently, hypovitaminosis D was believed to be nonexistent in the Brazilian population *(13)*. In the late 1990s, several studies reported hypovitaminosis D in tropical and subtropical countries *(8–11,29)*. Our study evaluated the prevalence of vitamin D deficiency in patients hospitalized in internal medicine wards of Hospital de Clínicas de Porto Alegre in early spring. Prevalence rate of hypovitaminosis D measured according to serum total 25(OH)D levels was very high, and serum 25(OH)D level correlated directly with serum albumin, calcium, and phosphorus levels, and inversely with serum PTH levels. Serum 25(OH)D levels were lower than 20 ng/mL in 77.8% of the patients, and lower than 10 ng/mL in 33.3%.

Measurement of serum total 25(OH)D is the most widely accepted parameter for hypovitaminosis D diagnosis, but the cutoff point to define it is not yet well established. Several studies have used different methods to measure serum total 25(OH)D, and have established several cutoff points for hypovitaminosis D. We measured serum total 25(OH)D concentrations by radioimmunoassay with low intra- and interassay coefficients. We classified serum 25(OH)D levels below 10 ng/mL as severe deficiency, and concentrations

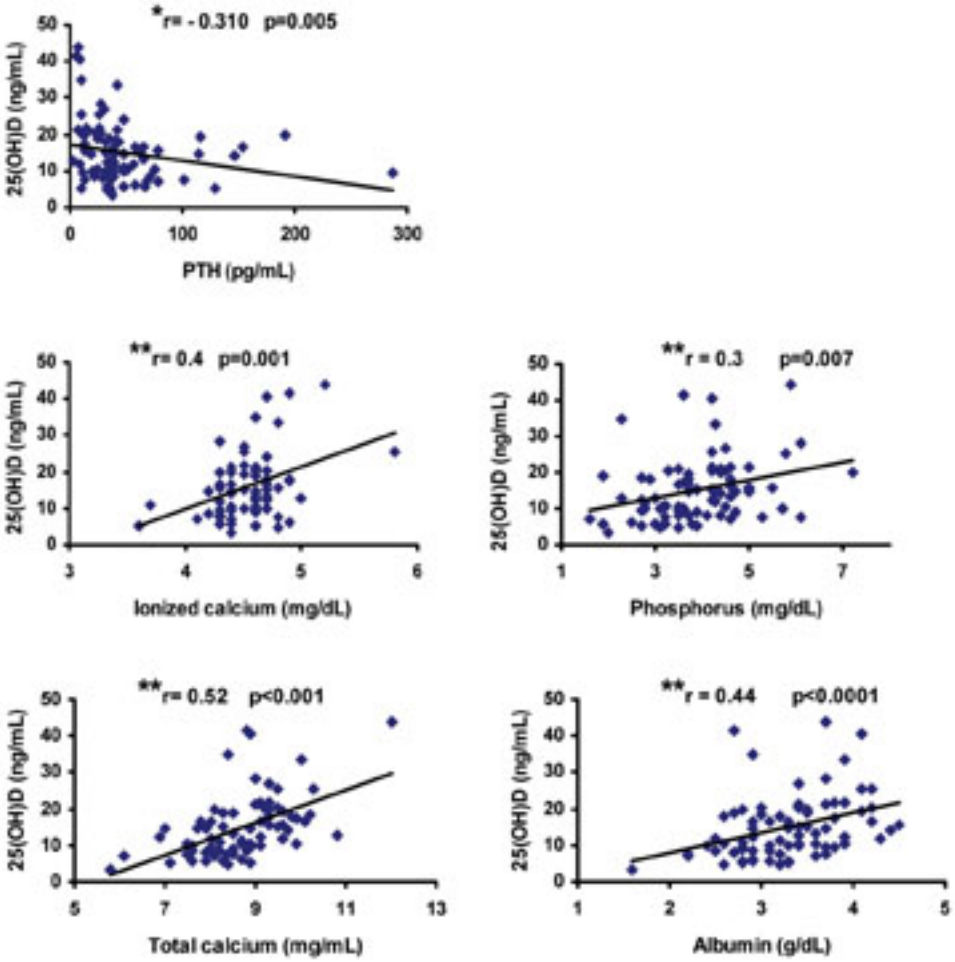

Fig. 2. Relationship between serum 25(OH)vitamin D and serum parathyroid hormone (PTH), ionized calcium, phosphorus, total calcium, and albumin, in 81 medical inpatients. *Pearson and **Spearman coefficients are shown.

Table 3
Multiple Linear Regression Analyses of Factors Affecting Variation of PTH in Relation to 25(OH)D[a]

Variable	B	Beta	*p*
25(OH)D	28.9		0.6
Magnesium	9	0.05	0.7
Calcium	–18.9	–0.4	0.01
Phosphorus	10.8	0.3	0.009
Albumin	30.6	0.4	0.009
Exposure to sunlight	–17.6	–0.2	0.2
Physical exercise	–14.7	–0.2	0.1

[a]Constant: 25(OH)vitamin D; dependent variable: parathyroid hormone; beta: intercept; B: coefficient.

between ≥10 ng/mL and <20 ng/mL as moderate. This cutoff point may be too high, and, consequently, prevalence of hypovitaminosis D might have been overestimated. However, we observed a moderate mean serum PTH increase in the group of patients with 25(OH)D < 20 ng/mL, and mean serum calcium and phosphorus levels were lower than for the other patients. We thus concluded that, in our region, patients with serum total 25(OH)D concentrations up to 20 ng/mL had metabolic and biochemical disorders compatible with hypovitaminosis D.

Thomas et al. were the first to describe hypovitaminosis D in patients in a general hospital. Their study was conducted in Boston in 1994, and revealed that 57% of the patients had 25(OH)D concentrations below 15 ng/mL; when patients were studied in winter, the prevalence rate rose to 63% *(27)*. A study conducted in Finland in 1998 reported very similar findings: 61% of the men and 70% of the women hospitalized in clinical wards of the hospital under study had 25(OH)D levels lower than 15 ng/mL *(28)*.

More than 45% of our patients were 65 yr or older; most of them were light skinned; about one third walked more than 3 h a week; and only a few were bedridden. Surprisingly, over 76% of the patients had 3 h or more a week of exposure to sunlight, which in Porto Alegre, 30° south latitude, should be enough for the skin to produce vitamin D. The characteristics of the patients that refused to participate in the study were similar to those of the study subjects.

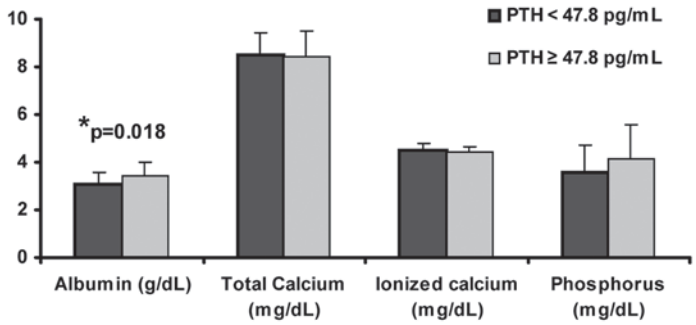

Fig. 3. Hypovitaminosis D, associated ($n = 23$) or not to secondary hyperparathyroidism ($n = 38$). Serum levels of albumin, total calcium, ionized calcium and phosphorus are shown as mean ± SD. PTH= parathyroid hormone; * for mean serum albumin level.

Therefore, their non-participation probably did not affect our results. What are, then, the factors that caused such high prevalence of hypovitaminosis D among our patients?

Exposure to sunlight was assessed by anamnesis, and may be overestimated, or maybe older and sick individuals need greater exposure to sunlight for adequate production of vitamin D. In the elderly the capacity to synthesize 25(OH)D is significantly reduced *(30)*, which may contribute to the fact that an apparently adequate exposure to sunlight may be insufficient to keep enough vitamin D stored. Other possible factors may be the quality of sunlight, pollution, and air humidity, which reduce the amount of UVB rays that reach the skin. Air humidity is very high in our region, and reaches 90% most days. This factor may contribute to a reduction of ultraviolet light that reaches the skin.

We did not evaluate vitamin D intake. However, we inferred that it was low among our patients because our population is not used to eating fish and there is no addition of vitamin D to foods in our country. Only three patients took oral vitamin D supplements. One of them had a serum 25(OH)D level above 40 ng/mL; the other two had serum 25(OH)D levels below 6 ng/mL.

A diet poor in calcium may contribute to hypovitaminosis D by increasing 25(OH)D clearance. Reduction of calcium absorption in the intestines causes an increase in PTH, and increases the conversion of 25(OH)D into $1,25(OH)_2D$. We do not know how much this factor has contributed to the high prevalence of hypovitaminosis D among our population because we did not measure calcium intake. However, two other studies conducted in poor urban areas of São Paulo found low calcium intake among the study population *(31,32)*.

Well-established factors associated with hypovitaminosis D, such as alcohol abuse or anticonvulsive drug use, were similar in both groups, possibly because the number of patients with such characteristics was small.

There was an inverse correlation between 25(OH)D and PTH, and a direct correlation between 25(OH)D and total calcium, ionized calcium, and phosphorus, as expected. It is difficult to define a cutoff point for insufficient serum 25(OH)D concentrations. The increase in serum PTH levels may be used as a parameter, but it follows a continuum, that is, the lower the serum 25(OH)D levels, the higher the serum PTH levels and the lower the serum total calcium, ionized calcium, and phosphorus levels. Kauppinen-Mäkelin et al. found progressively higher values of PTH for several vitamin D cutoff points, which corroborate this hypothesis *(28)*. The most useful method to define a cutoff point is to establish it as the value at which morbidity and mortality increase, but no studies have investigated this outcome.

Not all patients with serum 25(OH)D concentrations below 20 ng/mL had secondary hyperparathyroidism. Only 37% of those patients had serum PTH concentrations higher that 47.8 pg/mL. Our normal values may have been overestimated because they were calculated for a sample of only 18 patients. However, other authors, such as Souberbielle et al. and Marangella et al., found very similar values *(33,34)*.

Mean serum albumin levels were higher in the patients with hypovitaminosis D and secondary hyperparathyroidism, and this was the only factor that set these patients apart. Hypovitaminosis D patients with normal serum albumin levels (>3.5 g/dL) had mean serum PTH levels that were about 30 pg/mL above levels for patients with hypoalbuminemia. The mechanism why PTH increased less in hypoalbuminemic patients is probably a higher free 25(OH)D level in these patients, when compared to normoalbuminemic patients, with similar serum levels of 25(OH)D. Other hormones, like total T4, could be used as an example of this mechanism; total hormone serum level measurements can be very misleading when serum binding proteins are low. Circulating serum 25(OH)D is bound to vitamin D binding protein (VDBP) and to albumin *(35)*. We did not measure free serum 25(OH)D, but the documented PTH response suggests that patients with low 25(OH)D and hypoalbuminemia had free serum 25(OH)D normal or closer to normal. Multiple linear regression confirmed that albumin was a confounding factor that affected PTH response to hypovitaminosis D. This factor may be artificially elevating hypovitaminosis D prevalence in hospitalized patients in a general hospital because these patients often have hypoalbuminemia.

However, other factors that increase serum calcium concentrations and are not mediated by PTH, such as immobilization, use of thiazide diuretics, and cancer, could have prevented secondary hyperparathyroidism associated with hypovitaminosis D *(36–38)*.

Thomas et al. also found an association between higher albumin and higher 25(OH)D levels, but they did not evaluate patients separately *(27)*. Kauppinen-Mäkelin, in a Finnish study, measured VDBP and free vitamin D index, and found that VDBP was reduced in hospitalized patients. Their patients also had reduced total and free 25(OH)D, but no effects in PTH levels were observed *(28)*.

Hypovitaminosis D is a significant problem in patients in a general hospital. The role of hypoalbuminemia in these patients is not well known. For patients with albumin concentrations lower than 3.5 g/dL, serum ionized calcium, phosphorus, and PTH levels, and factors associated with PTH-independent increase in serum ionized calcium, should be carefully assessed before a diagnosis of 25(OH)D deficiency is made. Studies with methods that measure serum free 25(OH)D or its effects on target tissues would be useful for a better understanding of this problem.

Patients and Methods

All patients hospitalized in internal medicine wards of Hospital de Clínicas de Porto Alegre in October 2000 were invited to participate in this cross-sectional study. This month was chosen because it is the first month of spring in Brazil. Early spring is the time of the year when the lowest serum vitamin D concentrations were found in different regions of the world *(8)*. No patients were excluded from the study.

Blood and urine samples were collected between 6 and 8 AM in the first 24 h of hospitalization. Serum and urine were frozen at –70°C, and serum intact PTH and serum 25(OH)D levels were measured in the same sample. A radioimmunoassay (Nichols®, San Juan Capistrano, CA, USA) was used to measure serum 25(OH)D levels. The intra- and interassay coefficients of variation (CV) were 5.0% and 8.1%, respectively. Chemiluminescence (Immulite®, Los Angeles, CA, USA) was used for PTH, with intra- and interassay CV of 5.4% and 5%, respectively. Serum ionized calcium, total calcium, phosphorus, magnesium, creatinine, albumin, and alkaline phosphatase levels, as well as urinary creatinine and calcium levels, were measured by routine methods of the biochemistry laboratory of Hospital de Clínicas de Porto Alegre.

The following clinical aspects were evaluated: age, skin phototype, sex, smoking, alcohol abuse, type of housing, physical activity, and exposure to sunlight, according to a standard questionnaire *(39)*, and cause of hospitalization, length of underlying disease, medication, and body mass index [weight (kg)/height^2 (m)], according to the clinical charts.

Hypovitaminosis D was defined as severe when serum 25(OH)D level was lower than < 10 ng/mL (25 nmol/L), and as moderate when it was higher than or equal to ≥ 10 ng/mL and lower than 20 ng/mL (25 nmol/L and <50 nmol/L) *(1,19,20)*. Normal serum PTH levels were calculated as mean ± two standard deviation in patients with 25(OH)D higher than or equal to 50 nmol/L *(33,34)*.

Statistical Analysis

The prevalence rate of hypovitaminosis D was calculated. Possible associated factors were evaluated by means of the following tests, as applicable: Student's *t*, Mann–Whitney, ANOVA, Kruskal–Wallis, Fischer exact, chi square, and chi square with Yates correction. Pearson and Spearman coefficients were used to calculate correlations for normally and non-normally distributed data. Multiple linear regression was used to isolate possible confounding variables. Date were analyzed with the software SPSS® 10.0 for Windows.

Ethical Considerations

This study was approved by the Ethics Committee of Hospital de Clínicas de Porto Alegre. Informed consent was obtained from all patients.

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