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ORIGINAL PAPER

High prevalence of hypovitaminosis D and secondary hyperparathyroidism in elders living in nonprofit homes in South Brazil

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Abstract *Objectives* Hypovitaminosis D (HD) and secondary hyperparathyroidism (SHP) are common in elders, and many factors could contribute to them. The objectives of this study were to estimate the prevalence of HD, SHP, and its associated factors, in individuals living in nonprofit homes for elders in south Brazil. *Design* Cross-sectional study. *Methods* Serum 25-hydroxyvitamin D 25(OH)D, intact parathyroid hormone (PTH), total calcium, phosphorus, alkaline phosphatase, magnesium, creatinine, and albumin levels were measured in late spring, November, 2005. The presence of factors potentially related with HD and SHP—age, sex, weight, height, skin phototype, sun exposure, exercise, smoking, use of ≤5 medications or diuretics or alcohol, and daily calcium ingestion. *Results* 102 subjects age 77.8 ± 9.0 were included in the study. HD was found in 85.7% and SHP in 53% of the subjects. The estimated daily calcium ingestion was 720 mg. There was no association between serum 25(OH)D levels and any of the risk factors evaluated. Serum 25(OH)D levels were correlated with serum PTH ($r = -0.358$, $P = 0.000$), calcium ($r = 0.306$, $P = 0.002$), and albumin ($r = 0.253$, $P = 0.011$) levels. In univariate analysis, SHP was positively associated with age ($P = 0.006$), and female sex (0.007); and negatively associated with sunlight exposure ($P = 0.020$), GFR ($P = 0.000$), Ln25(OH)D ($P = 0.002$), and total serum calcium ($P = 0.024$). After multivariate model adjustment, age [OR 1.09 (CI 1.01–1.18); $P = 0.024$], Ln25(OH)D [OR 0.92 (CI 0.08–0.74); $P = 0.013$], GFR [OR 0.96 (CI 0.92–0.99); $P = 0.013$], and hydrochlorothiazide treatment [OR 7.63 (CI 1.67–34.9); $P = 0.008$] were independently associated with SHP. *Conclusions* HD and SHP are highly prevalent in elders living in old-age homes. No associations were established between common risk factors and low serum levels of 25(OH)D levels; however, SHP was independently related with age, 25(OH)D, GFR, and hydrochlorothiazide use.

Keywords Vitamin D deficiency · Secondary hyperparathyroidism · Aged · Thiazides

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Introduction

Hypovitaminosis D (HD) has been associated with bone mass loss, fractures, and muscle weakness [1]. There are also evidences that it increases the risk of cardiovascular disease, diabetes mellitus, cancer, and immunological abnormalities [1]. HD was frequently observed in older people, and many factors could contribute to it [2]. Everything that interferes with skin UVB light absorption, as latitude, season, daytime, ozone layer, clouds, aerosols,

altitude, surface reflectance, skin phototype, older age, clothing, and sunscreens can decrease the amount of vitamin D synthesized [3]. Chronic diseases, hospitalization, and immobilization are also associated with lower serum 25(OH)D levels in old people [4].

HD in the elderly has been detected all around the world including Latin America [5]. There are a few studies about the prevalence of HD in Brazil. It was not detected in children in Recife, latitude 8°S [6], however, it was evident in São Paulo, latitude 23°S [7, 8]. In south Brazil, due to its climate characteristics, a larger prevalence of HD is expected. A study in Porto Alegre, 30°S, in the early spring, identified HD in 78% of medical inpatients [9].

Secondary hyperparathyroidism (SHP) has not been observed in all individuals with HD [10], and several studies point to glomerular filtration rate (GFR) as the major determinant of the PTH response in these subjects [11, 12]. Furthermore, high calcium ingestion [13], low serum albumin levels [9], and magnesium deficiency [14] were also associated with a smaller PTH response to HD. Recently, SHP in HD individuals was associated with a higher mortality when compared to individuals with HD and without SHP [15]. SHP has been described in association with low calcium ingestion [16], higher body weight [17], hyperphosphatemia [17], and diuretic use [18].

The main objectives of this study were to estimate the prevalence of HD, SHP, and its associated factors in elderly subjects living in nonprofit homes for older people at Porto Alegre, a southern Brazilian city, during the spring.

Results

From 320 elders living in the two nonprofit old-age houses at Porto Alegre, 102 subjects agreed to participate. Two elders were excluded from the analysis, one due to primary hyperparathyroidism, and another one due to chronic renal failure. Serum 25(OH)D levels were not measured in two subjects, due to technical problems. All residents in the two houses were poor, and older than 65, and the subjects that accepted to participate had the same sex proportion than the others, so the sample was considered representative of this elderly population. The estimated calcium intake was 720 mg per day. Two subjects reported alcoholic beverages consumption, and two subjects were under vitamin D supplementation.

The prevalence of HD was 85.7%, and it was mild in 31.6%, and moderate/severe in 54.1%. There was no association among HD, and age, sex, weight, height, body mass index (BMI), skin phototypes I or II, exercise for more than 3 h per week, sunlight exposure for more than 3 h per week, smoking, use of five or more medications, or use of diuretics (data not shown).

Mean serum albumin, calcium, and PTH levels were different, when comparing normal subjects (N), in subjects with mild hypovitaminosis D (MHD), and subjects with moderate/severe hypovitaminosis D (MSHD). In the post hoc tests, no differences were detected among the mean serum albumin levels in the three groups. Mean serum PTH levels were higher in the MSHD group than in the MHD group. Mean serum calcium levels were lower in the MSHD group than in the other two groups. These data are shown in Table 1. Serum 25(OH)D levels were correlated with serum calcium, PTH, and albumin levels (Fig. 1).

SHP was observed in 54.8% of the individuals with hypovitaminosis D, and in 35.7% of the other subjects (data not shown).

SHP was detected in 53% of the subjects, and it was associated with age, female sex, and sunlight exposure for more than 3 h a week, GFR, serum 25(OH)D and calcium levels, in the univariate analysis. After the multivariate analysis, it was independently associated with age, serum 25(OH)D levels, GFR, and hydrochlorothiazide use. These data are shown in Table 2. There was no association among SHP, BMI ($P = 0.286$), phototypes I or II ($P = 0.564$), tobacco use ($P = 0.284$), exercise for more than 3 h a week ($P = 1.0$), ≥5 medications ($P = 1.0$), and furosemide use ($P = 0.210$). Serum phosphorus ($P = 0.422$), magnesium ($P = 0.153$), and alkaline phosphatase ($P = 0.509$) levels were similar in individuals with SHP or not. When we repeated this model defining SHP as a serum PTH level ≥65 pg/ml, the factors associated with it were similar [age (OR: 1.10 CI: 1.02–1.18; $P = 0.015$), serum 25(OH)D levels (OR: 0.27 CI: 0.09–0.84; $P = 0.024$), GFR (OR: 0.95 CI: 0.92–0.99; $P = 0.008$), and hydrochlorothiazide use (OR: 7.44 CI: 1.85–29.93; $P = 0.005$)]. These data are not shown.

Discussion

HD, defined as serum 25(OH)D level ≤20 ng/ml, was detected in 85.6% of 98 subjects living in two non profit homes for old people in Porto Alegre, (30°S), south of Brazil, in the spring. HD was mild in 31.6% and moderate/severe in 54.0%. There are only a few studies addressing this subject in Brazil. Nevertheless, the prevalence of HD was similar to the one observed in inpatients in São Paulo [7], where a seasonal variation of serum 25(OH)D levels was previously reported [8]. Since São Paulo is located closer to Equator than Porto Alegre, higher serum 25(OH)D levels would probably be found in summer and autumn in this population.

No risk factors associated with HD were identified. It could be, in part, because almost all subjects were vitamin D deficient in our study. This is its major limitation.

Table 1 Characteristics of the elderly residents of non-profit old-age houses at Porto Alegre, 30°S, Brazil, according to serum 25(OH) vitamin D (25(OH)D) levels

Group/subjects	All 98	Normal[a] 14 (14.3)	Hypovitaminosis D 84 (85.7)		
			Mild[b] 31 (31.6)	Moderate/severe[c] 53 (54.1)	P^e
Age (years)	77.8 ± 9.0($n = 90$)	78.2 ± 8.9($n = 14$)	76.3 ± 9.0($n = 26$)	78.6 ± 9.1($n = 52$)	0.54
Female sex	59(59.0)	9(64.3)	17(54.8)	32(64.4)	0.81
BMI (kg/m^2)	24.6 ± 4.2($n = 75$)	24.7 ± 4.0($n = 11$)	24.4 ± 4.1($n = 24$)	24.8 ± 4.6($n = 40$)	0.92
Phototype I or II	85(85.0)	12(85.7)	29(93.5)	44(83.0)	0.36
Smoking	17(17.0)	2(14.3)	7(22.6)	7(13.2)	0.52
Exercise[d]	21(21.0)	4 (28.6)	6(19.4)	10(18.9)	0.71
Sunlight[d]	41(41.0)	8 (57.1)	15(48.4)	2(33.7)	0.36
≥5 medications	21(21.0)	4(28.6)	9 (29.0)	7(13.2)	0.17
Furosemide	11(11.0)	2(14.3)	2(6.5)	7(13.2)	0.59
HCTZ	27(27.0)	5 (35.7)	8 (25.8)	14 (26.4)	0.76
GFR (ml/min)	51.4 ± 23.4($n = 92$)	49.0 ± 22.3($n = 14$)	55.0 ± 26.3($n = 26$)	50.7 ± 22.4($n = 52$)	0.68
25(OH)D (ng/ml)	9.8(6/16.9)	26.7(24/30.4)	13.9(11.5/17.4)	6.0(6.0/8.4)	0
Albumin (g/dl)	4.0 ± 0.3	4.1 ± 0.4	4.0 ± 0.3	3.9 ± 0.3	0.04
Ca (mg/dl)	9.5 ± 0.5	9.7 ± 0.4	9.6 ± 0.3	9.4 ± 0.6[f]	0.01
P (mg/dl)	3.5 ± 0.7	3.6 ± 0.5	3.3 ± 0.6	3.5 ± 0.8	0.28
Mg (mg/dl)	2.1 ± 0.2($n = 97$)	2.2 ± 0.2($n = 14$)	2.1 ± 0.3($n = 30$)	2.1 ± 0.2($n = 53$)	0.4
PTH (pg/ml)	51.6(41.5/78.1)	42.5(41.3/71.6)	46.5(34.6/59.1)	64.1(43.9/96.2)[g]	0.01
Alkaline P (U/l)	77.5(64.0/94.0)	46.0(62.5/92.5)	67.0(59.0/91.0)	82.0(68.0–98.5)	0.08

Data are shown as mean ± standard deviation, median (P25/75) or number (percentage). When a variable had a total number inferior than 98 the absolute number is showed as ($n = $)

Serum 25(OH)D levels: [a] >20 ng/ml, [b] from ≤20 to >10 ng/ml, and [c] ≤10 ng/ml

BMI: body mass index: [d] >3 h/week; GFR: glomerular filtration rate, as calculated using the Cockcroft-Gault equation [32]; HCZ: hydrochlorothiazide; 25 (OH)D, albumin, total calcium (Ca), phosphorus (P), magnesium (Mg), intact parathyroid hormone (PTH), alkaline phosphatase (Alkaline P): serum levels

[e] omparing the three groups: normal (N), mild hypovitaminosis D (MHD) and moderate or severe hypovitaminosis D (MSHD); [f] $P < 0.04$, when comparing MSHD vs. N; [g] $P = 0.01$, when comparing MSHD vs. MHD

Moreover, it was not possible to evaluate the effectiveness of oral supplementation of vitamin D, because only two subjects were using it. These subjects were not excluded because both had low serum 25(OH)D levels (12 and 6 ng/ml). The absence of a protective effect of exercise or sunlight exposure, for more than 3 h a week, could be explained by the daytime of sun exposure, the quality of the light in the month of the evaluation or preceding it, or the use of clothes covering the skin [3]. In addition, the low daily calcium ingestion in this population very probably contributed for the low serum 25(OH)D levels, due to increased utilization of 25(OH)D [19]. Even if an individual ingested all the food offered, the amount of calcium present in the diet was below the recommended. Moreover, it cannot be excluded that other factors, as genetic characteristics, or low ability of the skin to synthesize vitamin D could be also partly responsible for HD.

One of the limitations of this study was the inability to evaluate individual calcium intake. It was estimated based on the food offered to all subjects. A better measurement of the food intake would have allowed evaluating possible differences among subjects, as it is well known that the calcium intake decreases the SHP in HD subjects [13, 16].

Although recent studies have suggested serum 25(OH)D levels higher than 30 ng/ml as desirable, avoiding fractures, and other symptoms associated with HD [20, 21], the cut-off point used to define it in the present study was ≥20 ng/ml, which could have underestimated the prevalence of vitamin D deficiency.

Another limitation of the present study was the inability to identify a threshold level of serum 25(OH)D associated with increased serum PTH levels, as described by others[13, 22, 23]. The low number of subjects with serum 25(OH)D levels above 20 ng/ml could have contributed to

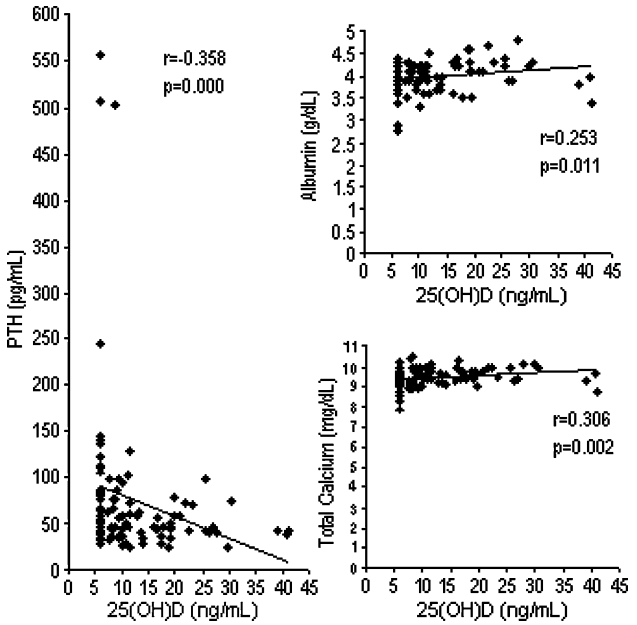

Fig. 1 Correlation of serum 25(OH) vitamin D [25(OH) D] and intact parathyroid hormone (PTH), albumin, and total calcium levels in elders resident in beneficent old age homes in southern Brazil

this limitation. Besides that, some studies reported that serum 25(OH)D and PTH levels are inversely related, until serum 25(OH)D attains a threshold of 48 ng/ml [13, 23].

The prevalence of SHP was 53% in our study. Despite the fact that serum 25(OH)D levels were correlated with serum PTH levels, only 54.8% of the subjects with HD had SHP. This phenomenon has been repeatedly reported, and some studies suggested other factors that could have a role. Sahota et al. called it "blunted PTH" [10] and tested the hypothesis that magnesium deficiency could be partly responsible by giving a magnesium load to individuals with HD without SHP [14]. Mean serum PTH levels increased 13.3 ng/l in their subjects. Our group found a positive correlation between serum PTH and magnesium levels in a group of young adults with HD [24]. In contrast, this correlation was not observed in the present study. A possible explanation for this negative result is the impact of the lower GFR of this older population on serum PTH levels. GFR was considered for some authors as the major determinant of SHT in HD especially in the elderly [12]. Other factors as higher calcium ingestion [13], and low serum albumin levels [9] were also associated with a smaller PTH response to vitamin D deficiency.

Furthermore, 35.7% of the subjects without HD had SHP. This data may suggest other causes for SHP. Low calcium intake [16], renal failure [12], higher body weight [17] and hyperphosphatemia [17] have been implicated in some studies. Low calcium ingestion by the subjects included in the present study could have contributed to SHP.

In this study, SHP was independently associated with age, GFR, serum 25(OH) levels, and hydrochlorothiazide use. A rise in serum PTH levels has been reported in individuals with thiazide diuretic use [25, 26]. It is well known that thiazide diuretic have the ability to increase calcium renal reabsorption [27]. Nevertheless, they modulated calcium uptake by intestinal cells [28], they induced calbindins gene expression [29], and they also stimulated the osteoblast differentiation markers [30]. The mechanism why thiazide diuretics use is associated with SHP is still unknown, as well as its true clinical significance.

In conclusion, HD and SHP were highly prevalent in the elderly living in nonprofit old-age houses at Porto Alegre, 30°S, Brazil. SHP was detected in 54.8% of individuals with HD and 35.7% of individuals without HD. No common risk factor was associated with the low serum 25(OH)D levels; however, SHP was associated with age, 25(OH)D, GFR, and hydrochlorothiazide use.

Table 2 Factors possibly associated with secondary hyperparathyroidism in elderly residents of non-profit old-age houses at Porto Alegre, 30°S, Brazil ($n = 92$)

Variables	Univariate analysis OR (CI95%)	*P*	Multivariate analysis[a] OR (CI 95%)	*P*
Age	1.08 (1.02–1.13)	0.006	1.09 (1.01–1.18)	0.024
Male sex	0.32 (0.14–0.73)	0.007	0.41 (0.12–1.38)	0.414
Sunlight[b]	0.38 (0.17–0.86)	0.020	0.92 (0.28–2.97)	0.887
GFR	0.95 (0.93–0.98)	0.000	0.96 (0.92–0.99)	0.013
Serum total calcium	0.34 (0.14–0.87)	0.024	0.61 (0.12–3.06)	0.551
LN25(OH)D	0.27 (0.12–0.62)	0.002	0.92 (0.08–0.74)	0.013
Serum albumin	0.28 (0.08–1.03)	0.055	0.64 (0.07–5.96)	0.691
Hydrochlorothiazide use	2.17 (0.86–5.46)	0.100	7.63 (1.67–34.9)	0.009

[a] Binary logistic regression model including age, sex, [b] Sunlight exposure >3 h/week, glomerular filtration rate (GFR), as calculated with the Cockcroft-Gault equation [32], serum total calcium, natural logarithm of serum 25(OH)-vitamin D [LN25(OH)D], serum albumin, and hydrochlorothiazide use. Dependent variable PTH > or ≤48 pg/ml; $n = 94$

Subjects and methods

A cross-sectional study was performed in the two nonprofit old-age homes of Porto Alegre, Brazil. All the subjects or their guardians signed a written consent, and the study was approved by the Ethics Committee of Hospital de Clínicas de Porto Alegre (HCPA). The calculated number of subjects to detect a 35% prevalence, with a precision of 10, for a significance level of 0.5 was 87.

Data about age, sun exposure, exercise, use of ≥5 medications, diuretics, tobacco, or alcohol were obtained by a standard questionnaire. The sunlight exposure was evaluated through a simple question: "Do you get sunlight for 30 min a day or at least 3 h a week?" Sex, weight, height and skin phototype were evaluated in the same day, by two members of the research team (MOP and RS). The calcium intake was calculated by a nutritionist based on the daily food offered in both institutions. Blood samples were collected in the morning, with at least 4 h fasting, in November 2005. The serum was stored at −20°C.

Skin phototype was classified from I to VI, as proposed by Fitzpatrick [31]. Sunburn and tanning history defines the phototype: (1) the skin burns easily and never tans, (2) the skin burns easily and tans minimally with difficulty, (3) the skin burns moderately and tans moderately and uniformly, (4) the skin burns minimally and tans moderately and easily, (5) the skin rarely burns and tans profusely, and (6) the skin never burns and tans profusely.

Serum 25(OH)D levels were assayed by chemoluminescence (LIAISON®—25(OH)vitamin D, Diasorin Inc, Stillwater, MN-USA, intra-assay coefficient of variation (CV) was 2% and inter-assay was 13%). Serum intact parathyroid hormone (PTH) levels were assayed by electrochemiluminescence (Elecsys-Modular E-170, Roche Diagnostics, Indianapolis-USA, CV intra-assay was 2.8% and inter-assay was 3.4%). Serum albumin, calcium, phosphorus, magnesium, alkaline phosphatase, and creatinine levels were measured by routine methods at HCPA (Modular-P, Roche Diagnostics, Indianapolis-USA). The GFR was calculated using the Cockcroft-Gault equation [32].

HD was defined as serum 25(OH)D levels ≤20 ng/ml. It was considered mild, when serum 25(OH)D levels were from ≤20 to 10 ng/ml, and moderate/severe when serum 25(OH)D levels were ≤10 ng/ml, as suggested by Lips [5]. Normal range for serum PTH levels were calculated in a prior study, by the mean ± two standard deviations, in patients with serum 25(OH)D levels ≥20 ng/ml. SHP was defined as serum PTH level >48 pg/ml [9] with normal or low serum total calcium level (normal range 8.6–10.3 mg/dl).

Statistical analysis

The prevalence of HD and SHP were calculated. The association with risk factors was evaluated using Student's *t*, Mann–Whitney's, chi-square, and Fisher's Exact tests, and Spearman's correlation coefficient. Analysis of variance, Kruskal-Wallis test and the Tukey post hoc test were used, when indicated. A binary logistic regression was used to evaluate factors associated with secondary hyperparathyroidism. In the multivariate model were included all the variables with $P < 0.1$.

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