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Comparative 25-OH-vitamin D level in institutionalized women older than 65 years from two cities in Spain and Argentina having a similar solar radiation index

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Abstract

Objective: The present study evaluated and compared vitamin D nutritional status and calcium–phosphorus metabolism in institutionalized women >65 y from two cities that have a similar sun irradiation index (heliophany).

Methods: The study was carried out in women living in similar social-status institutions from geographic cities having a similar solar radiation index (Lleida, Spain, $n = 49$, and suburban Buenos Aires, Argentina [BA], $n = 48$) at the end of summer.

Results: Fish consumption was higher in the Lleida group, as was red-meat consumption in the BA group. In both groups mean calcium intake was 800 mg/d. The daily intake of vitamin D was higher in the BA group ($P < 0.001$). A total of 90% in Lleida and 86% in BA had 25-hydroxyvitamin D (25OHD) levels <20 ng/mL. A significant inverse correlation between individual 25OHD and parathyroid hormone (PTH) levels was observed in the two groups of women ($r = -0.329$, $P = 0.035$). PTH levels >100 pg/mL were found in 24% and 20% of women in Lleida and BA, respectively. There was a marked increase in carboxy-terminal telopeptide cross-links of type I collagen levels and a decrease in 25OHD with an increase in PTH levels ($P < 0.05$). Conversely, bone alkaline phosphatase increased significantly only when the PTH concentration duplicated the reference range.

Conclusion: Even at the end of summer, vitamin D deficiency/insufficiency was prevalent in the two studied institutionalized elderly women. In the narrow range of the dietary calcium intake (close to 800 mg/d) of both studied groups, secondary hyperparathyroidism was absent when 25OHD levels were >17 ng/dL, indicating changes in the regulation control of serum PTH and consequently the changes in this threshold. As a result, vitamin D deficiency must be reversed to avoid the increment in bone turnover and to ensure the endocrine and paracrine functions of vitamin D for overall health and well-being.

Keywords: 25-Hydroxyvitamin D; Parathyroid hormone; Calcium; Elderly; Institutionalized women

Introduction

Vitamin D is involved in the regulation of various essential physiologic functions related to bone metabolism and maintenance of calcium–phosphorus (Ca-P) homeostasis. The body synthesis of vitamin D is molecularly well defined; it commences in the skin with the photoconversion of 7-dehydrocholesterol and continues further in the liver to

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produce the main circulating metabolite, 25-hydroxyvitamin D (25OHD). In the kidney, 25OHD undergoes the second hydroxylation to produce the biologically active 1,25-dihydroxyvitamin D (1,25[OH]$_2$D).

The level of 25OHD is the best indicator of vitamin D deficiency, insufficiency, sufficiency, and toxicity [1,2]. Although currently it is difficult and controversial to clearly define the cutoff values for each stage, there is no doubt that a 25OHD level <5 ng/mL in adults can result in bone diseases such as osteomalacia [3]. There is also evidence that 25OHD levels <10 ng/mL can result in bone diseases, whereas 25OHD concentrations <20 ng/mL could reflect vitamin D deficiency [4]. Recently, a 25OHD level close to 32 ng/mL has been proposed as a limit of vitamin D insufficiency in people >65 y of age [4], taking into account the observation that the parathyroid hormone (PTH) level in this concentration range can be slightly elevated, although remaining in the normal range [4].

Circulating 25OHD levels closely reflect the amount of sunlight to which the epidermis is exposed, plus the dietary intake of vitamin D [5,6]. When sunlight exposure is adequate, most of the total vitamin D requirement in white people can be obtained by the skin photoconversion, and only a low percentage is provided by the dietary sources. However, there are some foods, especially dairy products and some fatty fishes, that naturally contain vitamin D in relevant amounts.

Complications related to low vitamin D levels are more troublesome in the elderly population than in young adults, particularly in institutionalized subjects [7], in whom the incidence is about 60–80% [8]. The most important reasons could be the decreased vitamin D synthesis in the skin because of the aging process and limited outdoor activities. There exists abundant evidence that the evolution of hypovitaminosis D in elderly people involves an initial step of secondary hyperparathyroidism (2°HPT) that turns into irreversible bone loss, especially from the cortical area [3]. In addition to hypovitaminosis D, other reasons for the age-related PTH increase in the elderly have been suggested, such as impaired renal function with diminished 1α,25-hydroxylase enzyme activity, impaired Ca absorption owing to malabsorption, and parathyroid gland resistance to 1,25(OH)$_2$D-facilitated inhibition of PTH secretion.

Dietary Ca intake is considered an important confounder factor that influences serum PTH [8]. Accordingly, if serum 25OHD is low, then the increase in serum PTH level may be less prominent when Ca intake is high [9]. Conversely, low Ca intake aggravates vitamin D deficiency by increasing the turnover of vitamin D metabolites by 2°HPT [8]. Although the Ca requirement is observed to increase with age, the capacity to compensate for low Ca intake is found to decline with age [10]. The mean recommended daily Ca intake for healthy elderly people is 1200 mg [2,11].

Argentina is spread over 3700 km, from latitude 22°S to 55°S. Consequently, in such a wide range of parallels, a high prevalence of vitamin D levels <20 ng/mL in healthy elderly people living at home was documented [12]. Conversely, until a few years ago, this was not considered as a common problem in Spain, because of the high solar radiation, in addition to the high consumption of vitamin D–rich oily fish in the Mediterranean provinces. Moreover, mean Ca intake in both countries is observed to be lower than the international adequate intake for adults and is far lower than the recommended value for elderly people [2,11].

On these bases, the aim of this study was to evaluate and compare the vitamin D nutritional status and Ca-P metabolism in institutionalized women >65 y of age from two cities that have a similar solar radiation index (heliophany)—one in Spain [13] and the other in Argentina [14].

Materials and methods

Subjects

The data reported were collected from women 65 to 96 y of age living in similar social-status institutions from geographic cities having a similar solar radiation index—Lleida, Spain (43°NL) and suburban Buenos Aires, Argentina (BA; 34°SL). A total of 81 women (49 from Lleida and 48 from BA) were enrolled in this study. The recruitment was done during the end of the summer (2003–2004).

Age, weight, height, and clinical, dietetic, and pharmacologic histories were recorded. Women with malignancies, chronic renal (serum creatinine >1.4 mg/dL) or liver disease, malabsorption syndromes, or hypercalcemia owing to primary HPT were excluded. In addition, women who received vitamin D supplements, Ca, P, fluoride, bisphosphonates, or any other medication that could affect bone metabolism were excluded.

The study protocol was approved by the local ethics committee. All the patients gave informed consent before the onset of the study.

Dietary records and sun exposure

The mean intake of nutrients was calculated based on the weekly food served in each institution. All meals were prepared under the supervision of one nutritionist according to the cultural habits and food availability in each country. The menus were designed to provide daily balanced diets, covering energy and macronutrient requirements according to the recommendations of the dietary guides for elderly people [2,11,13,15].

The mean nutrient intake was calculated based on the size and consumption of the usual daily servings, using the tables of food composition of Spain and Argentina, respectively [16,17].

The average daily individual exposure time to sunlight in both cities was observed to be very brief. During a typical active day, the studied women were found to remain outdoors only for a few minutes between 10:00 and 16:00 h with head and arms covered with clothes, and only the face and hands were indirectly exposed to ultraviolet irradiation.

Samples and assays

Fasting blood was taken in the morning (08:00–09:30 h). An aliquot of whole blood was collected with ethylenediaminetetra-acetic acid to determine the hemogram with hematologic counters (Mega Bitex SA, Bs.As., Argentina). After centrifugation, the aliquots of serum were kept frozen until the analyses were performed. Although routine biochemistry and 25OHD analyses were done in each laboratory, an aliquot of the samples obtained in Spain were shipped in dry ice to the Laboratory of Metabolic Bone Diseases Section at the Clinical Hospital, Buenos Aires University, to assess the other determinations.

Routine biochemical determinations (glycemia, uremia, creatinine, cholesterol, and total and fractionated proteins) were carried out automatically using standard laboratory methods. Creatinine clearance was calculated according to the Cockcroft-Gault formula [18]. Serum P was assessed by a colorimetric method and calcemia was assessed by atomic absorption spectrophotometry. Total serum Ca was corrected when serum albumin levels were <4 g/dL [19].

The 25OHD levels were assayed by a competitive protein-binding method (Diasorin, Stillwater, MN, USA). The intra-assay coefficient of variation (CV) was observed to be 9%. The mid-molecular parathormone (PTH) was measured using radioimmunoassay employing the antiserum CH9 that recognizes the intact hormone and the mid-molecular and carboxy-terminal fragments with an intra-assay CV of 7% [20]. The bone alkaline phosphatase (BAP) was determined by a colorimetric method after wheat lectin precipitation. The intra-assay CV was observed to be 4–8%. Serum carboxy-terminal telopeptide cross-links of type I collagen (βCTX) was measured by an enzyme-linked immunosorbent assay (Crosslaps, Osteometer Biotech, Herlev, Denmark) with a 6% intra-assay CV. The biochemical determinations were measured within the same run to avoid interassay variations [21].

Statistical analysis

The data were expressed as mean ± standard deviation, and the normality was assessed by the Kolmogorov-Smirnov test. The two groups of women were compared using unpaired *t* test. The statistical significance among the BAP, βCTX, and 25OHD levels according to the ranges of PTH levels was analyzed by analysis of variance. The relation between PTH and 25OHD was expressed according to the Box-Tidwell model. The linear association was analyzed by Pearson's correlation coefficients (ρ) and multivariate linear regression. The statistical analysis was performed with SPSS (2006, SPSS Inc., Chicago, IL, USA), and $P < 0.05$ was considered statistically significant.

Results

In both institutions, the energy intake was adequate to maintain the body weight. The daily protein intake through the consumption of meat, fish, dairy products, and cereals was $1.2\ g \cdot kg^{-1} \cdot d^{-1}$ higher than the recommended safe level of $0.8\ g \cdot kg^{-1} \cdot d^{-1}$ [15]. According to cultural habits, fish consumption was higher in the Spanish group (70 versus 22 g/d); conversely, red-meat consumption was higher in the Argentine elderly women. Mean Ca intake was 800 mg/d without significant differences between the population groups, possibly because the consumption of dairy products was similar in both cities. However, daily intake of vitamin D was different (Lleida: 1.27 μg/d [61 IU/d], BA: 4.00 μg/d [160 IU/d], $P < 0.001$). Therefore, it is important to point out that, although women in Lleida showed greater fish consumption, the dairy products consumed in Spain were not fortified with vitamin D, as in Argentina.

There were no differences in age (82.0 ± 7.1 versus 81.3 ± 7.9 y), body weight (62.1 ± 9.7 versus 62.5 ± 16.6 kg), and other anthropometric measurements (data not shown) Table 1 presents no differences in means ± standard deviations of hemoglobin, total protein, albumin, creatinine, uremia, glycemia, cholesterol levels, and creatinine clearance, which ranged from 131 to 139 mL/min.

Table 2 presents means ± standard deviations of serum concentration of Ca corrected by albumin, P, PTH, 25OHD, βCTX, and BAP. Although serum concentration of Ca, PTH, 25OHD, and βCTX did not present any differences between cities, serum P and BAP levels were significantly lower in Lleida ($P < 0.01$).

Figure 1 shows the distribution of both populations of women (as percentages) according to the classification of McKenna and Freaney [1]: 25OHD levels <10, 10–19, 20–29, and >30 ng/mL. Forty-seven percent of the studied women in Lleida and 32% in BA had 25OHD levels <10 ng/mL, and the percentages increased to 90% and 86%, respectively, when the cutoff was 20 ng/mL. Further, none of them reached levels >30 ng/mL.

Figure 2 shows the significant inverse correlation between individual 25OHD and PTH levels in the two groups of women ($r = -0.329$, $P < 0.035$). PTH levels >100 pg/mL were found in 24% and 20% of women in Lleida and BA, respectively.

Table 1
Hemoglobin, total protein, albumin, serum creatinine, creatinine clearance, uremia, glycemia, and serum cholesterol levels in women from Lleida and Buenos Aires*

	Lleida	Greater Buenos Aires	*P*
Hemoglobin (g/dL)	12.6 ± 2.4	13.1 ± 1.4	NS
Total protein (g/dL)	6.8 ± 0.8	6.8 ± 0.6	NS
Albumin (g/dL)	3.73 ± 0.11	3.51 ± 0.35	NS
Total proteins (g/dL)	6.8 ± 0.8	6.8 ± 0.6	NS
Creatinine (mg/dL)	1.12 ± 0.36	1.23 ± 0.59	NS
Creatinine clearance (mL/min)	134.4 ± 1.4	134.9 ± 1.4	NS
Uremia (mg/dL)	54 ± 29	45 ± 15	NS
Glycemia (mg/dL)	99 ± 20	85 ± 11	NS
Cholesterol (mg/dL)	197 ± 38	202 ± 43	NS

* Values are means ± SDs.

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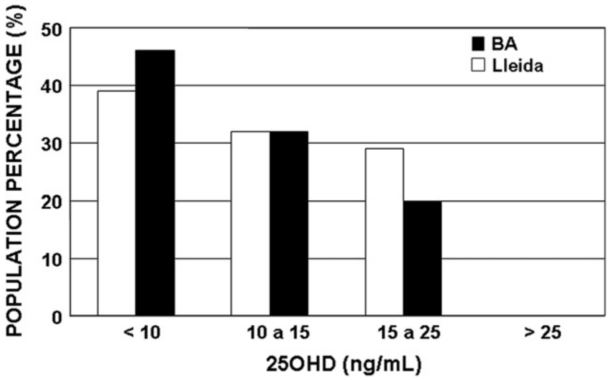

Fig. 1. Population distribution (percentage) according to ranges of 25OHD level. BA, Buenos Aires; 25OHD, 25-hydroxyvitamin D.

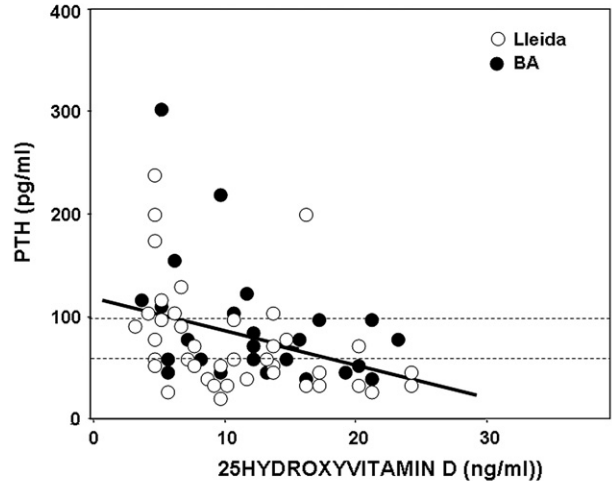

Fig. 2. Correlation between 25-hydroxyvitamin D and PTH levels. The linear association was analyzed by Pearson's correlation coefficients (ρ, $r = 0.329$, $P = 0.035$) and multivariate linear regression ($y = -3.01x + 109.98$, $r^2 = 0.109$). BA, Buenos Aires; PTH, parathyroid hormone.

No correlation was observed between the individual values of PTH and BAP in both groups of women, but a slight correlation was observed between PTH and βCTX levels ($r = 0.42$, $P < 0.05$). It must be noted that when only the PTH levels higher than the laboratory reference range were plotted against BAP and βCTX levels, a very high correlation was observed in both cases (0.73 and 0.62, respectively, $P < 0.01$).

Table 3 lists the mean values of BAP, βCTX, and 25OHD levels in both populations divided according to the increasing ranges of PTH (<50, 50–74, 75–99, 100–199, and ≥200 pg/mL). There was a marked increase in βCTX levels and a decrease in 25OHD with an increase in PTH levels. Conversely, BAP increased significantly only when the PTH concentration duplicated the reference range.

Discussion

The results of this study confirmed the poor vitamin D status, even at the end of summer, in the studied institutionalized elderly women from the two geographically different cities that present a similar heliophany index, located in South America (BA) and Europe (Lleida). In addition, the inverse correlation between 25OHD and PTH levels was demonstrated in a narrow range of Ca intake (close to 800 mg/d).

Table 2
Serum concentration of Ca, P, 25OHD, PTH, BAP, and βCTX in women from Lleida and Buenos Aires*

	Lleida	Buenos Aires	*P*
Ca corrected by albumin (mg/dL)	10.0 ± 0.6	10.1 ± 0.6	NS
P (mg/dL)	3.8 ± 0.5	4.5 ± 0.8	0.01
PTH mm (pg/mL)	77.9 ± 50.3	91.9 ± 55.0	NS
25OHD (ng/mL)	11.7 ± 5.8	13.6 ± 6.1	NS
βCTX (ng/L)	635.4 ± 250.4	544.5 ± 239.6	NS
BAP (IU/L)	55.5 ± 6.8	64.3 ± 13.6	0.01

25OHD, 25-hydroxyvitamin D; BAP, bone alkaline phosphatase; βCTX, carboxy-terminal telopeptide cross-links of type I collagen; Ca, calcium; P, phosphorus; PTH, parathyroid hormone

* Values are means ± SDs.

Vitamin D is an atypical nutrient, because it can be principally obtained from sunlight, through its interaction with the skin rather than from food. In this regard, about 85% of the total vitamin D requirement can be obtained from ultraviolet radiation. Thus, an adequate intake of vitamin D is observed to be related to sun exposure. The current recommendation for vitamin D intake in subjects without enough sunlight exposure is 10 μg/d for women 50–70 y of age, and for adults >70 y of age, the adequate intake is estimated as 15 μg/d [2]. Indeed, in aged people, a marked decrease in the capacity of human skin to produce vitamin D is observed when compared with the younger adults. This situation is aggravated by changes in lifestyle with little outdoor physical activity in addition to immobility, malnutrition, or dementia [22,23].

In this study, we found poor vitamin D status at the end of summer in the elderly population of both cities, which is in agreement with previous studies [24–26]. In this regard, none of the studied women showed a 25OHD level >30 ng/mL, and the prevalence of severe vitamin D deficiency (serum values <10 ng/mL) reached as high as 47% in Lleida and 32% in BA.

The severity of vitamin D insufficiency observed in both cities may not be owing to the underestimation of 25OHD levels, because a commercial radioimmunoassay test, currently considered the best validated method, was used [27]. Instead, the severity may be owing to the scant exposure to sunlight and insufficient vitamin D intake. With regard to ultraviolet irradiation, although both places experience a greater proportion of sunny days in summer, 40% and 100% of elderly women in Lleida and BA, respectively, had low or null sunlight exposure. This result was not unexpected, because elderly women traditionally dislike sun exposure during the hours when vitamin D synthesis is effective. Consequently, vitamin D insufficiency is not confined to the winter in this population, but exists throughout the year.

Table 3
Levels of BAP, βCTX, and 25OHD in the population divided according to increasing ranges of PTH*

PTH (pg/mL) (20–100)	BAP (IU/L) (21–95)	βCTX (ng/L)	25OHD (ng/mL)
38.7 ± 6.7 (<50) ($n = 16$)	59.4 ± 10.1^{a}	442.3 ± 196.9^{a}	15.9 ± 5.3^{a}
57.3 ± 7.8 (50–<75) ($n = 25$)	63.0 ± 22.0^{a}	586.6 ± 229.4^{ab}	12.6 ± 6.1^{a}
86.3 ± 6.2 (75–<100) ($n = 17$)	59.1 ± 9.5^{a}	646.9 ± 308.4^{ab}	14.3 ± 6.3^{a}
124.5 ± 23.9 (100–200) ($n = 15$)	53.0 ± 7.3^{a}	748.1 ± 422.5^{b}	8.5 ± 3.5^{b}
232.0 ± 41.5 (>200) ($n = 6$)	86.0 ± 46.3^{b}	866.8 ± 168.1^{b}	7.0 ± 2.2^{b}
P	0.05	0.025	0.025

25OHD, 25-hydroxyvitamin D; BAP, bone alkaline phosphatase; βCTX, carboxy-terminal telopeptide cross-links of type I collagen; PTH, parathyroid hormone.

* Values are means ± SDs (laboratory reference values). Different superscript letters indicate statistical significance at $P < 0.05$.

Vitamin D is very rare in unfortified foods and is present in the flesh of fatty fish and fish oils, including cod and tuna liver oils in varying amounts. However, dairy products and eggs contain only little vitamin D [28]. A higher amount of vitamin D is available from fortified foods, but fortification is not universal. Only a few of them are fortified with low amounts of vitamin D in Europe [29] and, particularly in Spain, foods are not fortified. Vitamin D intake was almost three times higher in the women studied in BA than in those living in Lleida, because not only skimmed milk, but also whole milk, is usually fortified in Argentina (400 IU/100 g). Although several studies have shown that <20% of the fortified milk samples contained the amount of vitamin D stated on the label [30], in Argentina, the fortified milk is considered to be the major food source of vitamin D. However, in both places, the intake of vitamin D was significantly lower than the recommended level of 15 μg/d.

Vitamin D is necessary for active Ca intestinal absorption and skeletal integrity. Therefore, a functional deficit of vitamin D or Ca would lead to a low serum Ca concentration and to an increase in PTH production. Because examination of Ca absorption is not widely available and PTH is the item that is usually measured, many investigators have examined the relation between serum PTH and serum 25OHD to best estimate the vitamin D status. Indeed, it is known that 25OHD and PTH present a strong negative correlation between each other [6,31], and the point at which PTH versus 25OHD reaches a plateau has been used to identify a lower 25OHD threshold level. Although this point widely varies among different studies [1,32], a value of 30 ng/dL has been agreed to be ideal [33]. However, despite the main limitation of this study regarding the limited number of elderly women studied, a negative correlation between PTH and 25OHD was observed in both cities, although none of the elderly women reached a 25OHD level of 30 ng/dL. It is well known that serum PTH often reaches levels above the upper reference limit in elderly people, indicating changes in the regulation control of serum PTH and consequently the changes in this threshold.

The low 25OHD level resulting in PTH increases may be modulated not only by age but also by Ca intake [34]. Accordingly, Reginster et al. [35] reported that serum PTH increases with increasing age in stratified patients, with respect to decreasing levels of 25OHD. However, different researchers have reported controversial results related to Ca intake. Steingrimsdottir et al. [36] demonstrated that Ca intake is not relevant in maintaining PTH levels if the 25OHD level is >10.0 ng/dL [37]. In contrast, Adami et al. [34] suggested that the effect of Ca intake was substantial for all 25OHD levels. The novelty of the present study was to demonstrate the interrelation between PTH and 25OHD in a narrow and reliable range of dietary Ca intake. Indeed, the menus were programmed to provide an individual mean daily amount of 800 mg of Ca, on the basis of dairy product consumption. In this narrow range of Ca intake, 2°HPT (defined arbitrarily as a PTH level above the standard laboratory reference range) was absent when 25OHD levels were >17 ng/dL. Moreover, these 25OHD levels were close to the 18 ng/dL reported by Steingrimsdottir et al. [36].

However, 2°HPT was observed in 33% and 25% of elderly women in Lleida and BA, respectively, when the 25OHD level was <16 ng/dL. The observed blunted PTH response in the presence of hypovitaminosis D was not unexpected, because not all patients with low circulating 25OHD levels manifest an increase in serum PTH, irrespective of the threshold level of 25OHD [3,32]. Instead, in general, the increase in PTH level associated with vitamin D deficiency is usually within the normal reference range [3]. However, the mechanisms underlying the PTH response still remain unclear, and the cutoff for the definition of an elevated PTH level requires further examination [37]. In addition, it is important to point out that serum Ca and P remained within the normal range without significant differences in serum Ca levels. In this regard, Haden et al. [38] reported an increase in PTH secretion in elderly people in response to changes in serum Ca, regardless of vitamin D status or renal function.

Although within normal ranges, serum P levels were higher in the BA women than in those living in Lleida. It is important to take into account that, in adults with an adequate renal function, serum P levels are directly related to P intake [2]. The individuals in this study had similar normal renal functions (although definite limitations of the Cockcroft-Gault formula must be underlined); therefore, differences in serum P levels could be related to the different P contents in the dietary patterns consumed by both studied populations.

The PTH is the main regulator of bone turnover, which in turn is a risk factor of fracture irrespective of bone balance

[39]. In this study, independent of the 25OHD levels, both studied bone markers showed no correlation with PTH in the reference range of the hormone. Moreover, when the mean bone marker levels were divided according to tertiles of PTH levels within the reference range, BAP levels did not show any changes, and βCTX increased with the increase in the PTH levels without reaching any significance (Table 3). This could be explained in the context that, at the level of Ca intake of the present study, it is possible to meet the body requirements with little active Ca transport in the gut, as in vitamin D insufficiency [40]. Conversely, a strong correlation between PTH levels and bone markers was found when 2°HPT was present. In this condition, all women examined showed 25OHD levels $<$12 ng/dL, and Ca and P concentrations remained within the normal range. This finding is in agreement with the fact that 2°HPT in vitamin D insufficiency maintains Ca homeostasis, but at the expense of increased bone turnover, which could lead to significant bone loss and increased risk of fracture [25].

Chronic vitamin D deficiency has also been related to several pathologic situations such as hypertension, multiple sclerosis, type 1 diabetes, colon, prostate, breast and ovary cancers, muscle weakness, pain, and osteoarthritis [5,41,42]. Recent research has demonstrated that various normal human tissues possess 25OHD-1α-hydroxylase activity and have the capacity to convert 25OHD directly into 1,25$(OH)_2$D to satisfy local needs in a paracrine way. This production probably depends on the availability of the circulating 25OHD, indicating the biological importance of establishing safe levels of this vitamin D metabolite. Although we did not measure levels of 1,25$(OH)_2$D, all patients with a serum creatinine level $>$1.4 mg/dL were excluded. Moreover, phosphate levels that may be increased in the presence of renal impairment were similar in both groups and within the laboratory reference range. These conditions decrease the probability of impaired 1-α-hydroxylation by the aging kidney but maintain the probability of this impairment by 25OHD substrate deficiency.

Conclusions

Even at the end of summer, vitamin D deficiency/insufficiency was prevalent in the two studied populations of institutionalized elderly women. In the narrow range of dietary Ca intake (close to 800 mg/d) of both studied groups, 2°HPT was absent when 25OHD levels were $>$17 ng/dL, indicating changes in the regulation control of serum PTH and consequently the changes in this threshold. As a result, vitamin D deficiency must be reversed to avoid the increment in bone turnover and to ensure the endocrine and paracrine functions of vitamin D for overall health and well-being.

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