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Vitamin D Status of an Outpatient Clinic Population

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Abstract. Vitamin D insufficiency contributes to bone loss and fracture risk. Low 25-hydroxyvitamin D (25OHD) levels are common in elderly people and in housebound and hospitalized patients. This study was conducted to assess wintertime 25OHD levels in relation to self-reported vitamin D supplement use in an outpatient thyroid clinic population. We assessed the medical history, vitamin D intake from milk and supplements, and serum 25OHD levels in 231 women and 41 men who attended a Thyroid Clinic between January and March, 1999. Of the 272 outpatients, 13.6% had 25OHD levels <40 nmol/l and 53.3% had levels below 80 nmol/l. Fewer than 15% of the patients consumed more than 200 IU per day of vitamin D from milk. Vitamin D supplement use was a positive determinant of serum 25OHD concentration ($P < 0.001$). For example, among the largest homogenous subset of patients, Caucasian women (n = 137), 30% of the unsupplemented women, and 65% of those taking 400 IU/day of vitamin D had levels of 25OHD as high as 80 nmol/l. Other significant determinants of 25OHD levels were race, weight, milk intake, and recent southern travel. Thyroid disorder, serum TSH level, and age were not predictors of serum 25OHD concentration. In conclusion, at their current dietary vitamin D intake levels, most patients at this latitude will need vitamin D supplements in the wintertime.

Key words: Vitamin D — Season — Supplements — 25-hydroxyvitamin D

Vitamin D deficiency is a significant risk factor for bone loss [1–3] and fracture [4–6] and low 25OHD levels are widespread in several segments of the population. Recent reports from the Boston area have indicated that half of the patients admitted to a local hospital with acute hip fractures had 25OHD levels below 30 nmol/l [7] and that over half of the patients admitted serially to the medical service of another local hospital had 25OHD levels of 37 nmol/l or below [8]. In elderly nursing home residents in Boston, 40% had 25OHD levels below 25 nmol/l and 80% had values below 37.5 nmol/l in the wintertime [9]. Each of these study populations could be considered vulnerable to vitamin D insufficiency on the basis that patients sick enough to require hospitalization or residing in nursing homes may have lower than average sun exposure and/or skin synthesis of vitamin D because of their advanced age. In Boston, the prevalence of low 25OHD levels varies widely with season because during the months of October through March, sun exposure does not promote the skin synthesis of vitamin D [10]. In one study, healthy male and female clinical study volunteers in Boston, aged 65 and older, had mean 25OHD levels that were about 40% lower in winter than in summer [11].

This study was conducted to determine the prevalence of different 25OHD levels in a Boston outpatient population and to determine the impact of self-selected vitamin D supplement use on 25OHD levels. We conducted the study in patients attending the Thyroid Clinic. This population was selected because none of the patients was acutely ill, this clinic provided access to a large patient population, and because most of the patients were having blood drawn anyway. In addition, thyroid conditions are not thought to affect vitamin D status [12]. All participants were assessed in the wintertime (January through March), when 25OHD levels are known to be lowest.

Methods

Subjects

All patients who attended the Thyroid Clinic at New England Medical Center between January 12, 1999 and March 31, 1999 were eligible to participate in this survey. Of the 377 people who attended, 66 refused to participate, 27 had incomplete data, and 12 were excluded from the analyses because of pregnancy (n = 7), visits to tanning salons (n = 2), and use of prescriptions for vitamin D (n = 3). The remaining 272 individuals are included in this report. The study was approved by the Human Investigation Review Committee at Tufts University and all subjects gave written informed consent.

Medical History and Examination

A physician interviewed each participant prior to his or her clinic appointment and obtained medical history of thyroid diagnosis,

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age, race as defined by the participant, current medication and supplement use, and pertinent medical and surgical history. Additional information was obtained from female participants regarding menstrual history, menopause, pregnancy, and current estrogen use. Height and weight were measured.

Diet and Travel

Dietary vitamin D intake from milk was estimated with a food frequency questionnaire [13]. With this questionnaire, milk contributed 67% of dietary vitamin D in a cohort of postmenopausal women [14]. Weekly use of multivitamins or other vitamin-D-containing supplements or cod liver oil was estimated by questionnaire. Any travel outside of New England during the 4 months prior to enrollment was recorded and the latitude of each destination was determined. Travel to latitudes lower than 35° North for > 1 day has been associated with higher 25OHD levels [11].

Biochemical Measurements

A blood sample was collected by venipuncture from each participant within 30 days of his or her clinic visit by a phlebotomist at New England Medical Center. Serum thyroid stimulating hormone (TSH) was measured by a second-generation immunometric assay in the New England Medical Center's Clinical Laboratory with use of Chiron ACS 180 automated analyzer assay kits (Bayer Diagnostics, Tarrytown NY). The inter- and intraassay coefficients of variation (CVs) were 4.63% and 2.78%, respectively. The laboratory reference range for TSH was 0.5–5.5 μU/ml. Subjects with undetectable TSH values were assigned the value of 0.05 μU/ml for the calculation of group means. Plasma was sent to the Smith Kline-Beecham Clinical Laboratory for determination of 25OHD concentration with radioimmunoassay kits (DiaSorin, formerly Incstar Corp, Stillwater, MN). The inter- and intraassay CVs were 14.6% and 9.6%, respectively. The normal reference range for this assay is 25–137 nmol/l.

Data Analysis

Characteristics of supplement users were compared by analysis of variance (continuous variables) and with Chi-squared tests (categorical variables). Factors significantly associated with 25OHD were identified by analysis of covariance (ANCOVA). The independent contributions of each of these factors to the predicted 25OHD concentration was estimated (from the same ANCOVA model) as the difference in mean 25OHD at each level of the factor relative to that in a specified reference group (Table 3). The same ANCOVA model was also used to calculate adjusted mean 25OHD concentrations by level of vitamin D supplement use (Fig. 1). *P* values less than 0.05 were considered to indicate statistical significance.

Results

The 272 subjects ranged in age from 18 to 86 years. The majority of participants were female 85% and Caucasian 73%. Four subjects currently used anti-seizure medications and their 25OHD levels ranged from 32.5 to 212.5 nmol/l. None currently used glucocorticoids. Thyroid disorders were 30.1% multinodular goiter, 27.9% Hashimoto's thyroiditis, 24.3% Graves, 12.1% thyroid cancer, and 5.6% other. In the group as a whole, the mean 25OHD concentration was 81.0 ± 37.2 nmol/l, and 3.3% of the patients had 25OHD levels <25 nmol/l (the lower bound of the reference range), 13.6% had levels <40 nmol/l, and 53.3% had levels <80 nmol/l.

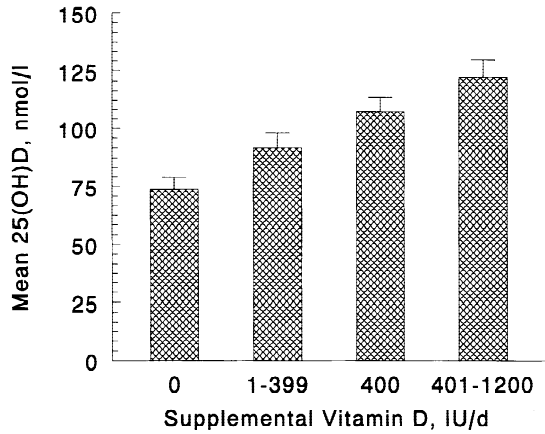

Fig. 1. Mean (±SD) 25OHD concentration (adjusted for race, weight, vitamin D intake from milk, travel, sex, and estrogen use) by category of vitamin D supplement intake in 272 subjects. Number of subjects in the supplement groups were, from left to right, 128, 49, 68, and 27. The *P* value for linear trend was <0.001.

Clinical and biochemical characteristics of the subjects, by pattern of vitamin D supplement use, are shown in Table 1. As expected, 25OHD levels increased with increasing supplement use. The users of higher supplement doses were older and more likely to be women. The supplement categories also differed significantly in racial composition, height, weight, and milk intake. Fewer than 15% of any supplement category had a vitamin D intake from milk greater than 200 IU/day.

Table 2 shows the estimated differences from a reference group in 25OHD concentration across levels of factors that were statistically significant or marginally significant predictors of 25OHD in an analysis of covariance. Mean 25OHD levels differed by race, with highest values in Caucasians (n = 198), lowest values in the smaller African-American (n = 23) and Asian subsets (n = 44), and intermediate values in the Hispanics (n = 7). Mean 25OHD levels were also significantly affected by vitamin D supplement use, weight, and southern travel. Neither thyroid disorder, plasma TSH concentration, nor age was a significant predictor of 25OHD concentration ($P > 0.20$). Mean 25OHD levels of the supplement groups, adjusted for race, weight, vitamin D intake from milk, sex, travel, and estrogen use are shown in Figure 1. The linear increase in mean 25OHD with increasing supplement use was significant ($P < 0.001$ for linear trend).

The distribution of 25OHD levels was examined in the largest relatively homogeneous subset of the study population, the 137 nontraveling Caucasian women. The percentage of women with serum 25OHD below selected levels is shown in Table 3. Among women who reported taking any supplemental vitamin D, none had levels below 20 nmol/l and one woman had a value <40 nmol/l. However, only

Table 1. Characteristics of 272 patients attending a thyroid clinic (mean ± SD or percentage)

	Vitamin D supplement use, IU/day				
	None (n = 28)	1-399 (n = 49)	400 (n = 68)	≥400 (n = 27)	*P*
Age yr	45.8 ± 16.1	47.8 ± 14.4	51.9 ± 15.0	56.0 ± 12.2	0.003
Sex % female	78.1	85.7	92.6	96.3	0.014
Height cm	162.6 ± 8.7	165.7 ± 9.4	161.0 ± 8.6	162.5 ± 6.1	0.036
Weight kg	76.3 ± 22.9	76.4 ± 19.2	69.9 ± 16.5	67.5 ± 13.6	0.048
25OHD nmol/l	24.7 ± 12.0	33.0 ± 13.3	40.9 ± 13.7	46.7 ± 13.5	<0.001
Vit D from milk IU/day, %					0.023
<100	68.8	77.6	51.5	59.3	
100–200	20.3	20.4	33.8	37.0	
>200	10.9	2.0	14.7	3.7	
Race %					0.003
Caucasian	61.7	79.6	88.2	74.1	
Asian	25.0	4.1	8.8	14.8	
African American	10.2	12.2	1.5	11.1	
Hispanic	3.1	4.1	1.5	0.0	
Serum TSH, μU/ml, %					0.433
Low < 0.5	17.2	22.4	10.3	11.1	
Normal 0.5 – 5.5	76.6	65.3	80.9	81.5	
High >5.5	6.3	12.2	8.8	7.4	
Estrogen use %[a]	20.3	24.5	22.1	33.3	0.065
Smokers %	14.8	10.2	8.8	22.2	0.292
Travelers %[b]	14.1	22.4	17.6	29.6	0.214

[a] Includes oral contraceptive pill and hormone replacement therapy
[b] Travel to latitude less than 35° North in the past 4 months

29.6% of the unsupplemented women and 65.2% of the women taking 400 IU/day had 25OHD levels as high as 80 nmol/l.

Discussion

This survey reveals that the mean 25OHD level in our Thyroid Clinic outpatients is far higher than that recently reported in patients admitted to a local hospital (81.0 nmol/l vs 37.5 nmol/l). The difference is particularly striking since half of the inpatients were measured in September when 25OHD levels are generally maximal [8]. Moreover, the self-reported use of multivitamins, most of which contain 400 IU of vitamin D, was greater in the inpatients than in our study. The lower mean 25OHD levels in the inpatients may be due in part to their older age and to the fact that 29% were either housebound or residents of nursing homes [8]. Alternatively, because the inpatients were generally sicker, they may have had lower levels of vitamin D binding protein than our outpatients. Hospitalized patients are known to have lower levels of other proteins, such as albumin, prealbumin, transferrin, and retinol-binding protein [14]. As expected, the mean 25OHD level of our outpatients was higher than that of elderly acute hip fracture patients [7] and Nursing Home residents [9] in Boston. It should be noted that the patients attending this clinic may not be representative of patients attending other clinics at this or other hospitals.

Table 2. Predicted differences in plasma 25OHD concentrations (±SE) across levels of factors in an analysis of covariance model

Variable	Mean 25OHD difference (nmol/l)	Significant factor
Race		0.007
Caucasian	reference	
Hispanic	−11.6 ± 11.6	
Asian	−15.2 ± 5.6	
African-American	−17.1 ± 6.8	
Weight/10 kg	−2.0 ± 1.1	0.027
Vitamin D supplement use		<0.001
>400 IU/day	reference	
400 IU/day	−14.7 ± 6.9	
1–399 IU/day	−30.6 ± 7.3	
None	−48.6 ± 6.6	
Vitamin D from milk		0.074
>200 IU/day	reference	
100–200 IU/day	−7.1 ± 7.1	
<100 IU/day	−13.5 ± 6.6	
Travel <35° N		<0.001
Yes	reference	
No	−20.9 ± 4.8	
Sex		0.070
Male	reference	
Female	−10.3 ± 5.7	
Exogenous estrogen use		0.097
Yes	reference	
No	−7.6 ± 4.5	

[a] Travel to latitude <35° North in the past 4 months able 2. Predicted differences in plasma 25OHD concentrations (±SE) across levels of factors in an analysis of covariance model

Table 3. Distribution of plasma 25OHD levels in nontraveling Caucasian women, by category of supplemental vitamin D dosage

	Women on vitamin D supplements, IU/day			
Plasma 25OHD (nmol/L)	0 (n = 54)	1–399 (n = 24)	400 (n = 46)	401–1,200 (n = 13)
<20	3.7	0	0	0
<40	27.8	0	2.2	0
<60	55.6	25.0	10.9	0
<80	70.4	54.2	34.8	15.4
<100	90.7	7.5	52.2	38.5
<120	94.4	91.7	78.3	69.2

Though it is reassuring that 25OHD levels in our outpatients compare favorably with those in the studies cited above [7–9], their 25OHD levels are not as high as may be desirable. Several studies have shown that serum PTH levels can be suppressed as 25OHD levels increase up to a plateau level of 75 nmol/l [15], 77 nmol/l [16], and 90 nmol/l [17] in postmenopausal women and at 110 nmol/l in elderly men and women [11]. Malabanan et al. [18] identified the plateau level to be at least 50 nmol/l whereas Ooms et al. [19] reported that the associations of 25OHD with PTH were significant only at 25OHD levels below 30 nmol/l. The consequence of having 25OHD levels below 80 and 100 nmol/l has been examined in two trials. In one study in 249 postmenopausal women, increasing 25OHD levels from 60 to 80 nmol/l by supplementation with vitamin D not only reduced serum parathyroid hormone levels but also reduced wintertime and net bone loss from the spine and total body over a 1-year period [1]. In a 2-year vitamin D intervention study in 247 postmenopausal women, wintertime and net bone loss from the femoral neck was greater in the women with a mean 25OHD level of 66 nmol/l than in the women with a mean level of 100 nmol/l [3]. Thus, we expect that the 30% of patients in this study with 25OHD levels below 60 nmol/l and probably the 53.3% who had 25OHD levels <80 nmol/l, may have been at increased risk of accelerated bone loss.

Vitamin D supplementation was a strong predictor of wintertime 25OHD levels in our study. This association was no doubt enhanced by the facts that the population had low dietary vitamin D intakes and were assessed in the wintertime. Multivitamins, most of which contain 400 IU of vitamin D, are often recommended for supplemental vitamin D. About 90% of the Caucasian women who reported taking 400 IU/day of supplemental vitamin D had levels of 60 nmol/l or greater and 65% had levels above 80 nmol/l. In contrast, among nonusers, 45% had levels above 60 nmol/l and 30% had levels above 80 nmol/l. Quantifying the association between self-reported intake and 25OHD levels may be of practical use to clinicians, as they make judgments about who should take supplements.

This study confirmed several other significant determinants of wintertime serum 25OHD concentration, including race, weight, and southern travel. Compared with Caucasians, the African-American, Hispanic, and Asian patients had lower wintertime 25OHD levels. Harris and Dawson-Hughes [20] have reported lower wintertime 25OHD levels in young African-American than in Caucasian women and there are reports, not season-specific, of lower 25OHD levels in African-Americans [21–23], Mexican-Americans [24], and Pacific Islanders [25] than in Caucasians. These differences have been attributed to lower rates of cutaneous vitamin D synthesis in skin with higher melanin content [26]. The finding that heavier people had lower 25OHD levels is consistent with some [11, 21] but not other [25] reports and the physiologic basis for the association is not clear. Southern travel in the wintertime was associated with significantly higher 25OHD concentrations in this study population. We have seen a similar impact of southern travel for periods as short as 1 day in healthy older men and women residing in the Boston area [11]. As expected, we could identify no association between either thyroid diagnosis or TSH level and serum 25OHD concentration.

In conclusion, mean 25OHD levels in an outpatient population were substantially higher than those reported recently in local hospital inpatients and nursing home residents. However, many of our outpatients, particularly those reporting no supplement use, had wintertime 25OHD levels below that needed, at least by some estimates, to minimize bone loss. Unless their dietary vitamin D intakes increase dramatically, many patients residing in the temperate zone will need supplemental vitamin D, at least in the wintertime. This study confirms that race, weight, southern travel, and vitamin D intake make contributions to wintertime serum 25OHD levels. We found no evidence that thyroid status influences the vitamin D requirement.

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