Hypovitaminosis D among Inpatients in a Sunny Country

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Abstract

Background: Hypovitaminosis D is an important risk factor for osteoporosis and its complications. Previous studies found that the incidence of hypovitaminosis D among patients in an internal medicine ward reached up to 57%.

Objective: To determine the prevalence and determinants of hypovitaminosis D among patients in internal medicine wards in a sunny country.

Methods: We measured 25-hydroxyvitamin D, parathyroid hormone and various other laboratory parameters, and assessed the amount of sun exposure, dietary vitamin D intake and other risk factors for hypovitaminosis D in 296 internal medicine inpatients admitted consecutively to the Soroka University Medical Center, which is situated in a sunny region of Israel.

Results: We found hypovitaminosis D (serum 25-HO-D < 15 ng/ml) in 77 inpatients (26.27%). The amount of sunlight exposure, serum albumin concentration, being housebound or resident of a nursing home, vitamin D intake, ethnic group, cerebrovascular accident and glucocorticoid therapy were all significantly associated with hypovitaminosis D. Multivariate analysis showed a significant association between hypovitaminosis D and Bedouin origin, sun exposure, vitamin D intake, and stroke. Hypovitaminosis D was also found among inpatients who reported consuming more than the recommended daily amount of vitamin D. Parathyroid hormone levels were significantly higher in patients with 25-OH-D levels below 15 ng/ml. In a subgroup of 74 inpatients under 65 years old with no known risk factors for hypovitaminosis D, we found 20.3% with hypovitaminosis D.

Conclusions: Hypovitaminosis D is common in patients hospitalized in internal medicine wards in our region, including patients with no known risk factors for this condition. Based on our findings, we recommend vitamin D supplementation during hospitalization and upon discharge from general internal medicine wards as a primary or secondary preventive measure.

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Vitamin D is an essential vitamin and hormone. It is produced in most plants and animals during exposure to the sun [1], but its physiologic role is known only in vertebrae, where it plays an important role in bone formation and maintenance and in the regulation of body calcium and phosphate levels.

Hypovitaminosis D is a major risk factor for osteoporosis and the fractures related to it, mainly hip and vertebral fractures [1–3]. The annual costs to the United States health system for treating osteoporosis were estimated to be 13.8 billion dollars in 1995 [4]. Studies have shown an association between vitamin D deficiency and osteoporosis [1,2,5] and have proved that the correction of hypovitaminosis D by vitamin D supplementation, with the addition of calcium supplements, increases bone density and decreases the incidence of osteoporosis and its complications [3,6,7]. Multiple studies have evaluated the prevalence of hypovitaminosis D in different populations, mainly those at high risk for vitamin D deficiency. In our area such high risk populations include the Bedouin and Ethiopians [3,8–12]. A recent study conducted in Boston [8], one of the few that examined vitamin D status in a more diverse population, found that 57% of patients in an internal medicine ward had hypovitaminosis D. The implications of the findings of that study were that vitamin D levels should be determined in all patients in internal medicine wards and that the diets of all patients on the service need to be supplemented with vitamin D. However, before universalizing the Boston findings and adopting into practice the implied recommendations in our region, we deemed it necessary to assess the prevalence of hypovitaminosis D in inpatients in our sunny country.

One important reason for doing so is the difference in the level of sun exposure in Israel (latitude 31 north) and Boston (latitude 42 north). Because of the importance of ultraviolet B exposure to the endogenous synthesis of vitamin D [1], a lower rate of hypovitaminosis D in our area is expected. Additional factors known to influence the vitamin D level [1,10,11] that might lead to a difference in prevalence of vitamin D deficiency in the two areas are skin color, diet and clothing habits, and the fact that milk products in the United States but not in Israel are enriched with vitamin D. Because vitamin D supplementation reduces the risk of osteoporosis and its complications, knowledge of the prevalence of vitamin D deficiency in our area might alter routine medical practice and have important public health implications.

Patients and Methods

Study population

We studied 144 patients admitted consecutively in September 1999 and 152 patients admitted consecutively in March 2000 to a department of internal medicine at the Soroka University Medical Center in Beer Sheva, Israel. We chose to study a total of close to 300 patients since this is the number of patients hospitalized in one ward during the months chosen for the study. Additionally, this was the number of patients in the Boston study [8] and was therefore optimal for the purposes of comparison. The months of March and September were chosen to represent the seasonal nadir and peak, respectively, of serum vitamin D [1,13]. The study was approved by

25-OH-D = 25-hydroxyvitamin D

the Helsinki Subcommittee on Human Studies at the Soroka University Medical Center and oral consent was obtained from the patients; eight declined to participate.

We identified a subgroup of 74 patients with no known risk factors for hypovitaminosis D by excluding patients who were older than 65 years of age, were housebound or living in a nursing home, and had no chronic liver or renal disease or debilitating illness (cancer, congestive heart failure, or chronic obstructive pulmonary disease).

Clinical characteristics

On the day of admission each patient's record was reviewed and data were collected on age, gender, country of origin, and medical diagnosis with an emphasis on debilitating illness, liver or renal disease, gastrointestinal surgery and other causes of malabsorption. Data were also collected regarding therapy with anticonvulsant agents (phenytoin, phenobarbital, lithium and carbamazepine), rifampin and glucocorticoids, which are known to affect the plasma vitamin D concentration [1].

Questionnaires

Each study participant filled out a questionnaire on personal details. Data including demographic details, functional status, sun exposure, and dietary habits with an emphasis on vitamin D-containing foods were collected by a single researcher trained in the use of a diet-recall diary validated in Israel. When there was a problem interviewing because of impaired mental status or language, a close caregiver or an interpreter were used, respectively.

- *Functional status*. Each participant was classified as independent, a nursing home resident or bedridden (at home or in a nursing home).
- *Sun exposure*. Sun exposure was determined based on self-report regarding hours spent outdoors, clothing, and the use of a hat and sunscreen, all known to influence plasma vitamin D [1]. The calculation of sun exposure and the conversion of that information to the amount of UVB exposure were deduced from the Bio-Meteorological study conducted in Beer Sheva in January 1995 to December 1997 by Dr. A. Kudish from the Solar Energy Laboratory at Ben-Gurion University. A sun-exposure grade ranging from 0 to 9 was calculated for each participant based on the data collected. This nine-point scale was developed on the basis of a similar previously validated scale [14].
- *Diet*. A dietary questionnaire was developed by an expert dietician and included a list of foods containing vitamin D in amounts of at least 0.25 μg (10 IU) per serving, and the average daily consumption of these foods was assessed using a dietary recall questionnaire. Regular use of vitamin D or calcium supplements was noted.

Laboratory tests

Morning blood samples were obtained from the study participants after an overnight fast within the first 24 hours of admission. General chemistry was performed for alkaline phosphatase, aminotransferases (alanine and aspartate), creatinine albumin, phosphate, total calcium, and bilirubin, using the Hitachi 747 Automatic Analyzer (Japan) with the use of Boehringer Mannheim reagents (Germany). Ionized calcium was determined by the STAT PROFILE 1, an electrolyte and blood gas analyzer. Serum 25-hydroxyvitamin D levels were determined by the competitive protein binding assay. Serum parathyroid hormone levels were measured by an immunoradiometric assay (kit developed by DiaSorin Inc., Stillwater, MN, USA). All laboratory tests were conducted in the Soroka Medical Center's laboratories and were performed separately from the routine tests in order to minimize variation in the results.

Hypovitaminosis D: definition

Hypovitaminosis D was defined as a serum 25-HO-D level below 15 ng/ml. This level was chosen as the cutoff level for the following reasons. First, evidence has been published that with serum 25-OH-D levels $\leqslant$ 15 ng/ml there is a rise in the parathyroid hormone levels [8,15]. This rise in PTH is a marker for the clinical significance of the hypovitaminosis D state on the bone. Second, this value was 2SD below the mean value of serum 25-OH-D levels in the healthy population of the Beer Sheva region and surroundings according to the Soroka Medical Center chemistry laboratory [16]. Third, we checked the levels of PTH in relation to serum 25-OH-D D levels (see below), as suggested elsewhere [17].

Statistics

The statistical analysis was performed using the SPSS program. The data were divided into qualitative and quantitative variables. The association between the serum 25-OH-D levels and qualitative variables was examined using Pearson's chi-square test. The association between serum 25-OH-D levels and quantitative variables was examined using analysis of variance. Linear association between serum 25-OH-D levels and sun-exposure grade was determined using analysis of variance. Multivariate analyses using logistic regression were performed in order to determine the influence of each variable.

Results

Clinical characteristics

Of the 293 patients, 157 (53.6%) were men and 136 (46.4%) women; 126 (43%) were of European or American origin, 127 (43%) of African or Asian origin, 37 (12.6%) were Bedouins and 3 (1%) were Ethiopians. Of the 293, 261 (89%) were independent, 25 (8.5%) were housebound and 7 (2.4%) were nursing home residents. The medical diagnoses of the patients were: ischemic heart disease in 50%, hypertension in 40%, heart failure in 14.3%, diabetes mellitus in 28%, previous stroke in 9.6%, anemia in 12.6%, chronic obstructive pulmonary disease in 17%, pneumonia in 9%, malignancy in 8%, and chronic liver disease in 4%. Infectious disease was the cause of admission in 18% and renal failure in 13%.

UVB = ultraviolet B

PTH = parathyroid hormone

Glucocorticoids were given as chronic treatment in 8.5% of patients. Other conditions known to be associated with hypovitaminosis D – such as malabsorption, intestinal resection, nephrotic syndrome and those requiring anticonvulsant therapy – were not found at all among the inpatient group.

25-OH-D levels and hypovitaminosis D

25-OH-D levels were obtained for 293 of the 296 inpatients. The three missing results were due to insufficient blood sample. The mean (±SD) for 25-OH-D levels was 21.1(±9.7) ng/ml in the entire inpatient group (293 inpatients), 19.9(±9) ng/ml in patients hospitalized in March, and 22.4(±10.6) ng/ml in those hospitalized in September. The difference in peak to nadir values was statistically significant ($P = 0.0298$).

Hypovitaminosis D was found in 77 patients (26.27%). There were no differences between the characteristics of the patients studied in March and those studied in September. In addition, since there was no significant difference in 25-HO-D levels (27.8% and 24.6%, respectively, $P = 0.538$) in the vitamin-deficient patients according to date of hospitalization, the two groups were combined for purposes of analysis.

Serum PTH rose steeply as serum 25-OH-D concentrations declined below 15 ng/ml [Figure 1]. The mean PTH levels were 34.6 pg/ml in the group of patients with 25-OH-D less than 15 ng/ml and 18.9 pg/ml in the group with levels higher than 15 ng/ml ($P = 0.00023$). The data indicate a physiologic response to the hypovitaminosis state, confirming the validity of the cutoff chosen to define physiologic hypovitaminosis D.

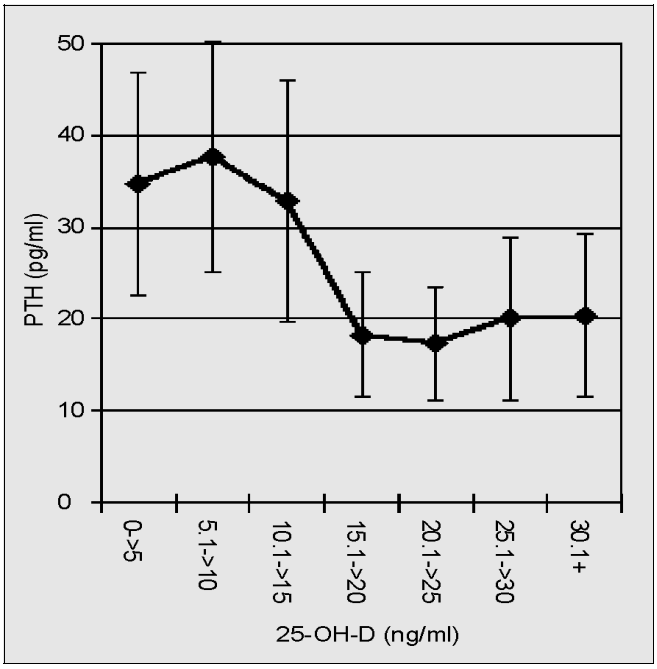

Figure 1. Relation between serum 25-hydroxyvitamin D concentrations and serum concentrations of PTH in the inpatient group (n = 285). The patients were categorized according to their serum 25-HO-D concentrations in increments of 5 ng/ml. (Since the group with 25-HO-D ranging from 0 to 5 ng/ml comprised only five inpatients, it is difficult to make true statistical conclusions about the PTH level in this group.)

Variables associated with hypovitaminosis D

Hypovitaminosis D was found to be significantly associated ($P < 0.05$) with sun-exposure grade, serum albumin level, functional status, vitamin D content in the diet, Bedouin origin, history of stroke, and glucocorticoid therapy [Tables 1 and 2]. There was a tendency toward an association ($P < 0.1$) with serum ionized calcium level and COPD. In a more conservative analysis defining a significant association as $P < 0.01$, we found an association of hypovitaminosis D with functional status, sun-exposure grade and stroke only.

- *Dietary vitamin D*. The mean daily (±SD) vitamin D intake was 24(±17) g. Twenty-five percent of the inpatients reported a vitamin D dietary intake that was less than the recommendation by age (5 g at 19–50 years old, 10 g at 51–70, and 15 g at age 71 and older) [18]. Hypovitaminosis D was significantly associated with low daily vitamin D intake. The prevalence of hypovitaminosis D in patients with a vitamin D dietary intake of 0–5, 5–10 and more than 10 g/day was 45.5%, 35% and 22.3% respectively ($P = 0.022$).
- *Origin*. The prevalence of hypovitaminosis D in the different ethnic groups was 47% among Bedouin, 28% among those whose family originated in Africa/Asia and 20% among those from Europe/America. Bedouin origin was therefore significantly

COPD = chronic obstruction pulmonary disease

Table 1. The association between serum 25-hydroxyvitamin D levels and qualitative variables

	25-HO-D levels (data in %)		
Variable	**0–15 ng/ml**	**>15 ng/ml**	***P* value**
Gender			
Male	48.1	55.6	0.257
Female	51.9	44.4	
Functional status			
Ambulatory	21.5	78.5	0.00001*
Housebound	64	36	
Nursing home	71.4	28	
Medical diagnosis (%)			
Ischemic heart disease	37.7	54.2	0.013*
Hypertension	35.1	42.4	0.278
Heart failure	17	13.4	0.457
Diabetes mellitus	27.3	28.2	0.87
Stroke	19.5	6	0.00056*
Anemia	13	12.5	0.912
COPD	23.4	14.8	0.086
Pneumonia	9.1	9.3	0.965
Malignancy	7.8	8.3	0.88
Chronic liver disease **	6.5	2.8	0.14
Renal failure ***	18.3	11.1	0.11
Infectious disease	20.8	17.1	0.475
Vitamin D supplements ****	18.4	17	0.8
Chronic steroid therapy	16.7	5.5	0.0017*

* $P < 0.5$
** Known chronic hepatitis or cirrhosis, or serum bilirubun >2 mg/dl
*** Serum creatinine > 1.5 mg/dl
**** Multivitamin, vitamin D + calcium or vitamin D alone

Table 2. The association between serum 25-hydroxyvitamin D levels and quantitative variables

Variable	25-HO-D levels mean (±SD) 0–15 ng/ml	>15 ng/ml	*P* value
Age (yrs)	63.77 (14.5)	62.9 (16.4)	0.684
Sun-exposure grade	3.58 (2.88)	5 (2.76)	0.0002*
Ionized calcium (nmol/L)	1.004 (0.17)	1.042 (0.14)	0.06
Serum phosphate (mg/dl)	3.71 (1.4)	3.48 (0.98)	0.12
Albumin (g/dl)	3.48 (0.85)	3.67 (0.512)	0.0295*
Total calcium (mg/dl)	8.7 (1.2)	9.36 (5)	0.2
Bilirubin (mg/dl)	0.885 (1.12)	0.68 (0.53)	0.041*
Alanine aminotransferase (mg/dl)	23.25 (16.8)	25 (32.6)	0.65
Aspartate aminotransferase (mg/dl)	28.5 (25)	27.8 (43)	0.8
Creatinine (mg/dl)	1.14 (0.76)	1.10 (0.63)	0.65

* $P < 0.5$

associated with hypovitaminosis D (P = 0.00273). We did not include Ethiopian patients in the statistical analysis since there were only three such patients.

- *Sun exposure.* Sun exposure was significantly lower in the hypovitaminosis D group [Table 2]. The association remained significant after analysis of variance was applied.

Multivariate analyses

Independent predictors of hypovitaminosis D were determined by multivariate analysis, which included all variables with statistical association ($P < 0.1$) on the univariate analysis: sun-exposure grade, serum albumin level, functional status, daily dietary vitamin D intake, ethnic origin, stroke, steroid therapy, COPD, and ionized calcium level. The significantly associated parameters on multivariate analysis were: Bedouin origin (P = 0.0001), sun-exposure grade (P = 0.0135), dietary vitamin D intake (P = 0.047) and stroke (P = 0.0418).

Hypovitaminosis D in patients without known risk factors for hypovitaminosis D

We subgrouped 74 inpatients with no known risk factors for hypovitaminosis D, defined by the absence of the following: age more than 65 years, housebound or living in a nursing home, chronic liver or renal disease (defined as serum creatinine >1.5 mg/dl) and debilitating illness (cancer, congestive heart failure, or COPD).

There was no significant difference in the prevalence of hypovitaminosis D between the subgroup (20.3% of 74) and the group as a whole (26.27% of 293 inpatients, P = 0.25) or the inpatients with risk factors (28.8% of 212, P = 0.17) [Figure 2].

The mean (±SD) 25-OH-D level in the no-risk factor subgroup was 20.2(±11.6) ng/ml, which was no different from the level in the inpatient group as a whole, 21.1(±9.7) (P = 0.181). The mean age in the subgroup was 46.4(±13) and there were more males than females, 64.5% and 35.5%, respectively (P = 0.037). Fifty percent of the subgroup had ischemic heart disease, but significantly less hypertension (27%) and diabetes (18.4%) than the total group of patients (P = 0.0083 and 0.031 respectively).

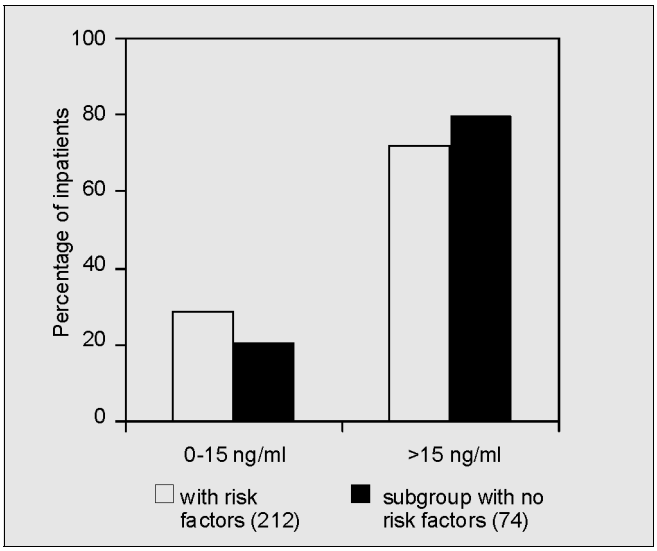

Figure 2. Prevalence of hypovitaminosis D and normal levels of serum 25-HO-D Concentrations in the subgroup of inpatients with no known risk factors (n = 74), compared to the rest (n = 212). The subgroup with no known risk factors is shown by solid bars, and the rest of the inpatients, i.e., with risk factors, by open bars (P = 0.17)

Discussion

The prevalence of hypovitaminosis D in the population we studied was 26.7%. Different studies have reported a prevalence ranging from 20 to 61% [8–12]. Most of those studies chose specific study populations, such as the elderly [19], the disabled [20], residents in institutions [21], specific ethnic groups such as the Bedouin [10], immigrants from Ethiopia [11], elderly women [12], women with specific dress customs [22], and other high risk populations. Our study targeted internal medicine patients, a more diverse, less specific population, and one more representative of the general population. A similar comprehensive study [8] examined medical inpatients in Boston, USA and found an extremely high prevalence of hypovitaminosis D (57%). Reasons for the markedly different results include the excess of UVB exposure in our area due to the geographic latitude (latitude 31N in Beer Sheva, Israel compared to 42N in Boston, USA), as well as differences in dietary habits and consumption of vitamin D-containing foods, which were proved to be associated with vitamin D deficiency in our study as well as in others [1,8,13]. The difference in population characteristics, e.g., the prevalence of debilitating diseases, can also explain the disparity in the prevalence of hypovitaminosis D. However, the disparity persisted even when younger patients without any known risk factors were compared.

We did not find a significant variation in the prevalence of hypovitaminosis D between summer and winter. Our sunny climate is such that there is sufficient UVB exposure during the winter as well, an exposure that makes the change of seasons inconsequential on the rate of hypovitaminosis D. It should be emphasized that we did find a lower mean 25-OH-D at the end of the winter, but not a higher rate of hypovitaminosis D, i.e., 25-OH-D less than 15 ng/ml. This lack of seasonal disparity was also found in other studies [8].

An important step in determining the prevalence of hypovitaminosis D is defining the minimal "normal" vitamin level. We expect that a rise in serum PTH level will act as a marker indicating the level of physiologic hypovitaminosis D, presumably through hypocalcemia resulting from low serum 25-OH-D. We found that PTH rose steeply as serum 25-OH-D declined below 15 ng/ml, therefore we set this value to be the minimal 25-OH-D level below which we defined a hypovitaminosis D state. Other studies also found that below this 25-OH-D concentration there was a rise in serum PTH levels [8,15] and a decrease in bone density [23].

We found an association between hypovitaminosis D and sun exposure, daily dietary intake of vitamin D, disability, and ethnic group. All these variables have been shown in other studies to effect 25-OH-D levels [1,8,10,11,19], and so corroborate our findings. The significance of the lower prevalence of hypovitaminosis D in the group of ischemic heart disease patients is unclear. It may be an incidental finding, or it may reflect awareness about the benefits of a balanced diet, physical activity, e.g., walking outdoors, as part of the treatment of these patients.

We conclude from our findings that hypovitaminosis D is common among patients hospitalized in internal medicine wards in our region; and that since the medical consequences are significant there is a need for comprehensive recommendations in order to raise vitamin D levels in this population. In view of the high prevalence of hypovitaminosis D and the difficulty to predict who will have a vitamin deficiency using clinical and routine laboratory parameters, as well as the high expenses and burden of testing 25-OH-D levels in all medical inpatients, we emphasize the need for an increased intake of vitamin D for all inpatients.

We have shown that hypovitaminosis D is common even in people with a self-reported dietary intake of vitamin D exceeding the minimum daily recommendation of the 1997 Food and Nutrition Board. Several steps should therefore be taken to increase vitamin D intake [24], such as encouraging dieticians, nurses and physicians in hospitals, clinics and nursing homes to advise and plan meals containing more vitamin D. The amount of vitamin D supplement in the preparations available on the market should be increased, as should the amount of vitamin D in milk products. It must be emphasized that the margin of safety from complications such as hypercalcemia is substantial [24]. An alternative solution – spending more time in the sun – is not advised because of the significant risk for skin cancer. As mentioned above, the correction of hypovitaminosis D enhances bone density and decreases fracture prevalence [3,7]. The simplicity of the solution for universal increase in vitamin D intake encourages us to recommend it for the entire medical inpatient population without conducting extensive screening tests for vitamin D deficiency, thus serving both primary and secondary prevention of osteoporosis. We believe that implementing this simple solution is crucial, especially given the tendency to overlook states of osteomalacia and vitamin D intake problems [25].

In the light of our findings as well as data from other countries that are sunny [10,12,22] and those that are not [5,8,9,20,21], these proposals are suitable for all countries, sunny or not, where the prevalence of hypovitaminosis D among medical inpatients is as high or even higher than in our population.

A limitation in our study was the fact that most inpatients were acutely ill. Although it is possible that acute illness could have suppressed endogenous vitamin D synthesis, the half-life of serum 25-HO-D is approximately 3 weeks [1] and thus its level is not influenced by the short period of illness prior to obtaining the blood sample for the study.

An important additional question is whether we can infer – from the high prevalence of vitamin deficiency in the population we studied – an equally high prevalence in the general healthy population. Though diseases known to be risk factors for hypovitaminosis D (renal failure, chronic liver disease and malabsorption) were not very common in our inpatient population, it could be argued that various parameters proven to influence the vitamin level, such as sun exposure and diet, are different in this group, especially in the chronically ill, than in the general population. In order to minimize the differences from the general population, we subgrouped 74 patients who were not chronically ill or disabled and who are seemingly more similar to the general population regarding variables influencing vitamin D level. In this subgroup we found a prevalence of hypovitaminosis D similar to that in the group of inpatients as a whole. We conclude from the data that although it is difficult to extrapolate to the general population, the prevalence of hypovitaminosis D, if measured in the general population, would not be significantly different. The implications and recommendations inferred from our study are therefore more likely to be applicable to the population of adults as a whole.

To summarize, it is not clear whether the prevalence of hypovitaminosis D found in our study population resembles the actual prevalence in the general healthy public. Because of the significant public health impact of hypovitaminosis D, we believe it necessary to determine its prevalence in the general population. Still, in view of the data from our research, and from similar studies conducted in our region and elsewhere, we recommend that milk products be enriched, as is customary in several countries, even before such data are obtained. Based on our findings, we advise vitamin D supplementation during hospitalization and upon discharge from general internal medicine wards.

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