

The New England Journal of Medicine

© Copyright, 1998, by the Massachusetts Medical Society

VOLUME 338

MARCH 19, 1998

NUMBER 12



HYPOVITAMINOSIS D IN MEDICAL INPATIENTS

MELISSA K. THOMAS, M.D., PH.D., DONALD M. LLOYD-JONES, M.D., RAVI I. THADHANI, M.D., M.P.H.,
ALBERT C. SHAW, M.D., PH.D., DONALD J. DERASKA, M.D., BARRETT T. KITCH, M.D.,
ELEFTHERIOS C. VAMVAKAS, M.D., PH.D., IAN M. DICK, M.Sc., RICHARD L. PRINCE, M.D.,
AND JOEL S. FINKELSTEIN, M.D.

ABSTRACT

Background Vitamin D deficiency is a major risk factor for bone loss and fracture. Although hypovitaminosis D has been detected frequently in elderly and housebound people, the prevalence of vitamin D deficiency among patients hospitalized on a general medical service is unknown.

Methods We assessed vitamin D intake, ultraviolet-light exposure, and risk factors for hypovitaminosis D and measured serum 25-hydroxyvitamin D, parathyroid hormone, and ionized calcium in 290 consecutive patients on a general medical ward.

Results A total of 164 patients (57 percent) were considered vitamin D-deficient (serum concentration of 25-hydroxyvitamin D, ≤ 15 ng per milliliter), of whom 65 (22 percent) were considered severely vitamin D-deficient (serum concentration of 25-hydroxyvitamin D, < 8 ng per milliliter). Serum 25-hydroxyvitamin D concentrations were related inversely to parathyroid hormone concentrations. Lower vitamin D intake, less exposure to ultraviolet light, anticonvulsant-drug therapy, renal dialysis, nephrotic syndrome, hypertension, diabetes mellitus, winter season, higher serum concentrations of parathyroid hormone and alkaline phosphatase, and lower serum concentrations of ionized calcium and albumin were significant univariate predictors of hypovitaminosis D. Sixty-six percent of the patients who consumed less than the recommended daily amount of vitamin D and 37 percent of the patients with intakes above the recommended daily amount were vitamin D-deficient. Inadequate vitamin D intake, winter season, and housebound status were independent predictors of hypovitaminosis D in a multivariate model. In a subgroup of 77 patients less than 65 years of age without known risk factors for hypovitaminosis D, the prevalence of vitamin D deficiency was 42 percent.

Conclusions Hypovitaminosis D is common in general medical inpatients, including those with vitamin D intakes exceeding the recommended daily amount and those without apparent risk factors for vitamin D deficiency. (N Engl J Med 1998;338:777-83.)

©1998, Massachusetts Medical Society.

VITAMIN D deficiency is a risk factor for osteopenia and bone fractures.¹⁻⁵ In ambulatory elderly people whose average serum concentration of 25-hydroxyvitamin D was slightly low, supplementation with 20 μ g (800 IU) of vitamin D and with calcium substantially reduced the risk of osteoporotic fractures, including hip fractures.^{6,7} Multiple studies have estimated the prevalence of hypovitaminosis D in selected populations at particular risk for vitamin D deficiency, such as residents of nursing homes and people over the age of 65, to be between 25 and 54 percent.⁸⁻¹¹ However, the prevalence of hypovitaminosis D in more diverse patient populations has not been well characterized. Conditions associated with hypovitaminosis D, such as poor dietary intake, inadequate sun exposure, and chronic liver and renal diseases, are common in general medical inpatients, as is therapy with drugs that impair vitamin D activation or accelerate its clearance, such as phenytoin, carbamazepine, and rifampin. Thus, such inpatients may be at risk for vitamin D deficiency. Because replacement therapy is simple and reduces the risk of fractures, an understanding of the prevalence of vitamin D deficiency may alter routine medical practice and have important public health implications.

METHODS

Study Subjects

We studied 150 patients admitted consecutively in March 1994 and 140 patients admitted consecutively in September 1994 to

From the Endocrine Unit (M.K.T., D.J.D., J.S.F.), Department of Medicine (D.M.L.-J., R.I.T., A.C.S., B.T.K.), and the Department of Pathology (E.C.V.), Massachusetts General Hospital and Harvard Medical School, Boston; and the Department of Medicine, University of Western Australia, Perth (I.M.D.), and the Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Nedlands (R.L.P.) — both in Australia. Address reprint requests to Dr. Finkelstein at the Endocrine Unit, Bulfinch 327, Massachusetts General Hospital, 55 Fruit St., Boston, MA 02114.

general medical wards at Massachusetts General Hospital. The months of March and September were chosen to represent the seasonal nadir and peak, respectively, of serum vitamin D concentrations in Boston.¹² The study was approved by the Subcommittee on Human Studies of Massachusetts General Hospital, and oral consent was obtained from the patients (3 of 293 declined to participate).

A subgroup of 77 patients with no known risk factors for hypovitaminosis D was defined by excluding patients who were more than 65 years of age, housebound or living in a nursing home, or taking anticonvulsant drugs, or who had a chronic debilitating illness (cancer, acquired immunodeficiency syndrome, congestive heart failure, or chronic obstructive pulmonary disease), renal disease (defined as a serum creatinine concentration >1.5 mg per deciliter [$133 \mu\text{mol}$ per liter], the presence of the nephrotic syndrome, or the need for dialysis), liver disease (defined as a serum bilirubin concentration >2.0 mg per deciliter [$34 \mu\text{mol}$ per liter] or the presence of hepatitis or cirrhosis), or a condition causing malabsorption of nutrients (inflammatory bowel disease, chronic pancreatitis, or gastric or small-bowel resection).

Evaluation of Clinical Characteristics

Within 24 hours after admission, each patient's record was reviewed. The data collected included age, sex, race, and diagnoses, with emphasis on any history of liver disease, renal disease, gastric or small-bowel surgery, inflammatory bowel disease, pancreatitis, malabsorption, and therapy with anticonvulsant agents (phenytoin, phenobarbital, and carbamazepine), rifampin, or glucocorticoids. Each patient was classified as ambulatory, housebound, living in a nursing home, or homeless. The patients were not followed during the hospitalization, except to determine mortality during the incident admission.

Dietary and Sun-Exposure Interviews

Study physicians were trained by a research dietitian to obtain standardized histories of dietary vitamin D intake. A questionnaire was developed that included a list of foods containing vitamin D in amounts of at least $1.25 \mu\text{g}$ (50 IU) per serving,¹³ and average daily and weekly consumption of these foods was assessed. Regular use of multivitamins, vitamin D, or calcium supplements was noted. Exposure to the sun was rated with the use of a previously validated nine-point scale,¹⁴ which measured the degree and extent of recent sun exposure, the use of sunscreens, and recent travel to southern locations. Two hundred six patients completed both the dietary and sun-exposure interviews. The remaining 84 patients were unable to provide complete dietary and sun-exposure information because of impaired mental status and were excluded from the multivariate analyses.

Laboratory Studies

Morning blood samples were obtained from the patients after an overnight fast within 24 hours after admission. Serum parathyroid hormone was measured by a two-site immunoradiometric assay.¹⁵ Serum 25-hydroxyvitamin D was measured by competitive protein-binding assay (Nichols Institute, San Juan Capistrano, Calif.). Serum vitamin D-binding protein was measured by radioimmunoassay.¹⁶ Routine chemistries were measured by a Hitachi multichannel analyzer, and serum ionized calcium was measured by a gas analyzer (Nova Biomedical, Waltham, Mass.). The samples were analyzed in multiple assays; the interassay coefficients of variation were less than 6 percent for the measurements of parathyroid hormone and 8 to 14 percent for 25-hydroxyvitamin D.

Definition of Hypovitaminosis D

The patients were divided into three diagnostic categories according to their serum 25-hydroxyvitamin D concentrations: those with severe hypovitaminosis D (serum 25-hydroxyvitamin D concentration, less than 8 ng per milliliter [20 nmol per liter]),

those with moderate hypovitaminosis D (serum 25-hydroxyvitamin D concentration, 8 to 15 ng per milliliter [20 to 37 nmol per liter]), and those with adequate vitamin D stores (serum 25-hydroxyvitamin D concentration, more than 15 ng per milliliter). The definition of severe hypovitaminosis D was based on the lower limit of normal of 9 ng per milliliter (22 nmol per liter) for serum 25-hydroxyvitamin D concentrations in New England as measured by chromatography in the reference laboratory (Nichols Institute). The definition of moderate hypovitaminosis D was determined according to the Nichols Institute's norms for serum 25-hydroxyvitamin D of 16 to 74 ng per milliliter (40 to 185 nmol per liter) in a competitive protein-binding assay (mean ± 2 SD calculated from measurements in 208 normal adult subjects in Southern California, Virginia, and New England in the summer and early fall) and from published data demonstrating that serum parathyroid hormone concentrations are increased in patients who have serum 25-hydroxyvitamin D concentrations that are less than or equal to 15 ng per milliliter.^{11,17,18}

Statistical Analysis

There were no differences between the characteristics of the patients studied in March and those of the patients studied in September, and the results were therefore combined. Associations between categorical variables and categories of serum 25-hydroxyvitamin D concentrations were examined by using Pearson's chi-square tests. Kruskal-Wallis nonparametric analysis of variance was used to examine associations between continuous variables and categories of serum 25-hydroxyvitamin D concentrations. For multivariate analyses, vitamin D deficiency was defined as a serum 25-hydroxyvitamin D concentration less than or equal to 15 ng per milliliter. Associations with categorical variables were examined with the use of two-tailed Fisher's exact tests, and associations with continuous variables were examined with Mann-Whitney rank-sum tests.

Stepwise discriminant analyses were used to identify the variables that best predicted vitamin D deficiency and to calculate the accuracy of those predictors.¹⁹ The accuracy of the computed discriminant function was estimated by a jackknifed classification matrix.²⁰ Variables associated with serum 25-hydroxyvitamin D concentrations in univariate analyses ($P < 0.10$) were eligible for inclusion in the multivariate models.

RESULTS

Clinical Characteristics

The characteristics of the patients are shown in Table 1. Few patients had conditions often associated with hypovitaminosis D or were taking medications known to alter vitamin D metabolism (Table 2). Three patients with serum 25-hydroxyvitamin D concentrations of less than 8 ng per milliliter, two patients with concentrations between 8 and 15 ng per milliliter, and three patients with values greater than 15 ng per milliliter died while in the hospital.

Prevalence of Hypovitaminosis D

The prevalence of hypovitaminosis D in the 290 patients was 57 percent (164 patients) (Fig. 1). Sixty-five patients (22 percent) had severe hypovitaminosis D, and an additional 99 patients (34 percent) had moderate hypovitaminosis D. Sixty-three percent of the patients studied in March and 49 percent of those studied in September had serum 25-hydroxyvitamin D concentrations of 15 ng per milliliter or less. The mean (\pm SD) serum 25-hydroxy-

TABLE 1. BASE-LINE CLINICAL CHARACTERISTICS OF THE 290 PATIENTS.

CHARACTERISTIC	VALUE
Age — yr	
Mean (\pm SD)	62 \pm 19
Range	18–95
Sex — M/F	152/138
Race or ethnic group — no. (%)	
White	229 (79)
Hispanic	25 (9)
Black	24 (8)
Asian	7 (2)
Other	5 (2)
Residential and functional status — no. (%)	
Housebound	60 (21)
Nursing home resident	23 (8)
Ambulatory	271 (93)
Homeless	10 (3)
Multivitamin user — no. (%)*	54 (21)
Major medical problems — no. (%)†	
Coronary artery disease	104 (36)
Hypertension	103 (36)
Diabetes mellitus	63 (22)
Chronic obstructive pulmonary disease	54 (19)
Congestive heart failure	41 (14)
Anemia	39 (13)
Atrial fibrillation	32 (11)
Substance abuse	31 (11)
Pneumonia	31 (11)
Gastrointestinal bleeding	29 (10)

*Percentage is based on the number of patients for whom information was available.

†Some patients had two or more of these problems.

vitamin D concentration for all 290 patients was 15 ± 9 ng per milliliter. Serum parathyroid hormone concentrations rose steeply as serum 25-hydroxyvitamin D concentrations declined below 15 ng per milliliter (Fig. 2), indicating a physiologic response, presumably through hypocalcemia, to the low serum 25-hydroxyvitamin D concentrations.

Variables Associated with Hypovitaminosis D

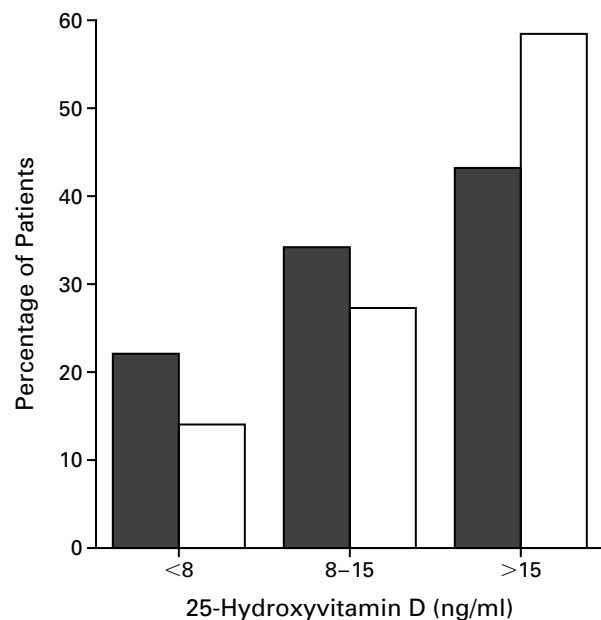
Anticonvulsant-drug therapy ($P=0.04$), renal dialysis ($P=0.007$), nephrotic syndrome ($P=0.04$), and winter season ($P=0.04$) were significantly associated with hypovitaminosis D. There were trends toward associations with housebound status ($P=0.07$) and female sex ($P=0.08$). Of the 60 housebound patients, 42 (70 percent) had serum 25-hydroxyvitamin D concentrations of 15 ng per milliliter or less. Of the 18 most frequently noted diagnoses (each affecting at least 20 patients), only hypertension ($P=0.009$) and diabetes mellitus ($P=0.04$) were significantly associated with hypovitaminosis D.

Lower vitamin D intake, exposure to ultraviolet light, and serum concentrations of ionized calcium and albumin, and higher serum concentrations of parathyroid hormone and alkaline phosphatase were associated with lower 25-hydroxyvitamin D concen-

TABLE 2. PREVALENCE OF CONDITIONS OFTEN ASSOCIATED WITH HYPOVITAMINOSIS D IN THE 290 PATIENTS.

DIAGNOSIS OR TREATMENT	VALUE
	no. (%)
Cirrhosis	10 (3)
Renal dysfunction*	24 (8)
Nephrotic syndrome	10 (3)
Gastric or bowel resection	7 (2)
Inflammatory bowel disease	3 (1)
Malabsorption	5 (2)
Rifampin therapy	1 (<1)
Glucocorticoid therapy	12 (4)
Anticonvulsant-drug therapy	9 (3)

*Renal dysfunction is defined as a serum creatinine concentration >2 mg per deciliter ($177 \mu\text{mol}$ per liter).

**Figure 1.** Prevalence of Hypovitaminosis D among 290 Medical Inpatients.

The percentages of patients with serum 25-hydroxyvitamin D concentrations of less than 8 ng per milliliter, 8 to 15 ng per milliliter, or greater than 15 ng per milliliter in the entire study population are shown by the solid bars, and the percentages among the subgroup of 77 patients with no known risk factors for hypovitaminosis D are shown by the open bars. To convert values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.50.

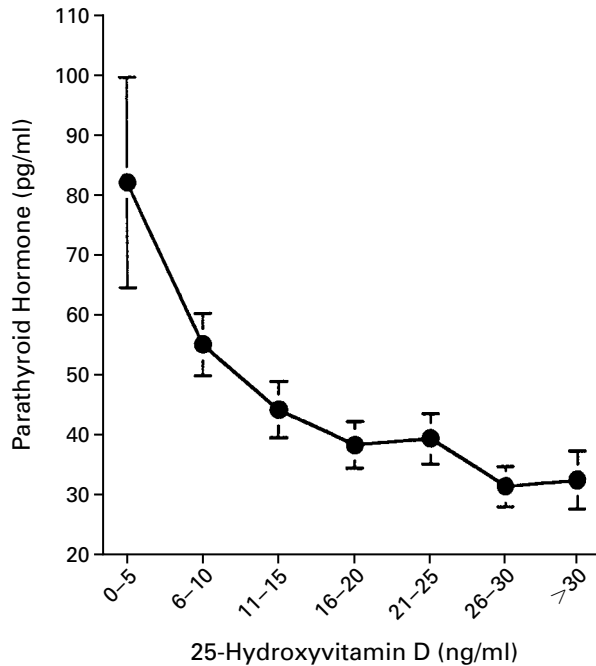


Figure 2. Relation between Serum 25-Hydroxyvitamin D Concentrations and Mean (\pm SE) Serum Concentrations of Parathyroid Hormone in the Study Patients.

The patients were categorized according to their serum 25-hydroxyvitamin D concentrations in increments of 5 ng per milliliter. The slope of the relation between serum 25-hydroxyvitamin D and parathyroid hormone concentrations was not significantly different ($P=0.13$) from zero for patients with serum 25-hydroxyvitamin D concentrations greater than 15 ng per milliliter. To convert values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.50. To convert values for parathyroid hormone to picomoles per liter, multiply by 0.11.

trations. There was no association between serum concentrations of vitamin D-binding protein and 25-hydroxyvitamin D (Table 3).

Vitamin D Intake and Sun Exposure

Serum 25-hydroxyvitamin D concentrations were higher in the patients with higher vitamin D intakes (Fig. 3). The mean (\pm SD) daily vitamin D intake reported was $7.5 \pm 7.3 \mu\text{g}$ (300 ± 292 IU). Sixty-seven percent of the patients reported vitamin D intakes less than the recommended daily amount for their age ($5 \mu\text{g}$ for adults 19 to 50 years old, $10 \mu\text{g}$ for adults 51 to 70 years old, and $15 \mu\text{g}$ for adults 71 or older²¹). Moderate or severe hypovitaminosis D was present in 66 percent of the patients reporting daily vitamin D intakes less than the recommended amount for their age and in 37 percent of the patients reporting daily vitamin D intakes in excess of the recommended amount for their age. Forty-six percent of the patients who reported taking multivitamins and 60 percent of those who reported not

TABLE 3. ASSOCIATION OF CONTINUOUS VARIABLES WITH VITAMIN D DEFICIENCY.

VARIABLE	SERUM 25-HYDROXYVITAMIN D CONCENTRATION*			P VALUE
	<8 ng/ml	8-15 ng/ml	>15 ng/ml	
Age (yr)	64 \pm 18	63 \pm 18	58 \pm 20	0.10
Vitamin D intake ($\mu\text{g}/\text{day}$)†	5.4 \pm 5.1	6.4 \pm 7.2	10.8 \pm 7.8	<0.001
Score for ultraviolet-light exposure‡	3.1 \pm 2.9	3.8 \pm 2.9	4.5 \pm 3.0	0.02
Serum ionized calcium (mmol/liter)	1.13 \pm 0.08	1.15 \pm 0.06	1.17 \pm 0.08	0.01
Serum inorganic phosphate (mg/dl)§	3.5 \pm 1.6	3.3 \pm 1.0	3.4 \pm 0.9	0.62
Serum albumin (g/dl)	3.1 \pm 0.8	3.3 \pm 0.7	3.5 \pm 0.6	<0.001
Serum alkaline phosphatase (U/liter)¶	159 \pm 125	145 \pm 132	111 \pm 158	<0.001
Serum parathyroid hormone (pg/ml)	66 \pm 69	48 \pm 43	36 \pm 25	<0.001
Serum vitamin D-binding protein (mg/liter)**	265 \pm 73	273 \pm 75	281 \pm 79	0.40

*Plus-minus values are means \pm SD. To convert values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.50.

†To convert values for vitamin D intake to international units, multiply by 40.

‡The scores for ultraviolet-light exposure ranged from 0 (little exposure) to 9 (substantial exposure).

§To convert values for inorganic phosphate to millimoles per liter, multiply by 0.32.

¶To convert values for alkaline phosphatase to microkatal per liter, multiply by 0.0167.

||To convert values for parathyroid hormone to picomoles per liter, multiply by 0.11.

**To convert values for vitamin D-binding protein to micromoles per liter, multiply by 0.017.

taking multivitamins had hypovitaminosis D. Increasing exposure to ultraviolet light was also associated with higher serum 25-hydroxyvitamin D concentrations (Fig. 3).

Predictors of Hypovitaminosis D

Independent predictors of hypovitaminosis D were identified by stepwise multivariate discriminant analysis in which risk factors for vitamin D deficiency that had a univariate association ($P<0.10$) with vitamin D deficiency were included in the model. These factors were inadequate vitamin D intake, insufficient sun exposure, winter season, older age, female sex, anticonvulsant-drug therapy, dialysis, nephrotic syndrome, and being housebound. Inadequate vitamin D intake, winter season, and being housebound were significant independent predictors of hypovitaminosis D and could correctly classify 59 percent of the patients ($P<0.001$). The addition of the other six variables to the model increased the accuracy of the classification to 68 percent.

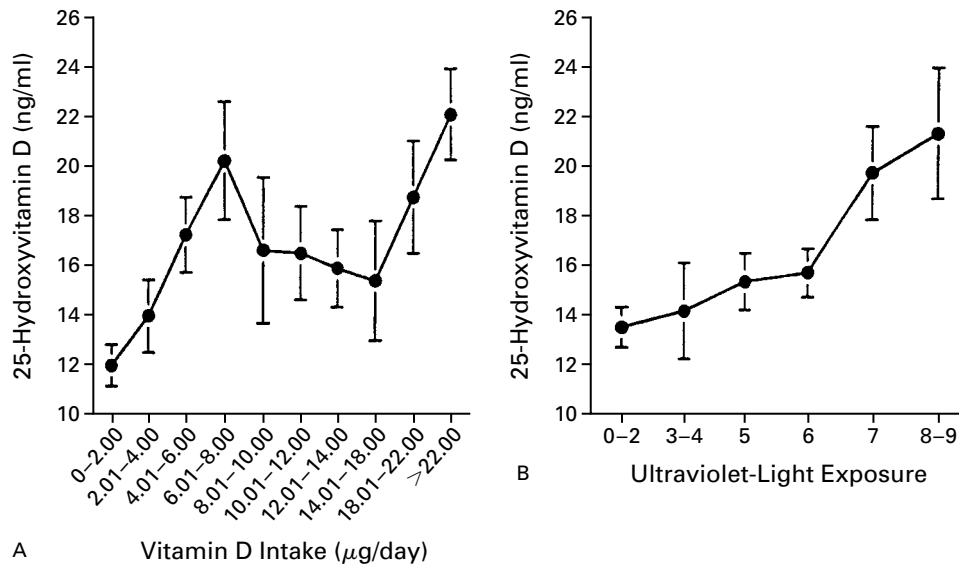


Figure 3. Relation between Daily Vitamin D Intake (Panel A) and Ultraviolet-Light Exposure (Panel B) and Mean (\pm SE) Serum 25-Hydroxyvitamin D Concentrations in the Study Patients.

The patients were categorized according to vitamin D intake or ultraviolet-light exposure. To convert values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.50. To convert values for vitamin D intake to international units, multiply by 40.

Prevalence of Hypovitaminosis D in the Patients with No Known Risk Factors

The mean age of the 77 patients in the subgroup with no known risk factors for vitamin D deficiency was 44 ± 14 years. Forty-eight (62 percent) were men and 29 (38 percent) were women. The most common diagnoses in this subgroup were coronary artery disease (39 percent), hypertension (29 percent), diabetes mellitus (17 percent), hypercholesterolemia (16 percent), substance abuse (16 percent), asthma (16 percent), atrial fibrillation (8 percent), and syncope (8 percent). Among these patients, 32 (42 percent) were vitamin D-deficient, of whom 11 had serum 25-hydroxyvitamin D concentrations of less than 8 ng per milliliter and 21 had values between 8 and 15 ng per milliliter (Fig. 1).

DISCUSSION

We found a high prevalence (57 percent) of hypovitaminosis D in unselected general medical inpatients. In previous studies of elderly housebound people and nursing home residents, one quarter to one half were vitamin D-deficient.⁸⁻¹¹ The patients we studied were younger than those in many previous studies, and only a minority were housebound or residents of a nursing home. Thus, our patients may have been more representative of the general population than those reported on previously.

It is unclear why the prevalence of vitamin D de-

ficiency was so high. Low levels of ultraviolet-light exposure and vitamin D intake are probably important factors. The definition of vitamin D deficiency may also affect estimates of its prevalence. We defined categories of severe and moderate hypovitaminosis D on the basis of a series of observations in the literature.^{11,17,18,22} Serum parathyroid hormone concentrations have been found to increase when serum 25-hydroxyvitamin D concentrations fall below 15 ng per milliliter in elderly housebound people,¹¹ and we found a similar relation in the patients we studied. In postmenopausal women, bone density is lower in those who have serum 25-hydroxyvitamin D concentrations of 15 ng per milliliter or less.²³ Thus, there is strong physiologic evidence that serum 25-hydroxyvitamin D concentrations of 15 ng per milliliter or less are insufficient to maintain adequate skeletal integrity.

In fact, other investigators have reported that serum 25-hydroxyvitamin D concentrations above 15 ng per milliliter may not be sufficient to exclude hypovitaminosis D. There are seasonal changes in both serum parathyroid hormone concentrations and bone density in patients with serum 25-hydroxyvitamin D concentrations of 37 ng per milliliter (92 nmol per liter) or less.^{24,25} Increasing patients' serum 25-hydroxyvitamin D concentrations to 20 ng per milliliter (50 nmol per liter) through supplementation with vitamin D increases serum 1,25-dihydroxyvita-

min D concentrations,²⁶ and some experts have suggested that serum 25-hydroxyvitamin D concentrations should exceed 30 ng per milliliter (75 nmol per liter). Had we used such a definition of vitamin D deficiency to categorize our patients, 93 percent of them would have been considered vitamin D-deficient.

Previous estimates of the prevalence of hypovitaminosis D in outpatients were substantially lower than in our study.^{9,27} The higher prevalence of vitamin D deficiency in this study may be related in part to the relatively low solar intensity in New England¹² or to the nature of our patients. Medical inpatients are more likely than outpatients to have conditions associated with vitamin D deficiency. However, 42 percent of our healthy subgroup were vitamin D-deficient, providing evidence that these results are not attributable to severity of illness.

A large number of patients with vitamin D intakes above the recommended daily amount were vitamin D-deficient. Because milk products contain variable amounts of vitamin D,²⁸ vitamin D intake may have been overestimated. Multivitamin therapy was not protective. This finding might reflect inaccurate self-reporting, because the majority of multivitamin supplements contain 10 μg of vitamin D. Our data support the conclusion that the current recommended daily intakes of vitamin D, which were recently revised upward,²¹ may be insufficient. For example, a daily intake of 5 μg of vitamin D was less effective in preventing bone loss than a daily intake of 20 μg in postmenopausal women.²⁹ Moreover, daily administration of 10 μg of vitamin D in patients with high dietary calcium intakes did not protect against fractures,³⁰ whereas 20 μg of vitamin D per day plus calcium decreased the risk of fractures in elderly women with lower dietary calcium intakes.^{6,7}

Our multivariate models could predict vitamin D deficiency with an accuracy of 59 to 68 percent, making them only slightly more accurate than predictions that would have occurred by chance. Because the assessment of common clinical risk factors failed to identify many patients with hypovitaminosis D, screening by using serum 25-hydroxyvitamin D concentrations may be required to identify patients with vitamin D deficiency.

The importance of vitamin D deficiency is related primarily to bone integrity. Because vitamin D is required for calcium homeostasis, secondary hyperparathyroidism may develop in patients with vitamin D deficiency. With increasing severity of hypovitaminosis D and secondary hyperparathyroidism, patients progress from states of increased bone turnover and decreased bone mass to states of impaired, and ultimately absent, mineralization with generalized osteomalacia.¹ Many patients with osteoporotic fractures have low serum 25-hydroxyvitamin D concentrations.^{4,5} Because treatment with vitamin D and

calcium increases bone mass and substantially reduces the risk of fractures,^{3,6,7,31} the diagnosis of vitamin D deficiency warrants attention. In addition to its effect on the skeleton, hypovitaminosis D may affect other organ systems adversely, resulting in muscle weakness and pain,² progression of osteoarthritis,³² or impaired macrophage activation.³³

Our study had several limitations. Many patients were acutely ill. Although it is possible that acute illness could have suppressed cutaneous vitamin D synthesis, the half-life of serum 25-hydroxyvitamin D is approximately three weeks,³⁴ so an arrest of synthesis should not have affected serum 25-hydroxyvitamin D concentrations rapidly. Substantial reductions in serum concentrations of vitamin D-binding protein are needed to lower serum 25-hydroxyvitamin D concentrations. Such reductions occur in only a few clinical conditions, such as severe hepatic failure, nephrotic syndrome, and severe malnutrition,^{2,35} which were rare in our patients. Furthermore, we found no relation between serum concentrations of 25-hydroxyvitamin D and those of vitamin D-binding protein in our patients. Thus, it seems unlikely that changes in concentrations of serum vitamin D-binding protein due to acute illness can explain our findings. Finally, the higher serum parathyroid hormone concentrations in the patients with low serum 25-hydroxyvitamin D concentrations attest to the physiologic importance of the latter. In fact, we may have underestimated the prevalence of hypovitaminosis D by not identifying patients with low serum 1,25-dihydroxyvitamin D concentrations despite adequate serum 25-hydroxyvitamin D concentrations.

In conclusion, we found a high prevalence of hypovitaminosis D in unselected medical inpatients in the United States. Standard clinical risk factors were poor predictors of vitamin D deficiency. Maintaining vitamin D intake at the level of the current recommended daily amount or using multivitamins may not be sufficient to ensure adequate vitamin D stores. Because of the potential adverse effects of vitamin D deficiency on the skeleton and other organ systems, widespread screening for vitamin D deficiency or routine vitamin D supplementation should be considered.

Supported by grants from the National Institutes of Health (RR-1066, R29-DK43341, DK07028, and DK02476) and the American Kidney Fund.

We are indebted to the nursing staff of the Mallinckrodt General Clinical Research Center at Massachusetts General Hospital for processing patient samples; to the resident physicians and staff of the Bigelow medical services for facilitating patient participation; to Deborah Lentz, R.D., Ellen Anderson, R.D., and Jane Hubbard, R.D., for conducting dietary analyses; to Dr. Gino Segre of the endocrine laboratory for assisting with measurements of serum parathyroid hormone and 25-hydroxyvitamin D; to Dr. Roger Bouillon for providing vitamin D-binding protein antiserum; to Dr. John T.

Potts, Jr., for encouraging and supporting research by house staff; and to Dr. Robert Neer for providing scholarly advice.

REFERENCES

1. Parfitt AM. Osteomalacia and related disorders. In: Avioli LV, Krane SM, eds. *Metabolic bone disease*. 3rd ed. San Diego, Calif.: Academic Press, 1998:327-86.
2. Gloth FM III, Tobin JD. Vitamin D deficiency in older people. *J Am Geriatr Soc* 1995;43:822-8.
3. Meunier PJ. Prevention of hip fractures. *Am J Med* 1993;95:Suppl 5A:5A-75S-5A-78S.
4. Boonen S, Aerssens J, Dequeker J. Age-related endocrine deficiencies and fractures of the proximal femur. II. Implications of vitamin D deficiency in the elderly. *J Endocrinol* 1996;149:13-7.
5. Baker MR, McDonnell H, Peacock M, Nordin BEC. Plasma 25-hydroxy vitamin D concentrations in patients with fractures of the femoral neck. *BMJ* 1979;1:589.
6. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D₃ and calcium to prevent hip fractures in elderly women. *N Engl J Med* 1992;327:1637-42.
7. Chapuy MC, Arlot ME, Delmas PD, Meunier PJ. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *BMJ* 1994;308:1081-2.
8. Omdahl JL, Garry PJ, Hunsaker LA, Hunt WC, Goodwin JS. Nutritional status in a healthy elderly population: vitamin D. *Am J Clin Nutr* 1982;36:1225-33.
9. McKenna MJ. Differences in vitamin D status between countries in young adults and the elderly. *Am J Med* 1992;93:69-77.
10. Goldray D, Mizrahi-Sasson E, Merdler C, et al. Vitamin D deficiency in elderly patients in a general hospital. *J Am Geriatr Soc* 1989;37:589-92.
11. Gloth FM, Gundberg CM, Hollis BW, Haddad JG Jr, Tobin JD. Vitamin D deficiency in homebound elderly persons. *JAMA* 1995;274:1683-6.
12. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D₃: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D₃ synthesis in human skin. *J Clin Endocrinol Metab* 1988;67:373-8.
13. Vitamin D (IU). In: Pennington JAT. *Bowes & Church's food values of portions commonly used*. 16th ed. rev. Philadelphia: J.B. Lippincott, 1994:411-4.
14. Salamone LM, Dallal GE, Zantos D, Makrauer F, Dawson-Hughes B. Contributions of vitamin D intake and seasonal sunlight exposure to plasma 25-hydroxyvitamin D concentration in elderly women. *Am J Clin Nutr* 1993;58:80-6.
15. Nussbaum SR, Zahradnik RJ, Lavigne JR, et al. Highly sensitive two-site immunoradiometric assay of parathyrin, and its clinical utility in evaluating patients with hypercalcemia. *Clin Chem* 1987;33:1364-7.
16. Wilson SG, Retallack RW, Kent JC, Worth GK, Gutteridge DH. Serum free 1,25-dihydroxyvitamin D and the free 1,25-dihydroxyvitamin D index during a longitudinal study of human pregnancy and lactation. *Clin Endocrinol (Oxf)* 1990;32:613-22.
17. Webb AR, Pilbeam C, Hanafin N, Holick MF. An evaluation of the relative contributions of exposure to sunlight and of diet to the circulating concentrations of 25-hydroxyvitamin D in an elderly nursing home population in Boston. *Am J Clin Nutr* 1990;51:1075-81.
18. Lips P, Wiersinga A, van Ginkel FC, et al. The effect of vitamin D supplementation on vitamin D status and parathyroid function in elderly subjects. *J Clin Endocrinol Metab* 1988;67:644-50.
19. Afifi AA, Clark V. *Computer-aided multivariate analysis*. Belmont, Calif.: Lifetime Learning, 1984.
20. Lachenbruch P, Mickey RU. Estimation of error rates in discriminant analysis. *Technometrics* 1968;10:1-11.
21. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Institute of Medicine. *Dietary reference intakes: calcium, phosphorus, magnesium, vitamin D, and fluoride*. Washington, D.C.: National Academy Press, 1997.
22. Bouillon RA, Auwerx JH, Lissens WD, Pelemans WK. Vitamin D status in the elderly: seasonal substrate deficiency causes 1,25-dihydroxycholecalciferol deficiency. *Am J Clin Nutr* 1987;45:755-63.
23. Villareal DT, Civitelli R, Chines A, Avioli LV. Subclinical vitamin D deficiency in postmenopausal women with low vertebral bone mass. *J Clin Endocrinol Metab* 1991;72:628-34.
24. Krall EA, Sahyoun N, Tannenbaum S, Dallal GE, Dawson-Hughes B. Effect of vitamin D intake on seasonal variations in parathyroid hormone secretion in postmenopausal women. *N Engl J Med* 1989;321:1777-83.
25. Dawson-Hughes B, Dallal GE, Krall EA, Harris S, Sokoll LJ, Falconer G. Effect of vitamin D supplementation on wintertime and overall bone loss in healthy postmenopausal women. *Ann Intern Med* 1991;115:505-12.
26. Peacock M, Selby PL, Francis RM, Brown WB, Hordon L. Vitamin D deficiency, insufficiency, sufficiency, and intoxication: what do they mean? In: Norman AW, Schaefer K, Grigoleit H-G, von Herrath D, eds. *Vitamin D: chemical, biochemical, and clinical update: sixth workshop on vitamin D*. New York: Walter de Gruyter, 1985:569-70.
27. Sherman SS, Hollis BW, Tobin JD. Vitamin D status and related parameters in a healthy population: the effects of age, sex, and season. *J Clin Endocrinol Metab* 1990;71:405-13.
28. Holick MF, Shao Q, Liu WW, Chen TC. The vitamin D content of fortified milk and infant formula. *N Engl J Med* 1992;326:1178-81.
29. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE, Falconer G, Green CL. Rates of bone loss in postmenopausal women randomly assigned to one of two dosages of vitamin D. *Am J Clin Nutr* 1995;61:1140-5.
30. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial. *Ann Intern Med* 1996;124:400-6.
31. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med* 1997;337:670-6.
32. McAlindon TE, Felson DT, Zhang Y, et al. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. *Ann Intern Med* 1996;125:353-9.
33. Gavison R, Bar-Shavit Z. Impaired macrophage activation in vitamin D₃ deficiency: differential in vitro effects of 1,25-dihydroxyvitamin D₃ on mouse peritoneal macrophage functions. *J Immunol* 1989;143:3686-90.
34. Holick MF. The use and interpretation of assays for vitamin D and its metabolites. *J Nutr* 1990;120:Suppl:1464-9.
35. Cooke NE, Haddad JG. Vitamin D binding protein (Gc-globulin). *Endocr Rev* 1989;10:294-307.