

Prevalence of Severe Hypovitaminosis D in Patients With Persistent, Nonspecific Musculoskeletal Pain

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• **Objective:** To determine the prevalence of hypovitaminosis D in primary care outpatients with persistent, nonspecific musculoskeletal pain syndromes refractory to standard therapies.

• **Patients and Methods:** In this cross-sectional study, 150 patients presented consecutively between February 2000 and June 2002 with persistent, nonspecific musculoskeletal pain to the Community University Health Care Center, a university-affiliated inner city primary care clinic in Minneapolis, Minn (45° north). Immigrant (n=83) and nonimmigrant (n=67) persons of both sexes, aged 10 to 65 years, from 6 broad ethnic groups were screened for vitamin D status. Serum 25-hydroxyvitamin D levels were determined by radioimmunoassay.

• **Results:** Of the African American, East African, Hispanic, and American Indian patients, 100% had deficient levels of vitamin D (≤ 20 ng/mL). Of all patients, 93% (140/150) had deficient levels of vitamin D (mean, 12.08 ng/mL; 95% confidence interval, 11.18-12.99 ng/mL). Nonimmigrants had vitamin D levels as deficient as immigrants ($P=.48$). Levels of vitamin D in men were as deficient as in women ($P=.42$). Of all patients, 28% (42/150) had severely deficient vitamin D levels (≤ 8 ng/mL), including 55% of

whom were younger than 30 years. Five patients, 4 of whom were aged 35 years or younger, had vitamin D serum levels below the level of detection. The severity of deficiency was disproportionate by age for young women ($P<.001$), by sex for East African patients ($P<.001$), and by race for African American patients ($P=.006$). Season was not a significant factor in determining vitamin D serum levels ($P=.06$).

• **Conclusion:** All patients with persistent, nonspecific musculoskeletal pain are at high risk for the consequences of unrecognized and untreated severe hypovitaminosis D. This risk extends to those considered at low risk for vitamin D deficiency: nonelderly, nonhousebound, or nonimmigrant persons of either sex. Nonimmigrant women of childbearing age with such pain appear to be at greatest risk for misdiagnosis or delayed diagnosis. Because osteomalacia is a known cause of persistent, nonspecific musculoskeletal pain, screening all outpatients with such pain for hypovitaminosis D should be standard practice in clinical care.

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ANOVA = analysis of variance; CI = confidence interval; PTH = parathyroid hormone

Prevalence surveys suggest that 9% to 20% of adults in the United States experience chronic pain.¹⁻⁴ Of these, 89% have some degree of long-term or short-term disability,⁵ and nearly all have substantially reduced health-related quality of life.⁶ Direct and indirect costs related to their chronic pain are estimated at \$50 billion annually.⁷

Of the many types of chronic pain, nonspecific or idiopathic musculoskeletal pain, such as noninflammatory arthritis, nonarticular rheumatism, and nonradicular low back pain, is seen frequently in medical and chiropractic clinics. Despite the prevalence, severity, and burdens of such pain, precise diagnosis and effective treatment are often elusive.

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Chronic nonspecific musculoskeletal pain is one consequence of hypovitaminosis D. For the past 30 years, published reports from Europe have documented persistent, nonspecific musculoskeletal pain in immigrant patients secondary to severe hypovitaminosis D.⁸⁻¹⁹ This study extends the European studies to include patients in the United States presumed to be vitamin D-sufficient, namely young ambulatory outpatients.^{20,21}

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PATIENTS AND METHODS

Study Population

Six broad categories of ethnic groups were divided into immigrant and nonimmigrant populations. The immigrant ethnic groups considered in this study are East African (primarily Somalian), Hispanic (primarily Mexican), and Southeast Asian (primarily Hmong, Cambodian, or Laotian). The Southeast Asian patients began translocating to Minnesota in 1975, most of whom arrived from refugee camps. The East African and Hispanic patients began arriving in Minnesota in 1995. The nonimmigrant ethnic groups

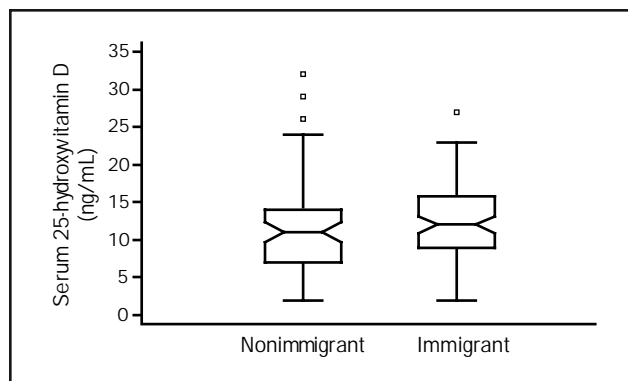


Figure 1. Mean serum 25-hydroxyvitamin D levels in nonimmigrant and immigrant patients. Notched box-and-whisker plot shows no difference in hypovitaminosis D between the 67 nonimmigrant and 83 immigrant patients. The central boxes represent values from the lower to upper quartile (25th to 75th percentiles). The middle line represents the median. The notches surrounding the medians represent confidence intervals (CIs) for the medians. The overlapping notches reveal that the medians are not significantly different at a 95% CI. The difference between the samples' mean serum 25-hydroxyvitamin D levels was 0.65 ng/mL (95% CI, -1.17 to 2.48 ng/mL; $P=.48$). The vertical line extends from the minimum to maximum values and shows the presence of outliers in both groups of patients. These were not excluded from analysis.

in this study are African American (Sub-Saharan Central and West African), white (Scandinavian and Northern European), and American Indian (Lakotan, Dakotan, and Ojibwe). Age categorizations were decadal, ie, 10 to 59 years, and 60 to 65 years.

In our cross-sectional study, 150 patients presented consecutively between February 2000 and June 2002 to the Community University Health Care Center in Minneapolis, Minn, with persistent, nonspecific musculoskeletal pain. None of the patients had fibromyalgia (as strictly defined by American College of Rheumatology criteria), temporomandibular disorder, or complex regional pain syndrome. The patients had no known medical condition that would decrease production, absorption, or hydroxylation of vitamin D, and they had no known condition associated with decreased action or increased clearance of 1,25-dihydroxyvitamin D. Two patients were seropositive for hepatitis C with normal serum transaminases; 2 had a history of prednisone use; and 2 were using inhaled corticosteroids. All patients had used maximum-dose over-the-counter and/or prescription analgesic agents with minimal improvement. Less than 10% were taking a vitamin supplement at the time of the study, and more than 90% had been medically evaluated for their persistent musculoskeletal pain 1 year or more before screening. None had been tested previously for hypovitaminosis D.

Methods

Serum 25-hydroxyvitamin D levels were obtained by radioimmunoassay (DiaSorin, Stillwater, Minn) in 83 immigrant and 67 nonimmigrant patients aged 10 to 65 years who presented consecutively between February 2000 and June 2002 with at least 2 months of nonspecific, persistent musculoskeletal pain refractory to standard interventions. Deficient 25-hydroxyvitamin D levels were grouped as follows: 4 ng/mL or less = profound deficiency; 5 to 8 ng/mL = severe deficiency; 9 to 12 ng/mL = moderately severe deficiency; 13 to 16 ng/mL = moderate deficiency; and 17 to 20 ng/mL = marginal deficiency. The definition of severe 25-hydroxyvitamin D deficiency (≤ 8 ng/mL or ≤ 20 nmol/L) is in accordance with that used in international studies.^{19,22,23} Levels below detection by radioimmunoassay (<3 ng/mL) were considered equal to 2 ng/mL for analysis.

Results were evaluated for statistical significance with Student *t* tests and analysis of variance (ANOVA) tests. All *t* tests were 2-sided, and $P<.05$ was considered significant. Univariate statistical analysis was performed using MedCalc 7.0.1 software (MedCalc, Mariakerke, Belgium). Multivariate tests were performed using SAS 6.0 software (SAS, Cary, NC). *P* values were adjusted using the Bonferroni procedure. Seasons were defined by the solar calendar. Normal childbearing age was defined as age 36 years or younger. The calculated coefficient of variation (interassay and intra-assay) was 10%.

RESULTS

The prevalence of hypovitaminosis D was unexpectedly high in this population of nonelderly, nonhousebound, primary care outpatients with persistent, nonspecific musculoskeletal pain refractory to standard pharmaceutical agents. Of all patients, 93% (140/150) had deficient levels of vitamin D (mean, 12.08 ng/mL; 95% confidence interval [CI], 11.18-12.99 ng/mL). Among the immigrant populations in this study, 100% of the East African ($n=34$), 100% of the Hispanic ($n=5$), and 89% (39/44) of the Southeast Asian immigrants with such pain had serum 25-hydroxyvitamin D levels of 20 ng/mL or less (mean, 12.37 ng/mL; 95% CI, 11.29-13.46 ng/mL). Unexpectedly, 100% of African American ($n=22$), 100% of American Indian ($n=10$), and 83% (29/35) of white patients with persistent pain also had hypovitaminosis D (mean, 11.7 ng/mL; 95% CI, 10.17-13.27 ng/mL). These mean values were not significantly different ($P=.48$) (Figure 1).

For patients with such musculoskeletal pain, vitamin D deficiency was not restricted to southern-to-northern latitude immigrant populations. African American and American Indian populations had a higher percentage of patients with profound or severe vitamin D deficiency (47%, 15/32)

Table 1. Ethnicity and Hypovitaminosis D*

Ethnicity	No. of patients	Mean ± SD 25-hydroxyvitamin D level (ng/mL)	Low deficiency (≤20 ng/mL) (%)	Severely low deficiency (≤8 ng/mL) (%)
African American	22	9.1±4.5	100	50
White	35	13.9±7.2	82	24
American Indian	10	9.9±4.1	100	40
East African	34	11.8±4.2	100	29
Hispanic	5	11.0±5.8	100	40
Southeast Asian	44	12.9±5.4	88	16

*Mean 25-hydroxyvitamin D levels among nonimmigrant (African American, white, and American Indian) and immigrant (East African, Hispanic, and Southeast Asian) patients. Nonimmigrant patients with persistent, nonspecific pain had 25-hydroxyvitamin D levels as deficient as immigrant patients (P=.48).

than either Southeast Asian patients (16%, 7/44) or East African patients (29%, 10/34). Although nonimmigrant patients accounted for 45% of the 150 patients, they represented 62.5% (5/8) of the patients with profound vitamin D deficiency (≤4 ng/mL) and 56% (19/34) of the patients with severe vitamin D deficiency (5-8 ng/mL) (Table 1).

Five patients with persistent pain had undetectable serum 25-hydroxyvitamin D levels by radioimmunoassay (<3 ng/mL). Osteomalacia had not been considered in their differential diagnosis until late in the course of their treatment, despite at least 6 months of considerable contact as inpatients and outpatients with the health care system. Of the 5 patients with undetectable serum 25-hydroxyvitamin D levels, 3 were nonimmigrants (Table 2).

The degree of severity of vitamin D deficiency was inversely disproportionate by age groups. Although 100% of the patients younger than 30 years and older than 60 years had deficient levels of vitamin D, the younger patients had significantly lower serum 25-hydroxyvitamin D

levels (Table 3). Among patients younger than 30 years, the mean serum 25-hydroxyvitamin D level was 9.18 ng/mL (95% CI, 7.53-10.85 ng/mL; n=33); among patients 50 years of age or older, the mean vitamin D level was 13.3 ng/mL (95% CI, 11.93-14.71 ng/mL; n=50; P<.001) (Figure 2). Of the 5 patients with undetectable serum 25-hydroxyvitamin D levels, 4 were 35 years of age or younger. For women of childbearing age, the mean 25-hydroxyvitamin D level was 9.56 ng/mL (95% CI, 7.80-11.33 ng/mL; n=39), significantly lower than the mean for perimenopausal and postmenopausal women at 14.09 ng/mL (95% CI, 12.29-15.88 ng/mL; n=35; P<.001) (Figure 3). By multivariate ANOVA, age was a significant factor in serum 25-hydroxyvitamin D levels (P=.02).

Only 29% (44/150) of the patients were male, but both sexes had equally deficient vitamin D levels. The mean vitamin D level for men (11.72 ng/mL; 95% CI, 10.41-13.03 ng/mL) was similar to that for women (12.22 ng/mL; 95% CI, 11.06-13.39 ng/mL; P=.62) (Figure 4). Multi-

Table 2. Patients With Undetectable 25-Hydroxyvitamin D*

Age (y)/sex	Ethnicity	Symptoms	Diagnoses	Medications
23/F	White	Nonradicular low back pain, weakness, fatigue	Dysthymia, nondegenerative joint disease, low back pain	OTC and Rx NSAIDs
26/M	Southeast Asian	Diffuse musculoskeletal pain, fatigue, insomnia	Dysthymia, stress reaction	OTC and Rx NSAIDs, TCA
27/F	African American	Severe nonradicular low back pain, fatigue, depressed mood, insomnia, weakness	Pregnancy 3rd trimester, gestational diabetes mellitus	OTC NSAID, prenatal vitamins, insulin
35/F	East African	Diffuse musculoskeletal pain, fatigue, insomnia, headache, weakness	Major depressive disorder, posttraumatic stress disorder	OTC NSAID, SSRI, neuroleptic agent
58/M	African American	Severe nonradicular low back pain, intermittent chest pain, depressed mood, insomnia, weakness	Dysthymia/major depressive disorder, degenerative joint disease refractory to surgery, angina refractory to percutaneous transthoracic cardiac angioplasty, somatoform disorder?	Rx NSAID, intermittent narcotic agents, SSRI, TCA, cardiovascular agents

*Each of 5 patients who had undetectable serum 25-hydroxyvitamin D levels by radioimmunoassay had frequent and resource-intense encounters with the medical system (for months to years) before the diagnosis of osteomalacia was considered. NSAID = nonsteroidal anti-inflammatory drug; OTC = over-the-counter; Rx = prescription agent; SSRI = prescription selective serotonin reuptake inhibitor antidepressant; TCA = tricyclic antidepressant agent.

Table 3. Age and Hypovitaminosis D*

Age (y)	No. of patients	Mean \pm SD 25-hydroxyvitamin D level (ng/mL)	Low deficiency (≤ 20 ng/mL) (%)	Severely low deficiency (≤ 8 ng/mL) (%)
10-19	6	8.3 \pm 5.5	100	66
20-29	27	9.4 \pm 4.5	100	52
30-39	38	12.3 \pm 5.6	86	29
40-49	29	12.9 \pm 6.8	89	28
50-59	39	13.4 \pm 5.2	89	10
60-65	11	13.0 \pm 3.6	100	9

*Mean 25-hydroxyvitamin D levels as calculated among patients in specific age groupings. The lowest mean 25-hydroxyvitamin D levels were found among the youngest patients, aged 10-29 years.

variate analysis revealed that sex was not a significant factor in determining serum 25-hydroxyvitamin D levels ($P=.16$). Also, there was a significant difference between the mean serum 25-hydroxyvitamin D levels of East African men (17.8 ng/mL; 95% CI, 16.03-19.64 ng/mL; $n=6$) and burqa-wearing (covered) East African women (mean, 10.5 ng/mL; 95% CI, 9.22-11.85 ng/mL; $n=28$; $P<.001$) (Figure 5).

African American status was associated with significantly worse vitamin D deficiency. African American patients had significantly lower mean values (9.1 ng/mL; 95% CI, 7.10-11.08 ng/mL; $n=22$) than either the white patients (13.9 ng/mL; 95% CI, 11.42-16.34 ng/mL; $n=35$; $P=.007$) or the East African patients (11.82 ng/mL; 95% CI, 10.35-13.30 ng/mL; $n=34$; $P=.02$) (Figure 6). Of the 5 patients with undetectable serum 25-hydroxyvitamin D levels, 2 were African American.

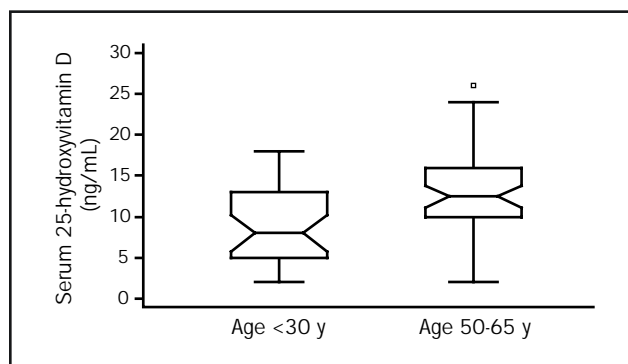


Figure 2. Mean serum 25-hydroxyvitamin D levels in patients younger than 30 years or 50 to 65 years of age. Notched box-and-whisker plot shows a significant difference in the severity of hypovitaminosis D between the 33 patients younger than 30 years and the 50 patients aged 50 to 65 years. The difference between the sample mean serum 25-hydroxyvitamin D level in younger and older patients was 4.14 ng/mL, with a 95% confidence interval of 2.00 to 6.27 ng/mL; $P<.001$.

By multivariate ANOVA, race was significant at $P=.02$. However, the interaction of race and sex had a more significant effect on 25-hydroxyvitamin D levels ($P<.001$). For example, 25-hydroxyvitamin D levels were lower in African American men than in East African men (adjusted P value, .048) and lower in African American women than in white women (adjusted P value, .03).

The percentage of patients found to have deficient levels of vitamin D ranged by season, from a low of 86% (summer) to a high of 96% (winter). More patients presented with chronic persistent musculoskeletal pain in winter ($n=47$) than summer ($n=30$). The mean winter 25-hydroxyvitamin D level was equivalent to a moderately severe deficiency at 10.49 ng/mL (95% CI, 8.91-12.07 ng/mL). The summer mean was statistically better at 14.03 ng/mL (95% CI, 11.77-16.30 ng/mL; $P=.009$). However, this improved level was still the equivalent of a moderate vitamin D deficiency (Figure 7). By multivariate ANOVA, season was not a significant factor in serum 25-hydroxyvitamin D levels ($P=.06$).

DISCUSSION

Severe hypovitaminosis D is not asymptomatic. Before the clinical presentation of osteomalacia bone pain, severe hypovitaminosis D results in a syndrome of persistent, nonspecific musculoskeletal pain, which has been well documented in European immigrants⁸⁻¹⁹ and recently in residents of Saudi Arabia.²⁴ In all such studies, women have been particularly at risk.

This study shows that in the United States, the risk of severe hypovitaminosis D extends beyond traditional risk categories to include nonelderly, nonhousebound, and non-immigrant persons of either sex. All outpatients with persistent, nonspecific musculoskeletal pain appear to be at risk. More than 90% of the patients in this study with persistent, nonspecific musculoskeletal pain were found to have deficient levels of 25-hydroxyvitamin D. Mean values were in the moderately severe to moderately deficient

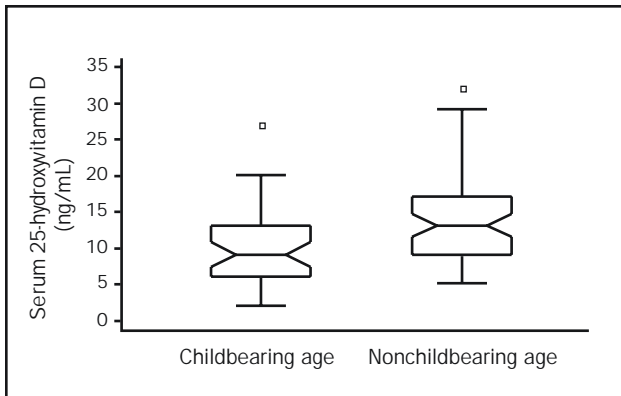


Figure 3. Mean serum 25-hydroxyvitamin D levels in women of childbearing vs nonchildbearing ages. Notched box-and-whisker plot shows a significant difference in the severity of hypovitaminosis D between the 39 women of childbearing age (≤ 36 years) and the 35 women aged 50 years or older. The difference between the sample means was 4.53 ng/mL with a 95% confidence interval of 1.78 to 6.64 ng/mL; $P < .001$.

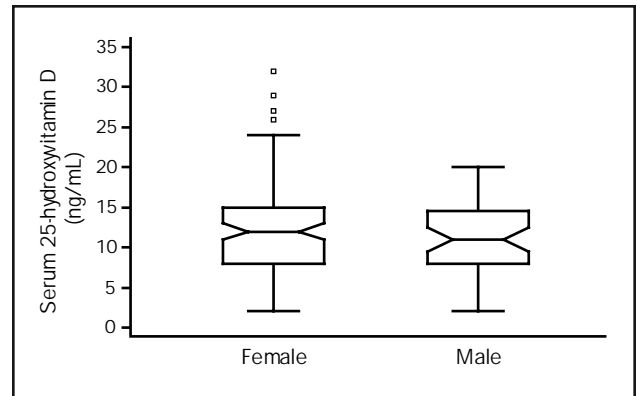


Figure 4. Mean serum 25-hydroxyvitamin D levels by sex. Notched box-and-whisker plot shows no significant differences in the degree of vitamin D insufficiency between the 107 female and the 43 male patients. The difference between the sample mean serum 25-hydroxyvitamin D levels in female and male patients was 0.51 ng/mL with a 95% confidence interval of -2.51 to 1.50 ng/mL; $P = .62$.

range. This was true regardless of immigrant status, sex, race, or season.

This study also showed an unexpected disparity in hypovitaminosis D severity: younger patients had significantly lower 25-hydroxyvitamin D levels than did older patients. As age increased, so did serum 25-hydroxyvitamin D levels. As a group, women of childbearing age had moderately severe vitamin D deficiency. Indeed, nearly half the women of childbearing age had severely or profoundly deficient 25-hydroxyvitamin D levels.

Furthermore, this study documented the discovery of 5 outpatients with immeasurable serum vitamin D levels by radioimmunoassay. Of these patients, 4 were aged 35 years or younger. For each of these patients, osteomalacia had not been suspected despite extensive contact with the health care system.

Unrecognized Risk

The levels of deficiency in women of childbearing age are consistent with increased risk for bearing children with adverse fetal effects²⁵⁻²⁷ or for severe neonatal illnesses.²⁸⁻³¹ The young adults in this study were found to be at high risk for failure to develop optimal peak bone mass.³² The older adults were found to be at high risk for excessive loss of skeletal integrity and osteoporotic fractures.³³⁻³⁵ All patients were at risk for misdiagnosis and suboptimal treatment of their pain condition.³⁶⁻⁴⁰

Delayed diagnosis of hypovitaminosis D may be due to its presumed rarity in the United States. Fortified milk is the most readily available dietary source, but there may be both cultural⁴¹ and physiological⁴² barriers to its consump-

tion. The per capita milk consumption by US teenagers in 2001 provided less than 25% of the recommended daily intake of vitamin D.⁴³

Even oral supplementation with vitamin D tablets may be inadequate at currently recommended doses.⁴⁴⁻⁴⁶ Up to 46% of persons found to be vitamin D-deficient have met the recommended daily intake.⁴⁷⁻⁴⁹ Also, oral supplements

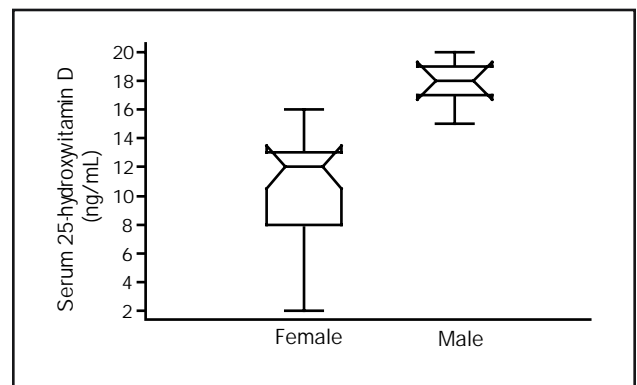


Figure 5. Mean serum 25-hydroxyvitamin D levels in East African female and male immigrant patients. Notched box-and-whisker plot shows a profound difference in the degree of vitamin D deficiency between the 28 East African female and 6 male patients with persistent nonspecific musculoskeletal pain. Every female patient adhered to traditional dress standards, which require covering exposed skin. The notched central boxes, representing the values from the lower to upper quartile, the medians, and the confidence levels for the medians, do not overlap. The difference between the sample mean serum 25-hydroxyvitamin D levels in female and male patients was 7.30 ng/mL with a 95% confidence interval from 4.38 to 10.21 ng/mL; $P < .001$.

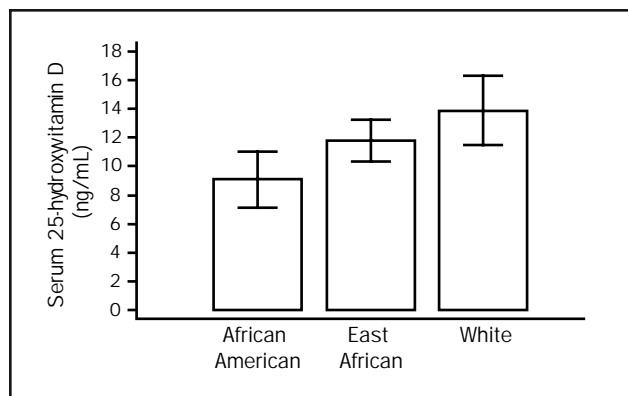


Figure 6. Mean serum 25-hydroxyvitamin D levels in African American, East African, and white patients; 95% confidence intervals (CIs) displayed for the mean serum 25-hydroxyvitamin D levels in the 22 African American, 34 East African, and 35 white patients. African American patients showed significantly lower mean serum levels than the other ethnic groups. The difference between the sample mean serum 25-hydroxyvitamin D levels in African American and East African patients was 2.73 ng/mL with a 95% CI of 0.36 to 5.10 ng/mL ($P=.02$). The difference between the sample mean serum 25-hydroxyvitamin D levels in African American and white patients was 4.80 ng/mL with a 95% CI of 1.37 to 8.22 ng/mL ($P=.007$). There was no significant difference between mean serum 25-hydroxyvitamin D levels for East African immigrant patients and white nonimmigrant patients, 2.06 ng/mL (95% CI, -0.77 to 4.90 ng/mL; $P=.15$).

may not provide sufficient compensation for patients with existing hypovitaminosis D.^{50,51}

Sun exposure may be required to prevent hypovitaminosis D.^{46,52,53} East African women, who adhere to traditional dress codes that require covering the head, arms, and legs, had profoundly lower levels of serum 25-hydroxyvitamin D than their uncovered male counterparts. For nonimmigrant residents at the same northern latitude, there was a significant difference in mean levels of serum 25-hydroxyvitamin D based on skin pigmentation. Persons with darker skin require increased ultraviolet B exposure for equal production of vitamin D compared with persons with lighter skin. However, current sun exposure guidelines do not emphasize the importance of clothing⁵⁴ and race⁵⁵ in limiting vitamin D production, nor do they acknowledge factors such as age,⁵⁶ season,⁵⁷ geographic latitude,⁵⁷ sunscreen used,⁵⁸ obesity,⁵⁹ smoking status,⁶⁰ and air pollution severity.⁶¹

Study Limitations

Serum 25-hydroxyvitamin D is the universally accepted measure of vitamin D status.⁶² However, there is no universal consensus about what constitutes vitamin D deficiency. The definition used here follows a peer-reviewed reference that is biological-based rather than population-based. Physiologi-

cal deficiency is defined by the 25-hydroxyvitamin D concentration below which parathyroid hormone (PTH) serum levels increase in a population.⁶³ The justification is that even slight increases in serum PTH levels result in increased bone turnover and accelerated bone loss.^{64,65} Two studies of more than 7700 patients using the same DiaSorin radioimmunoassay as was used in this study showed increased levels of serum intact PTH with 25-hydroxyvitamin D levels of 20 ng/mL (50 nmol/L) or less.^{66,67} Even at this level, calcium absorption is 35% lower than in levels averaging 34.6 ng/mL.⁶⁸

This study did not recruit age, sex, and ethnically matched patients for comparison purposes. The findings may simply reflect the background prevalence of hypovitaminosis D. The presence of nearly universal hypovitaminosis D in Minnesota (45° north) cannot be ruled out. However, the overall prevalence of hypovitaminosis D in this study (92.7%) is more than 40% higher than that found in 50 women with 2 defined pain conditions with risk factors for hypovitaminosis D: systemic lupus erythematosus and fibromyalgia.⁶⁹ For these patients, living at a similar latitude (London, Ontario, 42° north), the winter mean \pm SD serum 25-hydroxyvitamin D levels of 18.6 \pm 8.0 ng/mL (systemic lupus erythematosus) and 20.6 \pm 8.0 ng/mL (fibromyalgia) were significantly higher than the winter mean \pm SD serum 25-hydroxyvitamin D level of 10.5 \pm 5.4 ng/mL for the patients in this study with nonspecific musculoskeletal pain.

Furthermore, in the Framingham Heart Study, conducted at 42° north, the year-round mean \pm SD 25-

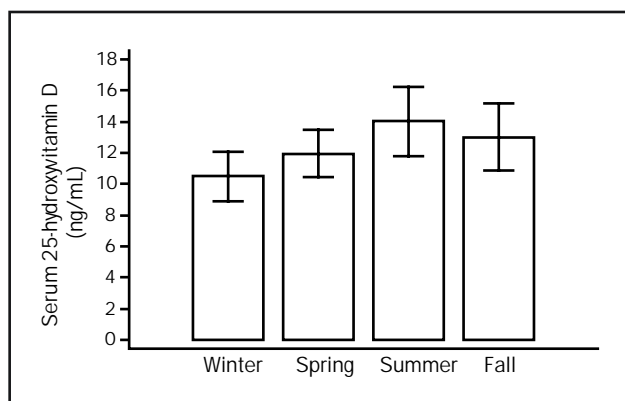


Figure 7. Mean serum 25-hydroxyvitamin D levels by season; 95% confidence intervals (CIs) display the mean serum 25-hydroxyvitamin D levels for each season, winter through fall: 10.49 ng/mL (95% CI, 8.91-12.07 ng/mL; n=47); 11.95 ng/mL (95% CI, 10.40-13.52 ng/mL; n=49); 14.03 ng/mL (95% CI, 11.77-16.30 ng/mL; n=30); and 13.0 ng/mL (95% CI, 10.80-15.20 ng/mL; n=24). Statistical significance exists only between the mean serum 25-hydroxyvitamin D levels for winter and summer. The difference between the sample means was 3.54 ng/mL (95% CI, 0.91-6.18 ng/mL; $P=.009$).

hydroxyvitamin D levels for 290 men and 469 women aged 67 to 95 years were 32.8 ± 11.6 ng/mL and 28.4 ± 11.6 ng/mL, respectively.⁷⁰ In contrast, the year-round mean \pm SD 25-hydroxyvitamin D levels for the 150 patients younger than 66 years were profoundly lower at 11.5 ± 4.4 ng/mL for men and 12.3 ± 6.0 ng/mL for women. Hence, the patients in this study appear to have profoundly lower serum 25-hydroxyvitamin D levels than those of either defined pain populations or in a population with a known high prevalence of hypovitaminosis D.

However, this study reports the serum 25-hydroxyvitamin D level at only 1 point in time. For this reason, the value cannot reflect the duration of deficiency. Symptomatic hypovitaminosis D might occur only with longstanding deficiency.⁷¹

The absence of a time dimension to the vitamin D measurement increases the importance of documenting secondary hyperparathyroidism and quantifying markers of bone formation and resorption. Future studies should include measurements of serum calcium, phosphorus, osteocalcin, and alkaline phosphatase isoenzymes, as well as urinary calcium, phosphorus, and cyclic adenosine monophosphate concentrations. Bone densitometry and bone x-ray films would also strengthen future studies. In the absence of an intervention to increase 25-hydroxyvitamin D levels, it is uncertain whether the musculoskeletal pain experienced by the patients in this study is secondary to their low vitamin D states. This study identifies the need for such an intervention study.

CONCLUSION

These results support screening of all outpatients with persistent, nonspecific musculoskeletal pain for hypovitaminosis D. These patients are at high risk for the consequences of unrecognized and untreated hypovitaminosis D, and this risk extends to those now considered at low risk, including nonelderly, nonhousebound, or nonimmigrant persons of either sex. Nonimmigrant women of childbearing age may be at particularly high risk for misdiagnosis or delayed diagnosis. Because osteomalacia is a known cause of persistent, nonspecific musculoskeletal pain, screening all outpatients with such pain for hypovitaminosis D should be standard practice in clinical care. A prospective US trial to assess management of persistent, nonspecific pain by prescription vitamin D replenishment is urgently needed.

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Mayo Clinic Proceedings

Editorial

Vitamin D Deficiency: What a Pain It Is

In the current issue of the *Mayo Clinic Proceedings*, Plotnikoff and Quigley¹ report that 100% of African Americans, East Africans, Hispanics, and American Indians in their Minnesota-based study had deficient levels of vitamin D; overall, 93% of the 150 children and adults in the study, which included 6 broad categories of ethnic groups, were vitamin D-deficient. Is this unexpected? No. Is this newsworthy? Yes.

It is inconceivable with all the advances in modern medicine that vitamin D deficiency should be a health concern in the United States. Most physicians assume that vitamin D deficiency, which plagued children from the 17th through 19th centuries, was eradicated with the fortification of milk with vitamin D. Indeed, from the 1930s through the 1950s, a wide variety of foods and beverages in the United States and Europe, including milk, bread, custard, hot dogs, soda, and even beer, were fortified with vitamin D.² However, the outbreak of vitamin D intoxication in a limited number of young children in Great Britain in the 1950s resulted in the banning of vitamin D fortification of dairy products and other foods in most European countries and the removal of vitamin D from most products except some breads, cereals, and milk in the United States.

Plotnikoff and Quigley¹ evaluated both children and adults who reported persistent musculoskeletal pain that did not meet the strict criteria for fibromyalgia defined by the American College of Rheumatology. Elderly patients with nonspecific musculoskeletal pain refractory to usual therapy, including the use of nonsteroidal anti-inflammatory drugs, had a high prevalence of vitamin D deficiency. Although the observation was not unexpected,^{2,3} the extent of vitamin D deficiency in the younger age group is noteworthy. Specifically, 100% of patients younger than 30

years and older than 60 years had vitamin D deficiencies, with the younger group having significantly lower levels of 25-hydroxyvitamin D. The association between nonspecific musculoskeletal pain and vitamin D deficiency was suspected because of a higher prevalence of these symptoms during winter than summer. The study patients ranged in age from 10 to 65 years, and all had symptoms of vitamin D deficiency. Of the more than 90% of patients who were medically evaluated for persistent musculoskeletal pain 1 year or more before screening, none had been tested previously for vitamin D deficiency.

[See also page 1463.](#)

Most physicians recognize that the elderly population is at risk for vitamin D deficiency.^{2,3} However, it is less appreciated that children, young adults, and middle-aged adults are also at high risk. Nesby-O'Dell et al⁴ reported that 42% of African American women in the United States aged 15 to 49 years were vitamin D-deficient; Tangpricha et al⁵ reported that 32% of healthy young white men and women in Boston aged 18 to 29 years were vitamin D-deficient at the end of winter in 2003. It is now recognized that mothers with darker skin, along with their newborns and young children who receive their total nutrition from breastfeeding, are at high risk of vitamin D deficiency. In Boston, 76% of 50 mother-infant pairs were found to be vitamin D-deficient, as were 69% of infants in the New York area (J. M. Lee, MD, B. L. Phillip, MD, D. S. Hirsch, MD, M. F. Holick, MD, unpublished data, 2003). Sullivan et al⁶ reported that 48% of girls in Maine aged 9 to 11 years were vitamin D-deficient at the end of winter in 2003.

Vitamin D is essential for the efficient utilization of dietary calcium. In a vitamin D-deficient state, the amount of calcium absorbed is inadequate to satisfy the body's calcium requirement,⁷ resulting in an increase in the production and secretion of parathyroid hormone (PTH). Parathyroid hormone conserves calcium by increasing tubular

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reabsorption of calcium in the kidneys, stimulating the kidneys to produce 1,25-dihydroxyvitamin D (the hormonally active form of vitamin D). However, in a vitamin D-deficient state, inadequate amounts of 1,25-dihydroxyvitamin D are produced to maintain intestinal calcium absorption. As a result, the skeleton, through a PTH-mediated process that involves osteoclast activation, serves as the surrogate source of calcium. This results in osteopenia and osteoporosis.^{2,7}

Another effect of PTH on mineral metabolism often goes unappreciated; it induces phosphaturia, which leads to hypophosphatemia. Thus, the calcium phosphate product in the circulation decreases and becomes inadequate to mineralize the bone properly. However, the osteoblasts continue to deposit collagen matrix on both the endosteal and periosteal surfaces of the skeleton, and the resultant rubbery matrix does not provide sufficient structural support. Instead, it hydrates and expands under the periosteal covering, causing an outward pressure on the periosteal covering that is innervated with sensory pain fibers. This is the likely explanation of why patients with osteomalacia often experience a dull unrelenting aching sensation in their bones. These symptoms are either dismissed or misdiagnosed as fibromyalgia by many physicians. A physical examination that includes application of minimal pressure with the thumb or forefinger on the sternum, anterior tibia, or radius and ulna often will elicit pain and discomfort, which is a helpful diagnostic sign for osteomalacia.

Vitamin D deficiency causes muscle weakness and muscle aches and pains in both children and adults. Glerup et al⁸ reported that 88% of Danish women of Arab descent who presented with muscle pains and weakness were severely vitamin D-deficient. Bischoff et al⁹ observed that adults with vitamin D deficiency have muscle weakness and are more likely to fall.

There are a multitude of reasons for why vitamin D deficiency has again become a major health problem for both children and adults of all ages and races. Extremely few foods naturally contain or are fortified with vitamin D. It has been estimated that 90% or more of our required vitamin D comes from exposure to sunlight.² Anything that interferes with the penetration of solar ultraviolet radiation into the skin, such as increased melanin pigmentation and sunscreen use, will diminish the cutaneous production of vitamin D.^{2,7} Thus, as noted by Plotnikoff and Quigley,¹ children and adults with darker skin are at higher risk of vitamin D deficiency. Application of a sunscreen with sun protection factor 8 reduces the capacity of the skin to produce vitamin D by 95%.^{2,10}

In 1997, the Institute of Medicine of the US National Academy of Sciences recommended new adequate intakes for vitamin D.¹¹ The recommendations, based on the assumption that young and middle-aged adults were more

likely than older adults to be exposed to sunlight, are as follows: 200 IU/d for children and adults to age 50 years, 400 IU/d for men and women aged 50 to 70 years, and 600 IU/d for those older than 70 years. However, a minimum of 1000 IU/d of vitamin D is needed to satisfy the body's requirement.¹²⁻¹⁴ Heaney et al¹⁴ estimated that the body uses 3000 to 5000 IU/d of vitamin D. What does the body do with all that vitamin D? Most organs in the body, including the brain, heart, pancreas, skin, and immune system, recognize 1,25-dihydroxyvitamin D.^{2,7} Furthermore, many of these organs also have the capacity to make 1,25-dihydroxyvitamin D.^{2,7} Besides regulating calcium homeostasis, 1,25-dihydroxyvitamin D is a potent inhibitor of cellular growth, stimulator of insulin secretion, modulator of immune function, and inhibitor of renin production.^{2,7} These functions are likely responsible for the numerous epidemiological observations that people who live at higher latitudes and who are more prone to vitamin D deficiency are at increased risk of developing prostate, colon, breast, and other solid tumors¹⁵; autoimmune diseases including multiple sclerosis and type 1 diabetes; hypertension; and cardiovascular heart disease.^{2,7}

The take-home message from Plotnikoff and Quigley's observations is that when patients with nonspecific skeletal-muscular pain are evaluated, their serum 25-hydroxyvitamin D levels should be obtained. Physicians should disregard the laboratory-reported lower limit of the normal range. A serum 25-hydroxyvitamin D level of at least 20 ng/mL is necessary to minimally satisfy the body's vitamin D requirement.^{14,16} Maintenance of a serum 25-hydroxyvitamin D level of 30 to 50 ng/mL is preferred.^{2,7,14,17}

The most cost-effective and efficient method for preventing vitamin D deficiency is to have adequate exposure to sunlight. Some dermatologists advise that people of all ages and ethnicities should avoid all direct exposure to sunlight and should always use sun protection when outdoors. This message is not only unfortunate, it is misguided and has serious consequences, ie, the risk of vitamin D deficiency and increased risk of many chronic diseases. There is little evidence that adequate sun exposure will substantially increase the risk of skin cancer; rather, long-term excessive exposure and repeated sunburns are associated with nonmelanoma skin cancers. The amount of time for adequate exposure depends on time of day, season, latitude, skin pigmentation, and the area of skin surface that has no sun protection. Typically, the sun exposure of a person in a bathing suit of 1 minimal erythema dose (which causes a slight pinkness to the skin) is equivalent to ingesting 20,000 IU of vitamin D.^{2,7} Thus, exposure of hands, face, and arms or arms and legs to 25% of a minimal erythema dose (about 5-15 minutes between 11 AM and 2 PM in Boston) will provide an adequate amount of vitamin D.

Vitamin D deficiency can be treated easily by giving the patient an oral dose of 50,000 IU of vitamin D once a week for 8 weeks.¹⁶ Long-term prevention of vitamin D deficiency can be accomplished by giving 50,000 IU of vitamin D once or twice a month.

Physicians should be alert to vitamin D deficiency, as noted by Plotnikoff and Quigley.¹ Patients should have their vitamin D status, ie, serum 25-hydroxyvitamin D levels, tested once a year, preferably at the end of the fall season, to ensure that they do not become vitamin D-deficient before winter. Prevention of vitamin D deficiency not only preserves bone and muscle health but also may help prevent many chronic diseases and preserve overall health and well-being.

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