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Low Vitamin D Status of Patients in Methadone Maintenance Treatment

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Abstract

Aim—To examine the prevalence and risk factors of low vitamin D status (vitamin D deficiency or insufficiency) among patients in a methadone maintenance treatment (MMT) program.

Design—Cross-sectional study of subjects recruited from an MMT program in a higher latitude (Boston, MA).

Measurements—Standardized survey and medical record review were used to assess patient characteristics. Serum was tested to determine vitamin D deficiency (25-hydroxyvitamin D <20 ng/mL) and insufficiency (25-hydroxyvitamin D between 20 and 30 ng/mL). Multivariable analyses were used to assess risk factors associated with vitamin D deficiency.

Findings—Low vitamin D status was found in 52% of the subjects (48 of 93), deficiency in 36%, and insufficiency in an additional 16%. Older age (OR = 3.47; 95% CI 1.31–9.22) and black or Hispanic race/ethnicity (OR 3.34; 95% CI 1.30–8.58) were significantly associated with higher risk of vitamin D deficiency.

Conclusion—Low vitamin D status was present in a majority of patients recruited from an MMT program. This raises the question as to whether this is a generalizable phenomenon and whether these patients are at higher risk of complications of low vitamin D status including bone pain, periodontal disease, osteomalacia, and cardiovascular disease.

Keywords

methadone maintenance; vitamin D; drug dependence; medical complications

The Institute of Medicine¹ recently stated that co-occurring medical conditions in drug-dependent populations are a reality that merit attention and action. Effective medical care is

often underutilized among individuals with substance-use disorders, due in part to unawareness of treatable medical conditions. Attending to physical health problems may be of particular importance to individuals enrolled in methadone maintenance treatment (MMT); opioid-dependent individuals in the United States tend to be older than opioid-dependent individuals in other forms of addiction treatment.²

Low vitamin D status, which we use to refer to either vitamin D deficiency or insufficiency, has been recognized in a variety of populations with medical conditions; yet, it has received little attention in drug-dependent populations.^{3–5} Examining vitamin D in individuals receiving MMT may be particularly important, because low vitamin D status can result in nonspecific musculoskeletal pain^{6,7} as well as periodontal disease and tooth loss,⁸ conditions common in MMT patients.^{9,10} Low vitamin D status can also lead to a higher risk of fracture by exacerbating osteoporosis,¹¹ a painless bone disease of low bone mass. Low bone density has also been noted in opioid-dependent populations.^{12,13}

Low vitamin D status is more common than previously thought, ranging from 21% in an elderly low-income African-American population in Boston³ to 71% in patients with severe peripheral arterial disease.¹⁴ The most important source of vitamin D is sunlight, the skin synthesis the vitamin from sunlight. Factors that affect vitamin D synthesis are the level of sunlight exposure (eg, season, latitude, and time of day), diet, skin pigmentation, sunscreen use, and age.

Better understanding of the contribution of vitamin D status to the bone health of MMT patients could lead to pragmatic interventions to identify patients in addiction treatment who are at risk for vitamin D deficiency and ameliorate the associated medical comorbidities. Thus, we sought to examine the prevalence and risk factors of low vitamin D status in a population enrolled in MMT.

Methods

Study Design and Sampling

This was a cross-sectional study of participants recruited from the 350 patients of the Boston Public Health Commission's MMT program. Flyers were posted at the MMT program's dosing and counseling sites inviting patients to participate in a study about bone health. Research associates were present at the program to schedule research appointments at the Boston University School of Medicine General Clinical Research Center. All patients who had received methadone for at least 30 days from the MMT program were eligible to participate. The study was conducted between August and December of 2003. The Boston University Institutional Review Board approved the study protocol.

Data Collection

After providing written informed consent, study participants met with trained research associates for a standardized interview assessing the following: demographics, vitamin D supplementation (“Have you taken vitamin D in the past week?”), medical conditions associated with low vitamin D status including chronic liver disease, chronic pancreatitis, and renal disease. Height and weight were measured to calculate body mass index (weight

[kg]/height² [m]), because obesity (body mass index ≥ 30) is associated with low vitamin D status in some populations.⁴ Data on alcohol use,¹⁵ opioid use,^{12,13} and HIV infection¹⁶ were collected, because they have been associated with low bone density. Medical record review was performed to ascertain the presence of medications that are associated with low vitamin D status including corticosteroids and antiepileptics (eg, phenytoin, carbamazepine, and phenobarbital).

We used the widely accepted definition of vitamin D deficiency or serum 25-hydroxyvitamin D of <20 ng/mL.¹⁷ We also report the prevalence of vitamin D insufficiency or 25-hydroxyvitamin D between 20 and 30 ng/mL. This is supported by the observation that elevated parathyroid hormone levels do not plateau until 25-hydroxyvitamin D levels are above 30 ng/mL. One source of confusion stems from the fact that older articles used different cutoffs for the terms vitamin D deficiency and insufficiency. Despite this source of confusion, we included the prevalence of insufficiency, because although there is no consensus on the optimal range of 25-hydroxyvitamin D, there is more agreement that levels between 20 and 30 ng/mL are still suboptimal.^{18,19}

Statistical Analysis

Analysis included descriptive statistics for all variables, such as using *t* tests for continuous variables and χ^2 analysis or Fisher exact test for categorical variables. We used logistic regression models to examine the relationship between independent variables and vitamin D deficiency. We used vitamin D deficiency as the outcomes in these analyses, because it is more widely known than vitamin D insufficiency. The limited number of vitamin D deficiency cases precluded models that adjusted for all independent variables simultaneously. Therefore, separate adjusted models were created for each independent variable; all adjusted analyses included age, gender, and race/ethnicity. All statistical analyses were performed using SAS version 8.2 (SAS System for Windows 2001; SAS Institute, NC).

Results

Sample Characteristics

Of the 350 patients enrolled in the MMT program, 106 volunteered to be included in the study. Thirteen (12%) were excluded due to inadequate venous access, which precluded serum collection. Of the remaining 93 subjects (Table 1), the majority were women (63%), black or Hispanic (58%), and overweight or obese (62%). Most of the subjects entered MMT after a median of 11 years of heroin use. About half had been heavy drinkers for at least a year, but only 14% reported recent (past month) heavy alcohol use. Many subjects reported past month medical conditions associated with low vitamin D deficiency status including liver disease (54%), kidney disease (7%), and chronic pancreatitis (1%). In addition, 12% of the sample was taking medications associated with vitamin D deficiency. Despite multiple risk factors for vitamin D deficiency, only 2 participants were taking any form of vitamin D supplementation. No differences were found between the entire MMT program population and the study sample in terms of age ($P = 0.48$), gender ($P = 0.65$), or race/ethnicity ($P = 0.5$).

The prevalence of vitamin D deficiency was 36% (95% CI 26%–45%). The prevalence of vitamin D insufficiency was found in an additional 16% (95% CI 9%–23%). Only 2 participants reported having been informed by a doctor of having vitamin D deficiency before this study. Participants were encouraged to give a letter with their 25-hydroxyvitamin D levels to his/her doctor.

Individuals older than 40 years were more than 3 times likely to have vitamin D deficiency (OR 3.47; 95% CI 1.31–9.22). In addition, those who were either black or Hispanic were more likely to be vitamin D deficient (OR 3.34; 95% CI 1.30–8.58). Recent heavy alcohol consumption, recent heroin use, and longer years in MMT were associated with a nonstatistically significantly higher OR of vitamin D deficiency (Table 2).

Discussion

More than half of the opioids-dependent population recruited from an MMT program had vitamin D status that is considered insufficient for optimal bone health. Although medical comorbidities of substance-use disorders have received greater recognition recently,²⁰ previous studies have not addressed vitamin D deficiency or insufficiency as a medical comorbidity. The findings in this study suggest that low vitamin D status is common among individuals with opioid dependence and deserves greater attention as a treatable medical issue in this population.

How does this estimate of low vitamin D status of patients on chronic methadone treatment compare with other populations in the literature? Methodological differences can often explain vitamin D differences between studies; the following similarities made it possible to compare healthy volunteers in a study by Tangpricha et al⁵: (1) study location in the Northeast, specifically, the city of Boston, (2) identical assay used to measure serum 25-hydroxyvitamin D levels,²¹ and (3) primary outcome or 25-hydroxyvitamin D deficiency <20 mg/dL. Our study, which was conducted predominantly at the end of summer (after maximal sun exposure), found more vitamin D deficiency (36%) compared with the study of Tangpricha et al (11%). Other studies of more debilitated populations have reported higher prevalence of vitamin D deficiency including adults with HIV infection (79%)²² elderly African-Americans in Boston (73%),³ and uninsured women in Michigan (67%).²³ In summary, our estimate of vitamin D deficiency is higher than a similar study of healthy volunteers but lower than potentially more debilitated populations.

Very few individuals knew of their vitamin D status despite a high proportion of patients with medical conditions or medications associated with low vitamin D. Our results underscore the pressing need to treat co-occurring medical conditions as well as the addiction needs of patients in substance use treatment so as to improve overall health. Primary care physicians should be aware that low vitamin D status could contribute to the chronic pain of patients with opioid dependence.

The finding that black and Hispanic individuals are at higher risk for vitamin D deficiency is consistent with other studies.^{3,11,23} One reason for this may be reduced skin synthesis of vitamin D in individuals with darker skin pigmentation. Among women of reproductive age

in the third National Health and Nutrition Examination Survey, the prevalence of 25-hydroxyvitamin D ≥ 15 ng/mL was 42% in African-American women versus 4% among white women.⁴ This biologic phenomenon could give rise to ethnicity-related health disparities. We also found that older patients were more likely to have vitamin D deficiency in our sample, which may be due to the skin's decreased ability to synthesize vitamin D with aging.²⁴ Older age may also be accompanied by lower physical functioning, which may result in less sun exposure.

Low vitamin D status in individuals in an MMT program is worthy of concern in light of the relatively high prevalence of chronic pain in drug-dependent populations.^{25–27} Patients in MMT experiencing chronic limb or joint pain are likely to attribute this pain to the effects of methadone.²⁸ Vitamin D deficiency causes osteomalacia, a bone disease of ineffective bone matrix mineralization and a syndrome of diffuse skeletal pain and muscle aches.²⁹ In a study of patients with chronic pain, 93% of them were of vitamin D deficiency.⁶ Long-term therapy with some medications such as corticosteroids, antiepileptic drugs, and some HIV antiretroviral therapies can lower vitamin D status by induction of the steroid and xenobiotic receptor.^{30,31} Whether methadone (or all opioids) activates steroid and xenobiotic receptor in a similar manner is not known. However, the high prevalence of low vitamin D status in this study raises the question of whether patients in MMT with chronic pain may have low vitamin D status.

Low vitamin D status for any population is important because of its role in a number of other medical conditions. Low vitamin D status is associated with muscle weakness that can lead to lower pulmonary function³² and higher risk of falls.³³ Vitamin D is vital for bone health. Low vitamin D status is also associated with cardiovascular disease^{34,35} and metabolic syndrome.³⁶ Moreover, vitamin D receptors are found in a variety of tissues in the body including colon, breast, ovarian, and prostate; sufficient vitamin D may be protective against cancers in these areas.^{37–39}

To treat vitamin D deficiency, 50,000 IU of vitamin D₂ once a week for 8 weeks is often effective. Reoccurrence of vitamin D deficiency can safely be prevented with 50,000 IU every other week. Another approach to prevention is daily supplementation of 1000 IU of vitamin D to maintain serum levels above 30 ng/mL.⁴⁰

The results of this study should be interpreted with the following limitations. First, because the study was conducted in the summer and fall when 25-hydroxyvitamin D levels are generally highest, a greater proportion of the study sample is likely to have low vitamin D at the end of winter when sunlight exposure is at its lowest. Second, although we did not find differences between the study sample and the clinic sample in terms of age, gender, and race/ethnicity, patients with bone pain may have been more likely to participate in a study on “bone health” leading to an overestimation of the incidence of low vitamin D. Third, the study did not include a comparison group of patients not receiving methadone, but rather notes a comparable historical control group. Thus, this study does not provide definitive evidence but rather suggests that the vitamin D status of MMT patients is worse than those not in MMT. Finally, it is possible that these findings may not generalize to other opioid-dependent populations, because most MMT patients are required to leave their house to

attend clinic for methadone dosing on a daily basis where they are potentially exposed to sunlight. Further study should examine low vitamin D status in other opioid-dependent populations including those in other forms of opioid treatment (ie, buprenorphine) and those not in addiction treatment.

In conclusion, low vitamin D status was common in patients receiving MMT and unawareness of vitamin D status was almost universal. Low vitamin D status is another largely unrecognized medical comorbidity of patients with addictions, a group with complex medical problems. These findings merit further investigation into the need and benefits of vitamin D supplementation in MMT patients.

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Table 1
Characteristics of Study Participants Recruited From a Methadone Maintenance Treatment Clinic (n = 93)

Variable	n (%)
Gender	
Female	59 (63)
Race/ethnicity	
Black	42 (45)
Hispanic	12 (13)
White	39 (42)
Body mass index (kg/m ²)	
< 18.5	1 (1)
18.5–24.9	35 (38)
25–29.9	23 (25)
30	34 (37)
HIV infection	25 (27)
Heavy alcohol use, 1 yr	48 (53)
Heavy alcohol use, past month*	13 (14)
Heroin use, lifetime years, median (range)	11 (0–38)
Heroin use, past month	21 (23)
Methadone maintenance treatment, lifetime years, median (range)	3.2 (0.08–25)
Age, years, median (range)	42 (21–66)
Condition associated with low vitamin D status	
Chronic liver disease [†]	50 (54)
Chronic kidney disease	6 (7)
Chronic pancreatitis	1 (1)
Medications (including prednisone, carbamazepine, phenytoin, and phenobarbital)	11 (12)

* Defined as more than 3 drinks/occasion, more than 3 occasions/wk.

[†] “Has a doctor ever told you that you had ongoing liver disease (eg, cirrhosis or chronic hepatitis B or C)?”

Table 2
Predictors of Vitamin D Deficiency in Adjusted*

Variable	% Vitamin D Deficiency	OR (95% CI)
Age [†] (yr)		
40	46	3.47 (1.31–9.22)
<40	19	1
Gender		
Female	37	1.24 (0.51–3.03)
Male	32	1
Race/ethnicity		
Non-white	46	3.34 (1.30–8.58)
White	21	1
Body mass index (kg/m ²)		
30	44	1.42 (0.54–3.73)
<30	31	1
HIV infection		
Yes	32	0.69 (0.24–2.01)
No	37	1
Liver disease		
Yes	34	0.83 (0.33–2.13)
No	37	1
Season		
November–April	35	1.15 (0.37–3.58)
May–October	36	1
Heavy alcohol use, past month		
Yes	46	1.47 (0.39–5.50)
No	33	1
Heavy alcohol use, lifetime (yr)		
1 yr	38	1.08 (0.42–2.82)
<1 yr	33	1
Heroin use, past month		
Yes	43	2.02 (0.67–6.07)
No	33	1
Heroin use, lifetime (yr) [‡]		
11	40	1.01 (0.37–2.76)
<11	30	1
MMT, lifetime (yr) [‡]		
3.2	43	1.60 (0.61–4.17)
<3.2	28	1

* Results of separate logistic regression models for each independent variable, adjusting for age, gender, and race/ethnicity.