

## ORIGINAL RESEARCH ARTICLES

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# Prevalence and Clinical Correlates of Vitamin D Inadequacy among Patients with Chronic Pain

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### ABSTRACT

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*Objective.* Vitamin D inadequacy is associated with medication refractory musculoskeletal pain and neuromuscular dysfunction. This vitamin deficiency could subsist as an unrecognized comorbid condition among patients with chronic pain. The primary objective of this study was to determine the prevalence and clinical correlates of vitamin D inadequacy in patients seeking treatment for chronic pain.

*Design.* Retrospective case series.

*Setting.* Multidisciplinary pain rehabilitation center at a tertiary referral medical center.

*Patients.* The study involved 267 chronic pain patients admitted from February to December 2006.

*Intervention.* Serum 25-hydroxyvitamin D (25[OH]D) was drawn at admission.

*Outcome Measures.* Patients with serum 25[OH]D levels  $\leq 20$  ng/mL were considered to have inadequate levels and those with levels  $>20$  ng/mL were considered to have adequate levels. Upon admission, opioid intake was documented and patients completed the Short Form-36 Health Status Questionnaire.

*Results.* The prevalence of vitamin D inadequacy was 26% (95% confidence interval, 20.6–31.1%). Among patients using opioids, the mean morphine equivalent dose for the inadequate vitamin D group was 133.5 mg/day compared with 70.0 mg/day for the adequate group ( $P = 0.001$ ). The mean duration of opioid use for the inadequate and adequate groups were 71.1 months and 43.8 months, respectively ( $P = 0.023$ ). Opioid users with inadequate levels reported worse physical functioning ( $P = 0.041$ ) and health perception ( $P = 0.003$ ) than opioid users with adequate levels.

*Conclusion.* The prevalence and clinical correlates identified in this pilot study provide the basis for the assertion that vitamin D inadequacy may represent an under-recognized source of nociception and impaired neuromuscular functioning among patients with chronic pain.

*Key Words.* Vitamin D; Chronic Pain; Opioids

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### Introduction

Cutaneous and dietary sources of vitamin D are important for the maintenance of calcium homeostasis. When vitamin D levels are low, intestinal absorption of calcium is inadequate,

resulting in a compensatory increase in parathyroid hormone (PTH) production. Calcium homeostasis is restored, in part, by a PTH-mediated increase in bone calcium reabsorption. Resultant musculoskeletal manifestations of vitamin D inadequacy include diffuse bone and muscle pain, which are poorly responsive to opioid and nonsteroidal anti-inflammatory analgesic medications [1]. Moreover, the vitamin D receptor has long been identified in muscle tissue [2], which could account for the association between vitamin D insufficiency and proximal muscle weakness [3]. These musculoskeletal and neuromuscular symptoms are ubiquitous in the clinical practice of pain medicine, wherein vitamin D inadequacy could subsist as an under-recognized source of persistent pain and impaired physical functioning in patients with chronic pain.

The unknown prevalence of vitamin D inadequacy among patients with chronic pain remains a fundamental barrier toward understanding the clinical significance of this vitamin deficiency in the clinical practice of pain medicine. Early vitamin D prevalence studies documented inadequacy in populations traditionally considered at risk, such as the homebound elderly [4], hospitalized patients [5], and postmenopausal women with osteoporosis [6]. More recent studies have found a high prevalence of vitamin D inadequacy among various community populations, including adolescent females [7] and African Americans of all ages [8]. Knowledge of the prevalence of vitamin D inadequacy in patients with chronic pain could raise awareness of this potential comorbid condition, which would, in turn, favorably impact the clinical care of patients with chronic pain.

The primary aim of this retrospective pilot study was to determine the prevalence of vitamin D inadequacy, as defined by a serum level of 25-hydroxyvitamin D (25[OH]D)  $\leq 20$  ng/mL, among patients with chronic pain. In light of previous studies that suggest pain-related symptoms of vitamin D inadequacy are poorly responsive to analgesic medications and that vitamin D inadequacy is associated with muscle weakness, the secondary aims of the present study included assessment of the associations between vitamin D inadequacy, opioid use, and self-report measures of physical functioning.

### Patients and Methods

This retrospective study involved 267 of 313 patients admitted to the Mayo Comprehensive

Pain Rehabilitation Center in Rochester, MN, from February 2006 to December 2006 for whom vitamin D levels were available. The study protocol was approved by the Mayo Foundation Institutional Review Board and informed consent was provided by all patients for use of medical records for research purposes.

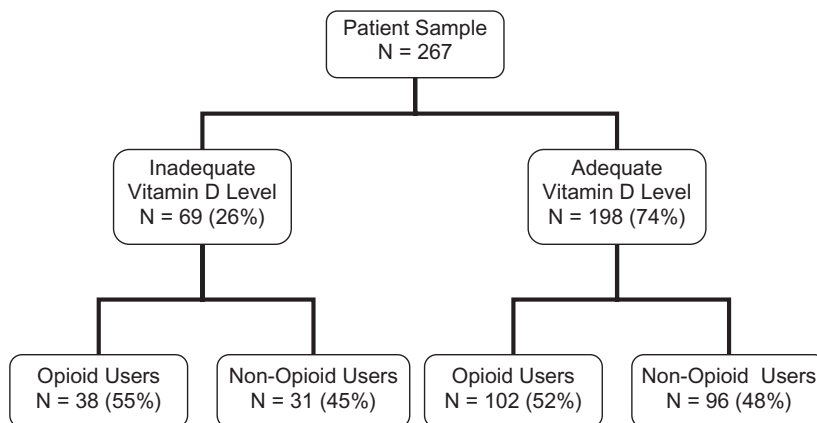
The duration of the outpatient pain rehabilitation program is 3 weeks. At the time of admission, relevant clinical and demographic data were collected, including age, comorbid medical conditions, body mass index (BMI), month of admission, pain duration, principal pain site or diagnosis, opioid intake, and duration of opioid use. The patient's residence above or below a latitude of 37°N was determined because sunlight above this latitude is insufficient to induce cutaneous production of vitamin D during winter months [9]. Opioid dosing at admission was determined from patient self-report and review of medical records. Opioid intake was then converted to oral morphine equivalents for analysis [10,11]. This is the established method of calculating oral morphine equivalents for patients with chronic pain at the rehabilitation center [12,13].

Serum levels of 25[OH]D were obtained at admission. The 25[OH]D serum level represents cutaneous and dietary sources of vitamin D and is the accepted measure for determining the adequacy of circulating vitamin D. Patients with serum levels  $\leq 20$  ng/mL were considered to have inadequate levels of vitamin D and those with levels  $>20$  ng/mL were considered to have adequate levels [9]. All patients with vitamin D inadequacy were prescribed a repletion schedule.

The Short Form-36 Health Status Questionnaire (SF-36) was administered at admission [14]. For purposes of the current study, four subscales were used including health perception, physical functioning, bodily pain, and role limitations related to emotional problems. Higher scores reflect a more favorable health status. These subscales have been used to measure health attributes among patients with chronic pain at the rehabilitation center [12,13,15].

### Statistical Analyses

Preliminary analyses were completed using univariate analyses of variance to compare vitamin D status on clinical and demographic characteristics, opioid intake, and SF-36 subscale scores. The raw SF-36 scores were converted to standardized T-scores with a normative value of 50 and a standard deviation (SD) of 10. The standardized



**Figure 1** Flow diagram of vitamin D adequacy and opioid use status.

T-scores were calculated using published age- and sex-specific mean scores and SDs for the SF-36 subscales in the general U.S. population [16]. Following these analyses, similar comparisons were completed for those patients using opioids. Categorical variables were compared using two-sided chi-square tests. In a post hoc analysis, multiple linear regression was completed utilizing a stepwise elimination procedure to identify independent correlates of serum vitamin D levels. Morphine equivalent use upon admission, duration of opioid use, and BMI were the independent variables and serum vitamin D level was the dependent variable. All analyses were completed using Statistical Package for the Social Sciences, release 15.0 (SPSS, Chicago, IL, 2006). The level of significance for all statistical tests was set at  $P < 0.05$ .

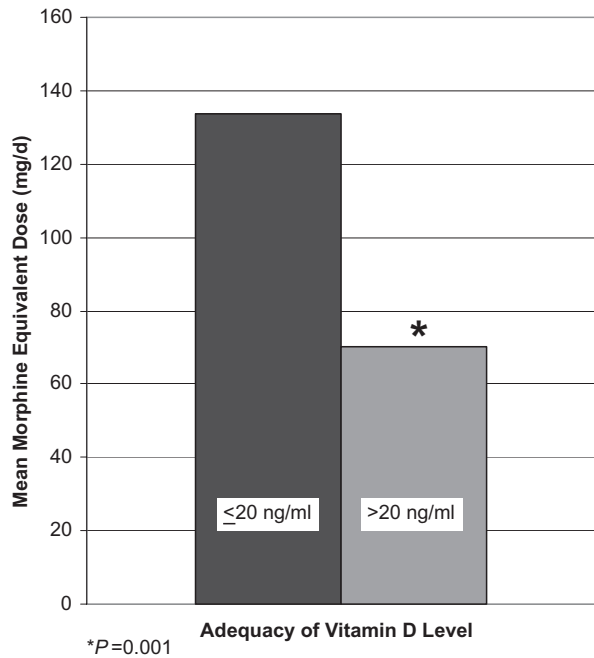
## Results

The prevalence of vitamin D inadequacy was 26% [95% confidence interval (CI), 20.6% to 31.1%] (Figure 1). The mean 25[OH]D serum level for the entire cohort was 28.7 ng/mL (SD = 11.6). Serum levels ranged from 6 ng/mL to 74 ng/mL and eight (3%) patients had serum levels  $\leq 10$  ng/mL. The mean age was 47.5 years (SD = 13.7), 75% (N = 200) were women, and 97.8% (N = 261) were Caucasian. Four patients were Hispanic, one was African American, and one was Asian. Seventy-nine percent (N = 210) of patients lived above a latitude of 37°N and 21% (N = 57) lived below this latitude. The mean 25[OH]D serum levels of patients living above and below a latitude of 37°N were 29.0 ng/mL (SD = 11.8) and 27.8 ng/mL (SD = 11.1), respectively. The mean pain duration was 10.8 years (SD = 12.5) and the mean BMI was 29.9 kg/m<sup>2</sup> (SD = 7.4). Fifty-two

percent (N = 140) of patients were using opioids at admission and the mean morphine equivalent dose was 86.6 mg/day (SD = 99.8). The mean duration of opioid use was 51.5 months (SD = 62.2). The principal pain site or pain diagnosis at admission included low back (N = 77), fibromyalgia (N = 66), upper or lower extremity (N = 29), chronic headache (N = 25), abdomen (N = 14), neck (N = 10), pelvis (N = 9), chest wall (N = 4), and face (N = 2). More than two anatomic regions were identified as the principal pain site for 31 patients.

The mean 25[OH]D serum level for patients in the vitamin D inadequate group was 15.7 ng/mL (SD = 4.0) and the mean serum level for the vitamin D adequate group was 33.3 ng/mL (SD = 9.8). Comparison between the two vitamin D groups showed no significant differences in age, sex, pain duration, pain diagnosis, or residence above or below a latitude of 37°N. The proportion of morbidly obese (BMI  $\geq 40$  kg/m<sup>2</sup>) patients with inadequate vitamin D levels was 20.3% (N = 14) compared with 6.0% (N = 12) of patients with adequate vitamin D levels ( $\chi^2 = 10.35$ ,  $P = 0.006$ ).

Several patients had comorbid medical or surgical conditions, or were taking medications that could potentially affect vitamin D levels. Ten patients had a history of gastric bypass, of whom two had inadequate vitamin D levels. Eight had a history of alcohol dependence in early remission, of whom three had inadequate levels. The two patients with celiac disease, two with ulcerative colitis, and one with a colostomy had adequate vitamin D levels. Five patients were taking carbamazepine, of whom three had inadequate vitamin D levels. Additionally, 27% (N = 72) of patients were taking some form of supplemental vitamin D, of whom 12 had inadequate vitamin D



**Figure 2** Opioid intake and vitamin D adequacy.

levels. No significant differences in the frequency of comorbid conditions were found between the two vitamin D groups. No patient had end-stage hepatic or renal disease.

Figure 1 compares the number of patients using daily opioids based on the adequacy of vitamin D levels. The proportion of patients using opioids with inadequate vitamin D levels was 55% (38/69) compared with 52% (102/198) of patients with adequate levels ( $P > 0.1$ ). However, the mean morphine equivalent dose was 133.5 mg/day (SD = 133.7) for patients with inadequate vitamin D levels, whereas the mean dose was 70.0 mg/day (SD = 78.0) for patients with adequate vitamin D levels ( $F_{1,139} = 12.09$ ,  $P = 0.001$ ) (Figure 2). The mean duration of opioid use among patients with inadequate vitamin D was 71.1 months (SD = 87.6) compared with 43.8 months (SD = 47.2) for opioid users with adequate levels ( $F_{1,129} = 5.31$ ,  $P = 0.023$ ). Duration of opioid use was

unknown for one patient in the vitamin D inadequate group and nine patients in the adequate group. No significant differences in age, sex, pain duration, pain diagnosis, or latitude of residence were identified between the two opioid groups. Six morbidly obese patients with inadequate vitamin D levels were taking opioids while four morbidly obese patients with adequate levels were using opioids. When the SF-36 subscale scores were compared, opioid users with inadequate vitamin D levels reported worse physical functioning ( $P = 0.041$ ) and health perception ( $P = 0.003$ ) compared with the opioid users with adequate levels (Table 1). The post hoc multiple linear regression analysis revealed higher morphine equivalent dosages at admission, and greater BMI were associated with lower serum vitamin D levels ( $R^2 = 0.092$ ,  $F = 6.57$ ,  $P = 0.002$ ).

## Discussion

The primary finding of this study was the 26% (95% CI, 20.6–31.1%) prevalence of vitamin D inadequacy among patients seeking treatment for chronic pain. To the authors' knowledge, this is the first reported prevalence of vitamin D inadequacy among patients with chronic pain of diverse etiologies. However, the prevalence of vitamin D inadequacy among our patients was lower than the prevalence reported for other cohorts of pain patients, which requires further explanation.

In a series of 150 patients undergoing evaluation for subacute and chronic widespread musculoskeletal pain in a primary care setting, the prevalence of vitamin D inadequacy was 93% [17]. None of the patients had fibromyalgia, and patients with other comorbid pain diagnoses were excluded. Fifty-five percent of patients in this particular study were of African, Hispanic, or Southeast Asian ethnicity, which is in marked contrast to our predominately Caucasian cohort. Increased skin pigmentation, which reduces cutaneous

**Table 1** SF-36 subscale scores for opioid users with adequate and inadequate vitamin D levels

Subscale	Inadequate (N = 38) Mean (SD)	Adequate (N = 102) Mean (SD)	$F_{1,139}^*$	P value
Health perception	34.06 (19.18)	47.28 (23.41)	9.208	0.003
Physical functioning	30.26 (19.77)	38.40 (20.37)	4.270	0.041
Bodily pain	21.32 (15.06)	23.85 (13.27)	0.905	0.343
Role emotional	37.72 (43.96)	34.67 (39.90)	0.125	0.697

\* Univariate analyses of variance.

SF-36 = Short Form-36 Health Status Questionnaire.

vitamin D production and is an established risk factor for vitamin D insufficiency, may have contributed to the high prevalence of vitamin D inadequacy in this subgroup of pain patients. In a separate study of 360 patients seeking treatment for low back pain in Saudi Arabia, the prevalence of vitamin D inadequacy was 83% [18]. Patients who were found to have a “mechanical” source for low back pain were excluded. As indicated by the investigators, direct sun exposure is generally avoided in Saudi Arabia by wearing clothing that covers the entire body. This cultural factor, which limits the cutaneous production of vitamin D, may have contributed to the high prevalence of inadequacy in this subgroup of low back pain patients. Compared with these previous cohorts, differences in study design, skin pigmentation, and cultural factors could account, in part, for the wide disparity in the prevalence of vitamin D inadequacy identified in the present study.

An important secondary finding of this study included a significant difference in opioid dosage and duration of opioid use between patients with inadequate and adequate vitamin D levels. Although vitamin D inadequacy contributes to defective bone mineralization and subsequent diffuse skeletal pain, the pathophysiological mechanism of pain generation remains undetermined. One proposed mechanism suggests that excessively collagenized osteoid deposited on periosteal surfaces expands following hydration, which places outward pressure on nociceptors innervating the outermost layers of the periosteum [19,20]. This mechanism could partially account for the clinical observations reported in two previous case series involving 11 patients with confirmed vitamin D inadequacy [1,21]. Among these patients, severe musculoskeletal pain involving the low back, neck, shoulders, hips, and legs was refractory to opioid analgesic and nonsteroidal anti-inflammatory medications but resolved following vitamin D repletion. Although these case series present more extreme examples of symptomatic vitamin D inadequacy, they provide the impetus for postulating that less severe states of insufficiency could remain an unrecognized but contributing source of nociception in patients with chronic pain. Furthermore, this postulate could explain why the inadequate vitamin D group reported similar pain levels compared with the adequate group despite use of greater dosages of opioids.

Additional secondary findings among our patients receiving opioids who had inadequate compared with adequate vitamin D levels included

significantly worse physical functioning, poorer health perception, and an increased frequency of morbid obesity. Worse physical functioning and poorer health perception could be indicative of vitamin D-associated myopathy, which can result in severely impaired neuromuscular function even in the absence of biochemical markers of associated bone involvement [3]. To the authors' knowledge, these findings have not been previously reported for chronic pain patients receiving maintenance opioid therapy. Our patient sample was also similar to other study cohorts in that elevated BMI was associated with vitamin D inadequacy, which is most likely related to sequestration of vitamin D in adipose tissue [22,23].

Our study has several limitations. All patients were specifically referred to the rehabilitation center and had health care resources to participate in the 3-week outpatient program. As a result of this selection bias, the study results may not be applicable to all patients with chronic pain. The mean pain duration of our cohort was 10.8 years; therefore, it was not possible to delineate the temporal impact of vitamin D status on the onset or maintenance of chronic pain. Furthermore, the study design does not allow for a causal relationship to be established between vitamin D inadequacy and the secondary findings reported herein.

The prevalence and clinical correlates identified in this pilot study provide the basis for the assertion that vitamin D inadequacy may represent an under-recognized source of nociception and impaired neuromuscular function among patients with chronic pain. In the clinical practice of pain medicine, knowledge of these findings could increase awareness of this potential source of comorbid pain and muscle weakness. Moreover, prospective trials utilizing a repeated measures design are warranted to assess the effects of vitamin D repletion on pain outcomes and physiological measures of neuromuscular functioning among patients with chronic pain and comorbid vitamin D inadequacy.

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