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Vitamin D and Central Hypersensitivity in Patients with Chronic Pain

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Abstract

Background. Low vitamin D is implicated in various chronic pain conditions with, however, inconclusive findings. Vitamin D might play an important role in mechanisms being involved in central processing of evoked pain stimuli but less so for spontaneous clinical pain.

Objective. This study aims to examine the relation between low serum levels of 25-hydroxyvitamin D3 (25-OH D) and mechanical pain sensitivity.

Design. We studied 174 patients (mean age 48 years, 53% women) with chronic pain. A standardized pain provocation test was applied, and pain intensity was rated on a numerical analogue scale (0–10). The widespread pain index and symptom severity score (including fatigue, waking unrefreshed, and cognitive symptoms) following the 2010 American College of Rheumatology preliminary diagnostic criteria for fibromyalgia were also assessed. Serum 25-OH D levels were measured with a chemiluminescent immunoassay.

Results. Vitamin deficiency (25-OH D < 50 nmol/L) was present in 71% of chronic pain patients; another 21% had insufficient vitamin D (25-OH D < 75 nmol/L). After adjustment for demographic and clinical variables, there was a mean ± standard error of the mean increase in pain intensity of 0.61 ± 0.25 for each 25 nmol/L decrease in 25-OH D ($P = 0.011$). Lower 25-OH D levels were also related to greater symptom severity ($r = -0.21$, $P = 0.008$) but not to the widespread pain index ($P = 0.83$) and fibromyalgia ($P = 0.51$).

Conclusions. The findings suggest a role of low vitamin D levels for heightened central sensitivity, particularly augmented pain processing upon mechanical stimulation in chronic pain patients. Vitamin D seems comparably less important for self-reports of spontaneous chronic pain.

Key Words. Chronic Pain; Central Nervous System; Central Sensitivity; Fibromyalgia; Vitamin D

Introduction

Low serum levels of 25-hydroxyvitamin D3 (25-OH D) have been implicated in various chronic pain conditions [1], including nonspecific musculoskeletal pain [2], chronic widespread pain [3], fibromyalgia [4], low back pain [5], headache [6], and lumbar spinal stenosis [7]. This is a general health concern as the average prevalence of vitamin D deficiency (25-OH D < 50 nmol/L) or insufficiency (25-OH D of 50–75 nmol/L [8] in chronic pain patients is at least 50% [2,6,7,9,10]. Nonetheless, the relationship between vitamin D levels and pain outcomes are not straightforward. Although some studies report an inverse relation between vitamin D deficiency and self-reports of pain intensity at different body sites [7,11], others do not [12–14]. A previous study in osteoarthritis patients found low levels of vitamin D to be predictive of increased mechanical pain sensitivity but not of self-reported clinical pain [12]. Therefore, low vitamin D levels might enhance central sensitivity to mechanically evoked pain, a core pathophysiological mechanism of pain processing that involves brain regions that are distinct from those being active in spontaneous pain [15]. This notion is supported by a study on rodents in which a vitamin D-deficient diet caused mechanical muscle hypersensitivity together with increased nociceptive skeletal muscle

innervation, even before muscle or bone pathology occurred [16]. As vitamin D has anti-inflammatory properties [17], pro-inflammatory cytokine production in states of vitamin D deficiency [18] might alter central pain processing, thereby increasing mechanical pain sensitivity [19]. Pain suppression by the central nervous system, including top down inhibition of musculoskeletal pain, might also become dysfunctional if vitamin D is low [20].

The primary aim of the present study was to further examine the relationship between 25-OH D serum levels and several measures of central hypersensitivity in a sample of patients with a chronic pain disorder with or without an initial biomedical cause at the beginning of the disease. As part of a larger project, we also assessed the preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity, which the American College of Rheumatology (ACR) found to be methodologically rigorous for making a clinical diagnosis of fibromyalgia without tender point examination [21]. These criteria refer to the widespread pain index (WPI) and the scale for symptom severity score (SSS) covering the previous week. The WPI denotes the number of areas in which a patient feels pain, and the SSS refers to the severity of fatigue, waking unrefreshed, and cognitive symptoms plus the extent of additional somatic symptoms [21]. In the realm of central hypersensitivity syndromes, to which fibromyalgia belongs [22], subjective pain and other somatic symptoms without objective clinical findings are deemed clinical manifestations of central sensitization [23]. In fibromyalgia, increased pressure pain sensitivity due to augmented central pain processing has been demonstrated [24]. To this extent, a secondary aim of our study was to investigate the association of 25-OH D levels with WPI, SSS, and a diagnosis of fibromyalgia.

Materials and Methods

Study Participants

Between March 2011 and April 2013, we enrolled a consecutive sample of 292 patients, referred to our tertiary clinic for multimodal pain therapy, aged 18 and older with pain of at least 3 months' duration. The main aim of the study project is to gain a better understanding on the role of central hypersensitivity as a pathophysiologic concept in patients with chronic pain not fully explained by a biomedical cause including fibromyalgia. An international classification of diseases (ICD)-10 diagnosis of somatoform pain disorder (F45.40) or chronic pain disorder with somatic and psychological factors (F45.41) was required for eligibility. The German version of ICD-10 introduced the F45.41 code in 2009 to address the relevance of psychological factors in those pain conditions with a clear biomedical cause at the beginning [25], whereas for the F45.40 code biomedical causes are irrelevant. The institutional review board approved the study protocol and all participants provided informed consent.

All patients were examined by internal medicine residents trained in Engel's biopsychosocial interview technique [26] and supervised by board-certified internists and psychiatrists trained in pain medicine. All patients underwent biopsychosocial history taking, physical examination, lab work-up, and if indicated, diagnostic imaging to assure a F45.40 or F45.41 diagnosis. Consultant physicians from the rheumatology, anesthesiology, neurology, neurosurgery, and orthopedic surgery clinics were called as needed.

For the vitamin D substudy presented here, we excluded 118 patients who had incomplete data for study outcomes (i.e., algometry scores, WPI, SSS, and fibromyalgia), 25-OH D levels, and covariates. This left 174 patients with a complete data set, allowing us to compute full regression models. The 174 patients did not significantly differ from the 118 excluded patients in terms of gender ($P = 0.66$), age ($P = 0.71$), immigrant background ($P > 0.05$), pain duration ($P = 0.52$), depression ($P = 0.31$), and posttraumatic stress disorder (PTSD) ($P = 0.67$).

Measures of Central Hypersensitivity

Mechanical Pressure Pain Sensitivity

To assess mechanical pain sensitivity, we used peg algometry that has been validated for clinical studies against an electronic pressure algometer in a sample of patients with somatoform/functional or orthopedic pain [27]. A calibrated "clothes peg" (i.e., clamping force of 10 N at an extension of 5 mm) was applied to the nail bed of the middle finger for 10 seconds after which patients rated pain intensity on a numeric scale ranging from 0 ("no pain") to 10 ("the most intense pain imaginable"). A "10" was also assigned if participants could not stand the clamping force for the entire 10 seconds ($N = 6$). If patients used a range between two integers to rate pain (e.g., "between 5 and 6"), the middle value was taken as the definite score (e.g., "5.5"). We performed algometry on both middle fingers to account for possible side-specific differences in pain perception [28]. The average of the two ratings was used for further analyses.

WPI

The number of areas in which a patient had pain over the last week was counted up to yield a WPI score ranging from 0 to 19. The following 19 locations are considered for the WPI score [21]: shoulder girdle left, right; hip (buttock, trochanter) left, right; jaw left, right; upper arm left, right; lower arm left, right; upper leg left, right; lower leg left, right; upper, lower back; neck; chest; abdomen.

SSS

The level of severity over the past week of fatigue, waking unrefreshed, and cognitive symptoms was indicated on a Likert scale from 0 (no problem) to 3 (severe) together with the number of somatic symptoms in general (0 = no symptoms, 3 = α great deal of symptoms). The final SSS is between 0 and 12 [21].

Fibromyalgia

In accordance with ACR 2010 criteria, we made a diagnosis of fibromyalgia if the WPI was at least 7 and the SSS was at least 5 *or* if the WPI was between 3 and 6 and the SSS was at least 9 [21]. Comorbid somatic conditions, which can also cause pain, as well as mental disorders being associated with pain complaints, were not exclusion criteria for fibromyalgia if judged to be not the primary cause of the patients' pain. By study design, all complaints had been present for at least three months.

Vitamin D Levels

Morning fasting blood samples to determine vitamin D levels were collected shortly after hospital referral. Vitamin D was measured as 25-OH D in serum (nmol/L) by an accredited laboratory with chemiluminescent immunoassay (Institute of Clinical Chemistry, Bern University Hospital, Switzerland).

Correlates of Vitamin D and Central Hypersensitivity

We assessed several important correlates of 25-OH D levels, as well as our primary (mechanical pain sensitivity) and secondary outcomes (WPI, SSS, and fibromyalgia) that might act as confounding variables. Potential confounders were selected a priori and based on the literature to be used as covariates in statistical analysis.

Demographic Factors

Age, gender, and immigrant status (mainly Eastern and Southern Europe) were assessed as part of history taking. Age was shown to impact pain sensitivity and report in several studies [29,30]. Compared with men, women show greater mechanical pain sensitivity [30] and higher prevalence of fibromyalgia [31], and they also report more numerous and more intense bodily symptoms [32]. Vitamin D decreases with aging and is found to be lower in individuals with immigrant status [33], the latter also being associated with increased pain reports at several body sites [34].

Pain History

The first manifestation of spontaneous pain was asked. We also collected information on current prescribed categories of pain substances (yes/no), namely paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), tramadol, strong opioids, antiepileptics, and antidepressants. All of these medications might affect pain sensitivity and reports [35,36]; moreover, anticonvulsants increase the catabolism of 25-OH D [33]. The total count of different pain substances (range 0–6) was used for the primary statistical analysis. A complementary analysis used the individual categories of pain medications. The presence of a comorbid somatic pain condition was categorized as yes or no.

Body Mass Index (BMI)

We obtained height and weight to calculate the BMI (kg/m^2). An elevated BMI is associated with lower vitamin D levels [33] and found in patients with fibromyalgia [37].

Psychiatric Comorbidity

The treating physicians made a diagnosis of a depressive disorder and PTSD in accordance with the usual clinical classification systems (ICD-10 and Diagnostic and Statistical Manual of Mental Disorders IV). Depressive mood has been associated with lowered 25-OH D [38], an elevated number of somatic symptoms, including pain [39], and fibromyalgia [40]. PTSD is also prevalent in fibromyalgia [40] and PTSD patients report pain more frequently and also have altered pain sensitivity thresholds [41].

Season

Relatively reduced 25-OH levels are found during the winter season [33]. To account for this seasonal effect on vitamin D levels, we defined the 6 months with the least (November to April) and the most (May to October) statistical sunshine hours in Switzerland as winter and summer seasons, respectively.

Data Analysis

Data were analyzed using PASW 18.0 statistical software package (SPSS Inc., Chicago, IL, USA). Two-tailed level of significance was set at $P < 0.05$. Values for algometry scores and WPI were square root transformed to obtain a normal distribution. We used Kruskal–Wallis and χ^2 tests for group comparisons on continuous and categorical variables, respectively. Spearman rank correlation coefficients were calculated to estimate the association between two variables. We applied recently proposed cutoffs for 25-OH D levels to estimate the prevalence of vitamin D deficiency (<50 nmol/L), insufficiency (50–75 nmol/L), and sufficiency/normal levels (>75 nmol/L) in clinical settings [8]. However, instead of these clinical cutoffs, we used continuously scaled 25-OH D levels in linear regression analysis to test for a significant relationship between vitamin D and measures of central sensitivity. This approach is preferred in regression-type models, as it increases statistical power [42] and because the severity of evoked pain and spontaneous chronic pain likely increases along a continuum of decreased vitamin D levels. We made multivariate adjustments for totally 10 covariates that were subsequently entered into the model in four blocks (i.e., age and gender in block 1; immigrant background, season, and BMI in block 2; depression and PTSD in block 3; pain duration, presence of a comorbid somatic pain condition, and the number of pain medication categories in block 4). Multivariate normality in regression models was assured using Cook's distance to verify the absence of outliers.

Table 1 Characteristics of 174 chronic pain patients per vitamin D status

Variable	All	Vitamin D Status (25-OH D)			P Value
		Deficiency (<50 nmol/L)	Insufficiency (50–75 nmol/L)	Sufficiency (>75 nmol/L)	
	N = 174	N = 124	N = 36	N = 14	
Age (years)	47.9 ± 12.4	47.0 ± 12.1	50.3 ± 11.7	49.2 ± 16.0	0.238
Female gender (%)	53.4	52.4	55.6	57.1	0.908
Winter season (%)	48.3	53.2	44.4	14.3	0.019
Immigrant background (%)	61.5	66.9	38.9	71.4	0.007
Pain duration (months)	93 ± 111	74 ± 88	127 ± 129	171 ± 179	0.025
Body mass index (kg/m^2)	27.5 ± 5.6	28.1 ± 5.8	26.1 ± 5.4	25.1 ± 4.1	0.064
Depression (%)	76.4	76.6	72.2	85.7	0.559
PTSD (%)	14.4	12.9	19.4	14.3	0.616
Pain medication categories	3.23 ± 1.37	3.19 ± 1.42	3.39 ± 1.32	3.14 ± 0.95	0.694
Paracetamol (%)	82.8	85.7	80.1	83.1	0.897
NSAIDs (%)	62.1	60.5	63.9	71.4	0.703
Tramadol (%)	52.9	50.8	63.9	42.9	0.282
Strong opioids (%)	33.9	32.3	41.7	28.6	0.520
Anticonvulsants (%)	34.5	35.5	33.3	28.6	0.864
Antidepressants (%)	56.9	57.3	55.6	57.1	0.983
Comorbid somatic pain (%)	44.3	41.1	55.6	42.9	0.306
Algometry score	3.40 ± 2.80	3.58 ± 2.82	3.10 ± 2.66	2.18 ± 2.53	0.136
Widespread pain index	5.38 ± 3.54	5.41 ± 3.56	5.64 ± 3.77	4.43 ± 2.77	0.662
Symptom severity score	6.98 ± 2.31	7.25 ± 2.23	6.44 ± 2.22	5.93 ± 2.84	0.071
Fibromyalgia (%)	46.6	47.6	47.2	35.7	0.698

Values are given as means ± SD or percentages. P values were calculated using χ^2 test or Kruskal–Wallis test for comparisons between the three groups for vitamin D status.
25-OH D; 25-hydroxyvitamin D3; NSAIDs = nonsteroidal anti-inflammatory drugs; PTSD = posttraumatic stress disorder; SD = standard deviation.

Results

Patient Characteristics

Table 1 shows the characteristics of the 174 study participants. The sample comprised somewhat more women than men and patients with an immigrant background than nonimmigrants. On average, pain had been present for 7.75 years (range 0.25–57) and patients had been prescribed three different categories of pain medications. The average BMI was in the overweight range. Almost half of the patients qualified for a diagnosis of fibromyalgia and about two-fifth had a comorbid somatic condition that may be painful. Three-fourth of patients had clinical depression and almost every sixth patient had clinical PTSD.

With regard to 25-OH D serum levels, 71% of patients had vitamin D deficiency and 21% had vitamin D insufficiency; only 8% had sufficient vitamin D. The unadjusted comparison of characteristics between patients with deficient, insufficient, and sufficient vitamin D levels showed significant group differences for season, immigrant background, and pain duration (Table 1). Post hoc comparisons revealed that patients with sufficient vitamin D were more often assessed during the summer season than those with vitamin D deficiency ($P = 0.009$). Immigrants were more frequent than nonimmigrants in patients with vitamin D deficiency than in those with vitamin D insufficiency ($P = 0.002$). Patients with vitamin D deficiency reported shorter pain duration than those with vitamin D insufficiency ($P = 0.034$) and those with sufficient vitamin D ($P = 0.047$). Vitamin D status did not significantly differentiate central hypersensitivity measures.

Associations among Central Sensitivity Measures

Expectedly, patients with fibromyalgia—compared with those without fibromyalgia—had a greater WPI ($7.86 ± 3.31$ vs $3.22 ± 1.97$, $P < 0.001$), higher SSS ($8.45 ± 1.57$ vs $5.57 ± 2.03$, $P < 0.001$), and higher algometry scores ($4.16 ± 3.05$ vs $2.68 ± 2.33$, $P = 0.002$). Higher algometry scores were also associated with greater WPI ($r = 0.33$, $P < 0.001$) but not with SSS

Table 2 Multivariate prediction of central hypersensitivity measures by vitamin D levels

	Algometry Scores	Widespread Pain Index	Symptom Severity Score	Fibromyalgia
Model 1	$r = -0.213$	$r = -0.058$	$r = -0.182$	$r = -0.047$
	$P = 0.005$	$P = 0.450$	$P = 0.017$	$P = 0.541$
Model 2	$r = -0.226$	$r = -0.065$	$r = -0.180$	$r = -0.051$
	$P = 0.003$	$P = 0.395$	$P = 0.018$	$P = 0.509$
Model 3	$r = -0.189$	$r = 0.032$	$r = -0.176$	$r = -0.013$
	$P = 0.014$	$P = 0.678$	$P = 0.022$	$P = 0.864$
Model 4	$r = -0.177$	$r = 0.010$	$r = -0.231$	$r = -0.049$
	$P = 0.022$	$P = 0.897$	$P = 0.003$	$P = 0.528$
Model 5	$r = -0.198$	$r = -0.017$	$r = -0.206$	$r = -0.051$
	$P = 0.011$	$P = 0.828$	$P = 0.008$	$P = 0.514$
	$R^2 = 0.141$	$R^2 = 0.190$	$R^2 = 0.259$	$R^2 = 0.134$
	$F_{11,162} = 2.42$	$F_{11,162} = 3.46$	$F_{11,162} = 5.15$	$F_{11,162} = 2.27$
	$P = 0.008$	$P < 0.008$	$P < 0.001$	$P = 0.013$

Values are given as covariate-adjusted correlation coefficients (r) with P values. Significant partial correlation coefficients are given in bold types. Model 1: No adjustment for covariates; Model 2: Adjustment for age and gender; Model 3: Adjustment for covariates in Model 2 plus immigrant status, season, and body mass index; Model 4: Adjustment for covariates in Model 3 plus depression and posttraumatic stress disorder; the fully adjusted Model 5 with model statistics: Adjusted for covariates in Model 4 plus pain duration, comorbid somatic pain condition, and number of pain medication categories.

($r = 0.10$, $P = 0.17$). In addition, greater WPI was associated with greater SSS ($r = 0.24$, $P = 0.001$).

Associations of Continuously Scaled 25-OH D Levels with Covariates

Lower levels of 25-OH D were found in patients with an immigrant background compared with nonimmigrants (38.5 ± 20.8 nmol/L vs 45.2 ± 22.2 nmol/L; $P = 0.034$) and during the winter relative to the summer season (36.9 ± 17.9 nmol/L vs 45.0 ± 23.9 nmol/L, $P = 0.033$). There were no significant associations between 25-OH D levels and age ($P = 0.61$), gender ($P = 0.69$), pain duration ($P = 0.19$), depression ($P = 0.21$), PTSD ($P = 0.44$), comorbid somatic pain conditions ($P = 0.24$), and the count of pain medication categories ($P = 0.31$). In terms of individual pain medication categories, 25-OH D levels also showed no significant relation with the use of paracetamol ($P = 0.57$), NSAIDs ($P = 0.35$), tramadol ($P = 0.92$), strong opioids ($P = 0.36$), anticonvulsants ($P = 0.53$), and antidepressants ($P = 0.96$).

Associations of Continuously Scaled 25-OH D Levels with Central Sensitivity Measures

Table 2 shows the results of the five linear regression models for the association of 25-OH D levels with measures of central hypersensitivity with subsequent adjustment for four blocks of covariates. In the final Model 5, which adjusted for all 10 covariates, lower levels of vitamin D were significantly associated with higher algometry scores ($P = 0.011$) and higher SSS ($P = 0.008$), explaining 3.9% and 4.3% of the respective variances. Figure 1 shows the partial regression plots of these relationships. Moreover, unstandardized coefficients B indicated a

mean $\pm$ standard error of the mean increase in algometry scores of 0.607 ± 0.253 and in SSS of 0.528 ± 0.197 for each 25 nmol/L decrease in the 25-OH D level. As an example, this would mean that the difference in 25-OH D levels between patients with 12 nmol/L and those with 94 nmol/L and 107 nmol/L, respectively, accounts for a 2-unit difference in algometry scores and SSS. In contrast, there was no significant association between 25-OH D levels and both the WPI ($P = 0.83$) and a diagnosis of fibromyalgia ($P = 0.63$).

The size and significance of the partial correlation coefficients changed little between the unadjusted Model 1 and Models 2–5 for all four central sensitivity measures. As shown in Table 3, this also was the case after adjustment for each pain medication category separately in lieu of the total count of categories of pain medications. Table 3 further shows that the individual categories of pain medications were not significantly related to algometry scores, WPI, SSS, and fibromyalgia.

In addition to 25-OH D levels, several covariates showed a significant relationship with measures of central sensitivity in the fully adjusted regression model (Model 5 in Table 2). Older patients had higher algometry scores than younger ones ($r = 0.183$, $P = 0.019$). Patients with an immigrant background ($r = 0.182$, $P = 0.20$) and those with a greater BMI ($r = 0.213$, $P = 0.006$) had a higher WPI. Patients with a comorbid somatic pain conditions had a lower SSS than those without a somatic pain conditions ($r = -0.214$, $P = 0.006$). Clinical depression was associated with a greater SSS ($r = 0.337$, $P < 0.001$) and fibromyalgia ($r = 0.219$, $P = 0.005$). Likewise, PTSD was also related to a greater SSS ($r = 0.169$, $P = 0.030$) and fibromyalgia ($r = 0.155$, $P = 0.047$).
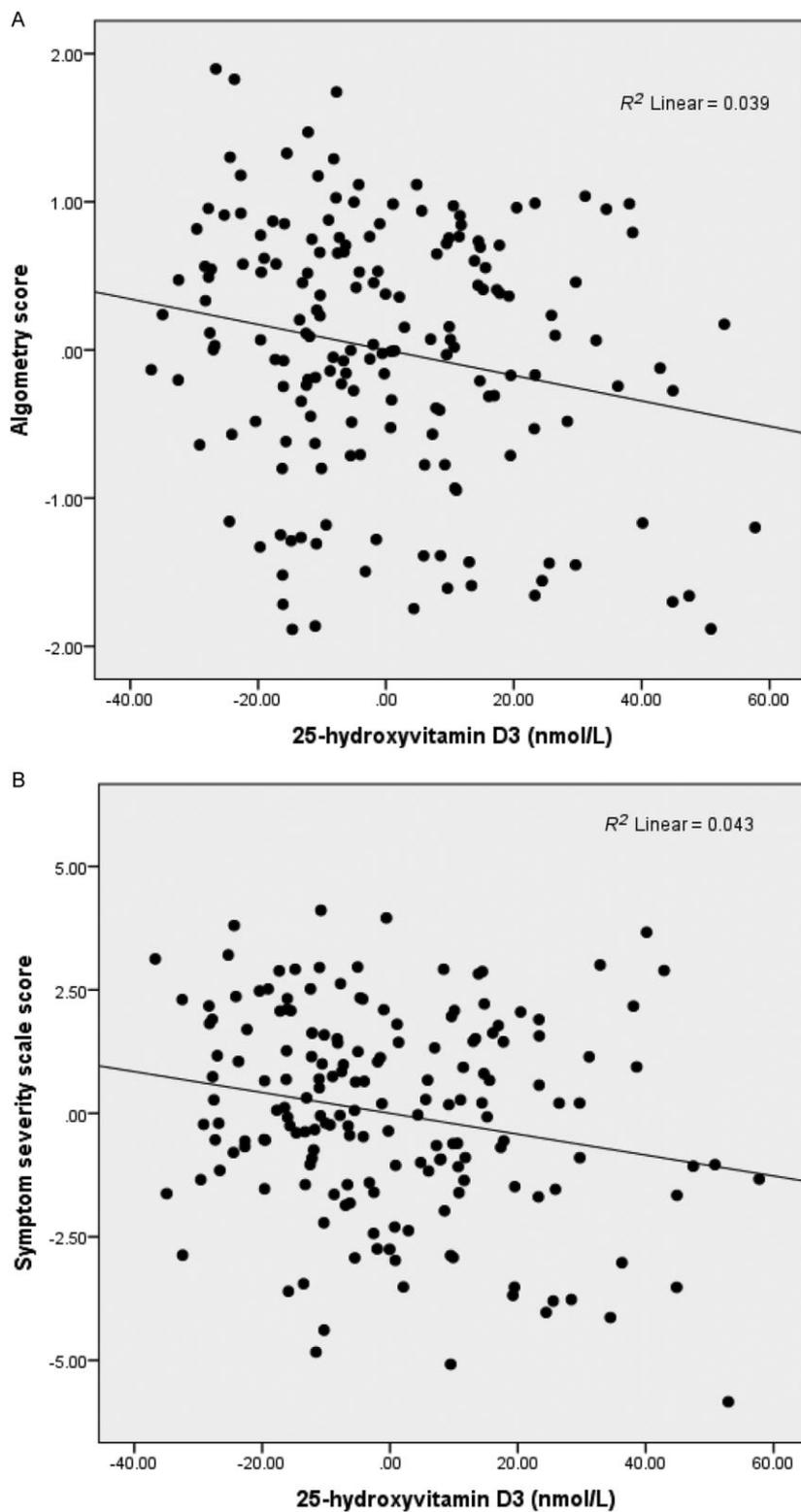
Figure 1 Multivariate association of vitamin D levels with central hypersensitivity.

The partial regression plots with fit line depict the significant associations of vitamin D levels with middle finger algometry scores (Panel A; $P = 0.011$) and symptom severity scale scores (Panel B; $P = 0.008$) across all 174 patients. Statistical adjustment was made for age, gender, immigrant status, season, body mass index, depression, post-traumatic stress disorder, pain duration, comorbid somatic pain condition, and total count of pain medication categories.

Table 3 Effect of pain medications on the link of vitamin D with central hypersensitivity

Medication Category	Algometry Scores	Widespread Pain Index	Symptom Severity Score	Fibromyalgia
Paracetamol	**r vit D = –0.204**	r vit D = –0.015	**r vit D = –0.212**	r vit D = 0.052
	r medi = 0.140	r medi = –0.038	r medi = 0.112	r medi = –0.037
NSAIDs	**r vit D = –0.198**	r vit D = –0.024	**r vit D = –0.198**	r vit D = 0.053
	r medi = 0.002	r medi = 0.083	r medi = –0.111	r medi = –0.025
Tramadol	**r vit D = –0.197**	r vit D = –0.013	**r vit D = –0.208**	r vit D = 0.050
	r medi = 0.035	r medi = 0.117	r medi = –0.031	r medi = –0.061
Strong opioids	**r vit D = –0.203**	r vit D = –0.019	**r vit D = –0.212**	r vit D = 0.055
	r medi = –0.115	r medi = –0.091	r medi = –0.113	r medi = 0.115
Anticonvulsants	**r vit D = –0.198**	r vit D = –0.016	**r vit D = –0.209**	r vit D = 0.051
	r medi = 0.010	r medi = 0.044	r medi = –0.109	r medi = 0.016
Antidepressants	**r vit D = –0.198**	r vit D = –0.016	**r vit D = –0.207**	r vit D = 0.051
	r medi = –0.036	r medi = –0.027	r medi = –0.035	r medi = –0.021

All models were fully adjusted for age, gender, immigrant status, season, body mass index, depression, posttraumatic stress disorder, pain duration, comorbid somatic pain condition, and the respective medication category. Read model output for partial correlation coefficients (r) as follows, e.g., upper box to the left: The "r vit D" value shows the association between vitamin D levels and algometry scores with paracetamol used as the medication category. The "r medi" value shows the association between paracetamol use and algometry scores in that model. Significant partial correlation coefficients are given in bold types ($P < 0.05$).

Discussion

We investigated vitamin D levels in relation to measures of central hypersensitivity, primarily mechanical pain sensitivity, in patients with chronic pain of whom 47% met preliminary diagnostic ACR criteria for fibromyalgia. The cutoffs to distinguish deficient from insufficient and sufficient/normal vitamin D levels are not uniformly discussed in the literature and, moreover, depend upon what is felt to be an adequate level for the index disease under study [8]. Consensus data on adequate 25-OH D levels in chronic pain patients are to our knowledge not available; however, it may seem reasonable to define values below 50 nmol/L as vitamin D deficiency and values above 75 nmol/L as normal in clinical settings [8]. We found that almost three-fourths of our patients were deficient in vitamin D and another one-fifth showed vitamin D insufficiency. In other words, less than 10% of our patients had normal vitamin D levels. This low prevalence of normal vitamin D levels is similar to other studies on chronic pain patients in primary [2] and tertiary [10] care settings. About 50% of the general population would be expected to have normal vitamin D levels [43]. Therefore, clinicians should be aware that lower than normal vitamin D levels are more the rule than the exception in patients with chronic pain.

We found a significant inverse association between continuously scaled 25-OH D levels and mechanical pain sensitivity. This finding is in agreement with experimental animal work on provoked pain sensitivity [16]. Specifically, in our sample, a decrease of about 100 nmol/L in 25-OH D corresponded to a 2-unit increase on the numeric rating scale ranging from 0 to 10 for pressure pain intensity. This effect size has been shown to be of clear clinical relevance for self-reports of spontaneous chronic musculoskeletal pain [44]. Statistical adjustment for a range of potentially confounding variables, including individual categories of different pain medications, retained the significant association of low vitamin D levels with heightened mechanical pain sensitivity.

We did not observe a significant association between low 25-OH D levels and both a diagnosis of fibromyalgia fulfilling ACR 2010 criteria and the WPI, even after adjusting for important confounding variables. However, the question as to whether low vitamin D contributes to the development of self-reported spontaneous (i.e., unprovoked) pain in humans is as yet unresolved [1]. One reason for the inconsistent findings could be that low vitamin D deficiency mainly reflects general characteristics of the local population such as low sunlight exposure and overweight; for instance, not all studies show lowered vitamin D levels in fibromyalgia patients [14]. Another explanation for the inconsistent findings regarding vitamin D levels in chronic pain patients might be that self-reports of spontaneous pain, including a count of body areas where "it hurts," are not specific to core pathophysiological processes of mechanically evoked pain.

We found that low 25-OH D levels were significantly associated with higher scores on the severity scale for somatic symptoms, even when taking psychiatric comorbidity into account. This is important because the number of somatic symptoms irrespective of whether they can be medically explained or not has been shown to be positively associated with anxiety and depressive symptoms [45]. In agreement, we found a clinical diagnosis of depression and PTSD both to be associated with elevated SSS in our chronic pain patients in the full multivariate-adjusted model. Those patients with a presumed additional somatic pain condition had a lower SSS. Therefore, the more severe the SSS, the greater might the probability be that symptom severity of chronic pain patients is an expression of their central hypersensitivity. Of course,

such a reasoning would not preclude the possibility that somatic pain conditions in their own right contributed to neuroplastic changes underlying central hypersensitivity at some time during the course of the disease. An approximate difference in 25-OH D levels of 100 nmol/L between patients with deficient and normal vitamin D levels would seem clinically relevant regarding somatic symptom severity. For instance, a 2-unit difference in the fatigue score would mean that over the past week, fatigue was perceived as either a severe, pervasive, and life-disturbing problem or as a mild problem only [21].

Central hypersensitivity to a range of sensory stimuli from both the environment and "milieu interieur" is a helpful concept to explain the accumulation of somatic symptoms without the existence of peripheral pathophysiological or structural tissue changes. Within such a framework, functional somatic syndromes, including fibromyalgia and chronic fatigue syndrome (CFS) are now understood as central sensitivity syndromes [22]. Fibromyalgia and CFS are highly overlapping conditions that is evident by the fact that core symptoms that went into the ACR 2010 criteria for fibromyalgia, namely fatigue, unrefreshing sleep, and cognitive impairment [21], are also part of the Fukuda criteria to define CFS [46]. Many of the symptoms that count for the SSS do not only serve the diagnostic criteria of fibromyalgia but also those of other central hypersensitivity syndromes [47]. The relation between low 25-OH D and increased SSS suggests that the role of low vitamin D for central hypersensitivity has implications for the severity of different somatic symptoms, i.e., above and beyond pain-related ones. Whether vitamin D supplementation is effective to alleviate spontaneously reported chronic pain compared with placebo is inconclusive [48]. However, future randomized controlled trials should also test for effects of vitamin D supplementation on mechanically evoked pain intensity.

Our study has several limitations. The cross-sectional and nonexperimental design preclude any causal and mechanistic inferences. Theoretically, low 25-OH D levels might contribute to increased central hypersensitivity of different organ systems or, alternatively, central processes could also inhibit vitamin D metabolism top down. The ultimate goal for future studies is to gain a better understanding of the mechanisms involved in transduction, transmission, and perception of somatic symptoms, including chronic pain, in relation to different levels of vitamin D. We adjusted our analyses for a range of important correlates of vitamin D levels and central hypersensitivity measures. However, the lack of information on vitamin D sources from sunlight exposure, diet, and supplements might act as an important confound of our findings. Our study also lacked formal evaluation of malabsorption and proper liver function, the latter being important for the hydroxylation of biologically inert vitamin D coming from the skin and diet to 25-OH D [8]. Prescribed pain medications were frequent and not stopped before algometry. We controlled for the total number of different medication categories and in complementary analysis also for individual categories, including anticonvulsants that enhance 25-OH D catabo-

lism and thus might have lowered vitamin D levels in our sample. However, the pharmacological interactions, potential impact on liver function, and individual effects on pain of these medications are all difficult to account for by statistical procedures. In the absence of a control group without chronic pain, it remains open to question whether the association between low vitamin D levels and increased algometry scores is specific to chronic pain patients. Because pain patients often are less mobile, physically active, and exposed to sunlight, the association of low vitamin D levels and higher algometry scores might reflect an epiphenomenon without necessarily having a cause–effect relationship. Whether our findings can be generalized to nonwhite populations and chronic pain conditions with a clearly defined primary biomedical cause remains unclear.

Taken together, we found in patients with chronic pain that lowered vitamin D levels are associated with elevated central hypersensitivity, namely increased mechanical pain sensitivity and severity of somatic symptoms. As the prevalence of vitamin D deficiency/insufficiency is high in this population, it may seem good clinical practice to screen for 25-OH D levels <75 nmol/L and to consider vitamin D supplementation following published guidelines [8,33].

Acknowledgment

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