

Vitamin D Levels Are Associated With Pain and Pain Catastrophizing in Patients With Fibromyalgia Syndrome

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ABSTRACT

Objective: Low vitamin D (VD) levels may increase pain sensitivity, particularly by enhancing central sensitivity. Fibromyalgia is associated with disruptions in neurotransmitters and inflammatory pathways within the central nervous system, leading to an increased sensitivity of pain signals. This study aimed to investigate the relationship between vitamin D levels and pain, pain catastrophizing, function, depression, and anxiety.

Materials and Methods: This study included 153 patients with Fibromyalgia Syndrome (FMS) and 153 healthy individuals. Vitamin D levels were measured using 5 ml blood samples obtained from both patients and healthy individuals. The Hospital Anxiety and Depression Scale (HADS), Pain Catastrophizing Scale (PCS), McGill Pain Questionnaire-Short Form (MPQ), and Fibromyalgia Impact Questionnaire (FIQ) were used to evaluate pain, pain catastrophizing, psychological symptoms, and function, respectively.

Results: VD levels were statistically lower in the FMS group (17.71 ± 9.32 ng/ml) compared to the control group (20.40 ± 9.33 ng/ml) ($p < 0.05$). No statistical difference was found among groups classified according to vitamin D subgroups in terms of FIQ, MPQ, PCS, and HADS scores ($p > 0.05$). There was a negative correlation between VD levels and MPQ, as well as all subgroups of PCS ($p > 0.05$), while no significant correlation was found between VD levels and depression, anxiety, or function.

Conclusion: VD levels in patients with FMS were found to be lower than those in healthy individuals, and VD levels were associated with pain and pain catastrophizing in this study. Physician-supervised VD supplementation may improve pain catastrophizing in patients with FMS.

Keywords: Fibromyalgia, pain, pain catastrophizing, vitamin D.



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INTRODUCTION

Vitamin D (VD), synthesized in the skin under the influence of ultraviolet light, is a steroidal, fat-soluble hormone. Given that the half-life of its active form is approximately four hours, the use of 25(OH)D is recommended in clinical practice to determine VD levels.¹ Vitamin D is known for its role in modulating various inflammatory pathways, which are linked to the onset



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and persistence of chronic pain. Moreover, it seems to have the potential to alter peripheral pain sensitivity through its anti-inflammatory properties.² Changes in cortical, immune, hormonal, and neuronal pathways involved in chronic pain are believed to be influenced by VD levels. Research has highlighted the impact of VD on pain symptoms, underscoring its role in the development of chronic pain conditions and associated comorbidities.³ These findings suggest a link between VD deficiency and chronic pain conditions such as Fibromyalgia Syndrome (FMS), proposing that low VD levels may exacerbate pain sensitivity, particularly by enhancing central sensitivity.² Animal studies have demonstrated that inadequate vitamin D levels can lead to an increased sensitivity of muscles to mechanical stimuli, accompanied by an elevation in nerve endings related to muscle pain, even in the absence of muscle or bone disorders.⁴ Vitamin D's anti-inflammatory effects imply that low levels may lead to an increased production of pro-inflammatory cytokines. This elevation in cytokines could potentially disrupt how pain signals are processed in both the peripheral and central nervous systems.⁵ Fibromyalgia patients, known for experiencing persistent pain, are among those greatly impacted by such conditions.

FMS is characterized by symptoms including widespread chronic muscle pain of unknown etiology, decreased sleep quality, fatigue, morning stiffness, and psychological issues such as anxiety and depression.⁶ The most important and characteristic symptom in FMS is chronic widespread musculoskeletal pain. Pain and other symptoms are always present, but their intensity varies from day to day and throughout the day.⁷

Persistent pain can predispose individuals to depression due to the feeling of restriction that accompanies it.⁸ In FMS, comorbid psychopathologies are more common than in other chronic pain syndromes, with almost all patients receiving at least one psychiatric diagnosis throughout their lives. The most common accompanying psychopathologies are anxiety and mood disorders. In addition, personality traits such as neuroticism, agreeableness, and conscientiousness observed in these patients have been found to be associated with high levels of pain anxiety and pain catastrophizing.⁹ Catastrophizing is defined as a negative cognitive-emotional response to pain and anticipated pain and is associated with pain-related emotional stress, anxiety, depression, analgesic intake, and hospitalization. It has been reported that the severity of depression, anxiety, and catastrophizing are interrelated but not directly correlated with pain intensity in FMS patients.¹⁰ High levels of catastrophizing thoughts have been found to be associated with a more intense perception of pain.¹¹

Studies have shown that VD deficiency is found in patients diagnosed with FMS compared to healthy controls, and this deficiency may be associated with chronic pain.¹² Considering the relationship between VD levels and central sensitization, we hypothesize that pain catastrophizing in patients with chronic pain may be related to VD levels. Therefore, this study aimed to compare vitamin D levels between FMS patients and healthy controls while exploring the correlation between vitamin D levels and pain, pain catastrophizing, quality of life, depression, and anxiety within the FMS patient group.

MATERIALS AND METHODS

Our study received approval from the Ethics Committee at Firat University (2022/14-32), and all patients were informed both verbally and in writing about the study, subsequently signing a consent form.

The study included 153 individuals diagnosed with FMS according to the American College of Rheumatology criteria¹³ and 153 healthy participants who volunteered for the research. The sample size was calculated using the formula $n = t^2pq/d^2$, which is used when the number of individuals in the population is unknown. Given the 3% prevalence of fibromyalgia in the general population,¹⁴ the minimum sample size was determined to be 125.

Inclusion criteria for the study were individuals aged 18–65 years with persistent pain lasting longer than six weeks, diagnosed with FMS through clinical and physical examination. Exclusion criteria included pregnancy, malignancy or infection, severe spinal stenosis, concomitant systemic inflammatory rheumatic disease, or a history of surgery within the last three months.

Outcome Measurements

Demographic information (age, height, weight, educational status, medication use) of the participants was collected. VD levels were determined using 5 ml blood samples from both patients and healthy individuals. Pain, quality of life, depression, anxiety, and pain catastrophizing were evaluated in the patient group.

Pain Level

The McGill Pain Questionnaire-Short Form (MPQ-SF) was used to assess both the type and severity of pain. Validated and proven reliable in Turkish, the questionnaire includes 11 sensory and 4 affective descriptors, totaling 15 words. Participants rated these descriptors on a scale of 0 to 3, indicating no pain, mild, moderate, or severe pain, thus generating three pain scores. Additionally, pain intensity at the time of evaluation was measured using both the Visual Analog Scale (VAS) and a 6-point Likert scale.¹⁵

Pain Catastrophizing

The Pain Catastrophizing Scale (PCS) includes 13 items designed to measure the extent of negative thoughts and emotions individuals experience in relation to their pain. The scale is divided into three subscales: helplessness, exaggerated perception, and rumination. High scores indicate a high level of negative impact. Subscale scores are obtained by summing the scores of the related items, while the overall score is derived from the sum of all 13 items, yielding a total score range from 0 to 52 points.¹⁶

Depression and Anxiety

The Hospital Anxiety and Depression Scale (HADS) is used to assess levels of anxiety and depression. This self-report questionnaire comprises 14 items, with half dedicated to assessing depression and the other half to anxiety. Higher scores on the scale indicate more severe levels of anxiety and depression.¹⁷

Function

The Fibromyalgia Impact Questionnaire (FIQ) assesses the functional abilities of patients with Fibromyalgia Syndrome (FMS). The questionnaire comprises 10 items, the first of which consists of 10 questions related to daily activities. The scores from these 10 sub-items are summed and then divided by the total number of valid responses to calculate a score that reflects physical functioning. A total score from 0 to less than 39 indicates a mild impact, more than 39 to less than 59 indicates a moderate impact, and more than 59 to 100 indicates a severe impact.¹⁸

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) (Version 22.0, SPSS Inc., Chicago, IL, USA) was utilized for statistical analysis of the data collected in the study. Descriptive statistics were presented as mean±standard deviation. The Kolmogorov-Smirnov test was employed to analyze the distribution for normality. Numerical data not exhibiting a normal distribution were analyzed using the Mann-Whitney U test and the Kruskal-Wallis test. If $p < 0.05$ after conducting the Kruskal-Wallis test, the Mann-Whitney U test was used to determine from which group or groups the difference originated. The Spearman correlation analysis was utilized to assess the relationship between the parameters. The correlation coefficient (r) was interpreted as follows: [0–0.30] indicated a weak correlation, [0.30–0.60] a moderate correlation, [0.60–0.75] a strong correlation, and [0.75–1] a very strong correlation.

RESULTS

The demographic characteristics and VD levels of the patients are listed in Table 1. No statistically significant differences were

Table 1. Comparison of demographic characteristic and clinical measurements between patients with Fibromyalgia Syndrome and healthy controls

Demographics	FMS patients (Mean±SD) (n=153)	Healthy controls (Mean±SD) (n=153)	p
Age (years)	44.37±8.17	44.40±8.78	0.980
BMI (kg/m ²)	28.39±4.93	28.08±5.11	0.548
Occupation, n (%)			0.359
No	75 (49%)	67 (43.8%)	
Yes	78 (51%)	86 (56.2%)	
Education level, n (%)			0.973
Literacy	19 (12.4%)	18 (11.8%)	
Primary school	75 (49%)	72 (47.1%)	
High school	36 (23.5%)	39 (25.5%)	
University	23 (15%)	24 (15.7%)	
Vitamin D, n (%)			0.009
Deficiency (<20 ng/ml)	105 (68.6%)	86 (56.2%)	
Insufficiency (20–30 ng/ml)	35 (22.9%)	46 (30.1%)	
Normal (>30 ng/ml)	13 (8.5%)	21 (13.7%)	

FMS: Fibromyalgia Syndrome; BMI: Body mass index; SD: Standard deviation; kg: Kilograms; m: Meters.

observed between the groups concerning age ($p=0.980$), body mass index ($p=0.548$), occupation ($p=0.359$), and education level ($p=0.973$). However, notable differences emerged in vitamin D levels, showcasing statistically lower values in the FMS group (17.71 ± 9.32 ng/ml) compared to the healthy controls (20.40 ± 9.33 ng/ml) ($p=0.009$). The comparison of clinical parameters according to VD subgroups in patients with FMS is presented in Table 2. When classified according to VD subgroups, no statistical differences were found between the three groups in the FIQ ($p=0.671$), MPQ ($p=0.054$), and PCS scores (Exaggerated Pain ($p=0.128$), Ruminations ($p=0.163$), Despair ($p=0.106$), Total ($p=0.073$)), as well as in the HADS Anxiety ($p=0.227$), HADS Depression ($p=0.893$), and HADS Total ($p=0.431$).

The relationship between VD levels and clinical parameters in patients with fibromyalgia is summarized in Table 3. A weak negative correlation was observed between VD levels and various clinical scales: MPQ ($r=-0.242$, $p=0.003$), PCS-Exaggerated Pain ($r=-0.214$, $p=0.008$), PCS-Ruminations ($r=-0.193$, $p=0.017$), PCS-Despair ($r=-0.184$, $p=0.023$), and PCS-Total ($r=-0.227$, $p=0.005$).

Table 2. Comparison of assessment parameters across subgroups with different vitamin D levels in patients with Fibromyalgia Syndrome

Parameters	Vitamin D deficiency (n=105)	Vitamin D insufficiency (n=35)	Normal level of vitamin D (n=13)	p
FIQ	74.99 [63.32; 78.67]	71.97 [66.24; 78.67]	68.34 [63.93; 75.00]	0.671
MPQ	60.00 [55.50; 65.50]	57.00 [49.00; 61.00]	58.00 [46.00; 63.50]	0.054
PCS-exaggerated pain	8.00 [5.00; 9.00]	6.00 [4.00; 8.00]	7.00 [3.00; 8.00]	0.128
PCS-ruminations	8.00 [6.00; 10.00]	7.00 [5.00; 9.00]	7.00 [3.50; 9.00]	0.163
PCS-despair	10.00 [8.00; 13.00]	9.00 [7.00; 11.00]	9.00 [6.50; 11.00]	0.106
PCS-total	25.00 [19.00; 31.50]	23.00 [17.00; 28.00]	22.00 [15.00; 26.00]	0.073
HADS-anxiety	9.00 [7.00; 12.00]	8.00 [6.00; 11.00]	9.00 [7.00; 17.00]	0.227
HADS-depression	10.00 [7.00; 12.00]	10.00 [7.00; 11.00]	9.00 [7.00; 12.50]	0.893
HADS-Total	19.00 [15.50; 24.00]	18.00 [15.00; 22.00]	19.00 [15.00; 27.00]	0.431

FIQ: Fibromyalgia Impact Questionnaire; HADS: Hospital Anxiety and Depression Scale; MPQ: McGill Pain Questionnaire; PCS: Pain Catastrophizing Scale.

DISCUSSION

This study aimed to evaluate VD levels in patients with FMS, compare these levels with those of healthy controls, and explore the relationship between VD levels and pain, pain catastrophizing, and psychosocial symptoms. Our findings reveal that FMS patients exhibited significantly lower VD levels compared to the age- and gender-matched healthy group. Specifically, 68.6% of FMS patients were found to have VD deficiency, compared to 56.2% in the healthy controls. Additionally, a weak negative correlation was identified between VD levels and both pain and pain catastrophizing in patients with FMS. No significant relationships were observed with quality of life, depression, or anxiety levels. When patients were categorized based on VD levels, no significant differences were found in assessment parameters between the groups. These results demonstrate that FMS is associated with VD deficiency, and such a deficiency may cause pain and pain catastrophizing in affected patients. Subsequently, VD supplementation may ameliorate pain catastrophizing in FMS patients.

Although some studies have reported VD deficiency in patients with FMS,^{19,20} others also have shown contrary results.²¹ In our research, 68.6% of FMS patients had VD deficiency and 22.9% had VD insufficiency, rates that were significantly different from those observed in healthy controls. Anxiety, depression, and physical inactivity are common symptoms among FMS patients.²² Anxiety and depression are linked to physical inactivity and obesity, which consequently reduce the likelihood of exposure to outdoor sunlight. Furthermore, adherence to vitamin D-poor vegan diets, a popular alternative medicine approach for FMS, may explain the observed VD deficiency in some studies.²² Significantly lower VD levels were reported in

FMS patients compared to healthy controls.^{19,20} For instance, a study examining VD levels in 75 white patients with FMS found that 13.3% had VD deficiency, 56.0% had insufficient levels, and 30.7% had normal vitamin D levels.²³ Olama et al.²⁴ conducted a study involving 50 premenopausal Egyptian women diagnosed with fibromyalgia, comparing them to a group of 50 healthy female controls matched for age; a significant deficiency in VD was found in the FMS group. McBeth et al.¹⁹ researched men aged 40–79 years across eight European cities in different countries. In their extensive cross-sectional investigation, patients with FMS exhibited notably reduced average vitamin D (VD) levels compared to their counterparts in the healthy control group. VD levels were found to be significantly lower in 410 pre- and postmenopausal women with FMS compared to healthy controls.²⁵ These studies are parallel to our study. On the other hand, the studies conducted by Pena et al.²⁶ and Maafi et al.²¹ found no association between VD levels and FMS. While Pena et al.²⁶ found no significant difference in VD levels between FMS patients and healthy controls, Maafi et al.²¹ unexpectedly concluded that 25-OHD levels in FMS patients were higher than those in the control group. The authors speculated that patients may have been using over-the-counter VD supplements.

In Fibromyalgia Syndrome (FMS), individuals often experience chronic neuropathic pain alongside widespread hypersensitivity of the skin.²⁷ Although the precise mechanisms behind the development of allodynia and hyperalgesia remain elusive, there are indications of the involvement of various levels within the pain processing system, from muscle nociceptors to the cortical regions. This heightened pain sensitivity appears to stem from central sensitization of nociceptive neurons in the dorsal horn, along with an imbalance between inhibitory

Table 3. The relationship between Vitamin D levels and assessment parameters in patients with Fibromyalgia syndrome

	Vitamin D	FIQ	MPQ	PCS-exa. pain	PCS-rum.	PCS-des.	PCS-total	HADS-anxiety	HADS-depression	HADS-total
Vitamin D										
r	1	-0.040	-0.242	-0.214	-0.193	-0.184	-0.227	-0.090	-0.015	-0.058
p	.	0.619	0.003	0.008	0.017	0.023	0.005	0.268	0.853	0.479
FIQ										
r	-0.040	1	-0.110	-0.103	-0.041	0.004	-0.046	0.317	0.168	0.277
p	0.619	.	0.175	0.203	0.618	0.958	0.569	<0.001	0.038	0.001
MPQ										
r	-0.242	-0.110	1	0.696	0.656	0.600	0.709	0.042	-0.074	-0.018
p	0.003	0.175	.	<0.001	<0.001	<0.001	<0.001	0.604	0.363	0.825
PCS-exaggerated pain										
r	-0.214	-0.103	0.696	1	0.752	0.610	0.887	0.166	0.002	0.087
p	0.008	0.203	<0.001	.	<0.001	<0.001	<0.001	0.040	0.977	0.284
PCS-ruminations										
r	-0.193	-0.041	0.656	0.752	1	0.542	0.850	0.151	-0.041	0.044
p	0.017	0.618	<0.001	<0.001	.	<0.001	<0.001	0.062	0.615	0.587
PCS-despair										
r	-0.184	0.004	0.600	0.610	0.542	1	0.845	0.075	-0.114	-0.022
p	0.023	0.958	<0.001	<0.001	<0.001	.	<0.001	0.355	0.615	0.786
PCS-total										
r	-0.227	-0.046	0.709	0.887	0.850	0.845	1	0.164	-0.046	0.057
p	0.005	0.569	<0.001	<0.001	<0.001	<0.001	.	0.043	0.159	0.484
HADS-anxiety										
r	-0.090	0.317	0.042	0.166	0.151	0.075	0.164	1	0.307	0.787
p	0.268	<0.001	0.604	0.040	0.062	0.355	0.043	.	<0.001	<0.001
HADS-depression										
r	-0.015	0.168	-0.074	0.002	-0.041	-0.114	-0.046	0.307	1	0.807
p	0.853	0.038	0.363	0.977	0.615	0.615	0.159	<0.001	.	<0.001
HADS-total										
r	-0.058	0.277	-0.018	0.087	0.044	-0.022	0.057	0.787	0.807	1
p	0.479	0.001	0.825	0.284	0.587	0.786	0.484	<0.001	<0.001	.

exa: Exaggerated; rum: Ruminations; des: Despair; FIQ: Fibromyalgia Impact Questionnaire; HADS: Hospital Anxiety and Depression Scale; MPQ: McGill Pain Questionnaire; PCS: Pain Catastrophizing Scale.

and facilitatory signals in the pathways from the brainstem to the dorsal horn.²⁸ In our investigation, a weak and negative correlation emerged between vitamin D levels and both the experience of pain and pain catastrophizing among FMS patients. It is known that VD levels affect pain in FMS. Our study demonstrated that VD levels have a weak association not only with pain but also with the catastrophizing of pain.

Fibromyalgia seems to correlate with an apparent disruption in neurotransmitters and inflammatory pathways in the central nervous system, leading to increased sensitivity in processing pain signals.²⁷ It is possible that insufficient vitamin D levels may reduce the activity of several inflammatory pathways linked to persistent pain, including interleukin-4 and Transforming Growth Factor Beta 1 (TGF-β1). Moreover,

vitamin D is involved in inhibiting Tumor Necrosis Factor Alpha (TNF- α) in astrocytes and microglia, both of which contribute to amplifying pain signals within both the peripheral and central nervous systems.²⁹ Findings from the European Male Aging Study (EMAS) suggest that high levels of physical activity do not significantly impact the likelihood of vitamin D deficiency, hinting at a potential intrinsic connection between vitamin D levels and pain. Moreover, both skeletal muscles and the brain have vitamin D receptors, and the central nervous system is capable of activating vitamin D.²⁸ These mechanisms may explain the observed association between VD levels and pain catastrophizing in our study. Future studies could explore the correlation between VD levels and pain catastrophizing due to the weak correlation and assess the changes in pain catastrophizing status with VD supplementation.

Fibromyalgia is a complex condition characterized by prominent symptoms such as anxiety and depression.²² Our study found no significant correlation between VD deficiency levels and function, anxiety, or depression levels. However, a cross-sectional study concluded that VD deficiency was correlated with both anxiety and depression in individuals diagnosed with fibromyalgia.²⁰ One study showed that patients with VD deficiency (<25 nmol/L) had higher HADS levels compared to those with insufficient or normal levels (≥ 50 nmol/L).²² Additionally, in research evaluating clinical symptoms of FMS and VD levels, a negative correlation was observed between levels of 25(OH)D and symptoms such as widespread body pain, headache, and sleep disturbance, suggesting a link between low VD levels and clinical symptoms of FMS.³⁰ Our study observed that patients with VD deficiency exhibited higher levels of anxiety and depression compared to those without deficiency. Literature suggests that depression and anxiety cause VD deficiency in FMS patients by reducing outdoor activities.²² However, data from the EMAS indicated no relationship between physical activity levels and VD levels. Similarly, our findings revealed no significant relationship between anxiety, depression, and VD deficiency, suggesting that different outcomes can be observed with different patient numbers.

No significant differences were found in depression, anxiety, function, pain, and pain catastrophizing scores between patients with and without VD deficiency or insufficiency in this study. Among our study participants, 66.8% had VD deficiency, 22.2% had insufficiency, and 8.5% had normal VD levels. This result is not surprising, as VD levels are generally low in patients with FMS. However, the large difference in the number of patients between the groups may be why a statistically significant difference was not observed. Studies with groups consisting of similar numbers of patients may yield different results. Karras et al.²³ reported that HADS anxiety and depression levels were higher in patients with VD deficiency than in those with normal or insufficient VD levels.

This study has some limitations. One limitation is that it did not examine the relationship between VD levels and symptoms commonly seen in FMS, such as sleep quality and fatigue. Additionally, studies involving similar numbers of patients with VD deficiency, insufficiency, and normal levels may produce different results.

CONCLUSION

In conclusion, this study demonstrated that patients with FMS had lower vitamin D levels compared to healthy individuals, and that VD levels were associated with pain and pain catastrophizing in this study. Our research is important as it is the first to examine the relationship between VD levels and pain catastrophizing in FMS patients. Pain catastrophizing, frequently observed in FMS, may be linked to VD deficiency. Physician-supervised VD supplementation may improve pain catastrophizing in patients with FMS. Further studies should explore the effects of VD supplementation on pain catastrophizing.

Ethics Committee Approval: The Firat University Non-Interventional Research Ethics Committee granted approval for this study (date: 01.12.2022, number: 2022/14-32).

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