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# The role of vitamin D therapy in patients with fibromyalgia and its effect on quality of life

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## Abstract

### Objective

To investigate the level of vitamin D and the effect of its therapy on quality of life in patients with fibromyalgia who had vitamin D deficiency.

### Patients and methods

Sixty patients presenting with fibromyalgia and 30 healthy controls were studied. Patients were grouped as deficient (<20 ng/ml), inadequate (20–30 ng/ml), and sufficient (>30 ng/ml) according to the levels of vitamin D. Vitamin D replacement was performed for patients with deficiencies and inadequacies and they were assessed before and after vitamin D therapy using the following scales: visual analog scale, fibromyalgia impact questionnaire, short form-36, Arizona sexual life questionnaire, and Beck depression scale and correlation were also calculated between vitamin D and different scores.

### Results

Sixty women with fibromyalgia were included in this study. The mean age of all fibromyalgia patients was 30.9±6.1 years. Vitamin D deficiencies and inadequacies were observed in 63.3% of the patients (n=42). The 25(OH)D levels increased significantly after 3 months of supplementation. In scales examined after vitamin D replacement therapy, statistically significant differences were observed in the fibromyalgia impact questionnaire, Beck depression inventory, visual analog scale, and short form-36 compared with pretreatment; also there is negative correlation between vitamin D levels and parameters of measuring quality of life.

### Conclusion

Vitamin D deficiency may be associated with fibromyalgia. Vitamin D supplementation seems to improve symptoms and quality of life in patients with fibromyalgia.

**Keywords:** Depression, fibromyalgia, quality of life, vitamin D, widespread pain

## INTRODUCTION

Fibromyalgia syndrome (FMS) is a noninflammatory disease characterized by widespread musculoskeletal pain, fatigue, and susceptibilities in the absence of another clinical disorder that could result in similar clinical manifestations, the cause of which is not fully understood [1].

FMS is observed in all ages, sexes, and races. It is 10 times more frequent in women [2]. Its prevalence increases with age but is most commonly seen between the ages of 20 and 55 years. Although symptoms concerning many systems may be observed, pain is the most disturbing symptom. This is an important issue not only for the patient but also for the physician [3].

FMS is not a life-threatening disease; however, it can lead to serious health expenses owing to the difficulties encountered in its therapy [4]. The symptoms of FMS are similar to symptoms observed in vitamin D deficiency. While there were factors that could cause confusion such as methodological differences and heterogeneous patient populations in these studies, vitamin D deficiency was reported in a considerable proportion of patients with FMS in almost every study [5].

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Although the interface of chronic pain and hypovitaminosis D remains limited, pathophysiological evidence demonstrate that low vitamin D affects pain manifestation, and play a role in the etiology and maintenance of chronic pain states and associated comorbidity [6]. Recent study found that the degree of 25(OH)D deficiency corresponded to the degree of pain sensitivity in patients with fibromyalgia [6].

The relationship between FMS and serum vitamin D levels is controversial; however, an important finding is that patients' pain can be reduced and thus the quality of life increased with an inexpensive therapeutic method such as vitamin D replacement [7].

### Aim

This study is conducted to assess the effect of vitamin D replacement on clinical symptoms and disease-associated scores in patients with FMS who were observed to have vitamin D deficiency.

## PATIENTS AND METHODS

Sixty female premenopausal patients diagnosed as FMS according to the 2010 FMS classification criteria set and 30 healthy age-matched and sex-matched controls were included in this prospective study [8].

The serum 25-OH vitamin D level were measured using an enzyme-linked immunosorbent assay method. A serum vitamin D level of up to 20 ng/ml was identified as vitamin D deficiency, a serum level of 21–29 ng/ml was identified as vitamin D inadequacy, and a serum level of at least 30 ng/ml was identified as normal.

All patients and healthy volunteers were informed about the study and informed consent was obtained. Before vitamin D replacement the patients were assessed using the following scales: fibromyalgia impact questionnaire (FIQ) [9], short form-36 (SF-36) [10], visual analog scale (VAS) [11], Arizona sexual life questionnaire (ASEX) [12], and Beck depression scale [13]. Patients with vitamin D deficiency and inadequacy were given a weekly dose of 50 000 IU vitamin D for 12 weeks orally. At the beginning of the fourth month after the initiation of therapy, serum vitamin D levels were measured.

It was observed that the vitamin D levels of all patients returned to normal ( $\geq 30$  ng/ml). After therapy, scoring that was performed before therapy was repeated. Vitamin D levels of the patients before and after replacement were compared.

### Assessment tools

- (1) Sociodemographic information form: We studied patient's age, sex, educational level, socioeconomic status, place of residence, marital status, and duration of illness.
- (2) FIQ: This was used to assess the health status of patients with fibromyalgia using three domains: one to describe physical functioning and work status; second domain to describe the overall impact of fibromyalgia over the last 7 days, and the third domain to indicate the intensity level of symptoms including the level of energy, depression,

anxiety, morning tiredness, stiffness, pain, fatigue, sleep, tender to touch, memory problems, balance problems and sensitivity to loud noises, bright lights, odors, and cold over the past week were measured.

- (3) SF-36: This is a developed scale for the measurement of quality of life. Its validity and reliability studies were performed.
- (4) VAS: This is a scale that measures the severity of pain. VAS is a continuous scale, usually 10 cm (100 mm) in length, and the score is determined by measuring the distance and consists of three parts (0–30 mm: mild; 40–60 mm: moderate; 70–100 mm: severe).
- (5) ASEX: ASEX experience scale, which was developed and the validity and reliability studies were carried out by Soykan [12]. In the validity and reliability study in Turkey, it was observed that the internal consistency and reliability of the scale was high with 0.89–0.90 Cronbach's values and as such valid in establishing the sexual dysfunction. The scale with separate forms for women and men was filled in by the patients, and there was no need for special training for its interpretation. The score range of the six-point Likert-type scale consisting of five items was 5–30; an increase in the total score indicates sexual dysfunction. According to Soykan, scale score of at least 11 is the breaking point for sexual dysfunction.
- (6) Beck depression inventory (BDI): It was used to determine the risk of depression in the test subject and to measure the level of depressive symptoms and the change in severity. It was developed by Beck *et al.* [13].

### Inclusion criteria

Female premenopausal patients diagnosed as FMS according to the 2010 FMS classification criteria set and 30 healthy age-matched and sex-matched controls will be included in this prospective study.

### Exclusion criteria

Patients who have additional diseases and conditions including obesity, smoking, alcohol use history, osteoporosis, and osteoarthritis as well as those with a history of drug use that may affect the calcium metabolism currently or earlier will be excluded from the study. Female patients in the postmenopausal or climacteric period will not be included in the study.

### Statistical analysis

The statistical analysis of the study data was conducted using the statistical package for the social sciences version 16.0. SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, USA, SPSS Inc. Descriptive statistics are presented as frequency, percentage, mean, and SD. Comparisons between patients and control groups will be done by using Student's *t*-test. For all statistical tests, significance will be done using the correlation coefficient (*r*) test in which significance is defined as the level of *P* value of less than 0.05.

## RESULTS

We studied 60 female premenopausal patients diagnosed as

FMS and 30 healthy age-matched and sex-matched controls; the average age of the patients with fibromyalgia was  $30.9 \pm 6.1$  years. Biochemical and demographic parameters of patients with FMS and controls are listed in Table 1.

The level of vitamin D was observed to be below 30 ng/ml in 63.3% of the patients ( $n = 42$ ) and in 10% of controls ( $n = 3$ ).

Among patients with low and normal levels of vitamin D, no statistically significant difference was observed in their values in the FIQ, BDI, VAS, and ASEX and SF-36 as shown in Table 2.

In scales examined after vitamin D replacement therapy for patients, statistically significant differences were observed in the FIQ, BDI, and pain scale (VAS) compared with pretreatment ( $P = 0.001$  for all). After vitamin D therapy, no significant difference was observed in the fields of ASEX ( $P \geq 0.05$ ; Table 3).

After vitamin D therapy, statistically significant improvements were observed in physical function, physical role limitations, emotional role limitations, social function, mental health bodily pain levels and general health fields in patients' quality of life forms (SF-36). No significant difference was observed in vitality, before and after therapy (Table 3).

In our study, we found that in patients with fibromyalgia after receiving vitamin D therapy there is negative significant correlation between vitamin D level and FIQ, BDI, VAS, and ASEX. Also, there is negative correlation between vitamin D level and SF-36 parameters (Table 4).

In our study, there are significant negative correlations between vitamin D levels and quality of life parameters.

## DISCUSSION

Vitamin D deficiency may negatively contribute toward a chronic pain state like that associated with fibromyalgia. Authors suggests that vitamin D may play a protective role against chronic pain development and modulation in various cellular activities. Briefly, vitamin D has been found to act as a neuroactive steroid, interfere with the creation and role of neurotrophins, influence prostaglandin action, affect inflammatory pathways, and inhibit nitric oxide synthase and T-helper cells [14]. Till now, there is no definitive understanding of how vitamin D or vitamin D supplementation precisely functions to prevent or ameliorate chronic pain [15].

FMS importance has been increasing in recent years due to the fact that its etiology has not been known and that patients are not totally satisfied with the current therapeutic approaches [16]. Although the pain observed in FMS is generally described as being burning, gnawing, throbbing, and sharp, sometimes patients cannot describe the character of the pain. The level of pain is greater than is expected from the painful stimulus. The pain lasts longer than expected, and it is commonly felt without indicating anatomical spread. The pain threshold value of patients with FMS is lower compared with healthy people [17].

**Table 1: Demographic and laboratory data of study groups**

Parameters	Patient (mean±SD)	Control (mean±SD)	P
Age	30.9±6.1	30.9±5.7	0.73
Disease duration (years)	7.1±0.35		
Number of children	1.1±1.0	1.6±0.9	
Hemoglobin (11.5-15.5 g/dl)	11.06±1.15	11.01±1.38	0.11
Calcium (8.4-10.2 mg/dl)	8.09±1.1	7.51±0.97	0.31
Phosphorus (2.5-4.5 mg/dl)	3.34±0.65	3.4±0.66	0.92
Alkaline-phosphatase (U/l)	71.06±22.0	75.6±18.5	0.43
Parathyroid hormone (10-69 ng/l)	95.23±27.39	78.8±28.7	0.18
Vitamin D>30 ng/ml	18.34±9.1	36.3±9.99	0.01

Values are presented as mean±SD.

**Table 2: Difference between patients with low and normal vitamin D level as regard parameters for measuring quality of life**

Parameters	Patients with low vitamin D level (n=22) (mean±SD)	Patients with normal vitamin D level (n=38) (mean±SD)	P
FIQ	66.27±14.40	64.84±19.14	0.22
BDI	37.26±10.5	37.52±8.2	0.9
VAS	62.68±11.1	63.8±12.9	0.30
ASEX	21.37±6.16	23.0±4.05	0.16
SF-36			
Physical function	18.9±4.8	18.36±4.73	0.4
Role physical	4.54±1.1	4.97±1.15	0.9
Role emotional	4.27±1.3	3.8±0.91	0.04
Bodily pain	6.0±1.1	6.15±1.4	0.1
Social function	6.8±0.9	6.7±1.1	0.06
Mental health	18.68±3.1	18.65±3.1	0.94
Vitality	14.09±2.2	14.9±2.6	0.26
General health	12.54±1.1	14.26±1.3	0.82

ASEX, Arizona sexual experience scale; BDI, Beck depression inventory; FIQ, fibromyalgia impact questionnaire; SF-36, short form-36; VAS, visual analog scale.  $P < 0.05$ , significant.

In our study we found that there is low level of vitamin D in patients with FMS with mean  $18.34 \pm 9.1$ , compared with the control group with mean  $31.3 \pm 9.99$  with statistically significant difference,  $P = 0.01$ . Most studies selected for meta-analysis were in agreement with our study. Makrani *et al.*[18] estimates showed that FM patients in comparison with the control groups had on average,  $-0.56$  units lower concentration of vitamin D.

Patients' quality of life is severely impaired because of the widespread pain. They become apathetic and enter into a vicious circle. Considering that the prevalence in adult society is 2–4%, it should be considered as a major health problem for people and society [19].

The aim of this study is to detect the possible cause of FMS to reach the useful therapy for treatment and improve patients'

**Table 3: Patients with fibromyalgia before and after vitamin D supplementation as regards parameters of measuring quality of life and laboratory data**

Parameters	Patients with low vitamin D	After vitamin D treatment	P
FIQ	64.8±19.1	51.9±15.6	0.002
BDI	37.5±8.21	33.8±9.3	0.03
VAS	63.8±12.9	52.9±18.4	0.001
ASEX	23.0±4.05	21.6±4.75	0.18
SF-36			
Physical function	18.3±4.3	15.9±4.1	0.06
Role physical	4.9±1.1	3.15±1.3	0.001
Role emotional	3.84±0.9	3.05±1.11	0.01
Bodily pain	6.1±1.44	4.71±1.5	0.001
Social function	6.78±1.2	5.26±1.51	0.02
Mental health	18.6±3.14	16.9±3.8	0.02
Vitality	14.97±2.66	14.02±2.48	0.05
General health	14.26±2.48	12.7±2.37	0.001
Calcium (8.410.2 mg/dl)	7.19±1.24	9.18±0.77	0.001
PTH (10-69 ng/l)	107±21.3	49.7±10.37	0.001
Vitamin D <sub>3</sub> >30 ng/ml	16.27±5.4	59.05±12.4	0.001

ASEX, Arizona sexual experience scale; BDI, Beck depression inventory; FIQ, fibromyalgia impact questionnaire; PTH, parathyroid hormone; SF-36, short form-36; VAS, visual analog scale. *P*<0.05, significant.

**Table 4: Correlations between vitamin D levels and quality of life parameters**

Parameters	Pearson correlation	P
FIQ	-0.420	0.09
BDI	-0.029	0.001
VAS	-0.359	0.02
ASEX	-0.605	0.001
SF-36		
Physical function	-0.397	0.015
Role physical	-0.393	0.005
Role emotional	-0.44	0.001
Bodily pain	-0.508	0.017
Social function	-0.385	0.004
Mental health	-0.45	0.009
Vitality	-0.38	0.01
General health	-0.58	0.001

ASEX, Arizona sexual experience scale; BDI, Beck depression inventory; FIQ, fibromyalgia impact questionnaire; SF-36, short form-36; VAS, visual analog scale. *P*<0.05, significant.

quality of life. One of the causes that plays a role in FMS's etiopathogenesis may be the deficiency in serum vitamin D. Likewise 1,25(OH) D (active vitamin D) functions in around 30 tissues and organs in the cell nucleus and cell membrane, the musculoskeletal system being one of them [20]. Therefore, vitamin D is important for the normal development and function of the musculoskeletal system. Bone and muscle pains are the well-known symptoms of vitamin D deficiency [21].

In our study, it was observed that vitamin D replacement had positive significant effects on scores associated with quality of life in patients with FMS. However, in ASEX experience

scale improvement with no statistically significant effects was observed after therapy. Other studies were not in agreement with our study where they found no changes in ASEX experience scale [22].

However, in our study we found that vitamin D replacement had positive effects on scores associated with quality of life in patients with FMS including bodily pain. Other studies found that no significant improvement was observed in bodily pain [22]. Even though vitamin D deficiency does not play a role in the etiopathogenesis of FMS, the positive effect seen with vitamin D replacement is important in terms of increasing a patient's quality of life and providing an increase in mobilization. Increasing vitamin D deficiency along with increased immobilization, depression, and consequently reduced exposure to the sun in FMS is the result of a vicious circle.

In our study we found a low level of vitamin D in patients with fibromyalgia with negative significant correlation between vitamin D level and score of pain assessed by VAS, score of symptoms of fibromyalgia assessed by FIQ, as well as score of depression assessed by Beck depression score. Also Dogru A *et al.* [23] investigated the serum levels of vitamin D in individuals with and without FM and found lower blood vitamin D levels in the patients group and a significant negative correlation between vitamin D level versus pain (assessed by the VAS score), Beck depression score, and lumbar bone mineral density. Others reported significant negative correlations between vitamin D blood level and pain intensity. In addition, there were significant impacts of vitamin D on the quality of life in patients with FM based on the FIQ [24].

Interestingly, more recent studies have found that there is an improvement of VAS scores at 3 months after vitamin D supplementation, 90 (0–100) versus 30 (0–80), *P* = 0.002. Eight (72.2%) patients experienced a very significant improvement in symptoms. In addition, a trend for reduction of the number of tender points was observed after 3 months, 17 (11–18) versus 10 (0–18), *P* = 0.07 and they concluded that the 25(OH) D levels and disease symptoms in patients with fibromyalgia and vitamin D deficiency/insufficiency seem to improve with vitamin D supplementation [25].

Some studies have found that vitamin D was not associated with pain in patients with widespread pain syndrome and that no response was received with vitamin D replacement [26]. Other studies were not in agreement with the previous results and the authors have found that vitamin D replacement for 30 patients with FMS whose vitamin D levels were below 32 ng/ml caused significant improvement in patients' VAS pain values. It was confirmed that optimizing the vitamin D level in patients with FMS would make positive contributions to the perception of pain [27].

In a meta-analysis consisting of 12 studies and 1854 patients, it was stated that vitamin D and chronic widespread pain syndrome were associated. In this meta-analysis, the use



of low values such as 8–10 ng/ml as a diagnostic threshold value in widespread pain syndrome instead of 20 ng/ml of hypovitaminosis physiological value was emphasized to be better [28].

More recent studies were performed in the form of a systematic literature review to determine if vitamin D contributes to the pathology and disability of patients with fibromyalgia. They found that patients with fibromyalgia have low levels of vitamin D compared with healthy controls. Conflicting results were obtained on the effect of vitamin D on pain or symptom control, with no clear consensus as to the role of supplementation in the management of fibromyalgia. They concluded that there is an association between vitamin D deficiency and fibromyalgia. However, its role in the pathophysiology of fibromyalgia and the clinical relevance of identifying and treating this requires further elucidation with appropriately controlled studies [29].

Another study found that vitamin D deficiency was frequently observed in patients with FMS, and an improvement was observed with vitamin D therapy. However, a higher reduction rates in the FIQ score and BDI score have been suggested as clinically significant by some authors [30]. In a study including patients with chronic nonspecific widespread musculoskeletal pain, it was reported that replacement of vitamin D improved the quality of life (SF-36) [31]. In another study, there were no correlations found between vitamin D and health status [5].

Inequalities between some primary studies and our study may be due to differences in the inclusion/exclusion criteria which might be responsible for a part of this heterogeneity. In addition, some of the studies had considered the season of the study conduction but most of them had not taken it into consideration. This might be another explanation for the observed heterogeneity.

Evaluation tools for determining the fibromyalgia are patient dependent, and some environmental factors and personal mood at that time may affect the questionnaire. There is no quantitative method. However, we excluded patients with factors that would affect the vitamin D level and the situations that caused chronic pain which strengthens our study.

Vitamin D deficiency seems to be associated with the pathogenesis of FMS. So, we recommend that serum vitamin D levels should be checked as a general health problem and patients' corroborations were necessary. Long-term randomized, prospective studies with larger populations are required for illustrating the relationship between FMS and vitamin D.

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#### Conflicts of interest

There are no conflicts of interest.

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