

Detection of serum 25(OH)-vitamin D level in the serum of women with fibromyalgia syndrome and its relation to pain severity

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Objective

The aim of our study is to determine serum 25(OH)-vitamin D level in patients with fibromyalgia syndrome and its relation to pain.

Patients and methods

Fifty-three women with fibromyalgia syndrome diagnosed according to the American College of Rheumatology 1990 fibromyalgia diagnostic criteria and 50 age-matched healthy women as a control group were included in this study. Serum 25(OH)-vitamin D levels were determined in both the patient and the control groups. Fibromyalgia Impact Questionnaire scores and pain intensity measured by the visual analogue scale were evaluated.

Results

We found a statistically significant decrease in serum vitamin D level in the patient group in comparison with the control group. There was a significant negative correlation ($P = 0.000$) between vitamin D level and Fibromyalgia Impact Questionnaire. The same results are found between vitamin D level and visual analogue scale. There was no significant correlation between vitamin D level and erythrocyte sedimentation rate or C-reactive protein.

Conclusion

We found a significant association between fibromyalgia and low 25(OH)-vitamin D levels as suggested previously in other studies. Also, there was a correlation between the level of vitamin D in serum and severity of pain. We recommend vitamin D screening in every patient with chronic nonspecific musculoskeletal pain, especially fibromyalgia, and extended research in this area with large numbers of patients.

Keywords:

chronic pain, fibromyalgia, vitamin D

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Introduction

Fibromyalgia syndrome (FMS) is a chronic pain syndrome that causes widespread body pain, stiffness, and tenderness points on specific anatomic regions. It is also characterized by restless sleep, tiredness, fatigue, anxiety, depression, and disturbances in bowel functions [1,2]. Low serum levels of 25(OH)-vitamin D are common in chronic widespread 'fibromyalgia-type' pain syndrome [3]. However, it is not clear whether the pain associated with low levels of 25(OH)-vitamin D is mainly proximal (as in the case of osteomalacia) [4], confined to the low back [5] or legs [6], or is widespread [7,8].

The pathophysiology of chronic, widespread 'fibromyalgia-type' pain syndrome is controversial. Emerging theories involve a combination of genetic and environmental factors leading to aberration of central sensitization of pain processing, with heightened responses to nonpainful and painful stimuli [9].

There is no strong evidence that vitamin D deficiency contributes toward fibromyalgia [10]; however, the

association between pain and vitamin D levels in fibromyalgia patients emphasizes that vitamin D deficiency in the FMS may have an augmenting impact on pain intensity and functional status [11].

Theories were postulated to explain the role of 25(OH)-vitamin D deficiency in the development and/or augmentation of pain intensity and deterioration of functional status. Recently, a new mechanism has been proposed by Tague *et al.* [12] for musculoskeletal symptoms because of vitamin D deficiency. The authors concluded that muscle hypersensitivity and sensory hyperinnervation may be responsible for the generation of musculoskeletal pain and this deep muscle pain may be in the early stage of vitamin D deficiency and may precede the development of gross bone or muscle pathology. This mechanism was based

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on the demonstration of vitamin D receptors in nociceptors (pain-sensing nerves) [13].

Another possible hypothesis for the generation of musculoskeletal pain associated with vitamin D deficiency may be the lack of the immunoregulatory and anti-inflammatory properties of vitamin D [14]. Alternatively, fibromyalgia could contribute toward vitamin D deficiency because of pain, poor mobility, or associated depression, potentially leading to less time spent outdoors, or high rates of adiposity leading to decreased synthesis of vitamin D [10].

There are conflicting results on the role of vitamin D supplementation in chronic nonspecific musculoskeletal pains [10]. Many studies report a beneficial effect on musculoskeletal diseases or complaints; they include not only well-described case reports [15–17], but also large intervention studies [5]. Other randomized-controlled trials show no therapeutic effect of vitamin D supplementation on muscle pain [10].

Objective

The aim of our study is to determine serum 25(OH)-vitamin D level in patients with FMS and its relation to pain.

Patients and methods

This study was carried out at the Rheumatology Outpatient Clinic, Physical Medicine and Rehabilitation Department, Menoufia University, Egypt, and was approved by its ethical committee after ethically informed consent from the patients. This study was carried out on 53 women (aged 20–64 years, average 37.71 ± 10.27 years) who visited the outpatient clinic. The patients were recruited from the period of January to August 2014 and fulfilled the 1990 American College of Rheumatology criteria for the diagnosis of FMS [18].

The control group included 50 age-matched healthy women (aged 21–61 years, average 37.01 ± 9.16 years) who had a normal physical examination and routine laboratory investigations. Serum 25(OH)-vitamin D level measurement was performed for the patient and control groups.

Patients who fulfilled our inclusion criteria were offered the opportunity to participate. The main inclusion criterion was the diagnosis of FMS on the basis of fulfillment of the 1990 American College of Rheumatology criteria for the diagnosis of FMS [18], which included:

- (i) A history of widespread pain; pain considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine, anterior chest, thoracic spine, or low back) must be present for more than 3 months.
- (ii) Pain on digital palpation must be present in at least 11 of following 18 tender points:
 - (1) Occiput: bilateral, at the suboccipital muscle insertion.
 - (2) Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5–C7.
 - (3) Trapezius: bilateral, at the midpoint of the upper border.
 - (4) Supraspinatus: bilateral, at origins, above the scapula spine near the medial border.
 - (5) Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces.
 - (6) Lateral epicondyle: bilateral, 2 cm distal to the epicondyle.
 - (7) Gluteal region: bilateral, in the upper outer quadrants of the buttocks in the anterior fold of the muscle.
 - (8) Greater trochanter: bilateral, posterior to the trochanteric prominence.
 - (9) Knee: bilateral, at the medial fat pad proximal to the joint line.

After physical examination and routine laboratory investigations, patients with the following conditions were excluded: renal disease, hepatic diseases, malabsorption syndrome, hyperparathyroidism, those who had recently taken vitamin D supplements, patients with rheumatic diseases (as they may have the same manifestations as FMS), malignancy, anemia, thyroid diseases, pregnant, or currently lactating.

The patient group was subjected to the following: assessment of history, general examination, which included digital palpation of the 18 previously mentioned tender points of FMS, visual analogue scale (VAS) from 0 to 10 [19], and the Revised Fibromyalgia Index Questionnaire (FIQR), which included 21 individual questions. All questions are based on an 11-point numeric rating scale of 0–10, with 10 being 'worst'. All questions are framed in the context for the past 7 days. The FIQR is divided into three linked sets of domains: (i) 'function' (contains nine questions), (ii) 'overall impact' (contains two questions), and (iii) 'symptoms' (contains 10 questions). The scoring of the FIQR is simple: the summed score for function (range 0–90) is divided by 3, the summed score for overall impact (range 0–20)

is not changed, and the summed score for symptoms (range 0–100) is divided by 2. The total FIQR is the sum of the three modified domain scores. The total maximal score of the FIQR is 100 [20].

Laboratory investigations

Serum samples were taken from the patients and control groups for assessment of vitamin D level (ng/dl), erythrocyte sedimentation rate, and C-reactive protein.

Assay of 25(OH)-vitamin D is a competitive protein-binding assay. It is based on the competition of 25(OH)-vitamin D tracer for the binding pocket of vitamin D-binding protein. As all circulating 25(OH)-vitamin D is bound to vitamin D-binding protein *in vivo*, samples have to be precipitated with a precipitation reagent to extract the analyte. The supernatant can be used without further treatment within the test. Normal 25(OH)-vitamin D serum levels were defined as values 30 ng/ml or more and deficiency as values below normal [21].

Routine immunological assays were performed to exclude certain rheumatic diseases; kidney function tests to detect any renal dysfunction; thyroid function tests to exclude thyroid diseases; hepatic viral tests to exclude liver infection; and assessments of parathyroid hormone level to detect parathyroid gland dysfunction.

Statistical analysis

Descriptive statistical methods were used to evaluate data in the form of mean \pm SD. The unpaired Student *t*-test was used to evaluate the significance of difference between groups. Pearson's correlation analysis was used to determine the correlation between findings. Data were analyzed using the SPSS-PC statistical software package (SPSS, version 20.0 for Windows; SPSS Inc. Chicago, Illinois, USA).

Results

Our study included 53 female patients ranging in age from 20 to 64 years with a mean age of 37.71 ± 10.27 years, diagnosed with fibromyalgia, with disease duration more than 6 months. Our control group included age-matched normal healthy 50 female patients ranging in age from 21 to 61 years, with a mean age of 37.01 ± 9.16 years. There was no statistically significant difference between the two studied groups in age (Table 1).

There was a statistically significant decrease in serum vitamin D levels in the patient group in comparison with the control group ($P < 0.05$) (Table 2).

There was a significant negative correlation between vitamin D level and Fibromyalgia Impact Questionnaire (FIQ) ($P < 0.05$) (Table 3). The same results were found between vitamin D level and VAS (Table 3), with a nonsignificant correlation between vitamin D level and erythrocyte sedimentation rate or C-reactive protein ($P > 0.05$).

Discussion

The aim of our study was to detect the level of serum 25(OH)-vitamin D in patients with FMS and its relation to pain. In the literature, findings on 25(OH)-vitamin D levels in FMS patients showed varying results. Many studies have reported low levels of 25(OH)-vitamin D in FMS patients [21,22].

In our study, we found a statistically significant decrease ($P < 0.01$) in serum 25(OH)-vitamin D level in the patient group in comparison with the control group (Table 2). This was in agreement with Olama *et al.* [23] who carried out a study on 50 female patients with FMS and 50 healthy control women age matched to the patients. They found that patients with FMS had significantly lower serum 25(OH)-vitamin D than the controls (15.1 ± 6.1 and 18.8 ± 5.4 ng/ml, respectively). Also, Baygutalp *et al.* [24] showed that the serum

Table 1 Mean, SD, and percentage values of clinical and laboratory findings in patients and control groups

	Number cases	Minimum	Maximum	Mean	SD
Age (patient group) (years)	53	20.00	64.00	37.7170	10.27203
Age (control group) (years)	50	21.00	61.00	37.0943	9.16151
Vitamin D level in the patient group (ng/dl)	53	4.10	22.10	10.7970	4.96072
Vitamin D level in the control group (ng/dl)	50	25.30	52.10	35.7247	6.23300
ESR	53	6.00	34.00	19.0943	6.264
CRP	53	0.00	17.00	4.3528	5.178
Fibromyalgia Impact Questionnaire	53	42.13	93.22	71.1719	13.75707
Visual analogue scale	53	3.00	9.00	6.5472	1.58801
Valid number of cases [n (%)]	53 (100)				

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Table 2 Comparison between vitamin D level in the patient and control groups (ng/dl)

	Mean	N	SD	t-Test	Significance (two-tailed)
Vitamin D level (patient group)	10.7970	53	4.96072	23.123	0.000
Vitamin D level (control group)	35.7247	50	6.23300		

Table 3 Correlation between vitamin D level in the patient group and Fibromyalgia Impact Questionnaire and visual analogue scale

Vitamin D level	VAS	FIQ
Pearson's correlation	-0.643**	-0.870**
Significance (two-tailed)	0.000	0.000
Number of patients	53	53

FIQ, Fibromyalgia Impact Questionnaire; VAS, visual analogue scale; **Correlation is significant at the 0.01 level (two-tailed).

vitamin D levels were significantly lower in the patient group compared with the control group. This was also similar to the study carried out by Altindag *et al.* [25], which found that there was a significantly higher prevalence of decreased vitamin D concentrations in women with FMS compared with age-matched controls.

Numerous studies and reports have suggested that vitamin D deficiency may play a role in chronic widespread pain, but none has as yet confirmed a clear biological mechanism by which deficiency or supplementation of vitamin D can modulate pain sensation [26].

Several attempts have been made to link FMS with vitamin D deficiency. Huisman *et al.* [27] found in a cross-sectional study that vitamin D levels in 25 White women with fibromyalgia were deficient. Two studies recently reported a significant reduction of vitamin D in patients with pain in comparison with the control group [28,29]. Six out of eight treatment studies that were not double blinded showed significant relief of pain after vitamin D supplementation (457 of 504 patients, 93%) [26].

A new study carried out in 2013 by McCarty *et al.* [30] evaluating vitamin D levels in patients with sleep disorder found that vitamin D deficiency is a reliable marker in patients with sleep disorders and chronic widespread pain, and suggested that chronic widespread musculoskeletal nonspecific pain can contribute toward subjective sleep disturbances.

Another study carried out by Prabhala *et al.* [17] suggested a mechanism of sleep disturbances because of vitamin D deficiency that leads to chronic pain and concluded that vitamin D deficiency has a

biologic potential in the development of obstructive sleep apnea through myopathy. McCarty [31] described a patient with a syndrome clinically indistinguishable from idiopathic central nervous system hypersomnia whose excessive daytime sleepiness resolved following treatment of severe vitamin D deficiency.

In contrast, Ulusoy *et al.* [32] found that the serum 25(OH)-vitamin D levels did not differ between patients (10.57 ± 10.46) and controls (10.87 ± 5.52 ng/l) ($P = 0.89$). Another study by Tandeter *et al.* [33] reported a nonsignificant difference between the fibromyalgia group and the matched control group in the vitamin D level, but they made no attempt to correlate the severity of fibromyalgia and vitamin D level.

In our study, we found that there is a significant negative correlation between vitamin D level and FIQ (Table 3). This was in agreement with Altindag *et al.* [23], who found that there was a significantly negative correlation with FIQ ($r = 0.344$, $P = 0.03$). Ulusoy *et al.* [32] found no relationship between vitamin D level and the FIQ score ($P = 0.707$). Also, Baygutalp *et al.* [24] found no significant correlation between FIQ and 25(OH)-vitamin D level in FMS.

In our study, we found that there was a significant negative correlation between serum 25(OH)-vitamin D levels and the intensity of pain measured by the VAS (Table 3). This result was similar to the study carried out by Olama *et al.* [23], which found that the serum level of 25(OH)-vitamin D is correlated inversely with pain measured by VAS ($P = 0.016$). This was in agreement with Baygutalp *et al.* [24], who found that there was a significant correlation between 25(OH)-vitamin D levels and widespread body pain measured by VAS ($r = 0.731$, $P < 0.01$). Altindag *et al.* [25] also obtained the same result ($r = 0.623$, $P < 0.000$). In contrast, Ulusoy *et al.* [32] found no relationship between 25(OH)-vitamin D levels and pain measured by VAS ($P = 0.414$).

All the results together suggest that chronic widespread pain in fibromyalgia and sleep disorder may be predictive of vitamin D deficiency and need for supplementation. Our findings would have a significant and better potential for the investigation and management of this syndrome in the future. It might be assumed that a decrease in 25(OH)-vitamin D level may be one of the possible mechanisms responsible for chronic widespread pain in FMS. We therefore suggested that treatment of women with FMS by vitamin D supplementation may be beneficial.

Conclusion

We found a significant association between fibromyalgia and low 25(OH)-vitamin D levels as suggested previously in some previous studies. Also, there was a negative correlation between the level of vitamin D in serum and severity of pain. We recommend vitamin D screening in all patients with chronic nonspecific musculoskeletal pain, especially fibromyalgia, and extended research in this area with larger numbers of patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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