

Vitamin D Supplementation Seems to Improve Fibromyalgia Symptoms: Preliminary Results

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ABSTRACT: **Background:** Vitamin D deficiency and insufficiency have been reported in fibromyalgia. However, to the best of our knowledge, only one study has evaluated the role of 25-hydroxyvitamin D [25(OH)D] supplementation on fibromyalgia symptoms.

Objectives: To analyze the effects of 3 months of 25(OH)D supplementation on symptoms of fibromyalgia.

Methods: This study included 11 female patient. Demographic and clinical data, tender points, visual analog scale results, and pre- and post-serum levels of 25(OH)D supplementation were analyzed. The levels of 25(OH)D were measured by a radioimmunologic test.

Results: Patients with fibromyalgia diagnosis and 25(OH)D values ≤ 30 ng/ml were recruited to receive 50,000 IU of oral vitamin D once every week for 3 months. The disease was diagnosed based on the American College of Rheumatology criteria. The median age of all patients was 48.5 (28–67) years and 63.4% were Caucasian. Disease duration varied from 1–10 years. The 25(OH)D levels increased significantly after 3 months, 18.4 (15.5–25.8) ng/ml vs. 33.8 (28–58) ng/ml, $P = 0.01$. Interestingly, an improvement of visual analog scale scores was observed at 3 months, 90 (0–100) vs. 30 (0–80), $P = 0.002$. Eight patients (72.2%) responded that they 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) vs. 10 (0–18), $P = 0.07$.

Conclusions: The 25(OH)D levels and disease symptoms in patients with fibromyalgia and vitamin D deficiency/insufficiency seem to improve with vitamin D supplementation.

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KEY WORDS: 25-hydroxyvitamin D [25(OH)D], fibromyalgia, pain, visual analog scale, vitamin D

to other disorders such as cancer, tuberculosis susceptibility, systemic hypertension, and autoimmune conditions [2-6]. Some studies have suggested that vitamin D may participate in the prevention of pathologies of autoimmune diseases [7] and even affect metabolic syndrome in patients with rheumatoid arthritis [8,9].

In fact, hypovitaminosis D is described as a treatment for rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid syndrome, and fibromyalgia [1-3].

Fibromyalgia is a chronic pain syndrome that presents with muscle tenderness and is often accompanied by fatigue, sleep disturbance, and depressive moods [10]. The prevalence of fibromyalgia in the population is reported to be between 0.66% and 4.4%, and may be more prevalent in women than in men, especially between the ages of 35 and 60 [11].

Several studies have demonstrated a negative association between 25(OH)D and fibromyalgia [12,13]. However, to the best of our knowledge, only one scientific paper has evaluated the role of vitamin D supplementation in this chronic disorder and evaluated the effect of one single dose of vitamin D [14].

In this study, our objective was to evaluate the effects of vitamin D supplementation on the symptoms of women with fibromyalgia.

PATIENTS AND METHODS

Our study was comprised of 11 female patients, all older than 18 years of age, who had been diagnosed with fibromyalgia according to the American College of Rheumatology (ACR) criteria. The diagnosis of fibromyalgia was confirmed by an experienced rheumatologist (JFC) [15]. Selected subjects had widespread pain in at least three quadrants of the body lasting for more than 3 months and identified a minimum of 11 tender points among the 18 points tested. Diffuse pain was defined as the presence of pain on the left and right sides of the body and above and below the waist.

In this study, we collected demographic data, reviewed medical charts, noted the presence of co-morbidities, and recorded medications taken.

Vitamin D deficiency or insufficiency is commonly associated to osteometabolic disorders such as osteoporosis and osteomalacia, in addition to being related to painful nonspecific musculoskeletal conditions [1]. This hormone has been linked

Exclusion criteria were the presence of systemic lupus erythematosus or other autoimmune systemic disease, the use of vitamin D supplementation, antidepressant therapy such as tricyclic, and serotonin reuptake inhibitors during the 6 months prior to this study. Thyroid dysfunction, muscle disorders as evaluated by muscle strength and creatine kinase levels, spondyloarthritis, and rheumatoid arthritis were also excluded. All patients had blood collected for laboratory analysis and all test results were normal, including thyroid function, creatine kinase, erythrocyte sedimentation rate, C-reactive protein, protein electrophoresis, calcium, phosphorus, blood count, liver enzymes, and renal function.

All patients received a 50,000 IU tablet once weekly during a period of 3 months.

INSTRUMENTS

The visual analog scale (VAS) is a 10 item number line on which subjects indicate the degree of pain perceived at that given moment and as a weekly average in which 0 = no pain and 10 = unbearable pain. Higher values indicate worse conditions. Subjects give a verbal gradation of pain by choosing a number from 0 to 10, with higher numbers corresponding to higher pain levels [16].

Tender points were evaluated and the number of positive points was reported.

VITAMIN D MEASUREMENT

The 25-hydroxyvitamin D [25(OH)D] was collected and measured by a commercial kit (DiaSorin, Minnesota, USA) that uses 125I radioimmunoassay (intra-assay coefficient of variation: 16.6%, inter-assay coefficient of variation: 22.6%).

STATISTICAL ANALYSIS

Results are presented as median (range) or percentage. Statistical analyses were performed using GraphPad InStat version 2.00 (GraphPad Software, La Jolla, CA, USA). A non-parametric Mann-Whitney test was used to compare medians, and a Fisher's exact test was used to compare frequencies. The results were considered significant when $P < 0.05$.

RESULTS

Eleven women with fibromyalgia were included in this study. Median age of all fibromyalgia patients was 48.5 (28–67) years and 63.4% were Caucasian. Disease duration was 10 (1–10) years. All patients completed the follow-up period of 3 months.

Features of fibromyalgia patients at baseline and after 3 months of vitamin D supplementation are summarized in Table 1.

The 25(OH)D levels increased significantly after 3 months of supplementation: 18.4 (15.5–25.8) vs. 33.8 (28–58) ng/ml, $P = 0.01$.

Table 1. Comparison between fibromyalgia and vitamin D features at baseline and after 3 months of vitamin D supplementation

	Pre-vitamin D supplementation N=11*	Post-vitamin D supplementation N=11*	P value
Median age, years	48.5 (28–67)	33.8 (28–58)	0.01
25(OH)D, ng/ml	18.4 (15.5–25.8)	33.8 (28–58)	0.01
Number of tender points	17 (11–18)	10 (0–18)	0.07
VAS			
Median score (range)	90 (0–100)	30 (0–80)	0.002

Data are shown as median (range) or percentage
25(OH)D = 25-hydroxy-vitamin D; VAS = visual analog scale

*All patients were female

An improvement of median VAS scores was observed at 3 months: 90 (0–100) vs. 30 (0–80), $P = 0.002$. In addition, a trend for a reduction in the number of tender points was seen: 17 (11–18) vs. 10 (0–18), $P = 0.07$.

Eight patients (72.7%) answered that they had a very significant improvement after vitamin D supplementation.

DISCUSSION

This study demonstrated that vitamin D supplementation seems to increase serum levels of 25(OH)D, and also improves symptoms of women with fibromyalgia.

An advantage of this study was that it included only fibromyalgia patients who did not have other autoimmune diseases, since these disorders may be influenced by 25(OH)D. Another strength of our research was to exclude patients currently taking antidepressants, vitamin D supplementation, or muscle relaxing agents. In our study, the same researcher determined the tender points in each patient.

Previous studies have demonstrated the presence of vitamin D deficiency or insufficiency in fibromyalgia [17,18]. Other studies used control groups, which suggested no association [19–21]. Some possible explanations for patients with fibromyalgia could show that hypovitaminosis D may be due to pain, poor mobility, obesity or overweight, and depression. Each of these factors could lead to less time outdoors, less sun exposure, and consequently vitamin D deficiency or insufficiency.

Some studies have evaluated serum levels of 25(OH)D in fibromyalgia and found inconclusive results. While other researchers suggest a positive association between fibromyalgia and low vitamin D levels [17,18]. Still others, using control groups, suggested no association [19–21]. Studies with larger populations showed conflicting results [22,23]. It should be noted that these last studies are population based studies, but only about 12% of the included subjects had fibromyalgia. Abokrysha [14] evaluated 30 Arab women with fibromyalgia and found that hypovitaminosis D was associated with widespread body pain. Of interest, Abokrysha found an improvement of symptoms and fatigue after 2 months of a single dose of vitamin D.

One limitation of this study was that it included a relatively small number of patients. This actuality was due to rigorous exclusion criteria that eliminated patients with other diseases and a history of drug use, who were treated with medications that could affect our results. Another limitation factor was the lack of a control group and data related to body mass index, sun exposure, and use of sunscreen. However, our research is preliminary and was designed as a pilot prospective study.

CONCLUSIONS

This study demonstrated that vitamin D supplementation seems to have a role in controlling symptoms in fibromyalgia patients with 25(OH)D deficiency. Other prospective and larger studies shall be conducted to confirm these findings.

Conflicts of interest

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References

1. Heidari B, Shirvani JS, Firouzjahi A, Heidari P, Hajian-Tilaki KO. Association between nonspecific skeletal pain and vitamin D deficiency. *Int J Rheum Dis* 2010; 13 (4): 340-6.
2. Andreoli L, Piantoni S, Dall’Ara F, Allegri F, Meroni PL, Tincani A. Vitamin D and antiphospholipid syndrome. *Lupus* 2012; 21 (7): 736-40.
3. Watad A, Neumann SG, Soriano A, Amital H, Shoenfeld Y. Vitamin D and systemic lupus erythematosus: myth or reality? *IMAJ* 2016; 18 (3-4): 177-82.
4. Belyaeva IV, Churilov LP, Mikhailova LR, et al. Vitamin D, cathelicidin, prolactin, autoantibodies, and cytokines in different forms of pulmonary tuberculosis versus sarcoidosis. *IMAJ* 2017; 19 (8): 499-505.
5. Dankers W, Colin EM, van Hamburg JP, Lubberts E. Vitamin D in autoimmunity: molecular mechanisms and therapeutic potential. *Front Immunol* 2017; 7: 697.
6. Grübler MR, März W, Pilz S, et al. Vitamin-D concentrations, cardiovascular

- risk and events – a review of epidemiological evidence. *Rev Endocr Metab Disord* 2017; 1 (2): 259-72.
7. Rosen Y, Daich J, Soliman I, Brathwaite E, Shoenfeld Y. Vitamin D and autoimmunity. *Scand J Rheumatol* 2016; 45 (6): 439-47.
8. Wimalawansa SJ. Associations of vitamin D with insulin resistance, obesity, type 2 diabetes, and metabolic syndrome. *J Steroid Biochem Mol Biol* 2018; 175: 177-189.
9. Haque UJ, Bathon JM, Giles JT. Association of vitamin D with cardiometabolic risk factors in rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012; 64 (10): 1497-504.
10. Moldofsky H SP, England R, Smythe H. Musculoskeletal symptoms and non-REM sleep disturbances in patients with fibrositis syndrome and healthy subjects. *Psychosom Med* 1975; 37 (4): 341-51.
11. Dohrenbusch R, Grüterich M, Genth E. Fibromyalgia and Sjögren syndrome—clinical and methodological aspects. *Z Rheumatol* 1996; 55: 9. [German]
12. Matthana MH. The relation between vitamin D deficiency and fibromyalgia syndrome in women. *Saudi Med J* 2011; 32 (9): 925-9.
13. De Rezende Pena C, Grillo LP, das Chagas Medeiros MM. Evaluation of 25-hydroxyvitamin D serum levels in patients with fibromyalgia. *J Clin Rheumatol* 2010;16 (8): 365-9.
14. Abokrysha NT. Vitamin D deficiency in women with fibromyalgia in Saudi Arabia. *Pain Med* 2012;13:7.
15. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990; 33: 160-72.
16. Bobey MJ, Davidson PO. Psychological factors affecting pain tolerance. *J Psychosom Res* 1970; 14 (4): 371-6.
17. Badsha H, Daher M, Ooi Kong K. Myalgias or non-specific muscle pain in Arab or Indo-Pakistani patients may indicate vitamin D deficiency. *Clin Rheumatol* 2009; 28 (3): 971-3.
18. Block SR. Vitamin D deficiency is not associated with nonspecific musculoskeletal pain syndromes including fibromyalgia. *Mayo Clin Proc* 2004; 79: 1585-6.
19. Huisman AM, White KP, Algra A, et al. Vitamin D levels in women with systemic lupus erythematosus and fibromyalgia. *J Rheumatol* 2001; 28: 2535-9.
20. Mouyis M, Ostor AJ, Crisp AJ, et al. Hypovitaminosis D among rheumatology outpatients in clinical practice. *Rheumatology (Oxford)* 2008; 47 (9): 1348-51.
21. Tandeter H, Grynbaum M, Zuili I, Shany S, Shvartzman P. Serum 25-OH vitamin D levels in patients with fibromyalgia. *IMAJ* 2009; 11: 339-42.
22. Erkal MZ, Wilde J, Bilgin Y, et al. High prevalence of vitamin D deficiency, secondary hyperparathyroidism and generalized bone pain in Turkish immigrants in Germany: identification of risk factors. *Osteoporos Int* 2006;17: 1133-40.
23. McBeth J, Pye SR, O’Neill TW, et al. Musculoskeletal pain is associated with very low levels of vitamin D in men: results from the European Male Ageing Study. *Ann Rheum Dis* 2010; 69: 1148-52.

Capsule

Infiltration inhibition of CTL

Type 1 diabetes (T1D) is associated with the infiltration of islet-specific autoreactive cytotoxic CD8+ T cells (CTLs) into pancreatic islets. This process leads to islet destruction and loss of insulin production. Most of the CTLs in islets are non-islet-specific, and their contribution to T1D is not well understood. **Christoffersson** and co-authors observed that the accumulation of these “bystander” CTLs was associated with

decreased activation and proliferation of islet-specific CTLs. The abundance of non-islet-specific CTLs in islets reduced the access of islet-specific CTLs to autoantigens, which led to a state of unresponsiveness. A similar form of nonspecific suppression by CTLs was observed in a viral meningitis model.

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Eitan Israeli

“It has always seemed strange to me that in our endless discussions about education so little stress is laid on the pleasure of becoming an educated person”

Edith Hamilton, (1868–1963), German author