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POSITIVE AND NEGATIVE ASSOCIATION OF VITAMIN D WITH FIBROMYALGIA SYNDROME

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ABSTRACT

Fibromyalgia syndrome (FMS) is a chronic, painful musculoskeletal condition marked by stiffness, exhaustion, disturbed sleep, cognitive impairment, and psychological distress. The role of vitamin D level in FM patients remains controversial. We therefore conducted internet searches for FMS papers to evaluate the relationship between the level of vitamin D and FM. Numerous studies have been conducted to evaluate the Effects of vitamin D in patients with fibromyalgia syndrome (FMS) and its association with FMS symptoms. A strong association between FM and vitamin D deficiency has been documented in several studies. In some trials, serum levels of 25(OH)D for FM were tested and incomplete findings were found. Vitamin D level was suggested to be associated with FM, but studies remain unclear. Therefore, in this study, we are attempting to elucidate the positive and negative relationship of vitamin D in FM patients, based on summarizing the evidence from the available observational and meta-analysis studies.

KEYWORDS: Fibromyalgia Syndrome, Vitamin D, Systematic review, Meta-analysis.

INTRODUCTION

Fibromyalgia is a commonly widespread chronic musculoskeletal pain condition with mechanical hyperalgesia at ≥ 11 tender points (1).Women are more likely to develop FMS and an estimated 2-4 percent of the population is affected, with a female to male incidence ratio of about 9:1 (2).Symptoms such as morning stiffness, fatigue, and multiple points of tenderness, sleep disorder, headache, and low threshold of pain, anxiety, and depression indicate FM (3). FM pathophysiology has not yet been properly understood (4).It may have mild to severe symptoms; with the worst cases of an invalidating condition that dominates daily life (5).FM is not considered a disease by many members of the medical community due to the lack of abnormalities in physical examination and the lack of objective diagnostic tests (6).FM is a chronic and potentially crippling condition that can interrupt the quality of life, thus impairing the capacity of the patient to work and their involvement in day-to-day activities that annoy patients and their families as a real burden in daily life (7).

However, vitamin D deficiency has been reported to be linked to musculoskeletal disorders such as autoimmune diseases, cardiovascular diseases, lung diseases, metabolic syndrome, cognitive function, psychiatric disorders, and several cancers (8-12).Vitamin D, which has a major role in both Calcium and Phosphate equilibrium and in bone health, is a steroid-structured hormone. The prevalence of vitamin D deficiency among the general population is 25-50 percent (13,8). The correlation of FM and vitamin D deficiency remains arguable. Some research reported ' positive association, ' while others found ' no relation ' between the deficiency of FM and vitamin D. We will therefore attempt to elucidate the positive and negative relationship between vitamin D and FM in this study (Table 1).

Positive studies related to Vitamin D level in FMS patients	**Negative studies related to Vitamin D level in FMS patients**
Study reported by Aires in 2018 onVitamin D supplementation, elevatedserum levels of 25 (OH) D improves the symptoms of FM. (33)	Gaikwad et al. 2017 Found no effect of vitamin D supplementation on pain symptoms of FMS patient. (53)

Table 1: Comparative Table for Positive and Negative Association of Vitamin D with FM

According to Mirzaei et al., 2018 Vitamin D supplementation reduced Chronic Widespread Pain in FM patients. (41)	Wu Z et al. 2016 reported that even supplementation of vitamin D, didn't improved FMS symptoms. (55)
Dogru A et al in 2017 found that vitamin D supplementation is capable of reducing pain scores in FM patients. (52)	Straube S et al. 2015 found no evidence to support vitamin D supplementation relief chronic pain Conditions. (54)
Badsha et al. in 2009 reported that 90% of patient's clinical symptoms improved after Vitamin D supplementation. (29)	Wepner et al. 2014 found that vitamin D levelshave a significant negative association with symptoms.(59)
Hooten WM et al. 2007 reported that Vitamin Ddeficiency may be a contributing factor in FM. (34)	Straube S et al. in 2010 reported no improvement in pain FMS patients. (61)
Plotnikoff and Quigley in 2003 reported that FM patients had lower levels of vitamin D and its supplementation, increased serum levels of 25(OH)D and improved condition. (38)	Warner et al. 2008 did not report any beneficial effects of vitamin D supplementation in a larger patient cohort study. (60)

Cont. Table 1: Comparative Table for Positive and Negative Association of Vitamin D with FM

Fibromyalgia and Vitamin D

Vitamin D is a lipid-soluble, secosteroid hormone, its receptor (vitamin D receptor, VDR), and the metabolizing enzymes involved in the production of the hormone's biologically active form, all of which play important roles in the endocrine system of vitamin D. Recently, the information on the position of the VDR and its role on the tissues has been expanded. VDR is found to have an effect on cell proliferation, differentiation, neurotransmission, and various neuroplastic functions, as well as neurotrophic and neuroprotective effects (14).Research has shown that vitamin D has physiological, metabolic, neurological and immunological impact on pain perception, as well as influence on etiology and chronic pain management and related comorbidities(15-17).

Vitamin D has been found to cause pain through different mechanisms in recent years. It is also suspected that the involvement of vitamin D in neuronal and glial cells, together with VDR and 1-a-hydroxylase enzyme complex, which causes pain through cytokine-mediated pathways, also promotes the production of central sensitization (18,19). Genes that encode the enzymes are present in brain and glial cells, playing a role in the metabolism of vitamin D (20). It is also suggested that the local synthesis of 1,25(OH)2D in microglial cells shape an antitumor response. Vitamin D makes an important contribution to neuroprotection by excreting specific neurotrophins such as nerve growth factor, neurotrophin-3, glial-derived neurotrophic factor, and c-glutamyl transpeptidase in astrocytes (21).Furthermore, Vitamin D regulates neuronal stimulation and plays a role in neurotransmitter (like dopamine, serotonin) regulation, functioning as a neuroactive steroid. Vitamin D is thought to play a role in the production of serotonin and dopamine, both of which are most likely to be involved as neurotransmitters in the pathogenesis of FM (22, 23). It was also established that VDR, which exists in neurons, especially in the hypothalamus, and 1-ahydroxylase enzyme, may contribute to the central sensitization that causes widespread chronic pain in FMS and has been suggested to play a role in causing migraine and chronic headache (18, 19).

The gene of the VDR is located on the 12q12–14.14 chromosome. There is several restriction fragment length polymorphisms (RFLP) identified for the VDR gene, including BsmI, ApaI, TaqI and FokI cleaved sites. Recently, a number of studies have confirmed that some diseases such as cancer, diabetes, and cardiovascular diseases are associated with VDR gene polymorphisms (24-28). Despite some knowledge of the function of VDR gene polymorphisms in chronic pain conditions such as osteoarthritis, (26) spinal pain (27) and migraine (26), their position in core hypersensitization pain pathways has not yet been established. In studies up to the VDR gene, several polymorphisms have been found. Yet FokI, BsmI, ApaI, yet TaqI are the most commonly studied (24). Contrary to the polymorphisms of BsmI, ApaI and TaqI, FokI is stated to induce important structural changes in VDR protein as it is located in the gene's

protein coding region and enhances pain sensitivity (25, 26). Again, insufficient research remains to fully understand the role of the genes of vitamin D in FM.

Positive association between FM and Vitamin D deficiency.

Badsha et al. 2009, found that Vitamin D supplementation indicated a satisfactory relief in among FM patients (29). At the Minnesota hospital, more than 90% of 150 people who presented with nonspecific muscle and bone aches and pains were found to be having Vitamin D deficiency (30). In clinical investigations, Vitamin D supplementation has been demonstrated to help relieve various pain symptoms either completely or partially, as well as providing other benefits such as increased stamina or strength, improvements in mood and quality of life (31).

Wu et al. 2018 performed 81 observational studies with a total of 50 834 participants relative to controls, mean 25(OH)D concentration was significantly lower in patients with arthritis, muscle pain and chronic widespread pain, but not in headache or migraine patients. Among patients with arthritis, muscle pain, and chronic widespread pain, a significantly lower concentration of 25(OH)D was found relative to those without it. Such results show that pain may be associated with low concentrations of 25(OH)D (32). It was demonstrated by Aires RB 2018 that Vitamin D supplementation seems to increase serum levels of 25(OH)D and also improves the symptoms of FM in women (33).

In this study, it is also noticed that 19 out of 61 Vitamin D deficient FM women, had found no evidence of improvement despite their blood level of Vitamin D exceeding 50.0 ng/ml. As their symptoms might be due to another problem rather than Vitamin D deficiency. Another explanation is that, Vitamin D deficiency in 61 women might be an association rather than a cause of FM. Some researchers have reported that Vitamin D deficiency may be contributing in FM with unrecognized factors yet not the main cause of pain and muscle weakness in FM (34). Other studies state that Vitamin D inadequacies can be strongly associated with FM even in cases where a specific etiology has been diagnosed, the potential for Vitamin D deficiency as a factor contributing to the pain. Vitamin D deficiency may play a role in chronic low back pain (35). Other researchers believe that Vitamin D receptors have different genetic makeup (polymorphism) and activity which may account for varying individual responses to Vitamin D therapy, (36) that carries a third explanation of absence of improvement in those 19 women. Therefore, many experts have recommended that Vitamin D deficiency should be considered during the differential diagnosis and treatment plans of FM (37).

Plotnikoff and Quigley note prevalence of vitamin D deficiency in patients with non-specific musculoskeletal pain. A total of 100% had low levels of vitamin D (< or= 20 ng / mL). 93% (140/150) of all patients had low levels of vitamin D (mean, 12.08 ng / mL; confidence interval of 95%, 11.18–12.99 ng / mL).Males and females had similarly low levels of vitamin D, while patients with 28 percent of non-specific musculoskeletal pain had lower levels of vitamin D than 8 ng / mL (38).In addition, a large European male cohort study (39) involved 2313 people with an average age of 58.8 years to assess the risk of developing CWP and the relationship between the levels of vitamin D for an average follow-up duration of 4.3 years. Results showed the greatest risk of developing CWP in individuals in the upper quintile of 25(OH)D (< 36.3 ng / mL) relative to those in the lower quintile (< 15.6 ng / mL), despite age and center change, physical performance and number of comorbidities(OddsRatio(OR)=1.93;95 percent CI=1.0–3.6).Furthermore, the depression modification (OR = 1.77; 95% CI = 0.98–3.21) or BMI (OR = 1.67; 95% CI = 0.93–3.02) made the relationship non-significant. The frequency of FM symptoms also associated with hypoVitaminosis D. Serum vitamin D concentrations were analyzed in the previous study of 75 Caucasian patients who met the ACR requirements for FM. However, a Hospital Anxiety Depression Rating (HADS) and an adapted FM effect questionnaire (FIQ) were also completed by these patients. HypoVitaminosis D was evident in 13.3 percent of patients; while inadequate was 56.0 percent and usual concentrations were 30.7 percent. Nonetheless, HADS (median, IQR, 31.0 (23.8–36.8)) was higher in patients with vitamin D deficiency (< 25 nmol / L) than in patients with inadequate levels (25–50 nmol / L; HADS 22.5 (17.0–26.0)) or normal levels (50 nmol / L or higher; HADS 23.5 (19.0–27.5); $p<0.05$) (40)

Vitamin D supplementation in FM, according to Mirzaei A et al., has important remedial advantages in the management of FM, especially in pain reduction. Patients suffering from vitamin D-deficient FM with a combination of vitamin D supplements and a traditional antidepressant that improves their physical and psychological symptoms (41).A recent meta-analysis of observational studies involves 12 trials, consisting of 1854 patients and 7850 controls (in 8 of which FM patients were diagnosed and CWP rest were diagnosed).Higher risk of patient group hypovitaminosis D relative to control group (OR, 1.63; 95% CI, 1.20–2.23).Since correcting confounders with a combined modified OR of 1.41 (95 percent CI, 1.00–2.00), the correlation was slightly diminished.By using a lower serum vitamin diagnostic

value (8and10ng / mL), HypoVitaminosis D ORs have improved. Based on the gender and interpretation of CWP, the sub-group study did not reveal any significance between group differences. It has been proposed that the levels of vitamin D < 10 ng / mL vary between the infected population and the control group. Furthermore, according to the findings of this meta-analysis, it may be proposed that patients with hypovitaminosis D may depend on such factors, such as sun exposure, seasonal variability, body mass index, and physical activity, and further research is required to examine such effects. (42)

This meta-analysis, covering 851 cases compared to 862 controls, about the serum vitamin D concentration, incorporates the contradictory primary study's findings that contrasted patients with control groups. The two groups standardized the mean difference between vitamin D and −0.56 (95% confidence interval: −1.05, −0.08). Based on the results of this meta-analysis, which found that control group serum levels of vitamin D were substantially higher than those of FM patients (43). Shawn D et al. 2018 notes that stable controls have elevated vitamin D levels relative to FM patients (44). Okyay et al. 2016found that patients with FM had a serious deficiency of vitamin D, close to (43) recorded by Olama et al. in 2013. Olama et al. stated that FM patients with levels of vitamin D are more likely to have memory loss, emotionally unstable, indecision, associated with the development or worsening of restless legs, sleep disorder, and palpitations.

A study conducted in Northern Spain by Mateos et al. 2014 with the highest sample size (205 cases and controls) observed a statistically significant reduction in levels of vitamin D after the summer months: 26.9 ng / ml and 23.3 ng / ml (p=0.03) in patients with FM relative to controls. Patients with FM and controls do not vary in average levels of vitamin D throughout the year; 23.0 ng / ml versus 24.0 ng / ml or PTH levels; 51.0 versus 48.0. Interestingly, vitamin D seasonal variation was found in patients with FM compared to healthy controls (45). There were 19 cases / controls with the smallest sample size in Baygutalp et al. 2014. Both of these studies found that FM patients had lower blood levels of vitamin D compared to controls (46).

Interestingly, a positive correlation between low vitamin D bold levels and FM was also recorded by Atherton et al. 2009 (47). Nonetheless, BMI, social and lifestyle variables were analyzed by Atherton et al. 2009, and the month of assessment of vitamin D was the most rigorous method in terms of exhaustive modification, including for established confounders. In Iranian women, Maafi et al. 2016 observed significantly higher levels of vitamin D in patients with FM relative to healthy controls (17.2 ng / ml vs. 9.91 ng / ml; p = 0.001) (48). Kasapoğlu Aksoy M et al. 2017 also found that with low levels of vitamin D, the FM group and the stable control group both affect. (49).

A research by Yilmaz R et al. 2016 also notes that in patients with non-specific CWP, Vitamin D replacement therapy has produced improvements in musculoskeletal symptoms, depression level, and quality of life for the patient. This is the first meta-analysis, according to our knowledge, to investigate the impact of vitamin D supplementation on FM and CWP pain management (50). In Yong WC et al.2017 recent meta-analysis, it is suspected that supplementation of vitamin D is capable of reducing pain scores and improving pain despite not being essential (51). Dogru A et al. 2017 also found that in patients with FM vitamin D deficiency was regularly observed and an improvement was observed via vitamin D therapy. Vitamin D deficiency seems to be associated with FM pathogenesis (52). The beneficial correlation between hypovitaminosis D and chronic pain conditions such as FM is thus strongly supported.

No association between FM and Vitamin D deficiency.

No effect of vitamin D supplementation has been found on chronic musculoskeletal pain (53) by Gaikwad et al. 2017 recent systematic review. A systematic review of Cochrane in 2015 (54) reviewed the impact of vitamin D supplementation on pain management of osteoarthritis, rheumatic polymyalgia, rheumatoid arthritis, and other CWPs, but only three RCTs examined the effect of vitamin D supplementation on FM or non-specific musculoskeletal pain included in this analysis. Cochrane authors concluded, including all the research, that there was no evidence to support the chronic pain conditions value of vitamin D supplementation in general. So, another meta-analysis (55) of RCTs using quantitative methods, following the Cochrane study, states that supplementation with vitamin D usually significantly decreases pain. The study includes patients with rheumatoid arthritis, osteoarthritis, dysmenorrhea, migraine, non-specific low back pain, CWP and FM; but in each individual medical condition, the authors did not report the impact of vitamin D supplementation (55).Recent large meta-analysis, including 11,321 participants with vitamin D supplementation, found occurrence of adverse events in both treated and placebo groups (56), according to Martineau AR et al. 2017 (56).Another study of vitamin D supplementation and pain management indicates that the marginal impact of supplementation in people with deficient levels (defined as 25-

hydroxyVitamin levels < 30 nmol / L) and those with sufficient levels (25-hydroxyVitamin levels > 50 nmol / L) is unlikely to benefit from additional supplementation (57).In Israeli premenopausal women, Tandeter et al. 2009 did not report any significant difference in mean levels of vitamin D between FM patients and controls (21.75 ng / ml vs 19.43 ng / ml, respectively)And there is also no significant difference between the two classes of individuals with low levels of vitamin D. Low levels of vitamin D in control patients were found to be slightly higher at 51.2% compared to 44.1% (58) of FM patients. Wepner et al. 2014 indicated that supplementing vitamin D in FM patients reduces pain, but also found that vitamin D levels have a significant negative association with the activities of the daily living portion of the FM effect questionnaire (59).Warner et al. 2008 did not report any beneficial effects of vitamin D supplementation in a larger patient cohort (60).

Numerous studies have been conducted in recent years to clear the link between low calciferol levels and FM, the two conditions prevalent and contributing to chronic pain. The proof for a correlation between them is still debatable given the many trials and efforts; with no improvement in pain when on a treatment of vitamin D (61-62,58,60,63-66)Many reports show that vitamin D deficiency may be involved in non-specific chronic pain or FM, and some studies have recommended a vitamin D supplement for FM treatment, but others did not confirm it (61-62, 58, 60-59,67).Two systematic reviews were conducted which concluded that the basis of evidence is rather weak for the contribution of vitamin D deficiency to FM and the use of a vitamin D supplement for treatment. As with de Rezende Pena et al. 2010 (61), there is no statistically significant difference in mean serum concentration of 25-OHD between the FM and control groups and no association between level of vitamin D and severity of pain. Warner and Arnspiger (60) and Straube et al. 2009 (16) reported similar results that did not confirm the correlation between vitamin D deficiency and chronic or FM pain.

CONCLUSION

There is no consensus on the relationship between vitamin D and FM. Some studies have listed the correlation between low concentration of vitamin D and non-specific musculoskeletal pain, while other studies have documented the apparent association of deficiency of vitamin D with clinical manifestations of FM. Other research, however, found no significant correlation between FM and vitamin D. Thus, tests on levels of vitamin D in FM patients showed conflicting results.

Conflict of interest: No conflict of interest

ABBREVIATION

FMS: Fibromyalgia syndrome

VDR: Vitamin D receptor

1,25(OH)2D: 1,25-Dihydroxyvitamin D

25(OH)D: 25-hydroxyVitamin levels

ng/ml: nanograms per milliliter

OR: OddsRatio

CI: Confidence Interval

BMI: Body mass index

ACR: American College of Rheumatology

CWP: Chronic Widespread Pain

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