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General

The Role of Vitamin D in the Management of Chronic Pain in Fibromyalgia: A Narrative Review

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Introduction

Fibromyalgia (FM) is a complex disorder characterized primarily by chronic, widespread musculoskeletal pain. Currently, the Food and Drug Administration (FDA) has approved the use of three medications to treat FM: pregabalin, duloxetine, and milnacipran. The pharmaceutical intervention has lacked consistent pain relief among all patients. Therefore, the investigation into alternative treatment options has grown in interest. This narrative review aims to evaluate the evidence regarding vitamin D for the treatment of FM.

Methods

Narrative review.

Results

Low serum vitamin D has been linked to various chronic pain states. An association between vitamin D deficiency and FM has been reported but is controversial in the literature. Some studies have documented the beneficial effects of vitamin D supplementation on reducing pain symptoms and improving the overall quality of life in those with FM. Despite these positive findings, many of the studies regarding this topic lack adequate power to make substantial conclusions about the effects of vitamin D on FM.

Conclusion

Existing studies provide promising results. However, additional high-quality data on vitamin D supplementation is needed before recommendations for pain management can be made. Vitamin D supplementation is inexpensive, has minimal side effects, and can benefit FM patients regardless of its efficacy in pain control. Additionally, high-quality studies are warranted to fully elucidate the potential of vitamin D to manage chronic pain in FM.

INTRODUCTION

Fibromyalgia (FM) is characterized primarily by prolonged, widespread musculoskeletal pain, often with accompanying fatigue, headaches, stiffness, genitourinary symptoms, disturbed sleep, and cognitive difficulties.[1] The exact etiology of FM remains unclear. However, factors such as adverse events, stressful environments, and emotional and physical distress have been documented as provoking variables.[1,2] The symptoms displayed in a patient can significantly differ throughout the disease from individual to individual. Symptoms also show discrepancies within the same patient throughout the progression of the disease.[1,3] Due to the variability, the syndrome's presentation can be challenging to identify. Physicians must have an adequate understanding of the requisite symptoms of FM for timely diagnosis and proper management.

Although anyone can be diagnosed with FM, it is most commonly found in middle-aged women. Studies show that 60-80% of individuals diagnosed with FM are women.[4,5]

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It is suspected that men may be underdiagnosed due to stigma, differences in perception of pain, pain tolerance, and health professionals lacking FM on their differential when treating men.[5]

FM often occurs with other conditions implicated by chronic inflammation or peripheral nerve damage.[6,7] Due to the culmination of symptoms present in FM, managing the syndrome is often complicated and takes a concerted effort by both the patient and physician. A multidisciplinary treatment plan that includes pharmaceutical intervention, supportive cognitive therapy, and lifestyle modifications (increasing exercise, teaching proper sleep hygiene, improving diet quality) provides better symptom management than any single treatment alone.[8,9] Nutrient supplementation may provide additional benefits in FM management and could play a role in the multidisciplinary approach to treatment. This review aims to evaluate the evidence regarding vitamin D supplementation to treat chronic pain in FM.

METHODS

This narrative review was carried out in 2020 via a comprehensive search using the PubMed database for literature associated with "Vitamin D Supplementation in the Management of Chronic Pain in FM." The following keywords were utilized in the search: vitamin D, FM, nutrient, diet, supplementation, supplements, pain. Recent manuscripts (within the last four years) were prioritized for inclusion; however, additional relevant papers (older than four years) were also included. An effort to utilize and cite primary manuscripts whenever possible was made. This manuscript is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any authors.

FIBROMYALGIA EPIDEMIOLOGY/ PATHOPHYSIOLOGY/RISK FACTORS/ PRESENTATION

EPIDEMIOLOGY/PRESENTATION/RISK FACTORS

FM's disease presentation is multifaceted. FM presents as chronic, widespread pain with fatigue, headache, cognitive disturbances, depression, stiffness, and genitourinary symptoms. FM's prevalence rate is 0.5%-5% worldwide and 2-4% in the United States.[10,11] The National Fibromyalgia Association (NFA) reported that many patients with FM also have associated comorbidities such as migraines, arthritis, irritable bowel syndrome, temporomandibular disorder, and major depressive disorder.[12,13] Some studies show increased FM rates in chronically ill patients with hepatitis C, human immunodeficiency virus (HIV), systemic lupus erythematous, Bechet, and those on hemodialysis.[10,14,15] Environmental factors such as physical trauma, microbial infections (i.e., Lyme disease, Parvovirus, and Epstein–Barr virus), and emotional stress have been shown to trigger FM in a small percent of individuals.[12,16] Numerous studies have shown that middle-aged women of a lower socioeconomic status or educational disparities are at an increased risk of being diagnosed with FM. There seems to be no association of FM with smoking or body mass index.[10]

It is difficult for the American College of Rheumatology (ACR) to establish concrete, comprehensive diagnostic criteria for FM because the associated symptoms are relatively common and nonspecific.[17] An accurate diagnosis heavily relies on ruling out disorders of rheumatic, psychiatric, hematologic, and endocrine origins, contributing to FM being an expensive diagnostic process.[18] Pain, the cardinal symptom of FM, also complicates its diagnosis. Pain is subjective and occurs with many disorders. Deciphering whether a person's pain is a symptom of a psychiatric disorder, FM, or another chronic pain condition is difficult. Studies have shown that the stigmatization of FM by society and dismissiveness and skepticism by healthcare professionals exacerbate diagnosis barriers.[12,19] The NFA estimates that it takes the average patient up to 5 years to receive an FM diagnosis.[13]

PATHOPHYSIOLOGY

The exact pathophysiology of FM is not yet completely understood. Continuous research has shown that environmental factors, neurotransmitter disturbances, genetics, neuroendocrine abnormalities, mitochondrial dysfunction, and inflammation contribute to its manifestation.[12,19–35]

PATHOPHYSIOLOGY- NEUROTRANSMISSION

Patients with FM tend to experience hyperalgesia (increased sensitivity to pain) and allodynia (pain elicited from innocuous baseline stimuli).[12] Although the exact pathophysiology behind FM is still unclear, functional magnetic resonance imaging (fMRI) elucidates dysfunctions in the central monoaminergic neurotransmission of substance P, serotonin, glutamate, and norepinephrine.[12,19] These disruptions cause decreased activity in the thalamus and other brain areas involved in the descending inhibitory pain pathways (i.e., amygdala, caudate nucleus, and anterior insula) and cause increased pain sensitivity in patients with FM.[12,20]

PATHOPHYSIOLOGY- GENETICS

Targeted gene studies are exploring the identification of genetic polymorphisms among patients with FM.[3,21] Although the genetic contribution to FM is still under investigation, and there is evidence that serotonin transporter (5-HTT), Catechol-O-methyltransferase (COMT), and dopamine D_4 receptor (DRD4) gene deletion and insertion polymorphisms are implicated in the pathogenesis of FM.[22–24] These proteins involve the metabolism or transport of monoamines, which play a critical role in the human stress response and heightening pain sensitivity in FM.[25,26] There is ongoing research using whole-exome sequencing, which shows that micro ribonucleic acids (mRNAs), specifically mir-145, are strongly associated with causing FM's cardinal symptoms.[27,28]

PATHOPHYSIOLOGY- NEUROENDOCRINE

Patients with FM are thought to have a disrupted hypothal-

amic-pituitary-adrenal axis (HPA axis).[29–32] HPA axis disruption can lead to abnormal levels of adrenocorticotropic hormone, follicle-stimulating hormone, and growth hormone.[12,25] The serotonin system significantly influences the functionality of the HPA axis. The reduced serotonin levels observed in patients with FM may facilitate the destruction of the HPA axis and lead to endocrine abnormalities.[33] These abnormalities result from the body's response to the stressor caused by the disease, rather than the stressor causing the disease process.[12]

PATHOPHYSIOLOGY- MITOCHONDRIAL DYSFUNCTION

Mitochondrial disruption with a concomitant reduction in mitochondrial chain activity has been observed in skin and muscle cells of patients with FM.[34,35] Mitochondrial dysfunction results in the release of pro-inflammatory signals, which stimulate oxidative stress and immune responses and have been correlated with peripheral nerve damage and subsequent allodynia.[34,35] Such signals include reactive oxygen species (ROS) and damaged mitochondrial deoxyribonucleic acid (mtDNA), which may accumulate and induce activation of a chronic innate inflammatory state.[34–36] Neural cells are highly susceptible to oxidative stress by ROS and lipid peroxidation because of their high lipid content, which also lends to the chronic neuroinflammation seen in FM as a result of mitochondrial dysfunction.[36]

PATHOPHYSIOLOGY- INFLAMMATION

Increased cytokines and chemokines play a significant role in the pathogenesis of FM.[34–38] Substance P is a neuropeptide that modulates pain through stimulation of mast cells and secretion of cytokines and is increased in FM.[36,37] Substance P, as well as brain-derived neurotrophic factor, glutamate, and nerve growth factor, also activate glial cells.[36,37] Upregulation of pro-inflammatory cytokines (tumor necrosis factor-alpha (TNF-a), interleukin (IL) -1, IL-6, and IL-8) via activated glial cells lead to central neural inflammation in FM.[36,37] These cytokines can further stimulate neurons to release more neuropeptides, thus, causing a robust amplification of neuron-inflammatory cell interactions.[37,38] This phenomenon increases the central processing of nociceptive input and contributes to chronic pain, allodynia, and hyperalgesia in FM.[34] Interferon-gamma (IFN-γ), which is increased in many FM patients, is believed to be the culprit of increasing the following pro-inflammatory chemokines: monokine induced by IFN-γ (MIG), monocyte chemoattract protein-1 (MCP), and eotaxin.[37] These chemokines are also involved in nociception and may contribute to the intense, widespread pain patients with FM experience.[37]

PATHOPHYSIOLOGY- SLEEP QUALITY

Poor sleep quality is associated with worsening symptoms of FM.[19,39,40] Sleep deprivation impairs descending pain inhibition pathways important in controlling pain modification.[19,39] Sleep disturbances are also linked to increased tender points in patients with FM; increased tender points are associated with increased severity of the disease.[16,19] Studies have found that slow-wave sleep (SWS) is diminished in FM patients.[19] SWS regulates heart rate, blood pressure, sympathetic activity, cerebral glucose consumption, and cortisol levels.[19] Compromised homeostatic regulation may result in reduced SWS, leading to fatigue and a decreased pain threshold as seen in FM.[16,19]

CURRENT TREATMENT OF FIBROMYALGIA

The treatment of FM is multifaceted. Current management of FM consists of both pharmacological and non-pharmacological approaches based on recommendations by various institutions such as the American Pain Society and the European League Against Rheumatisms (EULAR). However, despite the breadth of pharmacological approaches recommended, the Food and Drug Administration (FDA) has only approved the use of three medications to treat FM: pregabalin, duloxetine, and milnacipran.[41,42] Further complicating matters are the lack of consistency between various institutions and their guidelines.

Regardless of the discordance in recommendations, there are mainstays in FM management that are centered around patient education, non-pharmacological management, and targeted pharmacological therapy that is specific to the patient and limits a polypharmacy approach. As previously noted, the only FDA-approved medications are pregabalin, duloxetine, and milnacipran. Pregabalin is an anticonvulsant that binds to the alpha-2 subunit of the voltage-gated calcium channel, reducing synaptic transmission and neuronal excitability.[43] The Efficacy of this drug is significant, yielding improvements in pain and sleep quality, fatigue, and quality of life.[42,44,45] Duloxetine and milnacipran are both selective serotonin and norepinephrine reuptake inhibitors that are efficacious in relieving pain. Duloxetine, however, is limited since it was only found to be beneficial in treating the pain associated with FM but not other symptoms, such as fatigue or sleep quality.[42,46–49] In contrast, milnacipran has also improved fatigue and sleep quality.[41,50–52] Other drug classes that have been used off-label in the treatment of FM include tricyclic antidepressants, selective serotonin reuptake inhibitors, muscle relaxants, dopaminergic agonists, antioxidants, cannabinoids, benzodiazepine, and atypical antipsychotics. Analgesics, including non-steroidal anti-inflammatory drugs (NSAIDs), are commonly used in these patients despite the lack of efficacy.[46,53] Tramadol, a centrally acting analgesic, has been noted to have some efficacy in treating chronic pain associated with FM.[54,55] This benefit may result from the multimodal mechanisms of action of tramadol, specifically the weak serotonin and norepinephrine reuptake inhibition activity.[54–56] One drug class often used in treating chronic pain but has been discouraged in treating FM pain is opioids. This recommendation against opioids is in part due to their lack of efficacy, a result of the decreased opioid-mediated descending anti-nociceptive activity.[46,57,58]

Non-pharmacological treatments are designed to address the physical, emotional, and psychological effects of the disease on the patient. Ranging from physical exercise and alternative medicine to cognitive behavioral therapy and massage therapy, various non-pharmaceutical approaches have been studied and incorporated in the guide-

lines for management.[41,42,45,46,58] One relatively novel approach, hyperbaric oxygen therapy (HBOT), has gained traction as an alternative therapy due to the multitude of physiological mechanisms by which it diminishes nociception.[59] Specifically, HBOT targets a variety of the underlying pathophysiological processes that result in FM's chronic pain state, including reduced production of glial cells and inflammatory mediators.[59] Additionally, nutritional supplementation in the form of vitamins has gained popularity in pain management, especially vitamin D. However, the evidence regarding the efficacy of vitamins as a therapeutic adjunct remains inconclusive and requires further study.[42,60,61] Note that the effectiveness of these therapeutic approaches are not equal, and there are varying levels of evidence to support their use. Therefore, it is imperative to consider these modalities of management in the context of the patient.

ASSOCIATION BETWEEN LOW SERUM VITAMIN D AND CHRONIC PAIN

The effect of low serum vitamin D on the pathophysiology of chronic pain disorders has become an increasingly popular topic of investigation. Specifically, low levels of 25-hydroxy vitamin D (25(OH)D) have been identified as influencing the sensitivity to pain in the central nervous system (CNS) via augmentative properties. One study has documented an inverse relationship between 25(OH)D levels and pain sensitivity to mechanical stimuli.[62] This finding is especially notable given that FM has been identified as a central sensitivity syndrome. Furthermore, several studies have identified the role of steroids in modulating neuronal excitability, one of which is vitamin D.[62–64] These findings indicate that vitamin D can function to influence microglia, astrocytes, and spinal glia in the release of neuroexcitatory substances such as pro-inflammatory cytokines.[63,64] By controlling the release of pro-inflammatory cytokines, particularly TNF-a, vitamin D serves a neuroprotective role in reducing the extent of central sensitization to pain.[63,64] Vitamin D is also involved in suppressing macrophage-colony-stimulating factor (M-CSF), a cytokine that is involved in the activation of macrophages, cells responsible for releasing pro-inflammatory cytokines, including the TNF-a mentioned above.[65,66] In addition to neuromodulation, vitamin D has also been shown to play a role in nociceptor innervation and hypersensitivity to musculoskeletal pain.[62,67] Specifically, vitamin D has been reported to affect the nociceptive innervation of skeletal muscle, resulting in hyperinnervation when vitamin D deficiency is present.[67] Note, however, other studies have refuted the association between vitamin D deficiency and chronic pain, as evidenced by a randomized control trial (RCT) conducted in New Zealand, finding no significant associations between low vitamin D and chronic pain in older adults.[68]

VITAMIN D IN THE TREATMENT OF CHRONIC PAIN CONDITIONS

Multiple studies and systematic reviews have analyzed the existing data surrounding vitamin D supplementation in managing chronic pain conditions, with conflicting results being noted. In one literature review, vitamin D was found to be beneficial for chronic pain management in nonspecific pain and FM; however, these results were not consistent across all of the studies that were reviewed, indicating that there is significant heterogeneity that exists in the context of vitamin D and the treatment of chronic pain.[60,61] However, in a case series study of veterans with chronic musculoskeletal pain deficient in vitamin D, supplementation was found to have a statistically significant benefit in improving pain levels, sleep, and quality of life metrics.[69] Additionally, a 2017 meta-analysis described four separate studies where significantly lower visual analog scale (VAS) pain scores were reported in patients with widespread chronic pain when supplemented with vitamin D versus patients who were supplemented with placebo.[70] Despite the controversy, it may be argued that vitamin D supplementation can reasonably be incorporated into pain management regimens when deficient because of its known role in the nociceptive pathway and because it is inexpensive with minimal adverse effects.

SERUM VITAMIN D IN PATIENTS WITH FIBROMYALGIA

As with the association of vitamin D deficiency and chronic pain conditions, multiple studies have yielded varying results regarding whether there is an association between serum vitamin D levels and FM.[71–77] Mateos et al.[71] reported no significant difference between healthy controls and FM patients regarding both bone mineral density and vitamin D levels. Additionally, Beserra et al.[72] found no significant difference in vitamin D levels between FM patients and healthy individuals. In contrast, Okyay et al.[73] found a significant reduction in vitamin D levels between healthy controls and FM patients. Additionally, a negative correlation between vitamin D and VAS, tender point count (TPC), and FM impact questionnaire (FIQ) scores were found in FM patients by Beserra et al.[72] and Okyay et al.[73] Similar findings were also noted in a study of Saudi Arabian women with FM; specifically, a negative correlation between vitamin D levels and the widespread pain index (WPI) was found.[74] These findings echo the results found in the study mentioned above by Huang et al.[69]

Notably, a 2017 meta-analysis found no significant evidence to indicate that FM is associated with low serum vitamin D levels.[75] However, in reviewing the studies included in the meta-analysis, there are limitations secondary to the types of studies being conducted. Interestingly, Maafi et al.[76] found FM patients had significantly higher serum levels of vitamin D when compared to healthy controls.

It has been suggested that the association between serum vitamin D levels and FM is not associated with or due to any pathological causative effect but is instead a result of patients with chronic pain having limited sun exposure.[61,71] Regardless, there remains ambiguity regarding the significance of any association between serum vitamin D and FM. These conflicting findings call for additional studies on the topic.

THE ROLE OF VITAMIN D IN THE MANAGEMENT OF FIBROMYALGIA

Some studies that reported vitamin D supplementation in FM patients are notable for finding improvement in pain symptoms with vitamin D administration.[74,78–83] An even more significant impact on symptom relief has also been reported when serum levels of vitamin D surpassed 50 ng/mL in FM patients.[78] In one study, women with a diagnosis of FM were either treated with calcifediol or a placebo with the goal of > 32 ng/mL of calcifediol levels, in line with the Endocrine Society's guidelines for therapeutic serum 25(OH)D levels.[79,84] Patients who were part of the treatment group (TG) were noted to have significant improvement in their VAS pain scores; however, these benefits were found to dissipate 24 weeks after cessation of supplementation with vitamin D, further lending support to the argument of vitamin D improving the pain symptoms associated with FM.[79] Despite the breadth of information collected on this topic, and the studies mentioned above indicating the efficacy of vitamin D supplementation, there remains discordance about the benefit of vitamin D in the management of patients with FM.

Regardless of the underlying Efficacy, there are certain advantages to vitamin D supplementation that are especially beneficial in FM patients. Specifically, given the effects of chronic pain on physical activity levels and subsequently reduced exposure to sunlight, FM patients are at an increased risk for developing osteomalacia and decreasing muscular strength.[85,86] Therefore, supplementation with vitamin D would function to not only maintain long-term bone health but, as previously mentioned, also serve as a potential therapy for chronic FM pain with minimal adverse effects.

VITAMIN D SUPPLEMENTATION IN THE MANAGEMENT OF FIBROMYALGIA: CLINICAL STUDIES

FIBROMYALGIA ASSOCIATED WITH VITAMIN D LEVELS

Baygutalp et al.[87] investigated the relationship between FM and serum 25(OH) D levels. Nineteen premenopausal women diagnosed with FM were age and location matched to 24 control patients. The endpoints measured included widespread body pain, headache, fatigue, morning stiffness, sleep disorder, TPC, FIQ, and Beck depression inventory (BDI). Results showed a significant correlation in decreased serum 25(OH)D levels in patients compared to controls ($p=0.04$). Results also showed negative correlations between 25(OH)D levels and widespread body pain ($p < 0.01$), BDI scores ($p < 0.01$), headache ($p < 0.01$), and sleep disorder ($p < 0.01$) in FM patients, indicating a relationship between low vitamin D levels and clinical symptoms of FM.[87]

A similar study by Okumus et al.[88] compared 40 premenopausal women with and without FM and assessed the differences in symptoms and severity of symptoms related to 25(OH)D levels. Parameters tested included TPC; intensity of widespread pain, as measured by VAS; physical functional capacity, as measured by the activities of daily living components of the FIQ; and serum vitamin D levels. The study found no significant difference in vitamin D levels between the FM patients and the CG ($p=0.356$). However, there was a difference in pain intensity experienced by those with FM who were vitamin D deficient ($p=0.001$), indicating a possible effect on pain perception.[88]

A more extensive study of 410 pre-and post-menopausal women by Mateos et al.[71] looked at the relationship between FM, osteoporosis, and hypovitaminosis D. Compared to controls, this study did not a significantly lower vitamin D level in patients with FM ($p=0.06$). There was also no difference when pre-and post-menopausal women were considered separately. However, there was a lack of seasonal vitamin D fluctuation in FM patients. Their vitamin D levels did not rise in the summer leading to a relative hypovitaminosis D in FM patients. This difference may be due to behavioral factors or otherwise unrelated to their condition.[71]

VITAMIN D AS A TREATMENT FOR FIBROMYALGIA

The following studies are summarized in Table 1.

One preliminary study by de Carvalho et al.[80] investigated 11 female patients diagnosed with FM who were given 50,000 international units (IU) of vitamin D a week for three months. The study parameters included serum 25(OH)D levels and pain, as measured by VAS. At the end of the three months, vitamin D levels had increased significantly from 18.4 to 33.8 ng/mL ($p=0.01$). The VAS median and TPC decreased from 90 to 30 from 17 to 10, respectively ($p=0.07$). The study was limited by its lack of a CG and its small number of patients based on the exclusion criteria.[80]

In a randomized placebo-controlled study by Wepner et a.,[79] patients with FM who were vitamin D deficient were studied to assess the effect of becoming vitamin D replete on various parameters (72). Patients were split into a CG and TG and were evaluated at weeks 1, 5, 13, 25. Patients in the TG were given either 2400 IU or 1200 IU of oral cholecalciferol (vitamin D3) daily to reach optimal serum levels between 80 and 120 nmol/L (32 to 48 ng/mL). If patients exceeded 120nmol/L, treatment was discontinued to maintain optimal and safe serum concentrations. At week 25, both vitamin D and placebo treatments were stopped, and a follow-up exam was performed at week 49. Parameters studied included pain, as measured by VAS; quality of life, measured via the 36-item Short-Form Health Survey (SF-36); anxiety and depression; disease-related impairment, measured by FIQ; and somatization. Thirty patients completed the study, 15 people in each group. VAS scores were seen to significantly decrease in the TG ($p=0.025$) while excluding the follow-up time point as scores were similar at this time point ($p=0.999$). There were also significant increases in the physical role functioning scale ($p=0.022$), a subset of the SF-36 survey, and decreased morning fatigue on the FIQ ($p=0.007$). There were no significant changes in somatization, anxiety, and depressions or the SF-36 survey's remaining subsets. Although the study concluded that the results were promising, it was limited by its small, highly selective patient population.[79]

A study by Yilmaz et al.[81] included 58 patients to assess the effect of vitamin D supplementation in patients with chronic widespread musculoskeletal pain (CWMP), includ-

Table 1. Clinical Studies

Author	Groups Studied and Intervention	Results and Findings	Conclusions
J.F. de Carvalho, et al[80]	11 female patients were given 50,000 IU oral vitamin D supplementation weekly for 3 months to assess the effect on FM symptoms. Endpoints were measured using TPC and VAS to assess pain.	At the end of the 3-month period, VAS scores decreased from 90 to 30 (p=0.002) and TPC decreased from 17 to 10 (p=0.07).	The study concluded that disease symptoms of FM seemed to improve with vitamin supplementation.
F. Wepner, et al[79]	30 women with FM were evenly divided into a TG and CG. The treatment group was given vitamin D supplementation for 20 weeks with the goal of achieving a serum vitamin D level between 32 and 48 ng/mL. The CG was given a placebo. Endpoints were measured using VAS for pain, SF-36, Anxiety and Depression Scale, and FIQ.	Significant improvements were seen in the TG in VAS pain scores and physical role functioning scale of the SF-36.	The study concluded that adequate vitamin D levels in FM patients had a positive effect on the perception of pain.
R. Yilmaz, et al[81]	58 patients with chronic widespread musculoskeletal pain, including those with FM, were treated with 50,000 IU/ week of Vitamin D supplementation for 3 months. Endpoints were measured using serum levels of Ca, P, ALP, vitamin D, VAS for pain and asthenia, BDI, SF-36, TPC, and several others.	At the end of 3 months, patients showed decreased in VAS for pain and asthenia, severity of waking unrefreshed, TPC, and BDI.	The study concluded that vitamin D supplementation in those with CWMP, including those with FM, showed improvements in musculoskeletal symptoms, level of depression, and quality of life. It also stated that patients with CWMP should be screened for Vitamin D deficiency.
A. Mirzaei et al[82]	74 patients with FM were equally and randomly separated in a CG and TG. The TG was given 50,000 IU/week of oral Vitamin D and 25 mg of trazodone nightly for 8 weeks. The CG received the trazadone along with a placebo. Endpoints were measured using WPI, FIQ, PSQI, and SF-36.	At the end of 8 weeks, improvements in WPI< FIQ and PSQI scores were seen in both groups. Improvement in WPI and the physical component score of the SF-36 were more prominent in the TG. Overall scores on the SF-36 showed improvement in the TG compared to the CG.	The study concluded that vitamin D supplementation was useful in decreasing pain in FM patients. Supplementation of vitamin D combined with an antidepressant reportedly amplified the improvement in physical and psychological symptoms.
S. Abou-Raya et al[83]	72 FM patients were evenly and randomly distributed into a TG and CG. The TG received 2,000 IU/day of oral Vitamin D for 6 months. The CG received a placebo. Endpoints were measured using FIQ, BPI, BDI, VAS for pain, and SF-36.	At 6 months, results showed a decrease in VAS pain scores (p<0.001). There were also improvements in SF-36 and FIQ scores (p<0.005).	The study concluded that vitamin D supplementation had a positive effect on pain perception in FM patients.

Abbreviations: International Unit (IU); fibromyalgia (FM); tender point count (TPC); visual analog score (VAS); treatment group (TG); control group (CG); Fibromyalgia impact questionnaire (FIQ); 36-item Short Form Health Survey (SF-36); calcium (Ca); phosphate (P); alkaline phosphatase (ALP); Beck Depression Inventory (BDI); chronic widespread musculoskeletal pain (CWMP); Widespread Pain Index (WPI); Pittsburgh Sleep Quality Index (PSQI); Brief Pain Inventory (BPI)

ing those with FM. Patients were given 50000 IU/week oral vitamin D (calciferol) and elemental calcium daily for three months. The parameters studied included serum quantities of vitamin D, measured as 25(OH)D3, calcium (Ca), phosphate (P), and alkaline phosphatase (ALP). The study also measured quality of life, measured by the SF-36; depressive mood, measured by the BDI; pain and asthenia, measured by VAS; severity of waking unrefreshed; and TPC. At baseline, the frequency of meeting FM criteria within those with CWMP was increased in those with severe vitamin D deficiencies, as defined as <10 ng/ml. At the end of the three months, there was found to be a significant increase in 25(OH)D3 levels ($p < 0.001$) and a substantial decrease in ALP levels ($p < 0.001$). There was no significant change in the Ca or P levels. Pain and asthenia both saw significant reductions ($p<0.001$). Quality of life saw a significant increase in all categories measured on the SF-36. Out of the 58 patients with CWMP to complete the study, 30 met the criteria for FM before treatment compared to 20 after treatment ($p=0.013$). Forty-two patients had tibial tenderness before treatment, which decreased to 22 after treatment ($p < 0.001$). The study concluded that vitamin D supplementation leads to improved musculoskeletal symptoms and patients' quality of life. Patients with CWMP should be investigated for vitamin D deficiencies.[81]

An RCT by Mirzaei et al.[82] of 37 patients with FM combined vitamin D supplementation with Trazadone for 8 weeks and found similar results. Patients were given 50,000 IU of oral vitamin D weekly and 25 mg of trazodone at bedtime daily. Endpoints studied at baseline, week 4, and

week 8 included quality of life, measured by the SF-36; sleep quality, measured by the Pittsburgh Sleep Quality Index (PSQI); disease-related impairment, measured by the FIQ; and pain, measured by the WPI. Results at the end of 8 weeks showed a significant improvement in both the physical (p=0.001) and mental (p=0.04) component scores of the SF-36 survey in the TG compared with a decrease in the CG. There was a decrease in WPI scores in both the TG (from 12.2±2.3 to 4.47±2.5) and the CG (from 13.5±3.4 to 8±4.8), but the decrease was more significant in the TG (p=0.007). The FIQ showed improvements in all sub-scores in the TG, with the most improvement seen in morning tiredness, stiffness, anxiety, and depression. Total FIQ scores decreased from 52.4±16.6 to 29.7±14 in the TG compared to a decrease from 50.7±16 to 40.4±15.3 in the CG (p=0.064). PSQI scores decreased from 10 to 6.1 in the TG and from 10.4 to 8.1 in the CG (p=0.002). One limitation of this study is the short follow up time of 8 weeks.[82]

Another RCT by Abou-Raya et al.[83] studied the effects of taking 2000 IU of oral cholecalciferol daily for six months. Out of 72 patients diagnosed with FM, 36 patients received vitamin D treatment while the other 36 received a placebo. Endpoints included quality of life, measured by the SF-36 assessment; FMS symptoms, measured by FIQ scores; pain, measured by brief pain inventory (BPI) scores and VAS; and depression, measured by BDI scores. At six months, patients in the TG showed decreased pain as measured by VAS score from 6.6± 2.5 to 2.9± 2.7 ($p < 0.001$). The score also showed lower 25(OH)D levels correlated with higher scores of the FIQ with an r of 0.549 ($p < 0.005$). The study concluded that vitamin D supplementation had a positive effect on pain perception in FM patients.[83]

These studies conclude that patients with FM should be screened for vitamin D deficiencies and that vitamin D supplementation, especially in those that are vitamin D deficient, have a positive impact on the pain perception and quality of life of those with FM.[79–83] Mirzaei et al.[82] showed that vitamin D in combination with an antidepressant might show improvement in both physical and mental symptoms in those with FM. Another benefit of vitamin D supplementation as a treatment for FM is its low cost and low risk of significant side effects.

CONCLUSION

FM is an idiopathic, complex disorder that presents as chronic, widespread pain with fatigue, stiffness, cognitive impairment, and depressed mood.[12] It typically affects women more than men.[4,5] Most patients who suffer from FM also have other comorbid, chronic medical conditions.[6,7] Environmental, genetic, and neuro-hormonal factors can play a role in the pathogenesis of this disease.[19–35] The treatment of FM often involves a multidisciplinary approach involving pharmacological and non-pharmacological interventions.[8,9] Delayed diagnoses, expensive cost, insurance barriers, lack of consistency in treatment guidelines, and low treatment adherence heighten the barriers to effectively treating FM.[12]

FM's current pharmacological treatment options are pregabalin, duloxetine, and milnacipran, while the non-pharmacologic treatments are physical exercise, cognitive behavioral therapy, and alternative medicine.[8,9,12,41,42] One alternative option for symptom relief is vitamin D supplementation. Vitamin D plays a vital role in maintaining numerous homeostatic processes, regulating hormones, and nociceptor innervation in skeletal muscle.[16,19,65–67] Some studies show that low vitamin D levels facilitate increased sensitivity to pain in the CNS of patients with FM[67]; however, some studies refute these findings.[60,61] Some randomized control studies have shown that vitamin D supplementation helps alleviate pain, fatigue, and depression in patients with FM.[79,82,83] It is unclear if vitamin D proves to be fully efficacious because studies show conflicting results.

Vitamin D supplementation is inexpensive, has minimal side effects, and can benefit patients with FM regardless of its efficacy in pain control. Vitamin D may reduce the risk of developing osteomalacia and improve long-term bone health in patients with FM.[85,86] Vitamin D supplementation can improve the quality of life in patients suffering from FM, for a low cost thus should continue to be explored.

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COMPLIANCE WITH ETHICAL GUIDELINES

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any authors.

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