

The Role of Vitamin D in Pathophysiology and Treatment of Fibromyalgia

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Abstract Recent studies showed that most cells have receptors and enzymes responsible for metabolism of vitamin D. Several diseases have been linked to vitamin D deficiency, such as hypertension, diabetes, depression, Alzheimer's disease, Parkinson's disease, multiple sclerosis, and chronic pain syndromes such as fibromyalgia. The association between fibromyalgia and vitamin D deficiency is very controversial in the literature with conflicting studies and methodological problems, which leads to more questions than answers. The purpose of this article is to raise questions about the association of hypovitaminosis D with fibromyalgia considering causal relationships, treatment, and pathophysiological explanations.

Keywords Fibromyalgia · Pain · Hypovitaminosis D · Vitamin D deficiency · Pathophysiology

Introduction

Fibromyalgia (FM) syndrome (FMS) is a common chronic musculoskeletal disorder characterized by the presence of widespread pain and multiple tender points on physical examination [1•, 2]. Other important accompanying symptoms of FM are fatigue, sleep disturbance, psychological distress, and cognitive disturbance [1•, 2].

FMS has to be persistent for at least 3 months and distinct pain on digital palpation of at least 11 out of 18 defined tender points. FMS is the common final product of various etiological factors. Several factors are associated with the

pathophysiology of FMS, but the causal relationship is still unclear. This includes alterations of central pain pathways, hyporeactivity of the hypothalamus-pituitary-adrenal axis, increased systemic pro-inflammatory, and reduced anti-inflammatory cytokine profiles, and disturbance in the dopaminergic and serotonergic system [3•].

FMS affects an estimated 1 %–4 % of the general population [1•, 3•]; women are about nine times more likely to develop FMS than men [1•, 4].

Experiencing diffuse and persistent pain, which fits the American College of Rheumatology criteria for FM, occurs in many other medical conditions, such as migraine, chronic fatigue pain, myofascial pain, and irritable bowel syndrome, rendering the accurate diagnosis of these conditions troublesome. Several attempts have been made to link FMS with vitamin D deficiency [5].

Vitamin D was misclassified as a vitamin; it may be more appropriately considered as prohormone and its active 1,25-dihydroxyvitamin D (1,25(OH)₂D) metabolite functions as a hormone, since it has its own receptors which are found in all human tissues [3•].

Vitamin D deficiency might be clinically suspected if any of the following are present: chronic(>3 months) or recurrent musculoskeletal (muscle, bone, and/or joint) aches or pains at any age, which are largely unexplained by specific injury, disease, neuropathology or anatomic defect; persistent muscle weakness, fatigue, and possibly difficulty walking; history of minimal sunlight exposure and/or inadequate dietary or supplemental vitamin d intake; clinical signs/symptoms of clinical osteomalacia which most typically appear late in the course of the disease [3•].

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Vitamin D Deficiency Is Associated with Fibromyalgia

Plotnikoff and Quigley determined the prevalence of hypovitaminosis D in 150 patients in primary care outpatients with persistent, nonspecific musculoskeletal pain syndromes refractory to standard therapies. Of the African

American, East African, Hispanic, and American Indian patients, 100 % had deficient levels of vitamin D (<20 ng/mL). Of all patients, 93 % (140/150) had deficient levels of vitamin D (mean, 12,08 ng/mL). Nonimmigrants had vitamin D levels as deficient as immigrants concluding that all patients with persistent, nonspecific musculoskeletal pain are at high risk for the consequences of unrecognized and untreated severe hypovitaminosis D [6].

Gloth et al. described an unusual pain syndrome in 5 patients with vitamin D deficiency. The pain had a hyperesthetic quality and did not respond to analgesics, including opiate derivatives or tricyclic antidepressants. The pain resolved promptly and dramatically with the administration of ergocalciferol, and the patients also demonstrated improved vitamin D states [7, 8].

A case series in Western New York by Prabhala et al. demonstrated severe myopathy associated with vitamin D deficiency. These patients experienced prompt resolution of their pain and muscle weakness after vitamin D therapy [7, 9].

Straube et al. conducted a critical analysis and found 3 observational studies exploring differences in 25-hydroxyvitamin D (25-OHD) levels between patients with and without chronic musculoskeletal widespread pain. Two very small studies (104 patients in total) claimed significantly reduced 25-OHD levels in patients with pain compared with controls [5, 10, 11].

However, in a recent large study, a significant association between 25-OHD levels and increased pain was found in only 1 of the several analyses for 3495 women but not for 3365 men [5, 12].

Badsha et al. determined the prevalence of vitamin D deficiency (<20 ng/mL) among patients with FM or muscle pain in a musculoskeletal clinic in the United Arab Emirates. One hundred three (74 %) of these patients had a low vitamin D level. Vitamin D deficiency was most common among Arab patients (86 %) and Indo-Pakistani (87 %) and least common among Caucasians (8 %) and was equally prevalent among veiled and nonveiled patients. Treatment resulted in clinical improvement in 90 % of patients concluding that nonspecific muscle pains among Arab and Indian-Pakistani populations may indicate vitamin D deficiency, and prompt treatment can result in resolutions of symptoms [13].

Schwalfenberg revised 6 selected cases of improvement/resolution of chronic back pain or failed back surgery after vitamin D repletion, in a Canadian family practice setting, from a state of deficiency/insufficiency to sufficiency and concluded that insufficiency is common; repletion of vitamin D to normal levels in patients who have chronic low back pain or have had failed back surgery may improve quality of life or, in some cases, result in complete resolution of symptoms [14].

Chronic low back pain in Saudi Arabia was studied by Saud in Saudi Arabia. Initial assessment involved 360 patients attending spinal and internal medicine clinics over a 6-year period who had experienced low back pain that had no obvious cause for more than 6 months. 25-OHD level was

performed before and after treatment with vitamin D supplements. Findings showed that 83 % of the patients had an abnormally low level of vitamin D before treatment with vitamin D supplements. After treatment, clinical improvement in symptoms was seen in all the groups that had a low level of vitamin D [15].

Another prospective study in Saudi Arabia evaluated 100 women suffering from FMS. Blood level of 25-OHD was estimated at initial visit and every 4 weeks until its level exceeded 50 ng/mL. The patients with vitamin D deficiency were treated with ergocalciferol 50,000 IU once weekly until their blood level of 25-OHD exceeded 50 ng/mL. There were 61 women with 25-OHD deficiency; with vitamin D supplementation, 42 women showed a significant improvement when their blood level of 25-OHD became >30 ng/mL. This improvement became more significant when their blood level exceeded 50 ng/mL. Therefore the authors concluded that vitamin D deficiency has to be considered in the management of FMS [3•].

Vitamin D deficiency causes osteopenia, precipitates and exacerbates osteoporosis, causes the painful bone disease osteomalacia, and worsens proximal muscle strength and postural sway. Vitamin D deficiency and osteomalacia should be considered in the differential diagnosis of patients with musculoskeletal pain, FM, chronic fatigue syndrome, or myositis [16].

FM is a complex problem in which symptoms of anxiety and depression feature prominently. Seventy-five Caucasian patients who fulfilled the ACR criteria for FM had serum vitamin D levels measured and completed the FM Impact Questionnaire (FIQ) and Hospital Anxiety and Depression Score (HADS). Deficient levels of vitamin D was found in 13.3 % of the patients, while 56.0 % had insufficient levels and 30.7 % had normal levels. Patients with vitamin D deficiency (<25 nmol/L) had higher HADS than patients with insufficient levels or than patients with normal levels (50 nmol/L or greater). Vitamin D deficiency is common in FM and occurs more frequently in patients with anxiety and depression. The nature and direction of the causal relationship remains unclear, but there are definite implications for long-term bone health [17].

Mouyis et al. found that 25-OHD levels was substantially reduced among patients with inflammatory arthritis and chronic pain. 25-OHD levels were low in all rheumatology conditions when compared with a local healthy reference interval, including FM [18].

The European Male Ageing Study found low levels of vitamin D in a male population with musculoskeletal pain [19••]. Heidari et al. studied a total of 276 patients with nonspecific skeletal pain at different regions of the skeletal system diagnosed as leg pain, widespread pain, arthralgia, rib pain, back pain, and FM were compared with 202 matched controls with regard to mean serum 25-OHD level

and 25-OHD deficiency. The results of this study indicate a positive association of vitamin D deficiency with a variety of nonspecific bone pain, particularly in women [20••].

Egyptian women with FM study was assessed and compared serum vitamin D level and bone mineral density (BMD) value in patients with primary FMS (PFMS) and healthy controls. Serum level of the 25-OHD is inversely correlated with visual analogue scale (VAS) of pain ($P=0.016$), Beck score for depression ($P=0.020$), and BMD at lumbar spine ($P=0.012$) concluding that FMS is a risk factor for osteoporosis [21•].

Vitamin D deficiency causes muscle weakness and muscle aches and pains in both children and adults. Glerup et al. [22, 23] reported that 88 % of Danish women of Arab descent who presented with muscle pains and weakness were severely vitamin D-deficient. Bischoff et al. [22, 24] observed that adults with vitamin D deficiency have muscle weakness and are more likely to fall.

Al-Allaf et al. determined whether women with FM are at increased risk of developing osteoporosis or osteomalacia. Forty premenopausal women with FM and 37 age-matched female controls were studied. Broadband ultrasound attenuation (BUA) and velocity of sound (VOS) were measured at the calcaneum and bone mineral density was measured at the forearm and lumbar spine using dual-energy X-ray absorptiometry. Serum calcium, alkaline phosphatase, gamma-glutamyl transferase 25-OHD and plasma viscosity were measured in all subjects and parathyroid hormone was measured in subjects recruited in the latter part of the study. Seventeen patients with FMS and 7 controls had 25-OHD concentrations <20 nmol/l ($P<0.015$) and in 3 FMS patients serum parathyroid hormone was raised. Bone density in FM patients was slightly lower at the mid-distal forearm but comparable with that in controls at other sites. There is no reason to recommend routine bone densitometry in FM patients. However, vitamin D subnutrition is common in these patients and this should be sought [25].

Vitamin D Deficiency is not Associated with Fibromyalgia

Block criticized Plotnikoff and Quigley study (6) because the selected patients who had “at least 2 months of nonspecific, persistent musculoskeletal pain refractory to standard interventions” but none of whom “had FM as strictly defined by American College of Rheumatology (ACR) criteria” that require at least 3 months of symptoms. Furthermore, there were no controls [26].

Block evaluated 101 white patients with chronic, widespread musculoskeletal pain without an evident cause. Two thirds of the 101 patients fulfilled the ACR criteria for FM. Vitamin D levels were similar in all groups. Of the 9 patients

with vitamin D levels less than 10 ng/mL, 7 agreed to take 50,000 IU of vitamin D weekly for 8 weeks and 5 found the therapy of no benefit for their pain. A difference was not confirmed in vitamin D levels between those patients with chronic musculoskeletal pain who fit the ACR criteria for FM and those who did not; and there was no reason to suspect that vitamin D therapy would benefit this group of patients [26].

Tandeter et al. tested the levels of 25-OHD in patients 68 premenopausal women with a diagnosis of FM and 82 age-matched premenopausal women without. No statistically significant differences were found between the groups regardless of the cutoff levels used. A logistic regression model for predicting women with 25 OHD levels <20 ng/mL showed that all the variables examined in both groups (age, country of birth, education) were not statistically significant [27].

One study compared 25 women with systemic lupus erythematosus (SLE) with 25 women with FM. Serum 25-OHD levels did not significantly differ between SLE and FM patients but 1,25(OH)2D tended to be lower in the SLE compared with the FM patients. This difference could be attributed to hydroxychloroquine use [28].

The evidence regarding any association between vitamin D deficiency and FM, addressing whether general practitioners should be testing and treating these patients for vitamin D deficiency. A systematic literature review was performed, using MEDLINE as the primary database. The evidence for an association between FM and vitamin D deficiency is inconclusive, with no improvement in pain on supplementation. However, patients with concurrent risk factors for deficiency should be tested and treated for vitamin D deficiency to minimize osteoporosis risk and maximize muscular strength [29••].

Warner compared vitamin D levels in patients with diffuse musculoskeletal pain with controls and evaluation of the effect of treatment with vitamin D on diffuse pain. Low vitamin D levels were not associated with diffuse musculoskeletal pain, and treatment with vitamin D does not reduce pain in patients with diffuse pain who have low vitamin D levels [30].

A cross-sectional study aimed at evaluating 25-OHD serum levels in 87 patients with FM, compared with a control group composed of 92 age- and sex-matched subjects with no chronic musculoskeletal pain. There was no statistically significant difference between groups either with respect to mean serum concentration of 25-OHD or as to the classification of levels as deficient, insufficient, or sufficient. There was no correlation of 25-OHD levels with pain intensity [31••].

Pathophysiology of Vitamin D Deficiency in Fibromyalgia

The discovery that most tissues and cells in the body have a vitamin D receptor and that several possess the enzymatic

machinery to convert the primary circulating form of vitamin D, 25-OHD, to the active form, 1,25(OH)₂D, has provided new insights into the function of this vitamin [32].

Vitamin D from the skin and diet is metabolized in the liver to 25-OHD, which is used to determine a patient's vitamin D status; 25-OHD is metabolized in the kidneys by the enzyme 25-hydroxyvitamin D-1 α hydroxylase (CYP27B1) to its active form, 1,25(OH)₂D. The renal production of 1,25(OH)₂D is tightly regulated by plasma parathyroid hormone levels and serum calcium and phosphorus levels [32].

Lewis et al. believe that FMS may result from a physiologic blockade within the parathyroid axis, the endocrine system which produces activated vitamin D. If correct, this would put FMS in the same etiologic category as rickets, the bone-deforming disease of childhood [33••]. The authors suggest that FMS, like rickets, may suppress the production of activated vitamin D via the parathyroid axis. Rickets blocks the first step in that process, and they propose that FMS blocks the final step in the same process.

Whenever the parathyroid glands detect a drop in the body's ionized calcium level, they release into the blood a burst of parathyroid hormone (PTH). Arriving at the kidneys, the PTH triggers the renal release of phosphorus. This in turn signals specialized kidney cells to release 1 α -hydroxylase (1 α -OHase), the critical enzyme needed to convert 25-OHD into 1,25(OH)₂D. This sequence of events hinges very largely on the appropriate renal release of phosphorus. If this release does not occur, the creation of the hydroxylase enzyme may be suppressed, and with it the transformation of 25-OHD into 1,25(OH)₂D [33••, 34]. This is what may happen in FMS, since 2 factors known to suppress PTH release and/or the renal release of phosphorus are also prominent characteristics of FMS [33••]. The first of these factors is chronic sympathetic hyperactivity, a virtual hallmark of FMS [33••, 34]. Research indicates that sympathetic hyperactivity suppresses PTH release in humans. The second factor is more subtle than the first, and may account for the fact that women are more likely to be afflicted with FMS than men [33••, 35]. Women live for much of their lives under the influence of a strong central respiratory stimulant, progesterone [36]. By increasing respiration, progesterone creates a mild respiratory alkalosis. The kidneys compensate for this by mildly alkalizing the urine, which may account for the higher average urinary pH for women (5.37) than for men [36, 37]. The important fact here is that the formation of relatively alkaline urine in response to a mild respiratory alkalosis is highly anti-phosphaturic in humans [36]. This would not mean that men do not get FMS, but simply that women would be at much greater risk, which is indeed the case [38].

Significant evidence indicates that hypothalamic dysfunction occurs in FM, particularly involving the hypothalamic-pituitary-adrenal axis causing responses to stressors, increased

levels of neurotrophins in the cerebrospinal fluid (CSF), suggesting that this disorder is of central origin [39, 40].

There has been accumulating evidence that chronic pain is associated with changes in brain anatomy, particularly related to a decrease in the gray matter in chronic patients [39, 41]. The longer the patients had FM, the greater the matter loss, particularly in regions associated with pain modulation or stress, such as the cingulate, insular, and medial frontal cortices, parahippocampal gyri, and thalamus, thus reinforcing the concept that FM is a stress-related disorder related to the sensitization of CNS pain pathways [39].

A continuum of an increasing number of tender points with several painful body segments seems to occur. Some authors have hypothesized that FM represents 1 end of a spectrum of pain and tender points, and that both traits are probably continuous in the general population. Thus, a myofascial syndrome may progress to a severe FM [39, 42].

The probable mechanisms of allodynia and hyperalgesia are still unknown, although evidence suggests that several levels of the nociceptive system, from the nociceptors in the muscle to the cortex, are involved. The central sensitization of nociceptive neurons in the dorsal horn because of the activation of N-methyl-D-aspartic (NMDA) acid receptors and the resultant triggering of pain, due to an imbalance between inhibitory and facilitatory impulses in the descending tracts from the brainstem to the dorsal horn, appears to be the cause of hypersensitivity to pain [39, 43].

Eyles et al. studied the distribution of the 1,25(OH)₂D receptor (VDR), and 1 α -hydroxylase (1 α -OHase), the enzyme responsible for the formation of the active vitamin in the human brain. The strongest immunohistochemical staining for both the receptor and enzyme was in the hypothalamus and in the large (presumably dopaminergic) neurons within the substantia nigra. The widespread distribution of 1 α -OHase and the VDR suggests that Vitamin D may have autocrine/paracrine properties in the human brain [44].

Thus, the nuclear receptor for 1,25(OH)₂D has been localized in neurons and glial cells. Genes encoding the enzymes involved in the metabolism of this hormone are also expressed in brain cells. The reported biological effects of 1,25(OH)₂D in the nervous system include the biosynthesis of neurotrophic factors and at least 1 enzyme involved in neurotransmitter synthesis. 1,25(OH)₂D can also inhibit the synthesis of inducible nitric oxide synthase and increase glutathione levels, suggesting a role for the hormone in brain detoxification pathways. Neuroprotective and immunomodulatory effects of this hormone have been described in several experimental models, indicating the potential value of 1,25(OH)₂D pharmacological analogs in neurodegenerative and neuroimmune diseases [45].

Besides the effect on central nervous system, Vitamin D may improve muscle strength through a highly specific nuclear receptor in muscle tissue [45]. This effect may be

mediated by de novo protein synthesis [45–47] which affects muscle cell growth through a highly specific nuclear receptor expressed in muscle tissue [48–50]. In 1 study, treatment with 1 α -OHase increased the relative number and size of Type II muscle fibers in elderly women within 3 months of treatment [46, 48].

Therefore, the skeletal muscle and brain have a vitamin D receptor and the central nervous system has a capacity to activate vitamin D [50].

For the neuromuscular system 1,25(OH)₂D influences skeletal muscle calcium uptake, phosphate transport across the cell membrane, phospholipid metabolism, and muscle cell proliferation and differentiation. Furthermore vitamin D plays a key role in signal transduction by activating protein kinase C enhancing calcium release and increasing the calcium pool intracellularly which is essential for muscle contraction [51, 52, 53]. In the brain the prefrontal cortex, cingulate gyrus, hippocampus, basal forebrain, caudate/putamen, thalamus, substantia nigra, lateral geniculate nuclei, hypothalamus, and cerebellum express the VDR [44, 51, 54]. It has also been demonstrated that the cerebral cortex also expresses the 1 α -OHase and thus the central nervous system has the capacity to locally produce 1,25(OH)₂D [51, 55]. 1,25(OH)₂D has been shown to influence the production and activity of glial cell line-derived neurotrophic factor, neurotrophin, calcium binding proteins, proteins subunits for L-type voltage sensitive calcium channels, which are important for the proliferation and differentiation of neurons [45, 51, 56].

We hypothesized that hypovitaminosis D could be a risk factor (not necessarily the cause) for worsening of FM caused by peripheral and central mechanisms.

There would be both peripheral and central similar to what occurs in other chronic pains such as chronic migraine.

Even the relationship between chronic migraine and FM has been the focus of previous studies [39, 57–60].

We conducted a study to be presented at the International Headache Congress this year that compared the levels of vitamin d. Individuals were divided into 3 groups: healthy controls (79), episodic migraine (128), and chronic migraine (91). Patients had low 25 OHD levels compared with controls (25.1 ng/mL \pm 11.7 vs 27.3 ng/mL \pm 8.6, $P=0.03$). Chronic migraine patients (22.9 ng/mL \pm 11.2) had low levels compared with episodic migraine (26.1 ng/mL \pm 11.0, $P=.004$) and controls (27.3 ng/mL \pm 8.6, $P=0.003$). Significantly more chronic migraine patients were below 20 ng/mL, compared with controls ($P<0.001$), as well as episodic migraine vs controls ($P<0.001$); when migraine is linked to hypovitaminosis D, chronic migraine has even lower 25 OHD levels. Decrease in vitamin D may be cause or consequence of migraine. Further studies are necessary to verify the role of vitamin D in migraine and other headache disorders [61].

Conclusions

Over the past years, there has been renewed interest in vitamin D. This is due to the great epidemic of vitamin D deficiency that affects a large part the world's population, and the discovery of the presence of receptors and enzyme system of vitamin D in various cells in the body.

The causal relationship of hypovitaminosis D with fibromyalgia remains unknown. Treating vitamin D deficiency can benefit long-term bone health and muscle strength, both of which are important for patients with fibromyalgia and the general population; there is no doubt that it is necessary investigate the levels of vitamin D in general practice, not only in relation to fibromyalgia.

Compliance with Ethics Guidelines

Conflict of Interest Carlos A S Jesus declares that he has no potential conflicts.

David Feder declares that he has no potential conflicts.

Mario F P Peres serves as a Section Editor for Current Pain and Headache Reports.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. • Abokrysha NT. Vitamin D deficiency in women with fibromyalgia in Saudi Arabia. *Pain Medicine*. 2012;13:452–8. *This report consists of the prevalence of vitamin D deficiency among patients with fibromyalgia in a neurology clinic in the Kingdom of Saudi Arabia.*
2. Mease P. Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. *J Rheumatol*. 2005;75(Suppl):6–21.
3. • Matthana MH. The relation between vitamin d deficiency and fibromyalgia syndrome in women. *Saudi Med J*. 2011;32:925–9. *This article defines the relationship between vitamin D deficiency and fibromyalgia syndrome and evaluates the effect of replacement with vitamin D.*
4. Wolfe F, Ross K, Anderson J, et al. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum*. 1995;38:19–28.
5. Arnsion Y, Amital D, Amital H. The diverse world of vitamin D: does it also modulate pain sensation? *IMAJ*. 2009;11:371–2.
6. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin Proc*. 2003;78:1463–70.
7. Mascarenhas R, Mobarhan S. Hypovitaminosis D-induced pain. *Nutr Rev*. 2004;62:354–9.
8. Gloth III F, Lindsay JM, Zelesnick LB, et al. Can vitamin D deficiency produce an unusual pain syndrome? *Arch Intern Med*. 1991;151:1662–4.

9. Prabhala A, Garg R, Dandona P. Severe myopathy associated with vitamin D deficiency in Western New York. *Arch Intern Med.* 2000;160:1199–203.
10. Benson J, Wilson A, Stocks N, et al. Muscle pain as an indicator of vitamin D deficiency in an urban Australian Aboriginal population. *Med J Aust.* 2006;185:76–7.
11. Lofti A, Abdel-Nasser AM, Hamdy A, et al. Hypovitaminosis D in female patients with chronic low back pain. *Clin Rheumatol.* 2007;26:1895–901.
12. Atherton K, Berry DJ, Parsons T, et al. Vitamin D and chronic widespread pain in a white middle-aged British population: evidence from a cross-sectional population survey. *Ann Rheum Dis.* 2009;68:817–22.
13. Badsha H, Daher M, Kong KO. Myalgias or nonspecific muscle pain in Arab or Indo-Pakistani patients may indicate vitamin D deficiency. *Clin Rheumatol.* 2009;28:971–3.
14. Schwalfenberg G. Improvement of chronic back pain or failed back surgery with vitamin D repletion: a case series. *J Am Board Fam Med.* 2009;22:69–74.
15. Saud AF, Khalaf AM. Vitamin D deficiency and chronic low back pain in Saudi Arabia. *Spine.* 2003;28:177–9.
16. Shinchuk L, Holick MF. Vitamin D and rehabilitation: improving functional outcomes. *Nutr Clin Pract.* 2007;22:297–304.
17. Armstrong DJ, Meenagh GK, Bickle I, et al. Vitamin D deficiency is associated with anxiety and depression in fibromyalgia. *Clin Rheumatol.* 2007;26:551–4.
18. Mouyis M, Ostor AJK, Crisp AJ, et al. Hypovitaminosis D among rheumatology outpatients in clinical practice. *Rheumatology.* 2008;47:1348–51.
19. •• 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;69:1448–52. *A study was undertaken to test the hypothesis that musculoskeletal pain is associated with low vitamin D levels but the relationship is explained by physical inactivity and/or other putative confounding factors.*
20. •• Heidari B, Shirvani JS, Firouzjahi A, et al. Association between nonspecific skeletal pain and vitamin D deficiency. *Int J Rheum Dis.* 2010;13:340–6. *The results of this study indicate a positive association of vitamin D deficiency with a variety of nonspecific bone pain, particularly in women.*
21. • Olama SM, Senna MK, Elarman MM, et al. Serum vitamin D level and bone mineral density in premenopausal Egyptian women with fibromyalgia. *Rheumatol Int.* 2013;33:185–92.
22. Holick MF. Vitamin D, deficiency: what a pain it is. *Mayo Clin Proc.* 2003;78:1457–9.
23. Glerup H, Mikkelsen K, Poulsen L, et al. Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited. *J Intern Med.* 2000;247:260–8.
24. Bischoff HA, Stahelin HB, Dick W, et al. Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. *J Bone Miner Res.* 2003;18:343–51.
25. Al-Allaf AW, Mole PA, Paterson CR, et al. Bone health in patients with fibromyalgia. *Rheumatology.* 2003;42:1202–6.
26. Block SR. Vitamin D, deficiency is not associated with nonspecific musculoskeletal pain syndromes including fibromyalgia. *Mayo Clin Proc.* 2004;79:1585–91.
27. Tandeter H, Grynbaum M, Zuili I, et al. Serum 25-OH vitamin D levels in patients with fibromyalgia. *IMAJ.* 2009;11:339–42.
28. Huisman AM, White KP, Algra A. Vitamin D levels in women with systemic lupus erythematosus and fibromyalgia. *J Rheumatol.* 2001;28:2535–9.
29. •• Daniel D, Pirota MV. Fibromyalgia—should we be testing and treating for vitamin D deficiency? *Aust Fam Physicia.* 2011;40:712–6. *This review aims to synthesize the evidence whether general practitioners should be testing and treating these patients for vitamin D deficiency in fibromyalgia.*
30. Warner AE, Arnsperger AS. Diffuse musculoskeletal pain is not associated with low vitamin D levels or improved by treatment with vitamin D. *J Clin Rheumatol.* 2008;14:12–6.
31. •• 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;16:365–9. *This study showed that light to moderate deficient and insufficient 25(OH)D levels are not found more commonly in patients with FM.*
32. Holick MF. Vitamin D, deficiency. *N Engl J Med.* 2007;357:266–81.
33. •• Lewis JM, Coley JLB, Frontrier TH. Fibromyalgia syndrome and vitamin D. *J Musculoskeletal Pain.* 2011;19:164–6. *This article is an updated review on the association of fibromyalgia with hypovitaminosis D.*
34. Martinez-Lavin M. Is fibromyalgia a generalized reflex sympathetic dystrophy? *Clin Exp Rheumatol.* 2001;19:1–3.
35. Russell IJ. *Fibromyalgia Syndrome. Bonica's Management of Pain.* Ed. Loeser J. Lippincott Williams & Wilkins, Philadelphia, 2001; pp.543–56.
36. Bayliss DA, Millhorn DE. Central neural mechanisms of progesterone action: application to the respiratory system. *J Appl Physiol.* 1992;73:393–404.
37. Schimitt CP, Obry J, Feneberg R, et al. Beta-1 adrenergic blockade augments pulsatile PTH secretion in humans. *J Am Soc Nephrol.* 2003;14:3245–50.
38. Mostellar ME, Tuttle EP. Effects of alkalosis on plasma concentration and urinary excretion of inorganic phosphate in man. *J Clin Invest.* 1964;43:138–49.
39. Valença MM, Medeiros FL, Martins HA, et al. Neuroendocrine dysfunction in fibromyalgia and migraine. *Curr Pain Headache Rep.* 2009;13:308–13.
40. Macedo JA, Hesse J, Turner JD, et al. Glucocorticoid sensitivity in fibromyalgia patients decreased expression of corticosteroid receptors and glucocorticoid-induced leucine zipper. *Psychoneuroendocrinology.* 2008;33:799–809.
41. Kuchinaid A, Schweinhardt P, Seminowicz DA, et al. Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain? *J Neurosci.* 2007;27:4004–7.
42. Papageorgiou AC, Silman AJ, Macfarlane GJ. Chronic widespread pain in the population: a seven year follow-up study. *Ann Rheum Dis.* 2002;61:1071–4.
43. Nielsen G, Henriksson KG. Pathophysiological mechanisms in chronic musculoskeletal pain (fibromyalgia): the role of central and peripheral sensitization and pain disinhibition. *Best Pract Res Clin Rheumatol.* 2007;21:465–80.
44. Eyles DW, Smith S, Kinobe R, et al. Distribution of the vitamin D receptor and 1- α -hydroxylase in human brain. *J Chem Neuroanat.* 2005;29:21–30.
45. Garcion E, Wion-Barbot N, Montero-Menei CN, Berger F, et al. New clues about vitamin D functions in the nervous system. *Trends Endocrinol Metabol.* 2002;13:100–5.
46. Bischoff-Ferrari HA, Thomas Dietrich T, Orav EJ, et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged >60 years. *Am J Clin Nutr.* 2004;80:752–8.
47. Boland R. Role of vitamin D in skeletal muscle function. *Endocr Rev.* 1986;7:434–47.
48. Sorensen OH, Lund B, Saltin B, et al. Myopathy in bone loss of ageing: improvement by treatment with 1 α -hydroxycholecalciferol and calcium. *Clin Sci (Colch).* 1979;56:157–61.
49. Simpson RU, Thomas GA, Arnold AJ. Identification of 1,25 dihydroxyvitamin D3 receptors and activities in muscle. *J Biol Chem.* 1985;260:8882–91.
50. Bischoff HA, Borchers M, Gudat F, et al. In situ detection of 1,25-dihydroxyvitamin D3 receptor in human skeletal muscle tissue. *Histochem J.* 2001;33:19–24.

51. • Nimitphong H, Holick MF. Vitamin D, neurocognitive functioning and immunocompetence. *Curr Op Clin Nutr Metabol Care*. 2011;14:7–14. *Low vitamin D status has been linked to poor performance in neurocognitive testing in elderly, depression, schizophrenia, Alzheimer's disease, multiple sclerosis, and a lower motor neuron-induced muscle atrophy.*
52. Ceglia L. Vitamin D, and skeletal muscle tissue and function. *Mol Aspects Med*. 2008;29:407–14.
53. Dawson-Hughes B. Serum 25-hydroxyvitamin D and functional outcomes in the elderly. *Am J Clin Nutr*. 2008;88:537S–40S.
54. Zehnder D, Bland R, Williams MC, et al. Extrarenal expression of 25-hydroxyvitamin D(3)-1 alpha-hydroxylase. *J Clin Endocrinol Metab*. 2001;86:888–94.
55. Diesel B, Radermacher J, Bureik M, et al. Vitamin D(3) metabolism in humanglioblastoma multiforme: functionality of CYP27B1 splice variants, metabolism of calcidiol, and effect of calcitriol. *Clin Cancer Res*. 2005;11:5370–80.
56. McCann JC, Ames BN. Is there convincing biological or behavioral evidence linking vitamin D deficiency to brain dysfunction? *FASEB J*. 2008;22:982–1001.
57. Tommaso M, Sardaro M, Serpino C. Fibromyalgia comorbidity in primary headaches. *Cephalalgia*. 2009;29:453–64.
58. Peres MF, Young WB, Kaup AO, et al. Fibromyalgia is common in patients with transformed migraine. *Neurology*. 2001;57:1326–8.
59. Peres MF. Fibromyalgia, fatigue, and headache disorders. *Curr Neurol Neurosci Rep*. 2003;3:97–103.
60. Centonze V, Bassi A, Cassiano MA, et al. Migraine, daily chronic headache and fibromyalgia in the same patient: an evolutive 'continuum' of non organic chronic pain? About 100 clinical cases. *Neurol Sci*. 2004;25:S291–2.
61. Jesus CAS, Peres MFP. Low Vitamin D levels in migraine [Abstract]. *International Headache Congress*. Boston, USA. June 27–30, 2013.