

The relation between Vitamin D deficiency and fibromyalgia syndrome in women

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ABSTRACT

الأهداف: تحديد العلاقة بين نقص فيتامين د ومتلازمة الألم العضلي التليفي.

الطريقة: أجريت هذه الدراسة الاستطلاعية في مدينة الأمير سلطان بن عبدالعزيز للخدمات الإنسانية، الرياض، المملكة العربية السعودية، واستمرت خلال الفترة من مايو 2007م إلى مارس 2010م. شملت الدراسة 100 سيدة تعانين من متلازمة الألم العضلي التليفي. لقد قمنا بقياس نسبة هيدروكسي فيتامين د في الدم وذلك أثناء الزيارة الأولى، وأعيد قياسه كل 4 أسابيع حتى وصل مستواه إلى 50 نانوغرام/مل. وعولجت الحالات المصابة بنقص فيتامين د بإعطائهن حوالي 50000 وحدة دولية من إرغوكالسيفيرول (فيتامين د) مرة واحدة أسبوعياً وحتى وصل مستوى الفيتامين في الدم إلى 50 نانوغرام/مل. لقد تم تقييم متلازمة الألم العضلي التليفي سريرياً باستخدام عدد النقاط المؤلمة بالعضلات، ومحصلة عدد الأسئلة التي تصف معاناة المريضات من هذه المتلازمة قبل وبعد تعويض نقص فيتامين د.

النتائج: أشارت نتائج الدراسة إلى أن من أصل 100 سيدة مصابة بالألم العضلي التليفي وُجد أن هناك 61 سيدة مصابة بانخفاض مستوى فيتامين د في الدم، ومع علاجهن بمكملات الفيتامين لم يتحسن سوى 42 سيدة. وقد كان هذا التحسن ملحوظاً عندما أصبحت نسبة فيتامين د في الدم أكثر من أو تساوي 30 نانوغرام/مل، وكان هذا التحسن أكثر وضوحاً عندما تجاوزت نسبة فيتامين د في الدم 50 نانوغرام/مل.

خاتمة: أثبتت هذه الدراسة أنه يجب النظر في نقص فيتامين د عند علاج الحالات المصابة بالألم العضلي التليفي.

Objectives: To define the relationship between vitamin D deficiency and fibromyalgia syndrome.

Methods: This is a prospective cohort study for description of a medical disorder. The study was carried out in Sultan Bin Abdulaziz Humanitarian City, Riyadh, Kingdom of Saudi Arabia from May 2007 to March 2010. One hundred women suffering

from fibromyalgia syndrome were included. Blood level of 25-hydroxyvitamin D [25(OH) D] 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(OH) D exceeded 50 ng/mL. The number of tender points and the revised Fibromyalgia Impact Questionnaire (FIQR) score were used to assess the fibromyalgia before and after vitamin D repletion.

Results: Among the 100 fibromyalgia women, there were 61 women with 25(OH) D deficiency; with vitamin D supplementation, only 42 women showed a significant improvement when their blood level of 25(OH) D became ≥ 30 ng/mL, this improvement became more significant when their blood level of 25(OH) D exceeded 50 ng/mL.

Conclusion: Vitamin D deficiency has to be considered in the management of fibromyalgia syndrome.

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Fibromyalgia syndrome (FMS) is a medical disorder characterized by chronic widespread musculoskeletal pain, which 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.¹ Fibromyalgia syndrome 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 disturbances in the dopaminergic and serotonergic systems.² In adults, numerous clinical investigations have linked vitamin D deficiency to chronic aches and pains, muscle weakness, and fatigue.³⁻⁶ 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 hypocalcemia; signs/symptoms of clinical osteomalacia which most typically appearing late in the course of the disease.⁷ Vitamin D was misclassified as a vitamin; it may be more appropriately considered as prohormone and its active 1,25(OH)₂D metabolite function as a hormone, since it has its own receptors which are found in all human tissues.⁸ The aim of this study is to define the relationship between vitamin D deficiency and fibromyalgia syndrome.

Methods. One hundred women suffering from fibromyalgia syndrome (FMS) were collected from the outpatient clinics of Physical Medicine and Rehabilitation and Rheumatology of Sultan Bin Abdulaziz Humanitarian City, Riyadh, Saudi Arabia, from May 2007 to March 2010. Their ages ranged from 31-59 years. The study was approved by the Research and Ethical Committee, Sultan Bin Abdulaziz Humanitarian City, Riyadh, Saudi Arabia. All participants completed the informed consent, and the study was conducted in accordance with the Declaration of Helsinki. All patients fulfilled the American College of Rheumatology (ACR) 1990 Criteria for the Classification of Fibromyalgia,¹ which included: 1) History of widespread pain: pain considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine, anterior chest, thoracic spine or low back) must be present for more than 3 months. 2) Pain on digital palpation must be present in at least 11 of following 18 tender points. i) Occiput: Bilateral, at the suboccipital muscle insertion. ii) Low cervical: Bilateral, at the anterior aspects of the intertransverse spaces at C5- C7. iii) Trapezius: Bilateral, at the midpoint of the upper

border. iv) Supraspinatus: Bilateral, at origins, above the scapula spine near the medial border. v) Second rib: Bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces. vi) Lateral epicondyle: Bilateral, 2cm distal to the epicondyle. vii) Gluteal region: Bilateral, in upper outer quadrants of buttocks in the anterior fold of the muscle. viii) Greater trochanter: Bilateral, posterior to the trochanteric prominence. ix) Knee: Bilateral, at the medial fat pad proximal to the joint line.

All patients were subjected to the following examinations: 1) Thorough history including personal history (name, age, gender, occupation, marital status and residence), onset and duration of complaint, past history of trauma, surgery, psychic troubles, types of food that they were usually using and their habits in sun exposure. 2) General physical examination which included digital palpation of the above mentioned 18 tender points. 3) Blood level of total 25-hydroxyvitamin D [25(OH) D], which was determined by Quest liquid chromatography-mass spectrometry. It was estimated at initial visit with the diagnosis of fibromyalgia. In cases that were having vitamin D deficiency, blood level of 25(OH) D was determined every 4 weeks during the treatment period until its level exceeded 50 ng/mL. Vitamin D sufficiency was defined as 25(OH) D \geq 30 ng/mL, and toxicity was defined as 25(OH) D >150 ng/mL.⁹ 4) Blood level of calcium every 2-weeks and urinary calcium weekly for early detection of hypercalcemia. 5) Serum creatinine to detect any renal dysfunction.

All patients treated with vitamin D are instructed to avoid any pain medications during the study; they did not also change their lifestyle in terms of dietary habits and sun exposure. Patients with renal impairment were excluded from the study as it affects vitamin D metabolism. Patients with clinical manifestations of rheumatologic disorders were also excluded as they might give the same manifestations of fibromyalgia syndrome. None of the patients were pregnant or currently lactating. Medications which might interfere with vitamin D were reviewed before starting vitamin D repletion. The patients with vitamin D deficiency were treated with ergocalciferol 50,000 IU once weekly until their blood level of vitamin exceeded 50 ng/mL,¹⁰ then they were maintained on 800 IUs daily as a daily requirement.⁶ The number of tender points¹¹ and the revised Fibromyalgia Impact Questionnaire (FIQR)¹² were used to assess fibromyalgia patients with low vitamin D before starting vitamin D repletion (when the blood level of vitamin D became \geq 30 to <50 ng/mL and then when the blood level of vitamin D exceeded 50 ng/mL). The revised FIQR has 21 individual questions. All questions are based on an 11-point numeric rating

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scale of 0 to 10, with 10 being 'worst'. All questions are framed in the context for the past 7 days. The FIQR is divided into 3 linked sets of domains: (a) 'function' (contains 9 questions), (b) 'overall impact' (contains 2 questions) and (c) 'symptoms' (contains 10 questions). The scoring of the FIQR is simple: the summed score for function (range 0 to 90) is divided by 3, the summed score for overall impact (range 0 to 20) is not changed, and the summed score for symptoms (range 0 to 100) is divided by 2. The total FIQR is the sum of the 3 modified domain scores. The total maximal score of the FIQR is 100.¹²

The collected data were organized, tabulated, and statistically analyzed using SPSS Version 13. For quantitative data, range, mean and standard deviation were calculated. We used student t-test and paired t-test for comparison between means of 2 groups. Significance was adopted at $p < 0.05$ for interpretation of results of tests of significance.¹³ The confidence intervals was computed using the modified Wald method.¹⁴

Results. Our results showed that among the 100 fibromyalgia women, 61 were having vitamin D deficiency (95% confidence interval [CI] extends from 0.5119 to 0.6999). With vitamin D repletion, only 42 of the 61 showed improvement of their fibromyalgia (95% CI extends from 0.5636 to 0.7911), while 19 women has no evidence of improvement (95% CI 0.2089 to 0.4364). The improvement group (42 women) showed gradual improvement and when their blood level of vitamin D was ≥ 30 ng/mL, a significant ($p=0.000$) decrease of number of tender points and total FIQR was noticed. These patients maintained their treatment with ergocalciferol once weekly until their blood level of vitamin exceeded 50 ng/mL. We noticed that with this blood level of vitamin D (>50 ng/mL), the improvement was much better and on comparison of the number of tender points and total FIQR when the level of vitamin D was ≥ 30 and <50 ng/mL and when it exceeded 50 ng/mL, both number of tender points ($p=0.000$) and total FIQR had significantly decreased ($p=0.004$). This study also revealed that not all vitamin D deficiency cases were having hypocalcemia, in fact among the 61 vitamin D deficiency fibromyalgia cases only 32 (52.5%) were having hypocalcemia (95% CI 0.4016 to 0.6447).

Discussion. Many members of the medical community do not consider fibromyalgia syndrome a disease because of lack of abnormalities on physical examination and absence of objective diagnostic tests.¹⁵ The association between low levels of vitamin D and fibromyalgia syndrome remains controversial. Some researchers found no association between women with

fibromyalgia syndrome and low levels of vitamin D.¹⁶ Yet other researchers found a significantly greater prevalence of low vitamin D concentration in women with fibromyalgia compared to women without fibromyalgia (43% versus 19%). They also found that 90% of cases diagnosed with fibromyalgia and/or non-specific musculoskeletal pain treated with vitamin D showed an acceptable to maximal relief of their complains.¹⁷ In this study, the 61 vitamin D deficient fibromyalgia women were treated with ergocalciferol 50,000 IU once weekly. No standard repletion regimen is available; however some researchers reported that vitamin D in a dosage of 50,000 IU once a week for 8 weeks is an effective regimen to treat vitamin D deficiency.¹⁰ Ergocalciferol (vitamin D₂) was used as it was the commonly available orally administered vitamin D form in 50,000-IU dose strength as it is reported that vitamin D₂ and vitamin D₃ are equally efficacious in raising 25 (OH) D concentrations.¹⁸ An objective of such aggressively high dosing is to fill vitamin D reservoirs in adipose and other tissues, and also to provide ample amounts for conversion to the 25(OH) D and 1,25(OH)₂D metabolites.¹⁰ The number of tender points¹¹ and the revised FIQR¹² were used to assess fibromyalgia syndrome before starting vitamin D repletion and when the blood level of vitamin D became ≥ 30 and <50 ng/mL then when the blood level of vitamin D exceeded 50 ng/mL. While the universal consensus about the optimal serum level of 25 (OH) D is lacking, some researchers have agreed that, the optimal 25(OH) D concentration is considered to range from 30 to 50 ng/mL; however levels somewhat above 50 ng/mL also may be beneficial.^{7,19,20} When the blood level of vitamin D exceeded 50 ng/mL, cases were maintained on 800 IUs of vitamin D daily as a daily requirement.⁶ All cases did not use any calcium supplementation as it is reported. Extra calcium is not necessary in patients with vitamin D deficiency unless diet is insufficient and/or there are concerns on osteoporosis in postmenopausal women or in the elderly.⁷ The observed improvement of the 42 vitamin D deficient fibromyalgia women after vitamin D repletion indicates a strong connection between the disease and the function of vitamin D. Scientists believe that vitamin D deficiency results in hypocalcemia which in turn leads to elevated parathyroid hormones which impairs proper bone mineralization causing a spongy matrix to form under periosteal membranes covering the skeleton. This gelatin-like matrix can absorb fluid, expand, and cause outward pressure on periosteal tissues, which generates pain since these tissues are highly innervated with sensory pain fibers.²¹ But it is noticed in this study that, not all vitamin D deficient cases were having hypocalcemia, as among the sixty one vitamin D deficiency fibromyalgia cases, only 32 (52.5%) were

having hypocalcemia. Beyond the well-established role of vitamin D in bone health, vitamin D receptors have been identified in the skeletal muscle,²² which explains the fibromyalgia improvement noticed after vitamin D repletion. The anti-inflammatory properties of vitamin D had been demonstrated in animal experiments and recent clinical researches,²³⁻²⁵ which also explain the improvement of pain with vitamin D repletion. Various investigations have demonstrated benefits of vitamin D supplementation for reversing myopathic features and increasing physical endurance in fibromyalgia syndrome.²⁶ Another study of vitamin D levels in women with fibromyalgia found that half of the fibromyalgia patients were having low vitamin D.²⁷ At Minnesota hospital, more than 90% of 150 people who presented with nonspecific muscle aches and bone aches and pains were found to be vitamin D deficient.²⁸ 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, reductions in NSAID or opioid use, and improvements in mood and quality of life.²⁹ In this study, it is also noticed that 19 of the 61 vitamin D deficient fibromyalgia women had found no evidence of improvement despite their blood level of vitamin D exceeded 50 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 fibromyalgia. Some researchers reported that vitamin D inadequacy is not the principal cause of pain and muscle weakness in fibromyalgia. It could be a contributing, but unrecognized, factors.³⁰ Other studies stated that vitamin D inadequacies can be strongly associated with fibromyalgia even in cases where a specific etiology has been diagnosed, the potential for vitamin D deficit as a factor contributing to the pain should be respected.³¹ Another researchers believe that, vitamin D receptors have different genetic makeup (polymorphism) and activity which may account for varying individual responses to vitamin D therapy,³² which carry a third explanation of absence of improvement of those 19 women. Therefore, many experts have recommended that vitamin D inadequacy should be considered in the differential diagnosis and treatment plans of fibromyalgia syndrome.¹⁰

The relevant small number of cases was a limitation of this study as it was better if we used a greater number of cases which might give us more declaration of the relation between vitamin D deficiency and fibromyalgia syndrome. In England, 6,824 people who were 45 years old had a 25(OH) D test as part of a larger study. It was found that in women, but not men, vitamin D

levels of 30-40 ng/mL were associated with a 7.7% risk of having chronic widespread pain and a 14.6% risk for those with levels less than 30 ng/mL. They reported at the end of their study that, low vitamin D contributes to having fibromyalgia and suggested getting 2,000 units of vitamin D a day may be an optimal treatment to their fibromyalgia.³³ The short duration of our study was also another limitation as we had to follow up these cases after a long term maintenance therapy to see if there is a recurrence of manifestations or the improvement is permanent and what is the vitamin D dose needed to maintain the optimal blood level of vitamin D. The relation between vitamin D deficiency and fibromyalgia needs further investigation with a larger number of cases, longer duration for follow up of cases after vitamin D repletion, more investigations for the cases that did not show improvement with vitamin D repletion and also we have to study this relation in men.

In conclusion, there is a strong association between low serum levels of vitamin D and fibromyalgia syndrome. It may be a similarity in the clinical picture of both and so vitamin D deficiency is misdiagnosed as fibromyalgia or vitamin D deficiency itself may be a cause of fibromyalgia. Generally, vitamin D deficiency has to be considered in the management of fibromyalgia syndrome in women especially if they have a history of minimal sunlight exposure and/or inadequate dietary or supplemental vitamin D intake.

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