The Egyptian Rheumatologist xxx (xxxx) xxx

Contents lists available at ScienceDirect

The Egyptian Rheumatologist

journal homepage: www.elsevier.com/locate/ejr

Vitamin D deficiency and treatment in Iraqi patients with primary fibromyalgia syndrome

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ARTICLE INFO

Article history:
Received 8 May 2019
Accepted 27 May 2019
Available online xxxx

Keywords:
Fibromyalgia syndrome
Vitamin D
Hypovitaminosis D
Iraq

ABSTRACT

Aim of the work: To establish the frequency of vitamin D deficiency in patients with primary fibromyalgia syndrome (FMS) in Basrah, Iraq, and to evaluate the effectiveness of vitamin D supplements in managing disease symptoms.

Patients and methods: 160 FMS patients and 160 matched healthy controls were studied. Serum vitamin D levels were measured. Patients were randomly assigned to one of three treatment groups: Group 1 receiving antidepressant (amitriptyline 10 mg/day); group 2 treated with vitamin D (cholecalciferol 50,000 IU/week) and group 3 received both. All treatments were followed-up for 3 months.

Results: The frequency of vitamin D deficiency was high (95%). The mean age of patients was 34.3 ± 9.5 years and 92.5% were females. The widespread pain index (WPI) scores significantly improved after 12 weeks in groups 2 and 1 (5.3 ± 3.4 and 7.9 ± 3.4 respectively) compared to baseline (11.9 ± 2.8 and 13.4 ± 2.6 respectively; $p = 0.003$). The WPI scores of the patients in group 3 improved early into week 4 (3.3 ± 2.7) and continued to improve at weeks 8 and 12 (2.7 ± 2.6 and 1.96 ± 1.6). There were clinically significant improvement in the patients in all treatment groups, most notably in the symptoms severity score (SSS) of fatigue, waking unrefreshed and cognitive impairment. Effects were greatest in the group treated with vitamin D and antidepressants.

Conclusion: Vitamin D deficiency is common in FMS patients and it is associated with worsening of symptoms. Vitamin D supplementation in deficient FMS patients is associated with significant improvement. Screening of FMS patients for hypovitaminosis D is recommended.

1. Introduction

Fibromyalgia syndrome (FMS) is a common pain condition that manifests as chronic pervasive musculoskeletal pain, anxiety, depression, diminished cognition, fatigue, sleep disturbance, tenderness and other symptoms [1]. The prevalence of FMS varies depending upon the survey's methodology and the population evaluated. Prevalence ranges for females are typically 0.75%–10.45%, whereas for males it is 0% and 3.7% [2–4]. It could be primary or secondary to another existing rheumatic disease [5] and an association with Sjögren's syndrome has been reported [6].

Although the aetiology of FMS is unknown, it may arise from aberrations in the central nervous system (CNS) processing of pain and sensations [7]. Due to its multi-symptomatic nature, and because FMS has neurobiological and psychosocial aspects, recommended treatments favour a multimodal intervention [8]. It is a form of chronic widespread pain [9] and dyshomeostasis of the CNS is a primary mechanism associated with the pathophysiology of FMS [10]. In FMS, neurochemical imbalances and aberrant neural inflammatory pathways may amplify the sensations of pain, leading to increased signalling in ascending pathways, whilst simultaneously depressing descending signalling [11]. Patients with FMS display decreased tolerance to various sensory stimuli such as cold, heat, sound and electrical as well as lower pain thresholds [12]. FMS patients have elevated concentrations of the excitatory neurotransmitter, glutamate, nerve growth factor and substance P in the cerebrospinal fluid (CSF) [13].

Vitamin D is synthesised in the epidermis in response to UVB light exposure, or it is obtained from dietary sources. It has an essential role in brain development, applying neuroprotective effects, stimulating several nerve growth factors and potentially regulating neuron activity [14]. It has also been implicated in the synthesis of glial cell line-derived neural growth factor (GDNF); a neuropeptide that promotes neuron survival [15]. The concentra-

Peer review under responsibility of Egyptian Society of Rheumatic Diseases.
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https://doi.org/10.1016/j.ejr.2019.05.002
1110-1164/

Please cite this article as: H. A. ALdaoseri and M. B. Zubairi, Vitamin D deficiency and treatment in Iraqi patients with primary fibromyalgia syndrome, The Egyptian Rheumatologist, https://doi.org/10.1016/j.ejr.2019.05.002

tion of GDNF in CSF was significantly lower in FMS patients [16] suggesting that vitamin D may exert a beneficial, indirect modulation effect. Vitamin D upregulates interleukin-4 and transforming growth factor-β1 present in astrocytes and microglia [17], thus able to suppress the inflammatory pathways linked to chronic pain. By acting on nuclear receptors present in muscle tissue, vitamin D may exert anti-inflammatory properties that enhance muscle strength and modify sensitivity to peripheral pain [18]. However, the precise mechanisms by which vitamin D could influence FMS have yet to be fully elucidated [19]. A special attention was called for regarding vitamin D levels in RA patients with FMS with a decreased quality of life. Vitamin D should be corrected and considered among the management armamentarium in RA patients with FMS [20].

The purpose of this study was to determine the frequency of vitamin D deficiency in primary fibromyalgia patients in Basrah, Iraq, and to evaluate the effectiveness of vitamin D supplements in managing disease symptoms.

2. Patients and methods

This case-control, randomized non-blinded clinical trial study took place between April and October 2018 in a Rheumatology Consultation Clinic in the Basrah Teaching Hospital. 160 FMS patients (148 female and 12 male) and 160 healthy matched control (100 female, 60 male) were enrolled into the study. The patients had been diagnosed with FMS based upon the 2010/2011 American College of Rheumatology (ACR) diagnostic criteria [21]. The study was registered (nº: 22/358; 2017) by the Ministry of Higher Education and Science Research and Faculty of Pharmacy, Basrah University. The Local Institutional Ethical Committee of the Faculty of Medicine, Basrah University approved the study protocol. All patients signed an informed consent before participation.

The widespread pain index (WPI) scores between 0 and 19 during the preceding week. The symptom severity scale (SSS) (0 to 3 scale) was used to rate the severity of fatigue, feeling unrefreshed upon waking and cognitive symptoms during the preceding week. The sum of the tallied scores was calculated. FMS is diagnosed when the WPI was ≥ 7 and the SSS ≥ 5, or WPI 3–6 and SSS ≥ 9. FMS patients were randomly allocated to one of three treatment groups for 3 months: Patients received daily amitriptyline 10 mg in escalating dose (group 1), received weekly vitamin D3 cholecalciferol capsule 50,000 IU (group 2) or received both treatment of group 1 and 2 with the same doses (group 3).

The serum levels of 25-hydroxyvitamin D of patients were analysed using Hormone Analyzer (E411, Roche, Germany). The erythrocyte sedimentation rate (ESR), alkaline phosphates (ALP), calcium (Ca), phosphate (PO_4), thyroid stimulating hormone (TSH) and parathyroid hormone (PTH) were assessed for each patient. Participants were followed up at 4, 8 and 12 weeks. At follow up, laboratory and physical assessments were repeated. The study excluded FMS patients who co-presented with endocrine diseases (parathyroid, thyroid, Addison disease and Cushing syndrome), rheumatoid arthritis, lupus, Sjögren's syndrome, and patients who take lipid lowering agents, antivirals and corticosteroids**.** Normal reference range for vitamin D3 is 30–100 ng/ml; insufficiency (20.1–29.9 ng/ml), deficiency ($\leq$20 ng/ml) [22].

Statistical analyses were performed using GraphPad Prism 8 computer software. The study variables were analysed using descriptive statistics such as percentage, mean and standard deviation. To determine the difference between the follow-up periods for each group, repeated measures ANOVA and Tukeýs multiple comparisons test were used. To compare the differences between the groups at a certain time point through the follow-up periods, unpaired sample T test and two-way ANOVA test were used. Statistical significance was set as $p < 0.05$.

3. Results

The sociodemographic characteristics of the patients and control are presented in Table 1. The widespread pain index (WPI) and symptom severity score (SSS) for patients at baseline and different follow-up periods are presented in Table 2. Of the FMS patients, 5% (8/160) had insufficient vitamin D (22.9 ± 2.49 ng/ml) while the remaining 95% (152/160) were deficient (9.62 ± 3.93 ng/ml). None of the patients had a value >30 ng/ml. In the control, 3.8% (6/160) had insufficiency and 94.3% (151/160) were deficient; only 1.9% (3/160) were normal.

Serum vitamin D levels for patients treated by antidepressants, vitamin D and both at baseline were (10.9 ± 5.2, 11.1 ± 5.3, and 9.6 ± 4.04 ng/ml respectively). After 12 weeks treatment, vitamin D levels of antidepressant treated group were not changed (10.7 ± 5.1 ng/ml), while those treated by vitamin D or both showed a significant increase in serum levels (38.2 ± 7.6 and 38.4 ± 7.2 ng/ml respectively; $p < 0.001$). The response of WPI and (fatigue, waking unrefreshed and cognitive) SSS in treatment groups at baseline, 4, 8 and 12 week follow up are presented in Figs. 1 and 2.

4. Discussion

Vitamin D is a key contributor to the function of various inflammatory and pain pathway, making it essential to overall health. A relation between vitamin D level and FMS management has been suggested. In this study the demographic profile of the FMS participants was broadly consistent and the majority were female, unemployed and from urban areas. The study found no difference between the control and FMS patients' circulating serum level of vitamin D; the majority were deficient (controls 94.3%, FMS 95%). These findings are consistent with those of Block [22], who also failed to find a difference in the levels of vitamin D in patients with chronic musculoskeletal pain due to FMS and controls.

Table 1
Sociodemographic characteristics of the patients with primary fibromyalgia syndrome and control.

Characteristics mean ± SD or n(%)	FMS (n = 160)	Control (n = 160)
Age (years)	34.3 ± 9.5	35.1 ± 11.6
15–30	58 (36.3)	22 (13.8)
31–45	75 (46.9)	114 (71.2)
46–60	27 (16.8)	24 (15)
Female	148 (92.5)	100 (62.5)
Male	12 (7.5)	60 (37.5)
Employed	43 (26.8)	47 (29.3)
Residency		
Urban	138 (86.2)	146 (91.2)
Rural	22 (13.7)	14 (8.75)
Education		
Illiterate	27 (16.8)	42 (26.2)
Primary	78 (48.7)	58 (36.2)
Intermediate	26 (16.2)	37 (23.1)
Secondary	15 (9.37)	10 (6.25)
University/more	14 (8.75)	13 (8.12)
Social status		
Married	89 (55.6)	94 (58.7)
Unmarried	21 (13.1)	27 (16.8)
Divorcee/widow	50 (31.2)	39 (24.3)
No. of children	3.7 ± 2.24	2.95 ± 1.97

FMS: fibromyalgia syndrome.

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Table 2
Widespread pain index (WPI) and symptom severity score (SSS) for primary fibromyalgia patients at baseline and after 4, 8 and 12 weeks.

Treatment groups		FMS patients (n = 160)				
		Baseline	4 weeks	8 weeks	12 weeks	p
	WPI					
	Group 1 (n = 53)	13.4 ± 2.6	9.3 ± 3.6	8.4 ± 3.4	7.9 ± 3.4	**0.003**
	Group 2 (n = 53)	11.9 ± 2.8	7.8 ± 2.4	7.4 ± 2.4	5.3 ± 3.4	**0.003**
	Group 3 (n = 54)	12.4 ± 2.95	3.3 ± 2.7	2.7 ± 2.6	1.96 ± 1.6	**<0.001**
	SSS					
Gp 1	Fatigue	2.96 ± 0.3	2.3 ± 1.1	2.01 ± 1.1	2.03 ± 1.2	**0.01**
	Waking unrefreshed	2.9 ± 0.6	2.01 ± 1.2	2.03 ± 1.1	1.9 ± 1.1	**0.002**
	Cognitive symptom	2.8 ± 0.5	1.98 ± 1.01	1.8 ± 0.97	1.7 ± 0.9	**0.003**
Gp 2	Fatigue	2.84 ± 0.5	2.5 ± 0.5	2.4 ± 0.5	2.2 ± 0.7	**0.008**
	Waking unrefreshed	2.84 ± 0.45	2.5 ± 0.5	2.3 ± 0.5	1.7 ± 0.5	**0.002**
	Cognitive symptom	2.73 ± 0.52	2.15 ± 0.4	2.2 ± 0.5	1.98 ± 0.6	**0.003**
Gp 3	Fatigue	2.96 ± 0.2	1.7 ± 1.1	1.3 ± 1.1	0.7 ± 0.9	**0.001**
	Waking unrefreshed	2.9 ± 0.3	1.6 ± 0.96	1.1 ± 0.9	0.7 ± 0.9	**<0.001**
	Cognitive symptom	2.6 ± 0.7	1.7 ± 1.1	1.3 ± 1.1	0.5 ± 0.7	**<0.001**

FMS: fibromyalgia syndrome, WPI: widespread pain index, SSS: symptom severity scale. Group 1: antidepressant treated; Group 2: vitamin D treated; Group 3: Antidepressant plus vitamin D treated. All results in weeks 4, 8 and 12 were significantly different from the corresponding baseline values. Bold values are significant at $p < 0.05$.

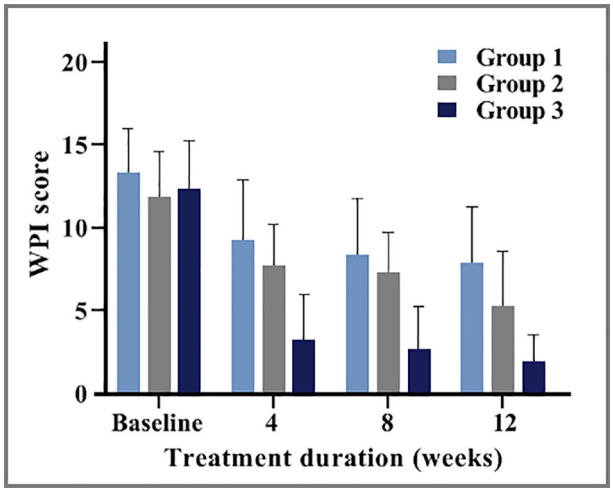

Fig. 1. Response of the widespread pain index (WPI) score in primary fibromyalgia patients treatment groups at baseline, 4, 8 and 12 week follow up. Group 1: antidepressant treated; Group 2: vitamin D treated; Group 3: antidepressant plus vitamin D treated.

The frequency of vitamin D deficiency is high in Basrah (95%). Levels of vitamin D vary between countries for multiple reasons, including latitude, altitude, clouds, pollution, season, surface reflectivity. Individual factors include skin pigmentation and extent of exposed skin [23–25]. In Basrah, the high frequency of vitamin D deficiency may be due to inadequate exposure to the sun at the appropriate time of the day, especially the majority of the patients were unemployed, in addition, they were veiled females. Also the deficiency in vitamin D levels extended to the control, and these required further studies to explain.

The findings of this study revealed that all FMS patients showed significant improvement in their pain score. This finding exceeds the goal for group 2 patients who received vitamin D supplements only; these are important in decreasing the WPI rating. In an experimental study, *Tague et al.* [26] found that before affecting bone health, a diet that was deficient in vitamin D resulted in a balance deficit and deep muscle hypersensitivity. The study's findings also noted that hyperinnervation of skeletal muscles, which is associated with increased sensitivity to pain stimuli and muscle pain could be selectively initiated by vitamin D deficiency. The observations of this study suggests that acute vitamin D deficiency has implications for muscle physiology and mitochondria, leading to alterations and defects that produce muscle disorders such as muscle tenderness, weakness and myalgia, all of which are common FMS symptoms.

Between group comparisons of WPI levels, show that group 3 participants began to improve at 4 week and their improvement continued at weeks 8 and 12. Where vitamin D is used as FMS treatment in conjunction with antidepressants, this finding is particularly important. This result is consistent with that of *Wepner*

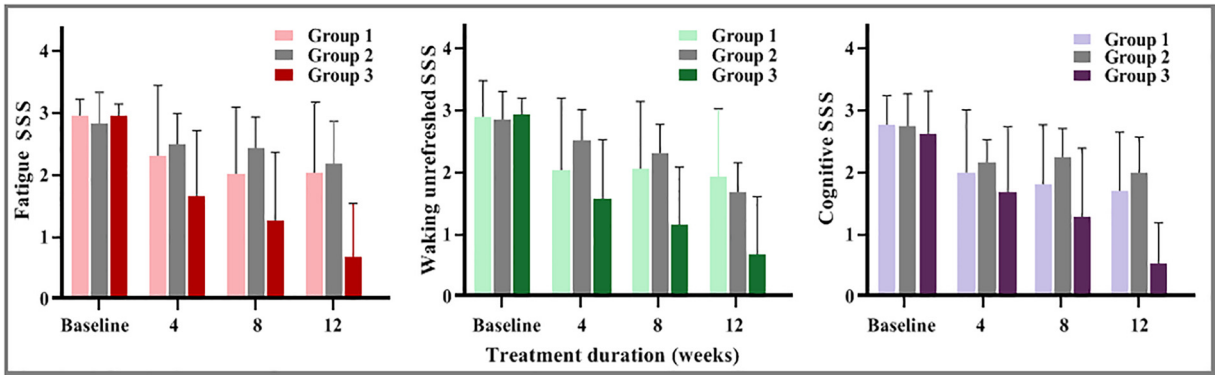

Fig. 2. Response of symptom severity score (fatigue, waking unrefreshed and cognitive) in primary fibromyalgia patients treatment groups at baseline, 4, 8 and 12 week follow up. Group 1: antidepressant treated; Group 2: vitamin D treated; Group 3: antidepressant plus vitamin D treated.

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et al. randomized 30 FMS patients with deficient vitamin D levels in a double-blinded fashion [27]. A VAS was used to assess progress; in the treatment group the score steadily decreased, whereas was unchanged for the control group. Vitamin D, as a pleiotropic hormone, has key roles in modulating calcium homeostasis and a number of inflammation and pain pathways. However, others failed to demonstrate pain reduction following vitamin D treatment in patients with low serum vitamin D values at baseline.

In all three groups of FMS patients, there was a significant improvement in their SSS at 4 weeks. This pattern persisted to the 12-week follow up. Taking the three groups of FMS patients together, the results indicate a highly significant improvement in SSS for group 3 who were received both antidepressant plus vitamin D. This result is partly consistent with others that found the symptoms of confusion, mood disturbance, restless-leg syndrome, short-term memory impairment and sleep disturbance more common in FMS patients who had vitamin D deficiency [28]. It has been noted that there were a significant clinical improvements in patients who were assessed using new clinical FMS diagnostic criteria that evaluate aspects other than cognitive symptoms [29,30].

In conclusion, in this study, vitamin D deficiency is common in FMS patients and is associated with worsening of FMS symptoms. Vitamin D supplementation for 12 weeks in deficient FMS patients is associated with significant improvement of symptoms. Screening of FMS patients for hypovitaminosis D is recommended.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None.

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