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Association between vitamin D serum levels and fibromyalgia disease activity

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Fibromyalgia (FM) is a chronic musculoskeletal disorder characterized by widespread, long-term pain and multiple tender points revealed in physical examination. Previous studies about the relationship between serum vitamin D level and FM have reported paradoxical results. This cross-sectional study aimed to evaluate levels of vitamin D and its relationship with the severity of FM. Based on the American College of Rheumatology (ACS) criteria, 100 female patients with FM were enrolled in this study, and their serum vitamin D levels were screened. Vitamin D deficiency is defined as a level less than 12 ng/mL; insufficiency is defined as a level between 12–29 ng/mL; and sufficiency is a level equal to or greater than 30 ng/mL. Disease severity was evaluated by symptom severity scale (SSS) score and documented using designed questionnaires.

Among the 100 female FM patients enrolled in this study, mean patient age was 35.60 years; 47% of them had vitamin D deficiency, 36% had vitamin D insufficiency, and only 17% had normal vitamin D serum levels. Vitamin D deficiency was reported among 50% of patients with an SSS score between 9 and 12, 49% of patients with an SSS score between 5 and 8, and 14.3% of patients with an SSS score between 1 and 4. There was no significant correlation between patient age and vitamin D level (p-value=0.12). Moreover, no significant correlation was found between patient age and SSS score (p-value=0.36). The current study demonstrated that there was no statistically significant relationship between FM disease activity and vitamin D serum level.

Keywords: Deficiency, Disease severity, Vitamin D, Widespread pain

Introduction

More than two decades have passed since the first classification of fibromyalgia (FM) by the American College of Rheumatology as a common disease with widespread and chronic pain [1, 2]. FM is mainly defined by pain, fatigue, and sleep problems. Sometimes it is associated with irritable bowel syndrome, memory and concentration problems, and mental issues such as depression. It affects 1-4% of the general population with a female-to-male ratio of 3:1 [3, 4]. Prevalence increases, peaking at age 60-70 years [5, 6]. This syndrome is common in obese individuals and people at lower socioeconomic levels [7].

Vitamin D is an essential regulator of the immune system. Its role in the incidence of rheumatoid arthritis, inflammatory bowel disease, diabetes, and multiple sclerosis is well understood [3, 8, 9]. Vitamin D deficiency is associated with musculoskeletal pain, wasting of type 2 muscle fibers, and proximal muscle atrophy; it plays an integral role in maintaining normal muscle size and strength [10]. In addition to its role in bone metabolism, vitamin D has been proven to be essential in other body organs, yet deficiency of this important vitamin is not rare [11]. Vitamin D deficiency can be assessed by checking 25-hydroxyvitamin D in the blood. Fortunately, it can be treated easily. Those who do not get regular sun exposure, such as people who stay at home or those who wear types of clothing that block sun rays, are susceptible to vitamin D deficiency [12, 13]. Various studies have reported that vitamin D might play a role in chronic pain syndromes; however, the exact biologic mechanisms are not fully understood. Several studies have evaluated the relationship between vitamin D and FM [14]. Due to pain, low activity, or depression, FM patients tend to stay at home most of the time, and this causes vitamin D deficiency. It has also been proposed that physiological blockade of the parathyroid axis, responsible for producing active vitamin D, is another reason for FM related to vitamin D [15, 16].

Fibromyalgia severity and activity are evaluated based on symptom severity scale (SSS) scores, including the extent of tiredness, restful sleep, cognitive problems, and somatic signs, which range from 0 to 12 [17, 18]. The curr-

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ent research investigated the correlation between different serum concentrations of vitamin D and FM severity.

Materials and Methods

Patient Population

This cross-sectional study evaluated 100 FM adult female patients who were visited in the Rheumatology Clinic of Imam Khomeini Hospital in Urmia between 23 August 2017 and 21 December 2017. Data was collected with checklists containing patients' demographic and disease information. FM was diagnosed according to the American College of Rheumatology 1990 [19] and/or 2010 criteria [20]. Vitamin D serum levels were assessed and disease severity was determined based on the designed questionnaires. Patients who had diseases other than FM were excluded. In total, 100 patients were included in this study.

Measurement of vitamin D serum levels

After their medical histories were taken and the disease was diagnosed, patients were sent to the specified central laboratory of Urmia Imam Khomeini Hospital to have their serum levels of vitamin D checked by enzyme-linked immunosorbent assay (ELISA) using a CALBIOTECH kit. The results were categorized into three groups. A vitamin D level lower than 12 ng/ml was considered a deficiency, between 12-29 ng/ml was considered insufficiency, and more than 30 ng/ml (inclusively) was considered normal [21]. Disease activity was assessed by symptom severity scale (SSS) score, comprised of the three main symptoms of fatigue, non-restful sleep, and cognitive symptoms. All symptoms were reported on a scale of 0-4; higher scores indicated severe symptoms. Validation of the fibromyalgia survey questionnaire within a cross-sectional survey is defined as 0 for no problem, 1 for slight or mild problems, 2 for moderate and considerable problems, and 4 for severe and life disturbing problems [22].

Statistical analysis

Mean ± SD (standard deviation) was calculated for continuous variables, and frequencies were measured for categorical variables. The independent *t*-test and Fisher's exact test were used to analyze continuous variables and categorical variables, respectively. One-way ANOVA was used to compare the mean of age in three categories, vitamin D level, and disease activity. Normality of the data was ensured by the Kolmogorov–Smirnov test, and Spearman's rho correlation test was applied to analyze correla-tions. Data analysis was performed using SPSS17 software, and a $p\ value < 0.05$ was considered statistically significant.

Ethical considerations

This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of Urmia University of Medical Sciences (IR. UMSU.rec.1392.131). No additional costs were imposed on patients, and their identities were not disclosed. All requested tests were based on indications, and written informed consent was obtained from patients before participation in the study.

Results

A total of 100 female patients with FM were surveyed. Mean patient age was 35.60 ± 7.7, and vitamin D serum levels were reported as normal, insufficient, and deficient in 17 (17%), 36 (36%), and 47 (47%) patients, respectively. Disease activity scores were 1-4 in seven patients, 5-8 in 51 patients, and 9-12 in 42 patients. The mean ages of patients with normal, insufficient, and deficient vitamin D serum levels were 38.35 ± 8.75, 36.25 ± 7.93, and 34.11 ± 7.13, respectively. There was no statistically significant difference among the groups ($p\ value = 0.12$). The mean ages of patients in different disease activity groups were 34.57 ± 8.85 in the 1-4 score group, 36.70 ± 8.20 in the 5-8 score group, and 34.45 ± 7.10 in the 5-9 score group; no significant difference was observed among the groups ($p\text{-}value = 0.36$) (Table 1).

Table 1. Mean patient age based on vitamin D serum level and disease activity status(analyzed using one-way ANOVA)

variable	status	Prevalence (%)	Mean ± SD	*P value*
Vitamin D serum level	normal	17 (17%)	38.35 ± 8.75	0.12
	insufficient	36 (36%)	36.25 ± 7.93	
	deficient	47 (47%)	34.11 ± 7.13	
Disease activity score	1-4	7 (7%)	34.57 ± 8.85	0.36
	5-8	51 (51%)	36.70 ± 8.20	
	9-12	42 (42%)	34.45 ± 7.10	

Vitamin D serum level was normal in three patients with a disease activity score of 1-4, in nine patients with disease activity score of 5-8, and in five patients with a disease activity score of 9-12. Vitamin D serum levels were deficient in 50% of patients with a disease activity score of 9-12, 49% of patients with a disease activity score of 5-8,

and 14.3% of patients with a disease activity score of 1-4. Nevertheless, the correlation between vitamin D serum level and disease activity score was not statistically significant (*p value* = 0.24) (Table 2).

Table 2. vitamin D serum level in fibromyalgia patients according to disease activity scores(Analyzed using Fisher test)

Vitamin D serum level	1-4 score	5-8 score	9-12score	*P value* (Fisher)
normal	3 (42.9%)	9 (17.6%)	5 (11.9%)	
insufficient	3 (42.9%)	17 (33.3%)	16 (38.1%)	0.24
deficient	1 (14.3%)	25 (49%)	21 (50%)	

The coefficient between disease activity scores and vitamin D serum levels in FM patients was negative (- 0.135), and disease severity was related to abnormal vitamin D amounts; however, this correlation was not statistically significant (*p value* = 0.18).

Figure 1 shows the vitamin D serum levels in different disease severity score groups in FM patients.

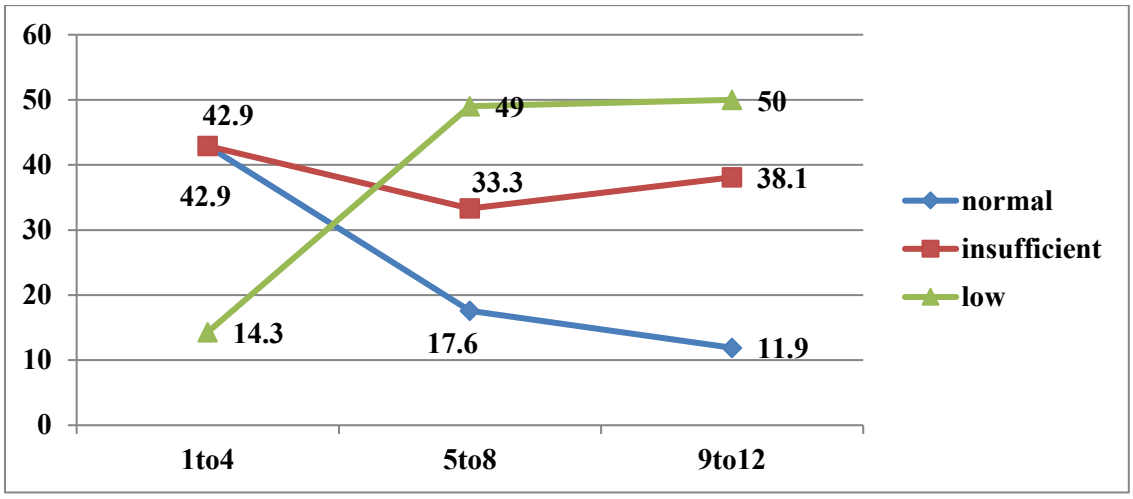

Figure 1. vitamin D serum level in different disease severity score groups in fibromyalgia patients.

Discussion

The biologically active form of vitamin D (1, 25 (OH) D), a fat-soluble vitamin, is present in the cell nucleus and membrane of more than 30 different tissues and organs of the human body [23, 24]. Muscles are considered target organs for vitamin D metabolites, and vitamin D receptors are present in these organs [25]. This vitamin is needed for the normal growth and function of muscles, and its deficiency in osteomalacia disease causes musculoskeletal pain [26, 27]. According to various reports on the association between vitamin D deficiency and chronic pain [28, 29] in the last decade and the fact that chronic diffuse pain is the most important feature of FM, the correlation between vitamin D deficiency and FM is emphasized more than before [30-32].

Pathophysiology of chronic and widespread pain in FM is not well-known, but it is controversial. A combination of environmental and hereditary factors is probably responsible for a change in the perception of pain in the central nervous system, which can intensify the response to stimuli [33]. More recent studies have mentioned the probability of peripheral and autonomic nervous system involvement in the pathogenesis of FM [34].

Activation of inflammatory cytokines triggered by an infection that changes the perception of pain in the CNS is another theory [35]. Considering the regulating role of vitamin D on the immune system [36] and the association between chronic pain and vitamin D is reasonable. Vitamin D deficiency is a worldwide health issue, and its main cause is insufficient sun exposure. The number of foods naturally containing vitamin D and vitamin D fortified foods are limited, so they are not enough to meet adults and children's needs [37, 38].

Several studies have demonstrated the correlation between vitamin D serum level and higher prevalence of chronic pain, but the biological mechanism underlying this relation is not well understood. As chronic pain is the most important feature of FM, it seems that vitamin D deficiency

influences the severity of pain in these patients. However, not enough studies have investigated the relationship between vitamin D and FM disease activity.

The current study included female patients with FM. Disease activity was measured by symptom severity score, and the relationship between the disease severity score and vitamin D serum level was evaluated. Although vitamin D was deficient among most patients with a disease severity score of more than 5, no statistically significant difference was observed. In a study conducted by Noha in Saudi Arabia, a negative relationship was presented between the widespread pain index and vitamin D serum levels in FM patients; however, the relationship was not statistically significant [3]. Another study done by Ryan S. 'D'Souza et al. showed that vitamin D deficiency was a risk factor for more severe symptoms of FM [39]. Furthermore, another cross-sectional study done by Yaseen et al. demonstrated that vitamin D deficiency is linked with disorders such as FM [40]. The correlation of vitamin D serum level and FM syndrome is paradoxical in different studies. In some studies, a positive correlation is reported [37], while in other studies, no relationship is reported [41-43]. In the present study, vitamin D serum level was lower in FM patients, but the difference was not statistically significant. The current results were consistent with other studies in which there was no relationship between vitamin D deficiency or insufficient vitamin D and the severity of FM [35, 36]. The current study showed that 47% of patients had vitamin D deficiency, 36% had vitamin D insufficiency, and 17% had normal vitamin D serum levels.

Previous studies have shown that vitamin D deficiency was more prevalent in developing countries [37]. Our clinical experience demonstrated that many women who do not suffer from FM have vitamin D deficiency. This means that vitamin D deficiency is something separate from FM and its prevalence is similar in the healthy women population. Because the current study had no control group, however, a decisive opinion cannot be expressed. Additionally, the mean age of patients in this study was 35.60 years, and vitamin D deficiency had a higher prevalence in patients under 45 years of age [37, 44, 45]. As FM is the disease of young women, the higher prevalence of vitamin d deficiency in these patients was an irrelevant finding which showed the simultaneous presence of vitamin D deficiency in younger women. Of course, more studies are needed for further evaluation of this issue.

Limitations

An important limitation of this study was the small sample size, which may have affected the serum vitamin D levels. Another limitation was that the study process (registering the topic with the Ethics Committee of Urmia University of Medical Sciences) was initiated in September 2014, but the major steps were not taken until September 2017. Additionally, no healthy control groups were included in this study to compare vitamin D serum levels with them.

Conclusion

The current study demonstrated that there is no clear relationship between vitamin D serum level and FM severity. However, obesity and insufficient sun exposure are risk factors for Vitamin D deficiency. Checking vitamin D serum levels to maintain bone density and optimal muscle function is necessary.

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Conflict of interest

The authors have no conflicts of interest to declare.

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