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# Does the levels of vitamin D correlate with the levels of vitamin B12 and ferritin in fibromyalgia?

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**Ethics Committee Approval**
The study was approved by the Eskisehir Osmangazi University Ethics Committee (14/07/20-34: E-25403353-050.99-77349). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
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## Abstract

**Background/Aim:** Considering the effects of inflammation on fibromyalgia and the small intestine, we hypothesize that vitamin D deficiency may contribute to inflammation and affect vitamin B12 and ferritin levels in patients with fibromyalgia. The objectives were: 1) to compare the levels of vitamin D, vitamin B12, and ferritin in patients with fibromyalgia and patients who have local painful conditions, and 2) to evaluate the correlation of vitamin D levels with vitamin B12 and ferritin levels.
**Methods:** The records of 299 patients with fibromyalgia (274 female, 25 male) and 128 patients with local painful conditions (114 female, 14 male) between April 2019 and 2020 were examined, including measurements of 25-hydroxy vitamin D, vitamin B12, ferritin, erythrocyte sedimentation rate, and C-reactive protein.
**Results:** The levels of 25-hydroxy vitamin D were low in both groups, with levels below 30 ng/ml in 90.3% of all patients. However, there was no significant difference in vitamin B12 and ferritin levels between the two groups, and the levels of these markers were within normal limits in both groups. Correlation analysis showed that vitamin D levels were significantly correlated with vitamin B12 ($P<0.001$, r=0.211) and ferritin ($P=0.005$, r=0.337) levels in patients with fibromyalgia but not in the other group.
**Conclusion:** Consistent with our hypothesis, an association was found between vitamin D levels and vitamin B12 and ferritin levels in fibromyalgia. However, this correlation was not found in patients with local painful conditions.

**Keywords:** fibromyalgia, neuroinflammation, vitamin D

## Introduction

Fibromyalgia is characterized by widespread chronic pain and fatigue [1], and its exact origin is unknown. It is speculated that vitamin deficiencies may play a role in its development, although it remains unclear whether they contribute to the underlying pathophysiology [2].

The relationship between iron and fibromyalgia has been investigated in previous studies, yielding varying results. A controlled study comparing fibromyalgia patients with healthy subjects suggested that iron, as a cofactor in the dopamine and serotonin pathways, may play a role in the etiology of fibromyalgia [3]. In contrast, another controlled study with healthy volunteers reported that patients with fibromyalgia do not have reduced iron stores [4]. Deficiency in vitamin B12 can lead to a decrease in neurotransmitter levels by affecting methylation reactions [5], and it has been associated with pain and other musculoskeletal disorders [6]. Therefore, several studies have examined the relationship between fibromyalgia and vitamin B12, finding normal serum levels of vitamin B12 [3,7].

Vitamin D has been extensively studied in relation to fibromyalgia, with many studies reporting low levels of this vitamin in individuals with the condition [8-10]. Akar et al. [8] suggested that patients with vitamin D levels below 25 ng/ml may be more prone to experiencing pain and developing fibromyalgia. Similarly, Özcan et al. [9] observed lower levels of 25-hydroxy vitamin D in 60 patients with fibromyalgia compared to 30 healthy controls. Özgen et al. [10] reported that only 11.48% of the patients with fibromyalgia had normal vitamin D levels (above 30 ng/ml).

There is evidence of both neuroinflammation and systemic inflammation in fibromyalgia [11-13]. Fibromyalgia often coexists with gastrointestinal dysbiosis and intestinal hyperpermeability [14-16], which can be attributed to the effects of systemic inflammation on the gastrointestinal tract, including barrier function, epithelial cells, villus structures, and intestinal absorptive area [17,18]. On the other hand, vitamin D has been shown to have anti-inflammatory properties [19], as well as the ability to reduce intestinal hyperpermeability [20] and improve intestinal dysbiosis [21].

Given the impact of inflammation on the small intestine, we hypothesize that vitamin D deficiency may contribute to inflammation and potentially affect vitamin B12 and ferritin levels in patients with fibromyalgia.

This study was conducted with the following objectives: 1) to investigate the levels of vitamin D, vitamin B12, and ferritin in patients with fibromyalgia, 2) to compare these results with patients who have local painful conditions, and 3) to evaluate the correlation between vitamin D levels and vitamin B12 and ferritin levels.

## Materials and methods

The study involved a retrospective analysis of patients with fibromyalgia and a local painful condition at the Physical Medicine and Rehabilitation Outpatient Clinic between April 2019 and 2020. This analysis was conducted by searching the computerized database and patient files. The medical records of 956 patients diagnosed with fibromyalgia, according to the American College of Rheumatology (ACR) 1990 Criteria (ICD-10: M79 and subgroups), were reviewed, along with the records of 350 patients with a local musculoskeletal problem (experiencing pain but without a systemic musculoskeletal problem) (ICD-10: M75.1, S83, G56.0, M17). The review focused on gathering information regarding age, gender, and blood test results.

Two-hundred-ninety-nine patients with fibromyalgia (274 female, 25 male) were included in Group 1, while 128 patients (114 female, 14 male) with only a local musculoskeletal problem (Group 2) and no systemic musculoskeletal problem were also included in the study. The inclusion criteria specified that patients must be aged between 20 and 75 years, with available records of age and gender, as well as 25-hydroxy-vitamin D (25(OH)vit D) and vitamin B12 values from blood tests. Patients who did not have both 25-hydroxy-vitamin D and vitamin B12 values, those with C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels higher than twice the normal upper limit, and patients who visited the hospital for control purposes and received vitamin therapy were excluded from the study. Additionally, patients with multi-joint osteoarthritis were excluded from Group 2.

The ACR 1990 Fibromyalgia Criteria defines fibromyalgia as the presence of widespread pain accompanied by tenderness at 11 or more of the 18 tender points for a duration of at least 3 months [1].

Blood tests were conducted to gather records of 25-hydroxy-vitamin D, vitamin B12, ferritin, ESR, and CRP levels. The following reference ranges were used: serum 25(OH)vit D values of 0–19.99 ng/ml (or 50 nmol/ml) indicated vitamin D deficiency, values of 20–29.99 ng/ml (or 50–75 nmol/ml) indicated mild deficiency and values of 30 ng/ml and above were considered within the normal serum concentration range. Vitamin B12 values between 190 and 880 pg/ml, ferritin values between 5–120 ng/ml, CRP values between 0 and 5 mg/l, and ESR values between 1 and 20 mm/h were regarded as normal serum concentrations. However, for geriatric patients, the normal upper limit of ESR values was calculated using the formula (age + 10)/2 for women and age/2 for men [22].

The study obtained approval from the Eskisehir Osmangazi University Ethics Committee (14/07/20-34: E-25403353-050.99-77349).

**Statistical analysis**

The distribution of each continuous variable was assessed using the Shapiro-Wilk test. Non-normally distributed variables were analyzed using the Mann-Whitney U test and are reported as median values with the interquartile range (25th-75th percentile). Categorical variables were compared using chi-square statistics and are presented as numbers and percentages. Spearman correlation analysis was employed to examine the relationships between variables. A significance level of $P < 0.05$ was considered statistically significant. All statistical analyses were conducted using SPSS version 22.0 software (SPSS Inc., Chicago, IL, USA).

## Results

No significant differences were found in age, gender, vitamin B12, ferritin, CRP, and ESR levels between the two

groups. The levels of these factors were within normal limits in both groups. However, both groups exhibited low vitamin D levels (Table 1). Table 2 displays the 25(OH)vit D levels for all patients. Only 11.6% of group 1 and 5.4% of group 2 had normal 25(OH)vit D levels.

Correlation analysis revealed significant correlations between vitamin D levels and vitamin B12 ($P<0.001$) as well as ferritin ($P=0.005$) levels in fibromyalgia patients. However, this correlation was not observed in patients with a local painful condition (Table 3).

Table 1: Comparison of age, gender, vitamin, c-reactive protein and erythrocyte sedimentation rate levels between groups

| | Group 1 | | Group 2 | | *P*-value |
|---|---|---|---|---|---|
| **Age, years, mean (range)** | 48.0 (40-56) | | 48.5(38-57) | | 0.857 |
| | n | % | n | % | |
| **Gender** | | | | | |
| Female | 274 | 91.63% | 114 | 89.06% | 0.212 |
| Male | 25 | 8.36% | 14 | 10.93% | |
| | Median (IQR 25-75%) | | Median (IQR 25-75%) | | |
| **25-hydroxy vitamin D** | 18.30 (12.90-25.10) | | 16.65 (9.65-22.97) | | 0.011 |
| **Vitamin B12** | 353.0 (265.25-434.0) | | 342.50 (265.50-412.0) | | 0.482 |
| **Ferritin** | 22.0 (6.50-44.0) | | 23.0 (6.0-51.0) | | 0.655 |
| **C-Reactive Protein** | 1.0 (0.10-3.10) | | 1.0 (0.20-2.90) | | 0.757 |
| **ESR** | 9.0 (6.0-15.0) | | 11.0 (5.0-17.0) | | 0.378 |

ESR: Erythrocyte Sedimentation Rate, IQR: inter quartile range

Table 2: Vitamin D levels of both groups

| | Group 1 (n=299) | | | Group 2 (n=128) | | |
|---|---|---|---|---|---|---|
| **Vitamin D categories** | <20ng/ml | 20-30ng/ml | ≥30ng/ml | <20ng/ml | 20-30ng/ml | ≥30ng/ml |
| **n (%)** | 163 (54.51%) | 102 (34.11%) | 35 (11.70%) | 82 (64.06%) | 39 (30.46%) | 7 (5.46%) |

Table 3: Correlation of vitamin levels in all patients

| | Group 1 (n=299) | | | Group 2 (n=128) | | |
|---|---|---|---|---|---|---|
| | **25-hidroxy-vitamin D (n=299)** | **Vitamin B12 (n=299)** | **Ferritin (n=68)** | **25-hidroxy-vitamin D (n=128)** | **Vitamin B12 (n=128)** | **Ferritin (n=45)** |
| **Vitamin B12** | r=0.211 *P*<0.001 | - | | r=0.073 *P*=0.411 | - | |
| **Ferritin** | r=0.337 *P*=0.005 | r=0.128 *P*=0.295 | - | r=0.223 *P*=0.141 | r=0.121 *P*=0.429 | - |

## Discussion

Vitamin deficiencies may play a role in the pathophysiology of fibromyalgia, although the mechanisms are still unclear [2]. On the other hand, many studies have compared the vitamin status of individuals with fibromyalgia to that of healthy controls, making it unclear whether vitamin deficiency is associated with fibromyalgia or simply a painful condition. To address this, we compared fibromyalgia with local painful conditions to evaluate the levels of vitamin D, ferritin, and vitamin B12. We found a deficiency in 25(OH)vit D levels but not in ferritin and vitamin B12 levels. Our results suggest that vitamin B12 and ferritin are not related to fibromyalgia. In our study, the level of 25(OH)vit D was below 30 ng/ml in 90.3% of all patients, indicating a relationship between painful conditions and vitamin D deficiency. These results are consistent with previous studies comparing patients with fibromyalgia and musculoskeletal pain. Block et al. [23] found low vitamin D levels in both patients with fibromyalgia and chronic musculoskeletal pain who do not meet the ACR criteria for fibromyalgia. These findings indicate that not only patients with fibromyalgia but also those with local painful conditions experience vitamin D deficiency. It is already known that low levels of vitamin D are associated with various musculoskeletal problems such as pain [8,24], myopathy, osteoporosis, and cognitive function [25]. Therefore, there is no doubt that vitamin D levels should be studied in general practice, physical therapy, and rehabilitation clinics, not only in relation to fibromyalgia.

According to our hypothesis, an association was found between the levels of vitamin D and the other vitamins, vitamin B12 and ferritin, in fibromyalgia. The impact of vitamin D levels on vitamin B12 and ferritin levels can be attributed to the effect of vitamin D on the gastrointestinal tract. Vitamin D receptors have been identified in various human tissues, including stomach and intestine cells [26]. Stumpf et al. [27] demonstrated the presence of vitamin D receptors in the digestive tract, including gastric glands and the absorptive epithelium of the small and large intestines. They suggest that vitamin D affects various digestive processes, such as parietal cell and intrinsic factor secretion. If a correlation were found only between vitamin D and B12 levels but not ferritin levels, it would indicate that vitamin D deficiency affects the parietal cells and intrinsic factors and reduces vitamin B12 levels.

Additionally, studies have shown a relationship between vitamin D deficiency and autoimmune gastritis [28]. However, vitamin D deficiency affects both vitamin B12 and ferritin levels. We believe that vitamin D deficiency may reduce absorption from the small intestine, which is the site of absorption for both vitamin B12 and ferritin. It is important to note that the association between vitamin D and ferritin, as well as vitamin B12 levels, was observed only in patients with fibromyalgia and not in those with a local painful condition. By examining the pathogenesis of fibromyalgia differently from local pain, we may have an opportunity for further discussion.

Evidence suggests the presence of both central neuroinflammation and neurogenic inflammation in peripheral tissues in fibromyalgia. Patients with fibromyalgia have been found to have elevated levels of neuropeptides associated with neuroinflammation, such as substance P [13], nerve growth factor [29], and brain-derived neurotrophic factor [30], in their cerebrospinal fluid (CSF). Additionally, increased levels of IL-8 have been reported in the CSF of fibromyalgia patients [31]. Furthermore, other studies have shown elevated levels of proinflammatory chemokines and cytokines in the blood of individuals with fibromyalgia [11,12]. While the exact cause of fibromyalgia remains unclear, these findings suggest a potential immune-related link to neuroinflammation. However, it is important to note that the presence of neuroinflammation alone is premature without considering the coexistence of small intestine bacterial overgrowth (SIBO), a type of gastrointestinal dysbiosis, and vitamin D deficiency.

Systemic inflammation has well-established effects on gastrointestinal function and morphology, including barrier function, epithelial cells, and the absorptive area of the intestines. Clinical and experimental evidence indicates systemic inflammation leads to reduced villus height, increased permeability, and disruptions in digestion and absorption processes [17,18]. Given the impact of inflammation on the gastrointestinal tract, it is common for neuroinflammation in fibromyalgia to coexist with gastrointestinal dysbiosis [14]. Pimentel et al. [16] reported that all 42 fibromyalgia patients in their study exhibited laboratory evidence of SIBO, and the severity of SIBO positively correlated with the severity of fibromyalgia symptoms. Additionally, Goebel et al. [15]

demonstrated that patients with fibromyalgia have increased intestinal permeability, a condition known as intestinal hyperpermeability.

Research has demonstrated that vitamin D supplementation can alleviate inflammation [19], reduce pain in fibromyalgia [32], improve intestinal hyperpermeability [20], address intestinal dysbiosis [21], and even inhibit experimental microglial activation [33], which is a crucial component of central sensitization and neuroinflammation. Furthermore, low vitamin D levels have been associated with high levels of lipopolysaccharide (LPS) [34]. LPS-induced stimulation of proinflammatory cytokines has been linked to chronic pain, and the presence of SIBO and increased intestinal permeability can lead to enhanced systemic absorption of LPS [35].

Neuroinflammation, SIBO, and vitamin D deficiency each have an additive or synergistic effect on the others [14]. Based on the aforementioned studies, we propose that in fibromyalgia, if vitamin D levels are low, the impairment of absorption for both vitamin B12 and ferritin from the small intestine may be further exacerbated by the additive inflammatory effects. Conversely, in patients with local musculoskeletal problems, low vitamin D levels may not cause absorption disorders due to the absence of SIBO and neuroinflammation. A study by Curic et al. [36] supports our hypothesis, as they found a significant association between 25(OH) vitamin D levels and vitamin B12 levels in obese middle-aged women. This study further strengthens our hypothesis, as neuroinflammation is also observed in obesity [37,38], similar to fibromyalgia.

**Limitations**

To our knowledge, this is the first study to investigate the relationship between levels of vitamin D and ferritin, as well as vitamin B12. This aspect represents a notable strength of our study. However, it is important to acknowledge certain limitations. First, our study has a retrospective design, which may introduce inherent biases and limitations in data collection. Additionally, a lack of a third control group consisting of healthy individuals is another limitation. This absence is because healthy individuals did not seek treatment at our clinic, thus restricting our ability to include them in the study.

**Conclusion**

In this study, our investigation revealed vitamin D deficiency in 90.3% of all patients with musculoskeletal problems. Additionally, we observed a positive correlation between vitamin D levels and the levels of vitamin B12 and ferritin in individuals with fibromyalgia. This finding suggests that vitamin D may play a role in the absorption of vitamin B12 and ferritin among fibromyalgia patients. However, further studies are necessary to explore this relationship in other diseases characterized by neuroinflammation and to determine the impact of vitamin D replacement therapy on vitamin B12 and ferritin levels.

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