The Relationship of Serum Vitamin B12 and Ferritin Levels with Disease Severity and Neuropathic Pain in Fibromyalgia Syndrome

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ABSTRACT

Objective: To investigate the relationship of serum vitamin B12 (vB12) and ferritin levels with disease severity and neuropathic pain in fibromyalgia syndrome (FMS).

Study Design: Observational study.

Place and Duration of the Study: Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Inonu University, Malatya, Turkiye, from October to December 2023.

Methodology: A total of 110 patients, aged between 18 and 65 years, diagnosed with FMS according to the 2016 ACR diagnostic criteria, were included in this study. The participants were evaluated using the Fibromyalgia Impact Questionnaire (FIQ) to measure symptoms impacting daily activities such as pain, sleep disturbances, and fatigue. The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) is a clinical scale used to investigate the neuropathic component of pain. The serum levels of vB12 and ferritin were compared between the patients with and without neuropathic pain symptoms and the impact of these parameters on disease severity and activities of daily life was analysed.

Results: Among the participants, 105 were females and 5 were males. Sixty-nine patients reported neuropathic pain, while 41 did not. Patients with neuropathic pain had significantly higher VAS and FIQ scores and significantly lower vB12 and ferritin levels ($p < 0.05$). A significant inverse relationship was found between FIQ scores and both vB12 levels ($p = 0.047$, $r = -0.190$) and ferritin levels ($p = 0.007$, $r = -0.256$).

Conclusion: In this study, fibromyalgia patients with neuropathic pain had higher pain and disease activity scores, and low serum vB12 and ferritin levels were found to be associated with disease severity and neuropathic pain.

Key Words: *Fibromyalgia syndrome*, *Neuropathic pain*, *Vitamin B12*, *Ferritin*, *Pain*.

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INTRODUCTION

Fibromyalgia syndrome (FMS) is a chronic condition characterised by widespread pain. Genetic, neurological, psychological, sleep-related, and immunological factors are listed among its possible causes.[1] In this syndrome, which is accepted as nociplastic pain among pain classifications, neuropathic pain component is also predominant in some patients. Studies conducted over the past decade have indicated that a significant proportion of patients with FMS have symptoms of small fibre neuropathy (SFN).[2]

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Vitamin B12 plays a role in protein production, neurotransmitter synthesis, cell membrane formation, and DNA maintenance. A deficiency in vB12 can cause nerve damage affecting the central and peripheral nervous systems. While the exact mechanisms are not fully understood, peripheral neuropathy (nerve damage in the peripheral nervous system) is a common complication, affecting about 25% of people with vB12 deficiency.[3]

The exact role of iron in regulating neurotransmitter function and pain perception remains unclear. Iron deficiency may decrease the function and level of these neurotransmitters in the central nervous system.[4] It has also been shown to cause sleep disturbance by decreasing dopamine synthesis.[5] Iron deficiency can affect emotional well-being by reducing levels of serotonin and norepinephrine. These neurotransmitters are important for mood regulation, and their decreased levels may lead to symptoms similar to FMS.[6] Low ferritin level is the initial finding indicating decreased iron reserve. Therefore, serum parameters that can be evaluated for all symptoms, especially

pain, in FMS patients and their replacement in treatment are an open field for study. The aim of this study was to evaluate the effect of serum vB12 and ferritin levels on disease severity and neuropathic symptoms in patients with FMS.

METHODOLOGY

The study included 110 patients aged 18-65 years who were diagnosed with FMS in the authors' outpatient clinic according to 2016 ACR diagnostic criteria, from October to December 2023. Exclusion criteria for the study were chronic liver and kidney disease, malignancy or rheumatic disease, diabetes mellitus and malabsorption, recent use of vB12 and iron supplements in the last year, smoking, and alcohol use. Ethical approval for the study was obtained from the local ethics committee (ID: 2023/48), and patients' written consent for participation in the study was obtained.

Demographic information (age, gender, occupation, employment status, marital status, and educational status) was collected. In addition to the tests ordered for the diagnosis of fibromyalgia, serum vB12 and ferritin levels were also evaluated. Visual Analogue Scale (VAS) was used to evaluate the severity of pain.

The Fibromyalgia Impact Questionnaire (FIQ) was used to test the extent to which the FMS affects the functional status of patients. In this scale, physical competence related to daily activities is tested with 11 items. These are daily labour loss, difficulty in working, fatigue, pain, morning stiffness, mood, depression, and anxiety. High values indicate functional limitations.[7]

Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale was used to determine the neuropathic component of the pain experienced by the patient. The scale ranges from 0 to 24, and a score of 12 or more is indicative of neuropathic pain. Turkish validity and reliability of the LANSS pain scale was performed by Yucel *et al*. in 2004.[8]

SPSS version 22.0 (Statistical Package for the Social Sciences) programme was used to analyse the data. The number of patients to be included in the study was determined by the power analysis. Normality analysis of the variables was evaluated using the Shapiro-Wilk's and Kolmogorov-Smirnov tests. Quantitative data were expressed as mean ± SD and qualitative data were presented as counts and percentages. Independent samples t-test was used to compare independent variables. The Pearson's correlation test was used to evaluate the relationships between continuous variables. Statistical significance was determined as $p < 0.05$.

RESULTS

A total of 110 (105 females and 5 males) patients were included in the study. The mean age of the participants was 44.13 ± 10.77 years. The educational status of the participants was; primary school graduates 54 (49.1%), high school graduates 22 (20%), and 34 (30.9%) were university graduates. Ninety-four (85.5%) were married and 75 (68.2%) were unemployed. Information about sociodemographic and clinical data is provided in Table I.

According to the LANSS scale, 41 patients (37.3%) had a neuropathic pain component. FMS patients with neuropathic pain had higher pain intensity and higher disease-activity scores than patients without neuropathic pain (VAS: 7.51 ± 2.15; 6.46 ± 2.22; $p < 0.017$- and FIQ: 68.8 ± 14.24; 52.65 ± 18.89; $p < 0.001$, respectively). On the other hand, they had lower vB12 and ferritin levels (vB12: 225.8 ± 108.79; 299.45 ± 161.06; $p < 0.011$ and ferritin: 14.05 ± 12.99; 28.82 ± 35.11; $p < 0.011$, respectively, Table II).

A significant negative correlation was found between FIQ score and levels of vB12 ($p = 0.047$, $r = -0.190$) and ferritin ($p = 0.007$, $r = -0.256$, Table III).

Table I: Sociodemographic and clinical characteristics.

Parameters	Mean ± SD
Age	44.13 ± 10.77
VAS pain	6.85 ± 2.24
FIQ score	58.67 ± 18.94
vB12 (pg/ml)	272 ± 147.67
Ferritin (ng/ml)	23.31 ± 29.71

SD: Standard deviation; VAS: Visual analogue scale. FIQ: Fibromyalgia impact questionnaire, vB12: Vitamin B12.

Table II: Comparison of FIQ, VAS, vB12, and ferritin levels with the presence of neuropathic pain.

Parameters	With neuropathic pain (n = 41)	Without neuropathic pain (n = 69)	p-value*
FIQ	68.8 ± 14.24	52.65 ± 18.89	<0.001
VAS	7.51 ± 2.15	6.46 ± 2.22	0.017
vB12	225.8 ± 108.79	299.45 ± 161.06	0.011
Ferritin	14.05 ± 12.99	28.82 ± 35.11	0.011

*SD: Standard deviation, VAS: Visual analogue scale, FIQ: Fibromyalgia impact questionnaire, vB12: Vitamin B12; *Independent sample t-test; p <0.05: Statistically significant.*

Table III: Correlation of FIQ with vB12 and ferritin levels.

Parameters		vB12	Ferritin
FIQ	r	-0.190	-0.256
	p*	0.047	0.007

FIQ: Fibromyalgia impact questionnaire; vB12: Vitamin B12; r: Pearson's correlation; p <0.05: Statistically significant.*

DISCUSSION

The study showed that low serum vB12 and ferritin levels were associated with disease severity and neuropathic pain in FMS patients.

Many factors continue to be investigated in the aetiology of fibromyalgia which is included in the nociplastic pain classification by the International Pain Society.[9] In a recent study, haematologic, biochemical, and inflammatory parameters were evaluated in 660 patients with nociplastic pain such as FMS. VAS activity score was found to be higher in patients with low haemoglobin and ferritin levels, and vB12 level was found to be lower in patients with widespread pain.[10]

The role of SFN in the onset and presentation of clinical symptoms in patients with FMS remains uncertain. One study has shown that rather than a direct relationship between SFN and neuropathic pain, there is an association between central sensitisation and both small nerve fibre dysfunction and neuropathic pain features in patients with FMS.[11] A very recent study has also found that SFN and autonomic fibres are affected in FMS patients. These new data highlight the complex role of SFN in the clinical presentation of FMS by providing additional information on its pathophysiology.[12]

In this study, patients with a score of 12 or higher on the LANSS scale were considered to have neuropathic pain. Neuropathic pain was observed in 37.3% of the patients. Estimates of the prevalence of neuropathic pain in the general population vary between 1 and 8%. In a study, neuropathic pain was found in 82.9% of the patients according to the DN4 scale and in 92.1% of the patients according to the LANSS scale in patients with FMS.[13] This suggests that the frequency of neuropathic pain in FMS is much higher than in the general population.

Vitamin B12 has a fundamental role in the activation of many metabolic processes in the metabolism of neurotransmitters, lipids and proteins, and in the protection of neuronal plasticity. In a study, it was found that vB12 levels measured in patients with FMS and healthy controls were significantly lower in the patient group than in the control group and it was suggested that vB12 levels may play a crucial role in the aetiopathogenesis of FMS.[14] Gunes *et al*. evaluated patients with vB12 deficiency in two groups–those with and without neuropathic pain–and measured intradermal fibre density histopathologically *via* skin punch biopsy. They showed that vB12 deficiency leads to symptomatic or asymptomatic SFN.[2] Another study demonstrated that the short-term use of 1000 mcg sublingual vB12 per day significantly improved FMS severity and anxiety scores in patients with a diagnosis of FMS. It was hypothesised that vB12 has strong potential to be considered at least as an adjunctive treatment of FMS.[15] It is thought that replacement therapy of nutrients with deficiency in FMS, for which there is currently no definite cure, may be beneficial to reduce symptoms and improve quality of life.[16] Recent studies have demonstrated that vB12 can help protect neurons from damage by promoting nerve repair and countering the harmful effects of glutamate.[17] However, studies on the effect of vB12 on nociplastic pain are very few.

The exact role of iron in regulating neurotransmitters and its influence on pain sensitivity remains unclear. Studies on animals and, to a lesser extent, on humans suggest that iron deficiency may lower pain tolerance, affect cognitive function and behaviour, and impair neuronal function. In this study, ferritin levels were statistically significantly lower in the group with neuropathic pain. No study examining the relationship between ferritin and neuropathic pain was found in the literature. It has been thought that this change may be due to the improvement of anaemia or saturation of intracellular enzymes with iron or both.[18] Although neuropathic pain was not directly investigated, all these studies have shown that deficiency of iron and iron parameters causes neuronal changes.

In this study, there was a negative correlation between ferritin levels and both the FIQ and VAS scores. FMS symptoms were more severe in the patient group with low ferritin levels. In a study conducted by Mader *et al*. in non-anaemic FMS patients, the prevalence of ferritin levels of 30 ng/mL or less was found to be significantly lower in the group of FMS patients compared to the control group.[6] Ortancil *et al*. showed the risk of FMS was 6.5 times higher in patients with serum ferritin levels <50 ng/mL, suggesting a potential role of iron in the aetiology of fibromyalgia and indicating that iron supplementation might improve symptoms.[4] Okan *et al*. reported that there was no correlation between serum ferritin levels and anxiety, depression, sleep quality, or physical function in patients with FMS.[19]

The main limitation of this research is the absence of a healthy control group and the relatively small sample size.

CONCLUSION

Fibromyalgia patients with neuropathic pain had higher pain and disease activity scores, and low serum vB12 and ferritin levels were associated with disease severity and neuropathic pain. Evaluation of serum vB12 and ferritin levels and supplementation in case of deficiency may contribute positively to the treatment of neuropathic pain in fibromyalgia.

ETHICAL APPROVAL:

Ethical approval was received for this study from Malatya Clinical Research Ethics Committee on 4.10.2023 with protocol code 2023/48.

PATIENTS' CONSENT:

Written consent was obtained from the patients for participation in the study.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

MKB: Conceptualisation and methodology, acquisition of data, formal analysis, and investigation.
SA, RB: Writing , reviewing, and editing.
RB: Writing the original draft.
SA, SZ: Supervision.
All authors approved the final version of the manuscript to be published.

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