

# Association of Vitamin B12, Vitamin D, and Thyroid-Stimulating Hormone With Fatigue and Neurologic Symptoms in Patients With Fibromyalgia

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## Abstract

**Objective:** To assess the association between vitamin B12 (B12) deficiency and the prevalence of fatigue and prespecified neurologic symptoms in patients with fibromyalgia.

**Patients and Methods:** A retrospective chart analysis of patients diagnosed with fibromyalgia in the years 2015-2020 was performed. The values of B12 were collected. The chart reviews assessed reported fatigue and neurologic symptoms, including brain fog, memory loss, cognitive impairment, paresthesias, numbness, and tingling, to assess their correlation with B12 levels. Concurrent vitamin D and thyroid-stimulating hormone levels were reviewed to assess their association with fibromyalgia.

**Results:** A total of 2142 patients with fibromyalgia with documented levels of B12 and vitamin D were included. Of them, 42.4% had B12 deficiency (<400 ng/L). Fatigue and memory loss were more common in the B12 deficiency group. After adjusting for vitamin D levels, B12 deficiency remained statistically significantly associated with the presence of fatigue (odds ratio, 1.39; 95% confidence interval, 1.11-1.75;  $P=.004$ ).

**Conclusion:** This is the first study to report the association of B12 in patients with fibromyalgia complaining of fatigue. This symptom was prevalent in our group of patients with fibromyalgia with B12 deficiency, regardless of whether the cutoff point was 400 or 350 ng/L.

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Fibromyalgia is a chronic medical condition with unknown etiology characterized by multiple somatic symptoms, which include fatigue, diffuse muscle pain, paresthesia, cognitive dysfunction, and nonrestorative sleep.<sup>1-5</sup> Patients generally have multiple nonspecific symptoms, without evidence of organic, endocrine, or inflammatory disorders. The prevalence of fibromyalgia has been estimated to be 2%-3% worldwide.<sup>2</sup> Although various conditions share the clinical presentation of fibromyalgia, there are no clear etiologies or diagnoses associated with fibromyalgia.<sup>1-3</sup>

The evidence of subclinical vitamin B12 (B12; cyanocobalamin) and vitamin D deficiencies and their association with overlapping symptoms of fibromyalgia remains unclear.<sup>1,6-11</sup> Additionally, subclinical

hypothyroidism has been associated with symptoms that overlap with fibromyalgia, including muscle pain and fatigue.<sup>12,13</sup> Published evidence has explored the mechanistic impact of vitamin deficiencies, including potential blockage of vitamin transportation across the blood-brain barrier<sup>12,13</sup>; downregulated, minimizing anti-inflammatory release (eg, prostaglandin E2)<sup>12,13</sup>; or the presence of certain antibodies.<sup>12,13</sup>

Subclinical B12 deficiency can often be overlooked in patients without classic anemia or neuropathic symptoms. Lower levels of B12 have been reported in a small series of patients with fibromyalgia.<sup>14</sup> Other subclinical deficiencies may also be overlooked in patients with nonspecific symptoms on the basis of B12 levels alone.<sup>15</sup>

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No clear relationship with subclinical vitamin deficiencies has been identified in fibromyalgia studies, and no large study has evaluated the prevalence and potential role of subclinical vitamin deficiencies and the symptoms of fibromyalgia. Although case reports and small studies have suggested a relationship between B12 deficiency and nonspecific symptoms of fibromyalgia, there is paucity of evidence from larger studies.<sup>16</sup>

To assess the association between subclinical B12 levels and specific symptoms in patients with fibromyalgia, we retrospectively evaluated the prevalence of symptoms of subclinical B12 levels in patients with fibromyalgia and compared them with those with fibromyalgia and normal B12 levels. Additionally, we assessed the concurrent vitamin D and thyroid-stimulating hormone (TSH) levels, along with B12 levels, in subclinically B12-deficient patients to assess whether there is an association with fibromyalgia.

## MATERIALS AND METHODS

### Population and Setting

This retrospective study was conducted at a tertiary care facility with integrated outpatient primary care and specialty clinics as well as an inpatient hospital. All patients with a diagnosis of fibromyalgia (International Classification of Diseases, 10th Revision, code M79.7) were enrolled from a database of all patients seen at our facility from January 1, 2015, through December 31, 2020. Patients were included if they had a documented diagnosis of fibromyalgia in the initial history and physical note. To include all patients who had a confirmed diagnosis of fibromyalgia and those with a suspected diagnosis on the basis of symptoms, we included patients with a new diagnosis on the basis of American College of Rheumatology 2016 criteria and those with a reported history of a prior diagnosis of fibromyalgia. Most, but not all, of the patients diagnosed with fibromyalgia in the past were confirmed during an initial evaluation by a clinician during the initial history and physical documentation.

### Variables of Interest

In addition to the patient demographic characteristics of age and sex, the date of history and

physical documentation associated with the diagnosis of fibromyalgia on the basis of International Classification of Diseases, 10th Revision, was recorded. The laboratory values of B12, hemoglobin, vitamin D, and TSH of the patients were extracted. There were not enough data on hemoglobin values to include in the statistical analysis, and therefore, this variable was excluded. Furthermore, TSH values were insufficient to pursue further statistical analysis, but TSH is noted as a variable and was considered in the analysis. The values most closely associated with the date of the documentation of fibromyalgia were used in this study. Patient charts were then reviewed for symptoms reported and documented in the history notes. The following symptoms were recorded if documented as positive: brain fog, memory loss, cognitive impairment, fatigue, paresthesias, numbness, and tingling. The data on symptoms were obtained from the history of present illness, past medical history, review of symptoms, or assessment and plan. The study was approved by the institutional review board at Mayo Clinic (IRB# 21-004276).

### Outcomes of Interest

Association between subclinical B12 deficiency and prespecified neurologic symptoms and fatigue in patients with fibromyalgia. Subclinical B12 deficiency was defined as a B12 level less than 400 ng/L vs a B12 level greater than or equal to 400 ng/L, the lower limit of normal at our institution. Vitamin B12 levels less than 350 ng/L were also used for analysis to confirm an association.

Association of vitamin D levels with B12 in subclinically B12-deficient patients with fibromyalgia.

### Statistical Analyses

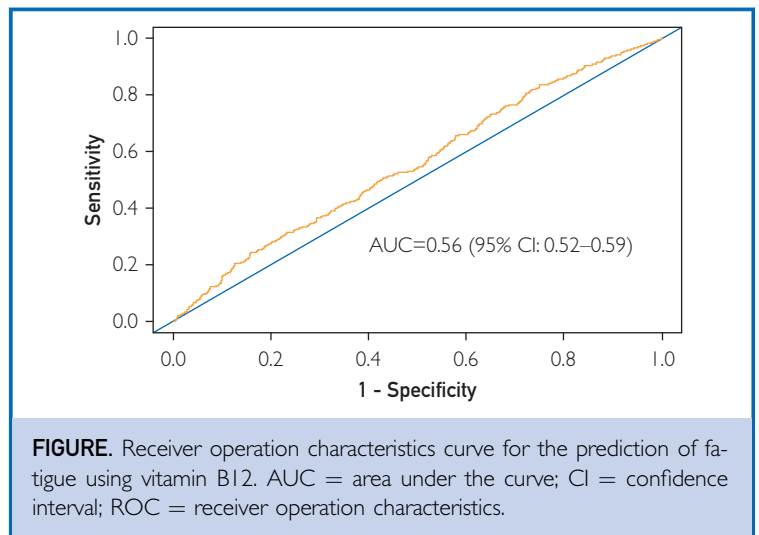
Categorical variables were summarized as frequency (percentage). The chi-squared test was used to compare categorical variables between patients with B12 deficiency and those without B12 deficiency. Multivariable logistic regression was used to evaluate the association between B12 and fatigue, with vitamin D levels adjusted. The receiver operation characteristics analysis was used to identify the best

cutoff point of B12 for the prediction of fatigue (Figure). All the tests were 2-sided, with a P value less than .05 considered statistically significant. The analysis was performed using the statistical computing package R3.6.2 (R Foundation for Statistical Computing).

**RESULTS**

A total of 2142 patients with fibromyalgia who also had documented levels of B12 and vitamin D were included in the study. Women accounted for 91.3% of the population (Table 1). Of the total, 42.4% patients had B12 deficiency (<400 ng/L). Fatigue was more common in the B12 deficiency group with a B12 level less than 350 ng/L (19.8% vs 15.7%, P=.01). A greater percentage of patients with a B12 level less than 400 ng/L reported memory loss (5.7% vs 4%, P=.058) compared with those with a B12 level greater than or equal to 400 ng/mL (Table 2), and although not statistically significant, a P value of .058 trends toward patients with B12 deficiency having memory loss. When the B12 levels were compared with both the cutoff ranges (<350 vs >350 ng/L or <400 vs >400 ng/L; 5.6%), there was no statistical significance between these levels and the symptoms of brain fog, cognitive impairment, numbness, or neuropathy.

After adjusting for vitamin D levels, B12 deficiency remained associated with the presence of fatigue (odds ratio [OR], 1.39; 95% confidence interval [CI], 1.11-1.75; P=.004) with both the subclinical cutoff levels (350



and 400 ng/L) (Table 3). Levels of vitamin D greater than 30 ng/mL were associated with fatigue (OR, 1.38; 95% CI, 1.06-1.83; P=.020; Table 3) and paresthesias (5.9% vs 3.5%, P=.02; OR, 1.74; 95% CI, 1.08-2.96; P=.031) (Tables 4 and 5). The best cutoff point identified using the receiver operation characteristics analysis was 765, with a sensitivity of 0.84 and specificity of 0.25, as shown in the Figure.

**DISCUSSION**

This is the first study to report the association of subclinical vitamin B12 levels with fatigue and prespecified neurologic symptoms in patients with fibromyalgia. Our study found

**TABLE 1. Patient Baseline Characteristics by Vitamin B12<sup>a</sup>**

	Total (N=2142)	B12<400 ng/L (N=908)	B12≥400 ng/L (N=1234)	P value	B12<350 ng/L (N=724)	B12≥350 ng/L (N=1418)	P value
Sex				.46			.65
Female	1955 (91.3%)	824 (90.7%)	1131 (91.7%)		658 (90.9%)	1297 (91.5%)	
Male	187 (8.7%)	84 (9.3%)	103 (8.3%)		66 (9.1%)	121 (8.5%)	
VD (ng/ mL)				<.001			<.001
<30	547 (25.5%)	289 (31.8%)	258 (20.9%)		232 (32.0%)	315 (22.2%)	
≥30	1595 (74.5%)	619 (68.2%)	976 (79.1%)		492 (68.0%)	1103 (77.8%)	
TSH (mIU/ mL)				.5			.67
N-Miss	865	399	466		328	537	
≤4.3	1184 (92.7%)	475 (93.3%)	709 (92.3%)		369 (93.2%)	815 (92.5%)	
>4.3	93 (7.3%)	34 (6.7%)	59 (7.7%)		27 (6.8%)	66 (7.5%)	

<sup>a</sup>B12 = vitamin B12; TSH = thyroid-stimulating hormone; VD = vitamin D.

TABLE 2. Patient Symptoms by Vitamin B12<sup>a</sup>

	Total (N=2142)	B12<400 ng/L (N=908)	B12≥400 ng/L (N=1234)	P value	B12<350 ng/L (N=724)	B12≥350 ng/L (N=1418)	P value
Fatigue				.01			.017
N	1777 (83.0%)	731 (80.5%)	1046 (84.8%)		581 (80.2%)	1196 (84.3%)	
Y	365 (17.0%)	177 (19.5%)	188 (15.2%)		143 (19.8%)	222 (15.7%)	
Confusion				.48			.71
N	2138 (99.8%)	907 (99.9%)	1231 (99.8%)		723 (99.9%)	1415 (99.8%)	
Y	4 (0.2%)	1 (0.1%)	3 (0.2%)		1 (0.1%)	3 (0.2%)	
Memory loss				.058			.09
N	2041 (95.3%)	856 (94.3%)	1185 (96.0%)		682 (94.2%)	1359 (95.8%)	
Y	101 (4.7%)	52 (5.7%)	49 (4.0%)		42 (5.8%)	59 (4.2%)	
Brain fog				.19			.34
N	2037 (95.1%)	857 (94.4%)	1180 (95.6%)		684 (94.5%)	1353 (95.4%)	
Y	105 (4.9%)	51 (5.6%)	54 (4.4%)		40 (5.5%)	65 (4.6%)	
Cognitive impairment				.18			.08
N	2081 (97.2%)	877 (96.6%)	1204 (97.6%)		697 (96.3%)	1384 (97.6%)	
Y	61 (2.8%)	31 (3.4%)	30 (2.4%)		27 (3.7%)	34 (2.4%)	
Paresthesia				.44			.21
N	2029 (94.7%)	864 (95.2%)	1165 (94.4%)		692 (95.6%)	1337 (94.3%)	
Y	113 (5.3%)	44 (4.8%)	69 (5.6%)		32 (4.4%)	81 (5.7%)	
Tingling				.26			.34
N	2103 (98.2%)	888 (97.8%)	1215 (98.5%)		708 (97.8%)	1395 (98.4%)	
Y	39 (1.8%)	20 (2.2%)	19 (1.5%)		16 (2.2%)	23 (1.6%)	
Numbness				.4			.53
N	2061 (96.2%)	870 (95.8%)	1191 (96.5%)		694 (95.9%)	1367 (96.4%)	
Y	81 (3.8%)	38 (4.2%)	43 (3.5%)		30 (4.1%)	51 (3.6%)	
Neuropathy				.57			.24
N	2040 (95.2%)	862 (94.9%)	1178 (95.5%)		684 (94.5%)	1356 (95.6%)	
Y	102 (4.8%)	46 (5.1%)	56 (4.5%)		40 (5.5%)	62 (4.4%)	

<sup>a</sup>B12 = vitamin B12; N = no; Y = yes.

that patients with fibromyalgia and subclinical vitamin B12 levels had more frequent symptoms of fatigue and, although not statistically significant, complained of memory loss compared with those with normal vitamin B12 levels. The association of fatigue persisted even after adjusting for vitamin D levels. These symptoms were prevalent in patients with fibromyalgia with vitamin B12 deficiency, regardless of whether the cutoff point was 400 or 350 ng/L. Vitamin B12 deficiency can cause neurologic symptoms that include neuropathy, spasticity, weakness, vibratory, and proprioceptive sensory loss along with cognitive changes, but the levels associated with these symptoms are lower than those used in our study.

Patients with fibromyalgia generally present with a myriad of organic and nonorganic

symptoms that often resemble the symptoms of low serum B12 levels. Küçük et al<sup>15</sup> compared 58 women with fibromyalgia with a control group of women without fibromyalgia and noted that the vitamin D, B12, and ferritin levels were lower in the patients with fibromyalgia than in the control group and that there was a negative correlation between the number of tender points and these levels. The levels also significantly impacted the patients' scores in the fibromyalgia impact questionnaire. They also found that low ferritin levels were an independent risk factor for fibromyalgia and that iron and B12 may play a role in the etiopathogenesis of fibromyalgia. Vitamin B12 deficiency has been associated with body aches, which may decrease with replacement.<sup>15</sup> However, de Carvalho et al<sup>17</sup> did not note B12 deficiency in 29 patients

**TABLE 3. Multivariable Logistic Regression Model Predicting Fatigue Using Vitamin B12<sup>a</sup>**

Term	OR (95 CI %)	P value
Model 1		
B12<400 ng/L	1.39 (1.11-1.75)	.004
VD≥30 ng/mL	1.38 (1.06- 1.83)	.02
Model 2		
B12<350 ng/L	1.37 (1.08-1.73)	.009
VD≥30 ng/mL	1.37 (1.05-1.81)	.024

<sup>a</sup>B12 = vitamin B12; CI = confidence interval; OR = odds ratio; VD = vitamin D.

with fibromyalgia, and Ortancil et al<sup>18</sup> found that B12 levels were similar in both patients with fibromyalgia and a control group without fibromyalgia. A systematic review of 16 randomized controlled trials, including 6276 participants, evaluated the effect of B12 on cognitive function, depressive symptoms, and fatigue, and only 1 study reported its effects on fatigue. Because of the limitation of 1 study, further analysis was not possible.<sup>19</sup>

Vitamin D has also been studied previously in patients with fibromyalgia. Ellis et al<sup>11</sup> conducted a systematic review and identified 6 studies with significantly lower vitamin D levels in patients with fibromyalgia than in healthy patients. Dogru et al<sup>20</sup> noted that 60% of patients with fibromyalgia had vitamin D levels less than 30 ng/mL and that scores on the fibromyalgia impact questionnaire improved with vitamin D replacement. Maafi et al<sup>21</sup> and Olama et al<sup>22</sup> noted vitamin D levels less than 20 ng/mL in both patients with fibromyalgia and in control groups, but in the study by Maafi et al,<sup>21</sup> the patients had higher vitamin D levels than the control group, and the study by Olama et al<sup>22</sup> reported that the vitamin D levels of patients with fibromyalgia were lower than those of the control group. Mateos et al<sup>19</sup> reported that the vitamin D levels were similar in both patients with fibromyalgia and in control groups.

One of the largest studies by Atherton et al<sup>23</sup> identified a positive relationship between vitamin D deficiency and fibromyalgia and noted that the greatest contrast was between patients with fibromyalgia with vitamin D levels less than 30 ng/mL and those with vitamin D levels of 30-40 ng/mL.<sup>11</sup> We did

not find that low vitamin D levels were associated with fatigue, and in fact, the converse was true in our study: we found that patients with vitamin D levels greater than 30 ng/mL had a higher incidence of fatigue.

Conflicting results have been noted in the literature regarding vitamin D levels in patients with fibromyalgia, and there are no studies in the literature indicating that vitamin D deficiency is an independent risk factor for the pathogenesis of fibromyalgia.<sup>4,6,17,18,20,21</sup> There is a considerable amount of heterogeneity among studies, which impacts the validity of the findings of these studies. Our results showing that patients with subclinical B12 levels had more fatigue and trended toward clinically significant memory loss suggest that treatment with B12 should be studied in these patients.

**TABLE 4. Patient Symptoms by Vitamin D Levels (pg/L)<sup>a</sup>**

	<30 ng/mL (N=547)	≥30 ng/mL (N=1595)	Total (N=2142)	P value
Fatigue				.045
N	469 (85.7%)	1308 (82.0%)	1777 (83.0%)	
Y	78 (14.3%)	287 (18.0%)	365 (17.0%)	
Confusion				.24
N	547 (100.0%)	1591 (99.7%)	2138 (99.8%)	
Y	0 (0.0%)	4 (0.3%)	4 (0.2%)	
Memory loss				.96
N	521 (95.2%)	1520 (95.3%)	2041 (95.3%)	
Y	26 (4.8%)	75 (4.7%)	101 (4.7%)	
Brain fog				.68
N	522 (95.4%)	1515 (95.0%)	2037 (95.1%)	
Y	25 (4.6%)	80 (5.0%)	105 (4.9%)	
Cognitive impairment				.47
N	529 (96.7%)	1552 (97.3%)	2081 (97.2%)	
Y	18 (3.3%)	43 (2.7%)	61 (2.8%)	
Paresthesia				.029
N	528 (96.5%)	1501 (94.1%)	2029 (94.7%)	
Y	19 (3.5%)	94 (5.9%)	113 (5.3%)	
Tingling				.066
N	542 (99.1%)	1561 (97.9%)	2103 (98.2%)	
Y	5 (0.9%)	34 (2.1%)	39 (1.8%)	
Numbness				.22
N	531 (97.1%)	1530 (95.9%)	2061 (96.2%)	
Y	16 (2.9%)	65 (4.1%)	81 (3.8%)	
Neuropathy				.63
N	523 (95.6%)	1517 (95.1%)	2040 (95.2%)	
Y	24 (4.4%)	78 (4.9%)	102 (4.8%)	

<sup>a</sup>N= no; Y = yes.

**TABLE 5. Univariable Logistic Regression Model Predicting Paresthesia Using Vitamin D Level<sup>a</sup>**

Term	OR (95% CI)	P value
VD $\geq$ 30 ng/mL	1.74 (1.08-2.96)	.031

<sup>a</sup>CI = confidence interval; OR = odds ratio; VD = vitamin D.

Our study has limitations. One limitation is the subjective reporting of symptoms because these are usually obtained using a questionnaire filled out by the patient before an encounter. Additionally, because this was a retrospective study, the limitations of comprehension, time, environment, fatigue, and cognitive issues impact the veracity or accuracy of the information. However, the strengths of our study are many, including the large population sample. Another strength of our study is that our institution follows the American College of Rheumatology criteria for the diagnosis of fibromyalgia. Patients diagnosed with fibromyalgia on the basis of other criteria were evaluated independently to confirm or negate the diagnosis, improving the validity of the diagnosis of fibromyalgia.

In summary, this large retrospective study reported some correlation between low serum B12 levels and specific symptoms of fatigue and memory loss. These findings suggest that the laboratory evaluation of B12, vitamin D, and TSH levels as well as the symptomatic impact of the treatment of patients with sub-optimal ranges should be considered. Although the testing of methylmalonic acid levels is not a routine screening test at our fibromyalgia clinic and was not included in this study to simplify the evaluation, these could be considered in the evaluation of patients with ambiguous B12 levels at the lower end of the normal range. Future prospective studies should be conducted to evaluate B12 supplementation in the cohort that reported a level of deficiency with these symptoms. Additional causes of similar symptoms in patients with fibromyalgia could also be investigated, including ferritin, copper, serum protein electrophoresis, and vitamin B6. Association with any potential deficiencies could be of value for treatment options while searching for the cause of these symptoms in patients with fibromyalgia.

**Abbreviations and Acronyms:** B12, vitamin B12; CI, confidence interval; OR, odds ratio; TSH, thyroid-stimulating hormone



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