

Original Article

## STUDY ON DIABETIC NEUROPATHY AND VITAMIN B12 DEFICIENCY IN PATIENTS TAKING METFORMIN

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### ABSTRACT

**Aim of the study:** The aim of this study was to assess the association between vitamin B12 deficiency and diabetic neuropathy, as well as the prevalence of vitamin B12 deficiency in patients receiving long-term metformin therapy.

**Materials and methods:** It was a cross-sectional study, conducted in the Dept. of Pharmacology in association with the Dept. of General Medicine in our tertiary care hospital, which included 100 patients, which are using metformin. Chemiluminescence immunoassay was used to determine vitamin B12 levels. Nerve conduction, the Michigan test, and patient records were used to assess diabetic neuropathy. Further information was gathered, encompassing demographic traits. The variables that were correlated with vitamin B12 levels and diabetic neuropath were assessed using a linear regression model.

**Results and Discussion:** Of all the patients, 9 % had low vitamin B12 levels. Vitamin B12 levels were found to be altered (low and borderline) in 66.66 % of patients with diabetic neuropathy and 22.64 % of patients without the condition. Vitamin B12 levels were lower in those taking a higher dose of metformin. Furthermore, vitamin B12 levels were higher in female patients than in male patients.

**Conclusion:** Deficiency of vitamin B12 is very common, particularly in those with diabetic neuropathy. This study discovered an inverse relationship between vitamin B12 plasma levels and diabetic neuropathy. Reduced vitamin B12 levels were associated with higher metformin dosages and male sex.

**Keywords:** Vitamin B12; Metformin; Diabetes mellitus; Prediabetic state, Malabsorption, Diabetic neuropathies

## **INTRODUCTION**

Vitamin B12, also known as cobalamin, is a water-soluble vitamin that is essential for hematopoiesis, the synthesis of DNA in every cell, and the proper operation of the central and peripheral nervous systems [8]. Megaloblastic anemia and peripheral neuropathy—which may be difficult to differentiate from diabetic neuropathy even with nerve conduction studies—are brought on by its deficiency. A B12 deficiency may also cause memory and cognitive impairments. [1,2]

One known side effect of long-term metformin use is vitamin B12 deficiency, which was first reported by Berchtold et al. in 1969 [1] and has since been confirmed in multiple studies [3, 4]. In patients taking metformin, the prevalence of vitamin B12 deficiency varies from 6 to 45% depending on the population.

Although the exact mechanism causing vitamin B12 deficiency in patients taking metformin over an extended period of time is unknown, some theories include changes to the small intestine's motility, which leads to bacterial overgrowth, and inhibition of the absorption of the vitamin B12 intrinsic factor complex. Competitive inhibition of vitamin B12 absorption and modifications to the intrinsic factor and cubilin (CUBN) receptor have also been suggested since it has been shown that the intrinsic factor, B12 complex is not absorbed in a calcium-dependent manner at the ileum level [5, 6].

Low vitamin B12 levels are linked to a variety of neurological and neurocognitive symptoms, such as axonal demyelination, delirium, dementia, combined subacute degeneration of the spinal cord, peripheral and autonomic neuropathy, and more [6, 7]. In diabetic patients taking metformin continuously, these neurological symptoms may be mistakenly diagnosed as diabetic neuropathy [8, 9, 10].

Since electrodiagnostic studies have achieved higher sensitivity and specificity in the diagnosis of diabetic neuropathy, there are a number of alternatives available with varying degrees of specificity and sensitivity. The best diagnostic technique for diabetic neuropathy in these patients is unknown [11, 12]. The Michigan diabetic neuropathy screening instrument is one of the most well-known research techniques [13, 14]

## **MATERIALS & METHODS:**

This cross-sectional study, conducted in the Dept. of Pharmacology in association with the Dept. of General Medicine in our tertiary care hospital, which included 100 patients, aimed to determine the prevalence of both low and normal vitamin B12 levels in patients with diabetic neuropathy, as well as the prevalence of vitamin B12 deficiency in patients using metformin on a long-term basis.

Further information, such as demographics, was gathered to assess the features of individuals suffering from diabetic neuropathy and vitamin B12 insufficiency.

The variables that correlated with vitamin B12 levels and the relationship between altered vitamin B12 levels and the presence of diabetic neuropathy were assessed using a linear regression model. 100 patients were included in this study which were diagnosed with diabetes mellitus or prediabetes who received metformin treatment for longer than three months were identified retrospectively.

**Inclusion criteria:** Adult patients who have been receiving metformin treatment for longer than three months and who meet the Standards of Medical Care in Diabetes Guidelines (16) for diabetes or prediabetes.

**Exclusion criteria:** Patients which had gastrointestinal surgery in the past, had malabsorptive syndrome, or were taking multivitamins containing vitamin B12.

**RESULTS:**

This study included a total of 100 metformin-using patients who were either pre-diabetic or diabetic. The average age was 61 years, with 55 men (55%) and 45 women (45%). Table 1 shows that the average duration of metformin use was 102 months, and the average daily dose taken was 1440 mg.

**Table 1:** Demographic & clinical characteristics

Variable	No.= 100
Age (years)	61
Female	45 (45%)
Male	55 (55%)
Vitamin B12 levels (pg/mL)	405
Metformin use time (months)	102
Metformin dose (mg)	1440
Diabetic neuropathy	24 (24%)

In 33 cases out of 100 / 33% (95% CI: 20–35%), altered vitamin B12 levels (borderline or low) were discovered out of 100 patients. Vitamin B12 levels were found to be borderline in 24% of cases (24 cases; 95% CI: 15–30%) and low in 9% of cases (9 cases; 95% CI: 5.0–12%).

**Table 2** shows that 3 women, out of 45 (6.66%) had low levels (95% CI: 1–15%) and 9 women (20%) had borderline levels (95% CI: 12–28%) of vitamin B12, while 8 men had low levels (14.5%; 95% CI: 6–21%) and 13 had borderline levels (23.6%; 95% CI: 20–35%). Vitamin B12 levels were higher in female patients than in male patients (coefficient: 48.3; 95% CI: 2.3–95).

**Table 2:** Vitamin B12 deficiency according to sex and age.

	Low B12 levels	Borderline levels
<b>Total population</b>	9% (95% CI: 8–15%)	24% (95% CI: 18–30%)
<b>Men</b>	14.5% (95% CI: 8–23%)	23.6% (95% CI: 20–35%)
<b>Women</b>	6.66% (95% CI: 2–10%)	20% (95% CI: 15–30%)
<b>Age &lt; 70 years</b>	6% (95% CI: 3–10%)	22% (95% CI: 14–29%)
<b>Age &gt; 70 years</b>	10% (95% CI: 7–25%)	24% (95% CI: 15–35%)

## FOR DIABETIC NEUROPATHY CASES

Using the clinical history, nerve conduction study, or MNSI, it was possible to determine whether or not diabetic neuropathy was present, in 74 of the 100 patients that were part of this study. Twenty-one (28.37%) of the seventy-four patients in this group had a confirmed diagnosis of diabetic neuropathy.

In patients with diabetic neuropathy, the prevalence of altered vitamin B12 levels (low or borderline) was 66.66% (95% CI: 47–78%). Vitamin B12 levels were found to be low in five patients (23.8%; 95% CI: 12–40%), borderline in nine patients (42.85%; 95% CI: 26–47%), and normal in seven patients (33.33%; 95% CI: 21–52%) (Table 3).

**Table 3:** Diabetic neuropathy according to vitamin B12 levels.

Vitamin B12 levels	Diabetic neuropathy		
	Present (n=21)	Absent (n=53)	Total
Low levels	5 (23.8%)	4	9
Borderline levels	9 (42.85%)	8	17
Normal levels	7 (33.33%)	41	48
<b>Total</b>	<b>21(28.37%)</b>	<b>53(71.62%)</b>	<b>74(100%)</b>

### DISCUSSION:

Compared to earlier studies that reported a prevalence of 39–50% of the diabetic population, our population's (28.37% of patients) diabetic neuropathy prevalence was lower [15,16]. Remarkably, we discovered a strong association between a positive diagnosis of diabetic neuropathy and reduced vitamin B12 levels. Furthermore, we discovered that patients with diabetic neuropathy had a high prevalence of both low and altered vitamin B12 levels, (66.66% of patients with diabetic neuropathy had low or borderline levels), with low levels occurring in 23.8 % of patients. A recently published meta-analysis found that the use of metformin is a risk factor for vitamin B12 deficiency in diabetic patients [17]

Although there has been some published research suggesting a link between vitamin B12 deficiency and diabetic neuropathy, the findings are descriptive in nature and have not reached a firm conclusion [8, 17, 18, 19]. Sun *et al.* [19] conducted a systematic review and found that while vitamin B12 and methyl cobalamin supplementation improved symptoms of neuropathy, including pain and paresthesia, electrophysiological measures showed inconsistent results. Our findings are similar to a study conducted by Alvarez M *et al.* [20]

In contrast to earlier research, we discovered that male patients had significantly different vitamin B12 levels. This finding is significant because males are also more likely to develop diabetic neuropathy; however, no physiological explanation for these findings was found. The variations in vitamin B12 deficiency by gender are not typically discussed in studies. We located one study [18], which indicated that vitamin B12 deficiency was more common in women. According to another study, having black skin protected against vitamin B12 deficiency (21).

Since metformin is the first line of pharmacological management for diabetes, which is highly prevalent, it is important to look into a common side effect of this treatment: vitamin B12 deficiency. This deficiency aggravates multiple complications of diabetes. The population at high risk of vitamin B12 deficiency caused by metformin is warranted for screening, as indicated by the study's results, particularly in higher-risk groups like those with diabetic neuropathy receiving high doses of metformin.

## **CONCLUSION:**

Vitamin B12 deficiency is highly prevalent, especially in patients with diabetic neuropathy. In this study an inverse correlation was found between diabetic neuropathy and the plasma level of vitamin B12. Higher doses of metformin and male sex were factors related to lower levels of vitamin B12. Therefore, Vitamin B12 levels should be monitored in patients taking metformin chronically, especially in patients with diabetic neuropathy. The association between diabetic neuropathy and Vitamin B12 deficiency is of great importance, since diabetic or prediabetic patients diagnosed with diabetic neuropathy may have neuropathy due to vitamin B12 deficiency. Thus, this condition should be ruled out before initiating diabetic neuropathy treatment.

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