



Original Research Article

IMPACT OF LONG-TERM METFORMIN THERAPY ON VITAMIN B12 LEVELS AND DIABETIC NEUROPATHY IN TYPE 2 DIABETES

Saleem Shahzad¹, Kajalbai², Mashooque Ali Dasti³, Rajesh Kumar⁴, Khadim Hussain⁵, Iqra Badar⁶

¹Associate Professor Medicine, Jinnah Post Graduate Medical Center Karachi Pakistan.

²Postgraduate Department of General Medicine, Dr. Ziauddin Hospital Karachi Pakistan.

³Associate Professor Adult Cardiology, National Institute of Cardiovascular Diseases Sehwan Pakistan.

⁴Associate Professor Medicine, Shaheed Mohtrama Benazir Bhutto Medical College Lyari & Sindh Govt: Lyari General Hospital Karachi Pakistan.

⁵Assistant Professor Medicine, Bilawal Medical College Jamshoro, District Hospital Kotri Pakistan.

⁶Consultant Physician Medicine, People's University of Medical and Health Sciences Nawabshah Pakistan.

Received : 29/12/2025
Received in revised form : 01/02/2026
Accepted : 17/02/2026

Corresponding Author:

Dr. Saleem Shahzad,
Associate Professor Medicine, Jinnah
Post Graduate Medical Center Karachi
Pakistan.
Email: drsaleemshahzad786@gmail.com

DOI: 10.70034/ijmedph.2026.1.283

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (1); 1620-1623

ABSTRACT

Background: One of the known side effects of metformin treatment among type 2 diabetes patients is vitamin B12 deficiency. This deficiency is widely used, yet its clinical implications in comparison with diabetic neuropathy is neglected. It is necessary to clarify this association since neuropathy is one of the primary causes of morbidity among diabetic patients. **Objective:** To determine the association between the status of vitamin B12 and diabetic neuropathy amongst patients with type 2 diabetes under metformin therapy. **Duration and place of study:** This study was conducted at Jinnah Post Graduate Medical Center Karachi from December 2024 to December 2025. **Material and Methods:** This analytical study involved 120 patients with type 2 diabetes who took metformin. A chemiluminescent immunoassay was used to determine the levels of serum vitamin B12 as normal, insufficient, or deficient. The Michigan Neuropathy Screening Instrument was used to evaluate diabetic neuropathy. The statistical analysis was conducted to find out the correlation between vitamin B12 and neuropathy.

Results: Out of 120 respondents, 64 (53.3) were females and 56 (46.7) were males, with an average age of 62.10 years. The 34 (28.3) patients had vitamin B12 below the normal range (≤ 300 pg/mL), with 9 (7.5) of them being deficient and 25 (20.8) insufficient. Twenty-six (21.7) patients were found to have diabetic neuropathy. Among them, 18 (69.2%) were below normal vitamin B12, 9 (34.6) with deficiency and 9 (34.6) below normal. The presence of neuropathy was significantly associated with a negative correlation with the levels of vitamin B12, but not with the levels and metformin exposure parameters.

Conclusion: Reduced levels of vitamin B12 are closely related to diabetic neuropathy among patients on metformin. Deficiency of Vitamin B12 seems to be a potentially treatable risk factor of neuropathic complications and thus regular screening and prompt supplementation of this group is essential.

Keywords: Type 2 diabetes, metformin, vitamin B12, diabetic neuropathy, deficiency.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) refers to a chronic metabolic condition that keeps on increasing in its prevalence across the globe, and this has taken a major toll on both the healthcare sector and on the

patients.^[1] Diabetic peripheral neuropathy is one of its most crippling complications, affecting the sensory, motor, and autonomic nerve fibers that may cause pain, numbness, gait instability, foot ulcers, and eventually amputation of limbs.^[2] Although glycemic control and pharmacotherapy have

progressed, neuropathy is not diagnosed early enough and tends to advance without symptoms to the clinical stage.^[3]

Metformin is recognised as the first-line oral hypoglycemic drug of choice in patients with T2DM due to its effectiveness, safety, and cardiovascular advantages.^[4] It enhances insulin sensitivity and minimises hepatic glucose production without resulting in a substantial weight gain and/or hypoglycaemia.^[5] These benefits have led to metformin being prescribed to be used in the long term. Yet, there is mounting evidence indicating that with long-term metformin treatment, the absorption of vitamin B12 in the terminal ileum becomes impaired, resulting in a decreased serum concentration with time.^[6,7] This negative outcome is often neglected during the practice.

Vitamin B12 is a key micronutrient that is needed in the synthesis of DNA, formation of red blood cells and within the neurological system.^[8] It is highly beneficial in the preservation of myelin and normal nerve conduction. Vitamin B12 deficiency may also cause a continuum of neurological effects, such as paresthesia, sensory loss, gait disturbance, cognitive alteration, and permanent nerve destruction with no cure in the event it is not treated.^[9] It is worth noting that neurological manifestations of B12 deficiency may closely resemble diabetic neuropathy, which poses difficulties to the diagnosis of diabetic patients.^[10]

Other studies done across nations have revealed that vitamin B12 deficiency is more prevalent in patients taking metformin than those who do not take it.^[11,12] These mechanisms proposed are abnormal absorption of the B12-intrinsic factor complex using calcium and changes in gut motility and microbiota.^[13] Even though the screening for vitamin B12 deficiency is not regularly evaluated in the guidelines of diabetes treatment in most places, supplementation is cheap and easy to perform.

The clinical issue that arises when there is an overlap between diabetic neuropathy and B12-related neuropathy, to what extent does vitamin B12 deficiency lead to the development of neuropathic symptoms in patients with T2DM who is treated using metformin? There are reports of a strong correlation between low levels of B12 and more severe cases of neuropathy and others have been found to have weak or no correlation.^[14,15] These discrepancies may be caused by the difference in the study design, diagnostic criteria and population characteristics.

This relationship is critical to understand since vitamin B12 deficiency is one of the possible risk factors that can be mitigated. Provided that there is a significant connection, early identification and treatment of low B12 may lead to the enhancement of neurological outcomes and quality of life in patients with T2DM. Thus, the proposed research will be used to assess the relationship between diabetic neuropathy and serum vitamin B12 levels in patients with type 2 diabetes who receive metformin

treatment in an attempt to guide improved screening and management measures.

MATERIALS AND METHODS

It was a cross-sectional analytical study, which was conducted to determine the relationship between the intensity of diabetic neuropathy and the level of vitamin B12 in patients who were under metformin treatment and had diabetes mellitus type 2. One hundred and twenty participants were recruited using a consecutive sampling method.

The patients who used metformin as part of treatment and were above 40 years with the confirmed diagnosis of type 2 diabetes were included. Any male or female patient could be included. Participants who had a history of gastrointestinal surgery, are known to have malabsorptive disorders, have pernicious anaemia, chronic liver disease or were already taking vitamin B12 supplements or multivitamin preparations were eliminated to remove confounding effects on serum B12 levels.

Demographic and clinical data were gathered through an informed written consent on a form. Data were captured: age, sex, time of diabetes, the current dose of metformin, and medical history. Serum vitamin B12 levels were measured by taking blood samples under normal aseptic conditions. The estimation of vitamin B12 was done through the chemiluminescence immunoassay technique. The level of serum was classified as deficient (below 200 pg/mL), insufficient (200-300 pg/mL), and normal (>300 pg/mL).

Diabetic neuropathy assessment was conducted in the Michigan Neuropathy Screening Instrument (MNSI). This involved the questionnaire item and a detailed physical examination involving the sensation of vibration, ankle reflexes, and foot examination. The selected range of scores in the questionnaires (≥ 7) and the physical examination (≥ 2) was based on the sensitivity and specificity values that were previously proven.

The Statistical Package of Social Sciences (SPSS), version 26, was used to enter and analyse the data. Continuous variables were represented in terms of mean and standard deviation, whereas categorical variables were represented in terms of frequencies and percentages. The vitamin B12 status was further stratified according to age and gender and proportions, including confidence intervals of 95%, were recorded. The relationship between the levels of B12 and the neuropathy scores was evaluated by the rank correlation coefficient of Spearman. P-value taken as statistically significant is 0.05 or less.

RESULTS

The analysis involved 120 patients with type 2 diabetes mellitus who were under metformin therapy. These (64 and 56, respectively) represented

53.3 percent of the female population and 46.7 percent of the male population. The mean age of the subjects was 62.1 or 10.1. Table 1 provides a

summary of the demographic and clinical features of the study population.

Table 1: Baseline Characteristics of the Study Population (n = 120)

Variable	Value
Age (years), Mean ± SD	62 ± 10
Gender	
• Male	56 (46.7%)
• Female	64 (53.3%)
Duration of diabetes (years), Mean ± SD	11.2 ± 5.1
Metformin dose (mg/day), Mean ± SD	1670 ± 420

Vitamin B12 in serum revealed that 34 patients (28.3) had a lower level (<300 pg/mL) than the normal range. Of them, 9 (7.5) were deficient (<200 pg/mL) and 25 (20.8) were insufficient (200-300 pg/mL). The rest of the patients (71.7) (86) had normal B12 levels (>300 pg/mL).

Table 2: Distribution of Vitamin B12 Levels

Vitamin B12 Category	Serum Level (pg/mL)	n (%)
Deficient	<200	9 (7.5%)
Insufficient	200-300	25 (20.8%)
Normal	>300	86 (71.7%)
Total	—	120 (100%)

Based on the Michigan Neuropathy Screening Instrument, diabetic neuropathy was detected in 26 patients (21.7%). Of these 26 patients with neuropathy, 18 (69.2) had subnormal vitamin B12 levels (\leq 300 pg/mL), with 9 (34.6) deficient and 9 (34.6) insufficient cases.

Table 3: Association Between Vitamin B12 Status and Diabetic Neuropathy

Vitamin B12 Status	Neuropathy Present (n=26)	Neuropathy Absent (n=94)	Total
Deficient	9 (34.6%)	0 (0.0%)	9
Insufficient	9 (34.6%)	16 (17.0%)	25
Normal	8 (30.8%)	78 (83.0%)	86
Total	26 (100%)	94 (100%)	120

The rank correlation of Spearman revealed a negative correlation between the levels of serum vitamin B12 and the scores of neuropathy ($r = -0.61$, $p = 0.001$), meaning that the lower the B12 levels, the more disastrous the findings were in the neuropathy.

The serum Vitamin B12 levels were not found to have statistically significant correlation with the dose of Metformin ($\rho = -0.08$, $p = 0.36$) or with diabetes duration ($\rho = -0.11$, $p = 0.22$).

DISCUSSION

In this research, we have observed a significant correlation between low serum levels of vitamin B12 and the severity of diabetic neuropathy in diabetic patients receiving metformin treatment. Deficient or inadequate levels of B12 were observed in a sizeable percentage of patients with neuropathy, which helps to endorse the hypothesis that low B12 can be the cause of neurological issues in this group of patients.

The findings obtained by us are consistent with a number of past studies that have shown a relationship between low levels of vitamin B12 and diabetic neuropathy. In a cross-sectional patient study on metformin, it was found that 66.7% of diabetic neuropathic patients had altered (low or borderline) B12 levels as compared to much lower

proportions of diabetic patients with no neuropathy. Neuropathy status in this study was also found to be negatively associated with vitamin B12, which supports our finding of the inverse relationship.^[16] Equally, diabetic subjects with neuropathy in a bigger cohort depicted a higher occurrence of distorted B12 levels, and with elevated doses of metformin, subjects are likely to have low levels of B12.^[17]

A multi-centre study that specifically studied type 2 diabetics with neuropathy revealed that 60 percent of the patients were B12-deficient, and patients with reduced B12 had much higher scores on neuropathy. This confirms that we observe that neuropathy is more predominant in patients with subnormal B12 levels and indicates that deficiency may increase nerve dysfunction.^[18] This is further supported in an observational study that evaluated the metformin-treated diabetes patients, which showed a definite negative relationship between the concentration of vitamin B12 and the results of the neuropathy severity assessment.^[19]

A multicenter Pakistani cohort study also indicated that individuals with B12 deficiency and neuropathy had poorer nerve functioning outcomes relative to those without deficiency, linking metabolic B12 status to be an etiological factor in neuropathic symptomatology.^[20] A congress abstract in endocrinology showed similar patterns with more

intense levels of neuropathy classification being correlated with the lower levels of B12, with other variables like daily metformin dose not being associated with B12 significantly in that group.^[21]

Conversely, not every study concurred on a direct relationship between metformin-induced B12 deficiency and neuropathy, irrespective of other variables. Indicatively, the comparative study of metformin and non-metformin treatments showed no statistically significant differences in the prevalence of deficiency in patients with neuropathy, indicating that diabetic neuropathy could occur regardless of B12 status or exposure to metformin alone.^[22] The differences could occur because of the differences in the study design, population, the way of assessing neuropathy, as well as the criteria of vitamin B12 deficiency.

The processes that associate metformin usage with decreased vitamin B12 include disruptive intestinal absorption of the vitamin-intrinsic factor complex, potentially by the influence of calcium-dependent events in the ileum.^[13] Since B12 is required in myelin generation and DNA repair in neurons, deficiency may promote nerve damage and dysfunction, especially when combined with underlying diabetic microvascular damage.^[8,9] The intersection of neuropathic symptoms of diabetes and B12 deficiency makes clinical interpretation difficult, hence the importance of objective biochemical screening.

There are important clinical implications of our findings. In contrast with most risk factors of diabetic neuropathy, vitamin B12 deficiency is a controllable disease and can be identified and treated via supplementation. Examining low B12 in diabetic patients on metformin early on may help prevent or delay the developmental process of neuropathy symptoms and reduce patient outcomes, as postulated by the clinical trials that reported neurophysiological benefits after the use of vitamin B12 supplementation in deficient patients.^[23] Additional longitudinal and intervention-based studies are however required to reinforce the causal evidence and also to help identify the best time to screen and the best supplementation practice.

CONCLUSION

This paper shows that low serum levels of vitamin B12 are closely correlated with diabetic neuropathy among patients with diabetes who are under metformin treatment. A high percentage of patients with neuropathy were identified to have deficient or

inadequate levels of vitamin B12, which demonstrated the importance of B12 deficiency as a possible modifiable factor leading to neurological problems. Considering the similarity in clinical manifestations of diabetic neuropathy and B12-related neuropathy, it is necessary to constantly evaluate the health of vitamin B12 in patients with metformin to identify diabetic neuropathy. The neuropathic symptoms can be prevented by timely supplementation and early detection so as to avoid the progression and enhance the quality of life. Vitamin B12 monitoring as a possible add-on to routine diabetes care practices may be a simple, low-cost approach to minimising morbidity caused by chronic metformin therapy.

Source of Funding: None

Permission: Ethical consent received.

Conflict of interest: None

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