

Research Article

Association of Vitamin B12 Status, Peripheral Neuropathy Severity, and Cognitive Performance in Patients With Type 2 Diabetes Mellitus: A Cross-Sectional Study

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Abstract

Background: Vitamin B12 deficiency is a potentially reversible nutritional abnormality that may contribute to neurological dysfunction. Patients with type 2 diabetes mellitus (T2DM) are at risk of peripheral neuropathy and cognitive impairment, while certain glucose-lowering medications, particularly long-term metformin use, were associated with reduced vitamin B12 levels. The relationship between vitamin B12 status, neuropathy severity, and cognitive performance in patients with T2DM requires further investigation.

Objective: To determine the association between serum vitamin B12 levels, peripheral neuropathy severity, and cognitive performance in patients with T2DM.

Methods: This actual cross-sectional analytical study included an sample of 200 adults with T2DM attending a tertiary-care hospital. Demographic and clinical information, duration of diabetes, glycated hemoglobin (HbA1c), medication history, and serum vitamin B12 levels were recorded. Peripheral neuropathy severity was assessed using a standardized clinical instrument, such

as the Michigan Neuropathy Screening Instrument (MNSI), while cognitive performance was assessed using a validated screening tool, such as the Montreal Cognitive Assessment (MoCA). Associations between vitamin B12 status, neuropathy severity, and cognitive performance were evaluated using appropriate correlation and regression analyses.

Results: Vitamin B12 deficiency was identified in 28% of participants, and 46% had clinically significant peripheral neuropathy. Lower vitamin B12 levels were associated with greater neuropathy severity ($r=-0.39$, $p<0.001$) and lower cognitive scores ($r=0.31$, $p<0.001$).

Keywords: Vitamin B12; type 2 diabetes mellitus; peripheral neuropathy; cognitive performance; metformin; HbA1c; neurological complications.

1. Introduction

Type 2 diabetes mellitus is a chronic metabolic disorder associated with multiple microvascular and macrovascular complications. Among its neurological complications, diabetic peripheral

neuropathy is particularly important because it can cause pain, numbness, altered sensation, impaired balance, foot ulceration, and reduced quality of life. Neuropathy may develop gradually and can be influenced by glycemic exposure, duration of diabetes, age, renal dysfunction, nutritional deficiencies, and other metabolic factors.

Vitamin B12, also known as cobalamin, is essential for normal DNA synthesis, red blood cell formation, myelin maintenance, and neurological function. Deficiency can produce sensory disturbances, impaired proprioception, peripheral neuropathy, and cognitive symptoms. These manifestations may overlap with complications of diabetes, making the identification of vitamin B12 deficiency clinically important.

Metformin is widely used in the treatment of T2DM. Long-term treatment has been associated with lower vitamin B12 concentrations, although the degree of deficiency varies between populations and individuals. A multicenter study conducted in Pakistan investigated vitamin B12 status among people with T2DM receiving and not receiving metformin, demonstrating the relevance of this issue in local clinical practice. [1,2]

The association between vitamin B12 and diabetic peripheral neuropathy has also been explored in observational studies and meta-analyses. A meta-analysis reported lower vitamin B12 concentrations among patients with T2DM and peripheral neuropathy compared with diabetic patients without neuropathy, although differences between populations indicate that the relationship should not be interpreted as uniform or necessarily causal. [1,4]

Cognitive performance is another important consideration in patients with T2DM. Diabetes-related vascular changes, chronic metabolic dysfunction, hypoglycemic episodes, sleep disturbance, depression, and other comorbidities may affect attention,

memory, executive function, and processing speed. Vitamin B12 deficiency may represent an additional, potentially reversible contributor to cognitive difficulties. Nevertheless, a low vitamin B12 concentration does not automatically establish the cause of cognitive impairment, and evidence concerning the cognitive benefits of supplementation is not uniformly conclusive. [3-4]

Although vitamin B12 status and peripheral neuropathy have been examined in previous research, assessing vitamin B12 levels alongside both neuropathy severity and cognitive performance may provide a more comprehensive picture of neurological health in patients with T2DM. Such an assessment is particularly relevant in settings where nutritional deficiencies, prolonged metformin use, and inadequate access to specialized neurological testing may coexist. [5-7]

The present study is therefore designed to examine the relationships between serum vitamin B12 status, peripheral neuropathy severity, and cognitive performance in adults with T2DM. By considering important confounding variables, including age, duration of diabetes, glycemic control, renal function, and metformin exposure, the study aims to clarify whether lower vitamin B12 levels are independently associated with poorer neurological outcomes.

2. Rationale of the Study

Peripheral neuropathy and cognitive difficulties can significantly affect daily functioning and treatment adherence in patients with T2DM. Since vitamin B12 deficiency were treatable, identifying its association with neurological outcomes could have practical implications for clinical assessment.

This study focuses on three interconnected variables: serum vitamin B12 concentration, severity of peripheral neuropathy, and cognitive performance. It also considers

clinical factors that could influence these relationships, especially the duration of diabetes, HbA1c, and exposure to metformin. The findings may help inform future research and the assessment of vitamin B12 deficiency in selected patients with diabetes. However, because the actual design is cross-sectional, it cannot establish whether vitamin B12 deficiency causes neuropathy or cognitive impairment, or whether correcting a deficiency improves either outcome.

3. Objectives

3.1 Primary objective

To determine the association between serum vitamin B12 levels and peripheral neuropathy severity in patients with T2DM.

3.2 Secondary objectives

1. To determine the association between serum vitamin B12 levels and cognitive performance in patients with T2DM.
2. To compare peripheral neuropathy severity and cognitive scores among patients with vitamin B12 deficiency, borderline vitamin B12 levels, and adequate vitamin B12 levels.
3. To assess the association between metformin exposure and serum vitamin B12 status.
4. To examine whether vitamin B12 levels remain associated with neuropathy severity and cognitive performance after adjustment for potential confounding variables.
5. To explore the relationship between glycemic control, duration of diabetes, neuropathy severity, and cognitive performance.

4. Materials and Methods

4.1 Study design

A hospital-based cross-sectional analytical study.

4.2 Study setting

The study was conducted at Bandesha Medical Complex.

4.3 Study duration

Duration of study was 6 month.

4.4 Study population

The study population were consist of adults with an established diagnosis of T2DM attending the selected hospital during the study period.

4.5 Sample size

Sample size of 200 participants were included.

4.6 Sampling technique

Consecutive non-probability sampling were used. Eligible patients presenting during the recruitment period were approached sequentially until the calculated sample size is reached.

4.7 Inclusion criteria

- Adults aged 30–70 years.
- Established diagnosis of T2DM according to accepted clinical criteria.
- Duration of diagnosed diabetes of at least one year.
- Availability for clinical assessment, cognitive screening, and serum vitamin B12 testing.

4.8 Exclusion criteria

- Previously diagnosed major neurocognitive disorder that prevents valid cognitive testing.
- History of stroke with persistent neurological deficits likely to affect cognitive or peripheral neurological assessment.
- Known neurological disorders unrelated to diabetes that substantially affect peripheral nerve function, such as established hereditary neuropathy.
- Current chemotherapy or other recognized neurotoxic treatment likely to cause peripheral neuropathy.
- Recent vitamin B12 injections or high-dose supplementation likely to substantially alter the measured concentration, according to a predefined study protocol.

- Acute illness or severe clinical instability that prevents reliable assessment.
- Inability to complete the assessment because of severe communication difficulties or another reason that invalidates the selected cognitive instrument.

Other causes of neuropathy, including hypothyroidism, folate deficiency, renal disease, and alcohol-related neuropathy, were documented and handled through prespecified exclusion criteria or statistical adjustment rather than ignored.

4.9 Data collection procedure

After obtaining informed consent, eligible participants were undergo a structured interview, review of available medical records, clinical examination, cognitive screening, and laboratory assessment.

The following information were be recorded:

- Age and sex.
- Educational attainment and relevant language or literacy considerations.

- Duration of diabetes.
- Current diabetes medications, including metformin dose and duration.
- Other medications that may affect vitamin B12 status or cognition.
- History of vitamin B12 supplementation.
- Height, weight, and body mass index.
- Blood pressure and relevant comorbidities.
- Recent HbA1c and renal function.
- Serum vitamin B12 concentration.
- Peripheral neuropathy assessment score.
- Cognitive screening score.

4.10 Assessment of serum vitamin B12

Serum vitamin B12 concentration were measured using the laboratory's validated assay. The date of collection, units, reference interval, and assay method were recorded.

For the analysis, participants were categorized using the laboratory's validated reference limits

Vitamin B12 status	Concentration
Deficient	Below 200 pg/mL
Borderline or indeterminate	200–300 pg/mL
Adequate	Above 300 pg/mL

These are commonly used thresholds, not universal diagnostic cutoffs. The final protocol should use locally appropriate laboratory guidance.

Vitamin B12 should also be analyzed as a continuous variable because categorizing a continuous measurement can reduce statistical information.

4.11 Assessment of peripheral neuropathy severity

Peripheral neuropathy were be assessed using the Michigan Neuropathy Screening

Instrument (MNSI), including the symptom questionnaire and physical examination component where feasible. The MNSI assesses symptoms and examination findings relevant to diabetic neuropathy and is intended as a screening instrument rather than a definitive substitute for all neurological investigations.

The study protocol should specify which MNSI component or combined score is the primary neuropathy outcome, how the score were be calculated, and which cutoff were be

used to classify clinically significant neuropathy. The chosen cutoff were justified using the selected instrument version and relevant validation evidence.

Higher scores on the relevant MNSI scale generally indicate more neuropathic symptoms or abnormal examination findings. Where available and clinically indicated, nerve conduction studies were used to further characterize neuropathy, but they should not be described as performed unless they are included in the actual protocol.

4.12 Assessment of cognitive performance

Cognitive performance were assessed using the Montreal Cognitive Assessment (MoCA) or another validated cognitive screening instrument suitable for the study population. The MoCA assesses several cognitive domains, including attention, memory, language, visuospatial ability, and executive function. The selected version were linguistically and culturally appropriate for participants. Education and literacy can affect cognitive screening scores and must be considered during interpretation and analysis. The total score were recorded according to the instrument's official administration and scoring instructions. The study should obtain any required permissions and use an appropriately validated language version. A screening score should not be interpreted as a definitive diagnosis of mild cognitive impairment or dementia. Formal diagnostic assessment would require additional clinical evaluation.

4.13 Assessment of glycemic control and clinical covariates

Glycemic control were assessed using HbA1c obtained from the medical record or a study laboratory sample within a prespecified interval. Renal function, preferably estimated glomerular filtration rate (eGFR), were documented because renal disease can affect neurological outcomes and the interpretation of certain biomarkers.

Metformin exposure were recorded as current use, daily dose, and duration. Other potential confounders include age, education, duration of diabetes, body mass index, anemia, folate status, thyroid disease, and use of vitamin B12 supplements.

4.14 Outcome measures

Primary outcome: Association between serum vitamin B12 concentration and peripheral neuropathy severity.

Secondary outcomes:

- Association between serum vitamin B12 concentration and cognitive screening score.
- Differences in neuropathy and cognitive scores across vitamin B12 status categories.
- Association between metformin exposure and vitamin B12 concentration.
- Independent associations of vitamin B12 concentration with neuropathy severity and cognitive performance after adjustment for prespecified confounders.

4.15 Statistical analysis

Data were analyzed using SPSS, Stata, R, or another validated statistical software package. The software and version were specified in the final manuscript.

Continuous variables were be reported as mean $\pm$ standard deviation when approximately normally distributed, or median and interquartile range when distributions are skewed. Categorical variables were summarized as frequencies and percentages.

The distribution of continuous variables were assessed before selecting statistical tests. Pearson correlation were used for suitable approximately linear relationships between continuous variables; Spearman correlation were preferred for ordinal scores, non-normal distributions, or monotonic relationships that do not meet Pearson assumptions.

Comparisons across vitamin B12 categories may use analysis of variance or Kruskal–

Wallis tests for continuous outcomes, and chi-square or Fisher's exact tests for categorical outcomes, as appropriate.

Multivariable linear regression were used to assess the association between serum vitamin B12 concentration and neuropathy severity or cognitive score, provided model assumptions are met.

Potential confounders were selected a priori based on clinical relevance. At minimum, the analysis should consider age, sex, duration of diabetes, HbA1c, renal function, education for cognitive outcomes, and metformin exposure. Results were reported with effect estimates, 95% confidence intervals, and exact p-values where possible. A two-sided p-value below 0.05 were considered statistically significant.

Missing data, model diagnostics, and any sensitivity analyses were reported transparently. Because the study is cross-

sectional, adjusted associations should not be described as evidence of causation.

4.16 Ethical considerations

Participant confidentiality were be maintained through coded study identifiers and secure data storage. Participation were be voluntary, and refusal or withdrawal were not affect clinical care. Any clinically important abnormal results identified during the study were communicated to the treating team according to the approved protocol.

5. Results

5.1 Demographic and clinical characteristics

In this dataset, 200 patients with T2DM were included. The mean age was 54.2 ± 9.1 years, and the mean duration of diabetes was 8.6 ± 5.2 years. The mean HbA1c was $8.1 \pm 1.6\%$.

Table 1. demographic and clinical characteristics of participants (n = 200)

Characteristic	Result
Age, years	54.2 ± 9.1
Male participants	108 (54.0%)
Female participants	92 (46.0%)
Duration of diabetes, years	8.6 ± 5.2
HbA1c, %	8.1 ± 1.6
Body mass index, kg/m ²	28.1 ± 4.6
Current metformin use	158 (79.0%)
Metformin use for at least 5 years	94 (47.0%)
Known hypertension	112 (56.0%)
eGFR below 60 mL/min/1.73 m ²	24 (12.0%)

Values are simulated. Continuous variables are shown as mean $\pm$ standard deviation and categorical variables as frequency (percentage).

5.2 Vitamin B12 status

For this example, 56 participants had vitamin B12 deficiency, 48 had borderline levels, and 96 had adequate levels.

Table 2. distribution of serum vitamin B12 status

Vitamin B12 category	concentration	Participants, n (%)
Deficient	Below 200 pg/mL	56 (28.0%)
Borderline	200–300 pg/mL	48 (24.0%)
Adequate	Above 300 pg/mL	96 (48.0%)
Total	—	200 (100%)

5.3 Peripheral neuropathy and cognitive performance

In the dataset, 92 participants (46.0%) met the predefined screening criterion for clinically significant peripheral neuropathy. The mean cognitive screening score was 23.8 ± 3.7 .

Table 3. neurological and cognitive assessment findings

Outcome	result
Participants screening positive for peripheral neuropathy	92 (46.0%)
Participants screening negative for peripheral neuropathy	108 (54.0%)
Mean MNSI examination score	2.8 ± 1.5
Mean cognitive screening score	23.8 ± 3.7
Participants with a cognitive screening score below the prespecified threshold	78 (39.0%)

5.4 Association between vitamin B12 levels and neurological outcomes

For the analysis, serum vitamin B12 concentration showed an inverse correlation with MNSI neuropathy severity and a positive correlation with cognitive screening scores. These directions indicate that lower vitamin B12 levels were associated with greater neuropathy severity and lower cognitive scores. [8-10]

The present study would add value by examining neuropathy severity as a graded outcome rather than relying solely on the presence or absence of neuropathy. This

approach may help identify whether lower vitamin B12 levels are associated with a greater burden of neuropathic findings. Nevertheless, diabetic neuropathy is multifactorial, and serum vitamin B12 alone cannot explain its development or progression. [11-13]

6.3 Vitamin B12 and cognitive performance

Cognitive performance is relevant to diabetes care because attention, memory, executive function, and information processing can affect medication management, self-

monitoring, and adherence to treatment recommendations. [14-17]

Vitamin B12 deficiency may contribute to neurological and cognitive symptoms. However, cognitive impairment in patients with diabetes may also reflect cerebrovascular disease, chronic hyperglycemia, recurrent hypoglycemia, depression, sleep disorders, medication effects, and other comorbidities. The relationship between low vitamin B12 concentrations and cognitive outcomes is therefore complex.

The literature on vitamin B12 supplementation also requires careful interpretation. Although treatment is indicated for confirmed deficiency, evidence that supplementation consistently improves cognition in people with low-normal or borderline concentrations is less certain.

Education, language, age, mood, hearing, vision, and other relevant factors were considered when interpreting screening scores. [18]

6.4 Potential role of metformin

Metformin is an important consideration because its long-term use has been associated with reduced vitamin B12 concentrations. The clinical relevance of this association were particularly important in patients who already have peripheral neuropathy or other neurological symptoms.

A multicenter Pakistani study examined vitamin B12 status in people with T2DM receiving metformin for more than two years and compared findings with participants not receiving metformin. This supports the relevance of recording medication exposure carefully when evaluating vitamin B12 status.

The study should collect metformin dose and duration rather than merely classifying participants as current users or non-users. Dietary intake, supplementation, gastrointestinal disorders, and other

medications may also influence vitamin B12 levels.

Importantly, an association between metformin exposure and low vitamin B12 does not mean that metformin should automatically be discontinued. Medication decisions were made by the treating clinician, taking account of glycemic needs and laboratory findings.

6.5 Importance of glycemic control and diabetes duration

Poor glycemic control and longer duration of diabetes are important potential contributors to peripheral neuropathy. If these variables are associated with both vitamin B12 status and neuropathy severity, they may confound the relationship under investigation.

HbA1c and diabetes duration should therefore be included in the planned analysis. Renal function also deserves attention because kidney disease can be associated with neurological dysfunction and may complicate the interpretation of certain biochemical markers.

An adjusted association between vitamin B12 and neuropathy would strengthen the evidence that the relationship is not fully explained by the measured confounders. It would not, however, eliminate the possibility of residual confounding or establish causality.

6.6 Clinical implications

The potential clinical implication is the value of considering vitamin B12 deficiency in the differential assessment of neurological symptoms in patients with T2DM, especially in those with relevant risk factors or prolonged metformin exposure.

The study may help characterize the relationship between biochemical vitamin B12 status and neurological assessment findings. If a clinically meaningful association is confirmed, the results could support further evaluation of targeted testing strategies in appropriate patient groups.

Vitamin B12 testing should not replace standard assessment and management of diabetic neuropathy. Likewise, cognitive screening were interpreted in the broader clinical context, and suspected cognitive impairment may require formal evaluation.

6.7 Strengths of the study

Potential strengths include:

- Simultaneous assessment of vitamin B12 status, peripheral neuropathy severity, and cognitive performance.
- Use of structured assessment instruments rather than relying exclusively on subjective symptom reports.
- Consideration of important clinical confounders, including HbA1c, diabetes duration, renal function, and metformin exposure.
- Potential relevance to clinical practice in Pakistan, where local data may help inform future research and assessment strategies.
- Use of continuous vitamin B12 concentrations alongside predefined deficiency categories.

6.8 Limitations

Several limitations were acknowledged.

First, the cross-sectional design prevents determination of whether vitamin B12 deficiency preceded neurological dysfunction. Second, a hospital-based sample may not represent all people with T2DM in the community. Third, a single serum vitamin B12 measurement may not fully characterize functional deficiency, particularly when concentrations are borderline.

Fourth, peripheral neuropathy in diabetes has multiple causes and contributing factors, making it difficult to isolate the role of vitamin B12. Fifth, cognitive screening instruments are influenced by education, language, cultural context, and other clinical factors. Finally, unmeasured confounders and incomplete clinical records may affect the findings.

6.9 Recommendations for future research

Future research should consider longitudinal follow-up to determine whether baseline vitamin B12 status predicts subsequent changes in neuropathy severity or cognitive performance. Studies using functional biomarkers, such as methylmalonic acid where appropriate, may help clarify the significance of borderline serum vitamin B12 results.

Multicenter studies with larger and more diverse samples may improve generalizability. Interventional studies could assess whether correcting confirmed vitamin B12 deficiency improves clinically meaningful neurological outcomes, while distinguishing biochemical correction from changes in symptoms, objective neurological findings, and cognitive performance.

7. Conclusion

This study aims to investigate the association between serum vitamin B12 status, peripheral neuropathy severity, and cognitive performance in patients with T2DM. The analysis were assess whether lower vitamin B12 concentrations are associated with more severe neuropathy and poorer cognitive screening scores after accounting for important clinical and demographic factors.

8. Recommendations

1. Consider vitamin B12 deficiency when evaluating patients with T2DM who have peripheral neuropathy or other compatible neurological symptoms, particularly when relevant risk factors are present.
2. Record metformin dose and duration when investigating vitamin B12 status.
3. Assess glycemic control, renal function, diabetes duration, and other relevant causes of neuropathy during clinical evaluation.
4. Use validated neuropathy and cognitive assessment instruments

appropriate to the population being studied.

5. Confirm and manage vitamin B12 deficiency according to clinical assessment and applicable guidance.
6. Conduct longitudinal or interventional research to determine whether correcting deficiency changes neurological outcomes.

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