ORIGINAL RESEARCH

A Comparative Study on the Prevalence of Vitamin B12 Deficiency and Peripheral Neuropathy in Type 2 Diabetes Patients: Metformin Users versus Non-Users

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ABSTRACT
Background: Metformin is the most commonly prescribed first-line therapy for Type 2 Diabetes Mellitus (T2DM), known for its effectiveness and safety. However, long-term use has been associated with Vitamin B12 deficiency, which may contribute to peripheral neuropathy, a common complication in diabetic individuals. **Aim:** To compare the prevalence of Vitamin B12 deficiency and peripheral neuropathy between metformin users and non-users in patients with T2DM and to evaluate the association between Vitamin B12 status and neuropathic symptoms. **Material and Methods:** This hospital-based cross-sectional observational study was conducted among 130 patients with T2DM aged 30–70 years. Participants were divided into two equal groups: metformin users (n=65) and non-users (n=65). Demographic data, clinical history, glycaemic status, and dietary patterns were recorded. Serum Vitamin B12 levels were assessed, and peripheral neuropathy was evaluated using clinical and neurological examination tools. A Vitamin B12 level <200 pg/mL was considered deficient. Data were analyzed using appropriate statistical tests with $p<0.05$ considered significant. **Results:** Vitamin B12 deficiency was observed in 40.00% of metformin users compared to 16.92% of non-users ($p=0.003$). Peripheral neuropathy was significantly more common among metformin users (47.69%) than non-users (27.69%) ($p=0.02$). A strong association was found between B12 deficiency and neuropathy, with 72.97% of B12-deficient individuals showing neuropathic symptoms ($p<0.001$). A significant increase in deficiency was also seen with longer metformin use ($p=0.04$). **Conclusion:** Metformin use in T2DM patients is associated with a significantly higher prevalence of Vitamin B12 deficiency and peripheral neuropathy. Longer duration of therapy further increases this risk. Regular screening and early intervention for B12 deficiency are recommended in metformin-treated patients to mitigate neurological complications.

Keywords: Type 2 Diabetes Mellitus, Metformin, Vitamin B12 Deficiency, Peripheral Neuropathy, Duration of Therapy

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance, relative insulin deficiency, and persistent hyperglycaemia. It has become one of the most pressing global health concerns of the 21st century, with rapidly increasing prevalence due to aging populations, urbanization, sedentary lifestyles, and dietary transitions. According to the International Diabetes Federation, the global burden of diabetes is expected to rise steeply in the coming decades, contributing significantly to morbidity, mortality, and healthcare costs.[1] Effective glycaemic control remains central to the management of T2DM, aiming not only to alleviate symptoms but more importantly, to

prevent or delay long-term complications such as neuropathy, nephropathy, and retinopathy.

Among the various pharmacological options available for T2DM management, metformin remains the first-line drug of choice and is widely recommended by international guidelines due to its proven efficacy, safety profile, and cardiovascular benefits.[2] It primarily acts by reducing hepatic gluconeogenesis and improving insulin sensitivity, thereby contributing to better glycaemic control without causing weight gain or hypoglycaemia.[3] In addition to these advantages, its affordability and ease of administration have further contributed to its widespread use globally. However, despite its clinical benefits, prolonged metformin therapy is increasingly being linked to certain adverse effects, notably the risk of Vitamin B12 deficiency.

Vitamin B12, or cobalamin, is an essential water-soluble vitamin involved in critical physiological processes such as DNA synthesis, erythropoiesis, and maintenance of neurological function. Its deficiency can lead to haematological abnormalities including megaloblastic anaemia and, more concerningly, neurological complications such as peripheral neuropathy. Metformin has been shown to interfere with the absorption of Vitamin B12 in the terminal ileum through mechanisms that may involve alteration of calcium-dependent membrane activity.[4] This interaction may not manifest clinically in the short term but becomes significant with long-term use, particularly when therapy exceeds several years or when high cumulative doses are involved.

The concern is especially relevant in the context of diabetes management, as diabetic patients are already at heightened risk for peripheral neuropathy due to chronic hyperglycaemia and microvascular damage. The superimposition of Vitamin B12 deficiency-related neuropathy may compound neurological symptoms, leading to earlier onset or more severe progression. Furthermore, the clinical overlap between diabetic neuropathy and B12-deficiency neuropathy can often lead to misdiagnosis or underdiagnosis, potentially delaying appropriate interventions. Neuropathy related to B12 deficiency tends to be symmetrical and involves sensory deficits, paresthesia, and sometimes motor dysfunction. In the absence of timely correction, these changes may become irreversible.

Epidemiological evidence suggests that the prevalence of Vitamin B12 deficiency among patients with T2DM on metformin varies widely, ranging from 6% to over 30% depending on population characteristics, duration and dose of metformin therapy, and dietary intake[5]. Vegetarian individuals, the elderly, and those with gastrointestinal disorders may be particularly susceptible due to lower baseline cobalamin stores. Despite these known risks, routine screening for Vitamin B12 levels in metformin-treated diabetic patients is not yet universally implemented in clinical practice, potentially allowing subclinical deficiency to progress undetected.

Recent consensus reports and management algorithms have begun to acknowledge this complication, recommending periodic assessment of Vitamin B12 levels, especially in high-risk individuals or those exhibiting symptoms of neuropathy[6]. However, the extent to which this is practiced varies across healthcare systems and regions. Moreover, clinical awareness regarding this association among both healthcare providers and patients remains limited. Early identification and supplementation can significantly reverse symptoms and prevent long-term damage, making it imperative to explore this association further through well-structured studies.

In the context of Saudi Arabia, a cross-sectional study demonstrated a significant association between metformin use and both Vitamin B12 deficiency and peripheral neuropathy in individuals with T2DM. This finding aligns with observations made in various other populations and reinforces the need for regional data to inform clinical protocols. However, Indian data on this topic, particularly comparing metformin users with non-users, remain scarce. Given the high prevalence of diabetes in India and the extensive use of metformin in its management, it is crucial to evaluate the potential risk of B12 deficiency and its clinical consequences in this demographic.[7]

AIM AND OBJECTIVES

Aim

To evaluate and compare the prevalence of vitamin B12 deficiency and peripheral neuropathy among type 2 diabetes mellitus (T2DM) patients using metformin versus those not using metformin, and to assess the association between vitamin B12 deficiency and peripheral neuropathy within this population.

Objectives

- Determine the Prevalence of Vitamin B12 Deficiency

- Assess the proportion of vitamin B12 deficiency (defined as serum levels <200 pg/mL) among metformin users and non-users with T2DM.
- Evaluate the Prevalence of Peripheral Neuropathy
- Compare the occurrence of clinically diagnosed peripheral neuropathy between metformin users and non-users.
- Analyze the Association Between Vitamin B12 Deficiency and Peripheral Neuropathy

MATERIALS AND METHODS

Study Design

This was a hospital-based, cross-sectional observational study aimed at comparing the prevalence of Vitamin B12 deficiency and peripheral neuropathy in Type 2 Diabetes Mellitus (T2DM) patients who were either on metformin therapy or not.

Study Population

The study included a total of 130 participants diagnosed with T2DM, aged between 30 to 70 years, selected using consecutive sampling from both outpatient and inpatient departments.

Study Place

The study was conducted in the Department of General Medicine in collaboration with Department of Physiology, Narayan Medical College and Hospital**,** Jamuhar, Rohtas, Bihar, India.

Study Duration

The study was carried out over a period of two year, from January 2020 to December 2021 after receiving Institutional Ethics Committee approval.

Inclusion Criteria

Participants had to meet the following criteria:

- Age between 30–70 years.
- Diagnosed with Type 2 Diabetes Mellitus (T2DM) for at least 1 year.
- Recent serum Vitamin B12 levels available (within the last 3 months).
- Willing to undergo clinical and neurological examination for peripheral neuropathy.
- Provided written informed consent.

Exclusion Criteria

The following were excluded:

- Patients with Type 1 Diabetes Mellitus or gestational diabetes.
- History of chronic alcohol use, pernicious anaemia, or gastrointestinal surgery.
- Use of Vitamin B12 supplements/injections within the past 6 months.

Known cases of neuropathy due to other causes, including hypothyroidism, chronic renal failure, or HIV infection.

Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee (IEC). All participants provided written informed consent prior to inclusion, ensuring voluntary participation and adherence to ethical standards.

Study Procedure

Participants were grouped as follows:

- Group A (Metformin Users): 65 T2DM patients on metformin therapy ≥1000 mg/day for at least 6 months.
- Group B (Non-Metformin Users): 65 T2DM patients not receiving metformin.

Data collected included:

- Demographics: Age, sex, BMI.
- Medical history: Duration of diabetes, comorbidities.
- Glycaemic control: Assessed via HbA1c levels.
- Dietary pattern: Classified as vegetarian or non-vegetarian.

Vitamin B12 assessment:

- Measured using chemiluminescent immunoassay.
- Levels <200 pg/mL were considered deficient.

Peripheral neuropathy assessment:

- Clinical neurological examination.
- Symptom scoring via Michigan Neuropathy Screening Instrument (MNSI).
- Vibration perception test using 128-Hz tuning fork.
- Pressure sensation via 10-g Semmes-Weinstein monofilament test.
- Ankle reflexes examination.

These tests provided both subjective and objective data on peripheral neuropathy.

Outcome Measures

- Primary Outcome: Prevalence of Vitamin B12 deficiency in metformin users vs. non-users.
- Secondary Outcome: Prevalence and severity of peripheral neuropathy in the same groups.

Statistical Analysis

- Data was entered in Microsoft Excel and analyzed using SPSS version 20.0.
- Continuous variables: Presented as mean ± SD.
- Categorical variables: Expressed as frequencies and percentages.
- Comparisons:

- Independent t-test for continuous variables.
- Chi-square test for categorical variables.
- p-value <0.05 was considered statistically significant.

RESULTS

Table 1: Baseline Demographic and Clinical Characteristics of the Study Population (n = 130)

Parameter	Metformin Users (n=65)	Non-Users (n=65)	p-value
Mean Age (years)	56.20 ± 8.40	54.90 ± 7.60	0.34
Male:Female Ratio	38:27	36:29	0.71
Mean Duration of T2DM (yrs)	8.10 ± 3.70	6.90 ± 4.20	0.05
Mean BMI (kg/m²)	26.50 ± 3.20	25.80 ± 2.90	0.18
Mean HbA1c (%)	8.20 ± 1.10	7.90 ± 1.30	0.09
Vegetarian Diet (%)	26 (40.00%)	23 (35.38%)	0.56

Table 1 shows the study included 130 participants equally divided into two groups of metformin users (n=65) and non-users (n=65). The mean age of the metformin users was 56.20 ± 8.40 years, slightly higher than the non-users at 54.90 ± 7.60 years, though the difference was not statistically significant (p=0.34). The gender distribution was comparable, with a male-to-female ratio of 38:27 in the metformin group and 36:29 in the non-user group (p=0.71). The duration of Type 2 Diabetes Mellitus (T2DM) was longer in metformin users (8.10 ± 3.70 years) compared to non-users (6.90 ± 4.20 years), approaching statistical significance (p=0.05). The mean BMI in both groups was similar (26.50 ± 3.20 kg/m² in users and 25.80 ± 2.90 kg/m² in non-users; p=0.18). Glycaemic control, as measured by HbA1c, was slightly poorer in metformin users (8.20 ± 1.10%) compared to non-users (7.90 ± 1.30%), but this difference was not statistically significant (p=0.09). Regarding dietary habits, 40.00% of metformin users and 35.38% of non-users followed a vegetarian diet (p=0.56), indicating no major dietary difference that could explain variations in Vitamin B12 levels.

Table 2: Vitamin B12 Status in Metformin Users and Non-Users

Vitamin B12 Status	Metformin Users (n=65)	Non-Users (n=65)	Total (n=130)	p-value
Deficient (<200 pg/mL)	26 (40.00%)	11 (16.92%)	37 (28.46%)	0.003
Normal (≥200 pg/mL)	39 (60.00%)	54 (83.08%)	93 (71.54%)	

Table 2 shows a notable difference was observed in the prevalence of Vitamin B12 deficiency between the two groups. Among metformin users, 26 out of 65 participants (40.00%) had Vitamin B12 levels below 200 pg/mL, indicating deficiency. In contrast, only 11 out of 65 non-users (16.92%) were deficient. This difference was statistically significant (p=0.003), clearly suggesting that metformin use is associated with a higher likelihood of Vitamin B12 deficiency. The overall prevalence of deficiency in the total study population was 28.46%, and 71.54% of participants had normal Vitamin B12 levels.

Table 3: Prevalence of Peripheral Neuropathy in Study Groups

Peripheral Neuropathy Status	Metformin Users (n=65)	Non-Users (n=65)	Total (n=130)	p-value
Present	31 (47.69%)	18 (27.69%)	49 (37.69%)	0.02
Absent	34 (52.31%)	47 (72.31%)	81 (62.31%)	

Table 3 shows the peripheral neuropathy was significantly more prevalent among metformin users. A total of 31 out of 65 (47.69%) metformin users showed clinical signs of neuropathy, compared to 18 out of 65 (27.69%) in the non-user group (p=0.02). Conversely, 52.31% of metformin users and 72.31% of non-users were free of neuropathy. These findings

suggest a potential link between metformin therapy and the development of diabetic peripheral neuropathy.

Table 4: Correlation Between Vitamin B12 Deficiency and Peripheral Neuropathy (n = 130)

Vitamin B12 Level	Peripheral Neuropathy Present	Peripheral Neuropathy Absent	Total (n)	p-value
Deficient (<200 pg/mL)	27 (72.97%)	10 (27.03%)	37	<0.001
Normal (≥200 pg/mL)	22 (23.66%)	71 (76.34%)	93	

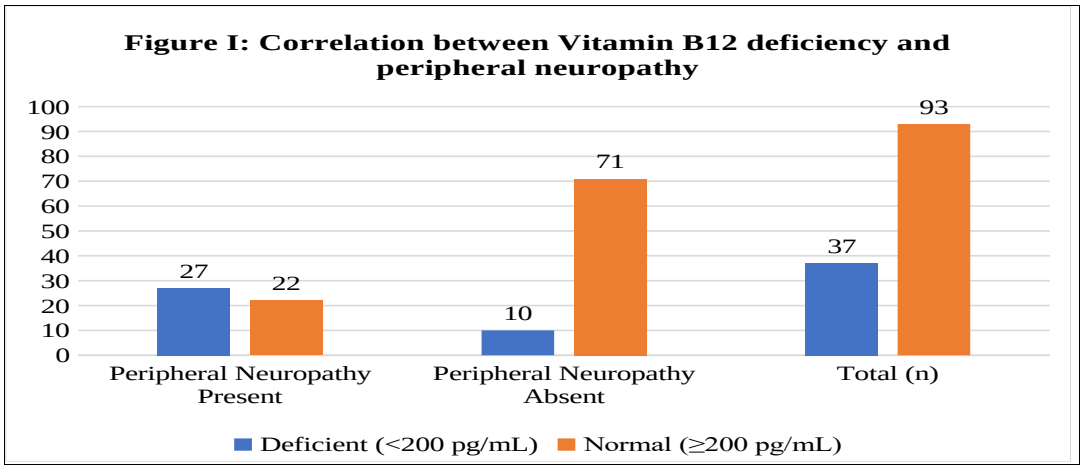

Table 4, figure I shows an important finding emerged when correlating Vitamin B12 status with the presence of peripheral neuropathy across the entire cohort. Among the 37 participants with Vitamin B12 deficiency, 27 (72.97%) had peripheral neuropathy, whereas only 10 (27.03%) did not. In contrast, among the 93 participants with normal Vitamin B12 levels, only 22 (23.66%) had neuropathy, while 71 (76.34%) did not. This association was highly statistically significant ($p<0.001$), suggesting that Vitamin B12 deficiency is strongly associated with the presence of peripheral neuropathy in patients with T2DM.

Table 5: Duration of Metformin Use and Vitamin B12 Deficiency (Metformin Users Only, n = 65)

Duration of Metformin Use	Vitamin B12 Deficient (n=26)	Vitamin B12 Normal (n=39)	p-value
<2 years	5 (19.23%)	12 (30.77%)	
2–5 years	8 (30.77%)	14 (35.90%)	
>5 years	13 (50.00%)	13 (33.33%)	0.04

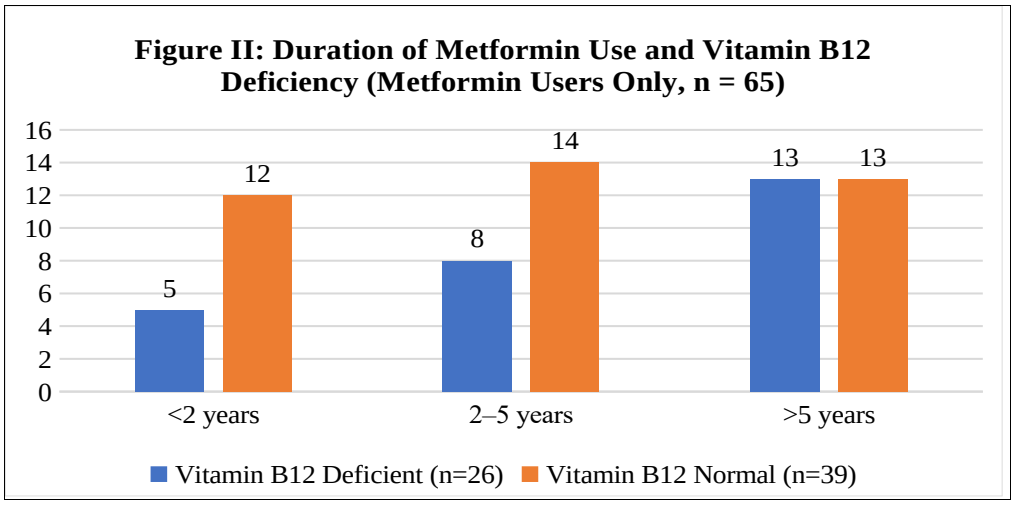

Table 5, figure II shows within the metformin user group (n=65), the association between duration of metformin therapy and Vitamin B12 deficiency was examined. Among those using metformin for less than 2 years, 5 out of 26 deficient individuals (19.23%) were affected. The deficiency rate increased to 30.77% for users between 2–5 years, and rose further to 50.00% in individuals using metformin for more than 5 years. In contrast, normal Vitamin B12 levels were found in 30.77% of users with <2 years of use, 35.90% in the 2–5 year group, and only 33.33% among long-term users (>5 years). The increasing trend of deficiency with longer metformin use was statistically significant (p=0.04), supporting a time-dependent effect of metformin on Vitamin B12 depletion.

DISCUSSION

In the present study, both metformin users and non-users were well-matched in terms of demographic and clinical characteristics, including age, gender, BMI, glycemic control, and diet (Table 1). The only marginal difference was a longer mean duration of T2DM among metformin users (8.10 ± 3.70 years) compared to non-users (6.90 ± 4.20 years), which is expected as metformin is typically continued for prolonged periods in diabetic management. A similar demographic profile was reported by **Jayashankar et al. (2021**), who conducted a comparable cross-sectional study and found no significant difference in baseline characteristics, affirming that the variations in Vitamin B12 status and neuropathy are not attributable to confounding baseline disparities.8

The current study found a significantly higher prevalence of Vitamin B12 deficiency among metformin users (40.00%) versus non-users (16.92%) (Table 2), which closely aligns with prior studies. **Jayashankar et al.**[8] reported a B12 deficiency prevalence of 35.7% in metformin users versus 13.2% in non-users, while **Khan et al.** found rates of 38.0% in metformin users compared to 18.0% in controls.[9] **Al Quran et al.** observed an even higher deficiency rate of 48.7% among metformin-treated patients. These consistent findings across geographic and ethnic populations highlight metformin's strong association with impaired B12 absorption, likely due to interference with the calcium-dependent uptake of the vitamin-intrinsic factor complex in the terminal ileum.[10]

In terms of peripheral neuropathy, our study found that 47.69% of metformin users experienced symptoms, significantly higher than the 27.69% observed among non-users (Table 3). **Jayashankar et al.**[8] also reported a higher rate of neuropathy in metformin users (45.7%) compared to non-users (25.0%). **Calvo Romero et al.**[11] and **Reinstatler et al.**[12] have emphasized that while diabetic neuropathy is multifactorial, B12 deficiency acts as an additive or even synergistic factor worsening neurologic outcomes. The higher neuropathy rate among metformin users in this and other studies suggests that Vitamin B12 screening may be critical to distinguish between true diabetic neuropathy and that caused or exacerbated by drug-induced deficiency.

The current study revealed a significant correlation between B12 deficiency and peripheral neuropathy, with 72.97% of deficient individuals exhibiting symptoms, as compared to only 23.66% of those with normal levels. This finding is consistent with the meta-analysis by **Stein et al.**[13], which showed that individuals with low B12 had a 2.5-fold higher risk of developing neuropathic complications. **Andrès et al.**[14] further emphasized that B12 deficiency leads to demyelination of peripheral nerves, contributing to paresthesia, weakness, and loss of proprioception, and that early supplementation can reverse these deficits.

The influence of metformin duration on B12 status was clearly evident in this study (Table 5). Among users of more than 5 years, 50.00% were deficient, compared to 19.23% among those with <2 years of use. **de Jager et al.**[15] conducted a randomized controlled trial over 4.3 years and found that long-term metformin therapy resulted in a mean B12 level reduction of 19%. **Aroda et al.**[16], analyzing the Diabetes Prevention Program Outcomes Study, showed that metformin users had a significantly higher risk of deficiency after 5 years of therapy (hazard ratio: 2.9), particularly in those not receiving B12 supplementation. These data collectively support a duration-dependent depletion of Vitamin B12 due to metformin therapy.

In our study, the overall prevalence of B12 deficiency among all T2DM patients was 28.46%, and the prevalence of peripheral neuropathy was 37.69%. These rates closely mirror findings from **Marar et al.**[17], who reported B12 deficiency in 31% and neuropathy in 35% of their metformin-treated diabetic cohort. Our findings also match those of **Sparre Hermann et al.**[18], who reported that nearly one-third of metformin users developed B12 depletion over time.

LIMITATIONS OF THE STUDY

- Cross-sectional design: Limits ability to establish causal relationships between metformin use and Vitamin B12 deficiency or neuropathy.
- Single-centre study: May limit generalizability to other settings or populations.
- Recall bias: Self-reported dietary patterns and medical history might introduce bias.
- Lack of longitudinal follow-up: Prevents assessment of progression or resolution of neuropathy over time.
- Possible confounders: Unmeasured variables such as genetic predisposition, other micronutrient deficiencies, or concurrent medications may influence results.

CONCLUSION

This study demonstrated a significantly higher prevalence of Vitamin B12 deficiency and peripheral neuropathy among metformin users compared to non-users with Type 2 Diabetes Mellitus. A strong correlation was found between B12 deficiency and the presence of neuropathic symptoms. Moreover, the risk of deficiency increased with longer duration of metformin use. These findings highlight the need for routine screening of Vitamin B12 levels in patients on long-term metformin therapy to prevent and manage potential neurological complications effectively.

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