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Metformin and Vitamin B12 Deficiency: Evidence of Progressive Decline With Higher Dose and Longer Duration

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ABSTRACT

Background: Metformin is the first-line therapy for type 2 diabetes mellitus (T2DM), yet long-term use has been consistently associated with vitamin B12 deficiency. This study evaluates serum vitamin B12 levels in patients receiving metformin and examines dose-response and duration-response relationships.

Methods: A cross-sectional study was conducted among 51 adults with T2DM on metformin therapy and 51 age- and sex-matched non-diabetic controls. Demographic, clinical, and biochemical parameters were recorded. Serum vitamin B12 levels were compared between groups and analyzed across metformin dose, duration of therapy, and diabetes duration. Pearson correlation analysis assessed associations between vitamin B12 concentrations and clinical variables.

Results: Mean serum vitamin B12 levels were significantly lower in diabetics than controls (258.84 ± 107.30 pg/mL vs 415.02 ± 158.04 pg/mL, $p<0.001$). Vitamin B12 deficiency (<200 pg/mL) was observed in 35.3% of diabetics compared with 3.9% of controls. Longer metformin use and higher daily doses were strongly associated with lower vitamin B12 levels. Duration of metformin therapy ($r = –0.58$, $p<0.001$), daily metformin dose ($r = –0.44$, $p=0.002$), and duration of diabetes ($r = –0.52$, $p<0.001$) showed significant negative correlations with vitamin B12 concentration. Peripheral smear abnormalities—macrocytosis and hypersegmented neutrophils—were more frequent in the diabetic group.

Conclusions: Vitamin B12 levels are significantly reduced in patients receiving metformin, with a clear dose-dependent and duration-dependent decline. These findings reinforce the need for routine B12 monitoring in long-term metformin users.

Keywords Metformin; Vitamin B12 deficiency; Type 2 diabetes mellitus; Dose-response; Duration-response; Correlation analysis; Macrocytosis; Peripheral smear; Hypersegmented neutrophils..

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance, progressive β-cell dysfunction, and sustained hyperglycemia. The American Diabetes Association (ADA) provides standardized diagnostic criteria using fasting plasma glucose, HbA1c, oral glucose tolerance testing, and random glucose measurements, and these remain the most widely accepted clinical tools for diagnosis [1]. India bears a substantial burden of diabetes, with prevalence rising rapidly over the past three decades due to urbanization, dietary transitions, sedentary behavior, and demographic changes. Epidemiological data indicate that India currently has over 77 million people living with diabetes, the second largest number globally, with projections showing a marked increase by 2045 [2]. Increasing life expectancy, high rates of prediabetes, and undiagnosed diabetes further contribute to the rising national burden.

Metformin, a biguanide derivative and the cornerstone first-line therapy for T2DM, has been in clinical use since the 1950s [3]. It lowers blood glucose primarily through suppression of hepatic gluconeogenesis, reduced intestinal glucose absorption, and improved insulin sensitivity mediated via activation of AMP-activated protein kinase (AMPK) [4]. Owing to its proven cardiovascular safety, weight neutrality, affordability, and glycemic efficacy, metformin is prescribed widely and often for prolonged durations [5]. However, despite its favorable therapeutic profile, long-term metformin use has been consistently associated with reduced serum vitamin B12 levels, an adverse effect that is frequently overlooked in routine clinical practice [6].

Vitamin B12 (cobalamin) is an essential water-soluble micronutrient required for DNA synthesis, red blood cell maturation, and neurological function. Absorption of dietary B12 involves multiple steps—gastric release from food proteins, binding to intrinsic factor (IF), and calcium-dependent endocytosis of the IF-B12 complex in the terminal ileum. Following absorption, transcobalamin II transports the vitamin to tissues, with nearly 90% of total body stores residing in the liver [7]. Disruption of any step in this pathway can lead to deficiency.

Multiple mechanisms have been proposed to explain metformin-associated vitamin B12 deficiency. The most widely supported mechanism is metformin's interference with calcium-dependent uptake of the IF-B12 complex in the terminal ileum. Additional theories include altered small bowel motility resulting in bacterial overgrowth and impaired intrinsic factor interactions. Notably, studies show that calcium supplementation can reverse metformin-induced B12 malabsorption, supporting a calcium-dependent mechanism. Several clinical studies and randomized trials have confirmed that higher metformin doses and longer duration of therapy significantly increase the risk of B12 deficiency. Reported prevalence ranges from 5.8% to 33% among metformin-treated T2DM patients, depending on dosage, duration, and diagnostic criteria [8,9].

Vitamin B12 deficiency is of particular clinical importance in individuals with T2DM because its neurological manifestations often resemble diabetic peripheral neuropathy. Symptoms such as distal paresthesias, impaired vibration sense, and reduced nerve conduction velocities may be misinterpreted as progression of diabetic neuropathy, leading to unnecessary escalation of neuropathic medications and delayed diagnosis of true cobalamin deficiency. Hematological manifestations include macrocytosis, megaloblastic anemia, and hypersegmented neutrophils, though these may remain occult for years due to large hepatic stores. Since India has a large vegetarian population and higher background prevalence of dietary B12 deficiency, the combined effect of low dietary intake and metformin therapy poses a significant risk [10-11].

Despite the accumulating evidence, routine screening for vitamin B12 deficiency in metformin-treated diabetics remains inconsistent across clinical guidelines. Some authors recommend annual screening in patients receiving metformin for ≥3–4 years, those on higher doses (≥2 g/day), elderly individuals, and those with neuropathy or hematological abnormalities [52–54]. The lack of clear guidance is particularly concerning in regions such as Himachal Pradesh, where diabetes prevalence has increased, especially in urban areas, and where dietary patterns may predispose individuals to lower B12 intake [12–14].

Given the rising burden of T2DM and widespread use of metformin, early identification of vitamin B12 deficiency may help prevent complications that significantly affect quality of life. However, regional data from North India, particularly Himachal Pradesh, remain limited.

The present study was therefore designed to measure serum vitamin B12 levels in patients with T2DM receiving long-term metformin therapy and compare them with non-diabetic individuals attending a tertiary care hospital in Solan, Himachal Pradesh. By analyzing associations with age, gender, duration and dose of metformin, hematological parameters, and microvascular complications, the study provides evidence that may guide screening practices and supplementation strategies in routine clinical care.

MATERIAL AND METHODS

We conducted a prospective, observational, case–control study at Maharishi Markandeshwar Medical College and Hospital, Kumarhatti, Solan, over an 18-month period, in the Departments of General Medicine and Biochemistry. A total of 102 participants were enrolled consecutively from outpatient and inpatient services, comprising 51 adults with type 2 diabetes mellitus (T2DM) receiving metformin for at least 1 year and 51 non-diabetic controls. Eligibility for the diabetes group required a diagnosis of T2DM based on American Diabetes Association criteria, including an HbA1c of at least 6.5%, fasting plasma glucose of at least 126 mg/dL, 2-hour plasma glucose of at least 200 mg/dL after a 75-g oral glucose load, or a random glucose level of at least 200 mg/dL with symptoms. Patients with type 1 or gestational diabetes, prior vitamin B12 injections, history of gastrectomy or colectomy, chronic liver disease or malignancy, or use of proton-pump inhibitors or H2-blockers were excluded. Controls were adults without diabetes who did not meet ADA criteria and had never received metformin. Written informed consent was obtained from all participants.

Demographic data, duration of diabetes, duration and dose of metformin therapy, alcohol history, and neuropathic symptoms were recorded. Physical examination included systemic, cardiovascular, and neurological assessments. Peripheral neuropathy was evaluated with a 10-g Semmes–Weinstein monofilament and a 128-Hz tuning fork, and fundus examination was performed using direct ophthalmoscopy to detect diabetic retinopathy. Peripheral blood smears were examined for macrocytosis and hypersegmented neutrophils suggestive of megaloblastic anemia.

Blood samples were analyzed in the institutional biochemistry laboratory. Serum vitamin B12 concentrations were measured using the COBAS e411 electrochemiluminescence immunoassay analyzer (Roche Diagnostics) and categorized as deficient (<200 pg/mL), borderline (200–300 pg/mL), or normal (>300 pg/mL). Hemoglobin, red-cell indices, liver and renal function tests, fasting and random blood glucose, and glycated hemoglobin were measured using standard automated procedures.

The sample size was determined using G*Power software for comparing two independent means, with an effect size of 0.5, a two-sided alpha of 0.05, and a power of 80%, yielding a requirement of 102 participants (51 per group). Statistical analyses were performed using SPSS version 27.0. Continuous variables are presented as means with standard deviations and compared using the independent t-test or one-way analysis of variance; categorical variables are presented as counts and percentages and compared using the chi-square test. Pearson correlation coefficients were calculated to assess associations between serum vitamin B12 concentrations and continuous variables. A two-sided P value of less than 0.05 was considered statistically significant.
Ethical approval for the study was obtained from the Institutional Ethics Committee, and confidentiality of participant data was maintained throughout.

RESULTS

A total of 102 participants were included in the study, comprising 51 patients with type 2 diabetes receiving metformin therapy and 51 non-diabetic controls. The baseline characteristics of the study population are summarized in Table 1. The mean age of participants was comparable between groups (55.68 ± 11.65 years in diabetics vs. 59.47 ± 11.70 years in controls; P=0.11). The distribution of participants across age categories was similar in both groups. Among diabetic participants, 29 (56.9%) were male and 22 (43.1%) were female, while controls included 21 (41.2%) males and 30 (58.8%) females. Alcohol use was reported by 18 (35.3%) diabetics and 17 (33.3%) controls.

Table 1. Baseline Characteristics of the Study Participants.

Characteristic	Cases	Controls	P Value
Age — yr, mean ± SD	55.68 ± 11.65	59.47 ± 11.70	0.11
Age categories — no. (%)			
30–40 yr	1 (2.0)	6 (11.8)	
41–50 yr	13 (25.5)	11 (21.6)	
51–60 yr	15 (29.4)	14 (27.5)	
61–70 yr	13 (25.5)	16 (31.4)	
71–80 yr	6 (11.8)	4 (7.8)	
81–90 yr	3 (5.9)	0 (0)	
Sex — no. (%)			
Male	29 (56.9)	21 (41.2)	
Female	22 (43.1)	30 (58.8)	
Alcohol use — no. (%)			
Yes	18 (35.3)	17 (33.3)	
No	33 (64.7)	34 (66.7)	
Neuropathy (Any cause)			
Sensory neuropathy	22 (43.14)	2 (3.92)	
Motor neuropathy	13 (25.49)	1 (1.96)	

Microvascular Complications			
Nephropathy	16 (31.37)	—	
Retinopathy	17 (33.33)	—	
Hemoglobin — g/dL, mean ± SD	16.55 ± 18.62	13.61 ± 1.81	0.27
MCV — fL, mean ± SD	87.44 ± 6.37	96.64 ± 10.93	<0.001
Fasting blood sugar — mg/dL	88.28 ± 8.54	180.06 ± 49.58	<0.001
Random blood sugar — mg/dL	112.98 ± 14.89	209.68 ± 73.80	<0.001
HbA1c — %	6.01 ± 0.34	9.31 ± 2.17	<0.001
Serum vitamin B12 — pg/mL	258.84 ± 107.30	415.02 ± 158.04	<0.001
<200 pg/mL— no. (%)	18 (35.3)	2 (3.9)	
200–300 pg/mL— no. (%)	18 (35.3)	5 (9.8)	
>300 pg/mL — no. (%)	15 (29.4)	44 (86.3)	
Continuous variables are expressed as mean ± SD. Categorical variables are expressed as number (percentage). Neuropathy represents any sensory or motor neuropathy irrespective of cause. Diabetic microvascular complications (nephropathy and retinopathy) were evaluated only in diabetic participants; control participants were not assessed for diabetic complications. P values represent comparisons between diabetic and non-diabetic participants.			

Neuropathy of any cause was more frequent among diabetics compared with controls. Sensory neuropathy was present in 22 (43.1%) diabetic participants and 2 (3.9%) controls, while motor neuropathy was present in 13 (25.5%) diabetics and 1 (2.0%) control. Diabetic microvascular complications (evaluated only among diabetic participants) included nephropathy in 16 (31.4%) participants and retinopathy in 17 (33.3%).

Hemoglobin concentration was similar between the two groups (P=0.27), while mean corpuscular volume was significantly higher in controls than in diabetics (P<0.001). Fasting blood sugar, random blood sugar, and HbA1c values were higher in diabetic participants, consistent with their disease status (all P<0.001).

The mean serum vitamin B12 concentration was 258.84 ± 107.30 pg/mL in the control group and 415.02 ± 158.04 pg/mL among diabetic (P<0.001). Vitamin B12 deficiency (<200 pg/mL) was present in 18 (35.3%) diabetics and 2 (3.9%) controls. Levels between 200–300 pg/mL were found in 18 (35.3%) diabetics and 5 (9.8%) controls, whereas concentrations above 300 pg/mL were observed in 15 (29.4%) diabetics and 44 (86.3%) controls. The full distribution of baseline parameters is presented in Table 1.

Associations between serum vitamin B12 levels and clinical variables among diabetic participants and controls are shown in Table 2. Among diabetics, mean vitamin B12 concentrations decreased progressively with increasing duration of diabetes. Participants with diabetes for less than 5 years had a mean B12 level of 435.20 ± 98.95 pg/mL, those with diabetes for 5–10 years had 306.41 ± 85.99 pg/mL, and those with diabetes for more than 10 years had 149.71 ± 45.65 pg/mL.

Table 2. Association of Serum Vitamin B12 Levels With Clinical and Laboratory Variables.

Variable	Cases (Mean ± SD)	Controls (Mean ± SD)	P Value
Alcohol Use			
Yes	243.92 ± 99.26	393.17 ± 147.00	0.001
No	267.24 ± 112.23	426.28 ± 164.49	0.001
Duration of Diabetes			
<5 years	435.20 ± 98.95	—	
5–10 years	306.41 ± 85.99	—	
>10 years	149.71 ± 45.65	—	
Duration of Metformin Use			
<5 years	435.20 ± 88.76	—	
5–10 years	306.41 ± 85.99	—	
>10 years	149.71 ± 45.65	—	
Daily Metformin Dose			
500 mg	360.30 ± 110.12	—	
1000 mg	343.24 ± 73.90	—	
1500 mg (1000+500 mg)	211.74 ± 100.16	—	
2000 mg (1000+1000 mg)	270.85 ± 107.28	—	
Peripheral Smear			
NCNC RBCs	318.00 ± 79.21	426.96 ± 149.67	0.012
NCNC + few macrocytes	194.95 ± 4.73	—	
Macrocytosis	128.34 ± 29.16	129.65 ± 13.08	0.001
Hypersegmented neutrophils	120.20 ± 23.31	128.70 ± 13.08	0.02

A similar pattern was observed with duration of metformin therapy. Participants using metformin for less than 5 years had a mean B12 value of 435.20 ± 88.76 pg/mL, those using it for 5–10 years had 306.41 ± 85.99 pg/mL, and those using it for more than 10 years had 149.71 ± 45.65 pg/mL.

Daily metformin dose was also associated with variation in vitamin B12 levels. Participants receiving 500 mg daily had the highest mean vitamin B12 concentration (360.30 ± 110.12 pg/mL), while those receiving 1000 mg had 343.24 ± 73.90 pg/mL, and those receiving 1500 mg and 2000 mg had mean concentrations of 211.74 ± 100.16 pg/mL and 270.85 ± 107.28 pg/mL,

respectively.
Peripheral smear findings were also associated with serum B12 levels. Participants with normocytic normochromic red blood cells had the highest mean vitamin B12 values (318.00 ± 79.21 pg/mL), whereas those with macrocytosis (128.34 ± 29.16 pg/mL) and hypersegmented neutrophils (120.20 ± 23.31 pg/mL) had substantially lower concentrations. Corresponding data for controls are presented in Table 2.

Pearson correlation analysis was performed to evaluate the association between serum vitamin B12 concentrations and selected clinical and biochemical parameters. The findings are summarized in Table 3.

Table 3. Correlation of Serum Vitamin B12 Levels With Clinical Variables

Variable	Correlation Coefficient (r)	P Value
Duration of metformin therapy	–0.58*	<0.001*
Daily metformin dose	–0.44*	0.002*
Duration of diabetes	–0.52*	<0.001*
Hemoglobin	0.41	0.003*
Mean corpuscular volume	–0.46*	0.001*
HbA1c	0.17	0.21 (NS)
Fasting blood sugar	0.03	0.78 (NS)
Random blood sugar	0.06	0.61 (NS)
"r: Pearson correlation coefficient. $p < 0.05$ considered statistically significant. Variables marked with * indicate statistically significant correlations."		

A strong negative correlation was observed between vitamin B12 levels and duration of metformin therapy ($r = –0.58$, $p < 0.001$). Daily metformin dose also showed a significant negative correlation ($r = –0.44$, $p = 0.002$). Similarly, duration of diabetes demonstrated a significant inverse relationship with vitamin B12 concentrations ($r = –0.52$, $p < 0.001$).
Among hematological variables, hemoglobin showed a significant positive correlation with vitamin B12 levels ($r = 0.41$, $p = 0.003$), whereas mean corpuscular volume (MCV) demonstrated a significant negative correlation ($r = –0.46$, $p = 0.001$). No significant correlations were found between vitamin B12 and HbA1c ($r = 0.17$, $p = 0.21$), fasting blood sugar ($r = 0.03$, $p = 0.78$), or random blood sugar ($r = 0.06$, $p = 0.61$).

Scatter plot analysis further illustrated the relationships identified through correlation testing. As shown in Figure 1A, serum vitamin B12 concentrations demonstrated a progressive decline with increasing duration of metformin therapy, with a clearly visible negative linear trend consistent with the strong inverse correlation observed ($r = –0.58$, $P < 0.001$). Figure 1B shows the association between daily metformin dose and vitamin B12 levels, also demonstrating a downward trend across higher dose categories, in accordance with the significant negative correlation obtained ($r = –0.44$, $P = 0.002$). These graphical representations complement the numerical findings and depict the dose- and duration-related decrease in serum vitamin B12 concentrations among individuals receiving metformin therapy.

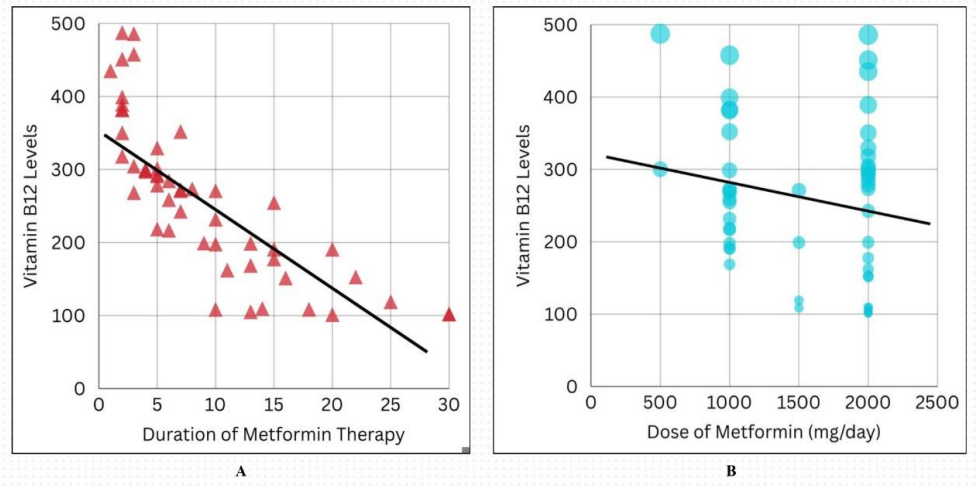

Figure 1. Association of Metformin Exposure With Serum Vitamin B12 Levels.

(Panel A shows serum vitamin B12 levels by duration of metformin therapy. Panel B shows serum vitamin B12 levels by daily metformin dose.)

In summary, serum vitamin B12 levels showed a consistent decline with increasing duration and dose of metformin therapy, supported by significant negative correlations demonstrated in both tabular and graphical analyses. These findings, together with the higher prevalence of biochemical deficiency among metformin users, outline a clear pattern of reduced vitamin B12 concentrations in this population. The implications of these observations are considered in the following Discussion section.

DISCUSSION

Metformin remains the cornerstone of first-line therapy for type 2 diabetes mellitus (T2DM) because of its proven efficacy, safety, and long-term cardiovascular benefits. However, over the past two decades, substantial evidence has accumulated linking prolonged metformin therapy to vitamin B12 deficiency—a clinically relevant adverse effect that often remains under-recognized. The present study provides further confirmation of this association, demonstrating significantly lower serum vitamin B12 concentrations among metformin-treated T2DM patients compared with non-diabetic controls. Importantly, the magnitude of deficiency in this cohort was not only statistically significant but also clinically meaningful, particularly when considering the potential neurological implications of chronic B12 depletion.

In our study, both the duration and daily dose of metformin exhibited strong, graded, and statistically significant negative correlations with serum vitamin B12 concentrations. Participants receiving metformin for more than 10 years had markedly lower vitamin B12 levels compared with those with shorter exposures. Likewise, higher metformin doses (1,500–2,000 mg/day) were associated with progressively lower B12 concentrations. These findings mirror results from large observational cohorts and randomized trials, which consistently demonstrate a dose-response relationship between metformin exposure and impaired vitamin B12 absorption.[15-18] The biological plausibility of this association is well-established: metformin interferes with calcium-dependent absorption of the intrinsic-factor–B12 complex at the terminal ileum, reduces ileal motility, alters small-bowel microbiota, and may impair enterohepatic B12 recirculation.[19,20]

Beyond biochemical reduction in B12 levels, the clinical relevance of this deficiency is highlighted by its association with neuropathy. In our study, a substantial proportion of metformin-treated individuals with low B12 levels also demonstrated sensory or motor neuropathy. Although diabetic neuropathy has multifactorial origins, emerging literature suggests that concomitant B12 deficiency may exacerbate or mimic diabetic neuropathy, leading to delayed recognition and suboptimal treatment outcomes.[21] The presence of neuropathy among some controls, unrelated to diabetes, underscores the importance of assessing B12 status even outside the context of glycemic control.

Peripheral smear findings in this study provided additional supportive evidence. Participants with macrocytosis or hypersegmented neutrophils exhibited significantly lower B12 concentrations—hematologic features that, although late manifestations, remain valuable clinical indicators of deficiency. Interestingly, not all B12-deficient individuals showed macrocytosis, consistent with literature suggesting that coexisting iron deficiency, chronic disease, or early-stage deficiency may mask classic hematologic changes.[22] This reinforces the importance of biochemical screening rather than reliance on morphology alone.

The observation of lower B12 levels among alcohol-consuming participants and among males further aligns with known risk modifiers. Alcohol interferes with B12 absorption and hepatic storage, while sex-related differences may be influenced by dietary patterns or differential metformin exposure. However, even after accounting for these variables, metformin remained the

dominant determinant of B12 status, emphasizing the robustness of the association.

Our findings carry important clinical implications. Given the high prevalence of metformin use in India and globally, coupled with the progressive nature of deficiency, routine B12 monitoring should be strongly considered in long-term metformin users, particularly those on higher doses, older adults, and individuals with neuropathic symptoms. Several guidelines now recommend periodic B12 screening after 4–5 years of therapy, although adherence to these recommendations remains low. Moreover, supplementation—either oral or parenteral—has been shown to reverse biochemical deficiency effectively without necessitating discontinuation of metformin.[23,24]

STRENGTHS AND LIMITATIONS

This study provides strong evidence of metformin-associated vitamin B12 reduction, supported by a clear dose-response and duration-response pattern, robust statistical correlations, and supportive graphical trends. Inclusion of a control group and peripheral smear findings further strengthens the observations. However, the cross-sectional design limits causal inference, and functional markers such as methylmalonic acid or homocysteine were not measured. Dietary factors and other confounders were not fully assessed. Despite these limitations, the consistency and magnitude of findings align with existing biological and epidemiological data, making the association compelling.

CONCLUSION

In conclusion, this study highlights a significant and clinically meaningful relationship between metformin therapy and vitamin B12 deficiency. The graded decline in B12 levels with increasing duration and dose of metformin therapy underscores the need for proactive screening and early supplementation strategies. Incorporating routine B12 monitoring into diabetes management protocols may help prevent underdiagnosed deficiency and reduce the risk of avoidable neurological morbidity.

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