

Prevalence and Clinical Predictors of Vitamin B12 Deficiency in Patients Receiving Long-Term Metformin Therapy

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ABSTRACT

Background: Metformin is a very common first-line drug for type 2 diabetes mellitus (T2DM). It works, is inexpensive and generally well tolerated, but has been linked to decreased absorption of vitamin B12 and subsequent deficiency when used for a long time. Vitamin B12 deficiency can cause symptoms such as anaemia, macrocytosis, and peripheral neuropathy and cognitive dysfunction that are potentially indistinguishable from diabetic neuropathy. The aim of this study was to establish a prevalence rate of vitamin B12 deficiency and its clinical predictors among patients on long-term metformin therapy.

Methods: This descriptive cross sectional study was carried out on the period of January 2022 to June 2023 at Department of Medicine, Dhaka Central International Medical College Hospital, Adabor, Dhaka, Bangladesh. In the present study, 85 adult patients of type 2 Diabetes mellitus (T2DM) having continued use of metformin therapy for at least 1 year from their last visit were recruited using non-probability consecutive sampling technique. Demographic parameters, diabetes duration, dose and duration of metformine, dietary pattern, use of proton pump inhibitors, haematological parameters and neurological symptoms were recorded. Vitamin B12 level <200 pg/mL was considered deficient, 200 to 300 pg/mL was considered borderline and >300 pg/mL was considered normal. Binary logistic regression was used to determine the independent predictors of B12 deficiency.

Results: The mean age of the participants was 55.6 ± 10.8 years, and 55.3% were male. Vitamin B12 deficiency was identified in 24 patients, giving an overall prevalence of 28.2%, while 25.9% had borderline vitamin B12 levels. Deficiency increased with longer metformin exposure, from 11.8% among patients treated for 1–3 years to 38.1% among those treated for more than six years. It was also more frequent among patients receiving more than 1,500 mg/day. Longer metformin duration, higher daily dose and concurrent proton-pump inhibitor use were independent predictors. Deficient patients had lower haemoglobin levels and higher frequencies of macrocytosis, anaemia and peripheral neuropathy.

Conclusion: Vitamin B12 deficiency was common among patients receiving long-term metformin therapy. The risk was particularly high among patients exposed to higher doses, longer treatment durations and concurrent acid-suppressive therapy. Periodic assessment of vitamin B12 status should be considered in high-risk patients, especially those presenting with anaemia or neuropathic symptoms.

Keywords: Vitamin B12 deficiency; metformin; type 2 diabetes mellitus; peripheral neuropathy; anaemia; prevalence.

INTRODUCTION

Type 2 diabetes mellitus is a primary chronic metabolic disease that involves chronic hyperglycaemia due to insulin resistance and a progressive decrease in the function of the pancreatic beta cells. Its long-term complications include cardiovascular disease, nephropathy, retinopathy and peripheral neuropathy. The combination of excellent effectiveness, affordability, a good safety profile and a low risk of hypoglycemia make metformin one of the most commonly used glucose-lowering medications. It is frequently employed as a first-line treatment and is frequently used in combination with other oral drugs or insulin or alone for many years [1-3].

Extended use of metformin has been linked with low levels of vitamin B12 in the blood, although clinical benefits have been noted. Proposed mechanisms are: impaired motility of intestines, bacterial overgrowth, alteration in bile-acid metabolism, and impaired calcium-dependent absorption of intrinsic factor-vitamin B12 complex in the terminal ileum [4, 5]. Since vitamin B12 levels in the liver can be maintained for many years, biochemical deficiency can only develop slowly and go clinically unnoticed. There are repeated reports of increased risk of deficiency with higher doses per day, longer periods of treatment and higher cumulative exposures [6-8].

Vitamin B12 plays an essential role in DNA synthesis, red blood cell production and maintenance of neurological function. Signs of deficiency include fatigue, pallor, macrocytic anaemia, glossitis, paraesthesias, difficulty walking, changes in cognitive function and peripheral neuropathy. In diabetes patients, neurological symptoms may be misdiagnosed as diabetic neuropathy as a result

of B12 deficiency. Furthermore, when anaemia or macrocytosis is evident, neurological problems may occur. Older age, vegetarian diet, malabsorption disorders and the concurrent use of proton-pump inhibitors or H₂-receptor blockers may further increase the risk [9-11].

Although vitamin B12 deficiency among metformin users has been reported in different populations, its prevalence varies considerably because of differences in study populations, laboratory cut-offs, dietary habits, metformin exposure and screening practices. Data from local clinical settings remain limited, and routine vitamin B12 monitoring is not consistently performed in patients receiving long-term metformin. Therefore, the present study was conducted to determine the prevalence of vitamin B12 deficiency and evaluate its clinical predictors among patients receiving prolonged metformin therapy. It also assessed the relationship of vitamin B12 deficiency with haematological abnormalities and peripheral neuropathic manifestations.

METHODOLOGY

This descriptive cross-sectional study was conducted at Department of Medicine, Dhaka Central International Medical College Hospital, Adabor, Dhaka, Bangladesh from January 2022 to June 2023 to determine the prevalence of vitamin B12 deficiency and identify its clinical predictors among patients receiving long-term metformin therapy. A total of 85 patients with type 2 diabetes mellitus were included through a non-probability consecutive sampling technique. Written informed consent was obtained from every participant after explaining the study purpose, procedures, potential benefits and confidentiality safeguards. Participants were informed that refusal to participate would not affect their routine medical care.

Patients, both males and females, who were 18 years or older, with a confirmed type 2 diabetes mellitus diagnosis and taking metformin for at least one year were eligible. Long-term metformin treatment was considered to be metformin use at least 12 months. Patients were excluded if they had a history of vitamin B12 deficient anaemia, were being treated with vitamin B12 injections or high dose oral vitamin B12, had undergone gastric or

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small intestinal surgery, or had a history of pernicious anaemia, inflammatory bowel disease, coeliac disease or other malabsorptive conditions. Patients who were pregnant, had an active malignancy, severe liver disease, end-stage kidney disease or were in an acute critical state with incomplete clinical and laboratory records were also excluded. Eligibility criteria included patient interviews, outpatient records, prescriptions and available laboratory reports.

A pre-designed structured proforma was used to collect data. The demographic variables were age, sex, BMI, place of residence, smoking status and pattern of diet. Diabetes-related data comprised duration of type 2 diabetes mellitus, glycated haemoglobin level, fasting blood glucose, Treatment regimen and documented diabetic complications. Metformin-related variables were current daily dose, duration of treatment, formulation and adherence to the treatment (use of metformin alone or in combination with other glucose-lowering medications). The daily dose of metformin was grouped as less than 1000 mg, 1000–1500 mg and over 1500 mg and duration of treatment was divided in 1–3 years, 4–6 years and more than 6 years groups. Other medications used at the same time as the PPIs were also documented: the use of H₂-receptor blockers, insulin, folate supplements, and multi-vitamins. Participants were evaluated for fatigue, weakness, glossitis, paraesthesias, numbness, burning feet, gait abnormalities and cognitive complaints, as well as impaired sensation of vibration.

Venous blood samples were taken from each participant under sterile conditions after clinical evaluation. Serum B12 levels were measured with a standard laboratory assay done at the study centre. Vitamin B12 deficiency was defined as serum vitamin B12 level less than 200 pg/mL, border line vitamin B12 level as 200–300 pg/mL, and vitamin B12 normal level as more than 300 pg/mL. A full blood count was conducted to determine haemoglobin, haematocrit, red blood cell (RBC) count, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and red cell distribution width (RDW). Anaemia was defined by the laboratory reference ranges and macrocytosis by an elevated mean corpuscular volume. Where available, glycated haemoglobin and serum creatinine were also noted. Peripheral neuropathy was diagnosed with compatible symptoms and clinical signs of decreased peripheral sensation and/or decreased vibration or position sense.

Data collected was entered and analysed in IBM SPSS Statistics 26. Continuous variables were analyzed for normality and then reported as mean $\pm$ standard deviation or median (interquartile range) depending on the normality. Categorical variables were summarised as frequencies and percentages. The prevalence of vitamin B12 deficiency was determined as the number of deficient patients divided by the total number of patients ($n = 85$) and then multiplied by 100. The independent-samples t-test or Mann-Whitney U test were used for continuous variables and the chi-square test or Fisher's exact test were used for categorical variables between patients with and without vitamin B12 deficiency. The variables that showed p values < 0.20 in the univariate analysis were included, together with clinically relevant data (age, dose of metformin, duration of the medication, dietary pattern, proton pump inhibitors) in a multivariable binary logistic regression model. The odds ratios and 95% confidence intervals were reported, and a p value < 0.05 was defined as statistically significant.

RESULTS

A total of 85 patients with type 2 diabetes mellitus who were taking long-term metformin therapy were included in the study. Participants' ages ranged from 32 to 76 years with a mean age of 55.6 ± 10.8 years. Of the total participants, 47 (55.3%) were male and 38 (44.7%) were female. The mean body mass index was 27.8 ± 4.2 kg/m². Forty-eight (56.5%) patients had hypertension, 17 (20.0%) had cardiovascular disease. Twenty-four (28.2%) participants reported taking proton-pump inhibitors.

Table 1: Demographic and Clinical Characteristics of the Participants

Variable	Frequency (%) or Mean $\pm$ SD
Age, years	55.6 $\pm$ 10.8
Male sex	47 (55.3)
Female sex	38 (44.7)
Body mass index, kg/m ²	27.8 $\pm$ 4.2
Hypertension	48 (56.5)
Cardiovascular disease	17 (20.0)
Current smoker	14 (16.5)
Proton-pump inhibitor use	24 (28.2)
Predominantly vegetarian diet	21 (24.7)
Vitamin supplementation	10 (11.8)

The duration of diabetes mellitus was 9.1 ± 4.7 years, while metformin treatment was 6.4 ± 3.1 years. Forty nine percent (42/42 patients) were taking metformin for over six years. The mean metformin dose per day was $1,486 \pm 462$ mg. Thirty-one (36.5%) participants were taking a daily dose $>1,500$ mg. Twenty-nine patients (34.1%) were treated with metformin alone, whereas 56 patients (65.9%) were taking metformin with other glucose-lowering drugs.

Table 2: Diabetes and Metformin-Treatment Characteristics

Variable	Frequency (%) or Mean $\pm$ SD
Duration of diabetes, years	9.1 $\pm$ 4.7
HbA1c, %	8.2 $\pm$ 1.4
Metformin-treatment duration, years	6.4 $\pm$ 3.1
Metformin use for 1–3 years	17 (20.0)
Metformin use for 4–6 years	26 (30.6)
Metformin use for >6 years	42 (49.4)
Daily metformin dose $<1,000$ mg	13 (15.3)
Daily metformin dose 1,000–1,500 mg	41 (48.2)
Daily metformin dose $>1,500$ mg	31 (36.5)
Metformin monotherapy	29 (34.1)
Combination therapy	56 (65.9)
Concurrent insulin therapy	19 (22.4)

The average serum vitamin B12 was 286.7 ± 131.5 pg/mL. Twenty-four patients were found to have a B12 level lower than 200 pg/mL, for an overall prevalence of 28.2% of vitamin B12 deficiency. 22 (25.9%) patients had borderline vitamin B12 levels (200–300 pg/mL), and 39 (45.9%) patients had normal vitamin B12 levels (above 300 pg/mL).

Table 3: Distribution of Serum Vitamin B12 Status

Vitamin B12 status	Frequency	Percentage
Deficient, <200 pg/mL	24	28.2
Borderline, 200–300 pg/mL	22	25.9
Normal, >300 pg/mL	39	45.9
Total	85	100.0

The duration of metformin therapy was significantly longer for patients with vitamin B12 deficiency compared with those with normal or borderline levels of vitamin B12 (8.2 ± 3.0 years versus 5.7 ± 2.8 years, $p < 0.001$). The deficient group also received a higher mean daily dose of metformin ($1,718 \pm 427$ versus $1,395 \pm 448$ mg/day, $p = 0.003$). The mean serum B12 level went down as the duration of metformin use increased, and with higher doses of the drug per day. Patients with vitamin B12 deficiency had a significantly lower mean haemoglobin level than those without (11.2 ± 1.5 g/dL vs. 12.5 ± 1.4 g/dL, $p < 0.001$). Likewise, MCV was increased in the deficient group compared to the non-deficient group (94.8 ± 7.9 fL vs. 87.1 ± 6.8 fL, $p < 0.001$). Vitamin B12 deficiency was associated with anaemia in 15 (62.5%) patients and 18 (29.5%) non-deficiency patients ($p = 0.005$). There was a statistical significance between macrocytosis in deficient and non-deficient patients (8 vs 5, $p = 0.004$). The nervous symptoms were

more common in patients with vitamin B12 deficiency. 16 (66.7%) deficient patients reported peripheral numbness or paraesthesia as compared to 20 (32.8%) non-deficient patients (p=0.005). Burning feet were reported by 13 (54.2%) and 15 (24.6%) patients, respectively (p=0.009). Peripheral neuropathy, confirmed in the clinic, was observed in 14 (58.3%) patients with vitamin B12 deficiency, and 17 (27.9%) patients without vitamin B12 deficiency (p=0.009).

Table 4: Comparison of Patients with and without Vitamin B12 Deficiency

Variable	B12 deficient n=24	Not deficient n=61	p-value
Age, years	60.1 ± 9.4	53.8 ± 10.8	0.013
Duration of diabetes, years	11.3 ± 4.8	8.2 ± 4.4	0.006
Metformin duration, years	8.2 ± 3.0	5.7 ± 2.8	<0.001
Daily metformin dose, mg	1,718 ± 427	1,395 ± 448	0.003
HbA1c, %	8.6 ± 1.5	8.0 ± 1.3	0.071
Haemoglobin, g/dL	11.2 ± 1.5	12.5 ± 1.4	<0.001
Mean corpuscular volume, fL	94.8 ± 7.9	87.1 ± 6.8	<0.001
Anaemia	15 (62.5)	18 (29.5)	0.005
Macrocytosis	8 (33.3)	5 (8.2)	0.004
Peripheral neuropathy	14 (58.3)	17 (27.9)	0.009
Proton-pump inhibitor use	11 (45.8)	13 (21.3)	0.023
Predominantly vegetarian diet	10 (41.7)	11 (18.0)	0.021

Vitamin B12 deficiency was more common in the highest duration of metformin (P=0.001). Deficiency was found in 2 of 17 patients (11.8%) treated for 1–3 years, 6 of 26 patients (23.1%) treated for 4–6 years and 16 of 42 patients (38.1%) treated for more than six years (p=0.041). Similarly, deficiency was present in 1 of 13 patients (7.7%) receiving less than 1,000 mg/day, 9 of 41 patients (22.0%) receiving 1,000–1,500 mg/day and 14 of 31 patients (45.2%) receiving more than 1,500 mg/day (p=0.008).

Table 5: Vitamin B12 Deficiency According to Metformin Duration and Dose

Metformin Exposure	Vitamin B12 Deficiency	p-value
Duration of Treatment	1–3 years	2/17 (11.8%)
	4–6 years	6/26 (23.1%)
	>6 years	16/42 (38.1%)
Daily Dose	<1,000 mg/day	1/13 (7.7%)
	1,000–1,500 mg/day	9/41 (22.0%)
	>1,500 mg/day	14/31 (45.2%)

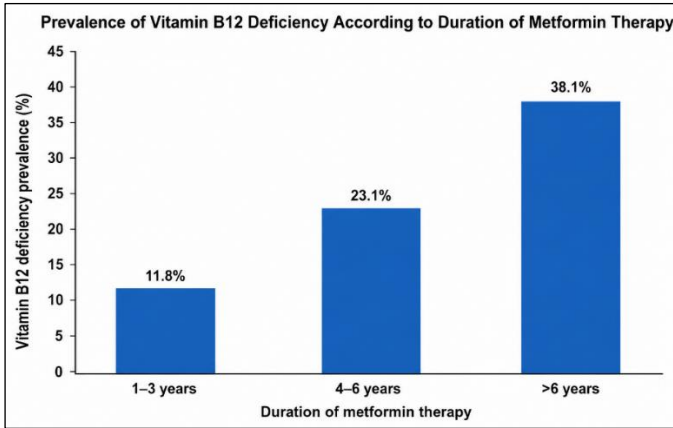
Variables with clinically significant associations in the univariate analysis were included in a multivariable binary logistic regression model. After adjustment for age, duration of diabetes, dietary pattern and proton-pump inhibitor use, metformin therapy lasting more than six years remained independently associated with vitamin B12 deficiency (adjusted odds ratio [AOR] 3.42, 95% confidence interval [CI] 1.11–10.56; p=0.032). A daily metformin dose greater than 1,500 mg was also an independent predictor of deficiency (AOR 4.08, 95% CI 1.27–13.12; p=0.018). The odds of having a vitamin B12 deficiency were nearly 3 times greater among those taking PPIs (AOR 3.01, 95% CI 1.02–8.91; p=0.046). There was a modest association with increasing age with the odds of deficiency increasing by around 5% with each year of age (AOR 1.05, 95% CI 1.00–1.10; p=0.048).

Table 6: Multivariable Logistic Regression Analysis of Predictors of Vitamin B12 Deficiency

Predictor	Adjusted odds ratio	95% confidence interval	p-value
Age, per one-year increase	1.05	1.00–1.10	0.048
Diabetes duration >10 years	1.84	0.65–5.24	0.251
Metformin duration >6 years	3.42	1.11–10.56	0.032
Metformin dose >1,500 mg/day	4.08	1.27–13.12	0.018
Proton-pump inhibitor use	3.01	1.02–8.91	0.046
Predominantly vegetarian diet	2.31	0.78–6.86	0.132
HbA1c ≥8.0%	1.39	0.49–3.96	0.536

Overall, approximately one in every four patients receiving long-term metformin therapy had biochemical vitamin B12 deficiency. The occurrence of deficiency was particularly high among older patients, individuals receiving higher metformin doses, those treated for more than six years and patients using proton-pump inhibitors. Vitamin B12 deficiency was also accompanied by a higher frequency of anaemia, macrocytosis and peripheral neuropathic manifestations.

Figure 1: Prevalence of Vitamin B12 Deficiency According to the Duration of Metformin Therapy.



The prevalence increased from 11.8% among patients treated for 1–3 years to 23.1% among those treated for 4–6 years and 38.1% among those receiving metformin for more than 6 years.

DISCUSSION

The present study found that 24 of 85 patients receiving long-term metformin therapy had vitamin B12 deficiency, resulting in an overall prevalence of 28.2%. A further 25.9% had borderline vitamin B12 concentrations, indicating that more than half of the participants had either deficient or potentially inadequate vitamin B12 status. These findings support the established association between prolonged metformin use and reduced serum vitamin B12 levels. Yang et al., in a meta-analysis of 31 studies, reported that metformin users had approximately twice the risk of vitamin B12 deficiency compared with patients not receiving metformin. Similarly, Chapman et al. found consistently lower vitamin B12 concentrations among metformin-treated patients across both observational studies and clinical trials. Variations in reported prevalence between studies may be related to differences in the definition of deficiency, metformin exposure, dietary habits, participant age, laboratory methods and the presence of gastrointestinal or nutritional disorders [12–14]. There was a significant association between metformin treatment duration with VD. The prevalence progressed from 11.8% in patients treated for 1-3 years to 23.1% in patients treated for four to six years and 38.1% in patients who were treated with metformin for more than six years. Treatment for over 6 years was an independent predictor of deficiency even when other clinical factors were taken into account. These results are similar to the Diabetes Prevention Program Outcomes Study, which found a greater risk of vitamin B12 deficiency with each year of metformin use. De Jager et al. also demonstrated in a placebo-controlled, randomised long-term study, that metformin treatment led to a sustained decrease in vitamin B12 levels and increased the prevalence of biochemical vitamin B12 deficiency. The progressive decrease could be due to the fact that some vitamin B12 absorption is interfered with over time, while the body continues to use up more of the vitamin B12 stored in the liver [15, 16] Another significant predictor was the dose of metformin per day. Among those consuming less than 1000 mg/day, 7.7% had vitamin B12 deficiency vs 45.2% of those consuming over 1500 mg/day. Multivariable analysis found an odds ratio of 4.0 for deficiency with a daily dose > 1,500 mg. Another study by Alharbi

et al. showed that lower levels of vitamin B12 were significantly related to higher metformin doses and longer duration of treatment (more than 4 years). Shivappresad et al. suggest the use of a drug use index for metformin that combines dosage and duration of treatment, and found increased exposure to metformin is correlated with decreased vitamin B12. The findings indicate that the total exposure to metformin, rather than either dosage or duration alone, might be more useful. Vitamin B12 is thought to be absorbed in the terminal ileum via a calcium-dependent process involving the binding of intrinsic factor to B12, and as a result of altered intestinal motility, bacterial overgrowth and interference with this process, the absorption of vitamin B12 is thought to be decreased by metformin [6, 17, 18].

The vitamin B12 deficient patients in the present study had lower level of haemoglobin, higher MCV, and higher percentages of anaemia, macrocytosis and peripheral neuropathy. The deficient group also had more cases of paraesthesias and numbness and burning feet. The clinical significance of these results is that neurological manifestations of B12 deficiency can closely mimic and/or deteriorate diabetic peripheral neuropathy even without the presence of significant macrocytic anaemia. Roy et al. found a correlation between peripheral neuropathy severity and vitamin B12 levels with metformin use. Yang's meta-analysis however, did not find consistent evidence of association between metformin and anaemia or neuropathy, due to the heterogeneity of the methods used and patient populations. Importantly, one year of oral methylcobalamin supplementation showed to improve vitamin B12 status, nerve-conduction parameters, pain and quality of life in metformin-treated patients with diabetic neuropathy and low vitamin B12 status in a 2021 randomised controlled trial (RCT) conducted by Didangelos et al. [19, 20]. Patients with vitamin B12 deficiency also were more likely to use proton-pump inhibitors, be older, and be primarily vegetarian. The use of PPIs decreases gastric acid secretion, which decreases the amount of vitamin B12 released from food and can increase the risk of deficiency, and the use of metformin decreases the amount of vitamin B12 absorbed from food, which may further increase the risk of deficiency. Miller concluded that metformin, proton-pump inhibitors and H₂-receptor antagonists all affect circulating levels of vitamin B12 and advised for monitoring in patients that develop abnormal biomarkers or compatible clinical features. Based on the present findings, it is recommended to routinely monitor vitamin B12 levels, especially in older patients, in those

receiving higher doses of metformin, patients treated for several years, patients taking acid-suppression medications, and patients with unexplained anaemia or neuropathic symptoms. However, the study was conducted in a single centre with a relatively small number of participants and without a non-metformin control group as well as not measuring methylmalonic acid or homocysteine to confirm the levels of vitamin B12. There is a need for larger prospective multicentre studies in order to establish appropriate screening timings and whether or not routine supplementation is effective in preventing neurological and haematological complications.

CONCLUSION

Vitamin B12 deficiency was common among patients receiving long-term metformin therapy, affecting more than one-quarter of the study population. Longer treatment duration, a daily metformin dose above 1,500 mg and concurrent proton-pump inhibitor use were identified as important independent predictors. Vitamin B12-deficient patients also had higher frequencies of anaemia, macrocytosis and peripheral neuropathic manifestations. Periodic assessment of vitamin B12 status should therefore be considered in patients receiving prolonged or high-dose metformin, particularly when anaemia, paraesthesia, numbness or other neurological symptoms are present. Early detection and appropriate supplementation may help prevent potentially reversible haematological and neurological complications.

Authors' Contribution

AS, MS: Concept & study design, data collection and drafting of the manuscript.

AS: Data entry, statistical analysis, interpretation of the results.

MGS: Manuscript editing and critical revision of the manuscript.

All authors approved the final version of the manuscript to be published.

Conflict of Interest

The authors declared no conflict of interest.

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Data Availability

Data is available with authors and can be provided on request.

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