Journal of MedVerse Research & Practice
nurexus.com

Prevalence of Vitamin B12 Deficiency Among Type 2 Diabetes Patients on Metformin Therapy

Dr. Vidhyavathi[1], Dr. Suriya[2]
Postgraduate, Associate Professor
Department of General Medicine, Government Medical College, Indore, Madhya Pradesh.
Email ID: vidhyavathi555@gmail.com

Submission Date: 27.04.2025	Accepted Date: 23.05.2025	Published Date: 31.05.2025
DOI: 10.65188/nurexus.1024		

Abstract

Introduction: Type 2 diabetes mellitus (T2DM) is increasingly prevalent worldwide, with metformin widely prescribed as the first-line therapy due to its efficacy and safety. However, prolonged use of metformin has been linked to vitamin B12 deficiency, a concern due to its potential to cause neurological and haematological complications, particularly in diabetic patients. This study aims to assess the prevalence of vitamin B12 deficiency among T2DM patients on metformin and examine its association with dosage and duration of therapy.

Materials & Methods: A descriptive cross-sectional study was conducted over 18 months (May 2023 to November 2024) at the Government Medical College, Indore. 150 adult T2DM patients on metformin for at least six months were selected via simple random sampling. Patients with confounding factors like strict vegetarian diet, B12 supplementation, or chronic diseases affecting absorption were excluded. Serum vitamin B12 levels were assessed using chemiluminescent immunoassay and classified as deficient (<200 pg/mL), borderline (200–300 pg/mL), or normal (>300 pg/mL). Data were analysed to determine the prevalence and associations with metformin dose and duration.

Results: Among 150 patients, those on 1000 mg metformin had significantly lower mean serum vitamin B12 levels (312.47 ± 223.97 pg/mL) compared to those on 500 mg (406.75 ± 309.79 pg/mL) ($p = 0.031$). Vitamin B12 deficiency was observed in 30% of participants, with a higher prevalence in the 1000 mg group (37.3%) versus the 500 mg group (22.7%) ($p = 0.027$). Deficiency rates also increased with treatment duration: 15.6% (6 months–1 year), 25.9% (1–3 years), and 46.2% (>3 years), showing a significant trend ($p = 0.004$). Glycaemic control remained similar across all groups.

Conclusion: The study demonstrates a clear association between both higher metformin doses and longer duration of use with lower vitamin B12 levels in T2DM patients. Despite effective glycaemic control, many patients developed vitamin B12 deficiency, reinforcing the need for routine monitoring and early intervention in long-term or high-dose metformin users.

Keywords: Type 2 diabetes mellitus, Metformin, Vitamin B12 deficiency, Dose-related effect, Treatment duration, Screening, Cross-sectional study.

Introduction

The global rise in type 2 diabetes mellitus (T2DM) presents a major public health concern, largely attributed to lifestyle shifts such as reduced physical activity, poor dietary habits, and an increasingly aging population [1,2,3]. Current statistics estimate that over 537 million individuals are living with diabetes worldwide, a number expected to increase substantially shortly. Among available treatment options,

metformin continues to be the first-line medication due to its well-documented ability to control blood glucose, its neutral effect on body weight, and its cardiovascular safety profile [4,5].

However, long-term administration of metformin has been associated with certain adverse effects, one of the most prominent being a reduction in vitamin B12 (cobalamin) levels. Vitamin B12 plays a critical role in maintaining neurological integrity, supporting red blood cell production, and facilitating DNA synthesis [6,7,8]. A deficiency in this essential micronutrient may lead to hematologic abnormalities such as megaloblastic anaemia, and neurological disturbances, including peripheral neuropathy, cognitive decline, and spinal cord degeneration. These complications can be particularly problematic for diabetic individuals who are already prone to nerve damage [9,10].

The proposed mechanism behind metformin-induced B12 deficiency suggests that the drug interferes with the absorption of vitamin B12 in the terminal ileum, particularly by affecting calcium-dependent pathways [11,12]. Research indicates that both the dosage and duration of metformin therapy are key factors influencing the likelihood of B12 depletion — higher daily doses and longer treatment periods are linked to a greater risk [13,14].

Several studies have documented a wide range in the prevalence of vitamin B12 deficiency among T2DM patients on metformin, with estimates ranging from 6% to as high as 30%. These variations are often influenced by patient demographics, treatment regimens, and healthcare practices [15-18]. Despite this, consistent screening for vitamin B12 levels in metformin-treated individuals remains uncommon in many clinical settings. Recognizing the implications, the American Diabetes Association (ADA) now recommends periodic evaluation of B12 levels, especially for patients exhibiting symptoms such as anaemia or peripheral neuropathy [19-22].

Given the widespread use of metformin and the serious implications of undetected B12 deficiency, it is critical to evaluate its prevalence among diabetic patients receiving this therapy [23-25]. This study aims to assess the frequency of vitamin B12 deficiency in individuals with T2DM who are on metformin, thereby underscoring the importance of proactive screening and early management to prevent potential complications.

Materials & Methods

This descriptive cross-sectional study was conducted over 18 months, from May 1, 2023, to November 1, 2024, at the Departments of General Medicine and Endocrinology, Government Medical College, Indore, Madhya Pradesh, to assess the prevalence of vitamin B12 deficiency among patients with type 2 diabetes mellitus on long-term metformin therapy. The study population included adult patients aged 18 years and above who had been diagnosed with type 2 diabetes mellitus and had been on metformin therapy for at least six months.

A total of 150 eligible participants were selected using simple random sampling from outpatient department records. Patients with type 1 diabetes, a history of bariatric surgery or gastrectomy, pregnancy, chronic liver or kidney disease, inflammatory bowel disease, a strict vegetarian diet, or prior vitamin B12 supplementation were excluded. Detailed demographic and clinical information, including age, sex, duration of diabetes, metformin dose and duration, comorbidities, and concurrent medications, was collected from both electronic and physical medical records. Serum vitamin B12 levels were measured using chemiluminescent immunoassay on an automated analyser in the hospital's central laboratory. Participants were classified as vitamin B12-deficient or normal based on standard reference ranges, and the prevalence of deficiency was calculated.

The study protocol was approved by the Institutional Ethics Committee of Government Medical College,

Indore and written informed consent was obtained from all participants. Confidentiality was maintained throughout, and all procedures adhered to the principles of the Declaration of Helsinki.

Ethical approval was obtained from the Institutional Ethics Committee of Government Medical College, Indore, Madhya Pradesh (Ref No: IEC/GMC-IND/2024/00638). All participants were provided with a detailed Participant Information Sheet, and written informed consent was obtained prior to their inclusion in the study.

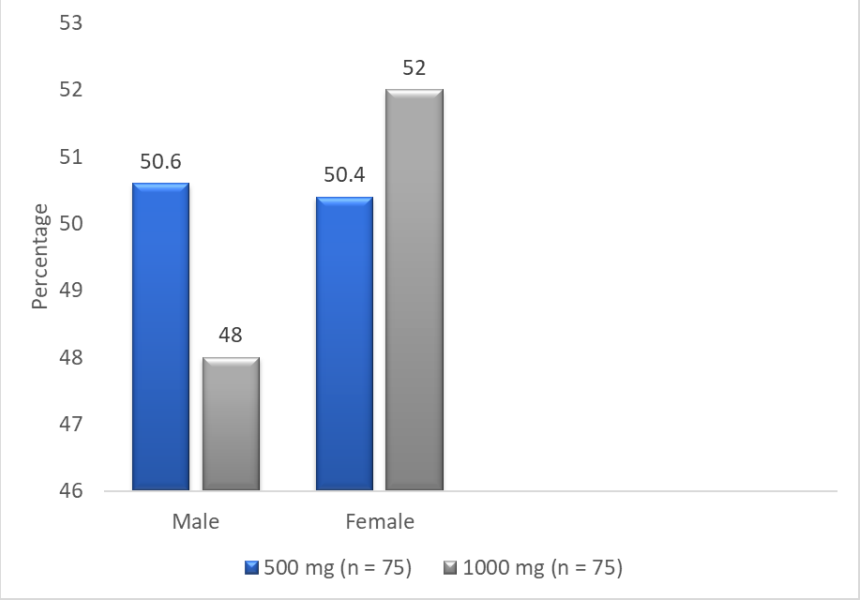
Results

Table 1. Demographic Details of the Patients (n = 150)

Parameter	500 mg (n = 75)	1000 mg (n = 75)
Gender	Male: 38 Female: 37	Male: 36 Female: 39
Age (years)	60.31 ± 5.12	60.74 ± 4.29
Height (cm)	168.88 ± 7.31	169.32 ± 7.48
Weight (kg)	77.42 ± 6.19	77.06 ± 5.10
Smoking	Yes: 42 No: 33	Yes: 35 No: 40

The demographic comparison between the two metformin dosage groups reveals a balanced gender distribution, with the 1000 mg group comprising 36 males (48.0%) and 39 females (52.0%). This near-equal gender ratio minimizes the risk of gender-related bias in comparing outcomes. The average age of participants was also similar across both groups—60.31 ± 5.12 years for the 500 mg group and 60.74 ± 4.29 years for the 1000 mg group—indicating comparable age-related influences on vitamin B12 metabolism and absorption. In terms of physical measurements, participants in the 500 mg group had an average height of 168.88 ± 7.31 cm and weight of 77.42 ± 6.19 kg, while those in the 1000 mg group measured 169.32 ± 7.48 cm in height and weighed 77.06 ± 5.10 kg. These closely aligned anthropometric values suggest minimal variability that could affect metabolic outcomes. Regarding smoking habits, 56.0% of the 500 mg group were smokers compared to 46.7% in the 1000 mg group. Although a slightly higher proportion of smokers was observed in the lower dose group, the difference is marginal and unlikely to significantly influence the comparative results.

Figure 1: Patient gender distribution



Among the participants, 75 patients received 500 mg of the medication and 75 received 1000 mg. In the 500 mg group, 50.6% were male and 50.4% were female, while in the 1000 mg group, 48% were male and 52% were female, showing a comparable gender distribution between the two groups**.s**

Table 2. Comparative Laboratory Parameters (n = 150)

Parameter	500 mg (Mean ± SD)	1000 mg (Mean ± SD)	p-value
RBS (mg/dL)	200.51 ± 10.17	200.18 ± 8.36	0.827
HbA1c (%)	8.19 ± 0.43	8.14 ± 0.29	0.364
Vitamin B12 (pg/mL)	406.75 ± 309.79	312.47 ± 223.97	**0.031**

Both groups showed comparable glycemic control, with no significant difference in random blood sugar (p = 0.827) or HbA1c levels (p = 0.364). However, vitamin B12 levels were significantly lower in the 1000 mg group compared to the 500 mg group (p = 0.031), indicating a potential dose-related impact of metformin on B12 status.

Table 3. Vitamin B12 Deficiency Status by Metformin Dosage Group

Vitamin B12 Status	500 mg (n = 75)	1000 mg (n = 75)	p-value
Deficient (<200 pg/mL)	17 (22.7%)	28 (37.3%)	**0.027**
Borderline (200–300 pg/mL)	21 (28.0%)	26 (34.7%)	
Normal (>300 pg/mL)	37 (49.3%)	21 (28.0%)	

Among the patients taking 500 mg of metformin, 22.7% were vitamin B12 deficient, 28.0% had borderline levels, and 49.3% had normal levels. In contrast, the 1000 mg group showed a higher deficiency rate of 37.3%, with 34.7% borderline and only 28.0% normal levels. Overall, 30% of the total 150 patients were deficient.

Table 4. Duration of Metformin Use and Vitamin B12 Deficiency

Duration of Metformin Use	Deficient (<200 pg/mL)	Non-deficient (≥200 pg/mL)	Total	p-value
6 months to 1 year	7 (15.6%)	38 (84.4%)	45	**0.004**
1 to 3 years	14 (25.9%)	40 (74.1%)	54	
>3 years	24 (46.2%)	28 (53.8%)	52	

The prevalence of vitamin B12 deficiency increased with the duration of metformin use: 15.6% in patients treated for 6 months to 1 year, 25.9% for 1–3 years, and 46.2% for over 3 years.

Discussion

This study highlights a significant association between both the dose and duration of metformin therapy and serum vitamin B12 levels in patients with type 2 diabetes mellitus. Our findings indicate that individuals receiving higher daily doses of metformin—specifically 1000 mg—had considerably lower mean vitamin B12 concentrations compared to those on a 500 mg dose. Additionally, a larger proportion of patients on the higher dose were vitamin B12 deficient, and this difference was statistically significant. These observations align with previous literature, which suggests a dose-related impact of metformin on vitamin B12 absorption. For instance, de Jager et al [13] reported that individuals taking more than 1 gram per day of metformin had a greater chance of developing B12 deficiency. Similarly, Aroda et al [21] noted that both the cumulative dose and extended use of metformin increase the risk of this deficiency.

We also observed a progressive decline in vitamin B12 levels as the duration of metformin use increased. The percentage of patients with B12 deficiency rose from 15.6% among those using metformin for less than a year, to 46.2% in those who had been on the drug for more than three years. This trend was statistically significant and supports earlier evidence suggesting that long-term exposure to metformin can

impair B12 absorption over time. Ahmed et al [22], in a meta-analysis, and Tomkin and Kelly et al [23] in their clinical review, have similarly highlighted this long-term risk and advocated for regular monitoring in chronic users.

Interestingly, while vitamin B12 levels declined with higher doses and longer use of metformin, glycaemic parameters such as RBS and HbA1c remained comparable across groups. This implies that although metformin continues to control blood glucose effectively, its adverse effect on B12 status may go unnoticed unless actively monitored. Reinstatler et al [24] also found no direct link between vitamin B12 levels and glycaemic outcomes in metformin-treated individuals.

The proposed mechanism behind this deficiency involves metformin's interference with calcium-dependent uptake of the B12-intrinsic factor complex in the terminal ileum (Bauman et al [6,25]; Adams et al [11]). This disruption becomes more pronounced over time, especially with increased dosage, ultimately reducing the body's ability to maintain adequate vitamin B12 stores. Taken together, these findings underscore the importance of incorporating routine screening for vitamin B12 levels in patients on long-term or high-dose metformin therapy. Early detection and timely supplementation may prevent the neurological and haematological complications associated with untreated deficiency.

Limitations: This study's cross-sectional design limits its ability to establish causality or monitor changes in B12 levels over time. Future longitudinal research involving larger sample sizes is needed to further clarify the timeline and clinical consequences of metformin-associated vitamin B12 deficiency and to assess the impact of preventive strategies.

Conclusion

Higher metformin doses and longer treatment durations were significantly associated with lower vitamin B12 levels in T2DM patients, despite similar glycaemic control. These results support the need for regular B12 screening in long-term or high-dose metformin users to prevent deficiency-related complications.

Conflict of Interest: Nil

Reference

1. World Health Organization. Global Report on Diabetes. Geneva: WHO; 2016.
2. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature*. 2001;414(6865):782–787.
3. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels: IDF; 2021.
4. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm. *Diabetes Care*. 2009;32(1):193–203.
5. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in T2DM, 2015 update. *Diabetes Care*. 2015;38(1):140–149.
6. Bauman WA, Shaw S, Jayatilleke E, et al. Increased intake of calcium reverses metformin-induced vitamin B12 malabsorption. *Diabetes Care*. 2000;23(9):1227–1231.
7. O'Leary F, Samman S. Vitamin B12 in health and disease. *Nutrients*. 2010;2(3):299–316.
8. Lindenbaum J, Healton EB, Savage DG, et al. Neuropsychiatric disorders caused by cobalamin deficiency. *N Engl J Med*. 1988;318(26):1720–1728.
9. Healton EB, Savage DG, Brust JC, et al. Neurologic aspects of cobalamin deficiency. *Medicine (Baltimore)*. 1991;70(4):229–245.
10. Sun H, Luo J, Jiang Y, et al. Vitamin B12 deficiency neuropathy: a clinical and electrophysiological retrospective study. *Clin Neurol Neurosurg*. 2018;173:1–4.
11. Adams JF, Clark JS, Ireland JT, et al. Malabsorption of vitamin B12 during biguanide therapy. *Diabetologia*. 1983;24(1):16–18.

12. Tomkin GH, Hadden DR, Weaver JA, et al. Vitamin B12 status of diabetic patients on long-term biguanide therapy. *BMJ*. 1971;2(5763):685–687.
13. de Jager J, Kooy A, Lehert P, et al. Long-term treatment with metformin and risk of vitamin B12 deficiency. *BMJ*. 2010;340:c2181.
14. Reinstatler L, Qi YP, Williamson RS, et al. Association of biochemical B12 deficiency with metformin therapy and diabetes. *Diabetes Care*. 2012;35(2):327–333.
15. Ting RZ, Szeto CC, Chan MH, et al. Risk factors of vitamin B12 deficiency in metformin-treated patients. *Arch Intern Med*. 2006;166(18):1975–1979.
16. Ahmed MA, Muntingh G, Rheeder P. Vitamin B12 deficiency in metformin-treated type-2 diabetes patients. *S Afr Med J*. 2016;106(4):384–387.
17. Nervo M, Lubini A, Raimundo FV, et al. Vitamin B12 in metformin-treated diabetic patients: a cross-sectional study. *Rev Assoc Med Bras*. 2011;57(1):46–49.
18. Pflipsen MC, Oh RC, Saguil A, et al. The prevalence of vitamin B12 deficiency in patients with type 2 diabetes. *J Am Board Fam Med*. 2009;22(5):528–534.
19. American Diabetes Association. Standards of Medical Care in Diabetes—2024. *Diabetes Care*. 2024;47(Supplement_1):S1–S290.
20. de Jager J, Kooy A, Lehert P, et al. Long-term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo-controlled trial. *BMJ*. 2010;340:c2181. doi:10.1136/bmj.c2181
21. Aroda VR, Edelstein SL, Goldberg RB, et al. Long-term Metformin Use and Vitamin B12 Deficiency in the Diabetes Prevention Program Outcomes Study. *J Clin Endocrinol Metab*. 2016;101(4):1754-1761. doi:10.1210/jc.2015-4068
22. Ahmed MA, Habib A, Abu-Sinna G, et al. Metformin therapy and vitamin B12 deficiency: A systematic review and meta-analysis. *Diabetes Metab Syndr*. 2019;13(3):2543-2553. doi:10.1016/j.dsx.2019.05.005
23. Tomkin GH, Kelly C. Metformin use and vitamin B12 deficiency. *Br J Diabetes Vasc Dis*. 2017;17(4):233-236. doi:10.1177/1474651417725653
24. Reinstatler L, Qi YP, Williamson RS, et al. Association of biochemical B12 deficiency with metformin therapy and vitamin B12 supplements: the National Health and Nutrition Examination Survey, 1999-2006. *Diabetes Care*. 2012;35(2):327-333. doi:10.2337/dc11-1582
25. Bauman WA, Shaw S, Jayatilleke E, et al. Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. *Diabetes Care*. 2000;23(9):1227-1231. doi:10.2337/diacare.23.9.1227.