VIA MEDICA
EDITORIAL
ISSN 2450–7458
e-ISSN 2450–8187

Gurusha Bahl[1], Md Sadique Hussain[1], Nikita Saraswat[1], Mohit Agrawal[2]
[1]School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan 302017, India
[2]Department of Pharmacology, School of Medical and Allied Sciences, K.R. Mangalam University, Gurugram 122103, India

Beyond Diabetes Management: Unraveling Metformin's Long-Term Effects on Vitamin B12

Introduction

The use of metformin has been associated with potential vitamin B12 malabsorption and deficiency, which can exacerbate distal symmetrical, autonomic, and cardiac neuropathy in diabetic patients. Numerous observational studies and meta-analyses have highlighted a significant association between metformin use and vitamin B12 deficiency [1, 2]. Prolonged and high-dose metformin treatment has been shown to have an inverse relationship with vitamin B12 levels [3]. Patients undergoing metformin treatment exhibit reduced B12 absorption, resulting in decreased serum total vitamin B12 and transcobalamin II (TCII-B12 levels). This outcome is attributed to a calcium-dependent ileal membrane antagonism, which can be counteracted through calcium supplementation [4]. Based on these findings, it is highly recommended that individuals using metformin, especially vegetarians, given the scarcity of Vitamin B12 in plant based diets [5], and those undergoing treatment for over 5 years, undergo routine monitoring of their vitamin B12 levels. This precaution is essential because prolonged metformin use may deplete hepatic vitamin B12 reserves [1].

Address for correspondence:
Mr. Md Sadique Hussain, Assistant Professor
School of Pharmaceutical Sciences, Jaipur National University,
Jaipur, Rajasthan, 302017, India
e-mail: sadiquehussain007@gmail.com
Clinical Diabetology 2023, 12; 5: 279–282
DOI: 10.5603/cd.97473
Received: 18.09.2023 Accepted: 27.09.2023
Early publication date: 12.10.2023

Mechanism of long-term metformin--induced vitamin B12 deficiency

The precise mechanism by which metformin induces vitamin B12 deficiency remains incompletely understood. However, a plausible explanation revolves around metformin's potential interference with calcium-dependent membrane functions in the terminal ileum, where vitamin B12-intrinsic factor absorption takes place. This absorption process relies on the calcium-dependent uptake of the B12-intrinsic factor complex by ileal cell membrane receptors, and metformin has shown the ability to affect calcium-dependent membrane functions. One of the clearest mechanisms for reversing metformin-induced B12 deficiency involves the calcium administration. The uptake of the vitamin B12-intrinsic factor complex by ileal cell surface receptors naturally relies on luminal calcium concentration to facilitate this vital process. Metformin is thought to introduce a positive charge to the membrane's surface, possibly displacing divalent cations such as calcium. This disturbance in calcium availability, attributed to metformin's activity, consequently disrupts the calcium-dependent mechanism responsible for vitamin B12 absorption [6].

Initial clinical observations suggested the presence of vitamin B12 malabsorption in individuals receiving prolonged metformin therapy (Fig. 1) [7]. Subsequent investigations have confirmed these observations by demonstrating that metformin can lead to a significant reduction in serum vitamin B12 levels, ranging from 14% to 30%. Notably, patients displaying vitamin B12 deficiency tend to have a lengthier history of metformin usage (≥ 4 years) and were prescribed higher daily doses

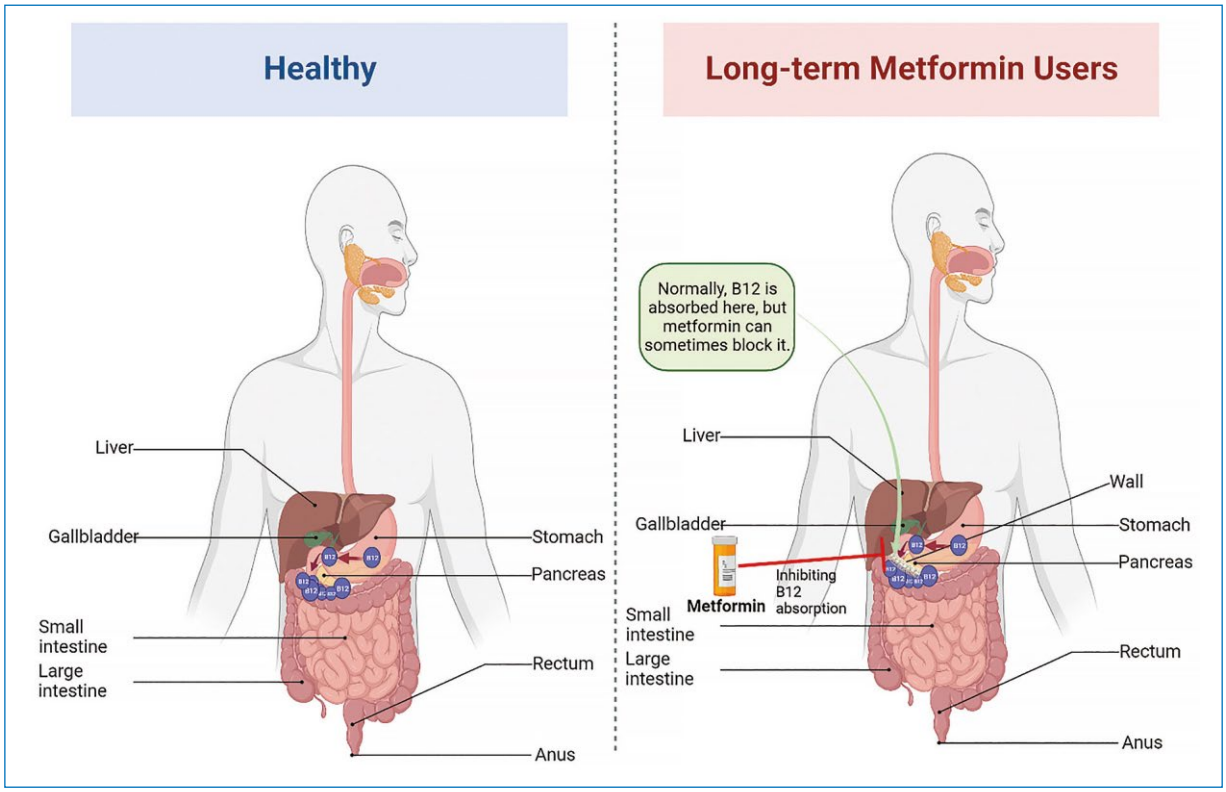

Figure 1. Absorption of Vitamin B12 in Healthy Individuals and Long-Term Metformin Users
In long-term metformin users, metformin induces a wall like structure which blocks the absorption of Vitamin B12 from foods

of metformin (> 1000 mg) compared to non-deficient patients [8].

From a clinical standpoint, vitamin B12 deficiency can present as changes in mental function, megaloblastic anemia, and neurological impairments. Notably, the symptoms of diabetic neuropathy, including paresthesias and compromised vibration sensation and proprioception, may overlap with those of peripheral neuropathy resulting from vitamin B12 deficiency. Consequently, peripheral neuropathy due to vitamin B12 deficiency can be mistaken for diabetic peripheral neuropathy or potentially exacerbate its symptoms. Timely identification and intervention through cobalamin supplementation can halt the progression of neurological damage associated with vitamin B12 deficiency. However, when misdiagnosed as diabetic neuropathy, this condition may lead to irreversible neurological impairments. It is worth noting that factors such as the daily dosage of metformin and the duration of treatment consistently emerged as significant risk factors for vitamin B12 deficiency [9].

Vitamin B12 deficiency can result in a diverse array of symptoms encompassing neurological manifestations such as tingling and numbness in the extremities, difficulties in maintaining balance, cognitive distress, including depression, confusion, dementia, compromised memory, as well as discomfort in the mouth or tongue. Additional indications might include fatigue, muscular weakness, constipation, diminished appetite, and weight loss [10]. Importantly, the symptoms associated with vitamin B12 deficiency tend to be broad and nonspecific, possibly not correlating with anemia or an elevated mean corpuscular volume [11]. It is noteworthy that these manifestations of vitamin B12 deficiency hold the potential for reversal with vitamin B12 supplementation [9, 11].

Left untreated, vitamin B12 deficiency can lead to severe and irreversible neurological impairment (Fig. 2), including peripheral neuropathy, cognitive decline, dementia, and psychiatric conditions like depression [12]. Additionally, vitamin B12 deficiency can result in hematologic anomalies, including the development of megaloblastic anemia [13]. In infants, neglecting vitamin B12 deficiency can contribute to developmental setbacks, movement irregularities, and failure to thrive. Importantly, symptoms associated with vitamin B12 deficiency have the potential to be reversed through the administration of vitamin B12 supplements [14, 15]. Therefore, a prompt diagnosis and effective management of vitamin B12 deficiency are of utmost importance in preventing prolonged complications.

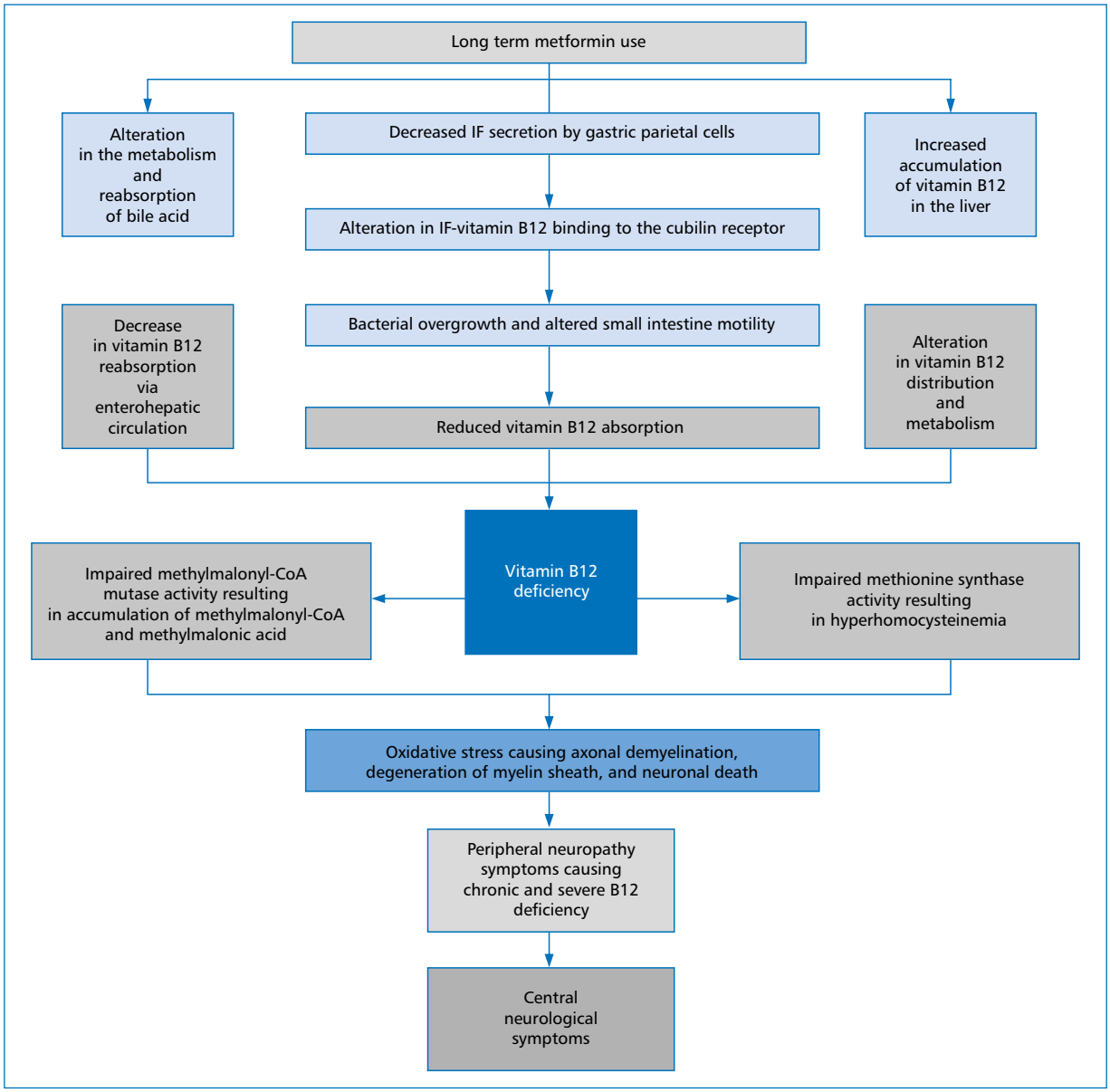

Figure 2. Exploring the Link: Long-term Metformin-Induced Vitamin B12 Deficiency

In summary, the link between metformin use and vitamin B12 deficiency, with potential implication for neuropathy and overall health, is a significant concern. Prolonged metformin therapy primarily impacts vitamin B12 levels by interfering with calcium-dependent processes in the ileal membrane. Calcium supplementation may potentially alleviate this issue. Clinical observations have indicated that a significant proportion of individuals on long-term metformin treatment may experience vitamin B12 deficiency, especially those with extended treatment durations and higher daily doses. Vitamin B12 deficiency can present with various neurological and general symptoms, sometimes resembling diabetic neuropathy. This underscores the importance of timely detection and intervention to prevent permanent neurological damage. It is important to note that the symptoms associated with vitamin B12 deficiency are multifaceted and non-specific, which can complicate diagnosis. Nevertheless, appropriate vitamin B12 supplementation typically leads to the reversal of these symptoms. Given these insights, it is highly advisable to regularly monitor vitamin B12 levels in all metformin users, particularly vegetarians, and those undergoing treatment for more than five years. This proactive approach can help prevent the depletion of hepatic vitamin B12 stores and mitigate potential long-term complications.

Clinicians must maintain a high level of awareness since vitamin B12 deficiency can manifest with

symptoms similar to diabetic neuropathy, emphasizing the importance of timely diagnosis and intervention. Additionally, factors including the daily metformin dosage and treatment duration significantly contribute to the risk of deficiency. The symptoms of vitamin B12 deficiency are wide-ranging, spanning neurological, cognitive, and physical aspects, all of which can be alleviated through cobalamin supplementation. Failure to promptly diagnose and treat this deficiency can result in severe and irreversible neurological damage, hematological irregularities, and developmental problems in infants.

Further research is imperative for a comprehensive understanding of the precise mechanism through which metformin hinders vitamin B12 absorption, providing insights for tailored interventions. Investigations should also focus on determining the optimal and cost-effective frequency for monitoring vitamin B12 levels in metformin users. Furthermore, researchers ought to explore genetic and dietary variables that may make individuals more susceptible to metformin-induced B12 deficiency, facilitating the creation of personalized preventative approaches. Equally important is the development of standardized treatment guidelines for addressing vitamin B12 deficiency in metformin users, considering the appropriate dosage and duration of supplementation.

Article information

Funding

None.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Bell DSH. Metformin-induced vitamin B12 deficiency can cause or worsen distal symmetrical, autonomic and cardiac neuropathy in the patient with diabetes. Diabetes Obes Metab. 2022; 24(8): 1423–1428, doi: 10.1111/dom.14734, indexed in Pubmed: 35491956.
2. Alhaji JH. Vitamin B12 Deficiency in Patients with Diabetes on Metformin: Arab Countries. Nutrients. 2022; 14(10), doi: 10.3390/nu14102046, indexed in Pubmed: 35631186.
3. Infante M, Leoni M, Caprio M, et al. Long-term metformin therapy and vitamin B12 deficiency: An association to bear in mind. World J Diabetes. 2021; 12(7): 916–931, doi: 10.4239/wjd.v12.i7.916, indexed in Pubmed: 34326945.
4. 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, indexed in Pubmed: 10977010.
5. Niklewicz A, Smith AD, Smith A, et al. CluB-12. The importance of vitamin B for individuals choosing plant-based diets. Eur J Nutr. 2023; 62(3): 1551–1559, doi: 10.1007/s00394-022-03025-4, indexed in Pubmed: 36469110.
6. Out M, Kooy A, Lehert P, et al. Long-term treatment with metformin in type 2 diabetes and methylmalonic acid: Post hoc analysis of a randomized controlled 4.3year trial. J Diabetes Complications. 2018; 32(2): 171–178, doi: 10.1016/j.jdiacomp.2017.11.001, indexed in Pubmed: 29174300.
7. Aroda VR, Edelstein SL, Goldberg RB, et al. Diabetes Prevention Program Research Group. 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.2015-3754, indexed in Pubmed: 26900641.
8. Hanumanthu A, Goswami S, Thimmegowda K, et al. A Study On The Prevalence Of Vitamin B12 Deficiency In Eastern Indian Type 2 Diabetes Mellitus Patients With Peripheral Neuropathy On Metformin Presenting To A Tertiary Care Hospital. Digital Journal of Clinical Medicine. 2023; 5(3): 102–113, doi: 10.55691/2582-3868.1138.
9. Ko SH, Ko SH, Ahn YB, et al. Association of vitamin B12 deficiency and metformin use in patients with type 2 diabetes. J Korean Med Sci. 2014; 29(7): 965–972, doi: 10.3346/jkms.2014.29.7.965, indexed in Pubmed: 25045229.
10. Arıcan P, Bozkurt O, Cavusoglu D, et al. Various Neurological Symptoms with Vitamin B12 Deficiency and Posttreatment Evaluation. J Pediatr Neurosci. 2020; 15(4): 365–369, doi: 10.4103/jpn.JPN_130_19, indexed in Pubmed: 33936299.
11. Serin HM, Arslan EA. Neurological symptoms of vitamin B12 deficiency: analysis of pediatric patients. Acta Clin Croat. 2019; 58(2): 295–302, doi: 10.20471/acc.2019.58.02.13, indexed in Pubmed: 31819326.
12. Silva EB, Bastos CS. Effects of Vitamin B12 Deficiency on the Central Nervous System. J Pathol Res Rev Rep. 2022; 4(1): 1–4, doi: 10.47363/jpr/2022(4)139.
13. Firat CK, Ozkan BN, Guler EM. Beneficial effects of vitamin B treatment in pediatric patients diagnosed with vitamin B deficiency regarding total-native thiol, oxidative stress, and mononuclear leukocyte DNA damage. Free Radic Res. 2022; 56(9-10): 631–639, doi: 10.1080/10715762.2022.2162392, indexed in Pubmed: 36571212.
14. D. S, Kalani R, Narayan K, et al. Prevalence of vitamin B12 deficiency among individuals with type 2 diabetes mellitus in a South Indian rural community. International Journal of Basic & Clinical Pharmacology. 2018; 7(2): 309, doi: 10.18203/2319-2003.ijbcp20180104.
15. Maghsoudlou P, Varlamova J, Pandit J. Patients with unexplained neurological symptoms and signs should be screened for vitamin B12 deficiency regardless of haemoglobin levels. Eye (Lond). 2022; 36(5): 1124–1125, doi: 10.1038/s41433-021-01589-9, indexed in Pubmed: 34035493.