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Long-Term Impact of Metformin Therapy on Vitamin B-12 Status: An Epidemiological Approach

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ABSTRACT

Metformin is the most popular drug to treat type 2 diabetes mellitus. It is common to prescribe metformin for long periods of time, sometimes for the entire life. While metformin is an effective, safe, and inexpensive treatment, long-term use may reduce vitamin B12 absorption, causing deficiency in some patients. Vitamin B12 is necessary for the formation of red blood cells, proper functioning of nerves, and the development of a healthy brain. Deficiency causes fatigue, anemia, numbness, cognitive problems, and neuropathy. Studies show that individuals with older age, longer treatment durations, high metformin doses, or a low B12 diet are more likely to develop vitamin B12 deficiency. Deficiency can be reduced by consuming vitamin B12-rich foods. Furthermore, there is a great need for a multidisciplinary approach to reduce, minimize, and inhibit long-term complications in people with type 2 diabetes.

Keywords: Diabetes, Metformin, Vitamin B12, Serum Cobalamin, Public Health, Food Sources

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Introduction

Diabetes mellitus (DM), characterized by long-standing hyperglycemia, is a chronic, progressive metabolic disorder that is caused by abnormalities in insulin production, insulin action, or both. There are common risk factors for diabetes, including increasing age, obesity, inactivity/physical inactivity; and poor lifestyle habits such as poor dieting. Diabetes mellitus is a significant public health concern and affects millions of people globally, contributing to the high levels of morbidity and mortality that accompany diabetes. The World Health Organization estimates that 415 million people have diabetes worldwide. According to the World Health Organization, 415 million people worldwide suffer from diabetes. Global data indicate that the prevalence rate is steadily increasing by roughly 2.5% annually. By 2030, this figure is estimated to rise to 439 million. In many regions of the world, the prevalence of diabetes is increasing due to rapid economic growth and urbanization. Diabetes significantly increases morbidity and early mortality by impairing people's functional abilities and quality of life (1). A medication called metformin was recommended as a first line of treatment for type 2 diabetes. The first-line treatment for diabetes has been metformin. In people with type 2 diabetes, this oral anti-hyperglycemic medication decreases plasma glucose levels both before and after meals. It works by reducing intestinal glucose absorption and hepatic glucose production in addition to raising insulin sensitivity. The use of metformin to help lower insulin resistance and reduce the risk of vascular complications in patients with diabetes has greatly improved the long-term prognosis of those diagnosed with diabetes. There are some limitations to the effectiveness of metformin based on recent clinical observations of patients taking metformin for an extended period of time, which indicate that 30% of all long-term metformin users experience vitamin B12 malabsorption syndrome. Studies have also found that patients taking metformin had their serum levels of vitamin B12 reduced by as much as 30% to 14%. Vitamin B12 is an important nutrient and is required for healthy red cell production and healthy functioning of both the nervous system and the brain. In addition to these conditions, vitamin B12 deficiency can enhance the development of peripheral neuropathy and anemia in people with type 2 diabetes. Approximately 60% of diabetic patients have peripheral neuropathy, which can lead to serious complications, including reduced productivity, increased risk of infection, fractures, amputations, leg ulcers, and increased healthcare costs. There are serious clinical implications as well as an impact on the overall health of diabetic patients, and it is essential to have a clear understanding of the relationship between metformin and vitamin B12 deficiency to develop population-based strategies that will result in the best long-term health outcomes for all diabetics. To improve long-term health outcomes, it is important to recognize the cause of the problem and develop preventive strategies (2).

Metformin and Vitamin B12: Biological Mechanism

Metformin, as the most used anti-diabetic drug, has few negative effects, although one that has been documented in type 2 diabetic patients is vitamin B12 malabsorption. Reduced intestinal motility with bacterial overgrowth, decreased intrinsic factor synthesis, increased vitamin B12 hepatic storage, and impaired enterohepatic B12 circulation. The most widely recognized explanation states that metformin inhibits calcium cation and halts the intrinsic factor-vitamin B12 complex (calcium-dependent) from attaching to the receptor(ileal cubilin), weakening the process of B12 endocytosis (2). Absorption of vitamin B12 is a complicated process involving multiple organs and steps. Firstly, in intragastric incidents, B12 is released from dietary proteins and bind by R-protein. Secondly, Jejunal and duodenal occurrences in which pancreatic proteases degraded the R-protein, and B12 binds via intrinsic factor. Thirdly, in Ileal incidents, B12 intrinsic factor binds to the receptor and is transported via enterocytes (B12 binds in portal blood via trans cobalamin II). Lastly, in enterohepatic circulation, biliary excretion of R-protein binds B12 and B12 analogues, and R-protein degradation by pancreatic proteases creates B12-intrinsic factor, then fecal excretion of B12 and ileal reabsorption of B12 happen. Because the liver stores several years' worth of vitamin B12, deficiency develops slowly, and symptoms don't show up until long-term treatment. Because of its delayed onset, the illness is quiet and frequently missed in standard clinical practice (3).

Epidemiological Evidence

Numerous epidemiological studies have looked into the connection between vitamin B12 deficiency and metformin use. Patients taking metformin have consistently had lower serum vitamin B12 levels than non-users, according to cross-sectional research. Table 1 summarizes a few studies on the connection between cobalamin status and metformin treatment.

A dose-response relationship has also been shown by cohort studies and randomized controlled trials, where a longer term of metformin medication and higher daily dosages are linked to an increased risk of deficiency. According to population-based surveys, 10–30% of patients on long-term metformin medication experience low or borderline vitamin B12 levels. Due to decreased food intake, poor absorption, and increased drug exposure, older people are more at risk. Vegetarians and those who eat less animal-based meals are likewise more vulnerable. Additionally, epidemiological statistics indicate that after three to five years of continuous metformin use, the risk of insufficiency increases. These results reinforce the necessity of routinely checking long-term users' vitamin B12 levels, particularly in high-risk populations. According to a number of observational and interventional studies, serum cobalamin concentrations and metformin medication have been linked. However, the literature started to concentrate on figuring out how metformin dosage and treatment duration affected serum cobalamin concentrations. (1).

Table 1: B12 status and **metformin therapy** among individuals **with diabetes mellitus** type 2

Study plan, location, and trial size	Properties/Attributes	Vitamin B12 or Methylmalonic Acidemia valuation	Main outcomes and inferences	References
A cross-sectional survey was conducted in Pakistan with a total of 932 participants (2020)	Adults with type 2 diabetes; 69.2% were receiving metformin therapy for more than two years, while the remaining were not using metformin	Serum vitamin B12 levels measured; deficiency defined based on low circulating B12 concentration	Vitamin B12 deficiency was observed more frequently in individuals using metformin compared with non-users (3.9% vs 2.1%), indicating an association between long-term metformin use and reduced B12 status	(4)
A retrospective cohort study carried out in the United States, including 13,489 patients (2021)	Patients with type 2 diabetes treated with metformin for at least one year; long-term follow-up available for several years	Serum vitamin B12 was assessed to determine deficiency status during follow-up	After one year of therapy, 3.3% of metformin users showed low or absent vitamin B12 (44.9% vs 2.2% in non-users). Over an average follow-up of 5.3 years, about 5% of patients developed vitamin B12 deficiency, supporting a time-dependent effect of metformin on B12 levels	(5)

Clinical and Public Health Implications

Numerous clinical symptoms might result from a vitamin B12 deficiency. Megaloblastic anemia, which shows as pallor, exhaustion, and dyspnea, is one of the hematological consequences. Numbness, tingling in the hands and feet, poor balance, and cognitive abnormalities are examples of neurological consequences. There may also be psychological signs like irritation and depression. Vitamin B12 deficiency-related neurological symptoms can resemble or aggravate diabetic neuropathy in diabetic patients. Treatment delays and incorrect diagnoses may result from this. Nerve injury may become irreparable and cause long-term disability if treatment is not received. From the viewpoint of public health, undiagnosed vitamin B12 deficiency leads to higher healthcare utilization, lower productivity, and worse quality of life. Seeing the extensive and prolonged use of metformin, this condition is a significant but frequently overlooked public health concern (6).

Table 2: Conditions Associated with Vitamin B12 Deficiency and Its Underlying Mechanism

Condition / Cause	Underlying Mechanism	References
Long-term metformin therapy	Interferes with calcium-dependent uptake of the intrinsic factor–vitamin B12 complex in the terminal ileum, reducing absorption.	(6)
High-dose metformin use	Dose-related inhibition of ileal B12 transport receptors, leading to progressive depletion.	
Prolonged duration of therapy (>3–5 years)	Chronic exposure impairs enterohepatic recycling of vitamin B12 and lowers body stores.	
Altered intestinal motility	Metformin-induced changes in gut motility promote bacterial overgrowth that competes for luminal vitamin B12.	
Changes in gut microbiota	Increased bacterial consumption of vitamin B12 reduces its availability for host absorption.	
Reduced calcium availability	In the ileum, insufficient calcium results in decreased binding of the intrinsic factor-B12 conjugate to cubilin.	
Elderly patients on metformin	Age-related Hypochlorhydria plus metformin further impairs the release and absorption of dietary vitamin B12.	
Concomitant PPI/H2-blocker use with metformin	Suppressed gastric acid decreases B12 release from food, compounding metformin-related malabsorption.	

Dietary Strategies Along with Metformin Therapy

Increased metformin use and decreased consumption of meat and milk, which are dietary sources of vitamin B12, may have contributed to the increasing prevalence of vitamin B12 deficiency in type 2 diabetes, given the correlation between metformin use and vitamin B12 deficiency. Meat, dairy, eggs, fish, shellfish, and animal products are the typical dietary sources of vitamin B12. Vitamin B12 bioavailability dramatically declines with increased consumption of vitamin B12 per meal because the intrinsic factor-mediated intestinal absorption pathway is thought to be saturated at roughly 1.5–2.0 micrograms per meal under physiologic settings. For vegetarians and older adults, fortified breakfast cereals are an especially beneficial source of vitamin B12. There are also plans to produce some crops enhanced with vitamin B12. There is a need for public health nutrition programs to highlight the importance of Vitamin B12, particularly among diabetic patients. Encourage early consultation, and awareness can be increased by simple educational messages about food sources and symptoms of deficiency (2).

Screening and Prevention

Detection of Vitamin B12 deficiency on time and following correction will prevent megaloblastic anemia and the development of potentially irreversible neuropathy and neuropsychiatric manifestations. People not at increased risk of Vitamin B12 deficiency should not be screened. Only patients with other conditions that put them at increased risk for Vitamin B12 deficiency (e.g., gastric bypass surgery, small intestine surgeries, inflammatory bowel disease) or those taking certain medications (e.g., metformin, proton pump inhibitors, H2 blockers) for more than 1 year, vegans/vegetarians, or individuals over the age of 75 need to be screened for the deficiency of vitamin B12**.** One of the most important requirements for preventing the deficiency is having access to high-quality foods**.** Long-term management of this deficiency is by the ingestion of foods rich in vitamin B12, mainly through animal products. However, there exist a multitude of variables that interfere with the access and consumption of foods high in vitamin B12 and include variables categorized as socioeconomic (cost of food), physiological (e.g., inability to swallow or chew), poor access to food (i.e., food deserts), dietary preference (i.e., vegetarian and/or vegan), and ecological, cultural, and religious factors, due to which the elderly rarely succeed in achieving the goal (5)**.**

Conclusion

Metformin therapy is highly effective for the management of type 2 diabetes, but in people with compromised intestinal absorption, its long-term use can cause a steady drop in the levels of Vitamin B12. This deficiency often develops silently and may remain undetected for years, eventually leading to anemia, neurological problems, and cognitive impairment. Because metformin is used by a large proportion of the global diabetic population, Vitamin B12 deficiency represents an important and preventable public health problem. Along with regular biochemical screening and supplementation when necessary, we need to make sure we are eating foods that are rich in Vitamin B12. Foods rich in vitamin B12 are liver, meat, fish, eggs, milk, yogurt, and some cereals. Dietary sources of Vitamin B12 will help maintain adequate levels of Vitamin B12 in both individuals with diabetes and the general public. By educating individuals with diabetes, providing a structured method of improving diet and evaluating diet on a regular basis, help to reduce diabetes significantly. Balanced diets, greater access to B12-rich foods, and nutritional counseling provided as part of routine diabetic care will greatly decrease the incidence of this preventable health issue. Overall, improving long-term health outcomes in individuals taking metformin will require a comprehensive strategy combining medical care, nutritional support, and general

population education. Therefore, both ensuring the safe and effective long-term use of metformin and improving the quality of life of people with diabetes will require assistance in all three areas (medical, nutrition, and public health).

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