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Review Article

A review on vitamin B12 deficiency induced by metformin

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ABSTRACT

Multiple studies have established a higher prevalence of vitamin B12 deficiency in patients who have type 2 diabetes mellitus (T2DM). Metformin is prescribed as the 1st line oral glucose-lowering medication for individuals with T2DM. However, metformin therapy has been linked to vitamin B12 malabsorption, which can result in both biochemical and clinical manifestations of vitamin B12 deficiency. The long-term use of metformin is associated with a significant decrease in vitamin B12 levels, particularly in doses greater than 2000 mg per day over a period of 4 years. Vitamin B12 is a water-soluble vitamin. It acts as a cofactor for enzymes involved in DNA synthesis and neuroprotection at the cellular level. Hence, vitamin B12 deficiency can lead to various clinical consequences, including hematologic abnormalities such as megaloblastic anemia and hypersegmented neutrophil formation, peripheral neuropathy, and progressive axonal demyelination, hyperhomocysteinemia (HHcy). The latest "standards of medical care in diabetes-2017" issued by the American diabetes association recommends periodic assessment of B12 status and, if necessary, the use of B12 replacement therapy in diabetic patients taking metformin. In order to address the vitamin B12 deficiency associated with metformin several therapies are available including prophylactic supplements of calcium and vitamin B12, discontinuation of metformin, and replenishment of vitamin B12 stores through intramuscular or oral therapy. It is important to regularly monitor vitamin B12 levels for at least annually to prevent complications of vitamin B12 deficiency and continue with supplementation if metformin is still being used.

Keywords: Deficiency, Malabsorption, Neuroprotection, Hematologic, Abnormalities, HHcy, Demyelination

INTRODUCTION

Metformin is a commonly prescribed drug for patients with T2DM and is considered as a first line agent in the management of diabetes.[1] It is an effective anti-hyperglycemic medication that is usually well-tolerated by most patients, with the exception of mild gastrointestinal side effects. Additionally, metformin [>1500 mg] has demonstrated significant improvement in cardiovascular morbidity and mortality associated with T2DM.[2] Metformin is also recommended for individuals with impaired fasting glucose and /or impaired glucose tolerance who meet certain criteria, including being under 60 years, having a BMI of 35 kg/m^2 or higher, having a family history of diabetes in first-degree relatives, elevated triglycerides, reduced HDL cholesterol, hypertension, and a hemoglobin A1c level above 6.0%.[3]

Metformin is a highly effective medication for controlling blood glucose levels, but its use has been found to lower the concentration of vitamin B12 in the body. Despite the significant clinical benefits of metformin, some of its side effects that could have potential adverse health effects are often overlooked and rarely investigated. One such side effect is vitamin B12 deficiency. Vitamin B12 also known as cobalamin, is a water-soluble vitamin that is primarily obtained from animal-based foods such as red meat, poultry, shellfish, milk, eggs, and other dairy products. Alternatively, vitamin B12-fortified foods can also provide a source of this vitamin.[4]

In terms of determining an optimal vitamin B12 status, low vitamin B12 status, which is a clear indication of Vitamin B12 deficiency, is typically defined as having total serum vitamin B12 levels of less than 148 pmol/L. Vitamin B12 levels between 148 and 221 pmol/L are generally regarded as "borderline" or indicative of "marginal deficiency."[5] Apart from Metformin use, there are other conditions that may lead to vitamin B12 deficiency. They include general malnutrition, chronic alcohol abuse, and following vegan or strict vegetarian diets. Other factors that increase the risk of vitamin B12 deficiency include older age, gastric bypass, partial or complete gastrectomy, gastric reduction, bariatric surgery, chronic gastritis due to *H. pylori* infection, and atrophic gastritis, which is an autoimmune disease characterized by the presence of antibodies directed against gastric parietal cells and intrinsic factor (IF).

LONG-TERM USE OF METFORMIN AND ITS UNDERLYING MECHANISM

Metformin-induced vitamin B12 deficiency is found to involve one or more of the following factors: Interference with the calcium-dependent binding of the IF-vitamin B12 complex to the cubilin receptor on enterocytes in the ileum, use of metformin with a dose of 1500 or more for a period of more than a year, interaction with the cubilin endocytic receptor. Alteration in small intestine motility, which can lead to small intestinal bacterial overgrowth and inhibit IF-vitamin B12 complex absorption in the distal ileum. Alteration in bile acid metabolism and reabsorption. Increased liver accumulation of vitamin B12 and reduced secretion of IF by gastric parietal cells.

PATHOPHYSIOLOGY OF METFORMIN INDUCED VITAMIN B12 DEFICIENCY

Metformin-induced vitamin B12 deficiency may involve multiple mechanisms affecting various organs and systems in the body. These may include:

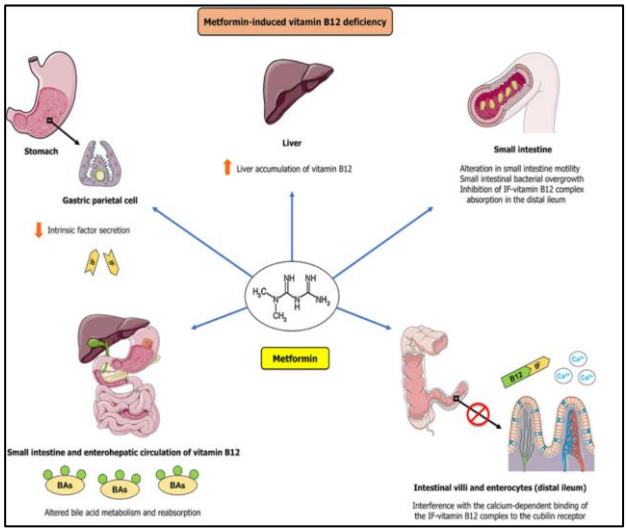

Figure 1: Metformin-induced vitamin B12 deficiency.

Figure 1 shows the various organs involves in the mechanism of metformin induced vitamin b12 deficiency.

Liver: Increased accumulation of vitamin B12 in the liver, leading to altered tissue distribution and metabolism of vitamin B12.

Small intestine: Altered motility in the small intestine may lead to bacterial overgrowth, which can inhibit the absorption of the IF-vitamin B12 complex in distal ileum.

Intestinal villi and endocytosis: Metformin may interfere with calcium-dependent binding of the IF-vitamin B12 complex to the cubilin receptor on enterocytes in ileum, and may also interact with cubilin endocytic receptor.

Small intestine and enterohepatic circulation: Impaired bile acid metabolism and reabsorption may result in the impaired enterohepatic circulation of vitamin B12.

Gastric parietal cells: The loss of gastric parietal cell mass may lead to reduced vitamin B12 absorption due to inadequate production of IF. This can result in profound hypochlorhydria and vitamin B12 deficiency.[6-8]

LABORATORY ASSESSMENT OF VITAMIN B12

Methods available to assess of vitamin B12 are: as follows-Table 1 includes the list of biochemical B12 assessments along with the traditional and evidence-based deficiency cutoffs. In clinical settings, serum B12 levels and mean corpuscular volume (MCV) are commonly utilized to assess B12 status, but their accuracy in diagnosing B12 deficiency is sometimes limited.[9]

Table 1: Laboratory assessment of vitamin B12.

Assessments	Traditional assessment cutoffs	Evidence-based assessment cutoffs
Serum B12	<148 pmol /l (<200 pg/ml)	<300 pmol/l (<405 pg/ml)
Homocysteine	>15 µmol/l	≥10 µmol/l
Holo TC II	<35 pmol/l	<50 pmol/l
Serum MMA	>260 nmol/l or >271 nmol/l	>260 nmol/l or >271 nmol/l
Urinary MMA	>4.3 µmol/l	>4.0 µmol/l
Urinary MMA/ creatinine	>4.8 mmol/l creatinine	>3.5 mmol/l creatinine
MCV	>98 μm^3/cell	>98 μm^3/cell

According to the national health and nutrition examination survey conducted in the United States from 1999 to 2006, serum B12 levels of 148 pmol/l or less were classified as indicating biochemical B12 deficiency, while levels greater than 148 to 221 pmol/l were considered indicative of borderline deficiency, and levels above 221 pmol/l considered normal. It is important to note that 400 pmol/l is equivalent to 550 pg/ml.

In the various study's authors discovered that with each increase of 1 g/d in metformin dosage, the risk of developing vitamin B12 deficiency was more than doubled.[10]

Clinical manifestation

Clinical manifestations of vitamin B12 deficiency are shown in the below Table 2.[11]

Table 2: Clinical manifestations of vitamin B12 deficiency.

Hematological	Neurological	Psychiatric	Gastrointestinal	Other side effects	Rare side effects	Clinical consequences
Megaloblastic anemia, thrombocytopenia, leucopenia	Peripheral neuropathy, tingling sensation in extremities, degeneration of the spinal cord	Irritability, mild memory impairment, personality change, dementia, depression	Diarrhea, nausea, vomiting, bloating, abdominal discomfort, flatulence, indigestion, constipation, heart burn, unpleasant metalic taste in mouth	Sneezing, cough, running nose, flushing of skin, nail changes	Lactic acidosis, chest pain, rash	Altered intestinal motility, bacterial overgrowth, decreased absorption of vitamin b12

Among the above-mentioned clinical presentation, Neuropathy, specifically pheripheral neuropathy without hematological symptoms are considered as the main clinical consequence of vitamin B12 deficiency induced by Metformin.

METFORMIN INDUCED VITAMIN B12 DEFICIENCY TREATMENT

Currently, there is no established guidelines or recommendations for the treatment of metformin-induced vitamin B12 deficiency. However, patients who are taking metformin and are found to have concurrent vitamin B12 deficiency should receive cobalamin supplementation to address the deficiency and mitigate the associated risk of peripheral nerve damage and other clinical complications. In particular, prompt administration of vitamin B12 should be considered for patients who are receiving metformin and have a vitamin B12 deficiency accompanied by neurological and/or hematological symptoms, such as peripheral neuropathy and megaloblastic anemia.

While treating vitamin B12 deficiency in metformin-treated patients may be a cost-effective measure, there is still a need to determine the most appropriate method of repletion. Metformin appears to impede vitamin B12 absorption in the small intestine through various mechanisms, making intramuscular or sublingual routes of administration potentially superior to oral supplementation by bypassing the gastrointestinal tract and intestinal absorption. However, it is also possible that high-dose oral vitamin B12 supplementation could be just as effective as other methods in addressing the malabsorption caused by metformin and properly correcting the cobalamin deficiency.

Further research is required to establish the most effective and convenient route of administration of vitamin B12 in metformin-treated patients who also have vitamin B12 deficiency. It may also be worthwhile to explore whether oral calcium supplementation could be a viable alternative, safe, and effective method of treating metformin-induced vitamin B12 deficiency, as it has been shown to reverse vitamin B12 malabsorption caused by metformin.[12]

CONCLUSION

Generally, metformin can cause serum vitamin B12 deficiency, but studies on the influence of its duration and dose are lacking. Hence this article demonarates regular screening for vitamin B12 is recommended in patients with long term use of Metformin and prophylactically use of vitamin B12 supplementation is recommended to prevent the complications of vitamin B12 deficiency.

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