

A REVIEW ON “METFORMIN INDUCED VITAMIN B12 DEFICIENCY IN PATIENTS WITH TYPE-2 DIABETES MELLITUS”

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Article Received on: 20/12/2024

Article Revised on: 10/01/2025

Article Accepted on: 30/01/2025



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ABSTRACT

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia, resulting from defects in insulin secretion, insulin action, or a combination of both. DM is classified into type 1 DM (insulin-dependent), type 2 DM (non-insulin-dependent), gestational diabetes, and other forms such as MODY and LADA. Type 2 DM (T2DM), a major subtype, involves progressive β -cell dysfunction and insulin resistance, often linked to metabolic syndrome (MDS). Oral hypoglycemic agents (OHAs) are the cornerstone of T2DM management, with metformin being the first-line agent. Metformin works by inhibiting hepatic gluconeogenesis, effectively lowering blood glucose levels. Despite its benefits, prolonged use of metformin is associated with vitamin B12 deficiency, affecting up to 30% of users. Symptoms may mimic diabetic neuropathy and cause irreversible neurological damage if untreated. Regular screening and timely intervention are critical for prevention and management. Treatment includes parenteral or high-dose oral vitamin B12 supplementation, with studies showing comparable efficacy of both methods. Preventive measures, including annual serum B12 level monitoring, are essential for at-risk populations.

KEYWORDS: Diabetes mellitus, Type 2 diabetes mellitus, Metformin, Oral hypoglycemic agents, Vitamin B12 deficiency, Neuropathy.

INTRODUCTION

Diabetes mellitus (DM): is a chronic metabolic disorder characterized by persistent hyperglycaemia, resulting from defects in insulin secretion, impaired insulin action, or a combination of both.^[1,2]

EPIDEMIOLOGY: Globally, an estimated 240 million people are living with undiagnosed diabetes, with nearly

half of all adults with diabetes unaware of their condition. This disease places a significant financial burden on healthcare systems worldwide. It is estimated that 537 million individuals, or 10.5% of people aged 20–79, are currently managing diabetes. In 2021, the International Diabetes Federation (IDF) estimated that 537 million people were living with diabetes.^[3]

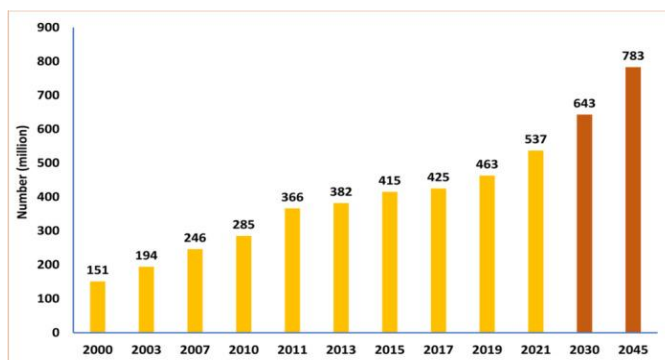


Figure 1: shows the epidemiology of diabetes mellitus.^[3]

Classifications: It include type 1 insulin-dependent, type 2 insulin-independent, gestational diabetes, and other less common types (e.g., MODY (Maturity onset diabetes of young), LADA (Latent AI diabetes of adult)^[4]

TYPE-2 DIABETES MELLITUS (T2DM): Type 2 diabetes (T2D) is a disease characterized by heterogeneously progressive loss of islet β cell insulin secretion usually occurring after the presence of insulin resistance (IR) and it is one component of metabolic

syndrome (MS), and we named it metabolic dysfunction syndrome (MDS)^[5]

ORAL HYPO-GLYCEMIC AGENTS

- A. **Biguanide:** Metformin (1st Line Agent)
- B. **Alpha-Glucosidase Inhibitor:** Acarbose, Miglitol
- C. **Sulphonyureas:** Tolbutamide, Glipizide
- D. **Di-Peptidyl Peptidase Inhibitor(Dpp-4) Inhibitor:** Alogliptin, Linagliptin
- E. **Meglitinide/D- Phenylalanine Analogues:** Repaglinide, Nateglinide
- F. **Thiazolidinedione:** Pioglitazone
- G. **Dopaminergic Antagonist:** Bromocriptine
- H. **Sodium Glucose Co Transport - 2 Inhibitor (Sglt-2):** Dapagliflozin, Canagliflozin.^[6]

Metformin: Metformin is a biguanide and inhibits glucose production in the liver, thus lowering levels of blood glucose.^[7] It is the first-line medication to treat type 2 diabetes mellitus (T2DM) in most guidelines and is used daily by >200 million patients.^[8] For children

(specialist use only) who are 10-17 years, initially a 500mg dosage of immediate-release medicines once per day is recommended through oral route. For adults, initially 500mg once daily is recommended that can be increased if necessary up to 2g once per day, except in Polycystic Ovary Syndrome (PCOS) Metformin gets absorbed quickly from the small intestine and the highest levels of plasma concentration are observed in about two hours. The administration of Metformin 30mins before a meal was found to work the best in decreasing postprandial hyperglycaemia.^[9]

Side effect are gastrointestinal (anorexia, nausea, vomiting, diarrhoea, abdominal discomfort), vitamin B12 deficiency (prolonged use), lactic acidosis (rare). Metformin using patient prevalence of vitamin b12 deficiency upto 30% are seen reduction in vitamin b12 levels as early as 3-6months who as to be used Metformin and symptoms are not seen. Vitamin b12 deficiency symptoms are seen in 4-6years.^[9, 10] Predictors of dose >2gm/day and duration > 4years.^[11]

HOW METFORMIN LEADS TO VITAMINE-B12 DEFICIENCY?

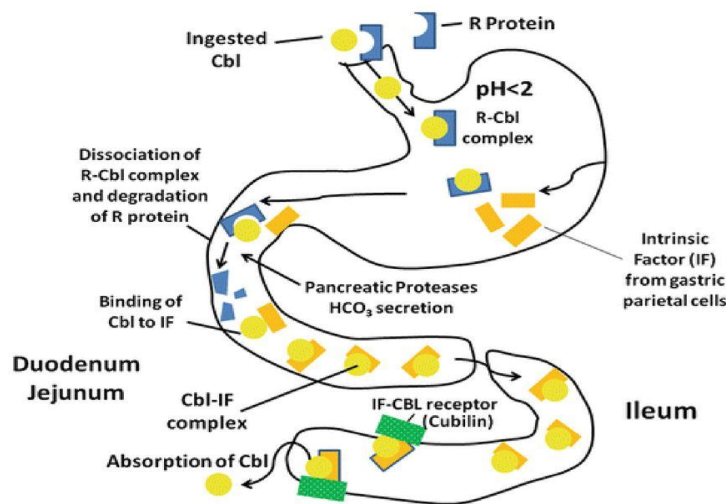
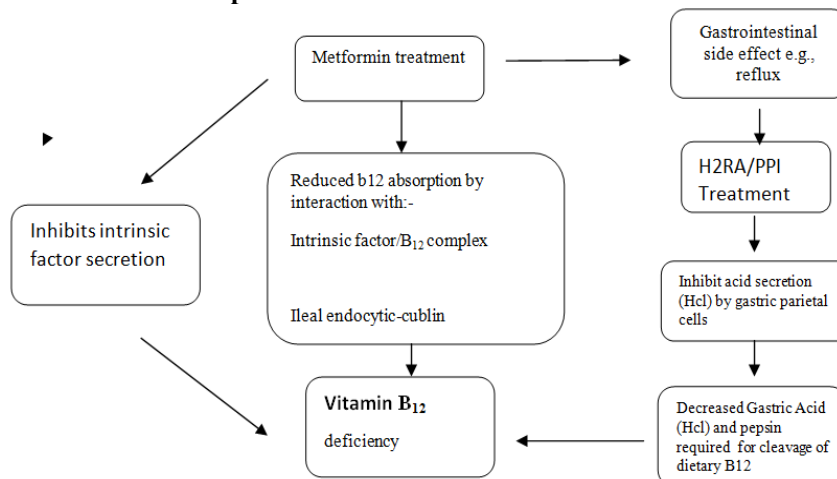


Figure: 2 shows the normal pathophysiology of vit B-12 absorption.^[12]

Metformin: Inhibit Vitamin B12 Absorption^[13]



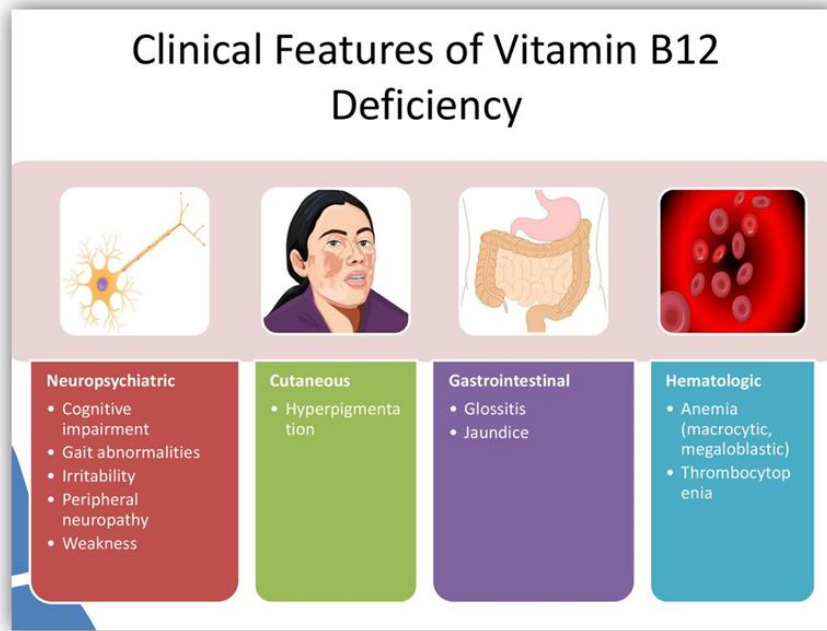


Figure: 3 shows the clinical features of vit B12 deficiency.^[14]

Importance of diagnosis vitamin b12 deficiency^[15,16]

- Neurological symptoms may present even in the absence of anaemia
- Mimic diabetic neuropathy

- Irreversible neurological damage, if left untreated.

Serum cobalamin (cbl) level^[17]

Serum cbl level	Type of result	Cbl deficiency
>400pg/ml	normal	Unlikely
200-400 pg/ml	borderline	Deficiency possible
<200pg/ml	Low result	Consistent with cbl deficiency

*Different laboratories use different methods to calculate the Cbl levels. As a re there is no common reference range or "gold standard test".^[18]

Treatment: VitB12 Parenteral route is the preferred route for patients with neurological defects 1080 mcg (1 mg) every day for one Followed by 1 mg every week for week initially weeks Duration of dose depends on the removal of Metformin.^[19]

What about Oral VitB12?

Few studies have shown equal efficacy with high dose oral B12 (1-2 mg) compared to Inj B12, even in patients with malabsorption (pernicious anemia)^[20]

Prevention

- Have a Serum VitB12 level: once a year or
- Inj. VitB12 1000 mcg: once a week daily and then a weekly dose for four week.^[21]

DISCUSSION

Diabetes mellitus (DM) is a chronic metabolic disorder marked by persistent hyperglycemia due to defects in insulin secretion, insulin action, or both. The main types include type 1 DM (insulin-dependent), type 2 DM (non-insulin-dependent), and gestational diabetes. Additionally, less common forms like Maturity Onset

Diabetes of the Young (MODY) and Latent Autoimmune Diabetes in Adults (LADA) are also recognized. These classifications highlight the diverse etiologies and manifestations of DM, necessitating tailored management strategies for each type. Metformin, a biguanide, is the most widely prescribed OHA for T2DM. Vitamin B12 deficiency affects up to 30% of patients using metformin and often develops without overt symptoms until 4–6 years of use. This deficiency can mimic diabetic neuropathy, leading to misdiagnosis and delayed treatment. Screening serum cobalamin levels is essential, especially for patients on high doses or long-term metformin therapy. Neurological damage caused by B12 deficiency can become irreversible if not promptly addressed, underscoring the importance of early detection and intervention. Regular screening and prophylactic supplementation can prevent deficiency, improving outcomes for metformin users. To mitigate the risk of vitamin B12 deficiency, annual serum level checks should be integrated into the care of patients on metformin. Prophylactic supplementation with injectable or oral B12 can also be considered. Further research into cost-effective screening and supplementation strategies

could help optimize care for vulnerable populations. Encouraging awareness among healthcare providers and patients regarding the link between metformin use and B12 deficiency is critical for reducing the burden of this preventable complication.

CONCLUSION

Diabetes mellitus is one of the most common chronic metabolic diseases with significant implications for health and the economy worldwide. Metformin is first-line pharmacotherapy for type 2 diabetes and has been prescribed to millions, but it is also associated with vitamin B12 deficiency, especially with long-term or higher-dose use. Monitoring serum vitamin B12 levels regularly, and timely supplementation, whether oral/injectable forms are essential to prevent and manage this problem. Based on evidence, raising awareness and acting accordingly can avoid complications and ensure better outcomes.

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