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REVIEW ON VITAMIN-B12 DEFICIENCY INDUCED BY LONG TERM TREATMENT OF METFORMIN

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ABSTRACT Metformin is said to be the first line drug for type2 diabetes mellitus. It improves the sensitivity of peripheral insulin and reduces the cardiovascular mortality rate. Abdominal distress, diarrhoea, lactic acidosis are the main side effects associated with metformin.. Many reports suggest that metformin causes vitamin-b12 deficiency due to malabsorption in the terminal ileum. Deficiency of vitamin-b12 particularly related to drug metformin, not the disease itself. The biomarker MethylMalonylCoA(MMA) is highly sensitive to interpret vitamin-b12 deficiency than Homocysteine.(HCY) The common oral symptom tongue pain erythema and beefy red patches are indications of vitamin-b12 deficiency. The vegetarian patients are more prone than non-vegetarians. Vitamin-b12 deficiency may lead to permanent neurological damage if it is misdiagnosed as diabetic neuropathy. Several studies reported that vitamin-b12 deficiency is related to a longer duration of treatment for more than 4 years and dose over 1000mg /day. According to the studies metformin competes with calcium mucosal membrane cause a lack of absorption of vitamin-b12 which can be reversed by oral calcium supplementation daily. Our review also confirmed that vitamin-b12 deficiency can be corrected by routine supplementation therapy. This review article offers a current perspective on vitamin B12 deficiency due to metformin therapy and vitamin B12 supplementation in diabetes mellitus type 2 patients.

KEYWORDS : Metformin, MMA, HCY

INTRODUCTION

Metformin is said to be one of the first line drugs for the type-2-diabetes patients as recommended by the American Diabetes Association And European Association For The Study Of Diabetes. Metformin is the preferred drug among type 2 diabetes patients, particularly those with overweight and having normal kidney function[1] . Metformin has an essential role in improving the sensitivity of peripheral insulin and reduces the cardiovascular mortality rate. It also plays an important role in carbohydrate metabolism, vascular protection, and weight loss. The side effects associated with metformin are mild such as abdominal distress, diarrhoea which may appear within first few days of admission but disappear after discontinuation of metformin therapy. Moreover, the evidence-based report suggests that metformin deprives vitamin-b_{12} uptake in terminal ileum which is considered as a major side effect in diabetes patients. Various studies have shown that vitamin-b_{12} deficiency is associated with an average of 10-30% of patients taking metformin for longer duration and higher dosage[2]

Vitamin-b_{12} commonly known as cyanocobalamin. It is one of the essential micronutrient found mostly in animal-derived foods. Vitamin-b_{12} deficiency is caused due to reduced dietary intake and reduced uptake due to intestinal malabsorption. Priorly, the deficiency may be asymptomatic for a longer duration. But it can be associated with the clinical manifestations like megaloblastic anemia, polyneuropathy, myelopathy, dementia, and optic neuropathy. Asthenia, glossitis, paresthesias are common symptoms with paraplegia and spasticity usually seen in advanced stages which may lead to irreversible condition. These symptoms could give rise to confusion between diagnosis of peripheral neuropathy due to vitamin B12 deficiency and diabetic peripheral neuropathy.[3] Some studies have shown that low vitamin-b_{12} level is associated with macrovascular (myocardial infarction, cerebral ischemia, coronary artery disease) and microvascular (neuropathy) complications which may worsen the existing symptoms due to other conditions such as diabetes.[4] To assess the vitamin-b_{12} level in metformin treated type-2-diabetes mellitus patients, researchers included the criteria based on the duration of diabetes, duration of metformin treatment and metformin with a dose of not less than 1.5g per day. The patients suffering from kidney, liver, thyroid disorders, alcoholics, smokers, vegetarians, history of nerve disease, malignancy, pregnancy and mentally impaired were excluded from their study. However diagnosis of vitamin-b_{12} malabsorption cannot be done easily without close attention.[5]

THERAPEUTIC IMPORTANCE OF METFORMIN

Metformin is one of the oral hypoglycemic agents belongs to the class of biguanides. Metformin acts by reducing the fasting plasma glucose concentration by decreasing the hepatic glucose production (gluconeogenesis) and also works by reducing the rates of hepatic glycogen metabolism (glycogenolysis).[6] Metformin has an essential benefit in overweight patients with T2DM. Unlike sulfonylureas, insulin, and thiazolidinediones, metformin does not alter body mass index but it significantly reduces total body fat and visceral fat in metformin treated overweight patients. It is indicated directly or indirectly in many other conditions such as polycystic ovarian syndrome related to a decreased level of total and free testosterone level and increased estradiol level. Metformin also possesses several cardiovascular protective effects like improving diastolic function, vascular relaxation and decreased oxidative stress in myocardial cells. Metformin enhances lipid metabolism by decreasing total cholesterol level, LDL, VLDL and decreasing HDL level.[7]

PHYSIOLOGICAL ROLE OF VITAMIN B12

Vitamin B12 is important in methylation of homocysteine to methionine and the conversion of methylmalonyl coenzyme A (CoA) to succinyl CoA. Methionine is then converted into S-adenosyl-methionine which acts as a donor of methyl group to myelin, membrane phospholipids and to various neurotransmitters.Dietary B_{12} binds with salivary protein haptocorrin for transportation of B12 into the small intestine where protein molecule is cleaved by the proteolytic enzymes present in the pancreas. A free form of B_{12} is then attached with intrinsic factor secreted by gastric parietal cells. B_{12}-IF complex is trapped into the ileal cells by calcium-dependent membrane transport (endocytosis) which binds to transcobalamin-II (TC-II) for transportation and reaches the circulation.vitamin-b_{12} present in animal foods like meat, milk, fish, shellfish is synthesized from certain bacteria by denova biosynthetic pathway which is not present in plant foods. The recommended daily intake of vitamin-b_{12} is 2.4mg.[8]

STATUS OF B_{12} DEFICIENCY

Vitamin-b_{12} acts as a cofactor for the enzymes like methionine synthase and methylmalonyl CoA mutase. Methionine synthase is involved in the methylation process which is essential for the conversion of dietary folate to its active metabolite form tetrahydrofolate. Deficiency of vitamin-b_{12} leads to the disruption of the methylation process. Hence there will be an accumulation of serum homocysteine. Hyperhomocysteinemia has toxic effects on neurons and vascular endothelium. In the fatty acid synthesis pathway. The initial precursor succinyl CoA is formed from the methyl malonyl CoA by the enzyme methylmalonyl CoA mutase which is mediated by vitamin-b_{12}. Vitamin-b_{12} deficiency leads to the defective fatty acid synthesis of neuronal membranes. Hence the accumulation of serum methylmalonic acid. Vitamin-b_{12} plays an important role in the synthesis of neurotransmitters like dopamine and serotonin. Its deficiency leads to decreased synthesis of neurotransmitters causing

neurocognitive or psychiatric manifestations.[9] The vitamin-b_{12} normal range is more than 300pg/ml. Its deficiency ranges about 200pg/ml and borderline deficiency is about 200-300pg/ml.[10]

METFORMIN INDUCED VITAMIN-B_{12} DEFICIENCY

In an Indian study conducted among 441 healthy middle aged mens to assess the frequency of vitamin B12 deficiency, defined by vitamin B12 concentrations <150 pmol/L was observed among 67% of the study participants.Some previous studies reported that vitamin-b_{12} deficiency may be caused due to decreased gastrointestinal motility or bacterial overgrowth. Over the period, more recent evidence suggests that vitamin-b_{12} deficiency is due to the disruption of ileal vitamin-b_{12} absorption. Absorption of B_{12}-IF complex is dependent on luminal calcium concentration which facilitates the uptake of B_{12} in ileal cell surface receptor.[11] Increase in metformin dose by 1g/day increases risk of vitamin B12 deficiency by greater than two fold. Subjects consuming metformin for more than ten to twelve years and daily dosage more than or equal to 2g showed that about a fourfold higher risk of vitamin B12 deficiency compared to those wih metformin use of less than four year and daily usage of less than or equal to 1g.[12] Metformin consists of a hydrophobic tail which extends into hydrocarbon core of the terminal ileal membrane. The membrane possesses a positive charge which in turn displaces divalent cations (Ca^{2+}) present in the luminal membrane. Metformin activity causes impaired calcium availability which would interfere with the calcium-dependent vitamin-b_{12} absorption.[13] The responsible mechanism for B12 deficiency in metformin users has been controversial;proposed contributors have included competitive inhibition or inactiation of CbI absorpion, alterations in intrinsic factor levels, bacterial flora, gastrointestinal motility, and interaction with the cubulin endocytic receptor.[14]Patients on metformin have low B12 levels because of a calcium dependent ileal membrane antagonism. Low B12 levels due to prolonged metformin use can cause or exacerbate diabetic peripheral neuropathy (DPN).Low serum B12 levels also alter cerebral functions like memory, cognition, alertness etc[15].

SCREENING APPROACHES FOR B_{12} DEFICIENCY

Vitamin-b_{12} deficiency can be indicated by two types of biomarkers. One is circulating biomarkers such as serum vitamin-b_{12} or holotranscobalamin and the other is functional biomarkers such as MMA or HCY. Circulating biomarkers measures vitamin-b_{12} concentrations which range from a high risk of severe deficiency. Functional (metabolic) biomarkers get accumulated when vitamin-b_{12} is insufficient. Moreover, HCY also gets accumulated in folate deficiency and a lesser degree of riboflavin and vitamin-b_6 deficiency. It is also useful to assess the subclinical b_{12} status.[16] The measurement of these biomarkers improves the sensitivity and specificity for the diagnosis of vitamin-b12 deficiency.[16,17] Although some studies reported that the B_{12} deficiency syndrome cannot be confirmed by the circulating biomarkers i.e low plasma levels of vitamin-b_{12}.[14] In most of the patients (98%) with clinical B_{12} deficiency indicates that MMA and HCY are shown to be elevated. In that MMA is the most specific biomarker than HCY.[18,19]

VITAMIN B12 DEFICIENCY AMONG PATIENTS WITH TYPE 2 DIABETES MELLITUS AND THE GENERAL POPULATION

It may be surprising that the first article describing metformin-associated B_{12} malabsorption was published in 1971.[20] Evidence-based studies showed that patient with T2DM are prone to vitamin-b_{12} deficiency particularly the deficiency is related to the drug metformin and not to the disease itself.[21] From several studies, it was concluded that low serum vitamin-b_{12} is related to longer duration of diabetes of more than 4 years and higher dose over 1000mg/day.[22,23] Studies reflect 1 in 10 patient with vitamin-b_{12} deficiency receiving metformin had shown low hemoglobin of less than 12g/dl and elevated glycated hemoglobin level of more than 7%.[24] Vitamin-b_{12} deficiency is related to neuropathic pain but it should be differentiated from that of diabetic neuropathy. Electromyography or nerve conduction test are used to detect diabetic neuropathy.[25] Some studies reciprocate that there is no significant difference in B_{12} levels between patients with or without peripheral neuropathy. Vitamin-b12 deficiencyalone does not elevate the frequency of peripheral neuropathy.[26]

Some evidence-based studies shown common oral symptoms like tongue pain, erythema, depapillation of the tongue, beefy red patches are used for the physical examination of vitamin-b_{12} deficiency.[27] This study strongly recommends gastroscopy as a special consideration in elderly, vegetarians and patients with digestive disorders and prolonged exposure to drugs like metformin.[28,29] Concomitant use of metformin with proton pump inhibitors or histamine-2-antagonists would cause B_{12} malabsorption in diabetic patients.[30] Vegetarians are more prone to vitamin-b_{12} deficiency and also have a risk of high HCY level after continuation of treatment with metformin.[31] In a study, patients who are taking metformin has a great influence on cognitive impairment than who are not taking metformin. Metformin alters vitamin-b_{12} level which has a great effect on cognitive performance.[32]An article suggests that sulfonylureas in contrast to insulin may affect the intestinal vitamin-b_{12} absorption or metabolism when combined with metformin particularly in patients taking a maximal dose for longer period.[33]

MANAGEMENT

According to this study, metformin competes with calcium for the mucosal cell membrane which is a reversible process. Hence vitamin-b_{12}malabsorption can be corrected by an oral calcium supplementation especially in patients who do not consume any milk or milk products daily .[34]The article suggests that multivitamin use has been associated with improved serum b_{12} concentrations.[35,36] Prevention of metformin-induced B_{12} deficiency includes annual vitamin-b_{12} assessment. Monthly injections of vitamin-b_{12} or large therapeutic daily doses (1000mcg) of vitamin-b_{12} and prophylactically administered calcium carbonate (1-2g/ day) are recommended. In severe cases, discontinuation of metformin therapy is recommended. Multivitamin use is convenient, non-invasive, inexpensive and effective in increasing serum B_{12} concentrations.[36] But multivitamin use which containing about 2.4mcg or 6mcg is not sufficient for those taking metformin for T2DM .[37]

CONCLUSION

Vitamin B12 deficiency occurs commonly among patients with type-2 diabetes taking metformin therapy for longer duration and at higher dosage. Hence routine annual screening of vitamin-b_{12} should be done especially in patients receiving metformin therapy for longer duration at higher dosage. However prevalence of diabetes is considerably increasing , it is difficult to screen B_{12} level in all diabetes patients. Administration of prophylactic vitamin-b_{12} supplementation for patients with long term and high dose metformin therapy seems to be clinically efficient and also considered as an cost effective approach. Our review also confirmed that vitamin-b_{12} deficiency can be corrected by supplementation therapy. This review aims to diagnose the vitamin-b_{12} status in T2DM patients treated with metformin in the future to prevent the clinical manifestations of vitamin-b_{12}deficiency.

CONFLICTS OF INTEREST

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTIONS

Both authors equally contributed to the development of the concept and manuscript, critically read and approved the final manuscript.

ABBREVIATIONS

T2DM – Type 2 Diabetes Mellitus
MMA- Methyl Malonic Acid
HCY- Homocysteine
B_{12}-IF – B_{12} Intrinsic Factor
CbI - Cyanocobalamin

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