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REVIEW: COBALAMINE STATUS IN TYPE 2 DIABETES MELLITUS PATIENTS ON METFORMIN THERAPY

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ABSTRACT

Consistently all researches have shown that metformin therapy improves glycemic response and lowers HbA1c levels. Besides causing gastrointestinal disorders at higher doses metformin is strongly related to vitamin B12 malabsorbtion and deficiency. The dose is an independent predictor of deficiency of vitamin B12 and longer duration is associated with higher prevalence. Recommendation by certain authors state that there should be regular screening of Vitamin B12 and supplementation including folate and calcium for patients on long term metformin use, especially the elderly who are at a higher risk of vitamin B12 deficiency. But there is not enough evidence showing adverse effects of vitamin B12 deficiency in patients on metformin drug. Thus there is contradiction, stating supplementation might be of no use if health benefits are not observed. Thus there is need for more research on effects of vitamin B12 deficiency on long term metformin use and effective ways in which this deficiency can be treated. From a public health perspective, it is most relevant to investigate whether metformin use causes nutritional deficiencies and if posing a health risk to the population at exposure by translating evidence based recommendations. The purpose of this article is to review existing data regarding the effects of long term metformin usage as monotherapy or in combination therapy for glycemic control causing vitamin B12 deficiency.

KEYWORDS: DIABETES, METFORMIN, VITAMIN B12.

INTRODUCTION

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels [ADA, 2010]. The number of people with diabetes is increasing due to population growth, aging, urbanization, and increasing prevalence of obesity and physical inactivity [Wild et al., 2004]. In 2005–2008, based on fasting glucose or hemoglobin A1c levels, 35% of U.S. adults aged 20 years or older had prediabetes (50% of adults aged 65 years or older).Applying this percentage to the entire U.S. population in 2010 yields an estimated 79 million American adults aged 20 years or older with prediabetes. About 215,000 people younger than 20 years had diabetes (type 1 or type 2) in the United States in 2010 [CDC, 2011].

Type-2 diabetes carries significant morbidity and is the leading cause of kidney failure, lower-limb amputations, and new cases of adult blindness. Moreover, it is the seventh leading cause of death in the U.S., primarily as a result of cardiovascular morbidity [Brunetti & Kalabalik, 2012]. The epidemic of type 2 diabetes mellitus and the recognition that achieving specific glycemic goals can substantially reduce morbidity have made the effective treatment of hyperglycemia a top priority [Nathan et al., 2009]. Controlled clinical trials involving patients with type 1 diabetes and those with type 2 diabetes have conclusively demonstrated that intensive diabetes therapy aimed at lowering glycemic levels reduces the risk of diabetic retinopathy, nephropathy, and neuropathy [DCCT, 2005]. Pharmacological therapy to prevent type 2 diabetes may be an important therapeutic modality in those patients in whom lifestyle interventions fail, are not sufficiently potent, or are not feasible [Padwal et al., 2005]. Metformin is a commonly prescribed first-line antidiabetic drug, has proven to be safe and efficacious when used as monotherapy or in combination with other oral antidiabetic agents or insulin in patients with type 2 diabetes [DeFronzo et al., 2005]. The use of metformin has extended in the last 2 decades to include diabetes prevention, gestational diabetes mellitus (GDM) and polycystic ovary syndrome (PCOS). There is accumulating evidence from observational studies to suggest a possible role for metformin in cancer prevention and in the management of non-alcoholic fatty liver disease [Fiad et al., 2013]. Metformin therapy throughout pregnancy in women with PCOS reduces the otherwise high rate of first-trimester spontaneous abortion seen among women not receiving metformin and does not appear to be teratogenic [Glueck et al., 2001]. Also, the initiation of treatment with metformin was associated with a significant reduction in the serum levels of TSH in diabetic patients with primary hypothyroidism [Cappelli et al., 2009].

MECHANISM OF ACTION OF METFORMIN DRUG:

Metformin (1, 1-dimethylbiguanide hydrochloride) is a biguanide commonly used in the treatment of type 2 diabetes mellitus. It is frequently referred to as an "insulin sensitizer" because in settings of insulin resistance and hyperinsulinemia, it lowers circulating insulin levels [Zakikhani et al., 2006]. The effect of metformin on glucose is mediated by improving insulin sensitivity in liver, muscle and fat. Conventionally, metformin is known to reduce glucose concentration through reduction in glucose liver output brought about primarily by reducing the rate of gluconeogenesis and to a lesser extent by reducing glycogenolysis. Metformin also augments peripheral glucose utilization in muscle and fat [Fiad et al., 2013].

More recent work showed that biguanides impair mitochondrial adenosine- 5′-triphosphate (ATP) production, which results in the activation of the liver kinase B1 (LKB1)–5AMP-activated protein kinase (AMPK) signaling pathway. This pathway is central to the regulation of cellular energy homeostasis, and its activation under conditions of energy stress leads to physiologic down regulation of energy-consuming processes, such as protein synthesis and fatty acid synthesis, to restore ATP levels. The system is involved in appetite control by the central nervous system, and in the special case of hepatocytes, activation of the LKB1-AMPK pathway down regulates gluconeogenesis, which represents the export of energy from hepatocytes to the organism in the form of glucose. This effect in turn reduces blood glucose concentration, which results in a secondary decrease in insulin level [Pollak, 2010]. Metformin activates AMPK in hepatocytes; as a result, acetyl-CoA carboxylase (ACC) activity is reduced, fatty acid oxidation is induced, and expression of lipogenic enzymes is suppressed. Phosphorylation and inactivation of ACC, as a result of AMPK activation, serves to inhibit the proximal and rate-limiting step of lipogenesis. Reduced synthesis of the ACC product, malonyl-CoA, is also predicted to relieve inhibition of CPT-1, resulting in increased fatty acid oxidation [Zhou et al., 2001]. Despite its efficacy, vitamin B12 deficiency is a noted side effect of long term metformin therapy.

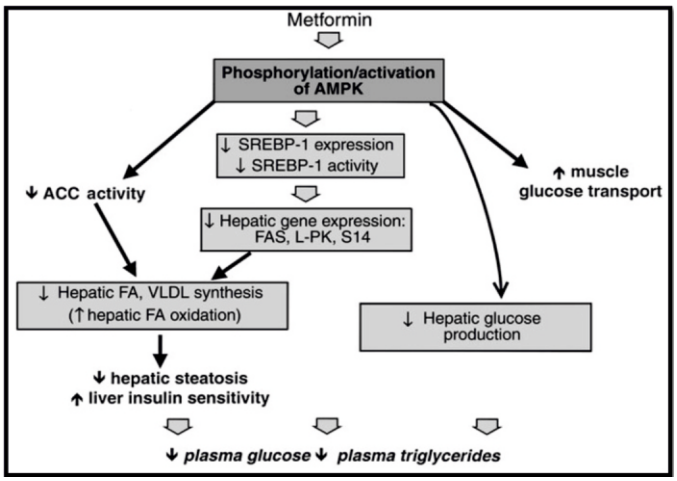

Figure 1: Metformin's Action Mechanism

VITAMIN B_{12}:

Vitamin B_{12} is a water-soluble essential vitamin. A member of vitamin B complex, vitamin B_{12} is also called *cobalamin* because it contains the metal cobalt. Vitamin B_{12} is synthesized by bacteria and is found mainly in meat, egg, and dairy products but lacks a reliable plant source. Vitamin B_{12} is an essential micronutrient required for optimal hemopoetic, neuro-cognitive and cardiovascular function. It is essential for the formation of red blood cells and maintenance of a healthy nervous system as well as for the rapid synthesis of DNA during cell division. Megaloblastic anemia is the common and serious illness associated with B_{12} deficiency, but it is believed that a mild decrease in the B_{12} level is associated with neurologic and psychiatric problems such as ataxia or mood disturbances. A common cause of vitamin B_{12} deficiency is poor intake or absorption. The protein-bound vitamin B_{12} is released by hydrochloric acid in the stomach during digestion. Once released, B_{12} combines with the gastric intrinsic factor, and this complex is absorbed in the intestinal tract. Biochemical and clinical vitamin B_{12} deficiency has been demonstrated to be highly prevalent among patients with type 1 and type 2 diabetes mellitus. [Hanna et al., 2009].

It is known that vitamin B_{12} deficiency is common and that its prevalence increases with age. Because typical signs and symptoms are frequently absent in early vitamin B_{12} deficiency, concern should be focused on persons with known risk factors. Lifestyle factors, such as smoking, alcoholism and vegetarian diet, may predispose to vitamin B_{12} deficiency. Gastrointestinal diseases, gastric acid suppressive drugs and metformin may increase the probability of cobalamine malabsorption [Loikas et al., 2007]. It is estimated that 10% to 30% of patients undergoing metformin therapy develops evidence of vitamin B_{12} deficiency. Another study showed a 22% prevalence of B_{12} deficiency in type 2 DM on metformin therapy [Kumthekar et al., 2012].

Vitamin B_{12} malabsorption has been described in diabetics on biguanides [Caspary et al., 1977]. Some evidence supported the hypothesis that metformin induced B_{12} malabsorption is due to enhanced bacterial overgrowth, especially because diabetic patients are known to exhibit alterations in small bowel motility as well as bacterial overgrowth. Also, vitamin B_{12} absorption is a calcium-dependent process. The hydrophobic tail of biguanides, such as metformin, extends into the hydrocarbon core of membranes. The protonated biguanide group gives a positive charge to the surface of the membrane, which acts to displace divalent cations. Thus, biguanides alter membrane potentials and affect divalent cation membrane functions, such as those that are calcium dependent, and may act in general as a calcium channel blocker. Adhesion of many substances to cell surface membranes is affected by calcium. Specifically, the cell surface TCII receptors on all DNA synthesizing cells are calcium dependent, and metformin may interfere with the delivery of vitamin B_{12} to these cells [Bauman et al., 2000 & Wulffele et al., 2003].

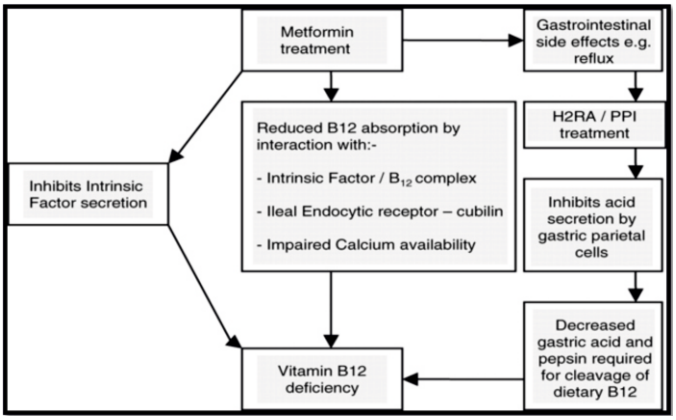

Figure 2: Possible Causes of B_{12} Deficiency due to Metformin Therapy

Some clinical studies have reported that metformin lowered vitamin B_{12} level. Therefore in this review the association between metformin treatment and vitamin B_{12} has been assessed [Liu et al., 2014].

Table: Research Studies on B12 Deficiency due to Metformin Therapy in Management of Diabetes Mellitus

REFERENCE & AIM	STUDY CHARACTERISTICS/ DESIGN	METHODOLOGY	RESULT	CONCLUSION
Ko et al., (2014) Aim: Association of Vitamin B_{12} Deficiency and Metformin Use in Patients with Type 2 Diabetes.	(n)-799; Age- 59yrs; Men (No %) - 354 (44.3); Diabetic duration (yr)- 11.3±7.9; Vitamin B_{12} deficiency was defined as vitamin $B_{12} \leq 300$ pg/mL without folate deficiency (folate > 4 ng/mL).	Vit.B_{12} and folate levels were quantified by chemiluminescent enzyme immunoassay. Alcohol intake was calculated. Diabetic retinopathy was assessed from retinal photographs at baseline, and the findings were reviewed by a board-certified ophthalmologist.	The prevalence of vitamin B_{12} deficiency in metformin-treated type 2 diabetes patients was 9.5%. Vitamin B_{12} deficient patients had longer duration of metformin use ($P < 0.001$) and higher daily metformin dose ($P < 0.001$). Compared with daily metformin dose of ≤ 1,000 mg, the adjusted odds ratio for 1,000-2,000 mg, and ≥ 2,000 mg were 2.52 ($P = 0.008$) and 3.80 ($P < 0.001$). Compared with metformin use of < 4 yr, the adjusted odds ratios for 4-10 yr, and ≥ 10 yr were 4.65 ($P < 0.001$) and 9.21 ($P < 0.001$), respectively.	It was demonstrated that daily metformin dosage and treatment duration were the most consistent risk factors for vitamin B_{12} deficiency. Higher metformin doses and longer treatment durations were independent risk factors.
Kang et al., (2014) Aim: To investigate the prevalence of Metformin-Induced Vitamin B_{12} Deficiency in Sulfonylurea Combination Compared with Insulin Combination in Patients with DM.	Cross sectional study; (n)-394; Duration of study - 2years; Males-179; Females- 215; Mean age- 59.4±10.4 years; Duration of diabetes- $_{12}$.2 years±6.7;	Metformin and sulfonylurea (S+M n = 299) or metformin and insulin (I+M group, n = 95) were consecutively recruited. The vitamin B_{12} and folate levels were quantified using the chemiluminescent enzyme immunoassay. The medication history was evaluated using a dietary supplement questionnaire.	The mean serum B_{12} levels were significantly lower in the S+M group compared with I+M group (600.0±266.5 vs.757.7±287.6 pg/mL, $P<0.001$). The prevalence of vitamin B_{12} deficiency in the metformin-treated patients was significantly higher in the S+M group compared with I+M group (17.4% vs. 4.2%, $P = 0.001$).	The study demonstrated that patients with type 2 diabetes who were treated with metformin combined with sulfonylurea require clinical attention for vitamin B_{12} deficiency and regular monitoring of their vitamin B_{12} levels.
Iftikhar et al., (2013) Aim: To determine prevalence and associations of Vitamin B_{12} deficiency in patients of type 2 diabetes mellitus treated with metformin.	Case control Study; (n)-219; Duration of study-1year; Age - 40-70 yr. Males-128; Females-91; Duration of diabetes (mean) - 8.96 to 8.82 years; Patients with vitamin B_{12} levels of less than 150 pg/ml were said to be B_{12} deficient.	114 outdoor patients of type 2 diabetes mellitus currently on metformin for at least $_{12}$ months were enrolled by consecutive sampling, and 105 age and sex matched patients taken as control. Samples were analyzed the same day for B_{12} levels & HbA1c. The results were analyzed on SPSS version 16.	Serum B_{12} levels were low in 31% on metformin as compared to 8.6% among controls, (p-0.002). Mean B_{12} levels were significantly low in metformin group, 311 pg/ml (±194.4), and p- 0.03. Dose of metformin had inverse correlation with B_{12} levels and the difference was statistically significant with value < 0.001.	Study demonstrated high prevalence of vitamin B_{12} deficiency in patients treated with metformin with significant effect of dose and duration of metformin use on B_{12} levels.

REFERENCE & AIM	STUDY CHARACTERISTICS/ DESIGN	METHODOLOGY	RESULT	CONCLUSION
Sato et al., (2013) Aim: To study Relationship between metformin use, vitamin B_{12} deficiency, hyperhomocysteinemia and vascular complications in patients with type 2 diabetes.	(n)- 84; Male-66; Female-18; Age (mean)-62 years; Patients were diagnosed as B_{12} deficient with a serum B_{12} concentration of <150 pmol/L and as borderline-deficient with 150-220 pmol/L [4]. Plasma HC ≥10 µmol/L was regarded as hyperHcy.	B_{12} status was analyzed in 62 consecutive metformin-treated patients. The relationship between B_{12}, HC and vascular complications was analyzed in 46 metformin-treated and 38 age- and sex-matched non-metformin-treated patients. HbA1c, B_{12} and HC were determined by HPLC and chemiluminescent enzyme immunoassay, respectively.	There were independent correlations between metformin use and B_{12} lowering (P=0.02); B_{12} lowering and elevation of HC (P<0.01). Elevation of HC was a risk for retinopathy (P=0.02). Correlation between B_{12} and HC was stronger in metformin-treated (P<0.01). In B_{12} deficient patients, B_{12} supplementation (1,500 µg/day) for 2.2±1.0 months with continued use of metformin raised B_{12} levels: 152±42 and 299±97 pmol/L before and after treatment, respectively (P<0.01).	Metformin induced B_{12} lowering in diabetes was associated with elevation of HC, and hyperHcy was independently related to retinopathy. Metformin-induced B_{12} deficiency was correctable with B_{12} supplementation.
Moore et al., (2013) Aim: To investigate the association of metformin, serum vitamin B_{12}, calcium supplements, and cognitive impairment in patients with diabetes.	There was insufficient information on use of other antidiabetic drugs, the duration of metformin use, and markers for socioeconomic status, diet, or exercise to investigate these variables. Patients with Alzheimer disease (AD) (n = 480) or mild cognitive impairment (n = 187) and those who were cognitively intact (n = 687) were included;	All participants with serum vitamin B_{12} measurements taken within 6months of cognitive assessment were included. Subgroup analyses were performed for participants who had either type 2 diabetes / IGT. An ordinal logistic regression model was formed with categories of cognitive performance as the response variable and diabetes as a predictor.	Participants with diabetes had worse cognitive performance. Among participants with diabetes, worse cognitive performance was associated with metformin use (2.23 [1.05–4.75]). After adjusting for age, sex, level of education, history of depression, serum vitamin B_{12}, and metformin use, participants with diabetes who were taking calcium supplements had better cognitive performance (0.41 [0.19–0.92]).	Metformin use was associated with impaired cognitive performance. Vitamin B_{12} and calcium supplements may alleviate metformin-induced vitamin B_{12} deficiency and were associated with better cognitive outcomes.
Reinstatler et al., (2012) Aim: To describe the prevalence of biochemical B_{12} deficiency in adults with type 2 DM taking metformin compared with those not taking metformin and those without diabetes, and explore whether this relationship is modified by vitamin B_{12} supplements.	NHANES 1999–2006 (Survey); (n) - 8488. Duration- 7 years. Type 2 diabetes was defined as clinical diagnosis after age 30 without initiation of insulin therapy within 1 year. B_{12} deficiency as serum levels <148 pmol/L, borderline deficiency as serum B_{12} >148 to <221 pmol/L.	Analysis of data on U.S. adults >50 years of age with (n = 1,621) or without type 2 diabetes (n = 6,867) was conducted. Serum B_{12} levels were quantified using the Quanta phase II folate/vitamin B_{12} radio assay kit from Bio-Rad Laboratories.	Biochemical B_{12} deficiency was present in 5.8% of those with diabetes using metformin compared with 2.4% of those not using metformin (P = 0.0026) and 3.3% of those without diabetes (P = 0.0002). Consumption of any supplement containing B_{12} was not associated with a reduction in the prevalence of biochemical B_{12} deficiency among those with diabetes; whereas consumption of any supplements containing B_{12} was associated with a two-thirds reduction among those without diabetes.	Metformin therapy is associated with a higher prevalence of biochemical B_{12} deficiency. The amount available in general multivitamins (6 mg) may not be enough to correct this deficiency among those with diabetes.
Nervo et al., (2010) Aim: Evaluate the presence of vitamin B_{12} deficiency and the factors associated with serum vitamin B_{12} levels in a sample of metformin- treated Brazilian diabetic patients.	Cross sectional study; (n)-144; Age (years)-63.7±11.30; Weight(kg)-80.3±15.4; Women n (%) 91 (63.2); Vitamin B_{12} deficiency was defined by a serum level < 125 pmol/L.	Intake of vitamin B_{12} was estimated by the 24-hour food recall method. Vitamin B_{12} levels were determined in a single batch by electrochemiluminescence - Modular E170 Roche.	Serum vitamin B_{12} levels were low (< 125 pmol/L) in 10 patients (6.9%) and possibly low (125 - 250 pmol/L) in 53 patients (36.8%). Serum vitamin B_{12} levels were negatively associated with age (p = 0.037) and duration of metformin use (p = 0.048), and positively associated with the estimated intake of vitamin B_{12} (p = 0.002).	High prevalence of Clb deficiency in metformin-treated diabetic patients. Patients in long term treatment with metformin and low vitamin B_{12} intake are probably more prone to this deficiency.
De Jager et al., (2010) Aim: To study the effects of metformin on the incidence of vitamin B_{12} deficiency (<150 pmol/l), low concentrations of vitamin B_{12} (150-220 pmol/l), and folate and HC concentrations in patients with type 2 diabetes receiving treatment with insulin.	Multicentre randomized placebo controlled trial. (n)-390; Age (years) - 30 to 80 years with type 2 diabetes. Patients randomized to metformin were older than those to placebo (64±10 years vs 59±11 years), were more likely to have a history of CVD and less likely to be a smoker (19%) vs (30%)).	Patients were randomly assigned to receive either 850 mg of metformin three times a day or 850 mg of placebo thrice daily. Percentage change in vitamin B_{12}, folate, and HC concentrations from baseline at 4, 17, 30, 43, and 52 months were analyzed. During visits, physical examination, medical history and laboratory investigations were performed. At baseline, and after 10 and 52months, dietary counseling was given to all patients.	Compared with placebo, metformin treatment was associated with a mean decrease in vitamin B_{12} concentration of −19% (P<0.001) and in folate concentration of −5% (P=0.033), and an increase in HC concentration of 5% (P=0.091). The absolute risk of vitamin B_{12} deficiency (<150 pmol/l) was 7.2 percentage points higher in the metformin group. Patients with vitamin B_{12} deficiency had a mean HC level of 23.7 µmol/l, compared with a mean HC level of 18.1 µmol/l (P=0.003) for patients with a low vitamin B_{12} concentration and 14.9 µmol/l for patients with a normal vitamin B_{12} concentration (>220 pmol/l).	Long term treatment with metformin increases the risk of Clb deficiency, which results in raised HC conc. Vitamin B_{12} deficiency, is preventable.

REFERENCE & AIM	STUDY CHARACTERISTICS/ DESIGN	METHODOLOGY	RESULT	CONCLUSION
Wile et al., (2010) Aim: The intent of this study was to clarify the relationship among metformin exposure, levels of Cbl, Hcy, and MMA, and severity of peripheral neuropathy in diabetic patients.	Prospective case-control study. There were no significant differences in demographic variables / disease severity between the two groups. A significantly higher no. of patients in the metformin treated group was concurrently treated with glyburide and significantly fewer with insulin.	Patients with type 2 diabetes and concurrent symptomatic peripheral neuropathy, comparing those who had received 6 months of metformin therapy (n=59) with those without metformin exposure (n=63). Comparisons were made using clinical, laboratory (serum Cbl, fasting Hcy, and fasting MMA), and electrophysiological measures (nerve conduction studies).	Median serum Cbl was significantly lower in the metformin treated group (231 vs. 486 pmol/l) with frank deficiency in 18 patients (31%) compared with 2 (3%) in the non–metformin-treated group (P 0.001).Metformin-treated patients had depressed Cbl levels and elevated fasting MMA and Hcy levels. Clinical and electrophysiological measures identified more severe peripheral neuropathy in these patients.	Metformin exposure may be an iatrogenic cause for exacerbation of peripheral neuropathy in patients with type 2 diabetes.
Pflipsen et al., (2009) Aim: Define the prevalence of Clb deficiency in a type 2 diabetic population within a primary care practice.	Cross-sectional study. (n)= 203 Age (yrs) (mean SD) - 61.5 (9.6); Male 104 (53.3%); Serum B_{12} levels <100 pg/mL or serum B_{12} levels of 100 to 350 pg/mL with elevation of serum MMA >243 nmol/L or HC >11.9 nmol/L defined B_{12} deficiency.	Patients completed a survey and had B_{12} levels measured. Patients with borderline B_{12} levels also had MMA acid and HC levels drawn. Descriptive statistics described frequency and means. X2 and student's t tests were used to analyze associations between categorical and continuous variables, respectively. Multivariate logistical regression identified covariates independently associated with B_{12} deficiency.	Twenty-two percent (n 44) of diabetic patients had metabolically confirmed B_{12} deficiency. Patients on metformin had lower serum B_{12} levels (425.99 pg/mL vs 527.49 pg/mL; P .012) and were at increased risk for B_{12} deficiency (P .04), as defined by a serum B_{12} level <350 pg/mL. Prevalence of B_{12} deficiency was significantly lower for patients using a multivitamin (odds ratio, 0.31; 95% CI, 0.15–0.63).	Results found a 22% prevalence of metabolically confirmed B_{12} deficiency in the primary care type 2 diabetic population.
Ting et al., (2006) Aim: Identification of risk factors for metformin related vitamin B_{12} deficiency has major potential implications regarding the management of diabetes mellitus.	Nested case-control study. 155 cases of diabetes mellitus and vitamin B_{12} deficiency secondary to metformin treatment. 310 controls from the cohort who did not have vitamin B_{12} deficiency while taking metformin. There were no significant differences in serum folate concentration between these 2 groups. Sex distribution, drinking, & smoking habits were similar among cases and controls. Vegetarians appeared to be more common among cases than controls, with borderline statistical significance (P=.04). A cutoff point 150 pmol/L for Clb deficiency was determined.	Serum Clb & folate concentrations were determined by electrochemiluminescent immunoassay. Serum MMA conc. evaluation was not routinely performed. Standardized data collection forms were used to abstract information. Data collected included demographic information, concentrations of serum vitamin B_{12}, folate, and blood hemoglobin. All statistical analyses were performed using The Statistical Package for the Social Sciences (Windows, version 13.0; SPSS Inc, Chicago, Ill).	Study found clinically important and statistically significant association of vitamin B_{12} deficiency with dose and duration of metformin use. Each 1-g/d metformin dose increment conferred an odds ratio of 2.88 (95% confidence interval, 2.15-3.87) for developing vitamin B_{12} deficiency (P .001). Among those using metformin for 3 years or more, the adjusted odds ratio was 2.39 (95% confidence interval, 1.46-3.91) (P=.001) compared with those receiving metformin for less than 3 years. After exclusion of 113 subjects with borderline vitamin B_{12} concentration, dose of metformin remained the strongest independent predictor of vitamin B_{12} deficiency.	Results indicate an increased risk of vitamin B_{12} deficiency associated with current dose and duration of metformin use despite adjustment for many potential confounders. The risk factors identified have implications for planning screening or prevention strategies in metformin-treated patients.

DISCUSSION:

It is evident from the above stated research papers that diabetic population is at an increased risk of B_{12} deficiency, majority of the population having borderline levels of this vitamin. Age is a factor for low levels of Vitamin B_{12} and the dietary intake of this vitamin is also low in general population. Long term treatment of type 2 diabetes with metformin due to its effectiveness increases the risk of B_{12} deficiency by causing malabsorbtion of cobalamine in the intestinal tract. There is a positive co-relation between dosage and duration of metformin use to the severity of deficiency of vitamin B_{12}. Diabetic patients are also at a risk of neuropathy, cardiovascular diseases, and lack of vitamin B_{12} may increase the risk of developing other health complications.

Since B_{12} is malabsorbed, whether oral supplementation will be effective in reversal of metformin induced B_{12} deficiency is yet unknown. Contradictory results have been seen in certain studies throwing light on the use of supplementation. In certain reported individual cases studies, intravenous cobalamine was given to provide relief from symptoms of the deficiency. It is thus essential to determine serum B_{12} levels for patient who are or will be on long term metformin therapy irrespective of age of the diabetic population. Also follow up with these patients and measuring their serum B_{12}, folate and homocysteine levels is recommended along with analysis of cognitive performance.

CONCLUSION:

Metformin provides a superior glycemic control effect in type 2 diabetes mellitus but causes vitamin B_{12} deficiency. Further research needs to be conducted to ensure dose at which metformin provides optimal benefits without inducing other health complication.

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