

Frequency of Vitamin B12 Deficiency in patients with Type 2 Diabetes Mellitus Taking Metformin

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ABSTRACT

Aim: To determine the frequency of vitamin B12 deficiency in patients with type 2 Diabetes Mellitus taking metformin.

Place & duration of study: The study was conducted from 1 Oct 2013 to 31 Mar 2014 at Department of Medicine Combined Military Hospital (CMH) Multan

Methods: A total of 135 cases with Type 2 Diabetes Mellitus, aged 40 or more, taking metformin for at least one year presenting to medical OPD were included in the study.

Results: Mean age as 54.53±8.56 years, 75(54.7%) were male and 62(45.3%) were females. HbA1C of patients were between 6.6 and 12.1% with a mean of 8.5% and standard deviation of 0.87. Mean fasting plasma glucose was calculated to be 208±46.3mg/dL, the duration of metformin use was between 1.5 years and 8.4 years with a mean of 5.1±1.9 years. The mean dose of metformin was calculated to be 1970 mg/day with a standard deviation of 727.0 Mean vitamin B12 levels among 137 patients taking metformin were found to be 311.6pmol/L. The standard deviation was 141.5. Serum vitamin B12 levels were found to be deficient (<150 pmol/L) in 19 patients (13.9%).

Conclusion: We concluded that a considerable percentage of diabetic patients treated with metformin have low vitamin B12 levels. So, physicians must recognize this important association of metformin with B12 deficiency.

Keywords: Vit B12, diabetes mellitus, metformin

INTRODUCTION

Diabetes Mellitus is an increasingly prevalent disease that affects 346 million people worldwide. Metformin has been recommended as first line oral monotherapy in the treatment of type 2 Diabetes Mellitus and reduces insulin resistance and risk of macrovascular disease^{1,2}. It is generally well tolerated apart from gastrointestinal side effects. The dreaded complication of lactic acidosis is rare with rational use of metformin.

Metformin has also been associated with vitamin B12 deficiency and it has generated much interest lately. A cross sectional study published in 2009 showed that 22% of diabetic patients had metabolically confirmed vitamin B12 deficiency.³ Vitamin B12 deficiency can manifest as macrocytic anemia, cognitive disorders and neuropathy.⁴ So metformin exposure may be the sole or contributory factor for exacerbation of peripheral neuropathy in patients with type 2 diabetes.⁵ The impaired vibration sense, proprioception and absent reflexes associated with vitamin B12 deficiency in diabetic patients may be wrongly attributed to diabetic polyneuropathy leading to delay in diagnosis and permanent nerve damage.⁶ Cognitive problems have also been reported with metformin induced B12 deficiency.⁷

The exact mechanism of vitamin B12 deficiency due to metformin is not known. The proposed mechanisms include competitive inhibition or inactivation of vitamin B12 absorption, alterations in intrinsic factor levels, bacterial flora, gastrointestinal motility and interaction with the cubulin endocyte receptor⁵. Other factors that may contribute to vitamin B12 deficiency in diabetic patients are ageing and use of H2-receptor antagonists or proton pump inhibitors⁸.

Serum vitamin B12 levels are the standard first investigation for detecting vitamin B12 deficiency. Values less than <125pmol/L are virtually diagnostic of deficiency. Values 125-250 pmol/L show possible B12 deficiency and should be followed with more sensitive tests like methylmalonic acid (MMA), homocysteine (HC) and holotranscobalamin (holoTC) levels⁸.

Considering the high prevalence of diabetes and its complications in Pakistan and widespread use of metformin, underlying vitamin B12 deficiency in such patients may represent a significant problem. The magnitude of this problem in our population is unknown. Estimation of vitamin B12 deficiency in type 2 DM patients taking metformin will help in the formulation of guidelines regarding vitamin B12 monitoring and supplementation in such patients.

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MATERIAL AND METHODS

A total of 135 cases with Type 2 Diabetes Mellitus, aged 40 or more, taking metformin for at least one year presenting to medical OPD were included in the study. Patients excluded from the study who had the history of pernicious anemia, inflammatory bowel disease or diseases of terminal ileum, gastrectomy (complete or partial), use of proton pump inhibitors or H2-receptor antagonists for last 04 weeks and use of vitamin B12 supplements. The study was conducted from 1 Oct 2013 to 31 Mar 2014 at Department of Medicine Combined Military Hospital (CMH) Multan.

After getting approval from hospital ethics committee, study was started. Patients with Type 2 diabetes mellitus presenting to the medical outpatient department of Combined Military Hospital Multan fulfilling inclusion criteria were invited to participate in the study. Informed consent of willing patients was taken. Characteristics of patients including age, gender, weight, height, body mass index, dosage and duration of metformin usage were recorded on a standardized data collection form. Blood samples were drawn and Vitamin B12 levels were determined by cobas e411 analyzer by electro chemiluminescence immunoassay. Glycosylated hemoglobin (HbA1c) levels were measured by DXC-600 analyzer. The results were verified by a pathologist.

Data was entered in SPSS version 17.0. Mean and Standard deviation were calculated for age, weight, height, BMI, dosage of metformin, duration of metformin intake, plasma glucose fasting, HbA1C and serum vitamin B12 levels. Gender and prevalence of vitamin B12 deficiency were calculated as percentages.

RESULTS

We recorded mean age as 54.53+8.56 years, 75(54.7%) were male and 62(45.3%) were females. Mean weight of the patients was 78.3Kg with a standard deviation of 9.76Kg. Mean height of patients was 1.61 meters with a standard deviation of 0.10 meters. Mean Body Mass Index was calculated to be 30.02Kg/m² with a standard deviation of 3.52. HbA1C of patients were between 6.6 and 12.1% with a mean of 8.5% and standard deviation of 0.87. Mean+SD fasting plasma glucose was calculated to be 208+ 46.3mg/dL The duration of metformin use was between 1.5 years and 8.4 years with a Mean+SD of 5.1+1.9 years. The mean dose of metformin was calculated to be 1970 mg/day with a standard deviation of 727.0 Mean vitamin B12 levels among 137 patients taking metformin were found to be 311.6 pmol/L. The standard deviation was 141.5.

Serum vitamin B12 levels were found to be deficient (< 150 pmol/L) in 19 patients (13.9%).

DISCUSSION

Metformin is the most commonly prescribed drug in diabetes mellitus. Apart from gastrointestinal adverse effects, it is a very safe drug. The dreaded complication of lactic acidosis is rare with rational use of metformin. Metformin is also known to cause vitamin B12 deficiency for more than last 3 decades.⁹ This topic has generated much interest lately and a number of studies have been published in international journal highlighting and focusing on this important aspect of metformin therapy^{3,5}.

Considering the high prevalence of diabetes and its complications in Pakistan and widespread use of metformin, underlying vitamin B12 deficiency in such patients may represent a significant problem. The magnitude of this problem in our population is unknown. Estimation of vitamin B12 deficiency in type 2 DM patients taking metformin will help in the formulation of guidelines regarding vitamin B12 monitoring and supplementation in such patients.

In our study, the patients (n=137) were between 40-70 years of age with a mean+sd of 53.45+7.03 years. 75(54.7%) were male and 62(45.3%) were females. The duration of metformin use was 5.1+1.9 years while the dose of metformin was 1970+727.0mg/day. Serum vitamin B12 levels were found to be deficient (<150 pmol/L) in 19 patients (13.9%). Mean vitamin B12 levels were found to be 311.6+141.5 pmol/L.

A study published by Pflipsen et al in 2009 showed vitamin B12 deficiency in 22% type 2 diabetic patients on metformin³. This study was superior as methylmalonic acid and homocysteine levels were also measured in patients with borderline vitamin B12 levels.

A cross sectional study in Brazil published in 2011 showed serum vitamin B12 levels were low (<125 pmol/l) and possibly low (125 pmol/L to 250 pmol/L) in, respectively, 6.9% and 36.8% of the 144 diabetic patients treated with metformin for more than one year¹⁰. So, the prevalence of vitamin B12 deficiency varies according to the cutoff for serum vitamin B12 level used. Similarly Ting et al, showed duration and dose of metformin as high risk factors for developing Vitamin B12 deficiency¹¹.

A randomized controlled trial by Jager and colleagues¹² followed type 2 diabetes taking metformin 2550 mg/day for 4.3 years and found that compared to placebo, metformin use was associated with a mean decrease in vitamin B-12 concentration of -19% (95% confidence interval -24% to -14%; P<0.001) and in folate concentration of -5% (95% CI

-10% to -0.4%; $P=0.033$), and an increase in homocysteine concentration of 5% (95% CI -1% to 11%; $P=0.091$). This study was the first placebo controlled trial which showed the effect of metformin on vitamin B12 deficiency and proved that long term treatment with metformin increases the risk of vitamin B-12 deficiency, which results in raised homocysteine concentrations.

Our study has important limitations. Its design only makes it possible to evaluate associations. The absence of a control group makes it impossible to compare prevalence of vitamin B12 deficiency in a similar population not using metformin, which may have vitamin B12 deficiency associated with other factors such as aging. Another limitation of our study was that methylmalonic acid levels were not measured. Methylmalonic acid levels can improve the sensitivity of results by identifying vitamin B12 deficiency in early stage¹³. We also did not evaluate for the presence of megaloblastic anemia in patients having low B12 levels. Therefore clinical implication of this deficiency cannot be predicted¹⁴.

Nevertheless our study showed significant number of patients being treated with metformin had low B12 levels. Vitamin B12 deficiency in the patients can lead to neuropathic symptoms mimicking diabetic neuropathy leading to diagnostic delay and permanent neurologic damage. So B12 testing and supplementation must be considered in metformin treated diabetic patients especially those presenting with neuropathy.

Our study demonstrated that a considerable percentage of diabetic patients treated with metformin have low vitamin B12 levels. So, physicians must recognize this important association of metformin with B12 deficiency. Diabetic patients especially those presenting with neuropathic symptoms must be screened for vitamin B12 deficiency. Further studies are required to evaluate

effect of B12 replacement in these patients towards reducing B12 deficiency and associated symptoms.

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