

Vitamin B12 Deficiency in Patients with Type 2 Diabetes Mellitus Taking Metformin

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ABSTRACT

Objective: To determine the frequency of vitamin B12 deficiency in type 2 diabetics taking metformin.

Methodology: It was a cross-sectional study conducted at Pathology Department of Sharif Medical City Hospital, Lahore. The study was approved by the ethical committee of the hospital. A total of 100 patients with type 2 diabetes mellitus taking metformin for more than two years were included in the study. Informed consent was obtained from all patients and history regarding medicine intake and any other illness was taken. Serum vitamin B12 levels of all study subjects were measured.

Results: The study included 40 males and 60 females. The mean age of the patients was 53 ± 5 years. The duration of metformin use was between 2-9 years with a mean value of 5.1 ± 2 years. The daily dose of metformin was noted in all patients and its mean value was 1490 ± 257 mg/day. Mean level of serum vitamin B12 was 161 ± 24 pg/mL and ranges from 120 pg/mL to 220 pg/mL. Level of serum vitamin B12 was normal in 5 (10%) patients and low in 45 (90%) patients. Mean level of vitamin B12 in patients taking metformin for 2-5 years was 160pg/mL whereas in patients on metformin for 6-9 years mean value was 145pg/mL. There was a significant association between serum vitamin B12 level and duration of metformin intake.

Conclusion: Vitamin B12 deficiency occurs in patients with type 2 diabetes treated with metformin for a longer duration.

Keywords: Vitamin B12, Diabetes mellitus, Metformin, Type 2 diabetes.

INTRODUCTION

The prevalence of diabetes mellitus is increasing worldwide. Management of diabetes mellitus involves lifestyle modification, oral hypoglycemics and insulin. Lifestyle modification and metformin are recommended as the first line treatment for type 2 diabetics. Metformin which belongs to a biguanide group is the most commonly given oral hypoglycemic drug in type 2 diabetes.¹ It reduces insulin resistance in the body and risk of development of macrovascular complications of diabetes. It is generally a well tolerated drug with few side effects like abdominal discomfort, nausea, diarrhea and lactic acidosis. In addition, prolonged metformin use causes vitamin B12 deficiency.²⁻⁴

Vitamin B12 binds with intrinsic factor and absorption of the vitamin B12-intrinsic factor complex occurs through cubulin receptors present in the ileum. The mechanism by which patients taking metformin develop vitamin B12 deficiency is still not clear. The proposed mechanisms include alteration in intestinal motility, bacterial overgrowth in the intestine, interaction with cubulin receptors and decreased vitamin B12 absorption. Use of proton pump inhibitors

or H2-receptor antagonists can also cause vitamin B12 deficiency. According to different studies, the most likely cause of metformin induced vitamin B12 deficiency is the alteration in calcium dependent vitamin B12-intrinsic factor complex uptake by cubulin receptors present in ileum.⁵⁻⁸

Vitamin B12 has a major role in the synthesis of DNA, haemopoiesis and neurological function. Clinical manifestations of vitamin B12 deficiency include megaloblastic anemia and neurological symptoms like paresthesias, numbness and tingling sensation in hands and feet. It can also cause sub-acute combined degeneration of the spinal cord in which degeneration of the posterior and lateral columns of the spinal cord occurs.⁹ These symptoms can be prevented by early diagnosis of vitamin B12 deficiency and appropriate B12 supplementation.³ Vitamin B12 deficiency is also associated with increased levels of homocysteine in the body. Elevated homocysteine levels have toxic effects on neurons and vascular endothelium and in turn are associated with an increased risk of cardiovascular disease.¹ Vitamin B12 deficiency is diagnosed by detecting serum vitamin B12 levels.⁵

The prevalence of diabetes and its complications is high in Pakistan. Metformin is the most commonly used oral hypoglycemic drug for the treatment of type 2 diabetes. So, diagnosis of vitamin B12 deficiency in type 2 diabetics taking metformin will help in the prevention of its complications.

METHODOLOGY

This was a cross-sectional study conducted at Pathology Department of Sharif Medical City hospital,

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Lahore. The study was approved by the ethical committee of the hospital. A total of 100 patients with type 2 diabetes mellitus taking metformin for more than two years were included in the study by probability random sampling technique. Informed consent was obtained from all patients and history regarding medicine intake and any other illness was taken. The blood sample of all patients was drawn by aseptic measures. Serum vitamin B12 level was performed on all subjects by chemiluminescence method. The normal range of serum vitamin B12 level was 187-883 pg/mL. Exclusion criteria included patients with newly diagnosed type 2 diabetes, pernicious anemia, pregnant women, type 1 diabetes, decreased renal function (serum creatinine levels >1.7 mg/dL for men and >1.5 mg/dL for women), prior vitamin B12 injections, gastrectomy, colectomy, inflammatory bowel disease and vegetarianism. Patients were also excluded if they had any severe medical illness such as sepsis, severe infection, malignancy, liver cirrhosis, heart failure or renal failure.

STATISTICAL ANALYSIS

The data was analyzed using SPSS 23.0. The quantitative variables were expressed as mean \pm SD whereas the qualitative variables were reported as frequency and percentage. A p-value of ≤ 0.05 was considered as statistical significance.

RESULTS

The study included 40 males and 60 females. The mean age of the patients was 53 ± 5 years. The duration of metformin use was between 2-9 years with a mean value of 5.1 ± 2 years. The daily dose of metformin was noted in all patients and its mean value was 1490 ± 257 mg/day. Mean level of serum vitamin B12 was 161 ± 24 pg/mL and ranges from 120 pg/mL to 220

pg/mL. Level of serum vitamin B12 was normal in 5 (10%) patients and low in 45 (90%) patients. Serum vitamin B12 levels of study subjects were compared on the basis of duration of metformin intake. Mean level of vitamin B12 in patients taking metformin for 2-5 years was 160pg/mL whereas in patients on metformin for 6-9 years mean value was 145pg/mL. A significant difference was found when mean levels of vitamin B12 in patients taking metformin for 2-5 years was compared with mean value in patients on metformin for 6-9 years. No significant association was found between dose of metformin and serum vitamin B12 levels.

DISCUSSION

The frequency of diabetes mellitus has increased significantly in the last three decades worldwide especially in Asia and is the ninth cause of death. Globally about 1 in 11 persons have diabetes mellitus and 90% of individuals have type 2 diabetes mellitus. The main factors predisposing to diabetes are genetic predisposition, unhealthy diet and sedentary lifestyle.¹⁰ Vitamin B12 is an important water soluble micronutrient which is essential to maintain haemopoietic, neurological and cardiovascular function. Different studies have shown that both the biochemical and clinical vitamin B12 deficiency are common in type 2 diabetic patients. The most important factor leading to vitamin B12 deficiency in type 2 diabetic patients is metformin use. The prevalence of vitamin B12 deficiency range from 5.8% to 33% in type 2 diabetic patients taking metformin.⁹ Twenty male and 30 female patients with the mean age of 53 ± 5 years were included in this study. Serum vitamin B12 levels in type 2 diabetes did not show any significant association with age and gender. Similar

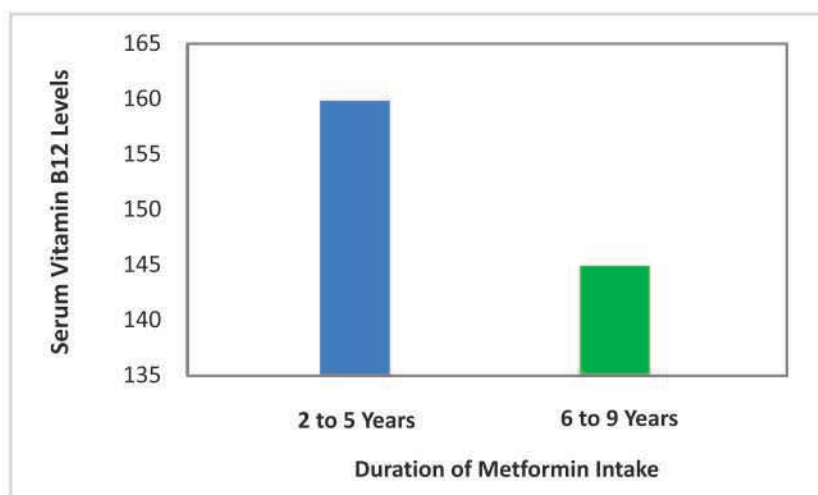


Figure 1: Association of serum vitamin B12 level with duration of metformin intake

results were observed in other studies.^{10,14}

Our results showed that 45 (90%) patients developed vitamin B12 deficiency after metformin use. Comparable results were found in other studies.^{8,15}

Another study found that patients with type 2 diabetes on long-term use of metformin had lower levels of serum cobalamin and holotranscobalamin.¹¹

A study conducted by Reinstatler et al. showed a strong association between metformin intake and decreased serum B12 levels in type 2 diabetics. They observed that intake of vitamin B12 in the form of multivitamins was associated with improvement in vitamin B12 levels.¹²

In this study, we found a significant association between duration of metformin intake and vitamin B12 deficiency. Serum vitamin B12 levels were more decreased in patients taking metformin for more than 5 years. Similar results were reported in another study which showed that use of metformin for more than 4 years increases the risk of vitamin B12 deficiency.⁸ Another study indicated that duration of metformin is strongly associated with risk of vitamin B12 deficiency.⁹

Our results showed no association between dose of metformin and vitamin B12 levels. This is in contrast to another study which indicated a strong association between dose of metformin and serum vitamin B12 level.^{8,9}

A study was conducted in Korea to evaluate the relationship between the duration of metformin use and vitamin B12 deficiency. It showed a negative correlation of vitamin B12 deficiency with the daily dose of metformin and the duration of metformin use.¹³

In another study, effects of dose and duration of metformin use on B12 levels in diabetics taking metformin were observed. Effects of dose of metformin on B12 deficiency among patients taking less than 1500 mg and more than 1500 mg were noted. According to them daily dose of metformin had an inverse correlation with vitamin B12 levels. Serum vitamin B12 levels of type 2 diabetic patients taking metformin for less than 24 months were compared with the patients on metformin for more than 24 months. Duration of metformin intake showed statistically significant association with B12 deficiency.^{12,16} Vitamin B12 levels start decreasing as early as the 4th months after using metformin. However, clinical manifestations of vitamin B12 deficiency occur after 5–10 years due to vitamin B12 stores in the liver.⁹

There is a limitation to this study that other indicators of vitamin B12 deficiency like

homocysteine or methylmalonic acid were not done due to financial constraints.

CONCLUSION

Vitamin B12 deficiency occurs in patients with type 2 diabetes treated with metformin with duration of more than 2 years.

RECOMMENDATIONS

Patients with type 2 diabetes taking metformin should be screened for vitamin B12 levels regularly to prevent the complications associated with vitamin B12 deficiency.

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