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ASSOCIATION OF BIOCHEMICAL SERUM VITAMIN B12 DEFECEINCY WITH METFORMIN THERAPY IN TYPE II DIABETES MELLITUS PATIENTS

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ABSTRACT

Background: Metformin is the only biguanide derivative used to treat type 2 diabetes mellitus (T2DM). Several studies documented that its use contributes to vitamin B12 deficiency in 10–30% of diabetics. The incidence of deficiency varies among populations and studies reported. There is limited data about the effect of metformin use on serum Vitamin B12 levels in type 2 diabetes patients from India. **Objective :** The objective of this study is to compare the prevalence of vitamin B12 deficiency between two groups of type 2 diabetes mellitus (T2DM) patients treated with or without metformin. **Design:** The study was a hospital based, case control type of analytical study. **Duration:** November 2016 to December 2017. **Setting:** Department of Biochemistry, Shadan Institute of Medical Sciences, Hyderabad. **Participants:** 200 patients recruited from the medicine outpatient department of Shadan Hospital. **Methods:** The study group had 100 patients with a diagnosis of T2DM and a prescription history of metformin for ≥15 months and control group has 100 patients with diagnosis of T2DM and no history of metformin use in the past five years. The following data was recorded for each patient: age, sex, weight, height, body mass index (BMI), years with diabetes, total daily dose of and years on metformin. Serum vitamin B12 was measured using an immunoassay method. Data was statistically analyzed. **Results:** The serum Vitamin B12 levels were 423.47 ± 194.4 in metformin group and 720.88 ± 197.2 in the no metformin group. The difference was statistically significant. Mean serum vitamin B12 levels in vegetarians (520.89 ± 289.009) were significantly lower than in non-vegetarian (661.986 ± 300.897). When adjusted for duration of diabetes, metformin use was associated with lower serum Vitamin B12 levels. **Conclusion:** Metformin use was associated with lower serum vitamin B12 levels. Based on our results, we strongly recommend the routine screening of subjects with T2DM on metformin for vitamin B12 deficiency due to its high prevalence and the significant clinical effects it may result in.

KEYWORDS: Vitamin B12 Defeceincy, Metformin, Type 2 Diabetes Mellitus.

INTRODUCTION

Diabetes mellitus is not a single disease entity but rather a group of metabolic disorders sharing the common underlying feature of hyperglycemia. Hyperglycemia in diabetes results from defects in insulin secretion, insulin action, or, most commonly, both. The chronic hyperglycemia and attendant metabolic deregulation may be associated with secondary damage in multiple organ systems, especially the kidneys, eyes, nerves, and blood vessels The prevalence of diabetes is increasingly sharply in the developing world as people adopt more sedentary life styles, with India and China being the largest contributors to the world's diabetic load. Type II diabetes mellitus, which accounts for ~90–95% of those with diabetes, previously referred to as non–insulin-dependent diabetes, type 2 diabetes, or adult-onset diabetes, encompasses individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency. There are probably many different causes of this form of diabetes. Metformin (1.1-dimethylbiguanide hydrochloride) is the only biguanide available and the recommended first line treatment for T2DM. Metformin is being used as monotherapy or in combination with other medications. In addition, lifestyle counseling, weight loss and exercise are usually recommended to every diabetic person. Metformin is probably one of the most commonly used medication on the planet given the incidence of T2DM reaching 5–10% of the population depending on the cohort studied. It has a long-standing evidence base for efficacy and safety, is inexpensive, and has been shown to reduce the risk of cardiovascular events. Its most common side effects include gastrointestinal upset and lactic acidosis. However, the associated vitamin B12 deficiency is less known and not routinely tested for by clinicians. Vitamin B12 also called cobalamin, is a water-soluble vitamin with a key role in

the normal functioning of the central and peripheral nervous systems, hematopoiesis, and the DNA synthesis of every cell. Its deficiency causes megaloblastic anemia, peripheral neuropathy that could be indistinguishable from the diabetic neuropathy even by nerve conduction studies. Memory and cognitive impairments could also result from B12 deficiency. Malabsorption of vitamin B12 in diabetic patients treated with metformin was first noted in 1969. Subsequent studies revealed a prevalence of vitamin B12 deficiency in the range of 10–30% of diabetic patients using metformin. The mechanisms are thought to be related to slowing of the bowel transit time resulting in bacterial overgrowth and interference of the Biguanide with the absorption of vitamin B12. The objectives of this study were to establish the incidence of vitamin B12 in our population, to investigate and characterize any specific associations between taking metformin and vitamin B12 deficiency to establish clear recommendations based on this data.

MATERIALS AND METHODS

The study included 200 patients recruited from the medicine outpatient department of Shadan Hospital. The study group had 100 patients with a diagnosis of T2DM and a prescription history of metformin for ≥15 months and control group has 100 patients with diagnosis of T2DM and no history of metformin use in the past five years. Patients with diagnosis of pernicious anaemia, vitamin B12 supplementation, malabsorption (celiac disease, inflammatory bowel disease, gastrointestinal surgery), malnutrition (pure vegans, anorexia nervosa), iron deficiency anaemia, history of thyroid disease and thyroxin treatment and/or a history of other organspecific autoimmune conditions (vitiligo, Addison's, primary ovarian failure, hypoparathyroidism) were excluded. The following data was recorded for each patient: age, sex, weight, height, body mass index (BMI), years with diabetes, total daily dose of and years on metformin. Serum vitamin B12 was measured using an immunoassay with a co-efficient of variation of approximately 10% or less. Data were analysed using student's t-test and Fisher's test.

OBSERVATIONS AND RESULTS

Table 1: Demographic Profile of The Patients.

Variables	Study Group	Control Group	P Value
Mean Age	50.89 ± 5.39	48.91 ± 5.00	0.12
Gender			
Male	86(.43%)	98(49%)	
Female	114(57%)	102(51%)	
Mean BMI	25.98 ± 3.11	23.67 ± 2.34	0.019*
Dietary Habits			
Vegetarian	136(68%)	136(68%)	
Non-Vegetarian	64(32%)	64(32%)	
Years With Diabetes	6.11 ± 3.91	3.55 ± 1.63	0.001*

*P value significant

Mean age of the study group was 50.89 ± 5.39 years, while it was 48.91 ± 5.00 in control group, which was statistically non-significant. 43% patients in study group and 49% patients in controls were male. Mean BMI in study group was 25.98 ± 3.11 and 23.67 ± 2.34 in control group. P value was significant for duration of diabetes parameter.

Table 2: Distribution of Mean Rbs and Glycated Hb Among The Patients.

	Study Group	Control Group	P Value
RBS	161.78 ± 35.88	179.01 ± 27.91	0.031*
Glycated Hb	8.19 ± 1.97	8.11 ± 1.75	0.039*

*P value significant

The mean RBS in cases was 161.78 ± 35.88 while mean RBS in control was 179.01 ± 27.91. The difference between two is significant. The mean glycated hemoglobin in study group (8.11 ± 1.75) was significantly lower than mean glycated hemoglobin in control group (8.19 ± 1.97) with p value of 0.039(Table 2).

Table 3: Distribution of Mean Serum Vitamin B12 Levels Between Study Group And Control Groups.

	Study Group	Control Group	P Value
Serum Vitamin B12 Levels	423.47 ± 194.4	720.88 ± 197.2	0.001*

*P value significant

Mean serum vitamin B12 levels in study group(423.47 ± 194.4) were significantly lower than in control group(720.88 ± 197.2).

Table 4: Distribution of Mean Serum Vitamin B12 Levels Between Vegetarian And Non-Vegetarian Groups.

	Frequency	Mean Serum Vitamin B12 Levels	P Value
Vegetarian	68	551.11 ± 298.55	0.028*
Non-Vegetarian	32	701.01 ± 303.15	

*P value significant

Mean serum vitamin B12 levels in vegetarians (551.11 ± 298.55) were significantly lower than in non vegetarian(701.01 ± 303.15).

Table 5. Distribution of Mean Serum Vitamin B12 Levels According To Duration of Diabetes.

Duration	Mean Serum Vitamin B12 Levels – Study Group	Mean Serum Vitamin B12 Levels –Control Group	P Value
≤ 5 years	501.11 ± 270.21	761.63 ± 253.09	0.0001*
> 5years	314.78 ± 218.92	641.09 ± 387.99	0.026*

*P value significant

The difference in mean vitamin B12 in both the groups was significantly different irrespective of duration of diabetes.

DISCUSSION

Metformin, a drug commonly sold under the trade name glucophage, is an important prescription medication used for the management of diabetes. It is currently sold worldwide and the American Diabetic Association recommends it as a first-line treatment for the prevention of T2DM individuals with pre-diabetes. As early as 1969 researchers began to speculate that one of the side effects of metformin use was vitamin B12 malabsorption. Vitamin B12, also known as cobalamin, is a water-soluble vitamin essential for hematopoietic and neurological functions in the body. It is obtained primarily from animal sources such as meat and fish. Many breakfast cereals and nondairy beverages such as soymilk are fortified with vitamin B12. Vitamin B12 is an essential cofactor in the conversion of homocysteine to methionine and regeneration of folate. This is a key step in the metabolic process that leads to DNA synthesis and formation and protection of the myelin sheath. Demyelination of nerve endings can lead to peripheral neuropathy. Symptoms begin to manifest as numbness and paresthesia in the feet. This tingling feeling is caused by pressure on the nerves. If the vitamin B12 deficiency is not corrected, weakness, ataxia, sphincter disturbance, and changes in mental status will follow. The objective of this study is to compare the prevalence of vitamin B12 deficiency between two groups of type 2 diabetes mellitus (T2DM) patients treated with or without metformin. The study included 200 patients recruited from the medicine outpatient department of Shadan Hospital. The study group had 100 patients with a diagnosis of T2DM and a prescription history of metformin for ≥15 months and control group has 100 patients with diagnosis of T2DM and no history of metformin use in the past five years. Mean age of the study group was 50.89 ± 5.39 years, while it was 48.91 ± 5.00 in control group, which was statistically non-significant. 43% patients in study group and 49% patients in controls were male. Mean BMI in study group was 25.98 ± 3.11 and 23.67 ± 2.34 in control group. P value was significant for duration of diabetes parameter. The serum Vitamin B12 levels were 423.47 ± 194.4 in metformin group and 720.88 ± 197.2 in the no metformin group. The difference was statistically significant. Mean serum vitamin B12 levels in vegetarians (520.89 ± 289.009) were significantly lower than in non-vegetarian (661.986 ± 300.897). When adjusted for duration of diabetes, metformin use was associated with lower serum Vitamin B12 levels. The mechanism of metformin inhibition of absorption is not fully understood. The current theory of inhibition is based on interference with intrinsic factor binding in the gut. It would be assumed that an increase in concentration of the inhibiting substance (metformin) would result in an increase in inhibition of said absorption.

CONCLUSIONS

Metformin use was associated with lower serum vitamin B12 levels. Based on our results, we strongly recommend the routine screening of subjects with T2DM on metformin for vitamin B12 deficiency due to its high prevalence and the significant clinical effects it may result in.

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