

## Original Research Article

# Vitamin B12 deficiency in patients with type 2 diabetes mellitus

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## ABSTRACT

**Background:** Vitamin B12 deficiency may occur consequent to long-term treatment with metformin but very few studies in India have assessed this risk. Metformin is considered the drug of first choice not only for the management of type 2 diabetes but also for prediabetes and polycystic ovary disease. The study was carried out to assess the serum levels of vitamin B12 in Indian patients with type 2 diabetes mellitus who were treated with metformin for a minimum duration of five years.

**Methods:** Serum vitamin B12 level was estimated in 39 patients with type 2 diabetes mellitus, who were on metformin for more than five years. vitamin B12 deficiency was defined as serum concentration less than 200 pg/dl. Apart from vitamin B12, fasting blood sugar, post prandial sugar and glycosylated hemoglobin were also estimated.

**Results:** 39 subjects in age group of 40-65 years, suffering from type 2 diabetes mellitus, for more than five years were recruited for the study. The mean serum level of vitamin B12 was  $153.27 \pm 46.01$ . Vitamin B12 deficiency was found in 35.89% subjects.

**Conclusions:** Patients suffering from long standing type 2 diabetes mellitus and taking large doses of metformin should be screened for Vitamin B 12 deficiency.

**Keywords:** Metformin, Neuropathy, Type 2 diabetes, Vitamin B12

## INTRODUCTION

India is facing a huge epidemic of type 2 diabetes mellitus. Rapid industrialization and urbanization have led to an increase in prevalence of overweight and obesity along with a decline in physical activity. This coupled with intake of convenient junk food has made Delhi, the Diabetic Capital of the World. Metformin, a biguanide derivative, is an indispensable drug as far as the management of type 2 diabetes is concerned. Its safety, efficacy and cost effectiveness has made it the drug of first choice in management of type 2 diabetes.<sup>1</sup>

Metformin is considered to be a safe drug, which is well tolerated by most of the patients except for mild gastro-

intestinal adverse effects. Its use is prohibited in a small group of patients with type 2 diabetes mellitus who are at risk of developing lactic acidosis. One major concern that has been unearthed with the prolonged use of metformin is vitamin B12 deficiency.

Although the association between vitamin B12 deficiency and metformin treatment had been reported for the first time way back in 1971, but there are very few studies from India looking at the link between the two.<sup>2</sup>

Indians due to religious and cultural reasons consume a predominantly vegetarian diet, hence the prevalence of vitamin B12 deficiency in general population ranges from 16% to 67%.<sup>3,4</sup> According to the estimates given by IDF,

India houses 65 million diabetics and Delhi is projected to become the diabetic capital of the World. Most of the diabetic patients in India are treated with metformin and such patients are at greater risk of developing vitamin B12 deficiency and therefore this study was undertaken to estimate serum vitamin B12 levels in the patients on long term therapy of metformin.

## METHODS

A total of 91 patients with type 2 diabetes mellitus, in the age group of 40-65 years, were recruited for this study. All these patients attended the health center of Institute of nuclear medicine and allied sciences (INMAS), Timarpur, Delhi, India and were on metformin for a minimum duration of five years. This study was approved by the institutional ethic committee.

### Inclusion and exclusion criteria

Inclusion criteria: patients with type 2 diabetes who were taking metformin for more than five years as monotherapy or in combinations with other agents.

Exclusion criteria: included patients with type 1 diabetes, those having a disease duration of less than five years, pregnant women, patients who have undergone gastrectomy or colectomy, those suffering from inflammatory bowel disease. All those suffering from severe medical illness like chronic liver disease, malignancy, renal failure and chronic alcoholics were excluded from the study. All patients who were on oral vitamin B12 supplementation were not included. Individuals with a history of treatment with vitamin B12 injection or multivitamin injections in the past 6 months were also excluded.

### Data collection

A pretested, structured questionnaire was filled by all subjects. The idea was to generate information about their diet, medication consumed by them and duration of diabetes. Vegetarians were defined as those who consumed only plant derived food. Lacto vegetarians were defined as those who consumed plant derived products along with milk and milk products. Lacto-ovo-vegetarians were defined as those who consumed plant food along with milk, milk products and eggs. Non-vegetarians were those who consumed fish, pork or meat, in addition to other food items.

### Blood sampling

Serum samples were collected after overnight fasting of 8 hours for estimation of blood sugar, HbA1C, complete blood counts, liver function test, kidney function test, TSH and Vitamin B12. Serum Vitamin B12 was estimated using chemiluminescence immunoassay. Biochemical Vitamin B12 deficiency was defined as Serum Vitamin B12 level <200 pg/dl.

## RESULTS

There were 91 patients with long standing type 2 diabetes mellitus taking metformin for more than 5 years were recruited for the study. Using a strict exclusion criterion, 52 patients were excluded from the study. 39 remaining patients underwent physical examination and biochemical evaluation. 28 subjects were males and 11 were females.<sup>7</sup> 17.9% patients were taking 2000 mg of metformin. 80% of patients were receiving metformin as monotherapy and 20 % as combination therapy with sulphonylureas, insulin/pioglitazone.

Vitamin B12 deficiency was seen in 35.89 % of the patients. 47.9% of subjects gave a family history of type 2 diabetes. The mean serum level of vitamin B12 was  $153.27 \pm 46.01$ . The mean value of vitamin B12 in those who were taking a high dose of (2000 milligrams) of metformin was  $111.42 \pm 47.66$ . The mean value of fasting plasma glucose was  $115.03 \pm 25.99$  and the mean value for postprandial plasma glucose was  $158.82 \pm 42.05$ . The mean HbA1c was  $7.22 \pm 1.46$ .

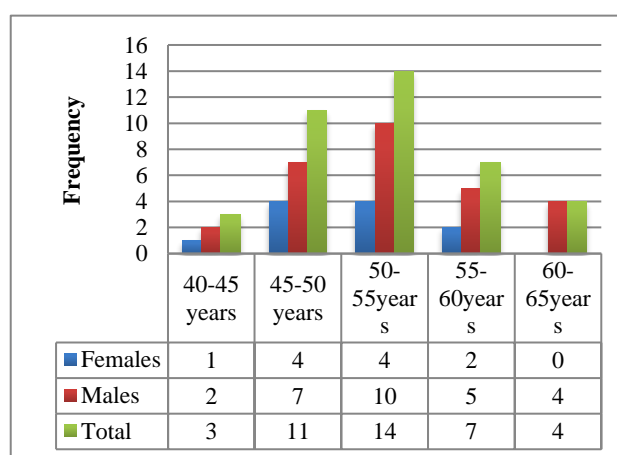


Figure 1: Age distribution of the cases.

Table 1: Daily dose of metformin in study population.

Daily dose of metformin	Female	Male	Total
1000	9	23	32
2000	2	5	7
Total	11	28	39

Figure 1 is showing the age distribution of cases. All the cases recruited for the study were in the age range of 40-65 years. 14 cases (35.8 percent) were in age group of 50 - 55 years.

Table 1 shows the frequency of cases taking more than 2000 milligrams of metformin. A total of seven patients including two females and five males were taking a higher dose of metformin. The mean value of vitamin B12 in these patients who were taking a higher dose of metformin was  $111.42 \pm 47.66$ .

## DISCUSSION

In the present study, vitamin B12 deficiency was observed in 35.89% of individuals with long standing diabetes mellitus and taking metformin for more than 5 years. The prevalence of vitamin B12 deficiency in another clinic based study from North India was found to be 19.9 %.<sup>5</sup> This was also a small study where the number of patients was 136 only. The higher prevalence of vitamin B12 deficiency in present study could be attributed to the longer duration of metformin treatment for type 2 diabetes mellitus. In other parts of the world, the prevalence of vitamin B12 deficiency ranges from 6.5% to 27.7%.<sup>6,7</sup>

In another study by Qureshi SA et al, a high prevalence of vitamin B12 deficiency to the tune of 33% was reported in adult patients with type 2 diabetes.<sup>8</sup> The patients enrolled in this study were those who were taking a higher dose of metformin more than 2 grams and were on a long-term metformin treatment.

The present study has also shown a similar high prevalence of biochemical vitamin B 12 deficiency. The probable reason could be that all patients were on metformin for the last 5 years and were not taking vitamin B12 supplements. Vitamin B 12 deficiency can manifest as megaloblastic anemia and peripheral neuropathy. Neuropathy caused by metformin induced vitamin B12 deficiency can be mistaken with the diabetic neuropathy and the patient may be put on anti convulsant and tricyclic antidepressants.<sup>9</sup>

In a rodent model, treatment with metformin resulted in an increase in accumulation of vitamin B12 in the liver and thereby decreased circulating vitamin B12 levels suggesting that metformin may alter tissue distribution of vitamin B 12 rather than causing a true deficiency.<sup>10</sup>

Despite accumulating evidence suggesting a possible link between metformin treatment and vitamin B12 deficiency, assessment of serum levels of vitamin B12 in type 2 diabetics treated with metformin has not become a practice, so far in India.

Since metformin is widely recommended as first line therapy not only for management of type 2 diabetes but also for treating pre-diabetics and polycystic ovarian disease and given the chronic nature of these diseases, routine estimation of vitamin B12 levels should be considered.

Apart from the small sample size of the present study there are certain other limitations, which are worth noting. The study involved biochemical assessment of vitamin B12 levels only, which may not necessarily indicate true tissue deficiency. We did not measure serum homocysteine, as elevated serum homocysteine levels suggest true vitamin B12 deficiency.

## CONCLUSION

Low serum levels of vitamin B12 have been found to be associated with the use of metformin therapy in the patients suffering from type 2 diabetes mellitus. All those patients who are taking a higher dose of metformin and for a longer duration should ideally be screened for vitamin B12 deficiency and should be supplemented if found to be deficient. Future research should be undertaken to evaluate the role of prophylactic vitamin B 12 supplementation in patients with type 2 diabetes mellitus treated with metformin.

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## REFERENCES

1. Kirpichnikov D, Ncfarlane SI, Sowers JR. Metformin: an update. *Am Intern Med.* 2002;137:25-33.
2. Tomkin GH, Hadden DR, Weaver JA, Montgomery DA. Vitamin-B12 status of patients on long-term metformin therapy. *Br Med J.* 1971 Jun 19;2(5763):685-7.
3. Khanduri U, Shamma A, Joshi A. Occult cobalamine and folate deficiency in Indians. *The National Med J India.* 2005;18(4).
4. Yajnik CS, Deshpande SS, LubreeHG, Naik SS, Bhatt DS, Uradey BS, et al. Vitamin B12 deficiency and hyperhomocysteine in rural and urban population in India. *Indians J Association Physicians India.* 2006;54:775-82.
5. Singh AK, Kumar A, Karmarkar D, Jha RK. Association of vitamin B12 deficiency and clinical neuropathy with metformin use in type 2 diabetes patient. 2013;59(4):253-7.
6. Farvid MS, Homayouni F. Factors associated with vitamin B12, folate and homocysteine levels in persons with type 2 diabetes. *Clin Chem Lab Med.* 2012;50:A48.
7. Calvo RSM, Lozano RJN. Vitamin B12 in type 2 diabetic patients treated with metformin. *Endocrine native.* 2012;59(8):487-90.
8. Qureshi SA, Ainworth A, Winocour PH. Metformin therapy and assessment of for vitamin b12 deficiency. is it necessary. *Practical Diabetes.* 2011;28(7):302-4.
9. Bell DS. Metformin induced vitamin B12 deficiency presenting as a peripheral neuropathy. *South Med J.* 2010;103(3):265-7.
10. Greibe E, Miller JW, Fortoushi SH, Green R, Nexo E. Metformin increases liver accumulation of vitamin B12-an experimental study in rats. *Biochem.* 2013;95:1063-5.

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