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Study On Prevalence of Vitamin B12 Deficiency in Type 2 Diabetes Mellitus Patients on Metformin Therapy

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Abstract
Background: Type 2 Diabetes Mellitus (T2DM) is a major global health problem. Metformin is the 1st-line oral hypoglycemic agent for its management. Long-term metformin therapy was associated with Vitamin B12 deficiency. This may contribute to anemia, peripheral neuropathy, and other neurological complications. Early detection of Vitamin B12 deficiency is important to prevent morbidity and improve patient outcomes.
Objectives: *To determine the prevalence of Vitamin B12 deficiency among patients with Type 2 Diabetes Mellitus receiving metformin therapy and to evaluate its association with duration and dosage of metformin therapy, duration of diabetes, glycemic control, and demographic factors.*
Materials and Methods: *The hospital-based cross-sectional observational study was done among 50 patients with T2DM receiving metformin therapy for at 6 months. Vitamin B12 levels were measured using Chemiluminescence Immunoassay (CLIA)/Electrochemiluminescence Immunoassay (ECLIA). Vitamin B12 deficiency was defined as serum levels <200 pg/mL.*
Results: *16 (32%) had Vitamin B12 deficiency, 12 (24%) had borderline deficiency, and 22 (44%) had normal Vitamin B12 levels. Vitamin B12 deficiency was significantly associated with longer duration of metformin therapy, more daily metformin dose (p=0.017), longer duration of diabetes (p=0.048), and poor glycemic control as indicated by elevated HbA1c levels (p=0.028). No significant association was seen between gender and Vitamin B12 deficiency.*
Conclusion: Vitamin B12 deficiency is common among patients with T2DM receiving metformin therapy. Routine screening and timely supplementation should be considered, particularly in patients on long-term and high-dose metformin therapy, to prevent hematological and neurological complications and improve overall diabetic care.
Keywords: *Type 2 Diabetes Mellitus, Metformin, Vitamin B12 Deficiency, Prevalence, HbA1c, Tertiary Care Hospital.*

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I. INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is one of the most common chronic metabolic disorders worldwide. It is characterized by insulin resistance, impaired insulin secretion, and persistent hyperglycemia. Global prevalence of diabetes may rise, posing a significant public health challenge due to its associated microvascular and macrovascular complications. Metformin is 1st-line pharmacological therapy for the management of T2DM due to its efficacy, safety profile, cardiovascular benefits, and cost-effectiveness. But prolonged metformin therapy was associated with vitamin B12 deficiency, which may adversely affect patient outcomes. [1]

Vitamin B12 (cobalamin) is an vital water-soluble vitamin involved in DNA synthesis, erythropoiesis, and neurological function. Deficiency of vitamin B12 can cause megaloblastic anemia, peripheral neuropathy, cognitive impairment, and other neuropsychiatric manifestations. Vitamin B12 deficiency can cause neurological manifestations may mimic or exacerbate diabetic neuropathy, causing delayed diagnosis and treatment. [2]

Metformin is interfere with calcium-dependent absorption of the vitamin B12–intrinsic factor complex in the terminal ileum, leading to reduced intestinal absorption and gradual depletion of body stores.[3] Both duration and dosage of metformin therapy are significant risk factors for the development of vitamin B12 deficiency.

The prevalence of vitamin B12 deficiency among metformin-treated patients with T2DM varies from 5% to 30%, depending on the diagnostic criteria used and patient characteristics.[4] One Korean study reported a prevalence of 9.5% among metformin users and demonstrated a strong association with higher doses and longer duration of therapy.

Inspite of growing evidence regarding metformin-associated vitamin B12 deficiency, routine screening is not universally practiced, especially in resource-limited settings. Early identification and appropriate supplementation may help prevent hematological and neurological complications, improve quality of life, and reduce morbidity among patients with T2DM. So, assessing the prevalence of vitamin B12 deficiency in patients receiving long-term metformin therapy is essential for developing screening strategies and optimizing patient care. [5]

Objective:

To determine the prevalence of vitamin B12 deficiency among patients with Type 2 Diabetes Mellitus receiving metformin therapy at a tertiary care hospital and to evaluate factors associated with its occurrence.

II. PATIENTS AND METHODS

Study Design

Hospital-based cross-sectional observational study

Study Population

Patients diagnosed with Type 2 Diabetes Mellitus attending the outpatient and inpatient departments of General Medicine and receiving metformin therapy were included in the study.

Sample Size

50 patients with Type 2 Diabetes Mellitus on metformin therapy were enrolled in the study after obtaining informed written consent.

Sampling Technique

Convenience sampling method was used

Inclusion Criteria

1. Patients aged 18 years and above.
2. Diagnosed cases of Type 2 Diabetes Mellitus.
3. Patients receiving metformin therapy for at least 6 months.
4. Patients willing to participate and provide written informed consent.

Exclusion Criteria

1. Patients with Type 1 Diabetes Mellitus.
2. Patients receiving Vitamin B12 supplementation within the last 6 months.
3. Patients with known pernicious anemia.
4. Patients with chronic kidney disease or chronic liver disease.
5. Patients with malabsorption disorders.
6. Patients with a history of gastrointestinal surgery affecting Vitamin B12 absorption.
7. Pregnant and lactating women.
8. Patients on long-term medications known to affect Vitamin B12 absorption, such as proton pump inhibitors and H2 receptor antagonists.

III. Methodology

The study was done from June 2025 to December 2025- for 6 months

After obtaining informed consent, a detailed history was taken using a predesigned proforma. Information regarding age, gender, duration of diabetes, duration and dosage of metformin therapy, dietary habits, and associated comorbidities was collected.

Complete general physical examination and systemic examination were performed for all participants.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using SPSS version 22.0

- Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were expressed as frequencies and percentages. Chi-square test was used to assess associations between categorical variables. A p-value <0.05 was considered statistically significant.

Ethical Considerations

The study was done after obtaining approval from the Institutional Ethics Committee. Written informed consent was obtained from all participants before enrollment. Confidentiality and anonymity of patient data were maintained throughout the study.

IV. RESULTS

Age Distribution:
36% of the patients were aged 51-60 years.

Age Group (Years)	Number of Patients	Percentage (%)
30–40	6	12
41–50	14	28
51–60	18	36
61–70	9	18
>70	3	6
Total	**50**	**100**

Table 1: Age distribution among patients

Gender Distribution:
56% of the patients were male.
Prevalence of Vitamin B12 Deficiency:
44% of the patients had normal vitamin B12 levels.

Vitamin B12 Status	Number of Patients	Percentage (%)
Deficient (<200 pg/mL)	16	32
Borderline (200–300 pg/mL)	12	24
Normal (>300 pg/mL)	22	44
Total	**50**	**100**

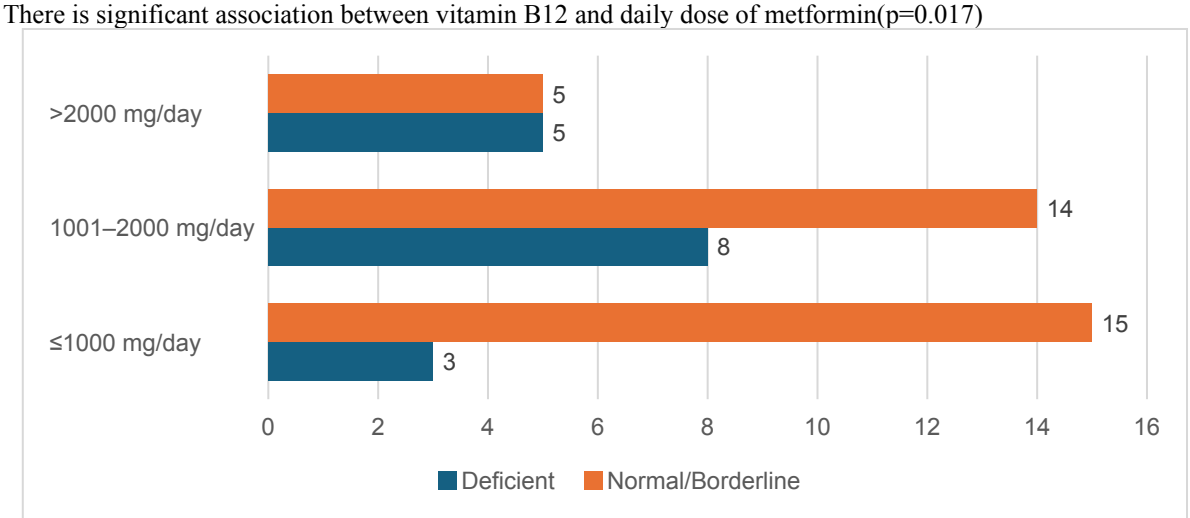
Table 2: Prevalence of vitamin B12 deficiency

Association Between Vitamin B12 Deficiency and Duration of Metformin Therapy:
There is significant association between vitamin B12 deficiency and duration of metformin therapy,

Duration of Metformin Therapy	Deficient	Normal/Borderline	Total
<5 years	4	18	22
5–10 years	7	10	17
>10 years	5	6	11
Total	**16**	**34**	**50**

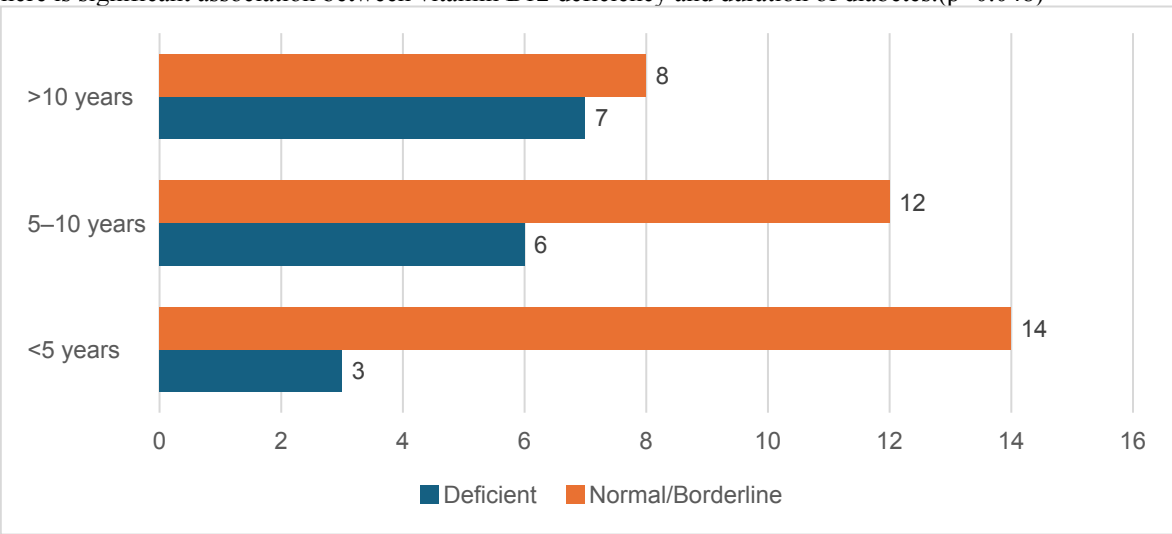
Chi-square = 6.42, p = 0.040
Table 3: Vitamin B12 deficiency and duration of metformin therapy

Association Between Vitamin B12 Deficiency and Daily Dose of Metformin:
There is significant association between vitamin B12 and daily dose of metformin(p=0.017)



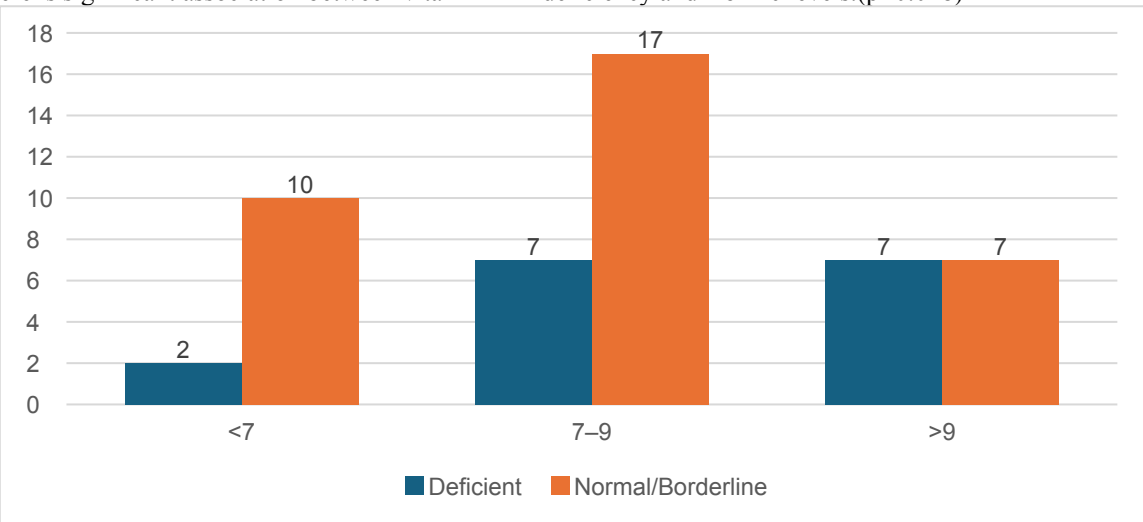
Graph 1: Vitamin B12 deficiency and daily dose of metformin

Association Between Vitamin B12 Deficiency and Duration of Diabetes:
There is significant association between vitamin B12 deficiency and duration of diabetes.(p=0.048)



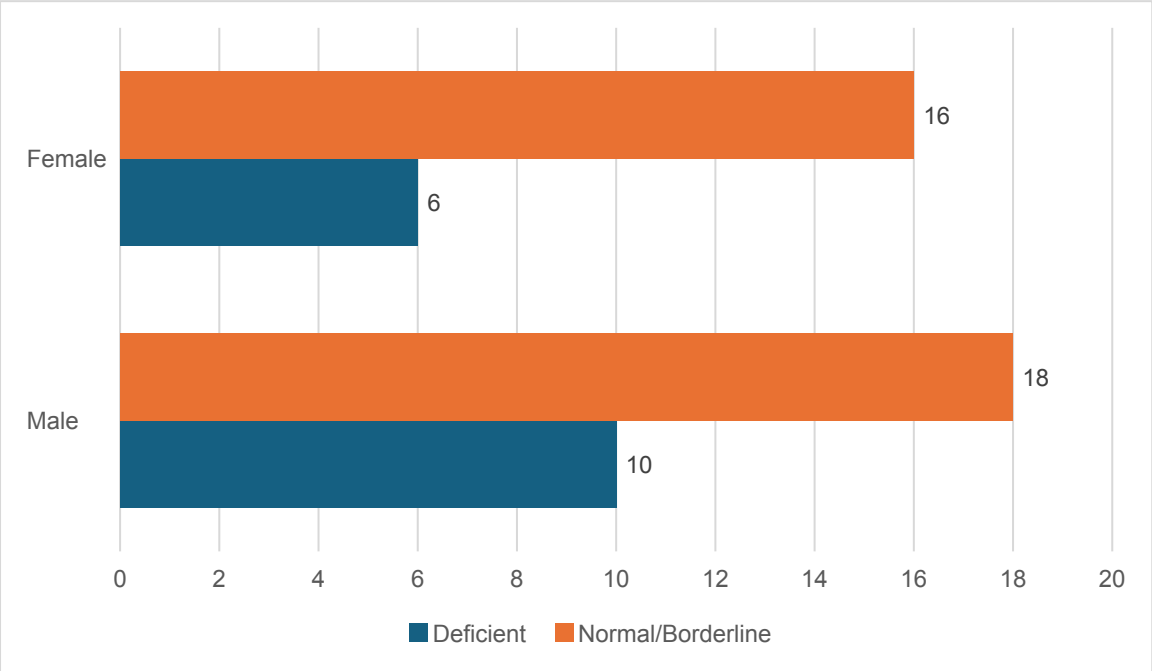
Graph 2: Vitamin B12 Deficiency and Duration of Diabetes

Association Between Vitamin B12 Deficiency and HbA1c Levels:
There is significant association between vitamin B12 deficiency and HbA1c levels.(p=0.028)



Graph 3: Association Between Vitamin B12 Deficiency and HbA1c Levels

Association Between Vitamin B12 Deficiency and Gender:
There is no significant association between vitamin B12 deficiency and gender.(p=0.071)



Graph 4: Association Between Vitamin B12 Deficiency and Gender:

V. DISCUSSION

The present study was done among 50 patients with T2DM receiving metformin therapy to determine the prevalence of Vitamin B12 deficiency and its association with various clinical parameters. In our study, the prevalence of Vitamin B12 deficiency was 32%, while 24% had borderline deficiency and 44% had normal Vitamin B12 levels.

The prevalence seen in the present study is comparable with the findings of Reinstatler et al.,[4] who reported a significantly higher prevalence of biochemical Vitamin B12 deficiency among metformin users compared to non-users in the NHANES population study. Similarly, Ko et al.[2] reported a Vitamin B12 deficiency prevalence of 9.5% among metformin-treated Korean patients and demonstrated that deficiency was significantly associated with higher cumulative metformin exposure. The higher prevalence observed in our study may be attributed to differences in dietary habits, ethnicity, sample size, and duration of metformin therapy.

In the present study, Vitamin B12 deficiency was significantly associated with the duration of metformin therapy (p=0.040). Patients receiving metformin for longer durations showed a higher frequency of deficiency. These findings are consistent with the randomized trial conducted by de Jager et al.,[1] who showed that long-term metformin therapy significantly reduced serum Vitamin B12 concentrations and increased the risk of Vitamin B12 deficiency.

We also observed a significant association between higher daily metformin dose and Vitamin B12 deficiency (p=0.017). Same findings were reported by Ko et al.,[2] who found that both duration and dose of metformin were independent predictors of Vitamin B12 deficiency.

The present study showed a significant relationship between Vitamin B12 deficiency and longer duration of diabetes (p=0.048). Patients with diabetes duration greater than 10 years had a higher prevalence of deficiency. This observation may be explained by prolonged exposure to metformin and cumulative metabolic disturbances associated with long-standing diabetes.[6]

A significant association was found between Vitamin B12 deficiency and poor glycemic control, with patients having HbA1c >9% showing a higher prevalence of deficiency (p=0.028). Similar observations have been reported in several studies, suggesting that patients with poor diabetic control require more doses and longer duration of metformin therapy, thereby increasing the risk of Vitamin B12 depletion.7

In our study, no significant association was observed between gender and Vitamin B12 deficiency (p=0.071). This finding is in agreement with studies by Reinstatler et al.[4] and Ko et al.,[2] which also failed to show significant gender-based difference in Vitamin B12 deficiency among metformin users.

The mean serum Vitamin B12 levels showed a progressive decline with increasing duration of metformin therapy. This finding supports the proposed mechanism whereby metformin interferes with calcium-dependent absorption of the Vitamin B12–intrinsic factor complex in the terminal ileum, resulting in gradual depletion of body stores over time. [8]

Significant associations with duration and dosage of metformin therapy inform the importance of periodic screening of Vitamin B12 levels, especially in patients receiving long-term treatment.

VI. CONCLUSION

The study showed that Vitamin B12 deficiency is a common finding among metformin-treated diabetic patients, with a prevalence of 32%. Routine screening for Vitamin B12 deficiency should be considered in patients on prolonged metformin therapy, especially those with long-standing diabetes, higher metformin doses, and poor glycemic control. Regular monitoring and timely intervention can reduce morbidity associated with Vitamin B12 deficiency and contribute to better overall diabetic care.

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