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ORIGINAL RESEARCH

A Study on Vitamin B12 Deficiency in Non-Vegetarian Diabetic Patients on Long-Term Metformin Therapy at a Tertiary Care Centre

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Abstract

Background: Type 2 Diabetes Mellitus (T2DM) is a prevalent chronic disease worldwide, and Metformin is one of the most commonly prescribed oral anti-diabetic drugs. While Metformin is effective, long-term usage is associated with Vitamin B12 deficiency, potentially leading to complications like neuropathy. Studies from India, especially among non-vegetarian populations, are limited.

Objective: To assess the prevalence of Vitamin B12 deficiency in non-vegetarian T2DM patients on long-term Metformin therapy and to correlate deficiency with Metformin dosage and duration.

Methods: This cross-sectional study involved 105 non-vegetarian T2DM patients on Metformin therapy for more than six months at a tertiary care center. Data on Vitamin B12 levels, Metformin dose, and duration were collected. Statistical analysis was performed to examine correlations.

Results: 25.7% of the patients exhibited Vitamin B12 deficiency. Higher Metformin doses (>1000 mg/day) and prolonged use (>5 years) were significantly associated with deficiency.

Conclusion: Vitamin B12 deficiency is prevalent among non-vegetarian T2DM patients on long-term Metformin. Monitoring and supplementation may be essential, especially for those on higher doses or prolonged therapy.

Keywords: Type 2 Diabetes, Metformin, Vitamin B12 deficiency, Non-vegetarian, India

Introduction

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterised by insulin resistance, hyperglycemia, and eventual β-cell dysfunction. The prevalence of T2DM has increased dramatically in recent years, particularly in rapidly urbanising countries like India, where lifestyle changes have contributed to its rise (1). T2DM is associated with numerous complications, including cardiovascular disease, neuropathy, and retinopathy (2).

Metformin is a biguanide and the first-line treatment for T2DM due to its efficacy in lowering blood glucose levels without the risk of hypoglycemia or significant weight gain (3). However, long-term use of Metformin has been associated with Vitamin B12 deficiency, a significant side effect that can exacerbate diabetes-related complications, such as peripheral neuropathy and cognitive decline (4,5).

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Vitamin B12 deficiency in diabetic patients on Metformin has been extensively studied in Western populations (6), but there is limited research from India, particularly among non-vegetarians, who are expected to have a diet rich in Vitamin B12 due to the consumption of animal products. Therefore, this study was conducted to evaluate Vitamin B12 deficiency in non-vegetarian diabetic patients on long-term Metformin therapy at a tertiary care center in North India.

Materials and Methods

Study Design and Setting

This cross-sectional study was conducted at the Integral Institute of Medical Sciences and Research (IIMSR), Lucknow, India. The study period spanned 18 months, from September 2022 to March 2024. The institute is a tertiary care center serving a large population from Lucknow and nearby districts.

Study Population

The study included 105 non-vegetarian T2DM patients attending the diabetic clinic at IIMSR. Inclusion criteria were:

- Age >30 years
- Diagnosis of T2DM
- On Metformin therapy for at least six months

Exclusion criteria included:

- Type 1 diabetes
- Renal impairment (serum creatinine >1.5 mg/dl for men and >1.4 mg/dl for women)
- Patients taking Vitamin B12 supplements
- Pregnant women

Ethical Approval

Ethical approval for the study was obtained from the Institutional Ethics Committee. Written informed consent was obtained from all patients before enrolment.

Data Collection

Serum Vitamin B12 levels were measured for all participants. Levels below 150 pg/ml were considered indicative of Vitamin B12 deficiency. Additional data collected included:

- Demographic information (age, sex, occupation, place of residence)
- Duration of diabetes
- Metformin dosage and duration
- Hematological parameters (HbA1c, hemoglobin levels)
- BMI and clinical symptoms

Statistical Analysis

Statistical analyses were performed using SPSS (version 25.0). Descriptive statistics were used to summarise the data, and chi-square and t-tests were used to examine associations between Vitamin B12 deficiency and Metformin dosage/duration. A p-value of <0.05 was considered statistically significant.

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Results

Metformin Use and Duration of Diabetes

The majority of patients (74.3%) had been diagnosed with diabetes for 1–5 years, and 75.2% had been using Metformin for the same duration. The most common dose of Metformin was 1000 mg/day, which was used by 34.3% of patients.

Table 1: Distribution of study population according to diabetic and Metformin use history

SN	Characteristic	No.	%
1.	Time since diagnosis of diabetes		
	≤1 Years	3	2.9
	>1-5 Years	78	74.3
	6-10 Years	20	19.0
	>10 Years	4	3.8
2.	Duration of Metformin Use		
	≤1 Years	15	14.3
	>1-5 Years	79	75.2
	6-10 Years	9	8.6
	>10 Years	2	1.9
3.	Dose of Metformin used		
	500 mg	31	29.5
	1000 mg	36	34.3
	1500 mg	28	26.7
	2000 mg	10	9.5

Glycemic Control

The mean HbA1c level among the participants was 8.37 ±1.78%, indicating poor glycemic control in most patients. The average fasting blood glucose level was 162.10 ±33.69 mg/dl, while post-prandial blood glucose was 202.81 ±32.65 mg/dl.

Table 2: Glycemic profile of the patients enrolled in the study

SN	Parameter	Mean	SD
1.	HbA1c (%)	8.37	1.78
2.	Fasting blood sugar (mg/dl)	162.10	33.69
3.	Post-prandial blood sugar (mg/dl)	202.81	32.65

Vitamin B12 Levels and Deficiency

The mean serum Vitamin B12 level was 596.15 ±495.93 pg/ml, with a range of 53 to 2000 pg/ml. A total of 25.7% of patients had Vitamin B12 levels below 150 pg/ml, indicating deficiency.

Table 3: Vitamin B12 status in the study population

SN	Variable	Statistic
1.	Range	53-2000 pg/ml
2.	Mean±standard deviation value	596.15±495.93 pg/ml
3.	Median value	525 pg/ml
4.	Vitamin B12 status	
	>150 pg/ml	78 (74.3%)
	≤150 pg/ml	27 (25.7%)

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Association Between Vitamin B12 Deficiency and Metformin Use

Significant associations were observed between Vitamin B12 deficiency and both the duration and dosage of Metformin use. Patients using Metformin for more than 5 years were more likely to have Vitamin B12 deficiency ($p < 0.001$), as were those taking doses greater than 1000 mg/day.

Table 4: Association of vitamin B12 deficiency with diabetic and Metformin use history

SN	Characteristic	Vitamin B12 deficiency (n=27)		No Vitamin B12 deficiency (n=78)		Statistical significance	
		No.	%	No.	%	c^2	p
1.	Time since diagnosis of diabetes						
	≤1 Years	0	0	3	3.8	30.41	<0.001
	>1-5 Years	11	40.7	67	85.9		
	6-10 Years	12	44.4	8	10.3		
	>10 Years	4	14.8	0	0		
2.	Duration of Metformin Use						
	≤1 Years	0	0	15	19.2	19.99	<0.001
	>1-5 Years	19	70.4	60	76.9		
	6-10 Years	6	22.2	3	3.8		
	>10 Years	2	7.4	0	0		
3.	Dose of Metformin used						
	500 mg	5	18.5	26	33.3	15.86	0.001
	1000 mg	5	18.5	31	39.7		
	1500 mg	10	37.0	18	23.1		
	2000 mg	7	25.9	3	3.8		

Discussion

Prevalence of Vitamin B12 Deficiency

The prevalence of Vitamin B12 deficiency in this study was 25.7%, which is consistent with other studies conducted on Metformin users. Al-Saeed and Baraja (7) reported a prevalence of 3.6% in non-vegetarian patients, but their study included patients who were taking Vitamin B12 supplements. In contrast, the present study excluded patients on supplements, leading to a higher observed deficiency rate.

Vitamin B12 deficiency in non-vegetarian populations suggests that dietary intake alone may not be sufficient to counteract Metformin's effect on B12 absorption (8). The mechanism involves impaired calcium-mediated absorption of Vitamin B12 in the terminal ileum, a process that Metformin disrupts over time (9).

Risk Factors for Vitamin B12 Deficiency

This study found that both the duration and dosage of Metformin were significantly associated with Vitamin B12 deficiency. Patients on higher doses (>1000 mg/day) or those using Metformin for more than 5 years were at greater risk of developing a deficiency. These findings are consistent with previous studies by Ting et al. (10) and de Jager et al. (11), which also reported dose- and time-dependent effects of Metformin on Vitamin B12 levels.

The longer the duration of diabetes, the higher the likelihood of Vitamin B12 deficiency. This highlights the need for regular monitoring of B12 levels in patients with long-standing diabetes who are on Metformin therapy.

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Clinical Implications

The clinical implications of Vitamin B12 deficiency are significant, especially for diabetic patients already at risk for neuropathy. Vitamin B12 deficiency can exacerbate neuropathy and other neurological complications (12). Therefore, routine screening for Vitamin B12 levels in patients on long-term Metformin therapy is recommended, particularly for those on higher doses. Early intervention with Vitamin B12 supplementation may help prevent long-term neurological damage.

Limitations

The limitations of this study include its cross-sectional design, which prevents causal inferences. Additionally, the study was conducted in a single tertiary care center, which may limit the generalisability of the findings. Future longitudinal studies are needed to confirm these results and explore the impact of Vitamin B12 supplementation on Metformin users.

Conclusion

This study demonstrates a significant prevalence of Vitamin B12 deficiency in non-vegetarian T2DM patients on long-term Metformin therapy. The deficiency was associated with both the duration and dosage of Metformin use. Given the clinical implications of Vitamin B12 deficiency, regular screening and early supplementation are recommended for patients on long-term Metformin therapy, particularly those on higher doses or with prolonged use.

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