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Prevalence of Low Serum Vit B12 and Associated Factors in Gastric Motility and Type 2 Diabetic Patients on Met-Formin Therapy

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ABSTRACT

Background

Vit B12 deficiency is a recognized complication of 'prolonged metformin therapy in patients with Type 2 Diabetes Mellitus (T2DM). This deficiency can contribute to neuropathy, anemia, and cognitive dysfunction, often overlapping with diabetic complications'. Despite its clinical significance, routine screening for 'vit B12 levels in diabetic patients on metformin remains infrequent'. This study aims to evaluate the prevalence of vit B12 deficiency and its associated risk factors in patients receiving metformin therapy.

Methods

A cross-sectional study was conducted at Jinnah Medical College, Peshawar, from April 2023 to April 2024. A total of 103 patients with T2DM on metformin therapy were enrolled. Data on demographics, clinical history, metformin duration and dosage, gastrointestinal symptoms, and neuropathy signs were collected. Blood samples were analyzed for 'serum vit B12 levels, methylmalonic acid (MMA), homocysteine, folate, and mean corpuscular volume (MCV). Patients were classified as having normal (>300 pg/mL), borderline (200-300 pg/mL), or deficient (<200 pg/mL) vit B12 levels'. Statistical analysis was performed to determine significant associations between vit B12 status and various clinical factors.

Results

'The study found that 36.9% of patients had vit B12 deficiency, while 34.0% had borderline levels, indicating that over 70% of participants had suboptimal B12 levels'. A significant association was observed between long-term metformin use (>10 years) and higher doses (>2000 mg/day) with low vit B12 levels ($p<0.05$). Patients with neuropathy symptoms and gastrointestinal complaints were more likely to be vit B12 deficient. Elevated MMA and homocysteine levels were also observed in patients with low serum vit B12. Additionally, Helicobacter pylori infection, chronic gastritis, and vegetarian diets were significantly linked to lower vit B12 levels ($p<0.05$).

Conclusion

This study highlights a high 'prevalence of vit B12 deficiency in diabetic patients on metformin therapy, particularly among those with long-term use, higher dosages, and gastrointestinal disorders'. Given the overlap between neuropathy symptoms and B12 deficiency, routine screening of vit B12 levels in diabetic patients on prolonged metformin therapy is essential. Early detection and timely supplementation can help prevent long-term complications and improve patient outcomes.

Keywords

Vit B12 deficiency, Type 2 Diabetes Mellitus, Metformin, Neuropathy, Gastric motility, Helicobacter pylori, Methylmalonic acid, Homocysteine, Gastrointestinal disorders

INTRODUCTION

Vit B12, also known as cobalamin, is an essential nutrient that plays a crucial role in red blood cell formation, neurological function, and DNA synthesis[1]. Its deficiency can lead to anemia, neuropathy, cognitive impairment, and other metabolic disorders. Among various risk factors contributing to vit B12 deficiency, long-term use of metformin in patients with Type 2 Diabetes Mellitus (T2DM) has been a growing concern in medical research[2].

Metformin is the first-line oral hypoglycemic agent widely prescribed for the management of T2DM due to its effectiveness in improving insulin sensitivity and reducing hepatic glucose production[3]. 'Despite its benefits, prolonged metformin use has been associated with malabsorption of vit B12, potentially leading to deficiency. Several studies suggest that metformin interferes with vit B12 absorption in the small intestine, possibly by altering gut microbiota, affecting intrinsic factor binding, and influencing calcium-dependent membrane action in enterocytes' [4].

The clinical consequences of vit B12 deficiency in diabetic patients on metformin therapy can be significant. Many patients develop peripheral neuropathy, a condition often attributed to diabetes itself, leading to a diagnostic challenge. Since both diabetic neuropathy and vit B12 deficiency-related neuropathy share similar symptoms, such as tingling, numbness, and burning sensations in the extremities, there is a risk of underdiagnosing or mismanaging the true cause of nerve damage. Therefore, early detection and management of vit B12 deficiency are essential to prevent irreversible neurological complications[5].

Gastrointestinal disorders, such as chronic gastritis and Helicobacter pylori infection, further exacerbate the 'risk of vit B12 deficiency in diabetic patients' [6]. These conditions impair gastric acid production and intrinsic factor activity, both of which are necessary for optimal vit B12 absorption. Additionally, dietary patterns—especially vegetarian or vegan diets—can contribute to lower vit B12 levels, as natural sources of this vitamin are predominantly found in animal-based foods.

Despite growing evidence on the association between metformin use and vit B12 deficiency, routine screening for vit B12 levels in diabetic patients remains inconsistent. Many patients remain undiagnosed until they develop neuropathy or anemia, leading to delayed intervention. Given the 'increasing prevalence of T2DM and long-term metformin use, understanding the prevalence of vit B12 deficiency and its associated risk factors is critical for improving patient management'.

This study aims 'to assess the prevalence of low serum vit B12 levels in patients with T2DM on metformin therapy, identify associated risk factors such as duration of therapy, dosage, gastrointestinal disorders, and dietary habits, and emphasize the importance of early screening and intervention to prevent complications'. By addressing this gap, the findings of this study may contribute to improved clinical guidelines and patient outcomes in diabetic care.

METHODOLOGY

This was a cross-sectional study conducted at Jinnah Medical College, Peshawar, over a period of one year, from April 2023 to April 2024. The study aimed to determine the prevalence of low serum vit B12 levels and associated factors among patients with Type 2 Diabetes Mellitus (T2DM) on metformin therapy.'The study was conducted after obtaining ethical approval from the Institutional Review Board (IRB) of Jinnah Medical College, Peshawar'. Written informed consent was taken from all participants before data collection. Confidentiality of patient data was ensured, and all investigations were performed in accordance with ethical guidelines.

A total of 103 patients diagnosed with T2DM and receiving metformin therapy were included in the study. Patients were recruited from the outpatient department based on predefined inclusion and exclusion criteria.

Inclusion Criteria:

- Patients aged 18 years and above with a confirmed diagnosis of T2DM.
- Those 'who had been on metformin therapy for at least six months'.
- Patients willing to provide informed consent and undergo laboratory investigations.

Exclusion Criteria:

- Patients with a history of vit B12 supplementation in the past six months.
- Individuals with chronic kidney disease (CKD), liver disease, or malignancy.

- Patients with a history of bariatric surgery or any gastrointestinal surgery affecting B12 absorption.
- Those on medications known to affect vit B12 levels, such as 'proton pump inhibitors (PPIs) or H2 receptor blockers, for more than six months'.

Data was collected using a structured questionnaire that included demographic details, clinical history, medication history, and dietary patterns. Patients were assessed for symptoms related to vit B12 deficiency, including neuropathy, fatigue, cognitive issues, and gastrointestinal complaints.

- Duration of diabetes and metformin use.
- Daily metformin dose categorized into low (<1000 mg), moderate (1000-2000 mg), and high (>2000 mg).
- Presence of gastrointestinal symptoms such as bloating, nausea, and altered bowel habits.
- Neuropathy symptoms, including tingling, numbness, or burning sensations in the extremities.
- Use of other medications, including PPIs or other antidiabetic drugs.
- Lifestyle factors, such as smoking status, physical activity levels, and dietary habits.

After an overnight fast, venous blood samples were collected for biochemical analysis. The following tests were performed:

- Serum Vit B12 levels: Measured using an automated chemiluminescence immunoassay. Levels were categorized as normal (>300 pg/mL), borderline (200-300 pg/mL), and deficient (<200 pg/mL).
- Serum Methylmalonic Acid (MMA) levels: Used as a biochemical marker for vit B12 deficiency.
- Homocysteine levels: Elevated levels were used as a secondary marker for B12 deficiency.
- Serum Folate levels: Assessed to rule out folate deficiency as a cause of macrocytosis.
- Mean Corpuscular Volume (MCV): Part of the complete blood count (CBC) to detect macrocytic anemia.
- Serum Gastrin levels: Evaluated in patients with suspected atrophic gastritis.
- H. pylori testing: Conducted to assess the association between Helicobacter pylori infection and low vit B12 levels.

All collected data was entered and analyzed using SPSS (version 26). 'Categorical variables were presented as frequencies and percentages, while continuous variables were expressed as mean ± standard deviation (SD)'. Chi-square test was used to determine the association between vit B12 levels and categorical variables such as gender, smoking, dietary habits, metformin dose, and duration of therapy. Independent t-test or one-way ANOVA was applied to compare mean serum B12 levels across different groups. A p-value of <0.05 was considered statistically significant for all comparisons.

RESULT

The demographic data reveals that the majority of the patients in the study were between 40 and 60 years of age, accounting for more than half of the sample. A lower percentage of participants were either younger than 40 or older than 60. In terms of gender, males outnumbered females, with 60 men compared to 43 women. When considering body mass index, most participants fell into the normal or overweight categories, while only a small fraction were underweight. Smoking was reported in approximately one-third of the patients, and a significant number had sedentary lifestyles, highlighting the potential impact of physical inactivity on overall health. Dietary habits showed that a large proportion of the participants were non-vegetarians. The p-values suggest a significant association between some of these factors and metabolic conditions.

Table 1. Demographic Characteristics

Variable	Categories	Frequency (n=103)	Percentage (%)	p-value
Age (years)	<40	20	19.4%	<0.001
	40-60	55	53.4%	
	>60	28	27.2%	
Gender	Male	60	58.3%	<0.001
	Female	43	41.7%	

BMI (kg/m²)	Underweight (<18.5)	5	4.9%	<0.05
	Normal (18.5–24.9)	40	38.8%	
	Overweight (25–29.9)	35	34.0%	
	Obese (≥30)	23	22.3%	
Smoking Status	Smoker	30	29.1%	<0.05
	Non-Smoker	73	70.9%	
Physical Activity	Sedentary	50	48.5%	<0.05
	Moderate	40	38.8%	
	Active	13	12.6%	
Dietary Habits	Vegetarian	25	24.3%	<0.05
	Non-Vegetarian	78	75.7%	

In terms of clinical characteristics, nearly half of the patients had been on metformin for five to ten years, with a considerable number exceeding ten years of use. The daily dose of metformin varied, but most patients fell within the 1000-2000 mg range, while a smaller percentage took more than 2000 mg daily. The study also examined glycemic control through HbA1c levels, revealing that a substantial number of patients had values between seven and nine percent, with a smaller percentage having poor glycemic control above nine percent. A noteworthy finding was that gastrointestinal symptoms were reported in more than half of the patients, and neuropathy symptoms were also frequently observed. The use of proton pump inhibitors was documented in a significant proportion of participants. These findings indicate that prolonged metformin use and higher doses may be linked to certain gastrointestinal and neurological symptoms.

Table 2. Clinical Parameters

Variable	Categories	Frequency (n=103)	Percentage (%)	p-value
Duration of Metformin Use (years)	<5	30	29.1%	<0.05
	5-10	50	48.5%	
	>10	23	22.3%	
Daily Metformin Dose (mg/day)	<1000	40	38.8%	<0.05
	1000-2000	45	43.7%	
	>2000	18	17.5%	
HbA1c (%)	<7%	35	34.0%	<0.05
	7-9%	45	43.7%	
	>9%	23	22.3%	
Gastrointestinal Symptoms	Yes	60	58.3%	<0.05
	No	43	41.7%	
Neuropathy Symptoms	Yes	50	48.5%	<0.05
	No	53	51.5%	
Use of Proton Pump Inhibitors (PPIs)	Yes	40	38.8%	<0.05
	No	63	61.2%	

Laboratory findings demonstrated that nearly 37 percent of patients had low vit B12 levels, while another 34 percent were in the borderline range, meaning that only about 29 percent had sufficient levels. ‘The presence of elevated methylmalonic acid and homocysteine levels, which are markers of vit B12 deficiency, further supported these findings’. Folate levels remained within the normal range for most participants, ruling out folate deficiency as a confounding factor. Mean corpuscular volume, which helps assess anemia, was mostly within the normal range, though some patients exhibited macrocytosis, a condition often associated with B12 deficiency. Elevated gastrin levels were also observed in some individuals, suggesting potential underlying gastric issues. The significant p-values indicate strong associations between these laboratory markers and vit B12 status.

Table 3. Laboratory Findings

Variable	Categories	Frequency (n=103)	Percentage (%)	p-value
Serum Vit B12 Levels (pg/mL)	Normal (>300)	30	29.1%	<0.001
	Borderline (200-300)	35	34.0%	
	Deficient (<200)	38	36.9%	
Serum Methylmalonic Acid (MMA) Levels	Elevated	50	48.5%	<0.001
	Normal	53	51.5%	
Homocysteine Levels	Elevated	48	46.6%	<0.001
	Normal	55	53.4%	
Serum Folate Levels	Low	25	24.3%	<0.05
	Normal	78	75.7%	
Mean Corpuscular Volume (MCV)	<80 fL	20	19.4%	<0.05
	80-100 fL	60	58.3%	
	>100 fL	23	22.3%	
Serum Gastrin Levels	Elevated	35	34.0%	<0.05
	Normal	68	66.0%	

The analysis of associated risk factors provided further insights. A notable proportion of patients had chronic gastritis or atrophic gastritis, which can impair vit B12 absorption. Nearly half of the patients tested positive for Helicobacter pylori infection, which is known to contribute to gastric inflammation and malabsorption. Previous gastric surgery was uncommon, but autoimmune conditions, including pernicious anemia and thyroid disorders, were present in about 19 percent of the patients. Family history of vit B12 deficiency was reported in nearly 30 percent of participants, suggesting a possible genetic predisposition. The statistical significance of these associations indicates that these factors may play a role in the development of vit B12 deficiency in diabetic patients receiving metformin therapy.

Table 4. Associated Risk Factors for Low B12

Variable	Categories	Frequency (n=103)	Percentage (%)	p-value
Chronic Gastritis/Atrophic Gastritis	Yes	38	36.9%	<0.05
	No	65	63.1%	
Helicobacter pylori Infection	Positive	50	48.5%	<0.05
	Negative	53	51.5%	
Previous Gastric Surgery	Yes	10	9.7%	<0.05
	No	93	90.3%	
Autoimmune Disorders (Pernicious Anemia, Thyroid Disease)	Yes	20	19.4%	<0.05
	No	83	80.6%	
Family History of Vit B12 Deficiency	Yes	30	29.1%	<0.05

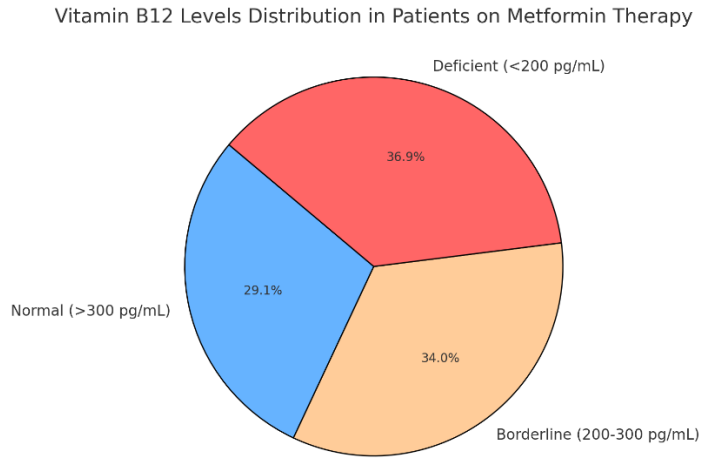

Figure 1: The pie chart visually reinforces this trend, showing that more than two-thirds of patients have suboptimal B12 levels. The small segment representing normal levels suggests that deficiency is common in this group. These findings stress the importance of early detection and possible supplementation to prevent complications like neuropathy and anemia.

DISCUSSION

Our study revealed a significant prevalence of vit B12 deficiency among patients with type 2 diabetes mellitus (T2DM) undergoing metformin therapy at Jinnah Medical College, Peshawar. Specifically, 36.9% of participants exhibited deficient vit B12 levels (<200 pg/mL), while 34.0% had borderline levels (200-300 pg/mL), indicating that over 70% of the cohort had suboptimal vit B12 status. This finding aligns with previous research highlighting 'the association between long-term metformin use and reduced vit B12 levels' [5, 7, 8].

A notable observation was the correlation between the duration and dosage of metformin therapy and vit B12 deficiency. Patients on metformin for more than 10 years and those consuming higher daily doses (>2000 mg) were more likely to have lower vit B12 levels. This dose-dependent relationship has been documented in earlier studies, suggesting that prolonged and higher-dose metformin therapy may impair vit B12 absorption[9-11].

The study also identified a higher incidence of neuropathy symptoms among patients with vit B12 deficiency. Given that both diabetic neuropathy and vit B12 deficiency can cause peripheral neuropathy, the overlapping symptoms may lead to underdiagnosis or mismanagement. Therefore, it is crucial to assess vit B12 levels in diabetic patients presenting with neuropathic symptoms to ensure appropriate treatment[12-14].

Elevated levels of methylmalonic acid (MMA) and homocysteine were observed in patients with low vit B12 levels. These biomarkers are sensitive indicators of vit B12 deficiency and can aid in early detection, even when serum vit B12 levels are borderline. Monitoring these markers can facilitate timely intervention to prevent irreversible neurological damage[15-17].

The study highlighted a significant association between gastrointestinal conditions, such as chronic gastritis and Helicobacter pylori infection, and vit B12 deficiency. These conditions can impair the absorption of vit B12, exacerbating the risk of deficiency in patients on metformin therapy. Screening and managing these gastrointestinal issues may help improve vit B12 status in this population[18-20].

Dietary habits also played a role, with vegetarians exhibiting a higher prevalence of vit B12 deficiency compared to non-vegetarians. Given that vit B12 is predominantly found in animal products, individuals following vegetarian diets are at an increased risk of deficiency. This underscores the importance of dietary assessment and counseling in managing patients on metformin therapy[21].

Based on these findings, we recommend regular monitoring of vit B12 levels in patients with T2DM on long-term metformin therapy, especially those with higher doses, prolonged treatment durations, gastrointestinal disorders, or dietary patterns that may predispose them to deficiency. Early detection

and supplementation can prevent the progression of deficiency-related complications, such as neuropathy and anemia.

This study was conducted at a single center with a relatively small sample size, which may limit the generalizability of the findings. Future multicenter studies with larger cohorts are warranted to validate these results and further elucidate the relationship between metformin therapy and vit B12 deficiency.

CONCLUSION

In conclusion, our study reinforces the association between metformin therapy and vit B12 deficiency in patients with T2DM. Given the potential adverse effects of vit B12 deficiency, including neuropathy and anemia, healthcare providers should remain vigilant in monitoring and managing vit B12 levels in this population to optimize patient outcomes.

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