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“Frequency of Vitamin B_{12}deficiency in Metformin-Treated type 2 Diabetic Patients”

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KEYWORDS

Type 2 Diabetes Mellitus, Metformin, Vitamin B12 Deficiency, Neuropathy, Glycemic Control, Supplementation, Diabetes Management

ABSTRACT:

Background: Type 2 Diabetes Mellitus (T2DM) is a prevalent chronic metabolic disorder characterized by insulin resistance and relative insulin deficiency. Metformin, a first-line pharmacological treatment for T2DM, is highly effective in glycaemic control but has been associated with Vitamin B12 deficiency, particularly in long-term and high-dose therapy. Vitamin B12 is critical for neurological function, DNA synthesis, and red blood cell production. Its deficiency can exacerbate complications such as neuropathy, anaemia, and cognitive impairments, which are already common in diabetic patients. This study investigates the prevalence and impact of Vitamin B12 deficiency among T2DM patients receiving metformin therapy at different dosages.

Methodology: This cross-sectional observational study was conducted in the Department of General Medicine and Endocrinology at the National Institute of Medical Sciences & Research, Jaipur, over 18 months. The study included 155 T2DM patients treated with metformin for at least six months. Participants were divided into two groups based on their metformin dosage: 500 mg and 1000 mg daily. Exclusion criteria included Type 1 diabetes, pregnancy, bariatric surgery, inflammatory bowel disease, chronic kidney or liver disease, and recent Vitamin B12 supplementation.

Blood samples were collected to measure Random Blood Sugar (RBS), Glycated Hemoglobin (HbA1c), and serum Vitamin B12 levels using chemiluminescent assays. Data were analyzed using SPSS software, with a p-value of <0.05 considered statistically significant. Comparative analysis was performed to evaluate Vitamin B12 levels between the dosage groups.

Results: The study population consisted of 155 patients, evenly distributed across the two metformin dosage groups (500 mg: 77, 1000 mg: 78). The mean age of participants was 60.338 ± 5.183 years (500 mg) and 60.795 ± 4.338 years (1000 mg). Gender distribution was balanced, with no significant differences in anthropometric measures or smoking status.

Laboratory analysis revealed no significant differences in RBS (p = 0.827) or HbA1c levels (p = 0.364) between the two groups, indicating comparable glycaemic control. However, a significant difference was observed in serum Vitamin B12 levels. Patients in the 1000 mg group exhibited lower mean Vitamin B12 levels (312.474 ± 223.979 pg/mL) compared to the 500 mg group (406.753 ± 309.793 pg/mL), with a p-value of 0.031.

The results suggest that higher doses of metformin are associated with a greater risk of Vitamin B12 deficiency. This finding aligns with existing literature, which highlights metformin’s impact on gut microbiota and its interference with the ileal absorption of Vitamin B12.

Conclusion: This study confirms a dose-dependent association between metformin therapy and reduced Vitamin B12 levels in T2DM patients. While metformin remains a cornerstone in diabetes management due to its efficacy and safety, its potential to induce Vitamin B12 deficiency requires attention. Routine monitoring of Vitamin B12 levels is essential, particularly for patients on high-dose or long-term therapy.

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Proactive screening and timely supplementation with oral or intramuscular Vitamin B12 can prevent complications such as neuropathy, anaemia, and cognitive impairments, thereby improving patient outcomes and quality of life. Further research is needed to explore strategies for mitigating this risk, including fortifying metformin formulations with Vitamin B12 or developing alternative therapies with fewer nutritional side effects.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and relative insulin deficiency. The pathophysiology of T2DM involves the inability of peripheral tissues, such as muscle and fat, to respond effectively to insulin, leading to impaired glucose uptake. Concurrently, pancreatic beta cells fail to compensate for this insulin resistance, resulting in hyperglycaemia. Over time, prolonged hyperglycaemia exacerbates beta-cell dysfunction, contributing to further insulin deficiency. Globally, T2DM is a leading cause of morbidity and mortality, with prevalence rising due to increasing obesity, sedentary lifestyles, and aging populations. According to the International Diabetes Federation, the number of adults living with diabetes worldwide is expected to rise from 537 million in 2021 to 643 million by 2030, making diabetes a significant public health concern (International Diabetes Federation, 2021)

Role of Metformin: Mechanism of Action, Dosage, and Widespread Use

Metformin is widely recognized as the first-line pharmacological treatment for T2DM. It belongs to the biguanide class of medications and works primarily by reducing hepatic glucose production (gluconeogenesis) through the activation of AMP-activated protein kinase (AMPK), a key regulator of cellular energy balance. Additionally, Metformin enhances insulin sensitivity in peripheral tissues, leading to improved glucose uptake in muscles and fat, and lowers intestinal absorption of glucose. Due to its effectiveness, relatively low cost, and favourable safety profile, Metformin is prescribed to millions of patients worldwide. The standard dosage ranges from 500 mg to 2000 mg daily, adjusted according to glycemic control and patient tolerance. Importantly, Metformin does not typically cause hypoglycemia, making it an attractive option for both monotherapy and combination therapy with other antidiabetic agents (Rojas & Gomes, 2013).

Importance of Managing Diabetes to Prevent Complications

Effective management of T2DM is critical to preventing both acute and chronic complications. Poorly controlled diabetes can lead to severe outcomes such as diabetic ketoacidosis and hyperosmolar hyperglycemic state in the short term, while long-term uncontrolled hyperglycemia is associated with microvascular complications like retinopathy, nephropathy, and neuropathy. In addition, T2DM significantly increases the risk of macrovascular diseases, including cardiovascular disease, stroke, and peripheral artery disease. These complications not only diminish the quality of life but also contribute to increased mortality. Therefore, maintaining optimal glycemic control through lifestyle modifications and pharmacotherapy, including the use of Metformin, is essential in reducing the burden of diabetes-related complications (American Diabetes Association, 2023).

METHODOLOGY

This study used a descriptive cross-sectional design to estimate the prevalence of vitamin B12 deficiency among a sample of 206 T2DM patients. Participants were selected using a simple random sampling technique and the electronic medical records of the outpatient clinic at the Diabetic and Endocrine Centre at Al-Noor Specialist Hospital in Holy Makkah. The study was conducted between August 30, 2020, and March 30, 2021. A web-based cross-sectional survey study was conducted to obtain responses from patients with T2DM attending the outpatient clinic at the National Institute of Medical Sciences and Research Hospital, Jaipur.

The main outcome measure was biochemical B12 deficiency. A blood sample was collected, and vitamin B12 levels were measured using chemiluminescent assays in an automated system. Based on this distinction, patients were categorized as vitamin B12 deficient or normal, and the clinical characteristics of the two groups were compared Study Design- It was an observational cross-sectional study

Study Area- The study was conducted in Department of General Medicine& Department of endocrinology at National Institute of Medical Sciences & Research, Jaipur, Rajasthan.

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Study population- All Type-2 Diabetes Mellitus patients treated with metformin of 18 years above age after applying the inclusion and exclusion criteria

Study period- 1st MAY 2023 to 1st NOVEMBER 2024

Time frame- 18 months

INCLUSION CRITERIA:

1. All patients older than 18 years diagnosed with T2DM and using metformin for 6 months or more were eligible to participate in the study
2. Patient who gave consent to participate in study.

EXCLUSION CRITERIA:

Patients with: -

1. Type 1 Diabetes Mellitus
2. Pregnancy or Previous bariatric surgery or gastrectomy.
3. Inflammatory bowel disease & vegetarian patients.
4. Chronic liver disease & chronic kidney disease
5. Patients on oral vitamin B12 supplementation or with a history of treatment with vitamin B12 injection or multivitamin injections

RESULT

DEMOGRAPHIC DETAILS

Table 1. Demographic details of the patients enrolled in the study.

Parameter	500 mg (Mean ± SD)	1000 mg (Mean ± SD)
Sample Size	77	78
Gender		
Male	39	38
Female	38	40
Age (years)	60.338 ± 5.183	60.795 ± 4.338
Height (cm)	168.922 ± 7.332	169.346 ± 7.507
Weight (kg)	77.429 ± 6.214	77.077 ± 5.162
Smoking		
Yes	43	37
No	34	41
All the data is presented in mean ± standard deviation, number n and percentage (%)		

A total of 155 patients were enrolled in the study, with 77 patients receiving 500 mg of metformin and 78 receiving 1000 mg. The gender distribution was balanced, with 39 males (50.6%) and 38 females (49.4%) in the 500 mg group, and 38 males (48.7%) and 40 females (51.3%) in the 1000 mg group.

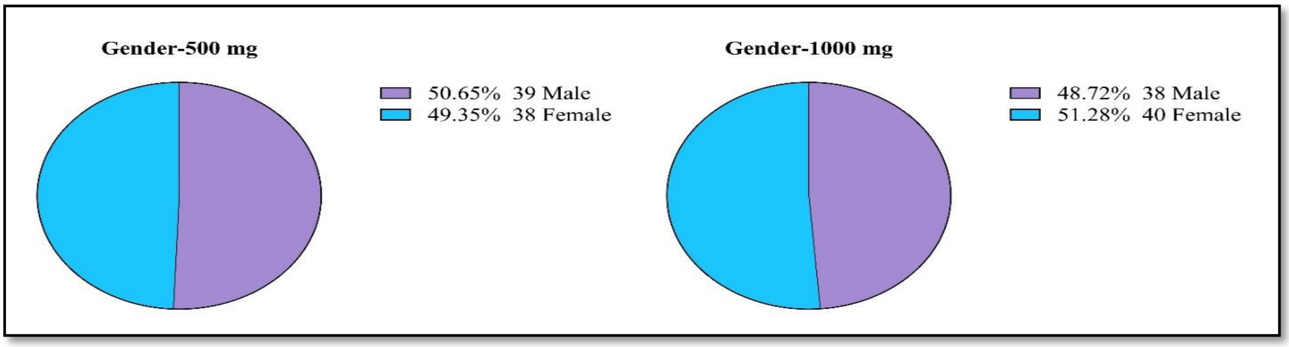

Figure 1. Gender distribution of the subjects enrolled in both the groups.

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The mean age of participants was similar across the two groups, with the 500 mg group having a mean age of 60.338 ± 5.183 years and the 1000 mg group having a mean age of 60.795 ± 4.338 years.

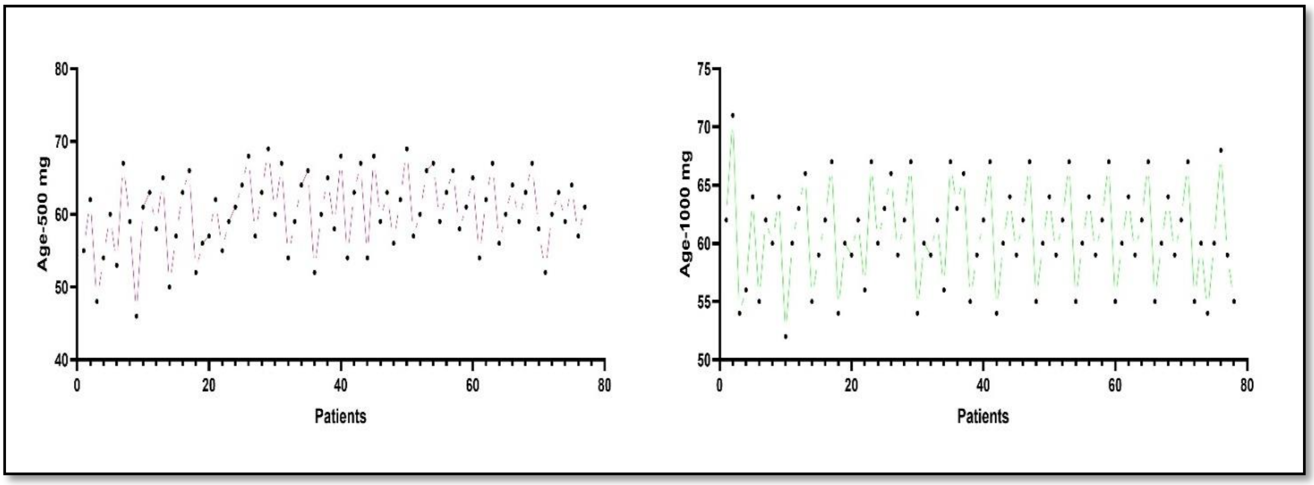

Figure 2. Age distribution of the subjects enrolled in both the groups.

The mean height was 168.922 ± 7.332 cm in the 500 mg group and 169.346 ± 7.507 cm in the 1000 mg group, while the mean weight was 77.429 ± 6.214 kg and 77.077 ± 5.162 kg in the respective groups.

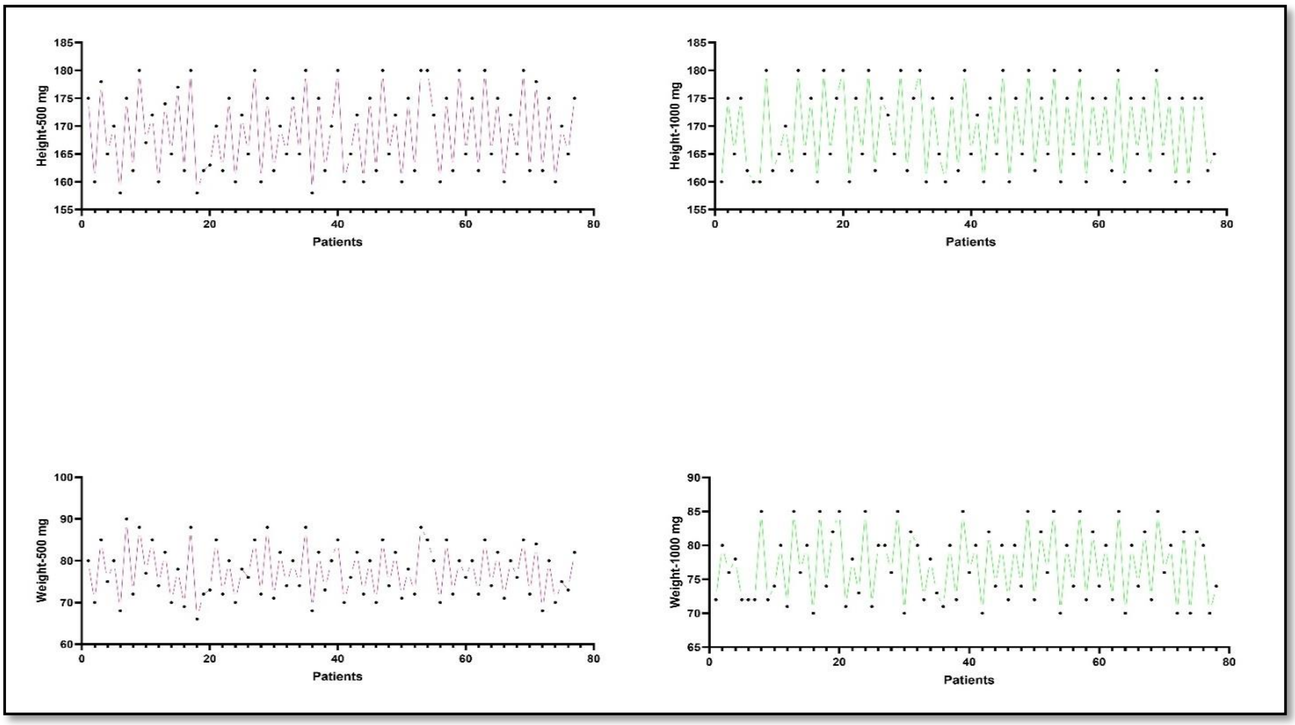

Figure 3. Anthropometric details of the subjects enrolled in both the groups.

Regarding smoking status, the 500 mg group included 43 smokers (55.8%) and 34 non-smokers (44.2%), while the 1000 mg group had 37 smokers (47.4%) and 41 non-smokers (52.6%).

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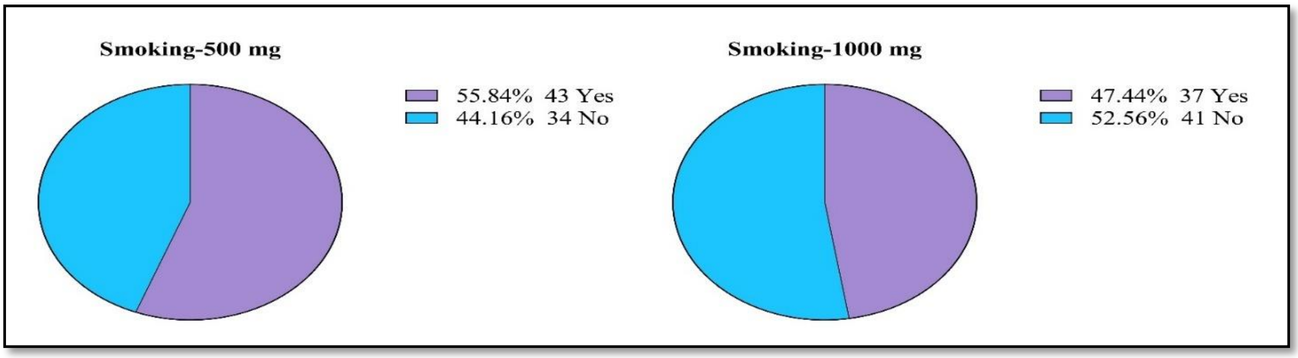

Figure 4. Prevalence of smoking among the subjects enrolled .in both the groups.

These demographic characteristics highlight a comparable distribution of age, gender, and anthropometric measures between the two metformin dosage groups. Such similarity ensures that any observed differences in outcomes related to vitamin B12 levels are unlikely to be confounded by demographic disparities.

LABORATORY PARAMETERS

Table 2. Comparative laboratory parameters of patient among both the groups.

Parameter	500 mg (Mean ± SD)	1000 mg (Mean ± SD)	p-value*
RBS (mg/dL)	**200.519 ± 10.182**	**200.192 ± 8.392**	**0.827**
HbA1c (%)	**8.197 ± 0.430**	**8.144 ± 0.294**	**0.364**
Vitamin B12 (pg/mL)	**406.753 ± 309.793**	**312.474 ± 223.979**	**0.031**
All the data is presented in mean ± standard deviation. ***The variance is significant at p<0.05**			

The laboratory parameters of the study population were compared between the two metformin dosage groups (500 mg and 1000 mg). The mean random blood sugar (RBS) levels were similar between the groups, with 200.519 ± 10.182 mg/dL in the 500 mg group and 200.192 ± 8.392 mg/dL in the 1000 mg group (p = 0.827). This indicates no significant difference in glycemic control based on the metformin dosage.

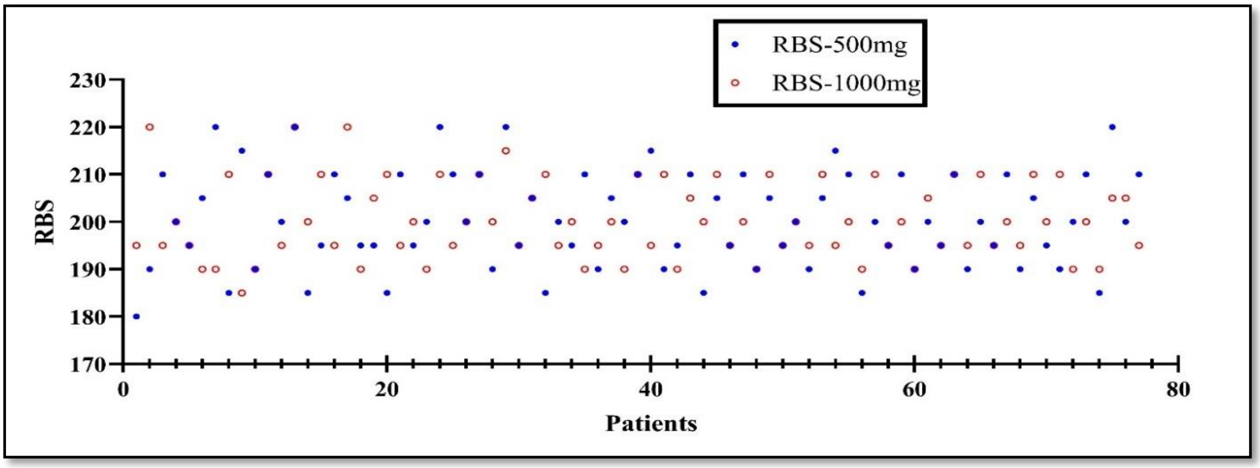

Figure 5. Random Blood Sugar of the subjects enrolled in both the groups.

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The mean HbA1c levels, which reflect long-term glycemic control, were also comparable, measuring 8.197 ± 0.430% in the 500 mg group and 8.144 ± 0.294% in the 1000 mg group (p = 0.364). Both groups demonstrated poor glycemic control, consistent with the inclusion criteria for type 2 diabetic patients.

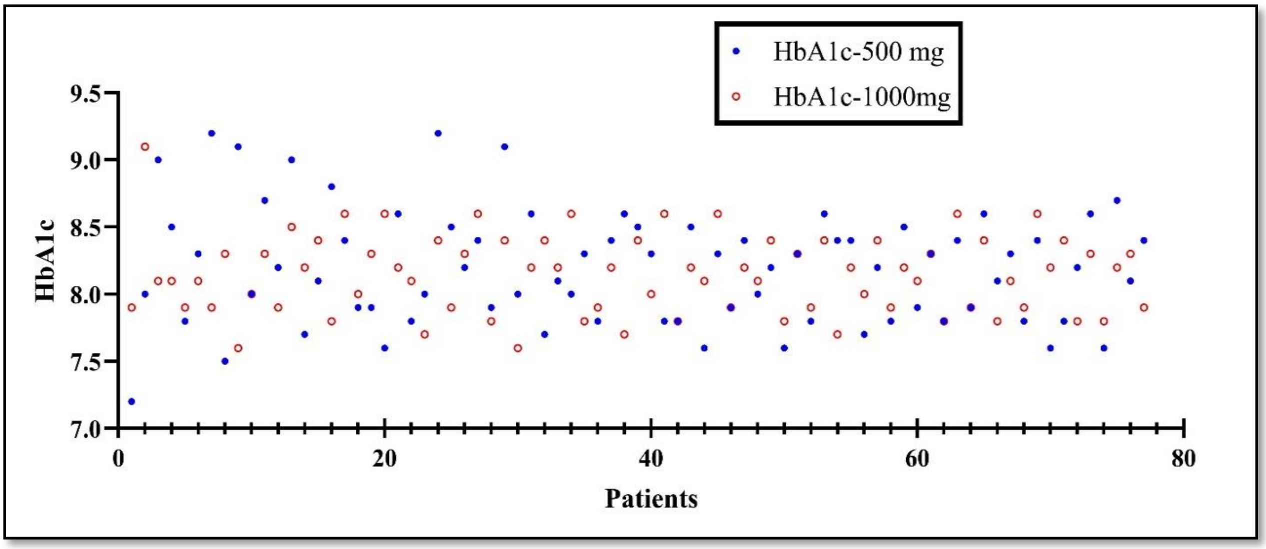

Figure 6. Glycated Hemoglobin of the subjects enrolled in both the groups.

However, a statistically significant difference was observed in mean serum vitamin B12 levels between the two groups. The 500 mg group had a higher mean vitamin B12 level (406.753 ± 309.793 pg/mL) compared to the 1000 mg group (312.474 ± 223.979 pg/mL), with a p-value of 0.031. This finding suggests that a higher dose of metformin (1000 mg) may be associated with a greater risk of reduced vitamin B12 levels in type 2 diabetic patients.

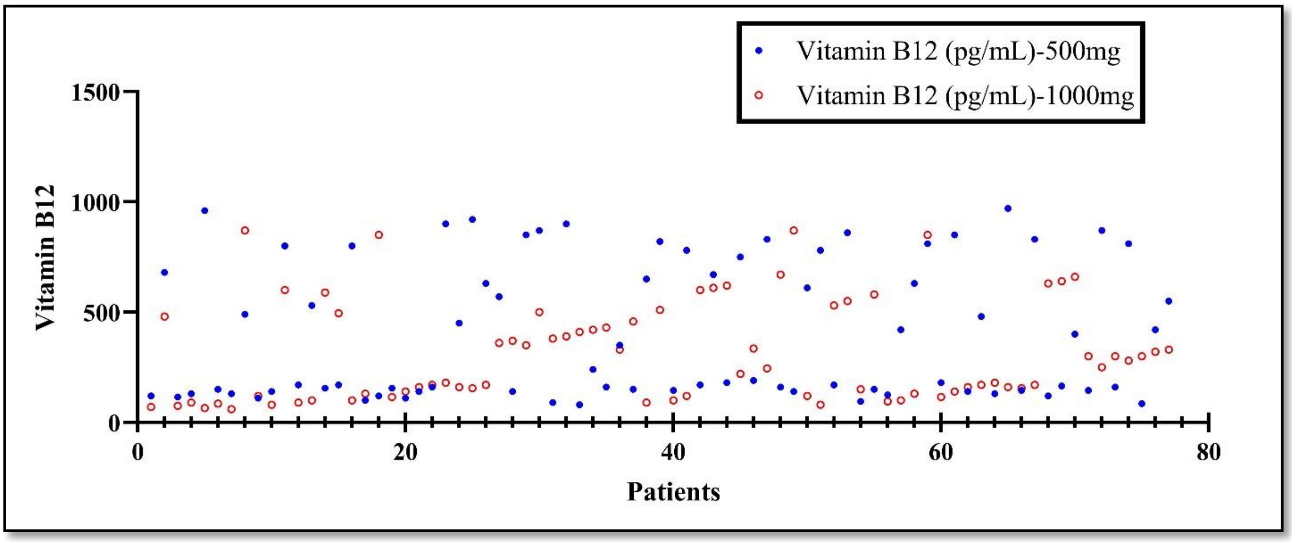

Figure 7. Vitamin B12 levels of the subjects enrolled in both the groups.

These results highlight the potential impact of metformin dosage on vitamin B12 status, warranting further investigation and consideration of routine vitamin B12 monitoring in patients on high-dose metformin therapy.

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DISCUSSION

This study evaluated the demographic characteristics, laboratory parameters, and their association with vitamin B12 levels in type 2 diabetic patients treated with two different doses of metformin (500 mg and 1000 mg). The findings provide valuable insights into the potential impact of metformin on vitamin B12 status, a crucial factor in managing diabetes and preventing long-term complications.

The demographic profile of patients was well-balanced between the two dosage groups, with similar distributions in gender, age, height, and weight. This comparability ensured that the observed differences in laboratory parameters, particularly vitamin B12 levels, could be attributed to metformin dosage rather than demographic disparities. Moreover, the distribution of smokers and non-smokers was comparable between the groups, eliminating smoking as a potential confounding factor in this study. Previous studies have reported that age and smoking status may influence vitamin B12 absorption (29,30), but our findings suggest that these factors did not play a significant role in the observed differences.

The glycemic control parameters, including random blood sugar (RBS) and HbA1c, were comparable between the 500 mg and 1000 mg groups. This indicates that both metformin doses were equally effective in managing blood glucose levels. Despite poor glycemic control observed in both groups (mean HbA1c > 8%), this was expected, as the study included patients with type 2 diabetes requiring metformin therapy (31).

A significant finding of this study was the difference in serum vitamin B12 levels between the two groups. The mean vitamin B12 level was significantly lower in the 1000 mg group (312.474 ± 223.979 pg/mL) compared to the 500 mg group (406.753 ± 309.793 pg/mL), with a p-value of 0.031. This finding aligns with existing evidence suggesting that higher doses and prolonged use of metformin are associated with reduced vitamin B12 levels (32,33).

Metformin is a cornerstone in type 2 diabetes management, but its role in vitamin B12 deficiency has been extensively documented. The proposed mechanism involves metformin altering the gut microbiota and reducing the absorption of vitamin B12 in the ileum (31,34). This effect is dose-dependent and more pronounced in patients receiving higher doses or long-term therapy. A meta-analysis by Ting et al. (2020) reported that patients on high-dose metformin had a 13-15% greater risk of vitamin B12 deficiency compared to those on lower doses.

Vitamin B12 deficiency is clinically significant because it is associated with neurological complications, including neuropathy, which can overlap with diabetic neuropathy, leading to diagnostic challenges (33,35). Additionally, deficiency in vitamin B12 can result in megaloblastic anemia and other systemic effects, potentially exacerbating the health burden of type 2 diabetes (29,31).

These findings emphasize the need for routine monitoring of vitamin B12 levels in patients on metformin therapy, especially those on higher doses. Clinical guidelines should advocate for regular screening, particularly in patients with symptoms of deficiency such as neuropathy, fatigue, or cognitive impairment (30). Supplementation with vitamin B12 may be a simple and effective strategy to mitigate the deficiency risk associated with metformin use (33).

Future studies should focus on the duration of metformin therapy and its cumulative impact on vitamin B12 levels. Additionally, exploring strategies to improve vitamin B12 absorption or developing metformin formulations with reduced impact on vitamin B12 metabolism could further enhance patient outcomes.

This study confirms that higher doses of metformin are associated with lower serum vitamin B12 levels in type 2 diabetic patients. While metformin remains indispensable in diabetes management, its impact on vitamin B12 status warrants attention. Proactive screening and timely intervention can prevent deficiency-related complications, improving the overall quality of care for diabetic patients.

CONCLUSION

This study provides compelling evidence that higher doses of metformin are significantly associated with lower serum vitamin B12 levels in patients with type 2 diabetes. While metformin remains a cornerstone in the management of type 2 diabetes due to its efficacy in controlling blood glucose levels and its favourable safety profile, the findings highlight a critical concern regarding its long-term use and its potential to induce vitamin B12 deficiency.

Vitamin B12 is essential for neurological function, DNA synthesis, and red blood cell production. A deficiency can lead to a spectrum of complications, ranging from mild symptoms such as fatigue and weakness to severe conditions like megaloblastic anemia and neuropathy. These complications can be particularly detrimental in diabetic patients, who may already face an elevated risk of neuropathy due to chronic hyperglycemia. The overlap between diabetic neuropathy and vitamin B12 deficiency-induced neuropathy underscores the importance of monitoring vitamin B12 levels to ensure accurate diagnosis and effective management of these conditions.

The dose-dependent association observed in this study underscores the need for proactive measures in patients receiving high doses of metformin, such as routine monitoring of serum vitamin B12 levels as part of their regular diabetes care. Early detection of vitamin B12 deficiency can facilitate timely intervention through dietary modifications, oral supplements, or intramuscular injections of vitamin B12, thereby preventing long-term complications and improving patient outcomes.

This study also reinforces the broader need for individualized patient care in diabetes management. While metformin's glycemic benefits remain unparalleled, its potential adverse effects, such as vitamin B12 deficiency, should not be overlooked. Physicians should adopt a holistic approach that balances the benefits of metformin therapy with the risks of nutritional deficiencies, ensuring that patients receive comprehensive care tailored to their unique needs.

Further research is warranted to explore the long-term impact of metformin therapy on vitamin B12 status, particularly in specific subgroups such as elderly patients, those with pre-existing gastrointestinal conditions, and those on prolonged therapy. Additionally, studies investigating the efficacy of different supplementation strategies and the potential benefits of fortifying metformin formulations with vitamin B12 are necessary to refine treatment protocols.

In conclusion, while metformin remains indispensable in the management of type 2 diabetes, its impact on vitamin B12 levels highlights an important aspect of patient care that warrants greater attention. Regular monitoring, early detection, and timely interventions can mitigate the risk of deficiency-related complications, ensuring better health outcomes and enhancing the overall quality of life for diabetic patients.

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