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Prevalence of vitamin B12 deficiency among diabetic patients on metformin therapy in a South Indian tertiary care hospital

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Abstract

Introduction: Metformin is one of the first-line drugs used for the management of Type 2 diabetes mellitus. Prolonged metformin therapy has been associated with reduced vitamin B12 absorption, potentially leading to biochemical deficiency and related clinical manifestations. This study aimed to assess whether long-term metformin use is associated with decreased serum vitamin B12 levels in diabetic patients.

Materials and Methods: A retrospective observational study was conducted using electronic medical records of diabetic patients attending a South Indian tertiary care hospital. Serum vitamin B12 values, duration of metformin therapy, and relevant demographic and clinical data were collected. Statistical analyses were performed to determine the correlation between metformin use and vitamin B12 deficiency.

Results: A statistically significant association was observed between the duration of metformin therapy and reduced serum vitamin B12 levels. Patients on long-term metformin therapy demonstrated a higher prevalence of vitamin B12 deficiency compared with those on shorter duration or minimal exposure to the same drug.

Conclusion: This study demonstrates a significant correlation between metformin therapy and vitamin B12 deficiency in diabetic patients. These findings emphasize the need for routine monitoring of vitamin B12 levels, particularly in individuals on prolonged metformin therapy, to enable early detection and appropriate management of deficiency manifestations and complications.

Keywords: metformin; vitamin B12; type 2 diabetes mellitus; deficiency; prevalence

Introduction

Diabetes mellitus is characterized by elevated blood glucose levels resulting from inadequate insulin secretion or impaired insulin action, leading to abnormal carbohydrate metabolism. According to the World Health Organization (WHO), in 2014, approximately 9% (about 1 in 10 adults) had diabetes, and this figure is projected to double by 2030, with nearly 1 in 5 adults being affected [1]. Complications of diabetes-particularly of Type 2 diabetes mellitus-are the seventh leading cause of death globally; in 2012, an estimated 1.5 million deaths occurred due to microvascular and macrovascular complications, about 50% of which were attributed to stroke, one of the major complications of diabetes [2]. The prevalence of diabetes varies across populations, being more common in developed countries and in individuals above 60 years of age, while in developing nations it commonly affects adults between 35 and 64 years of age [3].

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Vitamin B12 plays a crucial enzymatic role in methylation reactions that are essential for DNA synthesis and cellular metabolism. Deficiency of vitamin B12 can disrupt these processes and frequently manifests through symptoms involving rapidly proliferating cells [4]. Vitamin B12 is metabolized into two active forms, adenosylcobalamin in the mitochondria and methylcobalamin in the cytoplasm both of which regulate key biochemical pathways involving methylmalonic acid and homocysteine [5]. If left uncorrected, vitamin B12 deficiency can lead to significant neurological and hematological disturbances [6]. Therefore, timely recognition, diagnosis, and management of vitamin B12 deficiency are essential to reduce associated morbidity [7].

Metformin is widely used for glycemic control in Type 2 diabetes, primarily by reducing hepatic glucose production and enhancing peripheral insulin sensitivity. It is not primarily indicated for Type 1 diabetes, a condition characterized by absolute insulin deficiency [8]. Current international guidelines, including those from the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA), recommend metformin as first-line therapy for Type 2 diabetes [9]. Its widespread use is supported by its efficacy, affordability, weight neutrality, and overall safety profile. Additional benefits include improvements in lipid parameters, inflammatory markers, and reduction in cardiovascular events, seemingly independent of its glucose-lowering effect [10]. Early clinical observations suggested a 30% prevalence of vitamin B12 malabsorption in patients receiving long-term metformin therapy, and subsequent studies have shown a 14–30% reduction in serum vitamin B12 levels associated with metformin use [11].

This retrospective study aims to assess the risk of vitamin B12 deficiency among diabetic patients on metformin therapy. By identifying patterns and variations in vitamin B12 levels among these patients, the study seeks to provide insights that may aid in early diagnosis and improved clinical management of the subsequent deficiency manifestations.

Materials and methods

This retrospective study was conducted at PSG Hospitals, Coimbatore, using patient records from a 15-year period between November 2007 and November 2022. A convenient sampling strategy was employed, and primary data were collected from case sheets and hospital records of individuals diagnosed with diabetes mellitus during the study period. Approval for the study was obtained from the Institutional Ethics Committee.

Initially, a minimum sample size of 200 patients was targeted, including individuals diagnosed with diabetes mellitus and those who developed vitamin B12 deficiency during the course of metformin therapy, depending on the availability of eligible records. All data were collected anonymously to ensure patient confidentiality, and no personal identifiers were recorded. Patient information was handled securely, and confidentiality was strictly maintained.

Patient files meeting the inclusion criteria were retrieved through the Medical Records Department for detailed analysis. Records of diabetic patients who had been prescribed metformin for more than six months and who had documented serum vitamin B12 levels were examined. Relevant demographic and clinical information was extracted from the medical records for the purpose of analysis.

Patients consuming a non-vegetarian diet were included if they were adults diagnosed with diabetes mellitus and had been only on metformin therapy for more than six months with documented vitamin B12 levels indicating deficiency or otherwise. The dosage of metformin was fixed at 1000mg twice daily, for both cases and controls. Patients who were receiving oral or parenteral vitamin B12 supplementation were excluded from the study. After data collection, all variables were subjected to appropriate statistical analysis to determine the association between metformin use and vitamin B12 deficiency. Continuous variables were represented as mean ± standard deviation, median (min, max). Categorical variables were represented as absolute counts and percentages. The t-test was used to compare continuous variables and Chi Square for categorical variables (Fisher Exact for those with counts < 5). Pearson correlation method was used to calculate the correlation coefficients, P value of < 0.05 was considered statistically significant.

Results

The mean serum vitamin B12 levels were significantly lower in the cases (Type 2 diabetes patients on metformin therapy with reduced serum vitamin B12 levels) when compared with the control group. The mean vitamin B12 concentration in the case group was 101.46 ± 33.29 pg/mL, whereas the control group demonstrated a mean level of 524.07 ± 165.71 pg/mL. This difference was statistically significant, with a P value of <0.0001, indicating a strong association between metformin use and reduced vitamin B12 levels.

Among the study population, 55 individuals in the case group were metformin users, compared with only 22 metformin users in the control group. This distribution further supports the observed association between metformin exposure and decreased serum vitamin B12 concentrations. The corresponding P value of <0.0001 reinforces the statistical significance of this relationship (Table 1).

Table 1: Summary of biochemical parameters.

Parameter	*Cases*	*Controls*	*P value*
	N = 75	*N = 30*	
Vit B12	101.46 ± 33.29 106.5 (49.99, 150.3)	524.07 ± 165.71 517.5 (271, 898)	< 0.0001
Age	59.02 ± 10.19 61 (40, 74)	57.6 ± 9.84 54 (42,78)	0.5104
Gender			
Male	46 (44%)	17 (16%)	0.8255
Female	29 (28%)	13 (12%)	
Duration of diabetes	9.25 ± 4.76 9 (1, 18)	10.3 ± 6.71 8.5 (2, 29)	0.4405
Treatment			
Metformin	55 (52%)	22 (21%)	<0.0001
Metformin+Sulfonylurea	20 (19%)	0	
Metformin+Insulin	0	8 (8%)	
Duration of treatment	6.02 ± 3.06 6 (1, 15)	7.43 ± 3.54 7.5 (1, 15)	0.0632

The correlation analysis between serum vitamin B12 levels and various clinical parameters revealed no statistically significant associations in either the case or control groups. Among the cases, vitamin B12 levels demonstrated weak correlations with age (r = 0.0352, p = 0.7643), duration of diabetes (r = 0.117, p = 0.3174), and duration of treatment (r = –0.1105, p = 0.3483). Similarly, in the control group, weak negative correlations were observed for age (r = –0.2194, p = 0.2439), duration of diabetes (r = –0.252, p = 0.1784), and duration of treatment (r = –0.1389, p = 0.4641). None of these relationships reached statistical significance, indicating that vitamin B12 levels were not influenced by these variables in the study population (Table 2).

Table 2: Correlation between vitamin B12 and other clinical parameters.

Parameter	*Cases*	*P value*	*Controls*	*P value*
	Cor. Coeff		*Cor. Coeff*	
Age	0.0352	0.7643	-0.2194	0.2439
Duration of diabetes	0.117	0.3174	-0.252	0.1784
Duration of treatment	-0.1105	0.3483	-0.1389	0.4641

Importantly, other demographic and clinical variables including age, sex, duration of diabetes, and duration of treatment did not show any statistically significant correlations with vitamin B12 levels, as all P values were greater than 0.05. These findings indicate that these parameters are not significant confounders contributing to the reduced vitamin B12 levels observed in the case group compared with the controls. This strengthens the conclusion that the decrease in vitamin B12 is specifically associated with metformin therapy rather than influenced by these demographic factors.

Discussion

Multiple studies have examined the association between metformin therapy in diabetic patients and reduced serum vitamin B12 levels, consistently demonstrating a significant relationship between metformin use and vitamin B12 deficiency [12]. Several mechanisms have been proposed to explain the reduced absorption of vitamin B12 in patients undergoing metformin therapy. One hypothesis suggests that metformin interferes with the calcium-dependent uptake of the intrinsic factor–vitamin B12 complex, thereby impairing intestinal absorption [13]. Another proposed mechanism is that metformin may interact directly with the cubilin receptor, altering its membrane charge and subsequently reducing the binding affinity of the calcium-dependent intrinsic factor–vitamin B12 complex [13].

Despite the well-established association between metformin use and vitamin B12 deficiency, there

are limited formal guidelines regarding the routine screening, early detection, and management of deficiency in these patients [14]. As a result, many individuals are diagnosed only after developing clinical symptoms. The findings of this study highlight a notable prevalence of vitamin B12 deficiency among metformin-treated diabetic patients in Coimbatore, South India. This emphasizes the importance of proactive monitoring of vitamin B12 levels to prevent neurological and hematological complications that may arise from long standing untreated deficiency. Given that vitamin B12 supplementation is inexpensive and widely accessible in most countries, early management is both feasible and clinically beneficial [15].

In this study, patients with vitamin B12 deficiency typically exhibited a longer duration of diabetes, prolonged exposure to metformin therapy, and higher daily metformin dosages. Univariate logistic regression analysis demonstrated significant associations between each of these factors and reduced vitamin B12 levels. These findings align with previous research showing that longer diabetes duration correlates with a higher risk of vitamin B12 deficiency [16, 17]. Furthermore, multiple meta-analyses have identified both treatment duration and metformin dose as major determinants of vitamin B12 depletion[18]. Consistent with recent real-world clinical data [19], our analysis reinforces the importance of routine monitoring of vitamin B12 levels in individuals receiving long-term metformin therapy.

Conclusion

This study demonstrates a significant association between long-term metformin therapy and reduced vitamin B12 levels in patients with Type 2 diabetes mellitus. Routine screening for vitamin B12 deficiency should be considered in individuals receiving prolonged metformin treatment to enable early detection and timely supplementation. Future research should focus on identifying cost-effective biochemical markers for easier assessment of vitamin B12 status and developing standardized guidelines for monitoring and supplementation. Such measures could substantially reduce the burden of vitamin B12 deficiency and prevent related complications in metformin-treated patients.

Conflicts of interest

Authors declare no conflict of interest.

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