ORIGINAL ARTICLE

Exploring Hypovitaminosis B12 in New Onset Type 2 Diabetes Mellitus and Prediabetes

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Abstract

Background: Diabetics often develop vitamin B12 deficiencies, which are crucial for blood, nerve, cognitive, and cardiovascular functions. The impact of metformin on vitamin B12 levels, leading to complications such as peripheral neuropathy and anemia, is well-known; yet no studies focus on deficiency status at diabetes diagnosis or the start of treatment.

Methods: A cross-sectional study was conducted at 2 tertiary care institutions in India, Command Hospital (Western Command), Haryana, and Civil Hospital in Sirsi, Karnataka, from July 2022 to November 2023. The study included 326 newly diagnosed type II diabetes mellitus (DM) patients and prediabetes individuals attending outpatient and inpatient departments, collecting data on substance use, dietary practices, fasting blood sugar, random blood sugar, HbA1c, and vitamin B12 levels (CLIA method).

Results: The study population of 326 individuals showed significant regional differences in mean age, gender distribution, and dietary preferences. Vitamin B12 deficiency (<200 pg/mL) was prevalent in 43.4% of prediabetic and 51.9% of type II DM patients. Significant differences in fasting blood sugar, postprandial blood sugar, and HbA1c levels were observed between regions. However, no significant correlation was found between vitamin B12 levels and HbA1c, age, or fasting glucose levels. Vegetarian individuals exhibited significantly higher vitamin B12 deficiency.

Conclusion: This study revealed a high prevalence of vitamin B12 deficiency in newly diagnosed diabetes patients, emphasizing the need for early identification and treatment to prevent complications such as neuropathy. The study recommends incorporating initial vitamin B12 assessment into the diagnosis protocol for newly detected diabetes patients to improve patient care and prevent complications in the Indian population.

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Introduction

Diabetes is a major public health problem around the globe and in India.[1] These patients with diabetes develop multiple micronutrient deficiencies.[2] One of the important micronutrients is vitamin B12, which is important for blood function, nerve function, cognitive function, and cardiovascular functioning.[3] It is also known that metformin, the most common and most effective oral hypoglycemic drug used, causes vitamin B12 deficiency over a period of use.[4] According to the latest statements released in January 2019 by the American Association of Clinical Endocrinologists and the American College of Endocrinology, it has good antihyperglycemic efficacy at doses of 1,000–2,000 mg/day. However, in 16% of metformin users, metformin is responsible for vitamin B12 malabsorption and/or deficiency.[5,6] A review of existing literature has shed light on the impact of metformin and other OHAs on vitamin B12 levels.[7] Vitamin B12 malabsorption may lead to deficiency, which could be a causal factor in the development of peripheral neuropathy and anemia, further worsening the chronic disease.[8] It usually takes 4–6 months to start depletion of vitamin B12 and 5–10 years to show clinically the signs and symptoms of deficiency. Hence, there have been recommendations for annual screening for vitamin B12. However, there are no studies focusing on the deficiency status at the start of diagnosis or treatment.[9]

Hence, timely identification and treatment of the same are very essential. However, vitamin deficiency is very high in the general population itself,[10] hence patients are at risk of having vitamin B12 deficiency even before the start of antidiabetic treatment in those with new-onset diabetes. In such scenarios, the preexisting deficiency or insufficiency can add insult to injury and cause rapid progression of neuropathy or other symptoms of deficiency. This leads to severe damage earlier than expected. Hence, it is further important to identify and treat early so that complications such as neuropathy and worsening of overall health can be prevented. The preexisting vitamin B12 deficiency is high due to various reasons such as high PPI use and the increasing prevalence of NASH in the population.[11,12]

Thus, with this background, this study was conducted to assess the prevalence of low vitamin B12 in newly diagnosed type II diabetes mellitus (DM) patients.

Methods

This cross-sectional study was conducted at 2 tertiary care institutions, 1 North Indian center, Command Hospital (Western Command), Chandimandir, Haryana, and another in the South Indian population, the trust-run TSS Hospital in Sirsi, Karnataka. The study was conducted among new-onset or newly diagnosed type II DM patients or prediabetes patients attending OPD and IPD during the period from July 2022 to November 2023. Informed consent was obtained from all participants after explaining the study in detail in the local language.

Sample Size and Sampling

Sample size was calculated assuming the proportion of low serum vitamin B12 levels as 39.5% as per the study by Shahwan et al.[13] The other parameters considered for sample size calculation were 5.5% absolute precision and 95% confidence level. The following formula was used for sample size as per the study by Daniel and Cross.[14] The required sample size as per the abovementioned calculation was 303. However, 326 subjects were collected to increase precision and confidence in the findings. All newly diagnosed type II DM patients and prediabetes (IGT) subjects attending the OPD and IPD were included in the study, and those who were known cases of diabetes (chronic type II DM patients) were excluded. After informed consent, demographic details, substance use, and dietary practices were documented along with the FBS, RBS, and HbA1c. Vitamin B12 estimation was done

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by CLIA (chemiluminescence immunoassay) method using the Beckman Coulter machine.

Ethical and Informed Consent

Ethical approval was obtained from the Institutional Review Board (ref: IHEC: IEC/2022–23/002) of the center concerned. Informed written consent was obtained before the study started, and confidentiality was maintained throughout.

Statistical Analysis

Descriptive analysis was carried out using frequency and proportion for categorical variables. Continuous variables were presented as mean ± SD for normally distributed variables and median (IQR) for nonnormally distributed variables. The Chi-squared test was used to test the statistical significance of crosstabulation between categorical variables. The independent *t*-test was used to compare the mean ± SD of normally distributed continuous variables. Pearson correlation was used to assess the linear relationship between continuous variables. *p*-value < 0.05 was considered statistically significant. coGuide v 1.0.3 was used for statistical analysis.

Results

The demographic characteristics of a study population comprising 326 individuals from South and North areas were analyzed. The mean age exhibited a significant difference between the 2 regions ($p < 0.001$), with South area participants being older (52.4 ± 13.5) than those from the North area (42.9 ± 9.9). No significant differences in mean body mass index (BMI) were observed between the areas ($p = 0.841$). Gender distribution showed a substantial discrepancy between the South and North areas ($p < 0.001$), with a higher proportion of females in the South (52.5%) compared to the North (10.8%). Marital status exhibited no significant difference between the regions ($p = 0.196$), and the majority of participants were married (97.2%). Religious affiliation varied significantly ($p = 0.02$), with Hinduism being the predominant religion across both areas and combined (92.6%). Dietary preferences differed significantly between areas ($p < 0.001$), with a higher prevalence of nonvegetarian diets in the North (76.5%) compared to the South (55.6%). Smoking habits and alcohol consumption showed no significant differences between areas, with a predominant nonsmoking population (81.3%) and varying alcohol consumption patterns across regions (Table 1).

In the comparison of past medical history across 326 individuals from the South and North areas, no significant differences were observed in the prevalence of chronic liver disease, coronary artery disease (CAD), hypothyroidism, and old stroke between the 2 regions. For chronic liver disease, the positive cases were minimal and identical in both the South and North areas (1.2%, $p = 1.000$). Similarly, the occurrence of CAD did not significantly differ, with 4.4% in the South and 3.0% in the North, resulting in a combined rate of 3.7% ($p = 0.719$). However, differences emerged in the prevalence of hypertension (HTN), showing a higher proportion in the North (57.2%) compared to the South (43.1%), with a combined prevalence of 50.3% ($p = 0.015$). Hypothyroidism displayed no significant regional variance, with a combined prevalence of 8.6% ($p = 0.623$). Old stroke cases were minimal and comparable across regions, with a combined prevalence of 1.5% ($p = 1.000$). These findings suggest that while certain medical histories exhibit regional consistency, the prevalence of hypertension differs between the South and North areas in the study population (Table 2).

In the descriptive analysis of laboratory parameters for a study population of 326 individuals from the South and North areas, significant differences were observed across regions for fasting blood sugar ($p < 0.001$), postprandial blood sugar ($p < 0.001$), and HbA1c levels ($p < 0.001$). Participants from the South area exhibited higher mean levels of fasting blood sugar (178.3 ± 64.9) compared to those from the North area (125.4 ± 30.1), resulting in a combined mean of 143.9 ± 51.8. The mean postprandial blood sugar was higher in the South (264.9 ± 95.4) compared to the North (172.1 ± 50.1), yielding a combined mean of 204.0 ± 81.8. The HbA1c levels were higher in the South (8.3 ± 1.7) than in the North (6.5 ± 1.1), leading to a combined mean of 7.4 ± 1.7. One of the reasons for the

Table 1: Descriptive analysis of demographic characteristics across the area in the study population (*N* = 326)

Parameter	*Area*			*Combined (n = 326)*	*p-value*
	Level	*South (n = 160)*	*North (n = 166)*		
Age	Mean ± SD	52.4 ± 13.5	42.9 ± 9.9	47.6 ± 12.7	<0.001
Body mass index (in kg/m^2)	Mean ± SD	25.8 ± 3.3	25.9 ± 3	25.9 ± 3.2	0.841
Gender	Female	84 (52.5%)	18 (10.8%)	102 (31.3%)	<0.001
	Male	76 (47.5%)	148 (89.2%)	224 (68.7%)	
Marital status	Married	156 (97.5%)	161 (97.0%)	317 (97.2%)	0.196
	Single	2 (1.2%)	5 (3.0%)	7 (2.1%)	
	Unmarried	2 (1.2%)	0 (0.0%)	2 (0.6%)	
Religion	Hindu	150 (93.8%)	152 (91.6%)	302 (92.6%)	0.02
	Muslim	9 (5.6%)	4 (2.4%)	13 (4.0%)	
	Christian	1 (0.6%)	3 (1.8%)	4 (1.2%)	
	Sikh	0 (0.0%)	7 (4.2%)	7 (2.1%)	
Diet	Veg	71 (44.4%)	39 (23.5%)	110 (33.7%)	<0.001
	Nonveg	89 (55.6%)	127 (76.5%)	216 (66.3%)	
Smoker	Current	17 (10.6%)	19 (11.4%)	36 (11.0%)	0.935
	Past	13 (8.1%)	12 (7.2%)	25 (7.7%)	
	Never	130 (81.2%)	135 (81.3%)	265 (81.3%)	
Alcoholic	Current	20 (12.5%)	34 (20.5%)	54 (16.6%)	0.028
	Past	12 (7.5%)	21 (12.7%)	33 (10.1%)	
	Never	128 (80.0%)	111 (66.9%)	239 (73.3%)	

Table 2: Comparison of past history across area (*N* = 326)

Parameter	*Level*	*Area*		*Combined (n = 326)*	*p-value*
		South (n = 160)	*North (n = 166)*		
Chronic liver disease	Positive	2 (1.2%)	2 (1.2%)	4 (1.2%)	1.000
	Negative	158 (98.8%)	164 (98.8%)	322 (98.8%)	
Coronary artery disease	Yes	7 (4.4%)	5 (3.0%)	12 (3.7%)	0.719
	No	153 (95.6%)	161 (97.0%)	314 (96.3%)	
Hypertension (HTN)	Yes	69 (43.1%)	95 (57.2%)	164 (50.3%)	0.015
	No	91 (56.9%)	71 (42.8%)	162 (49.7%)	
Hypothyroidism	Yes	12 (7.5%)	16 (9.6%)	28 (8.6%)	0.623
	No	148 (92.5%)	150 (90.4%)	298 (91.4%)	
Old stroke	Yes	2 (1.2%)	3 (1.8%)	5 (1.5%)	1
	No	158 (98.8%)	163 (98.2%)	321 (98.5%)	

Table 3: Comparison of vitamin B12 category between types of diabetes in north and south populations

Vitamin B12 category	*North (160)*		*Total*	*South (166)*		*Total*
	Type of diabetes			*Type of diabetes*		
	Prediabetes (N = 117)	*Type 2 diabetes (N = 49)*		*Prediabetes (N = 14)*	*Type 2 diabetes (N = 146)*	
<200	50 (42.74%)	22 (44.9%)	72 (43.4%)	12 (85.71%)	71 (48.6%)	83 (51.9%)
200–300	37 (31.62%)	15 (30.61%)	52 (31.3%)	1 (7.14%)	26 (17.8%)	27 (16.9%)
>300	30 (25.64%)	12 (24.49%)	42 (25.3%)	1 (7.14%)	49 (33.6%)	50 (31.25%)

Table 4: Comparison of vitamin B12 category according to comorbidities (*N* = 326)

Comorbidities	*Vitamin B12 category*			*p-value*
	<200	*200–300*	*>300*	
Chronic liver disease				
Negative (*n* = 322)	154 (47.83%)	77 (23.91%)	91 (28.26%)	0.459
Positive (*n* = 4)	1 (25%)	2 (50%)	1 (25%)	
Coronary artery disease				
No (*n* = 314)	148 (47.13%)	78 (24.84%)	88 (28.03%)	0.423
Yes (*n* = 12)	7 (58.33%)	1 (8.33%)	4 (33.33%)	
Hypertension				
No (*n* = 162)	79 (48.77%)	39 (24.07%)	44 (27.16%)	0.890
Yes (*n* = 164)	76 (46.34%)	40 (24.39%)	48 (29.27%)	
Hypothyroidism				
No (*n* = 298)	147 (49.33%)	68 (22.82%)	83 (27.85%)	0.069
Yes (*n* = 28)	8 (28.57%)	11 (39.29%)	9 (32.14%)	
Old stroke				
No (*n* = 321)	154 (47.98%)	77 (23.99%)	90 (28.04%)	0.454
Yes (*n* = 5)	1 (20%)	2 (40%)	2 (40%)	

above difference in the results is the higher proportion of prediabetes in the North population compared to diabetes as per ADA guidelines.

The table presents a comparison of vitamin B12 categories between individuals classified with prediabetes (*N* = 117) and those diagnosed with type 2 diabetes (*N* = 49) within the North population (total *N* = 166). The distribution of vitamin B12 levels between the 2 diabetes types showed no statistically significant difference ($p = 0.967$). This suggests a comparable distribution of vitamin B12 levels in individuals with prediabetes and type 2 diabetes in the North population. Among individuals in the South population, with a total sample size of 160, differentiated by prediabetes (*N* = 14) and type 2 diabetes (*N* = 146), the results revealed a significant distinction in vitamin B12 levels ($p = 0.029$). A higher percentage of individuals with prediabetes fell into the <200 category compared to type 2 diabetes (85.71 vs 48.63%). Overall, there was a significant difference ($p = 0.01$) in vitamin B12 categories between North and South participants. There was no significant correlation between vitamin B12 and HbA1c ($r = 0.005$, $p = 0.923$), age ($r = -0.0039$, $p = 0.48$), or fasting glucose levels ($r = 0.017$, $p = 0.79$) (Table 3).

There was no significant relationship between various comorbidities such as chronic liver disease, CAD, hypertension, hypothyroidism, and old stroke and vitamin B12 deficiency (Table 4).

Table 5: Comparison of vitamin B12 category according to area and type of diabetes ($N = 326$)

Parameters	*Vitamin B12 category*			*p-value*
	<200	*200–300*	*>300*	
Alcoholic				
Current ($n = 54$)	22 (40.74%)	15 (27.78%)	17 (31.48%)	0.583
Never ($n = 239$)	115 (48.12%)	55 (23.01%)	69 (28.87%)	
Past ($n = 33$)	18 (54.55%)	9 (27.27%)	6 (18.18%)	
Smoker				
Current ($n = 36$)	14 (38.89%)	9 (25%)	13 (36.11%)	0.669
Never ($n = 265$)	127 (47.92%)	64 (24.15%)	74 (27.92%)	
Past ($n = 25$)	14 (56%)	6 (24%)	5 (20%)	
Type of diabetes				
Prediabetes ($n = 131$)	62 (47.33%)	38 (29.01%)	31 (23.66%)	0.159
Type 2 diabetes ($n = 195$)	93 (47.69%)	41 (21.03%)	61 (31.28%)	
Diet type				
Nonveg ($n = 216$)	87 (40.28%)	60 (27.78%)	69 (31.94%)	<0.001
Veg ($n = 110$)	68 (61.82%)	19 (17.27%)	23 (20.91%)	

Irrespective of smoking status, alcohol use, or prediabetes or newly diagnosed diabetes status, there was no difference in vitamin B12 level status. Significantly higher levels of insufficiency and deficiency of vitamin B12 were observed among vegetarians (Table 5).

There were significantly more prediabetics from the North side than the South side (70.48 vs 8.75%, $p < 0.001$) and more alcohol users, either current or past, in the North side than the South side (33 vs 20%, $p = 0.028$).

Discussion

This study revealed a very high prevalence of vitamin B12 deficiency (43.8–51.9%) during prediabetes or new-onset diabetes when metformin is not yet started. This is almost every alternate person having a deficiency of vitamin B12. Diabetes patients are known to develop neuropathy after 10–20 years, despite reasonable glycemic control, and sheer due to long-term dysglycemia. Thus, this preexisting deficiency adds insult to injury and further adds to the misery of diabetes patients. Studies on levels of vitamin B12 in the general population also indicate high levels of vitamin B12 deficiency.[10,15] One of the reasons for high levels of deficiency is increasing use of PPIs, worsening eating habits leading to frequent gastritis, increasing levels of alcoholism, and increasing NASH.[12,16,17]

Although it cannot be recommended to have a nonvegetarian diet, which is rich in vitamin B12, the area (North site) had higher nonvegetarians and lower deficiency of vitamin B12. However, animals are the only source of vitamin B12.[3,18] However, dietary practice alone may not determine B12 deficiency, as chronic gastritis can lead to intrinsic factor deficiency and hence decreased absorption of B12, eventually leading to B12 deficiency.[3]

This directs B12 assessment and treatment from the time of diagnosis itself to prevent or worsen neuropathy symptoms and prevent the early onset of neuropathy or anemia. Also, whether vitamin B12 deficiency is the cause or effect of NASH is still being investigated.[16] Similarly, preexisting vitamin B12 deficiency raises the question of whether it is bidirectional, both cause and effect, in diabetes. This leads to recommendations for meta-analysis and larger community-based studies to test the above hypothesis.

The prevalence of vitamin B12 deficiency (<200 pg/mL) in newly diagnosed diabetics (44%) is comparable to the general population of North India (47%), as reported by Singla et al.[10] Although the Standards of Medical Care in Diabetes—2022 state that there is no clear evidence that dietary supplements with vitamins, minerals, herbs, or spices can help with the management of diabetes,[19] deficiency requires management. The study recommends modifying existing guidelines by recommending initial assessment of vitamin B12 among newly detected diabetes patients and treating accordingly, so that patient care improves and complications, especially neuropathy, are reduced by diagnosing and treating as early as the time of diagnosis. Currently, although guidelines suggest annual screening for vitamin B12 deficiency, evidence reports that this is not being followed even in developed countries.[20,21] However, in a country like India, where high vitamin B12 deficiency exists,[15,18,22] there is a dire need for guidelines to be modified.

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