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Original research article

STUDY OF VITAMIN B12 DEFICIENCY IN TYPE 2 DIABETES MELLITUS AND ITS CORRELATION WITH PERIPHERAL NEUROPATHY

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ABSTRACT

Aim: The aim of the present study was to assess the deficiency of vitamin B12 in the patients of type 2 diabetes mellitus with peripheral neuropathy and its correlation.

Methods: The participants for the present study were recruited from patients with T2DM seen in the South Eastern Railway Central Hospital, Kolkata. The study was conducted for two years.

Results: Patients with diabetic neuropathy were older as majority had age between 61-70 years (55.40%) compared to those without neuropathy (majority had age between 51-60 years; 39.80%). The sex distribution between group was significantly different as revealed by the highly significant p value of <0.001. 9.60% of the patients with diabetes neuropathy had vitamin B 12 deficiency compared to control group (1.20%). Diabetes neuropathy patients had mean Vitamin B12 (471.33±168.992), diabetes with no neuropathy patients (479.11±208.121). Subjects in control group had higher Vitamin B12 level compared to remaining two groups.

Conclusion: Vitamin B12 deficiency is highly prevalent, especially in patients with diabetic neuropathy. In this study an inverse correlation was found between diabetic neuropathy and the plasma level of vitamin B12. The association between diabetic neuropathy and Vitamin B12

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deficiency is of great importance, since diabetic or prediabetic patients diagnosed with diabetic neuropathy may have neuropathy due to vitamin B12 deficiency.

Keywords: Diabetes mellitus, screening, Vitamin B12 deficiency

INTRODUCTION

Diabetes mellitus (DM) is associated with risk of cardiovascular diseases, which cannot be fully justified by important risk factors such as hyperglycemia,1 hypertension[2] and dyslipidemia.[3] Among all risk factors, homocysteine (Hcy) is recognized as an independent[4] and potentially modifiable,[5] risk factor that may be strongly linked to cardiovascular prognosis in Type 2 diabetes.[6] It can also be a determinant of microalbuminuria and diabetic retinopathy.

Hcy is produced during the demethylation of methionine. It is normally metabolized by two pathways, remethylation and transsulfuration. Remethylation acts as a catalyst for methionine synthase. In this reaction, 5‐ methyltetrahydrofolate is a methyl group donor and Vitamin B12 is a cofactor. Several studies found decreased serum Vitamin B12 level among metformin‐ treated diabetes patients[7] probably due to malabsorption.[8]

Type 2 diabetes is the most common type of diabetes, accounting for around 90% of all diabetes worldwide. In type 2 diabetes, hyperglycaemia is the result, initially, of the inability of the body's cells to respond fully to insulin, a situation termed 'insulin resistance'. During the state of insulin resistance, the hormone is ineffective and, in due course, prompts an increase in insulin production. Over time, inadequate production of insulin can develop because of failure of the pancreatic beta cells to keep up with demand. Type 2 diabetes is most commonly seen in older adults, but is increasingly seen in children and younger adults owing to rising levels of obesity, physical inactivity and inappropriate diet.[9] Type 2 diabetes may present with symptoms similar to those of type 1 diabetes but, in general, the presentation of type 2 diabetes is much less dramatic and the condition may be completely symptomless. In addition, the exact time of the onset of type 2 diabetes is usually impossible to determine. As a result, there is often a long pre-diagnostic period and as many as one-third to one-half of people with type 2 diabetes in the population may be undiagnosed. When unrecognised for a prolonged time, complications such as retinopathy or a lower-limb ulcer that fails to heal may be present at diagnosis.[10]

If attempts to change lifestyle are not sufficient to control blood glucose levels, oral medication is usually initiated with metformin as the first-line medicine. If treatment with a single

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antidiabetic medication is not sufficient, a range of combination therapy options is also prescribed. When oral medications are unable to control hyperglycaemia to recommended levels, insulin injections may be necessary.[11]

T2DM is a metabolic disorder that is increasingly becoming a public health concern. The disease is associated with a variety of systemic macrovascular and microvascular complications. Diabetic peripheral neuropathy (DPN) is the most common complication, and it may eventually develop in up to 50% of patients.[12]

5 million with type 2 diabetes, 60-70% will develop peripheral neuropathy (DPN)[13] and 22% are found to be vitamin B12 deficient.[14] Signs and symptoms of both DPN and vitamin B12 deficiency are similar and therefore patients undergoing testing for DPN must first eliminate vitamin B12 deficiency as the problem. In addition, patients consuming the diabetes medication, metformin, increase their risk of vitamin B12 deficiency by 74%[15], compared with patients taking insulin and other forms of biguanides. Other factors can also attribute to low vitamin B12 levels, including age, diet, malabsorption and other medication usage.[16] Many studies have focused on age and the use of metformin as the source of vitamin B12 deficiency.

Metformin is the number one recommended drug for individuals diagnosed with prediabetes and diabetes.[17] While most studies conclude that patients taking metformin have a 10-30% risk of developing vitamin B12 deficiency, there is not consistency in the timeline.[18] Bell et al stated that it takes 12 to 15 years of inadequate vitamin B12 intake in metformin users for serum B12 to reflect depleted stores.[17] The aim of the present study was to assess the deficiency of vitamin B12 in the patients of type 2 diabetes mellitus with peripheral neuropathy and its correlation.

MATERIALS AND METHODS

The participants for the present study were recruited from patients with T2DM seen in the South Eastern Railway Central Hospital, Kolkata. The study was conducted for two years.

Inclusion criteria

Cases of Type 2 diabetes mellitus or prediabetes patients with or without peripheral neuropathy

Exclusion criteria

Patients with type 1 diabetes mellitus, pregnant women, prior vitamin B 12 injections, gastrectomy, colectomy, IBD, chronic kidney disease, liver cirrhosis, with anaemia

Study groups

Group 1: non diabetic

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Group 2: Patients with diabetes but no peripheral neuropathy

Group 3: Patients with diabetic peripheral neuropathy

Study method

During the screening process, after written informed consent is obtained, the medical, family and neurological history of the subjects were taken. A vitals assessment of pulse, heart rate and blood pressure were noted down. Afterwards, various laboratory parameters like, CBC, FBS, PPBS,HbA1C, total cholesterol and serum vitamin B12 assay were carried out and noted. All the patients were examined physically for the presence of peripheral neuropathy as per the guidelines from the joint statement from American Diabetes Association.

Patients with symptoms like numbness, tingling sensation, poor balance, pain and burning sensation will be screened. Nerve conduction Velocity studies were done whenever required. Accordingly, the patients were allocated to one of the three groups as mentioned above. For each participant, serum vitamin B12 level was determined using a vitamin B12 immunoassay technique,

The following reflects serum vitamin B12 levels and interpretation

- Normal – above 300 pg/ml
- Borderline deficiency- 200 to 300 pg/ml
- Low- below 200 pg/ ml

Statistical analysis

Descriptive statistics were reported as mean (SD) for continuous variables, frequencies (percentage) for categorical variables. Independent t test was used. Chi square was used to fine the association between categorical variables. ANOVA is used to compare variances across the means (or average) of three groups. A binomial logistic regression was used. Data were statistically evaluated with IBM SPSS Statistics for Windows, Version 26.0., IBM Corp., Chicago, IL.

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RESULTS

Table 1: Age and sex distribution

S no	Age		Control	DN	DNN	Total	X^2 (df), p
1	29-40	Count	30	0	0	30	129.43 (10), <0.001
		%	36.10%	0.00%	0.00%	12.00%	
2	41-50	Count	26	3	25	54	
		% w	31.30%	3.60%	30.10%	21.70%	
3	51-60	Count	10	17	33	60	
		%	12.00%	20.50%	39.80%	24.10%	
4	61-70	Count	13	46	21	80	
		%	15.70%	55.40%	25.30%	32.10%	
5	71-80	Count	4	15	4	23	
		%	4.80%	18.10%	4.80%	9.20%	
6	>80	Count	0	2	0	2	
		%	0.00%	2.40%	0.00%	0.80%	
Total		Count	83	83	83	249	
		%	100.00%	100.00%	100.00%	100.00%	
Sex	F	Count	59	30	31	120	26.15(2), <0.001
		%	71.10%	36.10%	37.30%	48.20%	
	M	Count	24	53	52	129	
		%	28.90%	63.90%	62.70%	51.80%	
Total		Count	83	83	83	249	
		%	100.00%	100.00%	100.00%	100.00%	

Patients with diabetic neuropathy were older as majority had age between 61-70 years (55.40%) compared to those without neuropathy (majority had age between 51-60 years; 39.80%). Majority of the subjects in control groups were between 29-40 years (36.1%). This highlights that diabetic neuropathy develops among people living in their seventh to eight decade of life. The age distribution between group was significantly different as revealed by the highly

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significant p value of <0.001. Diabetes neuropathy is more common among males (63.90%). Similarly, those without neuropathy were males (62.70%). The sex distribution between group was significantly different as revealed by the highly significant p value of <0.001.

Table 2: Vitamin B12 between groups

			Group			Total	X^2 (df), p value
			Control	DN	DNN		
Vita12 level	<200	Count	1	8	3	12	17.76 (4), 0.001
		%	1.20%	9.60%	3.60%	4.80%	
	200-300	Count	2	14	11	27	
		%	2.40%	16.90%	13.30%	10.80%	
	>300	Count	80	61	69	210	
		%	96.40%	73.50%	83.10%	84.30%	
Total		Count	83	83	83	249	
		%	100.00%	100.00%	100.00%	100.00%	

9.60% of the patients with diabetes neuropathy had vitamin B 12 deficiency compared to control group (1.20%). Vitamin B12 deficiency is highly prevalent, especially in patients with diabetic neuropathy. In this study an inverse correlation was found between diabetic neuropathy and the plasma level of vitamin B12.

Table 3: Vitamin B 12 level as per metformin use

			Metformin		Total	X^2 (df), p value
			No	Yes		
Vita12 level	<200	Count	5	7	12	12.53 (2), 0.002
		%	3.00%	8.80%	4.80%	
	200-300	Count	12	15	27	
		%	7.10%	18.80%	10.80%	
	>300	Count	152	58	210	
		%	89.90%	72.50%	84.30%	
Total		Count	169	80	249	
		%	100.00%	100.00%	100.00%	

There was significant difference was obtained for metformin between groups as revealed by the significant p value of 0.002.

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Table 4: Mean Vitamin B 12 level between groups

	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean	
				Lower Bound	Upper Bound
Control	596.23	183.298	20.12	556.2	636.25
DN	471.33	168.992	22.844	433.66	524.55
DNN	479.11	208.121	18.549	434.42	508.23
Total	515.55	195.322	12.378	491.17	539.93

Diabetes neuropathy patients had mean Vitamin B12 (471.33±168.992), diabetes with no neuropathy patients (479.11±208.121). Subjects in control group had higher Vitamin B12 level compared to remaining two groups.

Table 5: Independent association of diabetic status and B12 level on neuropathy

S no	Diabetic status	Vitamin B12		OR (95% CI)	p
		Deficiency (n=39)	Normal (n=210)		
1	Control	3 (7.7)	80 (38.1)	1	-
2	Diabetic neuropathy	22 (56.4)	61 (29)	9.62 (2.75 to 33.62)	0.0004
3	Diabetic with no Neuropathy	14 (35.9)	69 (32.9)	5.41 (1.49 to 19.61)	0.01

The odds of vitamin b12 deficiency were 9.62 times more among diabetic neuropathy than control group. Similarly the odds of vitamin b12 deficiency were 5.41 times more among diabetic with no neuropathy than control group.

DISCUSSION

The present study was carried out with the aim to study the deficiency of vitamin B12 in the patients of type 2 diabetes mellitus with peripheral neuropathy as well as its correlations .It was a cross sectional study.

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Patients with diabetic neuropathy were older as majority had age between 61-70 years (55.40%) compared to those without neuropathy (majority had age between 51-60 years; 39.80%). This highlights that diabetic neuropathy develops among people living in their seventh to eight decade of life. The age distribution between group was significantly different as revealed by the highly significant p value of <0.001. In the current study, Diabetes neuropathy is more common among males (63.90%). Similarly, those without neuropathy were males (62.70%). The sex distribution between group was significantly different as revealed by the highly significant p value of <0.001. In our study a total 37.30% of the patients with diabetes neuropathy were smokers similarly, those without diabetic neuropathy, 34.90% were smokers. Significant difference was obtained in terms of smoking status between groups as revealed by the p value of <0.001.In the control group, 12% of the patients had smoking history while rest 88% patients didn't. This suggested the association of smoking and occurrence of diabetes. Subramani SK (2019) et al also recorded the same observation in their study.[19] Yeh HC (2010) et al established the direct relationships between smoking and diabetes mellitus.[20] It was shown in their study that a graded relationship existed between pack-years of smoking and incidence rates of type 2 diabetes. Wassink AMJ et al (2008) recorded in their study that smoking is a potentially confounding factor in the relation between metabolic syndrome and type 2 diabetes.[21]

In the present study, majority of the participants (96.40%) in the control group had the levels of B12 >300. One participant had the levels of B12 below 200 and only 2.40% had the B12 levels between 200 – 300. We observed the deficiency of B12 in 26% of the patients in DN group and 18% patients in DNN group. We observed that the odds of vitamin b12 deficiency were 9.62 times more among diabetic neuropathy than control group. Similarly the odds of vitamin b12 deficiency were 5.41 times more among diabetic with no neuropathy than control group. Vitamin B12 deficiency is a multifactorial condition caused by insufficient intake (nutritional deficiency) as well as acquired or inherited defects that disrupt B12 absorption and processing pathways.

Miyan Z et al (2020) reported in their study that significantly increased prevalence of B12 deficiency was observed in people with T2DM treated with metformin as compared with non-metformin users.[22] Fasipe OJ et al (2020) reported in their study that the prevalence rates for frank vitamin B12 deficiency state among the metformin-treated and metformin-naive type 2 diabetic patients were 41% and 20%, respectively, which revealed a statistically significant difference between both groups ($p < 0.001$).[23] There were statistically significant associations

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between the serum vitamin B12 categorization status versus pain sense ($p < 0.0001$), vibration sense ($p < 0.0001$) and light touch sense ($p < 0.0001$) among the participants. Alvarez M et al (2019) observed in their study that altered levels of vitamin B12 (borderline or low) were found in 29% of patients.[24] The prevalence of borderline levels of Vitamin B12 was 20.9% and the prevalence of low levels was 7.4% (12 cases; 95% CI: 4.0–11%). The prevalence of altered vitamin B12 levels (low or borderline) in patients with diabetic neuropathy was 64% (95% CI: 47–78%). Low levels of vitamin B12 were found in eight patients (23%; 95% CI: 12–40%) and borderline levels were found in 14 patients (41%; 95% CI: 26–47%); 12 patients had normal levels (35%; 95% CI: 21–52%).

As it is obvious, none of the participants in the control group were taking metformin. However, 60.20% and 36.10% patients in the DN and DNN group were already taking metformin. This higher percentage of patients in DN group suggests the association of the diabetic neuropathy and metformin consumption. In our study 27.5% of patient taking metformin found to have vitamin B12 deficiency compared to 10.06% who are not taking it. We observed that the odds of vitamin b12 deficiency were 3.39 times more among people with metformin therapy.

Reinstatler et al (2012) suggested in their study that among those with diabetes, 41% of the deficient cases were attributable to metformin use.[25] The prevalence of biochemical B12 deficiency was 4.1% among those taking metformin,1 year, 6.3% among those taking metformin 1–3 years, 4.1% among those taking metformin .3– 10 years, and 8.1% among those taking metformin .10 years ($P = 0.3219$ for ,1 year vs. .10 years). Kanyal L et al (2019) reported that 45% of patients were on Metformin Therapy. Glycated Hb is correlated with the duration of diabetes with a p value of 0.29, with metformin dose (p value of 0.87) and with metformin duration (p value of 0.12) which is not statistically significant.[26]

CONCLUSION

Vitamin B12 deficiency is highly prevalent, especially in patients with diabetic neuropathy. In this study an inverse correlation was found between diabetic neuropathy and the plasma level of vitamin B12. The association between diabetic neuropathy and Vitamin B12 deficiency is of great importance, since diabetic or prediabetic patients diagnosed with diabetic neuropathy may have neuropathy due to vitamin B12 deficiency. Thus, this condition should be ruled out before initiating diabetic neuropathy treatment.

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