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Prevalence of Vitamin B12 Deficiency in Type 2 Diabetes Mellitus and Its Correlation with Peripheral Neuropathy.

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Abstract

Background: Type 2 diabetes mellitus is a common metabolic disorder associated with several chronic complications, including peripheral neuropathy. Long-term metformin therapy, the cornerstone treatment for T2DM (Type 2 Diabetes Mellitus), has been linked to vitamin B12 deficiency, which may contribute to neurological dysfunction and worsen diabetic neuropathy. Early identification of vitamin B12 deficiency may help prevent progression of neuropathic complications and improve patient outcomes. ***Methods:*** A cross-sectional observational study was conducted in the Department of General Medicine, ESIC Medical College & Hospital, Bihta, Patna, Bihar, over a period of 18 months. A total of 200 adult patients with T2DM were enrolled and divided into two groups: Group 1 (diabetes without peripheral neuropathy, n=100) and Group 2 (diabetes with peripheral neuropathy, n=100). Clinical and demographic data, glycemic parameters, serum vitamin B12 levels, MNSI (Michigan Neuropathy Screening Instrument) scores, and NCV (Nerve Conduction Velocity) studies were assessed. Vitamin B12 levels were classified as inadequate (<200 pg/mL), borderline (200–300 pg/mL), and normal (>300 pg/mL). Student's t-test, chi-square test, and Mann-Whitney U test were used for statistical analysis; $p<0.05$ was deemed significant. ***Results:*** Patients with peripheral neuropathy were significantly older than those without neuropathy (52.14 ± 11.84 vs. 48.82 ± 11.44 years; p=0.045). HbA1c levels were significantly higher in the neuropathy group (8.50 ± 1.57% vs. 7.82 ± 1.71%; p=0.004). However, serum vitamin B12 levels did not differ significantly between groups (509.75 ± 185.15 pg/mL vs. 486.68 ± 176.80 pg/mL; p=0.333). Significant reductions in median sensory, ulnar motor, and left peroneal motor nerve conduction velocities were observed among patients with peripheral neuropathy. ***Conclusion:*** Peripheral neuropathy in T2DM was associated with older age, poorer glycemic control, and impaired nerve conduction parameters. Although vitamin B12 deficiency is recognized as a potential contributor to neuropathy, this study did not demonstrate a significant difference in serum vitamin B12 levels between diabetic patients with and without peripheral neuropathy. Routine monitoring of glycemic control and neurological status remains essential, while periodic assessment of vitamin B12 levels may be beneficial in patients receiving long-term metformin therapy.

Keywords: Type 2 Diabetes Mellitus, Vitamin B12 Deficiency, Peripheral Neuropathy, Metformin, Glycemic Control, Nerve Conduction Velocity, MNSI, Diabetic Complications.

INTRODUCTION

Persistent hyperglycemia brought on by decreased insulin secretion, action, or both is a hallmark of DM (Diabetes Mellitus), a chronic metabolic disease. About 90–95% of cases of diabetes are T2DM (Type 2 Diabetes Mellitus), which is mainly linked to insulin resistance and progressive pancreatic β-cell dysfunction. Obesity, sedentary lifestyles, ageing, genetic predispositions, and poor eating habits are common risk factors. Long-term harm to the eyes, kidneys, cardiovascular system, and peripheral nerves is a result of persistent hyperglycemia.

Vitamin B12 deficiency has emerged as an important comorbidity among patients with T2DM, particularly those receiving long-term metformin therapy. Metformin, the first-line treatment for T2DM, effectively improves glycemic control but can reduce intestinal absorption of vitamin B12, leading to biochemical and clinical deficiency over time. Vitamin B12 is essential for DNA synthesis, erythropoiesis, and maintenance of the nervous system through its role in myelin formation and neuronal repair. Deficiency promotes axonal degeneration, demyelination, and impaired homocysteine metabolism, resulting in elevated homocysteine and methylmalonic acid levels that contribute to neurotoxicity, oxidative stress, endothelial dysfunction, and impaired nerve conduction.[1]

The prevalence of vitamin B12 deficiency among individuals with T2DM varies from approximately 10% to 35%, depending on dietary habits, diagnostic criteria, and the duration and dose of metformin therapy. Studies conducted across different populations consistently identify long-term metformin use as a major risk factor for deficiency, emphasizing the need for regular monitoring.

Several studies have demonstrated a significant association between vitamin B12 deficiency and DPN (Diabetic Peripheral Neuropathy). Patients with concurrent deficiency often experience numbness, tingling, burning sensations, and reduced vibration sense, symptoms that may mimic or worsen diabetic neuropathy. Because vitamin B12 deficiency is both preventable and treatable, distinguishing it from neuropathy caused solely by chronic hyperglycemia has important clinical implications.

Routine assessment of vitamin B12 status in patients with T2DM receiving prolonged metformin therapy may facilitate early detection, timely supplementation, and reduction of neurological complications. However, inconsistencies in existing evidence warrant further research to refine screening and supplementation strategies in this population.[1–2]

Aims and Objectives

The current study intends to determine the incidence of vitamin B12 insufficiency and its correlation with peripheral neuropathy in patients with T2DM. The study specifically aims to determine how common diabetic peripheral neuropathy is in this cohort and investigate the relationship between vitamin B12 insufficiency and peripheral neuropathy in T2DM patients.

MATERIALS AND METHODS

Study Design

This study is designed as a hospital-based cross-sectional observational study conducted in the Department of General Medicine, ESIC Medical College and Hospital, Bihta, Patna, Bihar. The study will be carried out over a period of one year and six months.

Inclusion and Exclusion Criteria

Adult patients of any gender who are 18 years of age or older who have been diagnosed with type 2 diabetes mellitus or prediabetes in accordance with the Standards of Medical Care in Diabetes recommendations and who are willing to participate and give written informed consent were included in the study. Patients having a history of gastrointestinal surgery or malabsorptive syndrome, are receiving vitamin B12 supplementation or multivitamin preparations containing vitamin B12, are pregnant, have type 1 diabetes mellitus, follow a strict vegetarian diet, have a history of chronic alcohol consumption, are below 18 years of age, have pernicious anemia, renal insufficiency, or HIV infection, or have any known malignancy were excluded from the study.

Sample Size Calculation

Based on a previous study reporting a prevalence of 5.8% (Akinlade KS, 2015),[3] and with e=0.05, the calculated sample size was 84. After adjusting for a 15% attrition rate, the sample size increased to 97. To ensure adequacy and ease of group allocation, this figure was rounded up to 100 patients per group. For the sake of adequacy and ease of group allocation, this number was rounded to 100 participants per group. Accordingly, we included 100 patients in each group.

The sample size was estimated using the formula

$$n = \frac{Z^2_{\alpha} pq}{d^2}$$

=1.96*1.96*0.058*0.942
(0.05*0.05)
= 83.95

Where p is the observed prevalence of vitamin B12 deficiency in patients with type 2 DM.

q = 1 - p

d is the margin of error is the ordinate of standard normal distribution at α% level of significance.

Data Collection Procedure

All eligible subjects were included in the study and assessed using a systematic proforma following the acquisition of signed informed permission. Age, gender, length of diabetes, presenting complaints, medical history, medication history, and prior diagnosis of diabetic neuropathy were among the comprehensive clinical and demographic data that were

documented. FBS (Fasting Blood Sugar), PPBS (Postprandial Blood Sugar), RBS (Random Blood Sugar), HbA1c, and serum vitamin B12 levels were all measured in the lab. The American Diabetes Association (ADA) criteria were used to diagnose prediabetes and T2DM. Low (<200 pg/mL), borderline (200–300 pg/mL), and normal (>300 pg/mL) were the three categories for serum vitamin B12 levels. The MNSI, which comprises a 15-item self-administered questionnaire and a lower extremity examination evaluating foot appearance, ulceration, ankle reflexes, and vibratory sensation, was used to determine whether peripheral neuropathy was present. Diabetic neuropathy was thought to be indicated by an MNSI score of ≥2. In addition, available clinical records, previous nerve conduction studies, and neurological examination findings were reviewed and documented. All collected data were entered into a standardized database for subsequent statistical analysis while maintaining participant confidentiality.

Statistical Analysis

The SPSS (Statistical Package for the Social Sciences) program (IBM SPSS Statistics, Version 26.0) was used to analyse the data once it had been imported into Microsoft Excel. For continuous variables with a normal distribution, baseline demographic and clinical parameters were summarised as mean ± standard deviation (SD), and for categorical variables, as frequencies and percentages. The student's t-test was used to compare continuous variables that followed a normal distribution between groups, including age, fasting blood sugar, postprandial blood sugar, and HbA1c. The chi-square test was used to analyse categorical variables, such as sex, vitamin B12 deficiency categories, and the existence of diabetic neuropathy. The Mann-Whitney U test was used to compare variables that were not normally distributed, such as the length of diabetes and blood vitamin B12 levels. These variables were expressed as median with interquartile range (IQR). Based on the type and distribution of the data, the relationship between serum vitamin B12 levels and peripheral neuropathy was evaluated using the proper statistical tests. A p-value of less than 0.05 was deemed statistically significant, and all statistical tests were two-tailed.

RESULTS

Table 1 illustrates the comparison of baseline demographic characteristics between Group 1 and Group 2.

Table 1: Comparison of Baseline Demographic Characteristics

Characteristic	Group 1 (n=100)	Group 2 (n=100)	p-value
Age (years)	48.82 ± 11.44	52.14 ± 11.84	t = 2.016, p = 0.045*
Female	71 (71.0%)	50 (50.0%)	Chi^2 = 9.227, p = 0.002*
Male	29 (29.0%)	50 (50.0%)	
Test used: Student's t test (comparing means); Chi-square test (comparing proportions) *signifies significant p value<0.05			

Table 2 observes the comparison of fasting glucose, postprandial glucose and HbA1c between the two groups.

Table 2: Comparison of Glycaemic Parameters

Parameter	Group 1 (n=100)	Group 2 (n=100)	t, p-value
Fasting Glucose (mg/dL)	167.28 ± 47.60	163.10 ± 44.34	t = 0.642, p = 0.521
Postprandial Glucose (mg/dL)	232.93 ± 55.48	242.21 ± 66.43	t = 1.073, p = 0.285
HbA1c (%)	7.82 ± 1.71	8.50 ± 1.57	t = 2.924, p = 0.004*
Test used: Student's t test, *signifies significant p value<0.05			

Table 3 presents the comparison of duration of diabetes and vitamin B12 levels between the two groups.

Table 3: Comparison of Duration of Diabetes and Vitamin B12 Levels

Parameter	Group 1 Mean ± SD	Group 1 Median (IQR)	Group 2 Mean ± SD	Group 2 Median (IQR)	Test statistic (Z) with p-value
Duration of Diabetes (months)	90.78 ± 67.43	73.0 (30.0–153.0)	82.88 ± 67.17	61.5 (28.0–118.0)	Z = –1.006, p = 0.315
Vitamin B12 (pg/mL)	486.68 ± 176.80	500.5 (316.25–630.0)	509.75 ± 185.15	511.5 (356.75–656.0)	Z = –0.968, p = 0.333
Test used: Mann–Whitney U test					

Table 4 demonstrates the comparison of nerve conduction velocities between the two groups.

Table 4: Nerve Conduction Velocities

Nerve	Side	Group 1	Group 2	t-value	p-value
NCV Median Motor	Right	55.21 ± 8.90	54.55 ± 8.22	0.547	0.585
NCV Median Motor	Left	56.04 ± 7.98	54.52 ± 7.69	1.378	0.170
Median Sensory	Right	53.53 ± 7.61	49.96 ± 8.18	3.2	0.002*
Median Sensory	Left	52.72 ± 8.31	49.29 ± 8.49	2.891	0.004*
Ulnar Motor	Right	60.38 ± 9.22	56.63 ± 7.45	3.169	0.002*
Ulnar Motor	Left	59.68 ± 8.21	56.45 ± 6.95	2.995	0.003*
Peroneal Motor	Right	61.72 ± 10.32	60.97 ± 9.51	0.535	0.593
Peroneal Motor	Left	63.34 ± 9.53	59.64 ± 10.07	2.666	0.008*
Sural Nerve	Right	51.78 ± 9.04	53.03 ± 8.43	-1.011	0.313
Sural Nerve	Left	51.70 ± 9.38	52.17 ± 8.35	-0.376	0.708
Test used: Student's t test, signifies significant p value<0.05					

Table 5 highlights the comparison of MNSI questionnaire responses between the two groups.

Table 5: MNSI Questionnaire Results

Question	Group 1	Group 2	Chi-square value	p-value
1. Legs/feet numb	49%	60%	2.44	0.118
2. Burning pain	52%	43%	1.624	0.203
3. Feet too sensitive	36%	42%	0.988	0.610
4. Muscle cramps	45%	63%	6.522	0.011*
5. Prickling feelings	35%	41%	0.764	0.382
6. Pain when bed covers touch	28%	48%	8.489	0.004*
7. Hot vs cold water	51%	74%	11.285	0.001*
8. Open sore on foot	25%	45%	8.791	0.003*
9. Doctor told neuropathy	36%	66%	18.007	<0.001*
10. Weak all over	37%	45%	1.323	0.250
11. Symptoms worse at night	26%	61%	24.921	<0.001*
12. Legs hurt when walking	19%	43%	13.464	<0.001*
13. Sense feet when walking	42%	62%	8.013	0.005*
14. Skin cracks open	33%	34%	0.022	0.881
15. Amputation	30%	36%	0.814	0.367
Test used: Chi-square test, signifies significant p value<0.05				

Table 6 describes the comparison of physical assessment and sensory test findings between the two groups.

Table 6: Physical Assessment & Sensory Tests

Assessment	Group 1	Group 2	Chi-square value	p-value
Right foot ulceration	Present: 27 (27.0%)	Present: 45 (45.0%)	13.077	<0.001*
Ankle reflex	Present: 53 (53.0%) Reinforcement:26 (26.0%) Absent:21 (21.0%)	Present:45 (45.0%) Reinforcement:27 (27.0%) Absent:28 (28.0%)	1.672	0.433
Vibration perception (great toe)	Present:38 (38.0%) Reduced:36 (36.0%) Absent:26 (26.0%)	Present:34 (34.0%) Reduced:33 (33.0%) Absent:33 (33.0%)	1.183	0.553
10 gm filament	Present:40 (40.0%) Reduced:43 (43.0%) Absent:17 (17.0%)	Present:36 (36.0%) Reduced:42 (42.0%) Absent:22 (22.0%)	0.863	0.649
Test used: Chi-square test, signifies significant p value<0.05				

DISCUSSION

The chronic metabolic disease known as T2DM is typified by increasing β-cell dysfunction and persistent hyperglycemia brought on by insulin resistance. One of the most prevalent and incapacitating microvascular consequences of diabetes is diabetic peripheral neuropathy, which significantly increases the risk of foot ulcers, infections, and lower limb amputations.[1–6] The present study evaluated the association between vitamin B12 levels and peripheral neuropathy

among patients with T2DM using demographic characteristics, glycemic parameters, biochemical assessment, nerve conduction studies, and validated neuropathy screening instruments.

Demographic Characteristics

In the present study, patients with peripheral neuropathy (Group 2) were significantly older than those without neuropathy (Group 1), with mean ages of 52.14 ± 11.84 years and 48.82 ± 11.44 years, respectively (p = 0.045), as shown in Table 1. This observation is consistent with previous epidemiological studies demonstrating that advancing age is an important independent risk factor for diabetic peripheral neuropathy because of cumulative metabolic injury, progressive microvascular damage, and age-related neuronal vulnerability.[4-6]

Sex distribution also differed significantly between the two groups, with males constituting 50% of the neuropathy group compared with 29% in the non-neuropathy group (p = 0.002). Similar male predominance among patients with diabetic peripheral neuropathy has been reported by previous investigators, who attributed this finding to differences in occupational exposure, smoking habits, alcohol consumption, and delayed healthcare-seeking behavior among men.[7-9] These findings emphasize the importance of demographic characteristics in identifying individuals at higher risk of neuropathy.

Glycemic Control and Neuropathy

The present study demonstrated that fasting blood glucose and postprandial blood glucose levels did not differ significantly between patients with and without peripheral neuropathy (Table 2). Similar observations have been reported in previous studies, suggesting that single-point glucose measurements do not adequately represent cumulative glycemic exposure and therefore have limited value in predicting chronic microvascular complications.[10-12]

In contrast, glycated HbA1c levels were significantly higher among patients with neuropathy, with a mean HbA1c of 8.50 ± 1.57% compared with 7.82 ± 1.71% in patients without neuropathy (p = 0.004). This result is in line with important research like the UKPDS (United Kingdom Prospective Diabetes Study) and the DCCT (Diabetes Control and Complications Trial), which found poor long-term glycaemic control to be a significant factor in the development and progression of diabetic neuropathy.[13-15]

Peripheral nerve injury is caused by a number of biological mechanisms, including oxidative stress, activation of the polyol pathway, buildup of advanced glycation end products, mitochondrial failure, and microvascular ischaemia.[16-18] Therefore, the present findings reinforce the concept that sustained hyperglycemia, rather than isolated glucose measurements, plays a pivotal role in neuropathy development.

Duration of Diabetes

The duration of diabetes was comparable between patients with and without neuropathy (p = 0.315), as shown in Table 3. Although longer disease duration has traditionally been recognized as a risk factor for diabetic peripheral neuropathy, recent evidence indicates that neuropathy may develop relatively early in the disease course when poor glycemic control coexists with additional metabolic risk factors.[19] This may explain the absence of a statistically significant association between diabetes duration and neuropathy in the present study.

Vitamin B12 Levels and Neuropathy

Vitamin B12 deficiency has gained increasing attention as a potentially modifiable contributor to neuropathy, particularly among patients receiving prolonged metformin therapy, which impairs calcium-dependent vitamin B12 absorption in the terminal ileum.[20] However, in the present study, serum vitamin B12 levels did not differ significantly between patients with and without neuropathy (p = 0.333).

This finding is comparable with the observations of Kwape et al., who similarly reported that biochemical vitamin B12 deficiency does not always correlate directly with the presence of diabetic neuropathy.[21] Nevertheless, previous studies have suggested that patients with low-normal vitamin B12 concentrations may still exhibit functional deficiency characterized by elevated homocysteine levels and impaired nerve conduction, particularly among those receiving long-term metformin therapy.[22]

Nerve Conduction Study Findings

Electrophysiological evaluation demonstrated significant reductions in median sensory and ulnar motor nerve conduction velocities among patients with peripheral neuropathy (Table 4). Sensory nerve involvement was more pronounced than motor nerve involvement, a characteristic feature of diabetic peripheral neuropathy.[23]

These findings are in agreement with studies conducted by Didangelos et al., who demonstrated that patients with diabetic neuropathy-particularly those with vitamin B12 deficiency-show significant slowing of sensory nerve conduction

velocities.[24] The relative preservation of sural nerve conduction observed in the present study may reflect early or patchy small-fiber involvement, which is frequently undetected by conventional nerve conduction studies.[25]

Clinical Assessment Using the Michigan Neuropathy Screening Instrument

The MNSI questionnaire revealed significantly greater symptom burden among patients with neuropathy, particularly with respect to muscle cramps, allodynia, impaired temperature discrimination, nocturnal worsening of symptoms, and walking-related pain ($p < 0.05$), as shown in Table 5. These observations are consistent with previous validation studies demonstrating that the MNSI is an effective tool for identifying both clinical and subclinical diabetic peripheral neuropathy. Furthermore, Didangelos et al. demonstrated improvement in MNSI scores following vitamin B12 supplementation, highlighting the clinical relevance of these symptoms in metabolic and nutritional neuropathies.[24]

Foot Examination Findings

Clinical examination demonstrated that right foot ulceration was significantly more frequent among patients with neuropathy ($p < 0.001$), as shown in Table 6. This finding is consistent with established evidence linking sensory loss and impaired protective sensation to increased susceptibility to foot ulceration among diabetic patients.[26]

However, ankle reflexes, vibration perception, and monofilament testing did not differ significantly between the two groups, suggesting that these bedside examinations may have limited sensitivity for detecting early or moderate neuropathy.[27] Similar conclusions have been drawn in previous studies recommending that symptom questionnaires, detailed clinical examination, and nerve conduction studies should be used together to achieve comprehensive neuropathy assessment.

Limitations

The cross-sectional design limits the ability to establish a causal relationship between vitamin B12 deficiency and diabetic peripheral neuropathy. Functional biomarkers of vitamin B12 deficiency, such as methylmalonic acid and homocysteine, were not assessed. Additionally, the dose and duration of metformin therapy were not analyzed in detail, the evaluation of small-fiber neuropathy was limited, and the absence of long-term follow-up prevented assessment of disease progression and treatment outcomes over time.

CONCLUSION

The present study demonstrates that diabetic peripheral neuropathy in patients with type 2 diabetes mellitus is strongly associated with advancing age and poor long-term glycaemic control. Although serum vitamin B12 levels were not significantly associated with neuropathy in this cohort, monitoring vitamin B12 remains important, particularly in patients receiving long-term metformin therapy. Early detection through clinical screening and nerve conduction studies, along with timely management of modifiable risk factors, may help reduce neuropathic complications and improve patient outcomes.

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