



## EVALUATION OF SEVERITY OF PERIPHERAL NEUROPATHY IN TYPE 2 DIABETES MELLITUS PATIENTS WITH SPECIAL REFERENCE TO VITAMIN B12 DEFICIENCY

### General Medicine

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### ABSTRACT

**BACKGROUND:** Diabetic peripheral neuropathy (DPN) is the dysfunction of peripheral nerves attributed to chronic hyperglycemia after excluding other causes. Vitamin B12 deficiency is a potential comorbidity that is often overlooked in diabetic patients. Potentially reversible vitamin B12 deficiency induced neuropathy may be inappropriately labelled as diabetic peripheral neuropathy.

**METHOD:** 162 cases were included over a period of 1 year. After a detailed history and examination, severity of peripheral neuropathy was assessed by Toronto Clinical Scoring System. Presence of DPN was confirmed by Nerve Conduction Study. Vitamin B12 estimation was done by ELISA technique.

**RESULT:** DPN was found in 35.18% of patients. Longer duration of diabetes, poor glycemic control, higher daily dose and duration of metformin use, height of patients, low HDL were found to be risk factors. 25(15.43%) out of 162 and 10 (17.5%) of patients with DPN were vitamin B12 deficient. Mean vitamin B12 in patients with DPN was  $460.09 \pm 264.07$  pg/ml which is significantly lower than those without DPN ( $580.27 \pm 255.31$  pg/ml;  $p < 0.01$ ).

**CONCLUSION:** Vitamin B12 deficiency is found to be a potential comorbidity in type 2 diabetes mellitus patients and hence regular monitoring of its serum levels and supplementation must be considered especially in the patients on metformin therapy.

### KEYWORDS

Type 2 diabetes mellitus, peripheral neuropathy, Vitamin B12, Metformin.

### INTRODUCTION:

Diabetes mellitus type 2 is a heterogeneous group of disorders characterized by insulin resistance and impaired insulin secretion. It is fast gaining the status of a potential epidemic in India with more than 62 million individuals currently diagnosed with the disease<sup>1</sup>. Diabetic peripheral neuropathy (DPN), a well known microvascular complication is the dysfunction of peripheral nerves after exclusion of other causes<sup>2</sup> and can lead to foot infection, ulceration and non traumatic amputations<sup>3</sup>.

Vitamin B12 deficiency is a potential comorbidity that is often overlooked despite the fact that many diabetic patients are at risk for this specific disorder.<sup>4</sup>

Few such studies evaluating vitamin B12 deficiency as a contributing factor to diabetic peripheral neuropathy have been conducted in north eastern part of Indian and in Assam. Hence this study was conducted with the following aim and objective:

### AIM AND OBJECTIVE:

To study the peripheral neuropathy in type 2 diabetes mellitus patients and to correlate the vitamin B12 deficiency in these patients.

### MATERIALS AND METHODS:

After obtaining approval from Institutional Ethics Committee (H), known cases of type 2 diabetes mellitus, of age 13 years and above, who were admitted to Assam Medical College and Hospital or visited the OPD over a period of 1 year were included in this hospital based observational study. Detailed history for duration of diabetes, compliance with treatment, symptoms of neuropathy and potential risk factors was taken. This was followed by general and neurological examination. Presence of autonomic neuropathy was assessed bedside by presence of resting tachycardia, orthostatic hypotension, abnormal heart rate variability with deep breathing and history of erectile dysfunction in male patients. Routine biochemical investigations were done to assess glycemic control and coexisting nephropathy. Presence of retinopathy was confirmed by funduscopy.

The patients were excluded if the following comorbidities were present: patients with acute complication of diabetes, gestational diabetes mellitus, diagnosed cases of type 1 diabetes mellitus, maturity onset diabetes of young, pancreatic or endocrine causes of diabetes, patients on strict vegetarian diet, prior ileum resection/ bariatric

surgery, inflammatory bowel disease, pernicious anemia, known cases of chronic liver disease, malignancy, hypothyroidism, leprosy, patients on known neurotoxic drugs, HIV/ AIDS, patients of End Stage Renal Disease (eGFR < 15 ml/ min/ 1.73 metre square of body surface area), patients taking oral/ injectable vitamin B12 supplementation in last 3 months.

The severity of diabetic peripheral neuropathy was assessed with help of Toronto Clinical Scoring System (TCSS) which is a validated scoring system for DPN<sup>5</sup>. The criteria of classification were: 0 to 5 points without DPN, 6 to 8 points mild DPN, 9 to 11 points moderate DPN, 12 to 19 points severe DPN.

Presence of DPN was further confirmed by nerve conduction study. Motor conduction studies were done in median, ulnar, common peroneal and posterior tibial nerves. Sensory conduction studies were conducted at the median and sural nerve<sup>6</sup>.

The vitamin B12 analysis was done with the ELISA technique. Definite Vitamin B12 deficiency is defined as serum levels of B12 < 150 pg/ml and possible deficiency as 150- 220 pg/ ml and values > 220 pg/ml were taken to be sufficient.<sup>7</sup>

### RESULTS AND OBSERVATION:

After fulfilment of inclusion and exclusion criteria, 162 patients were included over a period of 1 year. In this study prevalence of DPN was found to be 35.18%.

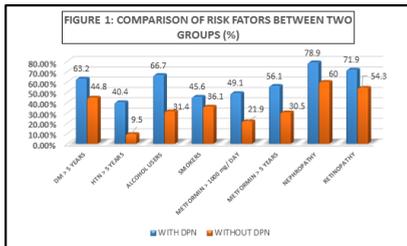
Out of 57 patients with DPN 35 (61.42%) were male and 22 (38.58%) were female. Among the 105 patients without DPN 62 (59.05%) were male and 43 (40.95%) were female. The M: F ratio was found to be similar in both groups. Mean age of patients with DPN was  $53.11 \pm 18.75$  years and those without DPN was  $52.99 \pm 10.98$  years. Metformin was found to be the most commonly used oral hypoglycemic agent being used in 150/ 162 (92.59%) patients.

Tingling/ paraesthesia had been found to be the most common symptom (75.4%) among patients with DPN followed by pain (42.11%) and numbness (36.8%). Erectile dysfunction was reported in 5 (14.29%) male patients. Foot ulcer and callus formation was noted in 14 (24.56%) of patients with DPN.

**Table 1: Types of diabetic neuropathy observed in this study**

TYPE OF NEUROPATHY	NUMBER OF PATIENTS (%)
DISTAL SYMMETRICAL SENSORY MOTOR POLYNEUROPATHY	49(85.96%)
MONONEUROPATHY	6(10.53%)
CRANIAL NEUROPATHY	1(1.75%)
AIDP	1(1.75%)
COEXISTING DIABETIC AUTONOMIC NEUROPATHY	28 (49.12%)

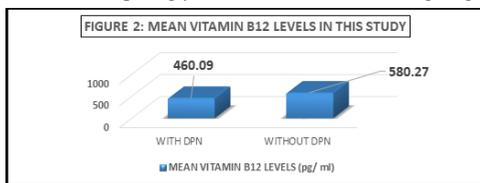
The most common type of peripheral neuropathy observed in this study was distal symmetrical sensory motor polyneuropathy in 85.96% patients, coexisting autonomic neuropathy was found in 49.12% patients with DPN.



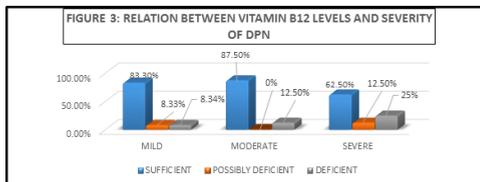
Daily dose of metformin > 1000 mg and use of metformin for more than 5 years were found to be statistically significant risk factors for development of neuropathy. In this study total cholesterol in patients with DPN was 174.54 ± 49.17 and those without DPN was 150.61 ± 49.34 mg/dL (p<0.01). HDL levels in patient with DPN 37.26 ± 8.41 mg/dL and in those without DPN it 41.59 ± 19.03 mg/dL (p< 0.01). Thus high total cholesterol and low HDL were found to be independent risk factors. The difference between LDL-C and triglyceride levels in the two groups was not found to be statistically significant.

Relation with smoking, BMI, LDL and triglyceride levels was not found to be statistically significant.

Out of 57 patients with DPN 1 had TCSS score of 3 (No DPN) but had features of DPN on NCS. 24 (42%) patients each were found to have mild and moderate DPN. 8 (14%) patients were found to have severe neuropathy. Severity of DPN was seen to increase with increasing duration of diabetes, poor glycemic control and increasing height.



Vitamin B12 level was found to be 580.27 ± 255.31 pg/ml in patients without peripheral neuropathy and 460.09 ± 264.07 pg/ml in patients with peripheral neuropathy with is significantly lower (p < 0.01). In this study prevalence of Vitamin B12 deficiency was found to be 15.43% (25 out of 162 cases). Out of them 11 (6.69%) had vitamin B12 levels between 150-220 pg/ml and 14 (8.64%) had levels below 150 pg/ml.



The proportion of patients with vitamin B12 deficiency was found to increase with increasing severity of peripheral neuropathy by TCSS score. 6 out 25 (24%) patients with vitamin B12 deficiency were found to have autonomic neuropathy.

**DISCUSSION:**

The prevalence of DPN have been found to vary from 9.6% to 78% in various populations<sup>8,9</sup>. Bansal et al in 2014 reported prevalence of 29.20%<sup>10</sup> which is similar to present study. A population based study

by Medhi RP et al in 2017 conducted in Dibrugarh, Assam reported majority of diabetic patients to belong to age group of 40- 60 years<sup>11</sup> which is similar to our study.

Bansal V et al quoted that distal symmetrical polyneuropathy is the most common type of DPN<sup>12</sup> and Basu AK et al in a study in Eastern India found prevalence of cardiac autonomic neuropathy to be 54%. These findings are comparable with our study<sup>13</sup>.

In studies conducted by Davies et al<sup>14</sup> and Gupta et al<sup>15</sup> using TCSS score, HbA1c was found to be higher in the group of patients with severe neuropathy thus supporting our findings, which is similar to the findings in our study.

The studies conducted by Adler AI et al<sup>16</sup> and Shaw et al<sup>17</sup> found height to be an independent risk factor for DPN which is noted in our study.

In this study the prevalence of vitamin B12 deficiency was found to be 15.43%. A study conducted by Pflipsen MC et al found 22% type 2 diabetic patients to have metabolically confirmed vitamin B12 deficiency which is comparable to our study.<sup>18</sup>

In this study 6 out of 25 (24%) of the patients with vitamin B12 deficiency had features of autonomic neuropathy. A study conducted by Beitzke et al in 2002 found a positive correlation between vitamin B12 deficiency and presence of autonomic dysfunction<sup>19</sup>. Vitamin B12 deficiency causes autonomic dysfunction and haemodynamic consequences similar to that caused by diabetes.

In studies conducted by Wile DJ et al and Singh AK et al, it was observed that median TCSS score was higher in the metformin treated group with a strong positive with cumulative increasing metformin dose which was attributed to lower serum vitamin B12 levels observed in these patients. Similar findings have been reported in our study.<sup>20,21</sup>

**CONCLUSION:**

Vitamin B12 deficiency is found to be a potential comorbidity in type 2 diabetes mellitus patients. It significantly worsens peripheral neuropathy in these patients. The type 2 diabetes mellitus patients on metformin should be tested for Vitamin B12 levels and Vitamin B12 supplementation should be considered in these patients.

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