

**Quality of Life and Role of Vitamin B<sub>12</sub> Levels in Patients with Peripheral Diabetic Neuropathy: A Cross-Sectional Study**Verma P<sup>1</sup>, Verma S<sup>2</sup>, Karoli R<sup>3</sup>, Singh M<sup>4</sup>, Singh V<sup>5</sup>, Gupta N<sup>6</sup>, Srivastava UK<sup>7</sup>, Pankaj J<sup>8</sup>, Kumar A<sup>9</sup><sup>1,3,4,5,6,7,8,9</sup>Dr. RMLIMS, Lucknow, Uttar Pradesh  
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Conflict of interest: Nil

**Abstract:****Background:** One of the most common microvascular effects of diabetes mellitus (DM) is diabetic neuropathy (DN), which is often underdiagnosed and undertreated in day-to-day clinical practice. So, this study compared the quality of life of diabetics with and without diabetic peripheral neuropathy (DPN). It also determines factors associated with DPN and correlation of Vitamin B<sub>12</sub> levels with metformin use in our region.**Methodology:** An analytical cross-sectional study was conducted in the Out-patient department tertiary care centre of northern India for a period of 12 months where all type 2 diabetics for more than 3 years were interviewed and thoroughly examined for diabetic neuropathy using a biothesiometer and quality of life using WHO-BREF scale.**Results:** 259 diabetics were divided into 2 groups i.e. with DPN (Group 1, 65) and without DPN (Group 2, 194). Mean age of the study participants in group 1 and 2 were 51.5 ± 9.2 and 53.3 ± 6.9 respectively. Higher duration of diabetes, use of metformin drug, longer duration of metformin use, Higher HbA<sub>1c</sub> levels and Lower levels of Vitamin B<sub>12</sub> were significantly associated with DPN. The correlation between levels of Vitamin B<sub>12</sub> (low or normal) and use of metformin was highly significant (p value- 0.009). The overall BREF score was significantly lower in the DPN group as compared to group 2. Physical and environmental subscales of the score were also significantly lower in the DPN group than group 1 (p<0.05).**Conclusion:** A lower quality of life was observed by the patients with DPN than those with no DPN. So, only right supplementation of Vitamin B<sub>12</sub> according to the recommended daily allowance and timely monitoring can give patient a better quality of life.**Keywords:** Diabetes mellitus, diabetic neuropathies, diabetes complications, quality of life, vitamin B<sub>12</sub> deficiency.

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**Introduction**

One of the most common microvascular effects of diabetes mellitus (DM) is diabetic peripheral neuropathy (DPN), which is worth noticing considering that in everyday clinical practice, it is often underdiagnosed and undertreated. [1] The estimated frequency of DPN in India varies greatly throughout groups, ranging from 9.6% to 78%. [2–5] While some diabetic individuals with peripheral neuropathy may have unbearably painful symptoms, others with more severe neuropathic impairments may not show any symptoms at all. [6]

Owing to its efficiency, safety and various metabolic and cardiovascular advantages, Metformin is usually the first line drug used to treat type 2 DM. [7] But, long term use of Metformin has some reported side effects with malabsorption of vitamin B<sub>12</sub> as one important one. [8]

Cobalamin, often known as vitamin B<sub>12</sub>, is a crucial element that is particularly needed for efficient hematological and cerebral function. [9] Ranging from 5.8 to 33%, type 2 diabetes individuals on metformin have been shown to be deficient in vitamin B<sub>12</sub>. [10,11] In contrast to those who did not take metformin, patients on metformin medication had an odds ratio of 2.45 (95% CI 1.74–3.44, p value=0.0001) for developing vitamin B<sub>12</sub> insufficiency, according to the results of a new meta-analysis based on 29 trials with 8089 participants. [8]

One of the effects of a vitamin B<sub>12</sub> shortage is peripheral neuropathy (PN), which responds quickly to early treatment. Long-term deficit can cause harm to the neurological system that cannot be repaired. [8] The quality of life may be significantly impacted by these. [12] A lot of

studies have been done to correlate the use of metformin in type 2 diabetes and vitamin B 12 levels but a very few of them have analysed the quality of life of these patients. So, here in this study we compared the quality of life of diabetics who had diabetic peripheral neuropathy (DPN) and who did not.

We also analysed the correlation between Vitamin B12 levels and metformin use in our region which was not done earlier. Factors associated with DPN were also determined.

### Methodology

**Study Design and Setting:** An analytical cross-sectional study was conducted in the Out-patient department tertiary care centre of northern India for a period of 12 months where all type 2 diabetics were interviewed and thoroughly examined for diabetic neuropathy and quality of life.

**Study participants:** Those type 2 diabetics for more than 3 years, who presented to the OPD were included in the study. Those who were taking any other medication like H2 blockers, proton pump inhibitors or antacids, were pregnant, had type 1 diabetes, were alcoholic or smokers were excluded from the study.

Those with past history of renal insufficiency, pernicious anemia, HIV infection or any other malabsorption conditions like syndrome or surgically after gastrectomy or bypass surgery involving the stomach or small intestines were also excluded from the study.

**Sample size:** For the purpose of sample size estimation, study used is **Rani PK et al (2021)[13]**.

Sample size formula used is:

$$n = ([Z_{\alpha/2}]^2 * p(1-p)) / d^2$$

- **Z $\alpha/2$**  -critical value of the normal distribution at  $\alpha/2$ (for a confidence level of 95%,  $\alpha=0.05$  and the **critical value is 1.96**)
- **p**= Proportion of diabetics suffering with diabetic neuropathy (value is **18.84%**)<sup>1</sup>
- **d**: Margin of error for desired precision (value is **0.05**).

To estimate the desired outcome in this study, significant with 95% confidence interval the required minimum sample size will be 235 patients. Taking 10% non-response, total sample size will be 259 diabetics.

### Data Collection

All diabetics who fulfilled the inclusion criteria were included in the study. A written informed consent was taken from the enrolled patients.

Basic demographic data, history of oral hypoglycemics or insulin used for the last 12

months, investigations like HbA1c, Vitamin B 12 levels were noted down. WHO-QoL BREF scale was also noted down. A peripheral neuropathy examination was done using biothesiometer and the patients were graded as group 1- with diabetic peripheral neuropathy (DPN) and group 2- without DPN.

Group 1 was further classified as mild, moderate, severe on the basis of Vibration perception thresholds (VPT). The biothesiometer estimates the threshold of appreciation of vibration and has a range of 0-50volt vibration output. Once the patient feels the vibration threshold value and receives the stimulus, the stimulus's recorded amplitude (volts) is increased gradually. [14] The values of VPT were gr as 'normal' (<15 v), 'mild' (15-20 v), 'moderate' (20-25 v) and >25 v as 'severe' neuropathy. [15]

Metformin use of at least 1 gm for last 12 months was taken into consideration as 'yes' for metformin use. Records of Vitamin B 12 assay below 200 pg/ml were considered deficient. [16] The WHO BREF, which consists of 26 items scoring from 1 to 5, was used to measure quality of life. It evaluated four domains: environment, social interactions, psychological health, and physical health. For every domain, a score between 0 and 100 was determined. [17] All the data was collected and was analysed.

**Statistical Analysis:** An Excel page from Microsoft was filled with data. Every research participant's confidentiality was upheld at all times. SPSS 26.0 was used to analyze the data. The study's findings were presented using a descriptive summary that included frequencies, percentages, means, and standard deviations. To assess statistical significance at the 5% level of significance, probability (p) was computed. The chi square test was used to analyze the categorical variable. The independent t test was used to calculate the continuous variable.

### Results

259 diabetics were included in the study and were divided into 2 groups i.e. with DPN (Group 1) and without DPN (Group 2). Group 1 had 65 patients which showed that the prevalence of Diabetic peripheral neuropathy is 25.1% in the study population. Out of these 65 patients maximum had moderate DPN (31, 11.9%) followed by mild DPN (21, 8.1%) and severe DPN (13, 5.1%). (Figure 1)

The mean age of the study participants in group 1 and 2 were  $51.5 \pm 9.2$  and  $53.3 \pm 6.9$  respectively, which was not significant. Higher number of females had DPN as compared to males, although this was also statistically insignificant.

Higher duration of diabetes, use of metformin drug, longer duration of metformin use, Higher HbA1c

levels and Lower levels of Vitamin B 12 were significantly associated with DPN. (Table 1)

The correlation between levels of Vitamin B12 (low or normal) and use of metformin was highly significant (p value- 0.009). (Table 2) The QOL in group 1 was affected than those of Group 2. The

overall BREF score was significantly lower in the DPN group as compared to group 2.

Physical and environmental subscales of the score were also significantly lower in the DPN group than group 1 (p value- 0.002 and 0.034 respectively). (Table 3)

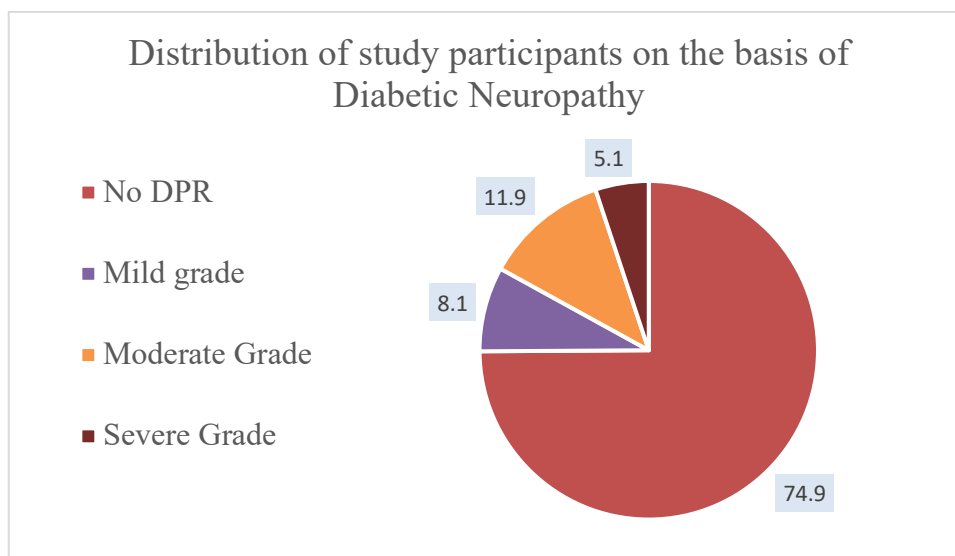


Figure 1: Distribution of study participants on the basis of Diabetic Neuropathy

Table 1: Different study variables across both groups

Variables	Diabetic Neuropathy		P value
	Yes (N=65)	No (N=194)	
Mean Age (yrs)	51.5 ± 9.2	53.3 ± 6.9	0.097
Gender	Male	26	0.142
	Female	39	
Duration of diabetes	7.9 ± 2.4	5.6 ± 3.1	<b>0.0001</b>
Metformin use	Yes	56	<b>0.0001</b>
	No	9	
Mean Metformin Dose (N=158)	1520.8±325.0	1367.6±420.6	<b>0.008</b>
Mean Metformin duration (N=158)	4.9±1.3	3.6±2.3	<b>0.0001</b>
Fasting Blood sugar levels (mg/dl)	134.8 ± 24.3	129.5 ± 42.8	0.344
HbA1c (gm%)	8.7±2.3	7.3 ± 1.9	<b>0.0001</b>
Vitamin B 12 levels	232.5±75.5	366.4±107.5	<b>0.0015</b>

Table 2: Correlation between Metformin use and Vitamin B12 levels in patients with Diabetic Neuropathy

Metformin use	Vitamin B 12 levels		Chi square value	P value
	<200 pg/ml	>200 pg/ml		
Yes (N=56)	38	18	6.717	0.009
No (N=9)	2	7		

Table 3: Comparison of Quality of life across both groups using WHO BREF Scale

Domains	Diabetic Neuropathy		F value	P value
	Yes (Mean SD)	No (Mean SD)		
Physical	54.2 ±12.5	60.4 ±13.8	10.287	0.002
Psychological	58.6 ±16.4	59.7 ±12.9	0.307	0.580
Social	49.4 ±10.3	53.4 ±17.4	3.070	0.081
Environmental	56.7 ±18.5	61.3 ±13.7	4.555	0.034
Mean Overall BREF Score	55.6 ±14.7	59.6 ±12.6	4.502	0.035

## Discussion

This study assessed the difference in quality of life of type 2 diabetics with diabetic neuropathy. World Health Organisation (WHO) defines QoL as the perception of an individual of their position in life with reference to the value system and the culture they follow and in relation to their expectations, concerns, goals and standards. [17] We observed a significantly lower QoL score in DPN than those with no DPN especially in the domains of physical and environmental personal conditions. Devi M et al., [14] that DPN patients with higher peripheral pain and higher grade of DPN had a poor QoL. They used a DN-4 (Douleur Neuropathique en 4) questionnaire. Amongst the diabetics similar to our study, Thomas Z et al., [17] also found that the mean WHO-QoL BREF score was 57.13 (9.69), 56.05 (9.93), 53.13 (20.14) and 60.83 (15.62) in the 4 domains i.e. physical, psychological, social and environmental domains, respectively. However they did not compare the quality of life with DPN.

Prajapati VB et al., [18] found that diabetics without co-morbidity had a superior QoL than those with QoL. They also visualised the association of duration of diabetes with the QoL, which was best in those diagnosed within 1 year as compared to 10year duration and thereon the QoL score decreased with the increase in duration of diabetes. Even patients with combination use of insulin and oral hypoglycemic agents had a better QoL.

Numerous lifestyle issues bother people with complications of diabetes mellitus. Ultimately, it impairs the kidneys, results in peripheral neuropathies, nephropathy, cardiac issues, eyesight loss, and others like erectile dysfunction that lower quality of life. In a cohort research, strict glycemic control was found to improve mental quality of life more than physical quality of life. [19] According to a research, individuals with diabetes had a lower quality of life than those without the condition, but a somewhat higher QoL than those with the majority of other chronic illnesses. Simply having diabetes can have a negative impact on the quality of relationships, family life, travel, and financial load. [21] One meta-analysis found that self-control education had a greater effect on managing the condition and enhancing quality of life. [22]

In our study, higher duration of diabetes, use of metformin drug, longer duration of metformin use, Higher HbA1c levels and Lower levels of Vitamin B 12 were significantly associated with DPN. The correlation between levels of Vitamin B12 (low or normal) and use of metformin was also significant. Many studies have proven the relationship of metformin use and Vitamin B12 deficiency in diabetics and hence its association with DPN. [9,12,23,24, 25] Darivemula s et al., [26] also

observed that DPN was significantly associated with duration of diabetes, hypertension, HbA1c value body mass index, age and sex. Similar to our study other studies have also shown that females were a strong predictor followed by longer duration of DM for DPN. [27-31]

The limitations of this study were that a control group without diabetes should have been included to get a better comparative result. Hence, relationship of cause effect cannot be established and so, generalisation of results cannot be done. Nerve conduction velocity is the gold standard test, better than biothesiometer, used to diagnose diabetic neuropathy, which was not used in our study due to follow-up issues.

## Conclusion

This study suggested that there exists a strong association of levels of Vitamin B12, DPN and use of metformin drug. A lower quality of life was observed by the patients with DPN than those with no DPN. So, with only right supplementation of Vitamin B12 according to the recommended daily allowance and timely monitoring can give patient a better quality of life. We also recommend regular checkup of diabetic neuropathy by a biothesiometer which can establish an early diagnosis and therapy to prevent progression to other grave situations like amputations.

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