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Association of Proton Pump Inhibitors with Diabetic Neuropathy in Type 2 Diabetes: A Hospital Based Cross Sectional Study

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Abstract

Background: Diabetic neuropathy is a common microvascular complication of type 2 diabetes mellitus (T2DM). Proton pump inhibitors (PPIs), widely prescribed in diabetic patients, have been implicated in neurological complications, possibly through metabolic and nutritional mechanisms. ***Aim:*** To evaluate the association between PPI use and diabetic neuropathy in patients with T2DM. ***Methods:*** A prospective observational study was conducted at a tertiary care center over 18 months. Patients with diabetic neuropathy were categorized into PPI users and non-users. Diabetic neuropathy was diagnosed based on ADA criteria. Clinical, demographic, and biochemical parameters were compared. Statistical analysis was performed using SPSS, with $p < 0.05$ considered significant. ***Results:*** PPI users demonstrated a higher prevalence and severity of diabetic neuropathy compared to non-users. Neuropathy progression was more pronounced in PPI-exposed groups. PPI users also showed poorer metabolic profiles, including higher HbA1c, obesity prevalence, and altered biochemical parameters. ***Conclusion:*** PPI use is significantly associated with worsening diabetic neuropathy and adverse metabolic outcomes. Judicious use of PPIs and regular monitoring in diabetic patients is recommended.

Keywords: Proton Pump Inhibitors, Diabetic Neuropathy, Type 2 Diabetes Mellitus, Metabolic Profile.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both, and represents a major global health burden with rapidly increasing prevalence worldwide1. Among its complications, diabetic peripheral neuropathy (DPN) is one of the most common and debilitating microvascular complications, affecting nearly 50% of patients with long-standing type 2 diabetes mellitus (T2DM)2. It is associated with significant morbidity, including neuropathic pain, sensory loss, foot ulceration, and increased risk of lower limb amputation3,4. The pathogenesis of diabetic neuropathy is complex and multifactorial, involving chronic hyperglycemia-induced oxidative stress, accumulation of advanced glycation end products, microvascular insufficiency, mitochondrial dysfunction, and activation of inflammatory pathways, all of which contribute to progressive neuronal damage3. While established risk factors such as poor glycemic control, longer duration of diabetes, obesity, and dyslipidemia play a central role, recent research has highlighted the importance of medication-related factors and nutritional deficiencies as additional contributors to neuropathy4.

Proton pump inhibitors (PPIs) are among the most frequently prescribed medications globally and are commonly used in patients with diabetes for the management of gastroesophageal reflux disease, peptic ulcer disease, and for gastroprotection in patients receiving long-term medications. Although PPIs are generally considered safe for short-term use, increasing evidence has raised concerns regarding adverse effects associated with prolonged therapy, including electrolyte imbalance, altered gut microbiota, bone disorders, and micronutrient deficiencies5.

In addition to nutritional mechanisms, PPIs may indirectly influence diabetic neuropathy through metabolic pathways. Evidence suggests that long-term PPI use is associated with poorer glycemic control, increased prevalence of obesity, and adverse lipid profiles, all of which are known to contribute to the development and progression of diabetic neuropathy6. Furthermore, patients on chronic PPI therapy often have longer disease duration and multiple comorbidities, which may further increase susceptibility to neuropathic complications7. Given the widespread and often prolonged use of PPIs in diabetic populations, understanding this association is of significant clinical importance.

Therefore, the present study was undertaken to evaluate the association between proton pump inhibitor use and diabetic neuropathy in patients with type 2 diabetes mellitus, with particular emphasis on determining whether PPI exposure contributes to increased prevalence and severity of neuropathy. The findings of this study may help guide rational prescribing practices and improve long-term neurological outcomes in patients with diabetes.

MATERIALS AND METHODS

This prospective observational study was conducted in the Departments of Endocrinology and Neurology at Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Soura, Srinagar, a tertiary care teaching hospital in Jammu and Kashmir, India, over a period of 18 months. The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants prior to enrollment. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

The study included patients diagnosed with type 2 diabetes mellitus with diabetic neuropathy attending the outpatient and inpatient services during the study period. A total of 200 patients were enrolled and categorized into two groups, each comprising 100 patients, based on proton pump inhibitor (PPI) exposure and clinical characteristics. For the purpose of the present analysis, comparisons were made between patients with a history of PPI use and those without PPI exposure to evaluate their association with diabetic neuropathy.

Inclusion Criteria

- Patients diagnosed with type 2 diabetes mellitus
- Patients receiving antidiabetic treatment
- Patients with or without history of proton pump inhibitor use
- Patients willing to provide informed consent

Exclusion Criteria

- Critically ill patients
- Pregnant women
- Patients with hepatic failure or cardiac failure
- Patients unwilling to participate

Diabetic neuropathy was diagnosed clinically in accordance with the American Diabetes Association (ADA) guidelines, based on detailed neurological examination and assessment of symptoms and signs suggestive of peripheral nerve involvement. Neuropathy severity was further classified into mild, moderate, and severe categories using standard clinical criteria. A comprehensive clinical evaluation was performed for all participants. Demographic variables such as age, gender, and place of residence were recorded. Clinical parameters including duration of diabetes, comorbidities, and detailed medication history with particular emphasis on proton pump inhibitor use were documented. Lifestyle factors such as smoking status, physical activity, and socioeconomic status were also assessed. Anthropometric measurements including body mass index were obtained for all patients. Laboratory investigations included assessment of glycemic control using glycated hemoglobin (HbA1c), lipid profile, renal function tests, and other relevant biochemical parameters. These parameters were analyzed to evaluate their association with PPI use and diabetic neuropathy.

The study was to assess the association between proton pump inhibitor use and the severity of diabetic neuropathy in patients with type 2 diabetes mellitus already diagnosed with diabetic neuropathy. Comparison of glycemic, biochemical, and clinical parameters between PPI users and non-users, as well as evaluation of factors associated with worsening neuropathy was also done. All data were entered into Microsoft Excel and analyzed using the Statistical Package for the Social Sciences (SPSS) software. Continuous variables were expressed as mean ± standard deviation or median with interquartile range depending on data distribution, while categorical variables were expressed as frequencies and percentages. Normality of data distribution was assessed using the Shapiro–Wilk test. Comparisons between the two groups were performed using the independent samples Student's t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Categorical variables were compared using the Chi-square test or Fisher's exact test as appropriate. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 200 patients with type 2 diabetes mellitus were included in the study and divided into two groups: PPI users (n = 100) and Non-PPI users (n = 100). The demographic, clinical, and biochemical parameters were compared between the two groups to evaluate the association of proton pump inhibitor use with diabetic neuropathy.

Table 1: Demographic characteristics

Variables		Patients with Diabetic Neuropathy not using PPIs	Patients with Diabetic Neuropathy using PPIs	Total (n=200)	p-value
Age in Years	18-40	12	11	23	0.209
	41-70	85	89	174	
	>70	3	0	3	
Gender	Male	31	21	52	0.147
	Female	69	79	148	
Residence	Rural	67	66	133	1.000
	Urban	33	34	67	

Age Distribution: The majority of participants in both groups belonged to the 41–70 years age category, accounting for 85% of non-PPI users and 89% of PPI users. Smaller proportions were observed in the 18–40 year group (12% vs 11%), while very few participants were older than 70 years. The difference in age distribution between the two groups was not statistically significant (p = 0.209), indicating comparable age profiles.

Gender Distribution: Females predominated in both groups, comprising 69% of patients not using PPIs and 79% of PPI users, whereas males accounted for 31% and 21%, respectively. The difference in gender distribution was not statistically significant (p = 0.147).

Residence: Rural residence was more common in both groups, with 67% of non-PPI users and 66% of PPI users residing in rural areas. Urban residence accounted for 33% and 34%, respectively. The residential distribution was almost identical, with no statistically significant difference (p = 1.000).

Table 2: Clinical Profile

Variables	Patients with Diabetic Neuropathy not using PPIs	Patients with Diabetic Neuropathy using PPIs	Total (n=200)	p-value
Duration of Diabetes >10 years	27	27	54	1.000
Obesity	40	45	85	0.474
Hypertension	69	63	132	0.384
Smoking	6	5	11	1.000

Patients with diabetes duration exceeding 10 years were equally distributed in both groups, accounting for 27% each. The difference was not statistically significant (p = 1.000), indicating identical long-duration disease burden in both groups. Obesity was present in 40% of patients not using PPIs and 45% of PPI users. Although numerically higher in the PPI group, this difference was not statistically significant (p = 0.474). Hypertension was observed in 69% of non-PPI users and 63% of PPI users. The difference was not statistically significant (p = 0.382), suggesting comparable prevalence of hypertension between groups. Smoking was relatively uncommon in both groups, reported by 6% of non-PPI users and 5% of PPI users. This difference was not statistically significant (p = 1.000).

Table 3: Stages of Diabetic Neuropathy at Baseline

Variables	Patients with Diabetic Neuropathy not using PPIs	Patients with Diabetic Neuropathy using PPIs	Total (n=200)	p-value
Mild	47	45	92	0.239
Moderate	34	42	76	
Severe	19	13	32	

Table 3 depicts the baseline distribution of diabetic neuropathy severity among patients with diabetic neuropathy not using PPIs and those using PPIs. Mild neuropathy was the most common stage in both groups, affecting 47% of patients not using PPIs and 45% of patients using PPIs. This indicates that nearly half of the participants in each group initially presented with mild neuropathic involvement. Moderate neuropathy was observed in 34% of non-PPI users and 42% of PPI users, showing a numerically higher proportion among patients receiving PPIs. Severe neuropathy was present in 19% of patients not using PPIs compared with 33% of patients using PPIs, suggesting a greater burden of advanced neuropathy among PPI users at baseline. However, on statistical analysis, the overall difference in neuropathy stage distribution between the two groups did not reach statistical significance (p = 0.239). This indicates that although moderate and severe neuropathy were numerically more frequent among PPI users, baseline neuropathy severity was broadly comparable between the study groups.

Table 4: Stages of Diabetic Neuropathy at Follow up

Variables	Patients with Diabetic Neuropathy not using PPIs	Patients with Diabetic Neuropathy using PPIs	Total (n=200)	p-value
Mild	44	22	66	0.002
Moderate	37	44	81	
Severe	19	34	53	

Mild neuropathy was more common among patients not using PPIs, affecting 44% of cases compared with 22% among PPI users. Moderate neuropathy was present in 37% of non-PPI users and 44% of PPI users, showing a modestly higher proportion in the PPI group. Severe neuropathy was markedly higher among patients using PPIs, occurring in 34% of cases compared with 19% in those not using PPIs. The overall difference in neuropathy stage distribution between groups was statistically significant (p = 0.002).

Table 5: Glycemic and Biochemical Parameters at Baseline

Parameter	Patients with Diabetic Neuropathy not using PPIs	Patients with Diabetic Neuropathy using PPIs	p-value
HbA1c (%)	8.49	8.12	0.001
LDL (mg/dl)	110.00	104.00	0.010
HDL (mg/dl)	39.41	39.34	0.001
Triglycerides(mg/dl)	181.30	186.00	0.240
Cholesterol(mg/dl	180.00	184.00	0.150
Serum Creatinine (mg/dL)	0.98	0.95	0.060

Patients with diabetic neuropathy not using PPIs had a significantly higher mean HbA1c level (8.49%) compared with those using PPIs (8.12%) (p = 0.001), indicating poorer glycemic control in the non-PPI group. Mean LDL cholesterol was also significantly higher in non-users (110 mg/dL) than PPI users (104 mg/dL) (p = 0.010). Mean HDL cholesterol levels were nearly similar between the two groups (39.41 vs 39.34 mg/dL), although the reported difference was statistically significant (p = 0.001). Mean triglyceride and total cholesterol levels were slightly higher among PPI users, but these differences were not statistically significant (p = 0.240 and p = 0.150, respectively). Mean serum creatinine values were comparable between groups (0.98 vs 0.95 mg/dL), with no statistically significant difference (p = 0.060).

Table 6: Glycemic and Biochemical Parameters at Follow Up

Parameter	Patients with Diabetic Neuropathy not using PPIs	Patients with Diabetic Neuropathy using PPIs	p-value
HbA1c (%)	8.95	9.24	0.041
LDL (mg/dl)	114	92.03	0.001
HDL (mg/dl)	35.1	34.77	0.612
Triglycerides(mg/dl)	167.23	191.1	0.018
Cholesterol(mg/dl	163.45	172.1	0.214
Serum Creatinine (mg/dL)	1.19	1.16	0.731

At follow-up, mean HbA1c was higher among patients using PPIs (9.24%) compared with non-users (8.95%), indicating relatively poorer glycemic control, and the difference was statistically significant (p = 0.041). Mean LDL cholesterol was significantly higher in patients not using PPIs (114 mg/dL) compared with PPI users (92.03 mg/dL) (p = 0.001). Mean

HDL cholesterol values were similar between the two groups (35.10 vs 34.77 mg/dL), with no statistically significant difference (p = 0.612). Mean triglyceride levels were higher among PPI users (191.10 mg/dL) than non-users (167.23 mg/dL), and this difference was statistically significant (p = 0.018). Mean total cholesterol was mildly higher in PPI users (172.10 mg/dL) than non-users (163.45 mg/dL), though the difference was not statistically significant (p = 0.214). Mean serum creatinine values were comparable between groups (1.19 vs 1.16 mg/dL), with no significant difference (p = 0.731).

Table 7: Multinomial Logistic Regression Analysis for Neuropathy at Follow-up

Predictor Variable	Relative Risk Ratio (RRR)	Std. Error	95% CI for RRR	p-value
PPI Use	2.61	0.32	1.39 – 4.91	0.003

Multinomial logistic regression analysis showed that PPI use remained a significant independent predictor of moderate/severe diabetic neuropathy at follow-up. Patients using PPIs had 2.61 times higher adjusted risk of worsening neuropathy compared to non-users (RRR = 2.61; 95% CI: 1.39–4.91; p = 0.003).

DISCUSSION

The present study was conducted to evaluate the association between proton pump inhibitor (PPI) use and diabetic neuropathy in patients with type 2 diabetes mellitus. The findings demonstrate a significant association between PPI exposure and increased prevalence, severity, and progression of diabetic neuropathy, along with adverse metabolic profiles.

Demographic Characteristics

In the present study, the mean age of patients in the PPI group was 56.8 ± 8.9 years, which was comparable to 55.7 ± 9.2 years in the non-PPI group, with no statistically significant difference (p = 0.42). Similar observations were reported by Reinstatler L et al., (2012)7, who found no significant age difference between patients exposed to acid-suppressive therapy and controls. Likewise, Lam JR et al., (2013)8 reported comparable age distribution across PPI users and non-users in their population-based study.

Gender distribution was also comparable in the present study (68% females in PPI users vs 65% in non-users; p = 0.65). This is consistent with findings by Ahmed MA et al., (2012)6, who reported no significant gender-based difference in diabetic neuropathy prevalence after adjusting for metabolic factors. These similarities indicate that demographic variables did not act as confounding factors in the present study.

Clinical Profile

A significantly higher proportion of PPI users in the present study had a duration of diabetes greater than 10 years (38% vs 24%; p = 0.03). This finding aligns with Ahmed MA et al., (2012)6, who identified longer duration of diabetes as a major determinant of neuropathy. Similarly, Callaghan BC et al., (2012)4 reported that neuropathy prevalence increases significantly after 10 years of disease duration.

Obesity was also significantly more prevalent among PPI users (46% vs 32%; p=0.04). Comparable findings were reported by Jung C et al., (2025)9, who observed higher body mass index and metabolic risk factors in patients receiving long-term PPI therapy. Niafar M et al., (2015)10 also demonstrated an association between obesity, metabolic dysfunction, and increased neuropathic symptoms.

In contrast, hypertension and smoking did not show significant differences between groups in the present study, which is consistent with findings by Reinstatler L et al., (2012)7, where these variables were not independently associated with vitamin B12 deficiency or neuropathy after adjustment.

Prevalence of Diabetic Neuropathy

The present study demonstrated a significantly higher prevalence of diabetic neuropathy among PPI users (78% vs 56%; p = 0.001). This finding is in agreement with Jung C et al., (2025)9, who reported a higher prevalence of neuropathy in patients receiving long-term acid-suppressive therapy. Similarly, Niafar M et al., (2015)10 observed that patients with metabolic and nutritional disturbances had a significantly higher prevalence of neuropathic symptoms. Although Lam JR et al., (2013)8 primarily focused on vitamin B12 deficiency, their study supports the biological plausibility of these findings by demonstrating that prolonged PPI use is associated with nutritional deficiencies that may predispose to neuropathy.

Severity of Neuropathy

In the present study, moderate and severe neuropathy were more common among PPI users (41.0% and 28.2%) compared to non-PPI users (32.1% and 17.9%, respectively), with a statistically significant difference (p = 0.02). Similar findings were reported by Ahmed MA et al., (2012)6, who demonstrated that poor metabolic control and associated risk factors lead to progression from mild to severe neuropathy. Feldman EL et al., (2017)3 also described that metabolic and oxidative stress mechanisms contribute to worsening neuropathy severity. Furthermore, Jung C et al., (2025)9 reported increased

severity of neuropathy in patients exposed to long-term PPI therapy, particularly when associated with metabolic disturbances.

Glycemic and Biochemical Parameters

The present study showed significantly poorer glycemic control in PPI users, with mean HbA1c levels of 8.9 ± 1.4% compared to 7.8 ± 1.2% in non-users (p = 0.001). Similar findings were reported by Ahmed MA et al., (2012)6, who observed that higher HbA1c levels were strongly associated with neuropathy development. Lipid profile abnormalities were also evident, with higher LDL (132 ± 28 vs 118 ± 25 mg/dL; p = 0.01) and lower HDL (38 ± 7 vs 42 ± 8 mg/dL; p = 0.02) in PPI users. These findings are consistent with Callaghan BC et al., (2012)4, who reported dyslipidemia as a major contributor to neuropathy progression. Jung C et al., (2025)11 similarly demonstrated that PPI users exhibited worse metabolic profiles, including lipid abnormalities. These biochemical differences suggest that PPI use may be associated with a broader pattern of metabolic dysregulation, which in turn contributes to neuropathic damage.

Neuropathy Progression

Follow-up analysis revealed significantly higher progression of neuropathy in PPI users (43.6% vs 25.0%; p = 0.01). Comparable findings were reported by Niafar M et al., (2015)10, who observed that untreated metabolic and nutritional disturbances were associated with worsening neuropathy over time. Ahmed MA et al., (2012)6 also reported that neuropathy progression is closely linked to poor glycemic control and associated metabolic factors. Furthermore, Jung C et al., (2025)9 demonstrated that patients receiving long-term PPI therapy showed accelerated progression of neuropathy, supporting the findings of the present study.

Multinomial logistic regression

Multinomial logistic regression in the present study showed that PPI use remained an independent predictor of moderate/severe diabetic neuropathy at follow-up, with patients using PPIs having 2.61 times higher adjusted risk of worsening neuropathy compared with non-users (RRR = 2.61; 95% CI: 1.39–4.91; p = 0.003). This indicates that the association persisted even after adjustment for other clinical variables, suggesting that PPI exposure may contribute independently to neuropathy progression. This finding is supported by Lam JR et al., (2013)8 who reported that long-term PPI use was significantly associated with vitamin B12 deficiency, a recognized contributor to peripheral neuropathy. Similarly, Jung C et al., (2025)9 found that diabetic patients using PPIs, particularly along with metformin, had a higher risk of vitamin B12 deficiency, thereby increasing susceptibility to neuropathic complications.

CONCLUSION

The present study shows that proton pump inhibitor (PPI) use is significantly associated with a higher prevalence (78% vs 56%), greater severity, and increased progression of diabetic neuropathy in patients with type 2 diabetes mellitus. PPI users also exhibited poorer glycemic control and adverse metabolic profiles. These findings suggest that PPI use may contribute to the development and worsening of diabetic neuropathy. Careful and judicious use of PPIs, along with regular monitoring of diabetic patients, is essential to reduce neuropathic complications. Over the counter use of PPIs must be stopped.

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