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Original Research Article

Correlation between HbA1c variability and diabetic neuropathy in type 2 diabetes mellitus

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Abstract

Background: Diabetic peripheral neuropathy (DPN) is one of the most common chronic complications of type 2 diabetes mellitus (T2DM). Emerging evidence suggests that long-term glycaemic variability, in addition to mean glycated haemoglobin (HbA1c), may contribute to the development of neuropathy.
Methods: This prospective observational study included 120 patients with T2DM attending a tertiary care centre. Clinical characteristics, glycaemic profile, and serial HbA1c measurements were recorded. HbA1c variability was assessed using standard deviation (SD) and coefficient of variation (CV). DPN was evaluated using clinical neurological examination together with the Michigan Neuropathy Screening Instrument (MNSI), Neuropathy Symptom Score (NSS), and Neuropathy Disability Score (NDS). Correlation analysis and multivariable logistic regression were performed to identify factors independently associated with DPN.
Results: DPN was present in 54 (45.0%) patients. Patients with DPN had significantly higher mean HbA1c (8.94 ± 1.18% vs. 7.89 ± 1.08%), HbA1c SD (1.02 ± 0.34% vs. 0.58 ± 0.24%), and HbA1c CV (11.56 ± 4.12% vs. 7.67 ± 3.62%) than those without DPN (all $p<0.001$). HbA1c SD demonstrated the strongest positive correlation with MNSI ($r=0.624$), NSS ($r=0.587$), and NDS ($r=0.608$). Multivariable analysis identified longer diabetes duration (adjusted OR 1.16, 95% CI 1.07–1.26), higher mean HbA1c (adjusted OR 1.42, 95% CI 1.03–1.97), HbA1c SD (adjusted OR 1.31, 95% CI 1.16–1.48), and HbA1c CV (adjusted OR 1.12, 95% CI 1.03–1.22) as independent predictors of DPN.
Conclusion: Greater long-term HbA1c variability is independently associated with the presence and severity of diabetic peripheral neuropathy. Assessment of HbA1c variability alongside mean HbA1c may improve risk stratification and facilitate earlier identification and prevention of diabetic neuropathy in patients with T2DM.
Keywords: Type 2 diabetes mellitus; Diabetic peripheral neuropathy; HbA1c variability; Glycated haemoglobin; Glycaemic variability; Michigan Neuropathy Screening Instrument; Neuropathy Disability Score.

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent chronic metabolic disorders worldwide and is associated with substantial morbidity, mortality, and healthcare expenditure. Persistent hyperglycaemia leads to progressive microvascular and macrovascular complications, including diabetic retinopathy, nephropathy, cardiovascular disease, and diabetic peripheral neuropathy (DPN), one of the most common and disabling complications of diabetes [1,2]. DPN is a chronic length-dependent sensorimotor neuropathy that predominantly affects the distal lower limbs and is associated with neuropathic pain, sensory loss, gait instability, diabetic foot ulceration, and lower-limb amputation. It affects approximately 30–50% of individuals with diabetes and significantly impairs quality of life, making early identification of modifiable risk factors essential [3].The pathogenesis of DPN is multifactorial, with chronic hyperglycaemia playing a central role. Sustained

elevation of blood glucose activates several metabolic pathways, including the polyol pathway, advanced glycation end-product formation, protein kinase C activation, and oxidative stress, leading to endothelial dysfunction, impaired nerve perfusion, mitochondrial injury, inflammation, and progressive neuronal damage [1,4]. Landmark studies such as the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that intensive glycaemic control, assessed by glycated haemoglobin (HbA1c), reduces the risk of diabetic microvascular complications [5,6]. However, many patients continue to develop neuropathy despite achieving recommended HbA1c targets, suggesting that mean HbA1c alone may not fully explain the risk of nerve injury [7].

HbA1c reflects average glycaemic control over the preceding two to three months but does not capture fluctuations in glucose levels. Patients with similar HbA1c values may experience markedly different patterns of glycaemic variability, which may influence the development of diabetic complications. HbA1c variability, commonly assessed using standard deviation (SD), coefficient of variation (CV), and other statistical indices, reflects long-term instability in glycaemic control [8].Emerging evidence indicates that glycaemic variability may independently contribute to diabetic complications beyond mean HbA1c levels. Repeated glucose fluctuations can induce greater oxidative stress, endothelial dysfunction, chronic inflammation, mitochondrial injury, and neuronal apoptosis than sustained hyperglycaemia alone [9,10]. Experimental studies have also demonstrated activation of inflammatory mediators such as nuclear factor-kappa B, interleukin-6, and tumour necrosis factor-alpha, together with impaired neurotrophic support, all of which may accelerate peripheral nerve damage [10–12].Clinical evidence regarding the association between HbA1c variability and DPN remains inconsistent. Several observational studies have reported that greater HbA1c variability is independently associated with a higher prevalence and severity of diabetic neuropathy [13,14], whereas other studies have found weaker associations after adjustment for age, diabetes duration, and mean HbA1c. These discrepancies may reflect differences in study populations, neuropathy assessment methods, and measures of glycaemic variability.Evidence from Indian patients with T2DM remains limited despite the country's high diabetes burden. Therefore, the present study was undertaken to evaluate the correlation between HbA1c variability and diabetic peripheral neuropathy in patients with type 2 diabetes mellitus and to determine whether long-term fluctuations in glycaemic control are associated with the presence and severity of neuropathy.

Methodology:

The present study was conducted as a prospective observational study to evaluate the correlation between HbA1c variability and diabetic peripheral neuropathy among patients with type 2 diabetes mellitus (T2DM). The study was carried out in the Department of Medicine at a tertiary care centre

Study Population

A total of 120 patients with type 2 diabetes mellitus who fulfilled the eligibility criteria were included in the study. Participants were recruited from the outpatient department and inpatient services of the hospital. All enrolled patients underwent detailed clinical evaluation, assessment of long-term glycaemic control, calculation of HbA1c variability, and evaluation for diabetic peripheral neuropathy.The study included 120 patients with type 2 diabetes mellitus. The sample size was determined considering the expected prevalence of diabetic peripheral neuropathy and the anticipated association between glycaemic variability and neuropathy parameters, with adequate statistical power to detect clinically meaningful correlations.

Study Duration

The study was conducted over a period of ___ months/years, during which eligible patients with T2DM were consecutively recruited and evaluated according to the study protocol.

Inclusion Criteria

Patients fulfilling the following criteria were included:

- Patients aged ≥18 years.
- Patients diagnosed with type 2 diabetes mellitus according to the American Diabetes Association (ADA) diagnostic criteria.
- Patients with available serial HbA1c measurements over the predefined period for assessment of HbA1c variability.
- Patients willing to participate and provide written informed consent.
- Patients attending the hospital outpatient or inpatient services during the study period.

Exclusion Criteria

Patients were excluded if they had:

- Type 1 diabetes mellitus or secondary diabetes.
- History of neurological disorders unrelated to diabetes (e.g., stroke, Parkinsonism, spinal cord disease).
- History of alcohol abuse or other causes of peripheral neuropathy.

- Vitamin B12 deficiency or other nutritional neuropathies.
- Chronic kidney disease with advanced renal failure.
- Active malignancy or severe systemic illness.
- Current use of medications known to cause neuropathy, such as chemotherapeutic agents.
- Incomplete medical records or insufficient HbA1c measurements for variability assessment.

Clinical Assessment and Data Collection

All participants underwent a detailed clinical evaluation. Demographic characteristics including age, sex, duration of diabetes, body mass index (BMI), and relevant medical history were recorded. Information regarding diabetes treatment, presence of hypertension, dyslipidaemia, smoking status, and other comorbidities was documented.

The duration of diabetes was calculated from the date of initial diagnosis to the date of enrolment. Details regarding antidiabetic medications, including oral hypoglycaemic agents and insulin therapy, were recorded.

Assessment of Glycaemic Control and HbA1c Variability

Glycaemic status was assessed using glycated haemoglobin (HbA1c) measurements obtained from medical records and laboratory investigations. For evaluation of HbA1c variability, multiple HbA1c values recorded during the predefined observation period were collected for each patient.

HbA1c variability was calculated using statistical parameters including:

- Standard deviation (SD) of HbA1c
- Coefficient of variation (CV) of HbA1c
- Average HbA1c value

The mean HbA1c represented overall glycaemic exposure, whereas HbA1c SD and CV were considered indicators of long-term glycaemic fluctuations.

Assessment of Diabetic Peripheral Neuropathy

All patients were evaluated for diabetic peripheral neuropathy using clinical examination and validated neuropathy assessment methods.

Neuropathy assessment included:

Clinical Neurological Examination

A detailed neurological examination was performed to assess:

- Symptoms of neuropathy including numbness, tingling, burning sensation, and neuropathic pain.
- Sensory abnormalities involving the lower limbs.
- Presence of muscle weakness or gait abnormalities.
- Deep tendon reflexes, particularly ankle reflexes.
- Peripheral Neuropathy Screening
- The presence and severity of neuropathy were assessed using standardized clinical tools, including:
- Michigan Neuropathy Screening Instrument (MNSI)
- Neuropathy Symptom Score (NSS)
- Neuropathy Disability Score (NDS)

Patients were categorised according to neuropathy severity based on clinical assessment scores.

Laboratory Investigations

Routine laboratory investigations were performed for all participants, including:

- Complete blood count
- Fasting plasma glucose
- Postprandial plasma glucose
- HbA1c
- Renal function tests
- Lipid profile
- Serum vitamin B12 levels (where indicated)

Additional investigations were performed whenever clinically required to exclude alternative causes of neuropathy.

Assessment of Associated Risk Factors

Potential risk factors associated with diabetic neuropathy were evaluated, including:

- Age
- Sex
- Duration of diabetes
- BMI
- Mean HbA1c level
- HbA1c variability indices
- Hypertension
- Dyslipidaemia
- Smoking status
- Insulin therapy

Statistical Analysis

The collected data were entered into a Microsoft Excel spreadsheet and analysed using SPSS statistical software 26.Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) depending on data distribution. Categorical variables were

presented as frequencies and percentages.Normality of continuous variables was assessed using the Shapiro–Wilk test. Comparisons between groups were performed using the independent sample t-test or Mann–Whitney U test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables.The correlation between HbA1c variability parameters and neuropathy scores was assessed using Pearson's correlation test or Spearman's rank correlation test depending on data distribution.Multivariable logistic regression analysis was performed to identify independent predictors of diabetic peripheral neuropathy after adjustment for potential confounding factors. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs).A p-value <0.05 was considered statistically significant.

Results:

A total of 100 patients with spirometry-confirmed A total of 120 patients with type 2 diabetes mellitus were included in the study. The mean age of the study population was 56.42 ± 10.86 years. Most patients belonged to the age group of 41–60 years (54.2%), followed by those aged >60 years (35.8%) and 18–40 years (10.0%). Males constituted 58.3% of the study population, while females accounted for 41.7%.The mean duration of diabetes was 9.84 ± 5.72 years, and the mean BMI was 27.68 ± 4.12 kg/m². Hypertension was present in 48.3% of patients, dyslipidaemia in 43.3%, and current smoking was reported by 20.8%. Insulin therapy was being received by 36.7% of patients, whereas 63.3% were treated with oral hypoglycaemic agents (Table 1).The mean fasting plasma glucose level was 157.46 ± 42.18 mg/dL, while the mean postprandial plasma glucose level was 232.74 ± 58.62 mg/dL. The mean HbA1c level was 8.36 ± 1.24%. The mean HbA1c standard deviation and coefficient of variation were 0.78 ± 0.36% and 9.42 ± 4.31%, respectively.The mean total cholesterol level was 189.82 ± 38.45 mg/dL, triglyceride level was 176.34 ± 61.28 mg/dL, LDL cholesterol was 112.46 ± 31.72 mg/dL, and HDL cholesterol was 42.18 ± 9.34 mg/dL. The mean serum creatinine and vitamin B12 levels were 0.96 ± 0.24 mg/dL and 382.56 ± 126.48 pg/mL, respectively (Table 2 and Figure 1)Diabetic peripheral neuropathy was present in 54 patients (45.0%), whereas 66 patients (55.0%) had no evidence of neuropathy. Regarding severity, mild neuropathy was observed in 22 patients (18.3%), moderate neuropathy in 21 patients (17.5%), and severe neuropathy in 11 patients (9.2%).Numbness was the most frequently reported neuropathic symptom, occurring in 40.0% of patients, followed by tingling sensation in 35.0%, burning sensation in 30.8%, and neuropathic pain in 25.8%. Reduced vibration perception was observed in 40.8%, absent or reduced ankle reflexes in 35.8%, and an abnormal 10-g monofilament test in 32.5% of patients (Table 3).Patients with diabetic peripheral neuropathy were significantly older than those without neuropathy (60.18 ± 9.42 vs. 53.35 ± 10.94 years; p<0.001). The mean duration of diabetes was also significantly longer among patients with neuropathy (13.24 ± 5.42 years) than among those without neuropathy (7.06 ± 4.31 years; p<0.001).The mean HbA1c level was significantly higher in patients with neuropathy compared with those without neuropathy (8.94 ± 1.18% vs. 7.89 ± 1.08%; p<0.001). Similarly, HbA1c standard deviation was significantly higher in the DPN group (1.02 ± 0.34% vs. 0.58 ± 0.24%; p<0.001), as was the HbA1c coefficient of variation (11.56 ± 4.12% vs. 7.67 ± 3.62%; p<0.001).Hypertension, dyslipidaemia, smoking, and insulin therapy were significantly more common among patients with diabetic peripheral neuropathy. However, no statistically significant differences were observed between the groups regarding male sex or BMI (Table 4 and Figure 2).Mean HbA1c demonstrated a moderate positive correlation with the MNSI score (r=0.468), NSS (r=0.421), and NDS (r=0.446), with all correlations being statistically significant (p<0.001).HbA1c standard deviation demonstrated the strongest correlations with neuropathy assessment scores, including MNSI (r=0.624), NSS (r=0.587), and NDS (r=0.608), all with p<0.001. HbA1c coefficient of variation was also positively correlated with MNSI (r=0.576), NSS (r=0.548), and NDS (r=0.563), with all correlations being statistically significant.Fasting and postprandial plasma glucose levels showed weaker but statistically significant positive correlations with all three neuropathy assessment scores (Table 5).On multivariable logistic regression analysis, longer duration of diabetes was independently associated with diabetic peripheral neuropathy, with an adjusted odds ratio of 1.16 for each additional year of diabetes duration (95% CI: 1.07–1.26; p<0.001).Higher mean HbA1c was independently associated with neuropathy (adjusted OR: 1.42; 95% CI: 1.03–1.97; p=0.032). HbA1c standard deviation was also an independent predictor, with each 0.1% increase associated with a 31% increase in the odds of neuropathy (adjusted OR: 1.31; 95% CI: 1.16–1.48; p<0.001). Similarly, each 1% increase in HbA1c coefficient of variation was associated with a 12% increase in the odds of neuropathy (adjusted OR: 1.12; 95% CI: 1.03–1.22; p=0.008).Increasing age was marginally associated with neuropathy (adjusted OR: 1.04; 95% CI: 1.00–1.09; p=0.046). Hypertension, dyslipidaemia, smoking, and insulin therapy were not independently associated with diabetic peripheral neuropathy after adjustment for other variables (Table 6 and Figure 3).

Table 1. Baseline Demographic and Clinical Characteristics of the Study Population (n = 120)

Variable	Value
Age (years), mean ± SD	56.42 ± 10.86
Age group, n (%)	
18–40 years	12 (10.0)
41–60 years	65 (54.2)
>60 years	43 (35.8)
Sex, n (%)	
Male	70 (58.3)
Female	50 (41.7)
Duration of diabetes (years), mean ± SD	9.84 ± 5.72
BMI (kg/m²), mean ± SD	27.68 ± 4.12
Hypertension, n (%)	58 (48.3)
Dyslipidaemia, n (%)	52 (43.3)
Current smoking, n (%)	25 (20.8)
Insulin therapy, n (%)	44 (36.7)
Oral hypoglycaemic agents, n (%)	76 (63.3)

Table 2. Glycaemic and Laboratory Profile of the Study Population (n = 120)

Variable	Mean ± SD
Fasting plasma glucose (mg/dL)	157.46 ± 42.18
Postprandial plasma glucose (mg/dL)	232.74 ± 58.62
Mean HbA1c (%)	8.36 ± 1.24
HbA1c standard deviation (%)	0.78 ± 0.36
HbA1c coefficient of variation (%)	9.42 ± 4.31
Total cholesterol (mg/dL)	189.82 ± 38.45
Triglycerides (mg/dL)	176.34 ± 61.28
LDL cholesterol (mg/dL)	112.46 ± 31.72
HDL cholesterol (mg/dL)	42.18 ± 9.34
Serum creatinine (mg/dL)	0.96 ± 0.24
Serum vitamin B12 (pg/mL)	382.56 ± 126.48

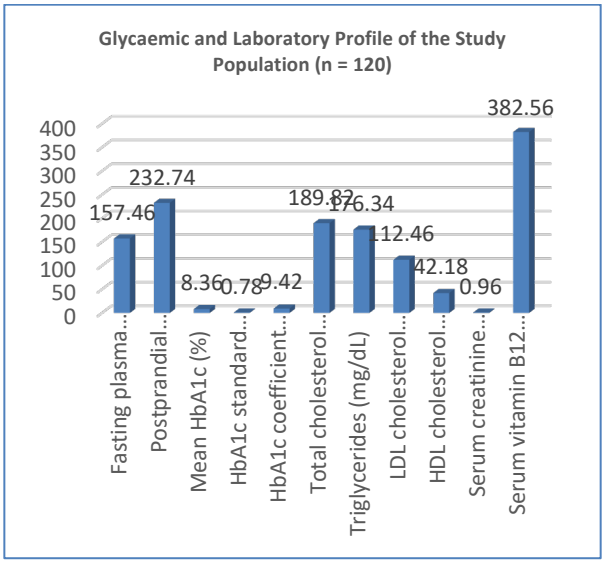

Figure 1 Glycaemic and Laboratory Profile of the Study Population (n = 120)

Table 3. Distribution and Clinical Severity of Diabetic Peripheral Neuropathy (n = 120)

Neuropathy Parameter	n (%)
Diabetic peripheral neuropathy	
Present	54 (45.0)
Absent	66 (55.0)
Neuropathy severity among total patients	
No neuropathy	66 (55.0)
Mild neuropathy	22 (18.3)
Moderate neuropathy	21 (17.5)
Severe neuropathy	11 (9.2)
Neuropathic symptoms	
Numbness	48 (40.0)
Tingling sensation	42 (35.0)
Burning sensation	37 (30.8)
Neuropathic pain	31 (25.8)

Reduced vibration perception	49 (40.8)
Absent or reduced ankle reflex	43 (35.8)
Abnormal 10-g monofilament test	39 (32.5)

Table 4. Comparison of Clinical and Glycaemic Parameters Between Patients With and Without Diabetic Peripheral Neuropathy

Variable	DPN Present (n = 54)	DPN Absent (n = 66)	p-value
Age (years)	60.18 ± 9.42	53.35 ± 10.94	<0.001
Male sex, n (%)	34 (63.0)	36 (54.5)	0.351
Duration of diabetes (years)	13.24 ± 5.42	7.06 ± 4.31	<0.001
BMI (kg/m²)	28.26 ± 4.20	27.21 ± 4.02	0.166
Mean HbA1c (%)	8.94 ± 1.18	7.89 ± 1.08	<0.001
HbA1c SD (%)	1.02 ± 0.34	0.58 ± 0.24	<0.001
HbA1c CV (%)	11.56 ± 4.12	7.67 ± 3.62	<0.001
Hypertension, n (%)	33 (61.1)	25 (37.9)	0.011
Dyslipidaemia, n (%)	30 (55.6)	22 (33.3)	0.014
Smoking, n (%)	16 (29.6)	9 (13.6)	0.031
Insulin therapy, n (%)	29 (53.7)	15 (22.7)	<0.001

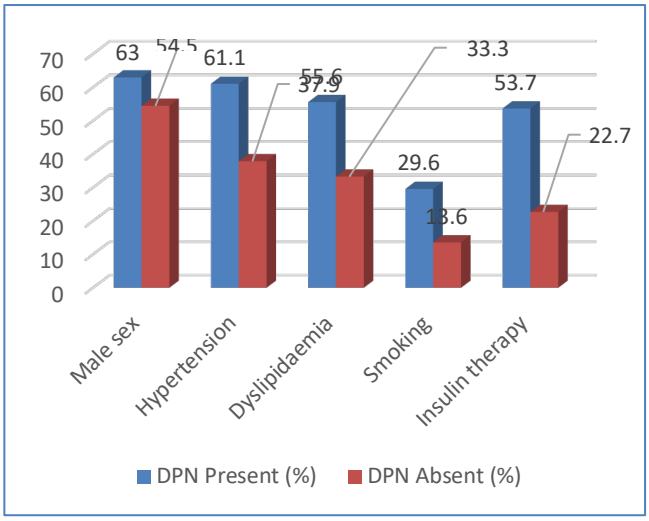

Figure 2 Comparison of Clinical and Glycaemic Parameters Between Patients With and Without Diabetic Peripheral Neuropathy

Table 5. Correlation of HbA1c Parameters With Neuropathy Assessment Scores

HbA1c Parameter	MNSI Score, r (p-value)	NSS, r (p-value)	NDS, r (p-value)
Mean HbA1c	0.468 (<0.001)	0.421 (<0.001)	0.446 (<0.001)
HbA1c SD	0.624 (<0.001)	0.587 (<0.001)	0.608 (<0.001)
HbA1c CV	0.576 (<0.001)	0.548 (<0.001)	0.563 (<0.001)
Fasting plasma glucose	0.284 (0.002)	0.246 (0.007)	0.262 (0.004)
Postprandial plasma glucose	0.316 (<0.001)	0.292 (0.001)	0.301 (0.001)

Table 6. Multivariable Logistic Regression Analysis for Predictors of Diabetic Peripheral Neuropathy

Variable	Adjusted OR	95% CI	p-value
Age, per one-year increase	1.04	1.00–1.09	0.046

Duration of diabetes, per one-year increase	1.16	1.07–1.26	<0.001
Mean HbA1c, per 1% increase	1.42	1.03–1.97	0.032
HbA1c SD, per 0.1% increase	1.31	1.16–1.48	<0.001
HbA1c CV, per 1% increase	1.12	1.03–1.22	0.008
Hypertension	1.78	0.79–4.04	0.165
Dyslipidaemia	1.63	0.72–3.69	0.241
Smoking	2.06	0.76–5.58	0.155
Insulin therapy	2.14	0.91–5.03	0.080

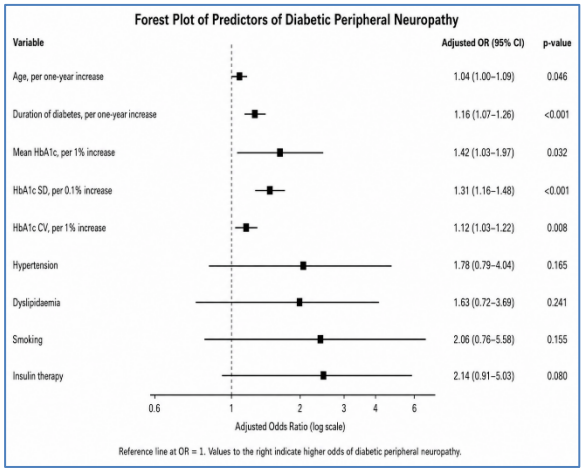

Figure 3 Multivariable Logistic Regression Analysis for Predictors of Diabetic Peripheral Neuropathy

Discussion

The present study evaluated diabetic peripheral neuropathy (DPN) and its association with long-term glycaemic control and visit-to-visit HbA1c variability among 120 patients with type 2 diabetes mellitus. DPN was present in 54 patients, giving a prevalence of 45.0%; 18.3% had mild, 17.5% moderate and 9.2% severe neuropathy. Patients with DPN were older, had a longer duration of diabetes and had significantly higher mean HbA1c, HbA1c standard deviation (SD) and HbA1c coefficient of variation (CV) than those without DPN.The observed prevalence was higher than the 29.1% reported by Bansal et al.[15]. Differences in diabetes duration, glycaemic control, referral patterns and diagnostic criteria may explain the higher prevalence in our tertiary-care population. Numbness was the most frequent symptom, followed by tingling, burning sensation and neuropathic pain. Reduced vibration perception, impaired ankle reflexes and abnormal monofilament testing were also common, indicating that painless sensory loss may occur frequently and may remain undetected without systematic screening.Patients with DPN were significantly older than those without DPN, and each one-year increase in age was associated with a 4% increase in the adjusted odds of neuropathy. Duration of diabetes was also substantially longer in the DPN group, and each additional year increased the odds of DPN by 16%. These findings support the cumulative effect of ageing, chronic hyperglycaemia, microvascular injury and oxidative stress on peripheral nerves.Mean HbA1c was significantly higher among patients with DPN and showed positive correlations with MNSI, NSS and NDS scores. Each 1% increase in mean HbA1c was associated with a 42% increase in the adjusted odds of DPN, confirming chronic hyperglycaemia as an important determinant of nerve damage.The principal finding was the strong association between visit-to-visit HbA1c variability and DPN. HbA1c SD and CV were markedly higher in patients with neuropathy and showed stronger correlations with neuropathy scores than mean HbA1c, fasting glucose or postprandial glucose. Each 0.1% increase in HbA1c SD increased the adjusted odds of DPN by 31%, while each 1% increase in HbA1c CV increased the odds by 12%.These findings are consistent with Su et al.[16], who reported progressively higher odds of DPN across increasing HbA1c CV tertiles and found that HbA1c CV had better discriminatory ability than mean HbA1c. Lai et al.[17] similarly demonstrated that greater HbA1c variability was independently associated with more severe electrophysiological neuropathy and poorer nerve-conduction parameters.

Hypertension, dyslipidaemia, smoking and insulin use were more frequent among patients with DPN, although they were not independent predictors after adjustment. BMI also did not differ significantly between groups.

Conclusion

Diabetic peripheral neuropathy was present in 45.0% of patients with type 2 diabetes mellitus. Patients with neuropathy had significantly higher mean HbA1c, HbA1c standard deviation and HbA1c coefficient of variation than those without neuropathy. HbA1c variability showed a stronger correlation with neuropathy severity than fasting or postprandial glucose levels. Longer diabetes duration, higher mean HbA1c and greater HbA1c variability were independent predictors of neuropathy. Regular assessment and reduction of

long-term glycaemic fluctuations may therefore help prevent or delay diabetic peripheral neuropathy.

Limitations

The study was conducted at a single tertiary-care centre with a relatively small sample size, which may limit the generalisability of the findings. HbA1c variability was calculated from available serial measurements, and differences in the number and timing of these measurements may have influenced the results. The observational design did not establish a causal relationship between glycaemic variability and diabetic peripheral neuropathy. Electrophysiological nerve-conduction studies were not performed in all patients to confirm subclinical neuropathy.

Ethical approval

Ethical approval for this study was obtained from the Institutional Ethics Committee prior to the commencement of the study. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and applicable institutional guidelines.

Informed Consent

Written informed consent was obtained from all participants prior to their enrolment in the study.

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Conflict of Interest Declaration

The authors declare no conflict of interest.

Data Availability Statement

All data generated or analysed during this study are available from the corresponding author upon reasonable request.

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