

Electrophysiological Phenotypes and Clinical–Metabolic Correlates of Neuropathy in Patients with Type 2 Diabetes Mellitus: An Original Cross-Sectional Study

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Abstract

Background: Diabetic peripheral neuropathy (DPN) is clinically and electro physiologically heterogeneous. Standard clinical screening scores and aggregate analysis frequently mask distinct metabolic profiles associated with isolated neurological patterns. We investigated the clinical-metabolic markers, vitamin B12 profiles, and diagnostic performance of bedside clinical scores across unique electrophysiological phenotypes in type 2 diabetes mellitus (T2DM). **Material and Methods:** An observational cross-sectional study of 80 participants with T2DM of >5 years' duration was conducted at SGT Medical College Hospital & Research Institute, Gurugram, India. Clinical assessments were conducted via the Diabetic Neuropathy Symptom Score (DNSS), Neuropathy Disability Score (NDS), and Neuropathic Pain Questionnaire (NPQ). Bilateral multi-nerve conduction studies (NCS) served as the standard gold benchmark. Abnormal electrophysiological findings were categorized into either generalized polyneuropathy-pattern or focal/other abnormalities. **Results:** Electrophysiological abnormalities were identified in 55/80 participants (68.8%), of whom 32 (40.0% of total cohort) exhibited a generalized polyneuropathy pattern and 23 (28.8%) presented with focal/other abnormalities. Within the electrophysiologically abnormal subset, participants with focal/other variants possessed highly elevated glycemic markers including HbA1c ($9.21 \pm 0.44\%$ vs $7.56 \pm 0.81\%$, $p < 0.001$), fasting blood sugar (180.75 ± 21.49 vs 139.41 ± 28.02 mg/dL, $p < 0.001$), and postprandial glucose (291.93 ± 30.21 vs 228.03 ± 33.46 mg/dL, $p < 0.001$). Conversely, the generalized polyneuropathy subgroup exhibited significantly higher painful sensory burden on the NPQ (4.94 ± 1.41 vs 3.30 ± 1.94 , $p = 0.001$). Serum vitamin B12 concentrations were lower in the overall abnormal NCS group compared to neurophysiological controls (457.94 ± 166.96 vs 592.41 ± 129.34 pg/mL, $p = 0.00023$). Against objective electrophysiology, the diagnostic sensitivity and specificity reached 100.0% and 96.0% for $\text{DNSS} \geq 1$, and 100.0% and 100.0% for $\text{NDS} \geq 3$. **Conclusion:** Diabetic neuropathy is highly heterogeneous. Distinct electrophysiological phenotypes display unique clinical and glycemic patterns. Poorer metabolic control strongly relates to localized focal lesions, whereas diffuse myelin/axonal stress yields a higher neuropathic pain burden. Pragmatic clinical screening programs must integrate phenotype-specific tracking with metabolic and vitamin B12 monitoring to guide clinical care.

Keywords: Diabetic Peripheral Neuropathy, Type 2 Diabetes Mellitus, Nerve Conduction Studies, Electrophysiological Phenotypes, Glycaemic Control, Glycated Hemoglobin, Neuropathic Pain, Vitamin B12, Neuropathy Disability Score, Diagnostic Accuracy.

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INTRODUCTION

Diabetes mellitus represents a global epidemic characterized by sustained metabolic dysregulation and microvascular target organ injury.^[1] Among its chronic sequelae, diabetic peripheral neuropathy (DPN) stands as a principal driver of neuropathic pain, loss of protective sensation, gait instability, and lower-extremity amputations.^[2,3] The basic Patho mechanisms of DPN involve a complex web of metabolic and vascular pathways. Prolonged exposure to excess intracellular glucose drives polyol pathway flux, accelerates the accumulation of advanced glycation end products (AGEs), elevates reactive oxygen species (ROS) output, and provokes chronic endoneurial ischemia via microangiopathy of the vasa nervorum.^[3] Standard clinical surveillance frequently models DPN as a uniform, binary phenomenon—classified simply as present or absent. However, contemporary neurophysiology demonstrates extreme structural heterogeneity, across which

patients may demonstrate generalized sensorimotor polyneuropathy, focal entrapment neuropathies (such as carpal tunnel syndrome or ulnar mononeuropathies), or distinct asymmetric motor features.^[4-9] Treating these diverse presentations under a single generic entity masks clinical-metabolic pathways, particularly regarding glycaemic toxicities, neuropathic pain scores, and reversible secondary nerve modifiers like subclinical vitamin B12 deficiency, which is

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common in Indian populations due to dietary restrictions and prolonged metformin exposure.^[5]

Bedside indices such as the Neuropathy Disability Score (NDS) and Diabetic Neuropathy Symptom Score (DNSS) are established, low-cost screening options in resource-limited Tier II and Tier III healthcare settings where advanced neurophysiology centers are unavailable.^[6,7] Yet, the diagnostic performance and phenotypic validity of these bedside tools when mapped against multi-nerve conduction studies (NCS) remain poorly characterized in South Asian cohorts.^[6] Therefore, this cross-sectional study evaluated the diagnostic accuracy of bedside screening instruments against objective gold-standard electrophysiology and characterized the clinical-metabolic variations between generalized polyneuropathy-pattern and focal/other electrophysiological variants.

MATERIALS AND METHODS

Study Design and Setting: This was an original, hospital-based, analytical cross-sectional study conducted over an 18-month duration at the Department of General Medicine, Faculty of Medicine and Health Sciences, SGT University, Budhera, Gurugram, Haryana, India. The study protocol received formal institutional review and ethics board approval under reference number SGT/FMHS/MED/2023-84, and written informed consent was acquired from all participants prior to screening.

Participant Selection Matrix: A cohort of 80 adult patients was consecutively enrolled using a convenient sampling methodology from outpatient clinics and inpatient general medicine wards. Inclusion criteria required a confirmed diagnosis of T2DM for a duration exceeding five years, an age range between 18 and 80 years, and the clinical presence of sensory or motor complaints in the limbs. Exclusion criteria were systematically enforced to eliminate non-diabetic causes of neuropathy, including: severe vitamin B12 deficiency (secondary to megaloblastic anemia), chronic alcoholism, active thyroid disease, chronic kidney disease (eGFR <60 mL/min/1.73 m²), liver failure, active malignancies, human immunodeficiency virus (HIV), leprosy, syphilis, pregnancy, and history of major mechanical spinal or post-traumatic nerve compression.^[5, 9]

Clinical and Bedside Neurological Assessments: Enrolled participants underwent a detailed bedside neurological examination to compute validated screening scores:

1) The Diabetic Neuropathy Symptom Score (DNSS), a 4-point questionnaire tracking unsteadiness, numbness, burning, and pricking sensations, with a positive threshold defined as a score ≥ 1 ^[7]

2) The Neuropathy Disability Score (NDS), a 10-point scale evaluating vibration perception (using a 128-Hz tuning fork), temperature discrimination, pinprick sensitivity at the great toe, and Achilles reflex preservation, with a score ≥ 3 operationalized as positive.^[6]

3) The Neuropathic Pain Questionnaire (NPQ), tracking pain intensity and burning, with a threshold of ≥ 3 establishing significant pain burden.^[8]

Objective Electrophysiological Phenotyping: Objective

nerve evaluation was conducted within the neurophysiology suite using the Medicaid System Neuro Stim (NS4) panel. Bilateral motor conduction assessments were processed for the median, ulnar, and posterior tibial nerves (evaluating distal onset latencies, compound muscle action potential amplitudes, and conduction velocities), alongside sensory nerve action potential (SNAP) recordings of the median, ulnar, and sural nerves.^[9] Abnormal studies were sub-classified into distinct phenotypes: a) Generalized polyneuropathy-pattern abnormalities, consisting of symmetric mixed axonal-demyelinating polyneuropathy, pure demyelinating polyneuropathy, or distal symmetric axonal polyneuropathy; b) Focal/other abnormalities, capturing median nerve compression at the flexor retinaculum (Carpal Tunnel Syndrome), ulnar mononeuropathies, or isolated radial compression.^[4]

Biochemical Evaluations & Biostatistical Architecture:

Venous blood samples were collected following an 8-hour overnight fast to establish standard metabolic profiles: fasting blood sugar (FBS), 2-hour postprandial blood sugar (PPBS), and glycated hemoglobin (HbA1c). Serum vitamin B12 concentrations were evaluated using automated chemiluminescent microparticle immunoassay channels [5]. Statistical computations were processed via IBM SPSS Version 26.0 and independent script repositories. Continuous parameters were evaluated for normality and expressed as mean $\pm$ standard deviation (SD). Subgroup variance was contrasted using Welch's two-sample t-test to mitigate potential Type I error inflation from unequal variances. Univariate diagnostic indicators (sensitivity, specificity, PPV, and NPV) were mapped against true neurophysiological confirmation. Exploratory Receiver Operating Characteristic (ROC) Areas Under the Curve (AUC) were generated with 95% confidence intervals utilizing 5,000 stratified bootstrap resamples to secure statistical stability. Categorical associations were evaluated using Pearson's chi-square test alongside Cramér's V. Statistical significance was defined as a two-sided p-value <0.05.

RESULTS

Cohort Demographics and Outcome Prevalence: The final analytical sample comprised 80 participants with type 2 diabetes mellitus, consisting of 58.8% female and 41.3% male subjects, with an overall mean age of 41.12 ± 12.13 years. The mean duration of documented T2DM was 8.48 ± 3.54 years, and the cohort demonstrated an overall pattern of suboptimal glycaemic exposure (mean HbA1c: $7.60 \pm 1.26\%$). Bilateral electrophysiological evaluation identified objective neurophysiological abnormalities in 55 out of 80 participants, establishing a high baseline prevalence rate of 68.8% for nerve conduction deficits.

Clinical-Metabolic Profiling by Binary NCS Status:

Contrasting participants across binary neurophysiological lines revealed significant differences in blood sugar exposure and micronutrient retention. Participants with abnormal NCS demonstrated significantly higher mean HbA1c ($8.25 \pm 1.06\%$ vs $6.25 \pm 0.38\%$, $p < 0.001$), fasting plasma glucose (156.70 ± 32.60 mg/dL vs 109.84 ± 11.17 mg/dL), and postprandial glucose (254.75 ± 45.01 mg/dL vs 184.95 ± 21.36 mg/dL) than neurophysiologically intact controls. Additionally, serum

vitamin B12 levels were significantly lower in the abnormal electrophysiological cohort (457.94 ± 166.96 pg/mL vs 592.41 ± 129.34 pg/mL, $p = 0.00023$) [5]. No significant

differences were identified regarding baseline chronological age ($p = 0.999$) or diabetes duration ($p = 0.169$) between the groups [Table 1].

Table 1: Comparison of Clinical and Biochemical Characteristics by Nerve Conduction Study Status

Clinical / Biochemical Variable	NCS Abnormal (n=55)	NCS Normal (n=25)	Mean Difference	p-Value
Age (years)	41.44 ± 12.92	41.44 ± 9.95	-0.00	0.999
Diabetes Duration (years)	8.79 ± 3.20	7.95 ± 2.11	0.84	0.169
Fasting Blood Sugar (mg/dL)	156.70 ± 32.60	109.84 ± 11.17	46.86	< 0.001
Postprandial Blood Sugar (mg/dL)	254.75 ± 45.01	184.95 ± 21.36	69.80	< 0.001
HbA1c (%)	8.25 ± 1.06	6.25 ± 0.38	2.00	< 0.001
Serum Vitamin B12 (pg/mL)	457.94 ± 166.96	592.41 ± 129.34	-134.47	0.00023
Neuropathic Pain Score (NPQ)	4.25 ± 1.83	1.40 ± 0.50	2.85	< 0.001
Neuropathy Disability Score (NDS)	5.80 ± 1.89	1.72 ± 0.46	4.08	< 0.001
Neuropathy Symptom Score (DNSS)	2.53 ± 1.12	0.04 ± 0.20	2.49	< 0.001

Electrophysiological Phenotyping and Structural Divergence: Sub-classification of the 55 abnormal nerve conduction records revealed structural heterogeneity. Thirty-two participants (40.0% of the entire cohort) presented with generalized polyneuropathy-pattern abnormalities (comprising mixed axonal-demyelinating or

pure symmetric variants).^[9] In parallel, 23 participants (28.8% of the cohort) demonstrated localized focal or mononeuropathic lesions (including carpal tunnel syndrome and isolated ulnar compression lines), confirming that focal entities accounted for 41.8% of all recorded electrophysiological abnormalities [Table 2].^[4]

Table 2: Distribution of Electrophysiological Phenotypes in the Study Cohort

Identified NCS Phenotype	Absolute Count (n)	Percentage of Cohort	Percentage of Abnormal Subset
Normal Neurophysiology Control	25	31.3%	—
Generalized Polyneuropathy Variant	32	40.0%	58.2%
Focal / Other Structural Neuropathy	23	28.8%	41.8%

Phenotypic Variations:

Generalized vs. Focal Pathologies: Direct statistical comparison between the generalized polyneuropathy-pattern group (n=32) and the focal/other group (n=23) revealed an unexpected phenotypic divergence. Participants with focal/other abnormalities exhibited significantly higher glycaemic levels, with a mean HbA1c elevation of $9.21 \pm 0.44\%$ versus $7.56 \pm 0.81\%$ in the generalized polyneuropathy variant, yielding a highly significant mean

difference of -1.65 percentage points (95% CI -1.99 to -1.31, $p < 0.001$).^[3,10] Fasting and postprandial glucose levels were similarly higher in the focal group. In contrast, the generalized polyneuropathy-pattern subgroup demonstrated a significantly higher painful sensory burden, with a mean NPQ score of 4.94 ± 1.41 versus 3.30 ± 1.94 in the focal group (mean difference: +1.63 points, 95% CI 0.67 to 2.60, $p = 0.001$).^[8] [Table 3].

Table 3: Comparison of Clinical and Glycaemic Measures Between Generalized Polyneuropathy and Focal/Other

Metabolic / Symptom Metric	Generalized (n=32)	Focal/Other (n=23)	Mean Difference	95% CI Bounds	p-Value
Neuropathic Pain (NPQ)	4.94 ± 1.41	3.30 ± 1.94	1.63	0.67 to 2.60	0.001
Fasting Blood Sugar (mg/dL)	139.41 ± 28.02	180.75 ± 21.49	-41.34	-54.74 to -27.94	< 0.001
Postprandial Glucose (mg/dL)	228.03 ± 33.46	291.93 ± 30.21	-63.90	-81.25 to -46.54	< 0.001
Glycated Hemoglobin [HbA1c] (%)	7.56 ± 0.81	9.21 ± 0.44	-1.65	-1.99 to -1.31	< 0.001

Microvascular Comorbidity Mapping: Retinopathy status was significantly associated with underlying neurophysiological classification ($\chi^2 = 7.91$, $df = 2$, $p = 0.019$; Cramér's $V = 0.314$).^[1]

Objective nerve conduction deficits were present in 67.9% of participants with normal fundus findings, increasing to 88.0% in those with non-proliferative diabetic retinopathy (NPDR), and dropping to 51.9% in advanced proliferative diabetic retinopathy (PDR) cases, reflecting a non-monotonic distribution among different microvascular territories.

Diagnostic Accuracy of Bedside Screening Scores: Evaluating bedside screening cut-offs against objective

gold-standard electrophysiology showed high diagnostic performance within this cohort. The Neuropathy Disability Score (NDS ≥ 3) demonstrated perfect classification, achieving a diagnostic sensitivity of 100.0%, specificity of 100.0%, and an area under the receiver operating characteristic curve (ROC AUC) of 1.000.^[6] The Diabetic Neuropathy Symptom Score (DNSS ≥ 1) correctly identified all 55 true positive cases, yielding 100.0% sensitivity, 96.0% specificity (1 false positive), and an AUC of 0.995 (95% CI 0.981 to 1.000).^[7] The pain-based Neuropathic Pain Questionnaire (NPQ ≥ 3) showed 83.6% sensitivity, 100.0% specificity, and an AUC of 0.922 (95% CI 0.861 to 0.972).^[8] [Table 4].

Table 4: Diagnostic Performance of Bedside Neuropathy Screening Scores Against Nerve Conduction Studies

Index Cut-off	TP	FN	TN	FP	Sensitivity	Specificity	PPV	NPV	ROC AUC (95% CI)
DNSS $\geq$ 1	55	0	24	1	100.0%	96.0%	98.2%	100.0%	0.995 (0.981–1.000)
NDS $\geq$ 3	55	0	25	0	100.0%	100.0%	100.0%	100.0%	1.000 (1.000–1.000)
NPQ $\geq$ 3	46	9	25	0	83.6%	100.0%	100.0%	73.5%	0.922 (0.861–0.972)

DISCUSSION

This study confirms that electrophysiological abnormalities in type 2 diabetes mellitus are highly heterogeneous.^[1,4] Importantly, focal entrapment neuropathies and isolated mononeuropathies accounted for over 41% of all objective neurophysiological deficits in this cohort.^[4] This structural distribution underscores that treating all abnormal nerve conduction results as generic diabetic peripheral neuropathy can obscure distinct metabolic and clinical relationships.

The primary finding of this investigation is the significant association between poorer glycaemic control and localized focal abnormalities within the electrophysiologically abnormal subset.^[3,10] Participants with focal variants possessed markedly higher HbA1c, fasting plasma glucose, and postprandial values than those with a generalized polyneuropathy pattern. Conversely, the generalized polyneuropathy group demonstrated a significantly higher sensory pain score on the NPQ, indicating that diffuse demyelinating and axonal strain across long peripheral fibers drives a more pronounced clinical pain burden.^[8,9] Furthermore, the finding of lower serum vitamin B12 levels among participants with abnormal NCS highlight the importance of regular micronutrient monitoring, particularly in populations receiving metformin-based regimens.^[5]

CONCLUSION

In conclusion, nerve conduction abnormalities in patients with type 2 diabetes mellitus are heterogeneous and show distinct clinical and metabolic patterns.^[4] Severe glycaemic exposure was linked to focal and mononeuropathic variants, whereas generalized polyneuropathy-pattern abnormalities presented with a greater neuropathic pain burden.^[3,8] Additionally, lower serum vitamin B12 concentrations were associated with objective electrophysiological deficits.^[5] These findings support systematic electrophysiological phenotyping and integrated metabolic screening to improve risk stratification and early clinical management.^[10]

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Conflicts of interest

There are no conflicts of interest.

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