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Correlation of Diabetic Peripheral Neuropathy with Glycaemic Variability Assessed by HbA1c - A Cross-Sectional Study from a Tertiary Care Teaching Hospital in South India.

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Abstract

Background: Diabetic peripheral neuropathy (DPN) is the most prevalent chronic complication of type 2 diabetes mellitus (T2DM). Beyond mean glycaemia, visit-to-visit variability in glycated haemoglobin (HbA1c) has been proposed as an independent determinant of micro vascular nerve injury, but data from Indian cohorts remain limited.

Objectives: To estimate HbA1c variability in patients with T2DM, to determine the frequency and severity of DPN, and to correlate HbA1c variability with the severity of DPN.

Methods: A hospital-based cross-sectional study was conducted on 100 adults with T2DM attending the outpatient and inpatient services of a tertiary care teaching hospital in Bengaluru between February 2021 and May 2022. Patients with chronic alcoholism, anaemia, hypothyroidism, vitamin B12 or folate deficiency, toxin exposure, or drugs affecting glycaemic variability were excluded. Neuropathy was screened with the Michigan Neuropathy Screening Instrument (MNSI) and graded by neurothesiometry using the vibration perception threshold (VPT). HbA1c variability was derived from sequential HbA1c estimations. Analysis used SPSS version 20, with significance set at $p<0.05$.

Results: Sixty-one participants (61%) were male. Mean age was 53±10 years, mean diabetes duration 7±4 years, and mean HbA1c 8.81±3.05%. DPN was detected in 76 participants (mild 37%, moderate 28%, severe 11%). Mean HbA1c variability was 1.50±3.21 and differed

significantly across severity strata (0.28±0.12 in no DPN, 2.73±4.99 in mild, 1.21±0.94 in moderate and 0.72±0.37 in severe DPN; p=0.001). An HbA1c of 7% or above was significantly associated with DPN (p=0.029). MNSI Part A and Part B scores both tracked VPT-defined severity (p=0.001 for each). Waist circumference also differed significantly across strata (p=0.035). The Pearson correlation between HbA1c variability and neuropathy grade was weak and non-significant (r=0.014, p=0.893).

Conclusion: HbA1c variability was significantly higher in patients with DPN than in those without, but did not increase monotonically with severity. Variability appears to flag the presence of early nerve injury rather than to grade its magnitude, and may be a useful adjunct to a single HbA1c value in routine screening.

Keywords: Type 2 diabetes mellitus, Diabetic peripheral neuropathy, HbA1c variability, Glycaemic variability, Michigan Neuropathy Screening Instrument, Vibration perception threshold.

Introduction

Diabetes mellitus is a group of metabolic disorders that share the common phenotype of hyperglycaemia arising from defective insulin secretion, defective insulin action, or both. It has become one of the defining chronic diseases of the present century. The International Diabetes Federation estimated that approximately 537 million adults aged 20 to 79 years were living with diabetes in 2021, with the figure projected to rise to 643 million by 2030 and 783 million by 2045, and with three of every four affected adults residing in low- and middle-income countries[1].

India carries a disproportionate share of this burden. The nationally representative Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) survey, which sampled adults aged 20 years and above across all states and union territories, reported a weighted national diabetes prevalence of 11.4% and a prediabetes prevalence of 15.3%, translating into more than 100 million people with diabetes and a comparable number in the prediabetic state[2]. These figures represent a substantial escalation over the earlier phase of the same programme, which had projected 62.4 million people with diabetes and 77.2 million with prediabetes for the country as a whole[3]. The implication for clinical practice is that the population at risk of chronic diabetic complications is expanding faster than the health system capacity to screen for them.

Among the long-term complications of diabetes, the neuropathies are the most prevalent. Diabetic neuropathy is a heterogeneous group of conditions affecting different parts of the somatic and autonomic nervous system with diverse clinical manifestations, of which distal symmetrical sensorimotor polyneuropathy is by far the commonest form[4]. The internationally accepted working definition for clinical practice is the presence of symptoms or signs of peripheral nerve dysfunction in a person with diabetes after the exclusion of other causes [5]. This definition is deliberately one of exclusion, because non-diabetic neuropathies occur in people with diabetes and may be independently treatable. Up to half of all diabetic peripheral neuropathies are asymptomatic at the time of detection, which is precisely why systematic screening rather than symptom-driven referral is recommende[4]. The reported prevalence varies widely with the diagnostic method and the population studied. In an early Indian series of 1000 consecutive patients with type 2 diabetes screened by biothesiometry, neuropathy defined by a vibration perception threshold above 25 volts was present in 19.1%, with age and

duration of diabetes emerging as the significant independent risk factors [15]. European screening programmes using clinical scoring have reported considerably higher figures, and studies using electrophysiology or quantitative sensory testing higher still.

The clinical importance of diabetic peripheral neuropathy lies less in the symptoms themselves than in what follows from the loss of protective sensation. Insensate feet permit unnoticed trauma, and neuropathy is the necessary antecedent in the causal pathway to foot ulceration, infection, Charcot neuroarthropathy and lower limb amputation. Gait instability, falls and fall-related injury add further morbidity, particularly in older patients with large-fibre involvement. Between a fifth and a third of patients experience neuropathic pain, which is typically burning, lancinating or shock-like, worsens at night, and is frequently accompanied by allodynia and hyperalgesia[4].

The condition substantially reduces quality of life and increases the direct and indirect costs of diabetes care. Despite considerable advances in understanding its pathogenesis, no disease-modifying therapy has been established, and management remains confined toglycaemicoptimisation, foot protection and symptomatic analgesia[6].

The pathogenesis of nerve injury in diabetes is multi factorial and involves both metabolic and micro vascular mechanisms. Chronic hyperglycaemia drives flux through the polyol pathway with intracellular accumulation of sorbitol, depletion of reduced nicotinamide adenine dinucleotide phosphate and consequent impairment of glutathione regeneration. Excess glycolytic intermediates are shunted into the hexosamine pathway, altering the transcription of housekeeping genes including transforming growth factor beta-1 and plasminogen activator inhibitor-1. Elevated diacylglycerol activates protein kinase C, with downstream effects on vasoconstriction, capillary permeability and basement membrane thickening. Non-enzymatic glycation generates advanced glycation end products that engage their receptor and activate nuclear factor kappa B. Poly-ADP-ribose polymerase activation in Schwann cells, endothelial cells and sensory neurons diverts glycolytic intermediates into these same injurious routes.

All of these converge on mitochondrial superoxide overproduction and oxidative stress, culminating in axonal degeneration and neuronal apoptosis [4,6]. Insulin resistance, dyslipidaemia, hypertension, visceral adiposity and the metabolic syndrome contribute independently, which is one reason why glycaemic control alone does not abolish the risk[6].

The evidence linking glycaemic control to neuropathy is strong but asymmetric between the two types of diabetes. In the Diabetes Control and Complications Trial, intensive insulin therapy in type 1 diabetes markedly delayed or prevented clinically manifest polyneuropathy, a benefit confirmed on objective nerve conduction testing[7]. In type 2 diabetes the effect is more modest. The United Kingdom Prospective Diabetes Study demonstrated that intensive blood-glucose control with sulphonylureas or insulin substantially reduced the risk of microvascular complications overall, although the effect specifically on neuropathy endpoints was considerably smaller than that observed in type 1 disease [8]. Systematic reviews have reached the same conclusion, namely that enhanced glucose control clearly prevents clinical neuropathy in type 1 diabetes while producing only a small and statistically uncertain

reduction in type 2 diabetes [6]. This gap between glycaemic control and neuropathy prevention in type 2 diabetes is one of the central unresolved problems in the field, and it is the point at which measures of glycaemic quality other than the mean become clinically interesting.

Glycated haemoglobin reflects average glycaemia over the preceding eight to twelve weeks, but two patients with identical HbA1c values may have travelled very different glycaemic paths to reach them. One may have been stable, the other may have oscillated between hypoglycaemia and marked hyperglycaemia. Glycaemic variability describes this dimension of glucose control that the mean conceals. It may be assessed over the short term using continuous glucose monitoring metrics such as the mean amplitude of glycaemic excursions, or over the long term using visit-to-visit fluctuation in HbA1c expressed as the standard deviation or coefficient of variation of serial measurements. Long-term variability has the practical advantage that HbA1c is already recorded routinely in most diabetes clinics and requires no additional technology, which makes it far more feasible in resource-constrained settings than continuous monitoring[9].

A growing body of evidence supports the prognostic value of HbA1c variability. A systematic review and meta-analysis of studies in both type 1 and type 2 diabetes found that higher HbA1c standard deviation and coefficient of variation were positively associated with micro vascular and macro vascular complications and with mortality, independent of mean HbA1c [9]. In a cross-sectional study of 563 patients with type 2 diabetes in whom neuropathy was confirmed by clinical manifestations together with nerve conduction abnormalities, the coefficient of variation of HbA1c was closely associated with the presence of diabetic peripheral neuropathy and was proposed as a potent indicator of it [10]. In a further study of 223 patients with type 2 diabetes in whom composite nerve conduction scores were used to quantify severity, HbA1c variability together with chronic glycaemic impairment was strongly associated with the severity of peripheral neuropathy, and the standard deviation of HbA1c emerged as an independent determinant on multiple linear regression alongside diabetes duration and estimated glomerular filtration rate [11]. A large linked-database analysis comparing several variability metrics found that variability measures were significantly associated with composite micro vascular disease risk, including neuropathy, and retained predictive value alongside a single baseline HbA1c value [12]. Taken together, these findings suggest that variability carries information about micro vascular risk that a single measurement does not.

Assessment of neuropathy in routine practice depends on simple, validated, bedside instruments. The Michigan Neuropathy Screening Instrument comprises a self-administered symptom questionnaire and a brief lower-extremity examination that includes foot inspection, assessment of vibration sensation with a 128 Hz tuning fork, elicitation of ankle reflexes and 10 g monofilament testing[13].

It has been extensively validated against neurological examination and standardised electrophysiology, and has been used in large clinical trials including the Diabetes Control and Complications Trial and its Epidemiology of Diabetes Interventions and Complications follow-up, where it was confirmed to be a simple, non-invasive and valid measure of distal symmetrical peripheral neuropathy.[14]

Quantification of severity, however, requires an instrument with a graded output. Neurothesiometry provides this by measuring the vibration perception threshold in volts and, in combined devices, by measuring warm and cold thermal perception thresholds that reflect small-fibre function. Vibration perception threshold measurement has been shown in Indian populations to be a reliable means of identifying patients at risk of neuropathic ulceration.[15]

Despite the accumulating international literature, several gaps remain. Most studies of HbA1c variability and neuropathy have been conducted in East Asian or European populations. Data from Indian cohorts, in whom diabetes develops at a younger age, at a lower body mass index and with a greater degree of central adiposity, are sparse. Furthermore, the majority of published work has examined variability against the binary presence or absence of neuropathy rather than against a graded measure of severity.

The present study was therefore designed to estimate HbA1c variability in patients with type 2 diabetes attending a tertiary care teaching hospital in South India, to determine the frequency and graded severity of diabetic peripheral neuropathy using the Michigan Neuropathy Screening Instrument for screening and neurothesiometry for severity grading, and to examine the relationship between HbA1c variability and neuropathy severity. The underlying clinical objective is to identify individuals at risk as early as possible, so that intensified glycaemicstabilisation and structured foot protection can be instituted before irreversible nerve loss occurs.

Aims and Objectives

The study was undertaken with the following objectives:

1. To estimate HbA1c variability in patients with type 2 diabetes mellitus attending a tertiary care teaching hospital.
2. To detect the frequency and graded severity of diabetic peripheral neuropathy in patients with type 2 diabetes mellitus using the Michigan Neuropathy Screening Instrument for screening and neuro the siometry for severity assessment.
3. To correlate the variability of HbA1c with the severity of diabetic peripheral neuropathy.

Materials and Methods

Study design and setting

This was a hospital-based, observational, cross-sectional study conducted in the Department of General Medicine of a tertiary care teaching hospital and its attached hospitals in Bengaluru, Karnataka, India. The study period extended from February 2021 to May 2022. Participants were recruited from both outpatient and inpatient services of the department.

Ethical considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee before the commencement of recruitment. Written informed consent was obtained from every participant in the language best understood by them after the purpose of the study, the tests and the procedures involved had been explained. Participants were informed of their right to withdraw at any stage without prejudice to their continuing treatment. Personal identifiers were not recorded in the analysis dataset, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Sample size estimation

The sample size was calculated using the formula for estimation of a mean in a single group, n = (Z alpha

squared multiplied by sigma squared) divided by d squared, where Z alpha was taken as 1.96 for a 95% confidence interval, sigma was the standard deviation of HbA1c and d the absolute precision. Taking the standard deviation of HbA1c among patients with type 2 diabetes as 1.0 from previously published work and setting the precision at 0.2, the calculated sample size was 96, which was rounded up to 100. One hundred participants were therefore enrolled.

Inclusion criteria

Patients were eligible if they were aged more than 18 years, had type 2 diabetes mellitus diagnosed according to American Diabetes Association criteria, and provided valid written informed consent.

Exclusion criteria

Patients were excluded if they declined consent, were aged less than 18 years, had a history of chronic alcoholism, were receiving drugs known to affect glycaemic variability such as corticosteroids, had anaemia defined as haemoglobin below 11 g/dL in women and below 12 g/dL in men, had a history of exposure to toxins or poisons, or had peripheral neuropathy attributable to another cause including hypothyroidism, vitamin B12 deficiency or folate deficiency.

These exclusions were applied so that the neuropathy observed could reasonably be attributed to diabetes, in keeping with the diagnosis-of-exclusion principle that governs the clinical definition of diabetic peripheral neuropathy.

Clinical assessment

All enrolled participants underwent a structured history and clinical examination recorded on a predesigned proforma. Variables recorded included age, sex, duration of diabetes, current antidiabetic treatment classified as oral hypoglycaemic agents alone, insulin alone or both, and the presence of comorbid conditions including hypertension, ischaemic heart disease, cerebrovascular accident, bronchial asthma, chronic obstructive pulmonary disease, obstructive sleep apnoea and past pulmonary tuberculosis. Blood pressure was recorded in the sitting position after five minutes of rest. Height, weight and waist circumference were measured using standard technique and body mass index was calculated and categorised as normal, overweight, obese or morbidly obese.

Laboratory investigations

Fasting blood glucose, postprandial blood glucose, complete blood count, liver function tests, renal function tests and serum electrolytes were estimated for all participants. HbA1c was measured in a laboratory using a method standardised to the Diabetes Control and Complications Trial assay.

Two sequential HbA1c values were obtained for each participant, and HbA1c variability was derived from the intra-individual difference between these sequential estimations, expressed as the variability value with its standard deviation for each neuropathy severity stratum.

Screening for neuropathy

All participants were screened using the Michigan Neuropathy Screening Instrument. Part A of the instrument is a self-administered questionnaire relating to the patient perception of symptoms such as numbness, burning pain, sensitivity to touch, cramps, prickling sensations, contact pain, impaired thermal discrimination, foot ulceration and nocturnal exacerbation. Part B is a brief physical assessment comprising inspection of the feet for deformity, dry skin, callus, infection, fissures and ulceration, assessment of vibration sensation at the dorsum of the great toe using a

128 Hz tuning fork, grading of ankle reflexes with the Jendrassikmanoeuvre where required, and 10 g monofilament testing. Neuropathy on screening was defined operationally as seven or more positive responses on Part A or a score above 2.0 on the Part B examination.

Grading of severity by neuro thesiometry

The severity of diabetic peripheral neuropathy was assessed using a combined neuropathy analyser providing bio thesiometric vibration perception threshold and thermal perception threshold measurement. Participants were first familiarised with the sensation by application of the probe to the distal palmar surface of the hand.

The vibration perception threshold was then measured at the distal plantar surface of the great toe of both feet. The voltage was increased slowly at a rate of 1 mV per second and the voltage at which the participant first perceived vibration was recorded as the vibration perception threshold. The mean of three readings was taken, and neuropathy was diagnosed when the vibration perception threshold exceeded 25 mV.

Thermal perception thresholds for cool detection, cold detection, warm detection and hot detection were measured at specified sites on the foot with the room temperature maintained between 28 and 32 degrees Celsius, in order to detect small-fibre involvement at an early stage. Taking the neuro thesio meter as the reference standard, participants were classified into four categories: no diabetic peripheral neuropathy, mild, moderate and severe diabetic peripheral neuropathy.

Statistical analysis

Data were entered into a Microsoft Excel spreadsheet and analysed using the Statistical Package for the Social Sciences version 20 (IBM SPSS Statistics, IBM Corporation, Armonk, New York, United States). Quantitative variables were summarised as mean with standard deviation and qualitative variables as frequencies and proportions. Comparison of continuous variables across the four neuropathy severity categories was performed using analysis of variance, and association between categorical variables was tested using the chi-square test. The relationship between HbA1c variability and neuropathy grade was examined using the Pearson correlation coefficient with a two-tailed test of significance. A p value below 0.05 was considered statistically significant.

Results

Demographic profile

One hundred patients with type 2 diabetes mellitus were enrolled and analysed. Sixty-one participants (61%) were male and 39 (39%) were female. The overall mean age was 53±10 years. The largest proportion of participants belonged to the 42 to 51 year age band (36%), followed by the 52 to 61 year band (29%), the 62 to 71 year band (16%), the 32 to 41 year band (14%) and the 72 to 81 year band (5%). The mean age was 54±11 years in participants without neuropathy, 54±9 years in the mild category, 55±12 years in the moderate category and 47±8 years in the severe category; this difference was not statistically significant (p=0.325). The distribution of sex across the four severity categories was also comparable, with males constituting 58.3%, 62.2%, 64.3% and 54.5% of the no, mild, moderate and severe neuropathy groups respectively (p=0.938). The demographic and baseline clinical profile is presented in Table 1.

Table 1: Demographic and baseline clinical characteristics of study participants stratified by severity of diabetic peripheral neuropathy (n=100).

Variable	No DPN (n=24)	Mild DPN (n=37)	Moderate DPN (n=28)	Severe DPN (n=11)	Total (n=100)	p value
Age, years (mean±SD)	54±11	54±9	55±12	47±8	53±10	0.325
Male, n (%)	14 (58.3)	23 (62.2)	18 (64.3)	6 (54.5)	61 (61.0)	0.938
Female, n (%)	10 (41.7)	14 (37.8)	10 (35.7)	5 (45.5)	39 (39.0)	0.938
Duration of diabetes, years (mean±SD)	6±3	8±4	8±6	6±3	7±4	0.326
Height, cm (mean±SD)	162±8	162±8	161±7	161±6	162±7	0.625
Weight, kg (mean±SD)	68.4±13.6	70.6±14.5	67.2±11.1	65.3±10.6	68.5±12.9	0.214
Waist circumference, cm (mean±SD)	104±14	100±13	95±7	99±7	99±12	0.035

DPN, diabetic peripheral neuropathy; SD, standard deviation. Severity graded by neurothesiometer vibration perception threshold. $p<0.05$ considered significant.

Glycemic parameters

The mean fasting blood glucose in the study population was 181.4±72.5 mg/dL and the mean postprandial blood glucose was 285.98±88.65 mg/dL. Fasting blood glucose exceeded 120 mg/dL in 96 participants (96%), including 97.3% of those with mild neuropathy and all participants with severe neuropathy, although the association between fasting glucose category and neuropathy severity was not statistically significant (p=0.613). Postprandial blood glucose exceeded 180 mg/dL in 99 participants (99%); no participant in the mild, moderate or severe neuropathy categories had a postprandial value below 180 mg/dL (p=0.362). The overall mean HbA1c was 8.81±3.05%.

On the first HbA1c estimation, 12 participants (12%) had a value below 7% and 88 (88%) had a value of 7% or above. Among those with HbA1c below 7%, nine had mild neuropathy, two had no neuropathy and one had moderate neuropathy. Among those with HbA1c of 7% or above, 28 had mild, 27 had moderate and 11 had severe neuropathy, while 22 had no neuropathy. This association was statistically significant (p=0.029). On the second estimation, only three participants (3%) had a value below 7% while 97 (97%) had a value of 7% or above, and the association with neuropathy severity did not reach statistical significance (p=0.153). The distribution of glycaemic parameters is shown in Table 2.

Table 2: Distribution of glycaemic parameters and their association with severity of diabetic peripheral neuropathy

Parameter	Category	No DPN n (%)	Mild DPN n (%)	Moderate DPN n (%)	Severe DPN n (%)	Total n (%)	p value
Fasting blood glucose (mg/dL)	<120	2 (8.3)	1 (2.7)	1 (3.6)	0 (0.0)	4 (4.0)	0.613
	>120	22 (91.7)	36 (97.3)	27 (96.4)	11 (100.0)	96 (96.0)	
Postprandial blood glucose (mg/dL)	<180	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0.362
	>180	23 (95.8)	37 (100.0)	28 (100.0)	11 (100.0)	99 (99.0)	
HbA1c, first estimation (%)	<7	2 (8.3)	9 (24.3)	1 (3.6)	0 (0.0)	12 (12.0)	0.029
	>=7	22 (91.7)	28 (75.7)	27 (96.4)	11 (100.0)	88 (88.0)	
HbA1c, second estimation (%)	<7	0 (0.0)	3 (8.1)	0 (0.0)	0 (0.0)	3 (3.0)	0.153
	>=7	24 (100.0)	34 (91.9)	28 (100.0)	11 (100.0)	97 (97.0)	

DPN, diabetic peripheral neuropathy; HbA1c, glycated haemoglobin. Mean fasting blood glucose 181.4±72.5 mg/dL; mean postprandial blood glucose 285.98±88.65 mg/dL; mean HbA1c 8.81±3.05%.

Frequency and severity of diabetic peripheral neuropathy

On neurothesiometer grading, 76 of the 100 participants (76%) had evidence of diabetic peripheral neuropathy. Mild neuropathy was present in 37 participants (37%), moderate neuropathy in 28 (28%) and severe neuropathy in 11 (11%), while 24 participants (24%) had no evidence of neuropathy. Among participants with mild neuropathy, the largest number (32.43%) fell within the 42 to 51 year age band. Participants with moderate neuropathy were distributed more evenly across the age bands, with the largest numbers (25% each) in the 52 to 61 and 62 to 71 year bands. Among those with severe neuropathy, 54.55% belonged to the 42 to 51 year age band. The overall mean duration of diabetes was 7±4 years, being 6±3 years in participants without neuropathy, 8±4 years in the mild category, 8±6 years in the moderate category and 6±3 years in the severe category (p=0.326). The distribution of neuropathy severity is presented in Table 3.

Table 3: Distribution of severity of diabetic peripheral neuropathy on neurothesiometer grading (n=100)

Severity category	Number of participants	Percentage (%)
No DPN	24	24.0
Mild DPN	37	37.0
Moderate DPN	28	28.0
Severe DPN	11	11.0
Total DPN (mild + moderate + severe)	76	76.0
Total	100	100.0

DPN, diabetic peripheral neuropathy. Neuropathy diagnosed when vibration perception threshold exceeded 25 mV.

HbA1c variability

The overall mean HbA1c variability in the study population was 1.50 with a standard deviation of 3.21. Variability was lowest among participants without neuropathy at 0.28±0.12. It was highest in the mild neuropathy group at 2.73±4.99, and progressively lower in the moderate group at 1.21±0.94 and the severe group at 0.72±0.37. The difference in mean HbA1c variability across the four severity categories was statistically significant on analysis of variance (p=0.001). These findings are presented in Table 4.

Table 4: HbA1c variability across categories of severity of diabetic peripheral neuropathy

Neuropathy category	n	Mean HbA1c variability	Standard deviation	p value
No DPN	24	0.28	0.12	0.001
Mild DPN	37	2.73	4.99	
Moderate DPN	28	1.21	0.94	
Severe DPN	11	0.72	0.37	
Total	100	1.50	3.21	

DPN, diabetic peripheral neuropathy. p value derived from comparison of means across the four categories; $p<0.05$ considered significant.

Comorbidities and antidiabetic treatment

Fifty-three participants (53%) had no co morbidity other than diabetes mellitus. Hypertension was the commonest associated co morbidity, present in 32 participants (32%), followed by the combination of hypertension with ischaemic heart disease in five (5%) and isolated ischaemic heart disease in three (3%). Bronchial asthma and chronic obstructive pulmonary disease were each present in two participants (2%), while the combination of ischaemic heart disease, old cerebrovascular accident and hypertension, old pulmonary tuberculosis and obstructive sleep apnoea were each present in one participant (1%). The distribution of co morbidities across neuropathy severity categories was not statistically significant (p=0.411).

With regard to antidiabetic therapy, 79 participants (79%) were on oral hypoglycaemic agents alone, 18 (18%) were on a combination of oral agents and insulin, and three (3%) were on insulin alone. The proportion on oral agents alone declined across severity strata from 87.5% in the no neuropathy group and 86.5% in the mild group to 64.3% in the moderate group and 72.7% in the severe group, while the proportion on combination therapy rose from 12.5% and 13.5% to 25% and 27.3% respectively. This gradient did not reach statistical significance (p=0.085). These data are presented in Table 5.

Table 5: Distribution of co morbidities and antidiabetic treatment by severity of diabetic peripheral neuropathy

Variable	No DPN n (%)	Mild DPN n (%)	Moderate DPN n (%)	Severe DPN n (%)	Total n (%)	p value
Hypertension	6 (25.0)	17 (45.9)	4 (14.3)	5 (45.5)	32 (32.0)	0.411
Hypertension + IHD	1 (4.2)	2 (5.4)	2 (7.1)	0 (0.0)	5 (5.0)	
Ischaemic heart disease	0 (0.0)	1 (2.7)	2 (7.1)	0 (0.0)	3 (3.0)	

IHD + old CVA + hypertension	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)	1 (1.0)	
Bronchial asthma	0 (0.0)	1 (2.7)	1 (3.6)	0 (0.0)	2 (2.0)	
COPD	0 (0.0)	0 (0.0)	2 (7.1)	0 (0.0)	2 (2.0)	
Old pulmonary tuberculosis	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	1 (1.0)	
Obstructive sleep apnoea	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	1 (1.0)	
No comorbidity	17 (70.8)	14 (37.8)	16 (57.1)	6 (54.5)	53 (53.0)	
Oral hypoglycaemic agents only	21 (87.5)	32 (86.5)	18 (64.3)	8 (72.7)	79 (79.0)	0.085
Insulin only	0 (0.0)	0 (0.0)	3 (10.7)	0 (0.0)	3 (3.0)	
Oral agents + insulin	3 (12.5)	5 (13.5)	7 (25.0)	3 (27.3)	18 (18.0)	

DPN, diabetic peripheral neuropathy; IHD, ischaemic heart disease; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease.

Blood pressure and anthropometry

Mean systolic blood pressure was 132±13 mmHg in participants without neuropathy, 133±12 mmHg in the mild category, 128±11 mmHg in the moderate category and 135±12 mmHg in the severe category, with an overall mean of 131±12 mmHg (p=0.211). Mean diastolic blood pressure was 80±11, 82±12, 81±8 and 85±9 mmHg respectively, with an overall mean of 82±10 mmHg (p=0.542). Neither systolic nor diastolic pressure differed significantly across the severity strata.

Mean height was approximately 162±7 cm and mean weight 68.5±12.9 kg, neither differing significantly across categories. Waist circumference did differ significantly, being 104±14 cm in participants without neuropathy, 100±13 cm in the mild category, 95±7 cm in the moderate category and 99±7 cm in the severe category, with an overall mean of 99±12 cm (p=0.035). On body mass index categorisation, only 26 participants (26%) were in the normal range, while 17 (17%) were overweight, 40 (40%) were obese and 17 (17%) were morbidly obese. The highest proportion of participants with severe neuropathy (63.6%) fell in the obese category, whereas the highest proportion of those without neuropathy (25.0%) fell in the normal body mass index category. The association between body mass index category and neuropathy severity approached but did not reach statistical significance (p=0.099). These findings are summarised in Table 6.

Table 6: Blood pressure and body mass index distribution by severity of diabetic peripheral neuropathy

Variable	No DPN	Mild DPN	Moderate DPN	Severe DPN	Total	p value
Systolic BP, mmHg (mean±SD)	132±13	133±12	128±11	135±12	131±12	0.211
Diastolic BP, mmHg (mean±SD)	80±11	82±12	81±8	85±9	82±10	0.542
BMI normal, n (%)	6 (25.0)	10 (27.0)	6 (21.4)	4 (36.4)	26 (26.0)	0.099
BMI overweight, n (%)	4 (16.7)	4 (10.8)	9 (32.1)	0 (0.0)	17 (17.0)	
BMI obese, n (%)	11 (45.8)	16 (43.2)	6 (21.4)	7 (63.6)	40 (40.0)	

BMI morbidly obese, n (%)	3 (12.5)	7 (18.9)	7 (25.0)	0 (0.0)	17 (17.0)	

DPN, diabetic peripheral neuropathy; BP, blood pressure; BMI, body mass index; SD, standard deviation.

Performance of the Michigan Neuropathy Screening Instrument

On Part A of the Michigan Neuropathy Screening Instrument, 72 participants (72%) scored between 0 and 6 while 28 (28%) scored between 7 and 10. All 24 participants without neuropathy (100%) scored in the 0 to 6 range, as did 29 of 37 with mild neuropathy (78.4%) and 18 of 28 with moderate neuropathy (64.3%), but only one of 11 with severe neuropathy (9.1%). Conversely, none of the participants without neuropathy, eight with mild neuropathy (21.6%), 10 with moderate neuropathy (35.7%) and 10 with severe neuropathy (90.9%) scored between 7 and 10. This association was highly significant (p=0.001).

On Part B, 42 participants (42%) scored between 0 and 1 and 58 (58%) scored between 2 and 5. A score in the 0 to 1 range was recorded in 22 of 24 participants without neuropathy (91.7%), 17 of 37 with mild neuropathy (45.9%), three of 28 with moderate neuropathy (10.7%) and none of those with severe neuropathy. Conversely, a score between 2 and 5 was recorded in 89.3% of participants with moderate neuropathy and in all 11 participants with severe neuropathy. This gradient was also highly significant (p=0.001). These findings are presented in Table 7.

Table 7: Michigan Neuropathy Screening Instrument scores and their association with neurothesiometer-defined severity of diabetic peripheral neuropathy

MNSI component	Score band	No DPN n (%)	Mild DPN n (%)	Moderate DPN n (%)	Severe DPN n (%)	Total n (%)	p value
MNSI Part A (questionnaire)	0-6	24 (100.0)	29 (78.4)	18 (64.3)	1 (9.1)	72 (72.0)	0.001
	7-10	0 (0.0)	8 (21.6)	10 (35.7)	10 (90.9)	28 (28.0)	
MNSI Part B (examination)	0-1	22 (91.7)	17 (45.9)	3 (10.7)	0 (0.0)	42 (42.0)	0.001
	2-5	2 (8.3)	20 (54.1)	25 (89.3)	11 (100.0)	58 (58.0)	

MNSI, Michigan Neuropathy Screening Instrument; DPN, diabetic peripheral neuropathy.

Correlation between HbA1c variability and neuropathy

The Pearson correlation coefficient between HbA1c variability and neuropathy grade was 0.014, indicating a very small positive association. The two-tailed p value was 0.893, which was not significant at the conventional alpha level of 0.05. Thus, while mean HbA1c variability differed significantly between the severity strata when analysed categorically, it did not demonstrate a significant linear relationship with neuropathy grade when analysed as a continuous correlation. This apparent discrepancy is accounted for by the non-monotonic pattern of variability across the strata, with the highest values occurring in the mild rather than the severe category. The correlation data are presented in Table 8.

Table 8: Pearson correlation between HbA1c variability and severity of diabetic peripheral neuropathy

Correlation	Pearson coefficient (r)	Significance (2-tailed)	n
HbA1c variability vs neuropathy grade	0.014	0.893	100

Neuropathy grade defined by neurothesiometer vibration perception threshold category. p<0.05 considered significan.

Discussion

This cross-sectional study of 100 patients with type 2 diabetes mellitus attending a tertiary care teaching hospital in South India examined the relationship between HbA1c variability and the graded severity of diabetic peripheral neuropathy. The principal findings were a high overall burden of neuropathy at 76%, a significant association between an HbA1c value of 7% or above and the presence of neuropathy, a statistically significant difference in mean HbA1c variability across severity strata, and a strong concordance between the Michigan Neuropathy Screening Instrument and neurothesiometer-defined severity. The correlation between variability and severity grade was, however, weak and non-significant.

Demographic and clinical profile

The mean age of 53±10 years in the present cohort is lower than that reported from most Western series. The Verona Diabetic Foot Screening Programme, which examined 1409 patients with type 2 diabetes, reported a mean age of 68±10 years [16], and a Korean study correlating polyneuropathy severity with HbA1c reported a comparable older profile [17]. This age difference is consistent with the well-documented earlier onset of type 2 diabetes in South Asian populations and reinforces the argument that screening for neuropathy in India cannot be deferred to later decades of life. Notably, the mean age of participants with severe neuropathy in our study was the lowest of all four strata at 47±8 years, and more than half of the severe cases fell within the 42 to 51 year age band. The absence of a statistically significant age gradient (p=0.325) contrasts with the earlier Indian biothesiometry series, in which age emerged as a strong independent risk factor with an odds ratio of 3.2 [15], and probably reflects the limited sample size and the referral character of a tertiary hospital population rather than a genuine absence of association.

The male preponderance of 61% and the absence of a significant sex difference across severity strata (p=0.938) are broadly consistent with published series. The mean duration of diabetes of 7±4 years is shorter than the 12±8 years reported in some comparison cohorts, yet 76% of our participants already had detectable neuropathy. This mismatch between duration and neuropathy burden is one of the more clinically arresting observations in the dataset. It is compatible with the recognized phenomenon that nerve injury may begin during the prediabetic phase and that a substantial proportion of patients have neuropathy at or shortly after diagnosis, and it argues for screening at the point of diagnosis rather than after an arbitrary interval [4].

Glycaemic control and neuropathy

The mean HbA1c of 8.81±3.05% in our cohort reflects substantially suboptimal glycaemic control, as does the finding that 96% of participants had a fasting glucose above 120 mg/dL and 99% a postprandial value above 180 mg/dL. The significant association between an HbA1c of 7% or above and neuropathy (p=0.029) is in keeping with a large body of literature. A Korean quantitative study using nerve conduction composite scores found significantly higher HbA1c in the polyneuropathy group and identified raised HbA1c together with older age as independent predictors of polyneuropathy [17]. A Japanese claims-database case-control study of patients with type 2 diabetes similarly reported that mean HbA1c discriminated for the presence of neuropathy, although the discriminative capacity was modest, with an area under the curve of

0.602 and an optimal cut-off of 7.12% that improved only slightly after adjustment for patient characteristics [19]. That modest discriminative performance is itself instructive: it indicates that a single mean value captures only part of the glycaemic risk, which is precisely the rationale for examining variability.

An Indian study examining the relationship between glycated haemoglobin and vibration perception threshold reported a strong positive relationship between the two, and proposed HbA1c as a predictor of subsequent foot complications in diabetic peripheral neuropathy [20]. Our data are consistent in direction. The interesting nuance in our cohort is that nine of the 12 participants with an HbA1c below 7% nonetheless had mild neuropathy, a finding that would be difficult to explain on the basis of mean glycaemia alone and which is compatible with a contribution from glycaemic fluctuation, from pre-diagnosis hyperglycaemia, or from non-glycaemic determinants such as adiposity and dyslipidaemia.

HbA1c variability and neuropathy

The central finding of the present study is that mean HbA1c variability differed significantly across neuropathy severity strata (p=0.001), being nearly ten times higher in participants with any neuropathy than in those with none (0.28±0.12 in the no neuropathy group compared with 2.73 ± 4.99, 1.21±0.94 and 0.72±0.37 in the mild, moderate and severe groups respectively). This supports the proposition that long-term glycaemic instability is associated with the presence of peripheral nerve injury. The direction of this finding aligns with the cross-sectional study of 563 patients with type 2 diabetes in which the coefficient of variation of quarterly HbA1c measurements was closely associated with nerve-conduction-confirmed neuropathy and was advanced as a potent indicator for it [10]. It is also consistent with the meta-analytic evidence that higher HbA1c standard deviation and coefficient of variation predict micro vascular complications independently of the mean [9], and with the linked-database finding that variability metrics were significantly associated with composite micro vascular disease risk including neuropathy [12].

Our results diverge from the published literature in one important respect. Variability in our cohort was highest in the mild neuropathy group and declined progressively through the moderate and severe groups, and the Pearson correlation between variability and severity grade was accordingly negligible (r=0.014, p=0.893). This contrasts directly with the study of 223 patients with type 2 diabetes in which patients in higher quartiles of HbA1c standard deviation had higher composite nerve conduction scores, and in which the standard deviation of HbA1c was an independent determinant of severity on multiple linear regression [11]. Several explanations deserve consideration. First, and most importantly, our variability measure was derived from only two sequential HbA1c estimations, whereas the comparison studies used four quarterly measurements over one year [10] or all measurements obtained over three years [11]. A two-point difference is a far less stable estimate of variability and is heavily influenced by measurement error and by the timing of the second sample relative to any therapeutic change. Second, patients with established severe neuropathy are more likely to have been identified as high-risk and escalated to intensified regimens, and indeed 27.3% of our severe group were on combined oral agents and insulin compared with 12.5% of the no-neuropathy group. Such therapeutic intensification stabilises HbA1c and would be expected to compress measured variability in exactly the group with the most advanced nerve damage, producing a

reverse-causality artefact. Third, the severe group contained only 11 participants, so the mean variability in that stratum is imprecisely estimated. Fourth, once axonal loss is advanced, the vibration perception threshold saturates and may no longer respond to further metabolic insult, so that a ceiling effect in the outcome measure attenuates any dose-response relationship. Taken together, these considerations suggest that HbA1c variability in this cohort behaved as a marker of the presence of early neuropathy rather than as a graded index of its severity.

A comparable pattern of divergence has been described elsewhere. A large Taiwanese case-control study of 2837 patients with type 2 diabetes that specifically examined newly proposed risk factors including hypoglycaemia and glycaemic variability found that DPN, defined by an MNSI examination score above 2, was present in 21.3% of patients, and reported that not all variability metrics behaved uniformly as determinants once traditional risk factors were entered into stepwise multivariate models [18]. The comparative analysis of several variability measures against micro vascular outcomes likewise found that different metrics of the same underlying construct did not perform identically, and that some retained significance only in models unadjusted for baseline HbA1c [12]. The methodological lesson is that the choice of variability metric, the number of measurements contributing to it, and the interval over which they are collected all materially affect the observed association.

Prevalence of neuropathy and screening performance

The neuropathy prevalence of 76% in the present cohort is considerably higher than the 19.1% reported by biothesiometry in an ambulatory South Indian diabetes centre population [15] and higher than most population-based estimates. Two factors explain this. The first is case mix: our participants were recruited from the outpatient and inpatient services of a tertiary teaching hospital, and inpatients in particular represent a group with more advanced disease. The second is ascertainment method. Studies that use questionnaires and clinical examination alone consistently report lower prevalence than studies using instrumented threshold testing. This has been demonstrated directly in a study of 106 patients with type 2 diabetes in which the MNSI identified neuropathy in 32.1%, electromyography in 46.2% and the neurothesiometer in 74.5% of the same cohort [21]. Our figure of 76% by neurothesiometry is almost identical to the 74.5% reported in that study using the same class of instrument, which lends external validity to our ascertainment and confirms that instrumented threshold testing detects a large reservoir of subclinical nerve dysfunction that clinical scoring misses.

The performance of the MNSI in our cohort was informative. Both Part A and Part B showed highly significant gradients across neurothesiometer-defined severity ($p=0.001$ for each). Part B, the examination component, performed better than Part A at identifying milder disease: 54.1% of participants with mild neuropathy already had a Part B score of 2 or above, whereas only 21.6% reached the Part A threshold of 7 or more positive responses. Every participant with severe neuropathy had a Part B score of 2 or above. This mirrors the DCCT/EDIC validation work, which found that the questionnaire component at the conventional cut-point of seven or more abnormal responses was insensitive and that lowering the threshold to four or more abnormal items improved performance [14]. Our data support the practical recommendation that the

examination component should not be omitted in favour of the questionnaire alone, and that the questionnaire cut-point of seven is too conservative for detection of early disease.

Associated risk factors

Hypertension was the commonest comorbidity in our cohort at 32%, followed by ischaemic heart disease. This is consistent with the well-established clustering of microvascular and macrovascular complications, and with the Verona screening programme finding that neuropathy in type 2 diabetes was significantly associated with other diabetic complications [16].

Obesity was strikingly prevalent, with only 26% of participants having a normal body mass index and 57% being obese or morbidly obese; the highest proportion of severe neuropathy (63.6%) occurred in the obese category, although the overall association fell just short of significance (p=0.099). Waist circumference did differ significantly across strata (p=0.035), though not in a monotonic direction. Given that central adiposity, insulin resistance and dyslipidaemia are recognised contributors to nerve injury independent of glycaemia [6], and given that the metabolic syndrome has been associated with peripheral neuropathy even in the absence of frank diabetes, these anthropometric findings support a multifactorial rather than purely glucocentric model of causation.

Neither systolic nor diastolic blood pressure differed significantly across severity strata in our cohort (p=0.211 and p=0.542 respectively), despite the high prevalence of diagnosed hypertension. This most likely reflects the fact that a third of participants were on antihypertensive treatment, so that recorded pressures represent treated rather than untreated values and do not capture cumulative hypertensive exposure.

Clinical implications

Three practical implications follow from these data. First, in a tertiary Indian setting, three of every four patients with type 2 diabetes have measurable peripheral nerve dysfunction, much of it not volunteered as a symptom; annual instrumented screening is therefore not a luxury but a necessity, and where neurothesiometry is unavailable the MNSI examination component with a lowered questionnaire threshold represents a reasonable substitute. Second, a single HbA1c value is an incomplete summary of glycaemic risk, and reviewing the pattern of a patient serial HbA1c record, which most clinics already possess, costs nothing and may identify patients whose glycaemic instability places them at risk despite an acceptable current value. Third, because variability in this cohort was greatest in the mildest disease, the window in which glycaemicstabilisation is likely to influence the natural history is probably early, which reinforces the case for screening at diagnosis rather than after a fixed interval of disease duration.

Limitations

Several limitations should temper the interpretation of these findings. The cross-sectional design permits the demonstration of association but not of causation, and the temporal sequence between glycaemic instability and nerve injury cannot be established. The sample size of 100 was adequate for the estimation of mean HbA1c with the specified precision but was underpowered for subgroup analysis, particularly in the severe neuropathy stratum which contained only 11 participants. HbA1c variability was derived from two sequential estimations rather than from the four or more serial measurements used in comparable published work, which makes it a less robust estimate and is the most likely explanation

for the divergence of our correlation analysis from the literature.

Nerve conduction studies, which remain the reference standard for the diagnosis of peripheral neuropathy, were not performed; the neurothesiometer, while quantitative and reproducible, assesses only vibration and thermal perception thresholds.

The single-centre tertiary hospital setting limits generalisability to community and primary care populations, in whom the prevalence and severity distribution would be expected to differ.

Finally, lipid parameters and estimated glomerular filtration rate, both established correlates of neuropathy severity, were not incorporated into the analysis.

Conclusion

In this cross-sectional study of 100 patients with type 2 diabetes mellitus at a tertiary care teaching hospital in South India, diabetic peripheral neuropathy was present in 76% of participants on neurothesiometer grading, comprising 37% mild, 28% moderate and 11% severe disease. An HbA1c of 7% or above was significantly associated with the presence of neuropathy (p=0.029), and mean HbA1c variability differed significantly across neuropathy severity strata (p=0.001), being approximately ten times higher in participants with any neuropathy than in those without.

HbA1c variability did not, however, increase monotonically with severity and showed no significant linear correlation with neuropathy grade (r=0.014, p=0.893); it was in fact highest in the mild category. The most plausible interpretation, given that variability here was derived from only two sequential estimations and that patients with advanced neuropathy were more likely to have been escalated to intensified therapy, is that HbA1c variability in this population functions as a marker of the presence of early nerve injury rather than as a graded index of established damage.

The Michigan Neuropathy Screening Instrument performed well against neurothesiometry, with both the questionnaire and the examination components showing highly significant gradients across severity strata (p=0.001 for each), and the examination component proving the more sensitive of the two for mild disease.

Hypertension was the commonest associated comorbidity at 32%, and 57% of participants were obese or morbidly obese, underlining the multifactorial nature of nerve injury in this population.

These findings support the incorporation of serial HbA1c review, which requires no additional investigation or expenditure, into the routine assessment of patients with type 2 diabetes as an adjunct to the current single-value approach.

They also support annual instrumented screening for neuropathy from the point of diagnosis rather than after an arbitrary duration of disease, given that 76% of a cohort with a mean diabetes duration of only seven years already had detectable nerve dysfunction. Prospective longitudinal studies with a larger sample, at least four serial HbA1c measurements per participant, nerve conduction confirmation and adjustment for lipid and renal parameters are required to establish whether glycaemicstabilisation, as distinct from glycaemic lowering, modifies the natural history of diabetic peripheral neuropathy.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from all participants.

Authors' contributions: NKN conceived and designed the study, acquired the clinical data, performed the neuropathy assessments and drafted the manuscript. YNS contributed to the study design, undertook the statistical analysis and interpretation of data, and critically revised the manuscript for important intellectual content. Both authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Data availability: The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

References

1. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022; 183:109119. PMID: 34879977.

2. Anjana RM, Unnikrishnan R, Deepa M, Pradeepa R, Tandon N, Das AK, et al. Metabolic non-communicable disease health report of India: the ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). Lancet Diabetes Endocrinol. 2023; 11(7):474-89. PMID: 37301218.

3. Anjana RM, Pradeepa R, Deepa M, Datta M, Sudha V, Unnikrishnan R, et al. Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: phase I results of the Indian Council of Medical Research-India DIABetes (ICMR-INDIAB) study. Diabetologia. 2011; 54 (12):3022-7. PMID: 21959957.

4. Pop-Busui R, Boulton AJM, Feldman EL, Bril V, Freeman R, Malik RA, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. Diabetes Care. 2017; 40 (1): 136-54. PMID: 27999003.

5. Tesfaye S, Boulton AJM, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. 2010; 33(10): 2285-93. PMID: 20876709.

6. Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL. Diabetic neuropathy: clinical manifestations and current treatments. Lancet Neurol. 2012; 11(6):521-34. PMID: 22608666.

7. The Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes therapy on the development and progression of neuropathy. Ann Intern Med. 1995; 122(8):561-8. PMID: 7887548.

8. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998; 352(9131):837-53. PMID: 9742976.

9. Gorst C, Kwok CS, Aslam S, Buchan I, Kontopantelis E, Myint PK, et al. Long-term glycemic variability and risk of adverse outcomes: a systematic review and meta-analysis. Diabetes Care. 2015; 38(12): 2354-69. PMID: 26604281.

10. Su JB, Zhao LH, Zhang XL, Cai HL, Huang HY, Xu F, et al. HbA1c variability and diabetic peripheral neuropathy in type 2 diabetic patients. Cardiovasc Diabetol. 2018;17(1):47. PMID: 29598819.

11. Lai YR, Chiu WC, Huang CC, Tsai NW, Wang HC, Lin WC, et al. HbA1C variability is strongly associated with the severity of peripheral neuropathy in patients with type 2 diabetes. Front Neurosci. 2019; 13:90. PMID: 30814926.

12. Yang CY, Su PF, Hung JY, Ou HT, Kuo S. Comparative predictive ability of visit-to-visit HbA1c variability measures for microvascular disease risk in type 2 diabetes. Cardiovasc Diabetol. 2020;19(1):105. PMID: 32631323.

13. Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N, Greene DA. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. Diabetes Care. 1994;17(11):1281-9. PMID: 7821168.

14. Herman WH, Pop-Busui R, Braffett BH, Martin CL, Cleary PA, Albers JW, et al. Use of the Michigan Neuropathy Screening Instrument as a measure of distal symmetrical peripheral neuropathy in Type 1 diabetes: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications. Diabet Med. 2012;29(7):937-44. PMID: 22417277.

15. Ashok S, Ramu M, Deepa R, Mohan V. Prevalence of neuropathy in type 2 diabetic patients attending a diabetes centre in South India. J Assoc Physicians India. 2002; 50:546-50. PMID: 12164406.

16. Salvotelli L, Stoico V, Perrone F, Cacciatori V, Negri C, Brangani C, et al. Prevalence of neuropathy in type 2 diabetic patients and its association with other diabetes complications: the Verona Diabetic Foot Screening Program. J Diabetes Complications. 2015; 29 (8):1066-70. PMID: 26227575.

17. Lee WJ, Jang S, Lee SH, Lee HS. Correlation between the severity of diabetic peripheral polyneuropathy and glycosylated hemoglobin levels: a quantitative study. Ann Rehabil Med. 2016;40(2):263-70. PMID: 27152276.

18. Pai YW, Lin CH, Lin SY, Lee IT, Chang MH. Reconfirmation of newly discovered risk factors of diabetic peripheral neuropathy in patients with type 2 diabetes: a case-control study. PLoS One. 2019; 14(7): e0220175. PMID: 31356602.

19. Nozawa K, Ikeda M, Kikuchi S. Association between HbA1c levels and diabetic peripheral neuropathy: a case-control study of patients with type 2 diabetes using claims data. Drugs Real World Outcomes. 2022; 9(3):403-14. PMID: 35725984.

20. Maiya AG, Parameshwar A, Hande M, Nandalike V. Relationship between glycated hemoglobin and vibration perception threshold in diabetic peripheral neuropathy. Int J Low Extrem Wounds. 2020;19(2):120-4. PMID: 31838926.

21. Mete T, Aydin Y, Saka M, Cinar Yavuz H, Bilen S, Yalcin Y, et al. Comparison of efficiencies of Michigan neuropathy screening instrument, neurothesiometer, and electromyography for diagnosis of diabetic neuropathy. Int J Endocrinol. 2013; 2013:821745. PMID: 23818897.