Original Article

Assessment of Neuropathy by Temperature Threshold Testing in Type 2 Diabetes Mellitus

Abstract

Introduction: Diagnosing diabetic neuropathy is a challenge at times as it is asymptomatic. Diagnosing diabetic neuropathy involves the use of quantitative sensory testing, nerve conduction study, and autonomic testing. Tempearture threshold testing (TTT) can aid in diagnosing small fiber neuropathy at early stages. This study aimed to assess the small fiber neuropathy using TTT in diabetes mellitus (DM) and correlate with age, duration of diabetes, and lipid profile. **Materials and Methods:** The study was commenced after obtaining ethics approval from the institute ethics committee. The study participants included 100 patients with type 2 DM of both genders between the ages of 40 and 65 years. The glycemic status and lipid profile were noted along with physical examination. Neuropathy assessment was done using Michigan Neuropathy Screening Instrument (MNSI) and TTT. **Results:** The prevalence of small fiber neuropathy based on TTT was 63%. The lipid profile was similar in both the groups. The MNSI B scale had significantly higher scores in the neuropathy group. In the neuropathy group, the thresholds for hot were significantly greater in all four limbs and cold were significantly lower. Age and years of DM were positively correlated with the neuropathy. Hot threshold in the lower limb had shown a strong positive correlation. **Conclusion:** The age and duration of diabetes are independent risk factors for diabetic peripheral neuropathy. Small fiber neuropathy is a prequel to the motor neuropathy. Hot threshold testing in the lower limb is more sensitive than cold threshold testing for diagnosing small fiber neuropathy.

Keywords: *Diabetes mellitus, neuropathy, small fiber, temperature threshold*

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Introduction

Diabetes mellitus (DM) has become a global health problem and is even designated as a "pandemic."[1] India is the epicenter of DM with the second-largest population, after China.[2] India has 77 million diabetics and this number is expected to increase to 134 million by 2045.[3] DM is associated with many long-term complications such as retinopathy, nephropathy, and neuropathy.[4]

Neuropathy is one of the dreadful complications affecting the peripheral nerves, autonomic nerves, and cranial nerves. Most DM patients with peripheral neuropathy are asymptomatic at early stages and only 20%–30% of patients have symptoms such as pain.[5,6]

Diagnosing diabetic neuropathy is a challenge at times as it is asymptomatic and is often diagnosed at later stages where it ends in limb salvage surgery. For the diagnosis of diabetic neuropathy, symptoms, signs, quantitative sensory testing, nerve conduction study, and autonomic testing are used; two of these five are recommended for clinical diagnosis.[7] All these tests help only in diagnosing large fiber neuropathy.

Tempearture threshold testing (TTT) can be an easy alternative and a noninvasive technique for early diagnosis of diabetic neuropathy, since small fibers are affected earlier. Some studies have used vibration perception threshold as an easy bedside noninvasive technique in evaluating diabetic peripheral neuropathy (DPN).[8] However, vibration perception is also accounts only to large fiber neuropathy. Furthermore, not many studies are available, using TTT in diagnosing small fiber neuropathy for early diagnosis.

Hence, we propose to study the small fiber neuropathy using TTT in DM and correlate with age, duration of diabetes, and lipid profile.

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Materials and Methods

The study was commenced after obtaining ethics approval from the Institute Ethics Committee (AIIMS/BBN/IEC/APR/2021/32/10.5.2021). The study participants included 100 patients with type 2 DM of both genders between the ages of 40 and 65 years. The study was conducted at All India Institute of Medical Sciences (AIIMS), Bibinagar. All the diabetic patients were recruited from the medicine outpatient department of AIIMS, Bibinagar. Patients with a history of thyroid disorder, any neurological problem, stroke patients, leprosy, any psychiatric illness, cancer patients, and patients not willing to participate in the study were excluded.

On the first visit to the hospital, sociodemographic data such as name, age, gender, religion, educational status and employment status, and socioeconomic status were obtained. A detailed medical history was taken regarding duration of diabetes and drugs. A complete general physical examination included height, weight, blood pressure (BP), pulse rate, and waist-and-hip circumference. Basal metabolic index (BMI) and waist–hip ratio were calculated. Five milliliters of blood was collected to assess the glycemic status, which included fasting blood sugar, postprandial blood sugar (PPBS), hemoglobin A1c (HbA1C) and lipid profile including total cholesterol, triglycerides, high-density lipoproteins (HDL), and low-density lipoproteins (LDL). Neuropathy assessment was done using Michigan Neuropathy Screening Instrument (MNSI) and temperature threshold testing. MNSI was administered to the participants and the scores were obtained. Temperature threshold testing was done as per the following protocol.

Tempearture threshold testing (TTT)

All the participants of the study were tested for cold and warm threshold using the digital thermal esthesiometer (v. 4.8.0) for the fingers and digits of foot of both sides. The digital thermal esthesiometer probe incorporated a Peltier sensor, which can be held against any part of the body. The testing was done in a temperature-controlled room at 22°C. The probe was held to the area being tested and the reference temperature was set at 32°C, and the temperature was increased or decreased at 1°C/s for warm or cold testing, respectively. The temperature was reversed and returned back to the initial or reference temperature when the participant felt either hot or cold and pressed the response button. The subjects were instructed to press the button whenever they started to feel warm or cold. At least 6 trials were given and the average of the trials was considered the mean threshold. The threshold value of warm and cold thresholds was obtained and reported as mean ± standard deviation (SD).

The data were expressed as mean ± SD/E and were analyzed statistically using the Statistical Package for the Social Sciences version 25.0 (SPSS Inc., Chicago, IL, USA). The thresholds were compared between neuropathy and nonneuropathy group. The thresholds were correlated with the duration of diabetes and other parameters using Pearson's correlation.

Results

The study population was divided into neuropathy and nonneuropathy group based on considering hot threshold ≥47°C and or cold threshold of ≤16°C as neuropathy. The prevalence of small fiber neuropathy based on temperature thresholds testing was 63%. A significant difference can be observed in the age of the two groups. The neuropathy group had significantly greater duration of DM. Although BP did not have significant difference in the groups, the systolic blood pressure (SBP) was on higher side in the neuropathy group. The diastolic blood pressure, PR, weight, height, waist circumference, hip circumference, and BMI did not show any significant difference among the groups [Table 1].

On comparing the neuropathy and nonneuropathy groups, the PPBS values were elevated in the neuropathy group though not significant. The lipid profile was similar in both the groups. The MNSI B scale had significantly higher scores in the neuropathy group. In the neuropathy group, the thresholds for hot were significantly greater in all four limbs and cold thresholds also were significantly lower [Table 2].

On correlating the neuropathy with other parameters, age and years of DM were positively correlated with the neuropathy [Figure 1]. The hot thresholds of both upper limb and lower limb showed a strong positive correlation with neuropathy [Figure 2]. The cold thresholds of both upper limb and lower limb showed a negative correlation with neuropathy [Figure 3 and Table 3].

Discussion

The study was conducted to assess the magnitude and risk factors of peripheral neuropathy in type 2 DM.

Table 1: Comparison of general parameters

	Neuropathy group (*n*=63)	Nonneuropathy group (*n*=37)	*P*
Age (years)	53.24±10.15	48.24±10.48	0.023*
Duration of DM (years)	7.37±6.45	4.30±4.83	0.008**
SBP (mm of Hg)	132.02±15.93	126.00±20.34	0.129
DBP (mm of Hg)	83.16±11.81	82.32±12.70	0.746
PR (rate/min)	81.92±13.55	85.22±12.54	0.219
Weight (kg)	62.06±10.61	62.92±13.56	0.743
Height (cm)	156.16±13.403	155.00±11.47	0.648
WC (cm)	90.79±18.15	87.97±11.37	0.342
HC (cm)	98.79±11.10	99.68±12.32	0.721
BMI (kg/m^2)	26.91±15.69	26.77±9.35	0.957

*P<0.05; **P<0.01. DM: Diabetes mellitus; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; PR: Pulse rate; WC: Waist circumference; HC: Hip circumference; BMI: Body mass index

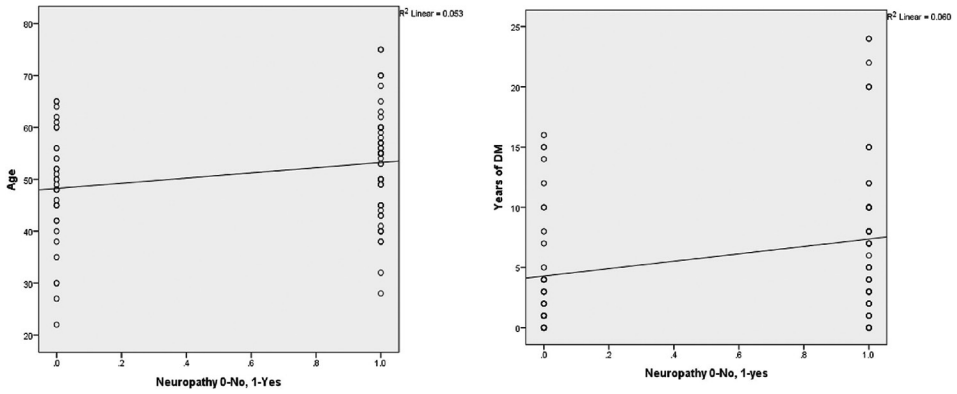

Figure 1: Correlation of age and duration of diabetes with neuropathy

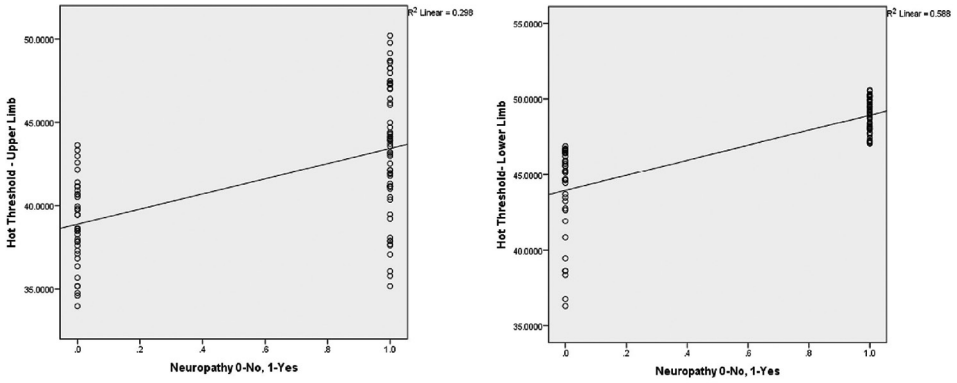

Figure 2: Correlation of hot threshold of upper limb and lower limb with neuropathy

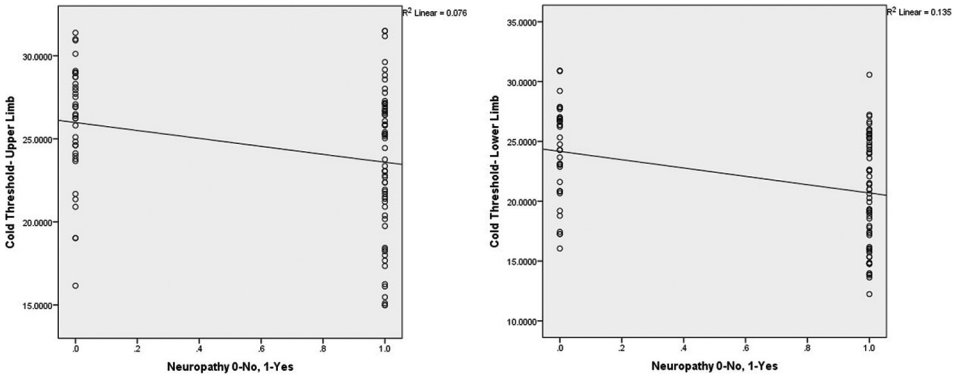

Figure 3: Correlation of cold threshold of upper limb and lower limb with neuropathy

We had included 100 patients with Type 2 DM. Their anthropometry parameters, glycemic parameters, lipid profile, and neuropathy assessment were done.

We observed that 63% of our population had neuropathy. A recent study reported 31.1% as DPN prevalence.[9] A study from South India reported the 39.3% as frequency of peripheral neuropathy, with males having 28.9% and females having 10.4%.[10] Another study reported a prevalence of 19.1%.[11] Patients with type 2 diabetes (42.2%) are afflicted more frequently compared to those with type 1 diabetes.[12] There is a wide variation in the prevalence of DPN from time to time. The variation in prevalence may be also because of the method used to assess the neuropathy. Semmes-Weinstein 10-g monofilament test, ankle reflex, and vibration perception thresholds test were used to assess neuropathy in these studies. We have used TTT to assess small fiber neuropathy. Therefore, we can explain the higher prevalence by claiming that small fibre neuropathy is a precursor to full-blown neuropathy detected through conventional tests.

The age of the neuropathy group was significantly higher than the nonneuropathy group. This sufficiently underscores

Table 2: Comparison of glycemic parameters and neuropathy assessment

	Neuropathy group (*n*=63)	Nonneuropathy group (*n*=37)	*P*
FBS (mg/dL)	177.79±77.47	162.78±68.16	0.315
PPBS (mg/dL)	305. 75±122.57	271±120.10	0.171
HbA1c	9.46±2.25	9.54±2.83	0.887
TC (mg/dL)	204.35±109.99	189.00±38.78	0.317
HDL (mg/dL)	47.35±14.2	48.49±9.43	0.632
LDL (mg/dL)	101.49±40.23	101.59±32.88	0.989
TG (mg/dL)	213.75±126.36	217±130.48	0.876
Michigan A	3.78±2.16	3.54±2.02	0.582
Michigan B	1.13±1.16	0.54±1.043	0.031*
Hot threshold (RUL) (°C)	43.35±3.97	38.95±2.7	<0.001***
Hot threshold (LUL) (°C)	43.56±4.047	38.31±3.10	<0.001***
Hot threshold (RLL) (°C)	49.03±1.29	43.73±3.40	<0.001***
Hot threshold (LLL) (°C)	48.79±1.35	44.16±3.43	<0.001***
Cold threshold (RUL) (°C)	23.62±4.69	25.76±4.08	0.019**
Cold threshold (LUL) (°C)	23.51±4.51	25.76±4.07	0.001**
Cold threshold (RLL) (°C)	20.46±4.71	24.49±4.11	<0.001***
Cold threshold (LLL) (°C)	20.89±4.48	24.05±4.27	0.001**

*P<0.05; **P<0.01; ***P<0.001. FBS: Fasting blood sugar; PPBS: Postprandial blood sugar; HbA1c: Glycated Hemoglobin; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglycerides; Michigan A: MNSI part A; Michigan B: MNSI part B; RUL: Right upper limb; LUL: Left upper limb; RLL: Right lower limb; LLL: Left lower limb

Table 3: Correlation of neuropathy with other parameters

Parameter	*r*	*P*
Age	0.231	0.021*
Duration of diabetes mellitus	0.245	0.014*
Hot (UL)	0.546	<0.001***
Hot (LL)	0.767	<0.001***
Cold (UL)	−0.276	0.005**
Cold (LL)	−0.368	<0.001***

*P<0.05; **P<0.01; ***P<0.001. LL: Lower limb; UL: Upper limb

that increasing age is a risk factor for the development of DPN. Increasing age is an independent risk factor for the development of DPN.[13] In fact, DPN prevalence increased with age from 11.9% aged ≤40 years up to >50% aged >70 years.[12] Similar results have been observed in other studies.[12,14]

In our study, the duration of DM was also significantly high in patients with neuropathy, similar to other studies where DPN incidence increased significantly between 5 and 10 years after diagnosis.[12] The mean duration of DM in patients with neuropathy was 7.37 ± 6.45 years. For every 5-year increment, the prevalence of DPN increases by odds ratio of 2.49.[15] This is line with other studies where the duration of diabetes is found to be an important risk factor for DPN.[16,17]

Although the BP in neuropathy group was not that high to be statistically significant, the SBP was substantially higher in the neuropathy group as can be observed from absolute P = 0.129. As such, hypertension is linked to neuropathy as evidenced by aberrant nerve conduction, increased vibration perception threshold, and decreased corneal nerve fiber density and length.[18] In another study, patients with neuropathy had high normal SBP.[19]

In our study, the PPBS values were elevated in the neuropathy group. Hyperglycemia has been recognized as a major, if not the primary, cause of the clinical manifestations of DPN.[20] Postprandial hyperglycemia is additionally one of the first variations of glucose homeostasis linked to type 2 diabetes.[21] There are reports as levels of FBS and PPBS increased dramatically as the severity of DPN increased.[22] Longstanding hyperglycemia causes peripheral nerve damage via an increased flux of the polyol pathway, higher advanced glycation end product production, excessive cytokine release, triggering of protein kinase C, and boosted oxidative stress.[23] Moreover, studies have shown that only rigorous glucose management is an effective method to reduce neuropathy risk in patients with type 1 DM.[24] Thus, the increased PPBS value in the neuropathy group is understandable. However, the HbA1c values were comparable to nonneuropathy group. This is in contrary to other studies, where higher HbA1c is associated with DPN.[25,26] It is said that long-term variations in HbA1c levels may be a risk factor for DPN rather than the mean HbA1c.[27,28]

Among the physiological indicators of DPN are variations in the serum lipid profile.[29] In one of the studies, HDL cholesterol alone was low by 14% in patients with neuropathy in comparison to a healthy control.[30] Increased LDL-C is linked to slower motor fiber conduction velocities along with higher HbA1c.[26] Oxidised low-density lipoprotein (LDL) increases the production of reactive oxygen species, which disrupts mitochondrial function and modifies the electrical properties of neurons, ultimately

leading to neuropathy.[31] However, in our study, there were no differences in the lipid profile among the neuropathy and nonneuropathy group. This could be because small fibre neuropathy is a precursor to full-blown neuropathy; although our data shows a distorted lipid profile, it is similar in both groups.

While the MNSI scores in part A of the questionnaire, which basically included questions on neuropathy symptoms, were identical for both groups, the neuropathy group scored significantly higher in part B of the assessment, which included the clinical examination. In our study, the MNSI scores were not more than 2 to diagnose neuropathy as per the ADA recommendation.[32] MNSI scoring is a valuable screening test for diabetic neuropathy in determining which individuals should be referred for electrophysiological investigations.[33] The late signs of DPN include loss of or a diminished response to tests of motor, vibration, proprioceptive and tactile, which are part of MNSI (part B) activities.[34] Thermal threshold testing, on the other hand, is a step ahead of MNSI since it is an electrophysiological test that looks for minor anomalies in the C and A nerve fibres of unmyelinated nerve fibres linked to temperature sensitivity, which are believed to occur earlier in DPN.[35]

The thermal thresholds were significantly greater for hot and significantly lower for cold thresholds in the neuropathy group in our study. TTT aids in the detection of small fiber peripheral neuropathy, particularly in early DPN.[36] The frequency of small fiber neuropathy detected by the TTT test was greater than that of large fiber neuropathy detected by the nerve conduction test, and it was discovered at a younger age.[37] This explains why the neuropathy group's MNSI scores were not extremely high despite having aberrant temperature thresholds.

The correlation statistics had shown age and years of DM to be positively associated with neuropathy. Independent of other risk factors, age determines the existence of DPN, even after controlling for other key risk factors such as blood glucose level and diabetes duration.[38,39] A recent meta-analysis is in line with our findings where age and duration of diabetes have a strong positive correlation with the presence of DPN.[16,40] The hot thresholds had a strong positive correlation with neuropathy. Similar findings were seen by Ijff *et al*., who advise using a warm threshold when detecting modest anomalies in small nerve fibre activity in diabetics.[41] Whereas, the cold thresholds had a weak negatively correlated. Moreover, the warm sensations are carried by unmyelinated C fibers which are smaller in diameter than Aδ fibers.[42] The smaller fibers of the hot threshold seem to be affected earlier. Further, it was the hot thresholds of the lower limb which were more strongly correlated with neuropathy in our study. An abnormal temperature threshold in the lower limbs was the most prevalent aberration in subclinical neuropathy.[43] Greater temperature-sensing thresholds in the lower versus upper regions of the body are most likely linked to the finding of a higher density of nerve terminals in the upper versus lower sections of the body.[38]

TTT can be an easy and early screening test to be utilized for early detection of neuropathy in type 2 DM. Further research is needed to standardize the technique to make it easily available routine screening test for the diagnosis of neuropathy.

Conclusion

The age and duration of diabetes are independent risk factors for DPN. The glycemic status and high BP are potential dangers for developing DPN. Small fiber neuropathy is a prequel to the motor neuropathy. Hot threshold testing is more sensitive than cold threshold testing for diagnosing small fiber neuropathy. Standardization of the technique and instrument is the need of the hour. Further research on this technique is warranted.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Institute (AIIMS/BBN/IEC/APR/2021/32/10.5.2021).

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Conflicts of interest

There are no conflicts of interest.

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