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Original Article

Diagnostic Accuracy of Different Bedside Clinical Methods in Evaluation of Peripheral Neuropathy in Patients of Diabetes Mellitus: Experience at a Tertiary Care Center in North India

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Abstract

Background and Objectives: At present, the gold standard for diagnosis of diabetic peripheral neuropathy is biothesiometry. Since the data are sparse comparing the biothesiometry with commonly used bedside tests, we conducted this study to evaluate the clinical accuracy of simple bedside clinical screening tools for evaluation of peripheral neuropathy in patients of diabetes mellitus.

Materials and Methods: A total of 120 patients with diabetes mellitus referred from the endocrinology department, from August 2014 to July 2017 were included in this study. A detailed clinical assessment including diabetic neuropathy symptom (DNS) score, diabetic neuropathy examination (DNE) score, ankle reflex, vibration sensation with a 128 Hz tuning fork, and 10 g Semmes-Weinstein monofilament, and biothesiometry was done in all the subjects.

Results: The prevalence of peripheral neuropathy was 36% with biothesiometry. Only 33.33% of patients followed foot care practices in the study population. Monofilament was the most sensitive and accurate of all the diagnostic tests for the evaluation of peripheral neuropathy in diabetes patients. On statistical analysis correlations observed between the biothesiometry and the DNE score (r = 0.572, P < 0.00018) and DNS score (r = 0.436, P < 0.0004) and absent tuning fork sensation (r = 0.510; P < 0.0007), monofilament sensation (r = 0.713; P < 0.0002) and ankle reflex (r = 0.456, P = 0.0002) were significant.

Interpretation and Conclusions: we concluded that simple bedside tests are useful for diagnosing peripheral neuropathy in diabetes patients including those in whom foot care practices are not followed.

Key words: Biothesiometry, Diabetes mellitus, Monofilament, Neuropathy, Tuning fork

INTRODUCTION

Diabetes mellitus has shown a marked rise all over the world, particularly in India. Diabetic persons have twice the incidence of having lower extremity disease, including peripheral neuropathy, foot ulceration, peripheral arterial disease, or lower extremity amputation, compared with non-diabetic persons and persons who are older than 40 years, about 30% are affected.[1] The annual population-based incidence of foot ulcer ranges from 1.0 to 4.1% and the prevalence ranges from 4 to 10%, in persons with diabetes mellitus, which suggests that the lifetime incidence may be as high as 25%.[1] Hence, screening and early identification of neuropathy in the patient with diabetes help them to actively modulate the course of suboptimal glycemic control to currently recommended targets, and to implement improved

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foot care before the onset of significant morbidity. The efficacy of screening strategies have demonstrated a reduced incidence of amputation and ulceration from various clinical trials and screening for neuropathy is now recommended in clinical practice guidelines.[2] Contrary to developed countries were foot care practices are widely followed, barefoot walking is still prevalent in developing countries and foot care practices are hardly followed,[3] which can result in alteration in cutaneous morphology which may influence the outcome of commonly used tools to identify neuropathy such as the diabetic neuropathy symptom (DNS)[4] Score, 10-g Semmes-Weinstein monofilament (SWMF), vibration testing by 128 Hz tuning fork, ankle reflex, and the diabetic neuropathy examination (DNE)[5] score. Therefore, we evaluated the usefulness of the above modalities with the standard well-validated screening method of measuring vibration perception threshold (VPT)[6] using a biothesiometer in a population where foot care practices are scantly followed.

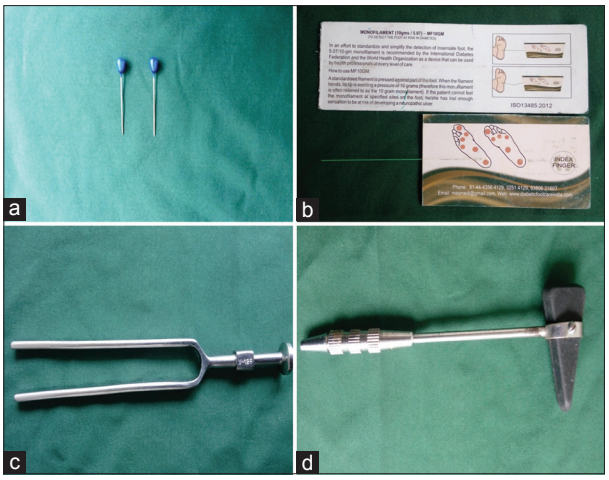


Figure 1: Instruments and tools we used for bedside evaluation of diabetic peripheral neuropathy (a) Stainless steel pins with a plastic cap used for doing pinprick test, (b) Semmes-Weinstein monofilament 5.07/10gm used to asses tactile and pressure sensation, (c) tuning fork (128 Hz) used for vibration test, (d) rubber hammer used for testing deep tendon reflexes

MATERIALS AND METHODS

The study was conducted in the Department of Plastic and Reconstructive Surgery at Sher-i-Kashmir Institute of Medical Sciences (SKIMS) Soura, a tertiary care hospital in Jammu and Kashmir, North India, from August 2014 to July 2017. The study was approved by the Institutional Ethical Committee.

The inclusion criteria were included in the study:

1) Presence of Type 1 or Type 2 diabetes mellitus.
2) Duration of diabetes >8 years.
3) Patient's consent.

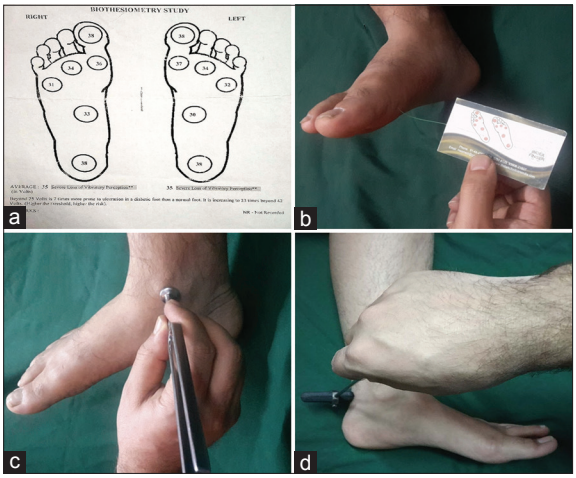
Exclusion criteria were excluded from the study:

1) Other causes of neuropathy such as vasculitis, amyloidosis, toxic neuropathy, AIDS, renal failure, and alcohol abuse.
2) Symptomatic lumbosacral spine disease.
3) Infected foot ulcers.
4) Refusal to participate in the study.

Complete history regarding the type, duration, and treatment of diabetes was recorded. Symptoms of diabetic neuropathy were scored with the DNS score[4] and a score ≥1 was considered significant [Annexure I].

Statistical Analysis

The data were analyzed using the SPSS statistical package, version 13 (Chicago, IL). Correlations were assessed with Spearman's correlation. BY constructing receiver operating characteristic curve, sensitivity, specificity, positive and negative predictive values, and accuracy were calculated for the various tests using VPT >25 mV as the gold standard



(Figure 2: Diagrammatic representation of different tests used to evaluate diabetic peripheral neuropathy (a) Biothesiometry report of a patient showing vibration perception threshold >25 mV suggestive of neuropathy, (b) testing for pressure and tactile sensation using Monofilament 5.07/10 g, (c) testing of vibration sense by using 128 Hz tuning fork, (d) testing of ankle reflex using a rubber hammer

definition of neuropathy. $P < 0.05$ was considered as statistically significant.

RESULTS

A total of 120 patients were included. The mean age was 55 ± 15 years (range 40–70 year) with almost equal gender distribution (Male:female: 1.4:1.0). Baseline characteristics of the study group are given in Table 1. The mean duration of diabetes mellitus was 10 ± 5 years. 48.2% were receiving insulin, 37% on OHA and 14.8% were on both insulin

and oral hypoglycemic agents. The mean body mass index was 22 ± 4 kg/m^2 (range18.4–26.1 kg/m^2). Most of our patients had controlled blood sugar (FPG: 130 ± 20 mg/dl, postprandial plasma glucose: 211 ± 40 mg/dl) and had raised HBA1c% (mean 7 ± 1.1). Hypertension was the main associated comorbidity with a mean systolic blood pressure of 140 ± 40 and diastolic BP of 84 ± 15 mmHg.

Foot care practices were followed by only 40 (33.33%) patients of the study population. While 20 (50%) were self-doing, in 15 (37.5%) foot care was done by a family member and only 5 (12.5%) patients of the study population had foot care done by a trained chiropodist. On evaluating for the symptoms of neuropathy with the DNS questionnaire, 48 (40%) patients were having a score of zero which indicated that they did not have symptoms of neuropathy, 19 (15.83%) had a DNS score of one, 19 (15.83%) had a score of two, 28 (23.33%) had a score of three, and 6(5%) had the maximum score of four; thus, 72 (66.05%) were having significant DNS score indicating that the vast majority of patients with diabetic neuropathy were symptomatic. In patients with a DNS score of zero, 78% had a VPT score of <25 mV and monofilament sensation, tuning fork sensation and ankle reflex were preserved in 39 (80.7%), 41 (86.1%), and 35 (73.3%) patients, respectively.

Evaluation for neuropathy with biothesiometry showed a VPT ≥25 mV in 43 patients, thus, showing a prevalence of peripheral neuropathy of 36% in the study population. Using other testing modalities, neuropathy was found in 28 (33.7%) patients with monofilament and 36 (30%) with tuning fork. The ankle reflex was absent in 48 (40%) patients. The DNE score was significant (>3) in 58 (48%) of patients.

Table 2 gives the sensitivity, specificity, and positive predictive value of each diagnostic modality compared with biothesiometry which is taken as the gold standard.

Table 1: Characteristics of the study population (*n*=120)

Characteristics	Mean±SD
Age (years)	55±15
Sex (Male:female)	70:50
DM 1/DM 2	0/110
Duration of DM (year)	10±5 years
Duration of treatment	10±5 years
BMI (kg/m^2)	24±4
Systolic BP (mmHg)	140±40
Diastolic BP (mmHg)	84±15
FPG (mg/dl)	130±20
PPPG (mg/dl)	211±40
HbA1c (%)	7±1.1

DM: Diabetes mellitus, BMI: Body mass index, BP: Blood pressure, FPG: Fasting plasma glucose, PPPG: Postprandial plasma glucose

Monofilament was the most sensitive and accurate of all the diagnostic tests and can be easily used as a bedside test for screening of diabetic peripheral neuropathy.

As shown in Table 3, there was significant correlation between the VPT score and the DNE ($r = 0.532$, $P < 0.001$) and DNS ($r = 0.546$, $P < 0.001$) scores and absent tuning fork sensation ($r = 0.590$; $P < 0.001$), monofilament sensation ($r = 0.573$; $P < 0.001$), and ankle reflex ($r = 0.377$, $P = 0.01$).

DISCUSSION

In this study, we used bioesthesiometry with VPT of >25 mV as the standard for the diagnosis of neuropathy and the prevalence of peripheral neuropathy was 36%. The use of VPT for the diagnosis of neuropathy has been well validated by clinical studies with a sensitivity and specificity of 80 and 98%, respectively.[7] This is further substantiated by large epidemiological prospective studies showing that a VPT >25 mV had a sensitivity of 83%, a specificity of 63%, a positive likelihood ratio of 2.2 (95% confidence interval [CI], 1.8–2.5), and a negative likelihood ratio of 0.27 (95% CI, 0.14–0.48) for predicting a foot ulceration over 4 years.[5]

Since peripheral sensory neuropathy is a pivotal element in the causal pathway to both foot ulceration and amputation, selecting a quick, inexpensive, and accurate instrument to evaluate the high-risk patient is essential to make decisions. Hence, apart from VPT, we also assessed monofilament, tuning fork, ankle reflex, the DNS, and DNE scores for evaluation of peripheral neuropathy.

The most frequently used modality for detecting neuropathy in clinical practice is the nylon SWMF.[8] Inability to perceive the 10 g of force a 5.07 monofilament applies is associated with clinically significant large-fiber neuropathy. Various case–control studies have reported variable sensitivity and specificity for monofilament sensation up to 95 and 82%, respectively.[9,10] However, another case–control study has shown sensitivity and specificity of 77 and 96%, respectively, which was attributed to the lack of blinding of examiners for individual screening maneuvers.[7] Our study has shown the sensitivity of 91% and specificity of 67% for monofilament sensation for the diagnosis of neuropathy which is lower as compared to the western data possibly due to lack of blinding of examiner for screening maneuver and the subjective variation in this modality. In three prospective studies, the SWMF identified persons at increased risk of foot ulceration with a sensitivity of 66–91%, a specificity of 34–86%, a positive predictive value of 18–39%, and a negative predictive value of 94–95%.[11-13]

Table 2: Diagnostic accuracy of different tests

TESTS	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
DNS score	89	43	67	75	69
DNE score	78	29	58	50	56
Pin prick	67	14	50	25	44
Monofilament	91	60	83	75	81
Ankle reflex	85	67	92	50	81
Vibration sense	75	25	75	25	62

PPV: Positive predictive value, NPV: Negative predictive value, DNE: Diabetic neuropathy examination, DNS: Diabetic neuropathy symptom

Table 3: Correlation between VPT score and absent tunning fork, monofilament and ankle reflex, and DNS score

VPT Score	Tuning fork absent	Monofilament absent	Ankle reflex absent	DNS score	DNE score
VPT score					
Correlation coefficient	0.510	0.713	0.456	0.436	0.572
$P \leq 0.05$	0.0007	0.0002	0.0002	0.0004	0.00018

VPT: Vibration perception threshold, DNS: Diabetic neuropathy score, DNE: Diabetic neuropathy examination

The 128 Hz tuning fork provides an easy and inexpensive test of vibratory sensation. The sensitivity and specificity of vibration testing for peripheral neuropathy have been estimated to be 53 and 99%, respectively.[1,7] The present study showed a better sensitivity (75%) but lower specificity (25%) compared to the above studies. A graded tuning fork is better than a conventional tuning fork and correlates more strongly with biothesiometer results.[14]

We also used ankle reflex for assessing peripheral neuropathy. Absent ankle reflex showed a significant correlation with VPT, though it was highly sensitive, ankle reflex had poor specificity and accuracy. However, in one study sensitivity and specificity for absent ankle reflex was 75 and 89%.[15] The disadvantage of relying purely on absent ankle reflex for peripheral neuropathy diagnosis is the high prevalence of absent ankle reflex even in normal population6. This possibly happens due to associated obesity, oedematous state, concurrent micronutrient deficiency, and various drugs like beta blockers. There is age-dependent increase in the prevalence of absent ankle reflex, which is substantiated by a study of 1074 normal adults, in which proportion of subjects with absent ankle reflex increased rapidly from 5% at 40 to 50 year of age to 80% at 90–100 years of age.[16]

The DNS and DNE scores are simple clinical scores useful to diagnose peripheral neuropathy in patients with diabetes. As expected, the symptom score was sensitive but was not specific for making the diagnosis of neuropathy. However, a study showed a sensitivity of 79% and specificity of 78% for DNS score as compared to VPT4. The DNE score was significant (>3) in 48% of patients and was well correlated with VPT score but had a low sensitivity compared to another study which showed a sensitivity of 96% and specificity of 51%.[6] However, both these scores are more subjective which may result in variability of these indices. Meijer *et al*.[17] have shown a strong relationship between the DNS and DNE scores and electro-diagnostic investigations in both nerve and muscle fiber conduction studies. However, the relatively time consuming DNE scoring did not give any additional specificity or accuracy in diagnosis compared to easy to use monofilament and tuning fork.

CONCLUSION

There is a good correlation between VPT score and monofilament test and the later can be used as a bedside screening tool for evaluation of diabetic peripheral neuropathy.

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(ANNEXURE I)

DNS SCORE QUESTIONAIRE

1. Are you suffering from unsteadiness in walking? Need for visual control, increase in the dark, walk like a drunken man, lack of contact with the floor.
2. Do you have a burning, aching pain or tenderness at your hands, legs or feet? Occurring at rest or night, not related to exercise, excluding intermittent claudication. The pain was graded on a visual analog scale from 0 (no pain) to 10 (most severe pain).
3. Do you have pricking sensations at your hands, legs, and feet? Occurring at rest or at night, distal >proximal, stocking-glove distribution.
4. Do you have places of numbness on your hands, legs or feet? Distal >proximal, stocking-glove distribution.
5. Do you have difficulty to form a fist, grasp small objects or perform other manual tasks.
6. Do you feel any decrease in muscle bulk of your hands and legs.

The questions were answered either "yes" (positive: 1 point) if a symptom has occurred during the past 2 weeks or "no" (negative: No point) if it did not. The maximum score is six and minimum 0.

Various diagnostic tests used to evaluate neuropathy in diabetic patients.

Biothesiometry

The biothesiometer is an instrument which measures the threshold of appreciation of vibration sense. VPT was measured with a biothesiometer – vibrometer. The biothesiometer probe, which vibrates at an amplitude proportional to the square of the applied voltage, was applied perpendicular to the test site with constant and firm pressure. Subjects were initially familiarized with the sensation by holding the probe against the distal palmar surface of the hand. VPT was then measured at the distal plantar surface of great toe of both the legs. If great toe was affected by an ulcer, VPT was measured at the base of the first, third or fifth metatarsals [Figure 2a]. The voltage was slowly increased until the subject indicated that he or she first felt the vibration sense. The mean of three records was taken and noted. Neuropathy was diagnosed if the VPT was ≥25mV.[6]

Pin Prick Test

A trial procedure was first performed with the eyes open. The tip of a sharp pin [Figure 1a] was pressed perpendicularly to the skin on the dorsum of the hand of the patient until the patient indicated that pain was experienced. With the use of the same force applied to the dorsum of the hand, the test was then performed with the same pin on the toes, forefoot, midfoot, and hind foot, and proceeding proximally up the ankle and leg to the knee. The patient was asked to respond if the sensation on foot was more (hyperesthesia), less (hypoesthesia), or comparable to that felt on the hand and the areas recorded.

SWMF Test

A 5.07 SWMF [Figure 1b]was employed to apply a consistent 10 g force on 10 different sites on foot. With the patients unable to see their feet, the monofilament was placed on the foot at right angles to the skin and pressure increased until the filament buckled. The patients were asked to say yes when they felt something. A foot is classified to have loss of protective sensation when less than seven sites were felt by the patient.

Vibration Sensing Test

A 128 Hz tuning fork [Figure 1c] was normally used. After being struck on the hard surface to initiate the vibration, it was not placed on the patient until the audible ring ceased. The patient was told that he would experience a buzzing sensation when the fork was applied to bony prominence, and a trial test was performed with both the fork vibrating and still so that the patient could differentiate between the two sensations. The test was conducted with the patient's eyes closed and he/she was instructed to verbally indicate when he/she no longer felt the vibration. The most common bony points used for this test were malleoli and ball of the big toe [Figure 2c].

Ankle Reflex

Patients were asked to take off their shoes and relax and sit on the table in an upright position with feet dangling. A small strike is given on the Achilles tendon using a proper hammer [Figure 1d], and the response is noted [Figure 2d]. A positive response was marked by a brisk plantar flexion of the foot.

DNE Score (DNE score)

It was used to quantify the neuropathy and a score >3 was considered significant for the presence of neuropathy.[5] [Annexure II].

(ANNEXURE II)

DNE SCORE

Muscle Strength

1. Quadriceps femoris: Extension of the knee 2. Tibialis anterior: Dorsiflexion of the foot

- Reflex: Ankle reflex

- Sensation: Index finger: Sensitivity to pinpricks
- Sensation: Big toe: Sensitivity to pinpricks, Sensitivity to touch.
- Vibration perception, sensitivity to joint position.
- Scoring from 0 to 2:

- 0=Normal
- 1=Mild/moderate deficit:
  Muscle strength: Medical Research Council scale 3–4,
  Reflex: Decreased but present,
  Sensation: Decreased but present.
- 2=Severely disturbed/absent
  Muscle strength: Medical Research Council scale 0–2,
  Reflex: Absent,
  Sensation: Absent.

Maximum score: 16 points.