Rapid Screening of Diabetic Polyneuropathy: Selection of Accurate Symptoms and Signs in an Outpatient Clinical Setting

Laily Najafi[1], Mohammad E. Khamseh[1], Mojtaba Malek[1], Hamid R Baradaran[1], Seyed Mojtaba Aghili[2], Maryam Kia[3], and Rokhsareh Aghili[1]

[1] *Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran*

[2] *Department of Emergency Medicine, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran*

[3] *Department of Internal Medicine, Ziaeian Hospital, Tehran University of Medical Sciences, Tehran, Iran*

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Abstract- Clinical assessment of distal symmetric polyneuropathy (DPN) involves the evaluation of symptoms and signs. Although there are numerous tools to evaluate DPN, there is still a need to determine the most sensitive, specific, and accurate tests to detect DPN in a busy outpatient clinical setting. A total of 107 patients with type 2 diabetes were examined using Michigan Neuropathy Screening Instrument (MNSI). Total score of the instrument was used as a standard to calculate sensitivity, specificity and diagnostic accuracy of every single item of MNSI to find the most accurate and applicable test for evaluation of DPN. In patients' history, the most sensitive (99.4%) and accurate (78%) symptoms were muscle cramp and weakness. Numbness and prickling had lower sensitivity (72.6% and 67.9%, respectively) but greater specificity (65.2% and 47.8%). In physical assessment, the most accurate signs were appearance of feet (81.3%), ankle reflexes (67.2%), and vibration perception (63.5%). Monofilament test had a sensitivity of 16.7%, accuracy of 31.7% with specificity of 87%. Findings show that symptoms such as a muscle cramp, weakness, numbness, and prickling, as well as signs such as ankle reflexes, appearance of feet, and vibration could be used as the most accurate tests for rapid diagnosis of DPN. In addition, the results suggest that monofilament examination may not be the optimum test to detect high risk patients.

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Introduction

Diabetic neuropathy is the most common long-term complication of diabetes (1). It has a heterogeneous pattern with diverse clinical manifestations. The most common form of neuropathy is chronic sensorimotor distal symmetric polyneuropathy (DPN) (2) which is ultimately characterized by a progressive loss of nerve fibers (3), leading to the presence of symptoms and/or signs of peripheral nerve dysfunction (4) and altered nerve conduction velocity (3). Determination of nerve conduction velocity is considered as an effective method for identifying DPN (5). This method is relatively simple; it is age, and temperature dependent (6) and the results vary according to the length and proximity of the limb (7).

In addition, determination of nerve conduction velocity is time-consuming and expensive in an outpatient setting; especially in developing countries without optimal podiatry service that health care professionals should provide standards of care in busy diabetes clinics (8,9).

The Michigan Neuropathy Screening Instrument (MNSI), Toronto Clinical Neuropathy Score (TCNS), Diabetic Neuropathy Symptom Score (DNS), modified Neuropathy Symptom Score (NSS), Diabetic Neuropathy Examination (DNE), and modified Neuropathy Disability Score (NDS) are available as alternative methods, in the assessment of DPN; however, there is a need to formulate a standard protocol for rapid and accurate diagnosis of DPN (10, 11).

Among the mentioned methods, MNSI is widely used for diagnosis of diabetic peripheral neuropathy (12). MNSI is a time consuming tool especially in a busy clinical setting. Thus, determining the most accurate diagnostic test(s) helps the clinicians to assess

Corresponding Author: R. Aghili
Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran
Tel: +98 21 88945172, Fax: +98 21 88945173, E-mail address: r-aghili@razi.tums.ac.ir

DPN precisely and rapidly.

The aim of this study was to determine the diagnostic accuracy of every single symptom and sign of MNSI, considering the total score as a standard to find the most accurate and applicable screening tests to detect DPN.

Materials and Methods

One hundred and seven type 2 diabetic subjects were enrolled in this study. Those subjects with severe peripheral arterial diseases, prior diagnosis of peripheral neuropathy, or secondary types of neuropathy were excluded. Secondary neuropathy was considered if any of the following conditions were present: alcohol consumption, renal failure, liver disease, previous cord injury, history of lumbar or cervical discopathy, inherited forms of neuropathy, occupational neuropathy, hypothyroidism, collagen vascular diseases, paraneoplastic disorders and immune-mediated disorders, and vasculitis.

MNSI was used for evaluation of DPN in these subjects. It comprised two parts, i.e.; "history" and "physical assessment"(13).

The history is a simple tool to assess subjective symptoms. The participants were asked to answer 15 questions. Responses were added to obtain the total score. A "yes" response to the items 1-3, 5-6, 8-9, 11-12, 14-15 was counted as one point for each item and a "no" response on items 7, and 13 counted as 1 point. Item number 4 which measures impaired circulation and item number 10 which measures general asthenia were not included in scoring.

Physical assessment was done by a trained physician considering the appearance of feet, ulceration, ankle reflexes, vibration perception at great toes, and monofilament. Possible obtainable score varied between 0 and 1 for each item. Appearance of feet was evaluated by the presence of deformities, dry skin, callus, infection, and fissure. Deformity was diagnosed if any of the following conditions was present: flat feet, hammer toes, overlapping toes, hallux valgus, joint subluxation, prominent metatarsal heads, medial convexity (Charcot foot), and amputation. All assessments were done in a room with the temperature around 30°C.

Test of vibration was performed bilaterally using a 128 Hz tuning fork placed over the dorsum of the great toe on distal interphalangeal (DIP) joint. A zero score showed that vibration sensation was intact while "0.5" represented a reduced sensation, and "1" was considered as lack of vibration sensation.

The ankle reflexes were examined using an appropriate reflex hammer. Tendon reflexes were scored bilaterally as 0 for normal, 0.5 for abnormal, and 1 for absent responses.

The monofilament was applied based on the protocol provided by Michigan Diabetes Research and Training Center (13); for this examination, the patient's foot was supported and we allowed the sole of the foot to rest on a flat, warm surface and the filament had initially been prestressed (4-6 perpendicular applications to the dorsum of the examiners' first finger). It was then applied to the dorsum of the great toe midway between the nail fold and the DIP joint. The toe was not held directly. The filament was applied perpendicularly and briefly, (<1 second) with even pressure. When the filament bended, the force of 10 grams had been applied.

The 10-g monofilament was applied for ten times on each foot, and a "yes" response was indicative of the filament sensation. Eight correct responses out of 10 applications were considered as normal; 1–7 correct responses as reduced sensation, and no correct answers as absent sensation.

The total score of the instrument was an ordinal numeric variable ranging from 0-10. A total score of >2 was considered as abnormal. Diagnostic accuracy of every single test was calculated considering total score as the standard for comparison using 2x2 tables (Table 1, 2). The basic measures to quantify the diagnostic accuracy of the test include sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

For each item, subjects were divided into four groups; true positive (a), false positive (b), false negative (c), and true negative (d).

In each subject, a symptom/sign was considered as true positive when it was present in accompany with an obtained total score of >2. False positive was considered if the symptom/sign was present on history/clinical examination, but the obtained total score was ≤2. When neuropathy was present based on the total score, but the symptom/sign was absent on history/clinical examination, it was considered as false negative. The symptoms/signs which were absent in both history/clinical examination were defined as true negative if the total score of the instrument was ≤2.

Diagnostic accuracy, PPV, and NPV of each test were derived from the same data.

The ethical approval was obtained from the ethics committee of the Tehran University of Medical Sciences, and all participants signed a written consent form.

Table 1. Comparison of symptoms with the total score as standard

Symptoms	Neuropathy based on total score	
	Present	Absent
Numbness		
Present	61 (a)	8 (b)
Absent	23 (c)	15 (d)
Prickling		
Present	57 (a)	12 (b)
Absent	27 (c)	11 (d)
Burning pain		
Present	45 (a)	6 (b)
Absent	39 (c)	17 (d)
Dry Skin		
Present	36 (a)	11 (b)
Absent	48 (c)	12 (d)
Hx of Amputation		
Present	0 (a)	0 (b)
Absent	85 (c)	22 (d)
Open Sore		
Present	12 (a)	1 (b)
Absent	72 (c)	22 (d)
Sensitive to touch		
Present	20 (a)	4 (b)
Absent	64 (c)	19 (d)
Muscle cramp		
Present	84 (a)	23 (b)
Absent	0 (c)	0 (d)
Hurt by touching with bed covers		
Present	23 (a)	6 (b)
Absent	61 (c)	17 (d)
Hurt legs by walking		
Present	17 (a)	4 (b)
Absent	67 (c)	19 (d)
Worse at night		
Present	39 (a)	7 (b)
Absent	45 (c)	16 (d)
Weakness		
Present	84 (a)	23 (b)
Absent	0 (c)	0 (d)

Data are n

Table 2. Comparison of signs with the total score as standard

Signs	Neuropathy based on total score	
	Present	Absent
Appearance of feet		
Abnormal	*84 (a)	20 (b)
Normal	0 (c)	3 (d)
Ankle reflexes		
Absent	64 (a)	15 (b)
Present	20 (c)	8 (d)
Ulceration		
Present	9 (a)	0 (b)
Absent	75 (c)	23 (d)
Vibration Perception		
Absent	52 (a)	7 (b)
Present	32 (c)	16 (d)
Monofilament		
Absent	14 (a)	3 (b)
Present	70 (c)	20 (d)

* Data are n

Table 3. Baseline characteristics of the study participants

Variables	
Age	57.6 (± 10.2)
Duration of DM	10.2 (± 7.3)
HbA1c	8.8 (± 1.8)
Gender	
Female	72 (67.3%)
Male	35 (32.7%)
BMI	
≤25 kg/m^2	27 (25.2%)
>25 kg/m^2	80 (74.8%)
Diabetes treatment	
Diet	3 (2.8%)
Oral agent ± diet	70 (65.4%)
Insulin ± Oral agent ± diet	34 (31.8%)
Smoking	
Yes	6 (5.6%)
No	94 (87.9%)
Former	7 (6.5%)

Mean ± SD are shown for continuous variables and % is shown for categorical variables

Results

A total of 107 patients participated in this study. Seventy-two (67.3%) were female. The mean age was 57.6 (10.2 SD), and the mean duration of diabetes was 10.2 (7.3 SD) years. The prevalence of DPN in the current study was high (78.5%). Table 3 illustrates baseline characteristics of the participants.

In patients' history, the most sensitive symptoms were muscle cramp and weakness (99.4%), followed by numbness (72.6%) and prickling feeling (67.9%). History of amputation (97.9%) and open sore (95.7%) had the greatest specificity.

To consider the effect of age on subjective parameters, the diagnostic accuracy of numbness was compared in patients less than 65 years old with those who were older (≥65yrs). The comparison showed that in both groups, the diagnostic accuracy of numbness was high; i.e. 67.5% in the former and 81.4% in the latter group.

In physical assessment, appearance of feet and ankle reflexes had the highest sensitivity: 99.9% and 76.2%, respectively. Ulceration (100%), monofilament sensation (87%) and vibration perception at great toes (70%) were the most specific tests.

Considering diagnostic accuracy, muscle cramp (78%),

weakness (78%), numbness (71%) and prickling feeling (63.5%) were the most accurate tests in the past history while, in the physical assessment appearance of feet (81.3%), ankle reflexes (67.2%), and vibration perception (62%) were the most accurate items (Tables 4 and 5).

Data analysis also indicated a diagnostic accuracy of 62.5% for absence of ankle reflexes in those less than 65 yr. old compared to 81.4% in participants who were older.

Table 4. Test Performance Characteristics of the Symptoms compared with the total score as standard

	Sensitivity (CI)	Specificity (CI)	PPV (CI)	NPV (CI)	LR (CI)	LR⁻ (CI)	Accuracy
	$\frac{a}{(a+c)} \times 100$	$\frac{d}{(b+d)} \times 10$	$\frac{a}{(a+c)} \times 1($	$\frac{c}{(a+c)} \times 100$	$\frac{\frac{a}{a \mid c}}{\frac{b}{b \mid d}}$	$\frac{\frac{c}{a \mid c}}{\frac{d}{b \mid d}}$	$\frac{(a+d)}{(a+b+c+d)} \times 100$
Numbness	72.6% (62.3 - 81)	65.2% (44.9 - 81.2)	88.4% (78.8 – 94)	39.5% (25.6 - 55.3)	2.088 (1.175-3.71)	0.42 (0.265- 0.66)	71%
Prickling	67.9% (57.3 - 76.9)	47.8% (29.2-67)	82.6% (72-89.8)	47.8% (29.2-67)	1.583 (1.055-2.376)	0.364 (0.186-0.709)	63.5%
Burning pain	53.6% (43 – 63.8)	73.9% (53.5 - 87.5)	88.2% (76.6 -94.5)	30.4% (19.9- 43.3)	2.054 (1.003-4.20)	0.628 (0.45-0877)	58%
Sensitive to touch	23.8% (16-33.9)	82.6% (62.9-93)	83.3% (64.1-93.3)	22.9% (15.2-33)	1.369 (0.52-3.60)	0.922 (0.738-1.15)	36.4%
Muscle Cramp	99.4% (94.6-99.9)	2.1% (0.2-17.5)	78.5% (69.8-85.2)	50% (5.5-94.5)	1.016 (0.955-1.08)	0.278 (0.006-13.6)	78%
Hurt by touching with bed covers	27.4% (19-37.7)	73.9% (53.5-87.5)	79.3% (61.6-90.2)	21.8% (14.1-32.2)	1.05 (0.485-2.27)	0.982 (0.746-1.29)	37.3%
Hurt legs by walking	20.2% (13-30)	82.6% (62.9-93)	81% (60-92.3)	22.1% (14.6-31.9)	1.164 (0.43-3.12)	0.966 (0.77-1.20)	33.6%
Worse at night	46.4% (36.2-57)	69.6% (49.1-84.4)	84.8% (71.8-92.4)	26.2% (16.8-38.4)	1.526 (0.79-2.94)	0.77 (0.55-1.07)	51.4%
weakness	99.4% (94.6-99.9)	2.1% (0.2-17.5)	78.5% (69.8-85.2)	50% (5.5-94.5)	1.016 (0.955-1.08)	0.278 (0.006-13.6)	78%
Dry Skin	42.9% (32.8-53.5)	52.2% (33-70.8)	76.6% (62.8-86.4)	20% (11.8-31.8)	0.896 (0.54-1.46)	1.095 (0.71-1.689)	45%
History of amputation	0.6% (0.1-5.4)	97.9% (82.5-99.8)	50% (5.5-94.5)	21.5% (14.8-30.2)	0.278 (0.006-13.64)	1.016 (0.955-1.08)	21%
Open sore	14.3% (8.4-23.3)	95.7% (79-99.2)	92.3% (66.7-98.6)	23.4% (16-32.9)	3.286 (0.45-23.96)	0.896 (0.79-1.014)	31.8%

CI: Confidence Interval
PPV: Positive Predictive Value
LR-: Likelihood Ratio for negative test results
NPV: Negative Predictive Value
LR+: Likelihood Ratio for positive test results

Discussion

The current study rigorously examined the sensitivity, specificity and diagnostic accuracy of various items of MNSI to determine the most accurate test(s) to screen distal symmetric polyneuropathy (DPN) in an outpatient clinical setting. The results showed that muscle cramp, weakness, numbness and prickling are the most accurate diagnostic tests in patient history, and appearance of feet, ankle reflexes, and vibration perception are the most accurate tests in physical assessment.

Diabetes may be accompanied by cramping of muscles in the legs and arms. The disturbance of glycogenolysis, as a result, of diabetes mellitus is one possibility which could justify the mechanism of muscle cramps. Depending on the cause, cramping may occur in one muscle or a group of muscles, and it may be accompanied by sharp pain (14). Precise mechanisms of positive neuropathic symptoms such as pain, muscle cramps and their significance in diagnosis of DPN have not yet been clarified (15).

In the present study, muscle cramp was the most sensitive and accurate test in the patient history; however, it had low specificity. This might be due to the presence of some other conditions such as dehydration, fatigue,

Table 5. Test Performance Characteristics of the Signs compared with the total score as standard

	Sensitivity (CI)	Specificity (CI)	PPV (CI)	NPV (CI)	LR^+ (CI)	LR^- (CI)	Accuracy
	$\frac{a}{(a+c)} \times 100$	$\frac{d}{(b+d)} \times 100$	$\frac{a}{(a+c)} \times 100$	$\frac{c}{(a+c)} \times 100$	$\frac{\frac{a}{a+c}}{\frac{b}{b+d}}$	$\frac{\frac{c}{a+c}}{\frac{d}{b+d}}$	$\frac{(a+c)}{(a+b+c+d)} \times 100$
Appearance of feet	99.9% (95.6 - 100)	13.1% (4.6 – 32.2)	80.8% (72.1 – 87.2)	99.7% (43.7 - 100)	1.15 (0.98 - 1.35)	0.01 (0.00- ~)	81.3%
Ankle reflexes	76.2% (66.1-84)	34.8% (18.8-55.1)	81% (71 – 88.1)	28.6% (15.3-47.1)	1.16 (0.84-1.61)	0.68 (0.34 -1.34)	67.2%
Ulceration	10.7% (5.7 - 19.1)	100% (85.6 - 100)	99.9% (70-100)	23.5% (16.2 – 33)	246.8 (0.00- ~)	0.89 (0.82 -0.96)	30%
Vibration perception	62% (51.2-71.6)	70% (49.1-84.4)	88.1% (77.5-94.1)	33.3% (21.7-47.5)	2.034 (1.07-3.85)	0.54 (0.37-0.80)	63.5%
Monofilament	16.7% (10.2-26.1)	87% (67.9-95.5)	82.4% (59-93.8)	22.2% (14.9-31.8)	1.278 (0.40-4.07)	0.958 (0.8-1.15)	31.7%

CI: Confidence Interval
PPV: Positive Predictive Value
NPV: Negative Predictive Value
LR+: Likelihood Ratio for positive test results
LR-: Likelihood Ratio for negative test results

poor peripheral circulation, and nerve compression.

Severe and advanced diabetic polyneuropathy leads to motor disturbances, distal weakness and atrophy of the muscles of the lower leg and foot (16). It might be associated with atrophy of muscle, probably because of inadequate reinnervation (17,18). Present results show that the weakness had sensitivity of 99.4% with diagnostic accuracy of 78%. However, the specificity of the test was poor.

Other studies (19-21) also reported an association between neuropathy and muscle weakness; present observation supports this finding. In another study conducted by Andreassen *et al*., on 30 diabetic and 30 matched control subjects, seven patients reported muscular weakness.

Clinical signs of muscular weakness were found in 10 of the diabetic subjects, of whom eight had symptomatic neuropathy (22). No follow-up study in diabetic neuropathy has been conducted concerning muscle weakness, even though motor function evaluated as part of the clinical assessment, is included in some studies (5,23).

Numbness is one of the most sensitive items in the patient history. Franse *et al*., in a study investigated whether sensory symptoms of neuropathy could be used as a diagnostic or screening tool for detection of diabetic polyneuropathy in general practice. Franse *et al*., reported that prediction of diabetic polyneuropathy with these symptoms is not convincing. The sensitivity and specificity of numbness were reported to be 28% and 93%, in patients less than 68 years old. Similar results were reported for older patients (24). It was concluded that neuropathic sensory symptoms are not useful as a diagnostic or screening tool in the evaluation of diabetic neuropathy in daily practice. The authors suggested an annual foot examination by a general practitioner. In contrast, current study revealed higher sensitivity in < 65 years' old participants and ≥ 65 years, but lower specificity in both groups Table 6 shows test performance characteristics of numbness by the age category.

This difference might be justified by different races and different geographic area being examined in these studies (24).

Table 6. Test Performance Characteristics of Numbness by the age category

	Numbness <65 yr	Numbness ≥65 yr
Sensitivity (CI)	67.8% (55-78.3)	95.5% (78.2-99.2)
Specificity (CI)	66.7% (45.4-82.8)	20% (3.6-62.4)
PPV (CI)	85.1% (72.3-92.6)	84% (65.3-93.6)
NPV (CI)	42.4% (27.2-59.2)	50% (9.5-90.5)
LR^+ (CI)	2.034 (1.08-3.81)	1.19 (76.3-1.86)
LR^- (CI)	0.48 (0.30-78)	0.22 (0.01-3.04)
Accuracy	67.5%	81.4%

CI: Confidence Interval
PPV: Positive Predictive Value
NPV: Negative Predictive Value
LR+: Likelihood Ratio for positive test results
LR-: Likelihood Ratio for negative test results

The current study showed that prickling feeling had sensitivity of 67.9% with specificity of 47.8%. The positive predictive value of the test was 82.6% and its negative predictive value was 47.8%. It was one of the most accurate tests in history to detect DPN. In another study conducted in Brazil, a questionnaire consisting of fifteen questions was applied to evaluate diabetic neuropathy. The most prevalent symptom reported by the patients was prickling (67%) (25) which is a prototypical symptom of diabetic neuropathy (26). Thus, it may be an accurate test for diagnosis of DPN in a busy clinical setting.

Ankle reflexes were also used for assessing peripheral neuropathy. In present study, absent ankle reflex was highly sensitive (76.2%) with accuracy of 67.2% and specificity of 34.8%. Another study reported almost the same sensitivity but higher specificity (89%) for absent ankle reflexes (27) . Meanwhile, Shehab et al(28) showed that ankle reflex is highly sensitive (91.5%) and specific (67.4%); taking nerve conduction studies (NCS) as the gold standard for comparison. Thus, ankle reflexes can be considered as a reliable option for DPN assessment.

Diagnosis of DPN based on absent ankle reflexes is a matter of debate because of the fact that absent ankle reflexes could be seen in the normal population (29). This possibly happens because of coexisting obesity, peripheral edema, concurrent micronutrient deficiency and taking various drugs including beta blockers. In addition, there is an age dependent increase in the prevalence of absent ankle reflexes. In a study of 1074 normal adults, the proportion of subjects with absent ankle reflexes increased rapidly from 5 per cent in the age group of 40-50 to 80 per cent in those over 90 years old (30) . In contrast to this report, the results of this study indicated that ageing could not significantly affect the performance characteristics of this test in evaluation of DPN. Table 7 presents test performance characteristics of ankle reflex by the age category.

Table 7. Test Performance Characteristics of Loss of Ankle Reflex by the age category

	Loss of ankle reflex < 65 yr	Loss of ankle reflex ≥65 yr
Sensitivity (CI)	74.6%(62.2-84)	80%(61-91)
Specificity (CI)	28.6%(13.8-50)	99.9%(34.-100)
PPV (CI)	74.6%(62.2-84)	100%(83.8-100)
NPV (CI)	28.6%(13.8-50)	28.6%(8.3-64)
LR^+ (CI)	1.044(0.76-1.42)	161.6(0.0- ~)
LR^- (CI)	0.89(39.8-1.99)	0.201(0.09-0.44)
Accuracy	62.5%	81.4%

CI: Confidence Interval
PPV: Positive Predictive Value
NPV: Negative Predictive Value
LR+: Likelihood Ratio for positive test results
LR-: Likelihood Ratio for negative test results

Appearance of feet was the most sensitive item (99.9%) to detect DPN in the current study with diagnostic accuracy of 81.3%. Peripheral neuropathy interferes with normal protective mechanisms and puts patients at risk of major or repeated minor trauma to the foot. Disordered proprioception causes misjudgment of foot position, resulting in increased risk of fall (31) and abnormal weight bearing leading to callus formation or ulceration (32). Motor and sensory neuropathy result in abnormal foot muscle mechanics and turn into structural changes in the foot (hammer toe, claw toe deformity, prominent metatarsal heads, and Charcot joint) (32). Thus, the presence of changes of the leg and foot, abnormal hair loss, infection, fissures, calluses (including the heels and web spaces), and deformities should be noted while assessing diabetic neuropathy (33).

The 128 Hz tuning fork provides a simple, applicable and inexpensive test of vibration. In some studies, the sensitivity and specificity of vibration testing for peripheral neuropathy are 53 and 99 per cent, respectively (34, 35). In the study conducted by Jayaprakash et al. a better sensitivity (62.5%) and a lower specificity (95%) are reported (36). Current study showed a high sensitivity (62%) and specificity (70%), making this test as one of the most useful modalities to detect DPN.

As vibration perception (VP) testing is not significantly affected by the presence of foot callus or by limb temperature (37), it can provide clinically important information about large nerve fiber dysfunction in diabetes. The neurological deficits associated with large fiber neuropathy account for 80% of the morbidity associated with DPN (38). The majority of long-term complications of diabetes such as ulceration and

amputation are preceded by abnormal VP values (39). However, VP testing is not sufficiently specific to large fiber or even to peripheral nerve dysfunction, and the results are influenced by subject attentiveness, motivation, and fatigue (37,40-42) . In other words, its reproducibility may vary in non-diabetic and diabetic patients (37,42) . VP can be an optimal option for DPN assessment in a busy clinical setting, considering the pros and cons of VP and the presence of standard algorithms,

The most commonly used modality for evaluating neuropathy in daily clinics is the Semmes-Weinstein monofilament examination (43). Various case-control studies reported variable sensitivity and specificity for monofilament sensation up to 95 and 82 per cent, respectively (44,45). In the study conducted by Jayaprakash et al (36) in India, results showed sensitivity of 63 per cent and specificity of 93 per cent for monofilament sensation for the diagnosis of neuropathy. Other studies, indicated that abnormal results of Semmes-Weinstein monofilament examination, increase the likelihood of peripheral neuropathy (35,46,47). Despite differences in technique and threshold values, an abnormal test has a likelihood ratio in favor of the neuropathy (48).

In contrary to the above studies, monofilament examination had poor sensitivity in this study, though it was highly specific. Regarding the results of this study and the systematic review done by Dros et al, despite the common use of monofilament examination, the accuracy of the test for evaluating neuropathy in feet without frank ulcers is questionable. It should be emphasized that the results of monofilament testing depends on "Optimal test application" and "defining a threshold" (49). In a study by Miranda-Palma et al. the number of testing sites and the proportion needed to be insensate for the optimal assessment of foot ulcer risk was assessed. They showed that the sensitivity of monofilament examination was less than NDS and biothesiometer (50).

Feng et al. in a systematic review concluded that there is great variation in the current literature regarding the diagnostic value of monofilament examination because of different methodologies (51).

Taking the above evidence into consideration, monofilament examination should not be used as the optimum modality to diagnose peripheral neuropathy as its accuracy is low.

Although present study assessment showed muscle cramp, weakness, numbness, prickling, and appearance of feet, ankle reflexes, and vibration perception as the most accurate tests in a busy outpatient clinical setting, further studies using nerve conduction velocity tests are needed to confirm these results. In addition, using monofilament examination as the optimal test to detect patients at risk of DPN is controversial and there is still a need to formulate a standard protocol for the test application.

The high prevalence of DPN in current study might be attributed to the fact that this study was conducted in a tertiary referral center; therefore, the results could not be generalized to all diabetic patients.

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