Original Article

Role of bedside methods in evaluation of diabetic peripheral neuropathy

Javed Ahmed Phulpoto, Kouro Mal Gurbakhshani, Abrar Shaikh

Department of Medicine, Ghulam Mohd Mahar Medical College, Sukkur and Chandka Medical College, Larkana, Pakistan

ABSTRACT
Objective

To assess the role of bedside methods in evaluation of diabetic peripheral neuropathy in diabetic patients attending diabetic clinic at Ghulam Mohammad Mahar Medical College Hospital, Sukkur, Pakistan.

Methods

This cross-sectional study was carried out at Diabetes Clinic, Ghulam Mohammad Mahar Medical College Hospital, Sukkur, from January 2010 to May 2011. A total of 1044 patients with diabetes mellitus were included in this study. All subjects had 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, 10g Semmes-Weinstein monofilament and vibration perception threshold (VPT).

Results

The prevalence of peripheral neuropathy was 34.9 % with VPT. Foot care practices were followed by only 214 (20.5%) patients. When compared with VPT, ankle reflex was the most sensitive (90.7%) but least specific (37.3%). The tuning fork and monofilament tests respectively had lower sensitivity (62.5 and 62.8%) but better specificity (95.3 and 92.9%) and accuracy (78.9 and 77.9%). Significant correlations were observed 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).

Conclusions

The findings show that simple bed side tests are useful for assessing peripheral diabetic neuropathy, even in those subjects in whom foot care practices are not followed. (Rawal Med J 2012;37:137-141).

Key Words

Ankle reflex, monofilament, neuropathy, VPT.

INTRODUCTION

The number of patients with diabetes mellitus (DM) is increasing by epidemic proportions in the world. Lower extremity disease, including peripheral neuropathy (PN), foot ulceration, peripheral arterial disease, or lower extremity amputation, is twice as common in diabetic persons compared with non diabetic persons and affects 30% of type II diabetic persons older than 40 years.[1] In persons with DM, the annual population-based incidence of foot ulcer ranges from 1.0 to 4.1% and the prevalence ranges from 4 to 10%, which suggests that the lifetime incidence may be as high as 25 percent.[1] Screening and early identification of PN offer a crucial opportunity for the patient with diabetes to actively modulate the course of suboptimal glycemic control to currently recommended targets, and to implement improved foot care before the onset of significant morbidity.

Most of the available modalities have been evaluated in developed countries where foot care practices are widely followed. Contrary to it, in developing countries barefoot walking is still prevalent and foot care practices are hardly followed,[2,3] which can result in alteration in cutaneous morphology. This may influence the outcome of commonly used tools to identify neuropathy like the Diabetic Neuropathy Symptom (DNS) Score, 10-g Semmes-Weinstein monofilament, vibration testing by 128 Hz tuning fork, ankle reflex and the Diabetic Neuropathy Examination (DNE) score. Therefore, this study was performed to evaluate the usefulness of the above modalities with the standard validated screening method of

measuring vibration perception threshold (VPT) with a biothesiometer in a population where foot care practices are scantly followed.

PATIENTS AND METHODS

The study was conducted in the Diabetes clinic, Ghulam Mohammad Mahar Medical College Hospital, Sukkur, Pakistan from January 2010 to May 2011. Patients with DM, according to the American Diabetes Association (ADA) criteria[2] and who had at least two visits in the last six months were included in the study. Institutional Ethics Committee approved the protocol and an informed written consent was obtained from the study participants. Detailed history regarding the type, duration and treatment of diabetes was recorded. History regarding foot care was taken-whether using footwear or not, the type of footwear(s) used and whether foot care practices were followed daily or not, were assessed by a questionnaire. Symptoms of DN were scored with the DNS score[4] and a score ≥ 1 was considered significant (Annexure I). VPT was measured with a biothesiometer (Vibrometer, VPT® Diabetic Foot Care, Madras Engineering Service, India) in a standardized fashion by a single observer. The biothesiometer probe was applied perpendicular to the test site with a constant and firm pressure. If great toe was affected by ulcer, VPT was measured at the base of the first, third or fifth metatarsals. The voltage was slowly increased at the rate of 1 mV/Sec and the VPT value was defined as the voltage level when the subject indicated that he or she first felt the vibration sense. A mean of three records was taken and neuropathy was diagnosed if the VPT was $\geq$ 25m V.[5]

Evaluation for PN was done using 10 g Semmes-Weinstein monofilament. The filament was placed perpendicular to the skin and pressure was applied until the filament just buckles with a contact time of 2 seconds. The patient was prevented from seeing if and where the examiner applied the filament. Monofilament was applied to the plantar surface of great toe and base of first, third and fifth metatarsals of both feet. Areas affected by ulceration or thick callus formation were omitted. The patient was asked to say whether he can feel the pressure applied (yes/ no) and in which foot it was applied (right/ left foot). Inability to perceive the sensation at two or more sites were considered abnormal. Assessment of vibration

sensation was also done with a 128 Hz tuning fork applied at the distal plantar surface of big toe of both legs. The response was considered abnormal when the patient loses vibratory sensation while the examiner still perceived it for more than ten seconds. Ankle reflex was assessed with a tendon hammer and was recorded as either present or absent. The DNE score was used to quantify the neuropathy (Annexure II) and a score >3 was considered significant for presence of neuropathy.[6]

The data were analyzed using SPSS v 13. 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 definition of neuropathy. P<0.05 was considered as statistically significant.

RESULTS

A total of 1044 patients were included. The mean age was 53.3 ± 11.8 years, (range 13-86 yr) with almost equal gender distribution (M:F 1.02:1.0). Baseline characteristics of the study group are given in the Table 1.

Table 1. Characteristics of the study population (n=1044).

Variable	Mean + SD
Age (yr)	53.3+11.8
Sex (M:F)	532:512
Duration of DM (yr)	7.18 ±6.92
BMI (kg/m^2	25.22 ± 4.96
BMI (kg/m^2	92.39 ± 10.59
Waist Circumference (cm)	136.57 ±16.97
Systolic BP (mmHg)	84.02 ±10.96
Diastolic BP (mmHg)	149.12±57.56
FPG (mg/dl)	211.95±74.27
PPPG (mg/dl)	8.79±2.54
HbAlc (%)	8.79±2.54
24 h Urinary protein (mg)	274.36 ±13.93*
TC (mg/dl)	184.19 ± 47.01

LDL (mg/dl)	108.05 ± 39.52
HDL (mg/dl)	47.72± 31.75
TG (mg/dl)	163.10 ±76.89

*Value in SEM. BMI, body mass index; FPG, fasting plasma glucose; PPPG, postprandial plasma glucose; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides.

Among the study group, 37 (3.5%) had type I DM and the rest had type II diabetes. The mean duration of DM was 7.18±6.92 year and 42.2% were receiving insulin and/or oral anti diabetic drugs.

Table 2. Diagnostic accuracy of different tests compared to vibration perception threshold (VPT).

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy %
DNS Score	86.2	55.4	83.1	16.9	59.3
Ankle reflex	90.7	37.3	56.1	81.9	62.3
Tuning fork	62.5	95.3	93.0	71.7	78.9
Monofilament	62.8	92.9	90.0	71.4	77.9
DNE score	68.6	74.0	72.5	70.2	71.3

PPV, positive predictive value, NPV, negative predictive value: DNS diabetic neuropathy symptom: DNE, diabetic neuropathy examination

Foot care practices were followed by only 214 (20.5%) patients. 182 (17.4%) patients were self doing and in 20 (1.9%) foot care was done by a family member and only 13 (1.2%) patients had foot care by a trained chiropodist. Twenty three (2.2%) subjects were not using any footwear outdoor while 473 (45.3%) did not use any footwear indoor.

Table 3. Correlations between VPT score and absent tuning fork, monofilament and ankle reflex, and DNS and DNE score.

		Tuning fork absent	Monofilament absent	Ankle reflex absent	DNS Score	DNE Score
VPT score	Correlation coefficient	0.590	0.573	0.377	0.546	0.532
	P (2-tailed)	<0.001	<0.001	0.011	<0.001	<0.001

VPT, Vibration perception threshold; DNS, diabetic neuropathy symptom: DNE, diabetic neuropathy examination.

Only 242 (232%) patients were using closed footwear like shoes while the remaining were using open footwear, majority (64.6%) of which was sandals. On evaluating for the symptoms of neuropathy with the DNS questionnaire, 375 (35.9%) patients had a score of zero which indicated that they did not have symptoms of neuropathy, 148 (14.2%) had a DNS score of one, 187 (17.9%) had a score of two, 267 (25.6%) had a score of three and 67 (6.4%) had the maximum score of four; thus 669 (64.1%) 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, 91.1 percent had a VPT score of <25 mV and monofilament sensation, tuning fork sensation and ankle reflex were preserved in 895 (85.7%), 909 (87.1%) and 765 (73.3%) patients, respectively.

Evaluation for neuropathy with biothesiometry showed a VPT $\geq$ 25 mV in 364 patients, thus showing a prevalence of peripheral neuropathy of 34.9 per cent in the study population. Using other testing modalities, neuropathy was found in 321 (30.9%) with tuning fork. The ankle reflex was absent in 471 (45.1%) patients. The DNE score was significant (>3) in 496 (47.5%) of patients. Table 2 shows the sensitivity, specificity and positive predictive value of each diagnostic modality compared with biothesiometry which is taken as the gold standard. Tuning fork test and monofilament were the most specific and accurate of all the diagnostic tests. Though the ankle reflex was most sensitive it had poor specificity and positive predictive value. 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= 0.573; p<0.001) and ankle reflex (r=0.377, P=0.01).

DISCUSSION

The present study has used VPT of > 25 m V as the standard for the diagnosis of neuropathy and the prevalence of PN was 34.9 percent. The use of VPT for the diagnosis of neuropathy has been well validated by clinical studies with sensitivity and specificity of 80 and 98 percent respectively.[7] This is

further substantiated by large epidemiological prospective studies showing that a VPT more than 25 mV had a sensitivity of 83 percent, a specificity of 63 percent, a positive likelihood ratio of 2.2 (95% 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 four years.[6] 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. Thus, 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 Semmes-Weinstein monofilament.[8] Inability to perceive the 10 g of force a 5.07 monofilament 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 study has shown sensitivity and specificity of 77 and 96% respectively, which was attributed to lack of blinding of examiners for individual screening maneuvers.[7] Our study has shown sensitivity of 63 per cent and specificity of 93 per cent for monofilament sensation for the diagnosis of neuropathy which is lower as compared to the western data, possibly because of lack of blinding of examiner for screening maneuver and the subjective variation in this modality. In three prospective studies, the Semmes-Weinstein monofilament identified persons at increased risk of foot ulceration with a sensitivity of 66 to 91%, a specificity of 34 to 86%, a positive predictive value of 18 to 39%, and a negative predictive value of 94 to 95%.[10-13]

The 128 Hz tuning fork provides an easy and inexpensive test of vibratory sensation. The sensitivity and specificity of vibration testing for PN has been estimated to be 53 and 99%, respectively.[7] The present study showed a better sensitivity (62.5%) but a lower specificity (95%) compared to the above studies. A graded tuning fork is better than a conventional tuning fork and correlates more strongly with biothesiometer results.[14]

Our study had also used ankle reflex for assessing PN and absent ankle reflex showed a significant correlation with VPT, though it was highly sensitive, ankle reflex had poor specificity, positive predictive value and accuracy. However, in one study sensitivity and specificity for absent ankle reflex was 75 and 89 percent.[15] The disadvantage of relying purely on absent ankle reflex for PN is the high prevalence of absent ankle reflex even in normal population.[6] This possibly happens because of associated obesity, edematous state, concurrent micronutrient deficiency and various drugs like beta blockers. There is age dependent increase in 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 to 100 year of age.[16]

The DNS and DNE scores are simple clinical scores useful to diagnose PN 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 VPT.[4] The DNE score was significant (>3) in 47.5 per cent 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 have shown a strong relation between the DNS and DNE scores and electro-diagnostic investigations in both nerve and muscle fiber conduction studies.[17] But 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 was good correlation between VPT score with tuning fork, monofilament and ankle reflex show that simple bed side tests are useful in clinical practice, even in those subjects in whom foot care practices are not followed.

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Annexure 1

DNS Questionnaire

1. Are you suffering of unsteadiness in walking? Need for visual control, increase in the dark, walk like a drunken man, lack of contact with floor.
2. Do you have a burning, aching pain or tenderness at your legs or feet? Occurring at rest or at night, not related to exercise, exclude intermittent claudication.
3. Do you have prickling sensations at your legs and feet? Occurring at rest or at night, distal> proximal, stocking glove distribution.
4. Do you have places of numbness on your legs or feet?
   Distal>proximal, stocking glove distribution.

The questions were answered either "Yes" (positive: 1 point) if a symptom has occurred during the last 2 weeks or 'No' (negative: no point) if it did not. Maximum score is 4 and minimum 0.

Annexure II

DNE scoring

Muscle strength:
1. Quadriceps femoris: extension of the knee;
2. Tibialis anterior: dorsiflexion of the foot
   Reflex: Triceps surae
   Sensation: index finger: Sensitivity to pinpricks
   Sensation: big toe: Sensitivity to pinpricks, Sensitivity to touch, Vibration perception, Sensitivity to joint position.
   Only the right leg and foot are tested.
   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