Original Research Article

Comparison Of The Diagnostic Yields Of Some Methods Of Screening For Diabetic Peripheral Neuropathy In North Central Nigeria.

ABSTRACT

BACKGROUND

Peripheral neuropathy is one of the microvascular complications of diabetes mellitus, a risk factor for diabetic foot, and a major cause of disability world wide. Several authors have variedly reported on the efficacies of the different simple and sophisticated methods used in the diagnosis of peripheral neuropathy. The aim of this study is to compare the diagnostic yields of different simple methods of screening for diabetic peripheral neuropathy.

METHODOLOGY

This is a multi-center cross-sectional study involving 1040 participants recruited consecutively, following consent. Relevant biodata and medical history were obtained, while physical examinations including anthropometry, and blood glucose levels were done for each participant. History of paresthesia, 10g monofilament test, vibration test using 128Hz tuning fork, and ankle reflex assessment were the methods used to screen for diabetic peripheral neuropathy. Student 't' test and chi square were used to compare continuous and categorical variables respectively. Significant p-value was put at less than or equal to 0.05.

RESULTS

The percentage of participants with positive screen for diabetic peripheral neuropathy based on the different methods include: positive neuropathic symptoms (64%), negative neuropathic symptoms (50.7%), 10g monofilament testing (31.9%), vibration sensation by tuning fork (21.8%), and ankle reflex impairment (13.1%). A total of 80.1% of the participants were screened positive for diabetic peripheral neuropathy when all the methods were used.

CONCLUSION

Positive and negative neuropathic symptoms have higher diagnostic yields for diabetic peripheral neuropathy screening than 10g monofilament testing, vibration sensation using tuning fork, and ankle reflex examination. However, it is encouraged to use all available methods to screen for diabetic peripheral neuropathy, as this increases the diagnostic yield, and ensure early adoption of preventive and therapeutic strategies.

Keywords: diabetes mellitus, diabetic peripheral neuropathy, screening, diagnostic yield

INTRODUCTION

According to the World Health Organization, Peripheral Neuropathy is “the involvement of peripheral nerve in disease states”. It is a risk factor for diabetic foot and a major cause of disability world wide. The etiology of peripheral neuropathy include malnutrition, toxins, genetic disorders, and metabolic conditions like diabetes mellitus. Peripheral neuropathy may be asymptomatic or present with symptoms of paresthesia. Paresthesia are positive or negative symptoms due to peripheral neuropathy. Positive symptoms include pain, tingling, burning, or crawling sensation, etc. while negative symptoms include numbness. Painful paresthesia is due to small fibre neuropathy and can diminish the quality of life in persons with DM resulting in anxiety, depression, and insomnia. The prevalence of diabetic peripheral neuropathy varies from 14% to 65%. This variation may be attributable to differences in the methods of diagnosis and heterogeneity of study populations. [1,2]

Various methods useful in the diagnosis of peripheral neuropathy include history of paresthesia, physical examination methods like checking for pinprick sensation, position sense, reflexes, vibration sensation using tuning fork, and the use of 10g or 1g monofilament. More sophisticated investigative techniques used for the diagnosis of peripheral neuropathy include neurobiothesiometry, nerve conduction studies, skin biopsy for intra-epidermal nerve density, and corneal confocal microscopy. [1,2] Suda et al.,[3] Zhang et al.,[4] and Yildrim et al.[5] concluded that Semmes-Weinstein Monofilament (SWM) test was reliable for detecting peripheral neuropathy in persons with chronic stroke, DM, and for electrophysiologically grading carpal tunnel syndrome respectively. Olaiya et al. [6] also demonstrated that SMWs can help in identifying subclinical peripheral neuropathy. In the same vein, Widasmara et al. [7] reported a strong positive correlation between some biomarkers of nerve damage and SWM scores in a research study.

Brown et al. [8] however, posited that though, vibration and 10g monofilament may assist in the screening for diabetic peripheral neuropathy, they have lower yields than the 1g monofilament. Similarly, Malik et al., [9] Wang et al., [10] and Azmi et al. [1] reported that the 10g monofilament has limited sensitivity in diagnosing early diabetic peripheral neuropathy, and may not detect small fiber mediated painful neuropathy. In a similar vein, Jayaprakash et al. [11] reported that vibration and monofilament tests had better specificity but less sensitivity when compared to ankle reflex.

However, Lanting et al. [12] recommended the use of more than one method to screen and monitor progression of peripheral neuropathy in persons with diabetes. This will result in increased yield in the diagnosis of peripheral neuropathy. Several studies have tried to compare the diagnostic yields of various investigative tools used in the diagnosis of peripheral neuropathy. None of the literature searched specifically compared the diagnostic yields of positive and negative neuropathic symptoms, reflexes, vibration sensation, and Semmes-Weinstein 10g monofilament. This study is therefore aimed at comparing the diagnostic yields of history of positive and negative neuropathic symptoms, reflexes, vibration sensation, and Semmes-Weinstein 10g monofilament.

MATERIALS AND METHODS

This is a multi-center cross-sectional study that is aimed at comparing the diagnostic yields of some methods of diagnosing diabetic peripheral neuropathy in North Central Nigeria. This research was

undertaken as part of the routine clinical activities of several hospitals, thus with waiver of ethical approval. The study was done in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Inclusion criteria included all adult outpatients with DM who attend the Diabetic Clinics while exclusion criteria included presence of other neurological problems not related to DM, dyselectrolytemia, nutritional deficiencies, and non-diabetic status. Written consent was obtained from the participants to allow their clinical data to be utilized in this study with no form of identity disclosure. The participants were enrolled consecutively from their various clinics over the period of the study resulting in a total of one thousand and forty (1040) enrollees. Clinical data was obtained from each participant including bio-data, history of systemic hypertension, and duration of diabetes from the time of diagnosis.

A combined weight-height scale (model RGZ-120, by Jiangsu Suhong Medical Instruments Co. LTD, Jiangsu, China, June 2016) was used to measure the participants' weight and height. Each participant was instructed to stand vertically on the board facing the examiner without headscarf or footwear, with feet together, heels against the back of the board, looking straight ahead such that the inferior orbital margin was at the same level with the external auditory meatus. The adjustable head of the board was pressed gently on the participant's head, then instructed to breathe in. The height was then, measured to the nearest 0.1cm. Subsequently, each participant with only light clothings on without footwear, was instructed to stand still on the scale with each foot on either side of the scale. He or she was further instructed to stand still, with arms by the side, then the weight was measured to the nearest 0.5kg. Body mass index (BMI) was calculated by dividing weight (kg) by the square of height (m^2) and the answer recorded in kg/ m^2. [22]

Subsequently, waist circumference was measured with a non-stretchable tape. The examiner stood by the side of the participant, then located a point mid-way between the inferior margin of the lowest rib and the iliac crest top. With the help of an assistant, the tape was wrapped around the waist of the participant over the marked midpoint ensuring the tape is horizontally placed and parallel to the flat ground. The participant was then, instructed to stand with his or her feet placed together, arms by the sides, palms facing inwards, and gently exhaling. At the end of expiration, the waist circumference was measured to the nearest 0.1 cm. [22] Each participant was asked to relax in a sitting position, legs uncrossed, for at least five (5) minutes, then, the blood pressure was measured with a mercury sphygmomanometer and recorded to the nearest 2mmHg.

Semmes-Weinstein 10gm monofilament was used to test for sensation. At first, the filament was applied to the participant's forehead so he or she knows how it feels. The participant was then, asked to close his or her eyes, and the filament was applied perpendicular to the skin's surface at the plantar surface of the 1^{st} and 3^{rd} toes and metatarsal heads. Minimal force was applied just sufficient enough to allow the filament to buckle; and the approach, application, and removal did not exceed two (2) seconds. Care was taken not to apply the filament on a callus, ulcer, or a necrotic tissue; and not to allow the filament to make repeated contacts or slide across the skin. The participant was instructed to say, "Yes," when he or she feels the filament. The procedure was repeated twice at each site with at least one "mock" application in an irregular pattern with varied timing, to avoid stimulus anticipation by the participant. A participant was said to have peripheral neuropathy if he or she failed to feel the filament at two or more sites on either foot. [13]

In order to test for vibration sensation, a 128Hz tuning fork was struck against the palm of the examiner's hand hard enough to vibrate for about 40 seconds. The base of the tuning fork was then applied to the participant's forehead to enable him or her understands the vibration sensation and not just the touch sensation. With the participant's eyes closed, the tuning fork was applied to the bony prominence at the dorsum of the first toe just proximal to the nail bed. He or she was then asked if the vibration sensation was perceived. Then, the participant was asked to tell when the sensation stopped, before the vibration was dampened with the other hand. This procedure was repeated twice on each foot with at least one "mock" application in an irregular pattern with varied timing, to prevent stimulus anticipation by the participant. The participant that failed to perceive vibration sensation or tell when it stopped in 2 or more sites of either foot was said to have peripheral neuropathy. [13]

Ankle reflex was assessed using a long reflex hammer with the participant relaxed and positioned symmetrically in a supine position. The hip was slightly externally rotated, and the foot gently dorsiflexed, then the Achilles tendon was tapped with a reflex hammer. If the reflex was absent, it was attempted again after re-enforcing by instructing the participant to interlock and pull flexed fingers (Jendrassik maneuver). Participants with reduced or absent reflex contraction of the gastrocnemius muscle and reduced or absent plantar flexion were said to have peripheral neuropathy. [13]

For each participant, blood sample for Fasting plasma glucose (FPG) was taken after fasting overnight for 8-12 hours. Then, a second blood sample was obtained two (2) hours after ingestion of 75g anhydrous glucose in 250mls of water within 5 minutes. Plasma glucose was detemined using the glucose oxidase method. The American Diabetes Association criteria for blood glucose control target was used to classify participants into "Good control" and "Poor control" i.e good control was taken as HbA1c <7.0% (<53 mmol/mol), preprandial capillary plasma glucose 80-130 mg/dL (4.4-7.2 mmol/L), peak postprandial capillary plasma glucose <180 mg/dL (<10.0 mmol/L). [26] The data was entered into Microsoft Excel, then the analysis was done using IBM SPSS version 23 (IBM SPSS Co. LTD., New York, USA; March 4, 2015). Results were expressed as means ± standard deviation at 95% confidence interval. Student 't' test and chi square were used to compare continuous and categorical variables respectively. Significant p-value was put at less than or equal to 0.05.

RESULTS

This study was aimed at comparing the diagnostic yields of some methods of diabetic peripheral neuropathy screening. The total number of participants was one thousand and forty (1040) which comprised six hundred and eight (608) females and four hundred and thirty two (432) males with a male to female ratio of 1.0 to 1.4. The mean age (standard deviation) of the participants was 52.9 (11.8) years with no significant difference in the mean age for the men and women (p=0.084). The mean duration of diabetes mellitus was significantly higher in the men compared to the women (102 vs 89 months, p=0.014). However, the mean body mass index (BMI) was significantly higher in the women than the men (29.0 vs 26.2 Kg/m^2, p<0.001). However, there were no significant gender differences in systolic blood pressure (SBP), diastolic blood pressure (DBP), plasma glucose levels and glycated hemoglobin (HbA1c) [Table 1].

Table 1 showing some clinical and laboratory parameters of participants

	Female	Male	Total	P
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (yrs)	52.38 (11.81)	53.66 (11.82)	52.91 (11.82)	.084
Duration (months)	89.00 (75.37)	102.15 (96.98)	94.46 (85.22)	.014
BMI (Kg/m^2)	28.95 (5.82)	26.28 (4.94)	27.84 (5.62)	<.001
WC (cm)	96.31 (15.17)	93.07 (15.43)	94.96 (15.35)	.001
SBP (mmHg)	130.14 (21.01)	130.49 (20.02)	130.29 (20.60)	.790
DBP (mmHg)	79.97 (12.12)	79.31 (10.63)	79.69 (11.52)	.368
FPG (mmol/L)	9.33 (4.32)	9.57 (4.71)	9.43 (4.49)	.388
2HrPP (mmol/L)	12.74 (6.48)	12.86 (6.21)	12.79 (6.37)	.763
HbA1c (%)	8.18 (2.40)	8.67 (2.69)	8.39 (2.53)	.221

BMI=body mass index, WC=waist circumference, SBP=systolic blood pressure, SBP=diastolic blood pressure, FPG=fasting plasma glucose, 2HrPP=2-hour postprandial glucose, HbA1c=glycated hemoglobin, SD=standard deviation, P=level of significance.

However, the women had significantly higher prevalence of generalized obesity than the men (24.5% vs 9.0%, p<0.001). Central obesity prevalence was also higher in the women than men (52.4% vs 21.4%, p<0.001). However, there was no significant difference in the percentage of men and women with poor control of systolic blood pressure, diastolic blood pressure, FPG, 2HrPP, and HbA1c. The percentage of statins and antiplatelets use were also not significantly different among the female and male participants (Table 2).

Table 2 showing gender difference of some clinical and therapeutic variables

	Female	Male	Total	Chi square	P
Htn	31.2%	19.5%	50.7%	4.349	.037
Obesity (BMI)	24.5%	9.0%	33.5%	52.088	<0.001
Central obesity	52.4%	21.4%	73.8%	189.001	<0.001
SBPpc	19.5%	13.1%	32.6%	0.418	0.518
DBPpc	17.8%	10.2%	28.0%	4.349	0.037
FPGpc	30.6%	20.8%	51.4%	1.146	0.564
2HrPPpc	36.4%	25.5%	61.9%	0.808	0.668
HbA1cpc	27.3%	21.2%	48.5%	1.188	0.756
Statin	13.4%	8.9%	22.3%	3.134	0.053
Antiplatelet	5.1%	3.3%	8.4%	2.976	0.087

Htn=known hypertensive, BMI=body mass index, SBPpc=poor systolic blood pressure control, DBPpc=poor diastolic blood pressure control, FPGpc=poor fasting plasma glucose control, 2HrPPpc=poor 2-hour postprandial plasma

glucose control, HbA1cpc=poor glycated hemoglobin control, P=level of significance.

The percentage of participants screened positive for diabetic peripheral neuropathy based on the different methods include: positive neuropathic symptoms (64%), negative neuropathic symptoms (50.7%), 10g monofilament testing (31.9%), vibration sensation by tuning fork (21.8%), and ankle reflex impairment (13.1%). A total of 80.1% of the participants were screened positive for diabetic peripheral neuropathy when all the methods were used. (Table 3)

Table 3 showing diagnostic yields of some methods of screening for diabetic peripheral neuropathy

	Frequency	Percent
PosNeuro	667	64.0
NegNeuro	528	50.7
Monofilament	332	31.9
Vibration	227	21.8
Reflexes	136	13.1
Combined	835	80.1

PosNeuro=positive neuropathic symptoms, NegNeuro=negative neuropathic symptoms

Following a gender-based analysis, there was a significantly higher percentage of females who had positive neuropathic symptoms compared to men (39.0% vs 24.9%, p=0.044). There was however, no significant gender difference in the percentage of peripheral neuropathy diagnosed by other methods of assessing peripheral neuropathy. There was also no significant gender difference in the total percentage of participants who had peripheral neuropathy (female vs male: 47.3% vs 32.6%, p=0.497) [Table 4].

Table 4 showing gender distribution of the diagnostic yields of some methods of screening for diabetic peripheral neuropathy

Methods	Female	Male	Total	P
Monofilament	17.1%	13.9%	31.1%	0.215
Vibration	12.1%	9.7%	21.8%	0.393

Reflexes	7.1%	6.0%	13.1%	0.570
PosNeuro	39.0%	24.9%	64.0%	0.044
NegNeuro	29.9%	20.5%	50.7%	0.321
Combined	47.3%	32.6%	80.1%	0.497

PosNeuro=positive neuropathic symptoms, NegNeuro=negative neuropathic symptoms

DISCUSSION

The main aim of this study was to compare the diagnostic yields of some methods of assessing diabetic peripheral neuropathy in North Central Nigeria. The presence of positive neuropathic symptoms as a method of diagnosing peripheral neuropathy had the highest diagnostic yield of 64%, followed by negative neuropathic symptoms 50.7%, and 10g monofilament testing 31.9%. The methods with the least diagnostic yields included vibration sensation using tuning fork 21.8%, and ankle reflex 13.1%. None of the studies in the literature searched had specifically compared these simpler methods of assessing peripheral neuropathy. However, some studies had compared other methods including more sophisticated methods of diagnosing peripheral neuropathy.

In contradiction to our finding, Jayaprakash et al. [11] reported that ankle reflex was more sensitive than vibration and monofilament tests in the diagnosis of peripheral neuropathy among some Indians with diabetes mellitus. This may be due to practitioner's differences in the techniques of applying these tests, subjectivity in the responses by the participants, thickness or ruggedness of stratum corneum of skin, or even possible racial differences in the threshold for detecting abnormal sensation.

The 10g monofilament testing detected 31.9% out of a total of 80.1% of the participants found to have peripheral neuropathy which portrays a relatively limited diagnostic yield. This may be due to its inability to detect small fiber mediated painful neuropathy and diagnose early neuropathy. Similar reasons have been adduced by Azmi et al.,[1] Malik et al.,[9] and Wang et al.,[10] for the limited sensitivity of Semmes-Weinstein 10g monofilament in diagnosing peripheral neuropathy. However, several studies had reported on the usefulness of the 10g monofilament in the screening for peripheral neuropathy. [3-6,8] Widasmara et al. [7] even reported a strong positive correlation between some biomarkers of nerve damage and SWM scores. Though, the 1g monofilament has been reported by some studies as a better tool for diagnosing peripheral neuropathy than the 10g monofilament. [8]

It is worthy of note that the combined use of the various modalities led to the best diagnostic yield of 80.1% in this study which is in keeping with the report by Lanting et al. [12] where they recommended the use of more than one method to screen and monitor the progress of peripheral neuropathy in persons with diabetes mellitus. Further more, there was no significant gender difference in the diagnostic yields of all the methods used to diagnose peripheral neuropathy except for positive neuropathic symptoms where the females had significantly higher number of participants who complained of positive neuropathic symptoms than the male participants. This may be explained by the greater tendency for women to visit hospitals when they feel pain or discomfort than men. Additionally, men tend to have higher threshold for complaining of pain or discomfort than women.

However, there was no significant gender difference in the diagnostic yields of the combined methods of diagnosing peripheral neuropathy. This may be due to lack of significant gender difference in glycemic

control (fasting plasma glucose and 2-hour postprandial glucose), use of statin and platelets. The higher prevalence of obesity among the women may have been neutralized by the longer duration of diabetes mellitus among the men, thereby eroding any significant gender difference in the prevalence of peripheral neuropathy. The limitations of this study include the inability to calculate the sensitivity and specificity of these methods of assessing peripheral neuropathy, as this requires measurement against the gold standard of diagnosing peripheral neuropathy i.e., nerve conduction studies.

CONCLUSION

Positive and negative neuropathic symptoms have higher diagnostic yields for screening for diabetic peripheral neuropathy than 10g monofilament testing, vibration sensation using tuning fork, and ankle reflex examination. Additionally, only positive neuropathic symptoms had significant female gender preponderance. However, it is encouraged to use all available methods to screen for diabetic peripheral neuropathy. This helps to increase the diagnostic yield, and ensure early preventive and therapeutic strategies.

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