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Objective Peripheral Neuropathy and its Predictors in Type 2 Diabetic Subjects with Symptoms of Peripheral Neuropathy in Nnewi, South-Eastern Nigeria

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ABSTRACT

Peripheral neuropathy (PN) is a risk factor for foot disease in type 2 diabetes mellitus (T2DM).This study aims to evaluate the prevalence and predictors of objective PN in T2DM subjects with symptoms of PN. 78 South-Eastern Nigerian T2DM subjects with symptoms of PN were assessed for objective PN using tuning fork and two biothesiometers. Prevalence of objective PN with tuning fork, analog and digital Biothesiometers were 66.7%, 38.5% and 38.5% respectively. Hypertension and triglyceride levels were significant predictors of PN using Biothesiometry.

Keywords: *Objective, Peripheral Neuropathy, Predictors, Type 2 Diabetes Mellitus, Biothesiometer*

INTRODUCTION

Peripheral neuropathy (PN) is a major complication of DM which contributes immensely to the development of foot disease [1]. This is associated with increasing lower extremity amputation rates and mortality in DM patients [2].

Although symptoms of PN are very common in T2DM patients, there is paucity of data on PN diagnosed using different objective methods in T2DM patients with clinical symptoms of PN in South-East Nigeria. Data are even more scarce on the predictors of objective PN in DM subjects with symptoms of PN. The objective of this study is to evaluate the prevalence and predictors of objective PN in T2DM subjects with symptoms of PN.

MATERIALS AND METHODS

This is a cross-sectional study involving T2DM subjects attending the Diabetes Clinic of Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, South-Eastern Nigeria. Study subjects were recruited consecutively over a three month period and those with DM foot disease were excluded from the study. Biodata, duration of DM, medications used, and presence of symptoms suggestive of PN were obtained from study subjects. Weight (in kilogrammes) was measured using a weighing balance with their footwear off and their height (in metres) measured with a stadiometer. The Body Mass Index (BMI) in kilogrammes per square metre (kg/m^2) was determined by dividing weight by the square of the height. Using a non-stretch tape, waist circumference (WC) was measured midway between the lower ribs and the highest point of the iliac crest while hip circumference (HC) was measured at the widest diameter of the hip (in centimetres). The waist-to-hip ratio (WHR) was taken as the ratio of WC to HC. Blood pressure measurement was done on the right arm using an Accosson Mercury Sphygmomanometer with the patient in a sitting position.

Objective peripheral neuropathy was diagnosed using three methods- 128 Hz vibration tuning fork, and two Biothesiometers (a digital type and an analog type).

The Diabetic Neuropathy Symptom Score (DNS) was used to identify subjects with neuropathic symptoms as a DNS $\geq$ 1 confirmed presence of neuropathic symptoms [3]. Table 1 shows the Diabetic Neuropathy Symptom Score.

Table1. *The Diabetic Neuropathy Symptom Score (DNS)*

DNS items	Score
Unsteadiness in walking	0=absent, 1=present
Numbness	0=absent, 1=present
Burning, aching pain or tenderness in legs or feet	0=absent, 1=present
Prickling sensations	0=absent, 1=present

DNS $\geq$ 1 defines PN

The Biothesiometer objectively measures vibration sensation and determines the vibration perception threshold (VPT) and each of the two types were used on study subjects. With the subject lying in a supine position on an examination couch, testing was commenced by applying the vibrator of each Biothesiometer to the pulp of the big toe of each foot. The vibrator was held in such a way that the weight of the vibrator furnished a standard pressure on the vibrator button with the probe balanced vertically on the pulp of the great toe. The vibrator was held steady and the subject instructed to concentrate all attention at the test site and to verbally report the first appearance of the sensation of vibration by saying "yes". The amplitude of the vibrator button was set as low as possible at the start of testing and increased until the patient perceived vibration. The voltage on the Biothesiometer display at that instant was recorded as Threshold 1 (TH_1). This threshold is usually higher than the actual threshold due to the reaction time of the patient. Two further threshold readings (TH_2 and TH_3) were obtained at the test site and the mean of the last two readings used to determine the VPT for each foot.

Records of fasting plasma glucose (FPG) done on the day of assessment and records of the following investigations done within the preceding three months-glycated haemoglobin (HbA1c), and fasting lipid profile [(total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C)], were obtained from the subjects' clinic folders.

Global obesity was defined as BMI greater than or equal to 30 kg/m^2 while Overweight was defined as BMI of greater than 25 kg/m^2 in study subjects [4]. Abdominal obesity was defined as WC$\geq$94cm for males and $\geq$80cm for females [5]; or WHR $\geq$0.90 for males and $\geq$0.85 for females [4]. Hypertension was defined as BP $\geq$ 140/90 mmHg or use of anti-hypertensive medications [6]. Poor glycaemic control was defined as HbA1c $\geq$ 6.5% [7]. Peripheral neuropathy was defined as vibration loss to 128 Hz tuning fork; or Vibration Perception Threshold (VPT) >25 Volts [8] with any of the digital or analog biothesiometers.

Data collection was done using researcher-administered study proforma and analyzed using SPSS version 20. Continuous variables were presented as Mean $\pm$ SD while categorical variables were presented as proportions (in percent). Continuous variables were compared using student t-test. Binary logistic regression model was used to determine predictors of peripheral neuropathy. $p<0.05$ defined statistical significance.

RESULTS

106 subjects [44 (41.5%) males and 62 (58.5%) females] were recruited for the study. 78 (73.6%) of these subjects [26 males (24.5%) and 52 females (49.1%)] had PN symptoms and their data analyzed (N=78/106). Table 2 shows the clinical characteristics of subjects with neuropathic symptoms. There was no significant gender difference in all the clinical variables evaluated.

Table2. *Clinical Characteristics of Subjects with Neuropathic Symptoms*

	Mean ± SD			
Variable	**Males (n=26)**	**Females (n=52)**	**t**	**p-value**
Age (years)	62.05 ± 12.53	63.90 ± 10.88	1.23	0.73
DM duration (months)	164.36 ± 36.84	121.74 ± 45.30	1.63	0.32
SBP (mmHg)	136.23 ± 17.59	142.67 ± 25.00	-0.69	0.34
DBP (mmHg)	85.91 ± 12.82	85.33 ± 15.12	0.16	0.88
WC (cm)	100.47 ± 9.30	98.05 ± 10.62	-1.00	0.32
HC (cm)	103.27 ± 9.13	104.33 ± 8.72	-1.26	0.25
WHR	0.95 ± 0.07	0.96 ± 0.06	0.11	0.92
BMI (kg/m^2)	28.29 ± 4.71	31.12 ± 5.67	0.34	0.43
HbA1c (%)	9.09 ± 2.79	7.73 ± 2.41	0.45	0.52
FPG (mmol/L)	7.65 ± 3.19	6.59 ± 2.34	-1.83	0.07
TC (mmol/L)	4.59 ± 0.95	4.94 ± 0.94	-1.91	0.64
TG (mmol/L)	1.13 ± 0.51	1.24 ± 0.48	-0.84	0.41
LDL-C (mmol/L)	2.81 ± 0.91	3.10 ± 1.00	-1.58	0.12
HDL-C (mmol/L)	1.19 ± 0.37	1.30 ± 0.31	-1.57	0.12
Right VPT (Analog)	22.27 ± 8.35	20.73 ± 7.20	0.51	0.65
Left VPT (Analog)	21.00 ± 8.02	21.07 ± 7.62	-0.03	0.98
Right VPT (Digital)	20.77 ± 7.50	21.10 ± 6.64	-0.34	0.73
Left VPT (Digital)	19.14 ± 7.01	21.30 ± 8.53	-0.07	0.85

BMI, Body Mass Index; DBP, Diastolic Blood Pressure; DM, Diabetes Mellitus; FPG, Fasting Plasma Glucose; HC, Hip Circumference; HDL-C, High Density Lipoprotein Cholesterol; LDL-C, Low Density Lipoprotein-Cholesterol; TC, Total Cholesterol; TG, Triglycerides; VPT, Vibration Perception Threshold; WC, Waist Circumference; WHR, Waist-to-Hip Ratio

The PN prevalence with tuning fork, analog and digital biothesiometers were 66.7%, 38.5% and 38.5% respectively. Table 3 shows univariate logistic regression analysis of PN in T2DM subjects with symptoms of PN. There was no association between PN diagnosed with tuning fork and clinical variables. Age, duration of DM, hypertension and triglycerides were significant predictors of PN diagnosed with both biothesiometers.

Table3. *Univariate logistic regression analysis of PN in T2DM subjects with neuropathic symptoms*

	Tuning Fork		Analog Biothesiometer		Digital Biothesiometer	
Variable	**OR**	**p-value**	**OR**	**p-value**	**OR**	**p-value**
Age>65years	1.23	0.54	5.43	*0.03	4.72	*0.02
Male Sex	1.00	0.32	1.00	0.57	1.01	0.52
Duration of DM	1.00	0.17	10.24	*<0.01	22.11	*<0.01
DM drug compliance	0.97	0.53	0.98	0.58	0.98	0.58
Hypertension	1.00	0.52	9.23	*0.03	5.34	*0.02
Global obesity	0.93	0.44	1.00	0.15	0.94	0.37
Abdominal Obesity using WHR	1.03	0.32	0.85	0.38	1.01	0.44
Abdominal Obesity using WC	0.88	0.64	0.98	0.37	0.98	0.67
TG	1.00	0.63	7.84	0.02	11.24	<0.01
Use of medications for neuropathic pains	1.01	0.74	1.01	0.88	0.91	0.19

*DM, Diabetes Mellitus; OR, Odd Ratio; TG, Triglyceride; WC, Waist Circumference; WHR, Waist-to-Hip Ratio; *Statistical Significance*

Table 4 shows multivariate logistic regression analysis of PN in symptomatic patients after replacement of significant predictors in the logistic regression model. Hypertension and triglycerides remained significant predictors of PN diagnosed with both biothesiometer types.

Table4. *Multivariate logistic regression analysis of PN in T2DM subjects*

	Analog Biothesiometer		Digital Biothesiometer	
Variable	**OR**	**p-value**	**OR**	**p-value**
Age>65years	1.03	0.30	0.73	*0.59
Duration of DM	1.01	0.43	1.00	0.71
Hypertension	8.27	*0.01	5.34	*0.01
TG	12.31	*<0.01	11.06	*<0.01

*DM, Diabetes Mellitus; TG, Triglyceride; *Statistical Significance*

DISCUSSION

This study showed that PN diagnosed using three objective methods- tuning fork, analog and digital biothesiometers- is common in T2DM subjects with symptoms suggestive of PN in South-East Nigeria. It showed that presence of neuropathic symptoms may indeed indicate presence of objective PN. These findings are similar to reports from previous studies[9-11].

Literature reports show that evaluating for Diabetic Peripheral Neuropathy (DPN) using symptom scores may be highly subjective in its ability to indicate presence of objective PN. Many patients who are diagnosed to have PN using "symptoms" assessment, may not have PN when assessed using more objective methods and instruments.

Our study involved 78 (73.6%) diabetic subjects out of a pool of 106 study population with symptomatic PN diagnosed using DNS scoring method. Further evaluation of this population with symptoms of PN with more objective diagnostic tools showed that tuning fork detected PN in 66.7% and Biothesiometry in 38.5%. The high prevalence of PN detected by tuning fork assessment reflects its relative subjectivity compared to the more objective, more sensitive and more specific methodology of Biothesiometry[8].

The objectivity of the symptoms of DPN in Nigerian T2DM subjects assessed using a symptoms score (the United Kingdom Screening Test, UKST) and Biothesiometer was reported by Oguejiofor et al in 2009[10]. The study, similar to the present study, showed that using symptoms scores to diagnose PN was very subjective. Among their study subjects that had symptomatic DPN using the UKST (61.7%), 79.7% had PN diagnosed using Biothesiometer indicating that most symptoms of PN were really objective. Both studies disagreed about duration of DM being a predictor of PN diagnosed using Biothesiometer in symptomatic subjects. Our study on univariate logistic regression analysis, similar to the report of Oguejiofor et al, found that duration of DM, Age, Hypertension and Triglycerides were significant predictors of PN. However, on further testing with multivariate logistic regression analysis, only hypertension and triglycerides remained significant predictors of PN diagnosed with both Biothesiometry models.

Our study additionally showed that age greater than 65 years was not a significant predictor of PN diagnosed by Biothesiometry, contrary to the finding of Ogbera et al[11] in Lagos. They reported that age greater than 60 years was a significant predictor of PN diagnosed with Biothesiometer in T2DM subjects. The disagreements in duration of DM and age greater than 60 years being significant predictors of PN between the ourt study, Oguejiofor et al[10] and Ogbera et al[11] may have resulted from different diagnostic VPTs used in the various studies. The former used a diagnostic VPT of 20 volts and the latter an even lower value (15 volts) to diagnose PN by Biothesiometry. We used a VPT of 25 volts which has been found to have a higher sensitivity and specificity in diagnosing PN[8].

CONCLUSION

Objective peripheral neuropathy diagnosed using tuning fork and biothesiometry is prevalent in South-Eastern Nigerian T2DM subjects with symptoms of DPN and presence of symptoms of PN indeed indicates presence of PN objectively. Tuning fork detected PN much more than Biothesiometry, reflecting its apparent subjectivity in diagnosing PN in Nigerian diabetic subjects with symptoms of PN compared to Biothesiometry. Biothesiometry with VPT of $\geq$ 25V is more sensitive and more specific in diagnosing PN. Hypertension and triglyceride levels were the only significant predictors of peripheral neuropathy.

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