Diabetic peripheral neuropathy and its risk factors in a Nigerian population with type 2 diabetes mellitus

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Abstract

Diabetic peripheral neuropathy (DPN) is a common complication of diabetes, which increases diabetes-related morbidity and mortality. Vibration perception threshold is considered a gold standard for diagnosis of DPN. However, the data are sparse using vibration perception threshold (VPT) to assess the frequency of diabetic peripheral neuropathy in Nigeria. Hence, this cross-sectional study investigated the prevalence and associated risk factors of DPN in patients with type 2 diabetes (T2DM) in Nigeria. We used a vibrometer to assess VPT in both feet of 250 adults with T2DM. A vibration threshold greater than 15 Volts in one or both feet was used to diagnose neuropathy. All participants underwent a standardised questionnaire about diabetes duration, height and weight and history of hypertension. Blood pressure was measured and fasting glucose, glycosylated hemoglobin, and fasting lipids were determined. We examined the independent association between DPN and these factors. There were 82 (33%) males and 168 (67%) females. The mean age was 48 + 12 years and mean duration of diabetes mellitus was 14 + 12 years. Overall 86.8% (n= 217) of the patients with T2DM were classified as having neuropathy; while 40 (16%), 37 (15%) and 140 (56%) had mild, moderate and severe neuropathy respectively. Neuropathy was significantly associated with age, diabetes duration, systolic blood pressure and diastolic blood pressure. We conclude that there is a high prevalence of peripheral neuropathy in Nigerians already diagnosed with T2DM who are on oral antidiabetic agents, and those patients were far more likely to have complications or co-morbidities. The proper management of DPN deserves attention from clinicians to ensure better management of diabetes in Nigeria.

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Introduction

Diabetes mellitus is a common metabolic disorder, and is known for its peripheral complications such as neuropathy and retinopathy. It has become one of the largest global health-care problem of the 21st century. Diabetic polyneuropathy (DPN) is the most prevalent complication of diabetes mellitus, affecting over 50% of individuals diagnosed with type 1 or type 2 DM (T2DM). 1 DPN affects up to 50% of patients with T2DM in their lifetimes, resulting in a considerable reduction of quality of life. 2 Enhanced glucose control can prevent or retarad DPN intype 1 diabetes (T1DM), though advantages are less clear in T2DM, and factors other than glycaemia may be important.3- 5 T2DM affects more than 400 million people around the world. In 2040, there will be more than 640 million people with diabetes worldwide. 6 The prevalence of T2DM is expected to double within the next 20 years, due to the increase in age, obesity and the number of ethnic groups of high risk in the population, 7 with significant increases in cardiovascular disease, 8 end-stage renal disease, 9 retinopathy and neuropathy. DPN is the most common diabetic complication. 10-14 and is a leading cause of disability due to foot ulceration and amputation, gait disturbance and fall-related injury.

Approximately one-fifth to a third of patients with DPN suffer from neuropathic pain, 13-16 and it significantly lowers quality of life and substantially increases health costs associated with diabetes. 2 Despite the different pathophysiology underlying type 1 and type 2 diabetes, there has been a longstanding assumption that the mechanism leading to DPN is shared. T2DM has a slightly lower lifetime incidence of neuropathy compared with T1DM. 17 Whereas treating hyperglycemia in type 1 DM can significantly reduce the incidence of neuropathy by up to 60% to 70%, 18, 19 glucose control in T2DM has only a marginal 5% to 7% reduction in the development of neuropathy. 20, 21 Also, over 40% of patients with diabetes develop neuropathy despite good glucose control, suggesting that other factors are driving nerve injury. 22

T2DM is inseparably linked to the obesity epidemic; about 90% of diabetic risk is attributably linked to excess weight. 23 The longstanding notion that DPN occurs after longstanding hyperglycemia has been replaced by the observation that even those with good glycaemic control (HbA1c of less than 5.4%) are at risk. 24 Studies have implicated cardiovascular risk factors, including

Table 1 Characteristics of study population (n = 250)

Variable	Mean ± SD
Age (yr.)	50 ± 12
Sex (M/F)	82(33)/168(67)
Diabetes duration (yrs.)	13 ± 5
Body mass index (Kg/m2)	27.2 ± 2.7
Waist circumference (cm)	89 ± 8
Systolic BP (mmHg)	139 ± 14
Diastolic BP (mmHg)	87 ± 11
Fasting blood glucose (mmol/l)	7.8 ± 1.7
HbA1c (%)	8.1 ± 1.2
Total cholesterol (mmol/l))	4.9 ± 0.7
LDL cholesterol (mmol/l))	2.9 ± 0.6
HDL cholesterol (mmol/l))	1.1 ± 0.2
Triglyceride (mmol/l))	3.1 ± 1.0
Smokers (%)	44 (18%)
Hypertensive (%)	124 (50%)
Hyperlipidemia (%)	79 (32%)
Right foot (volts)	27.78 ± 11.74
Left foot (volts)	28.25 ± 11.58

obesity, 25 hypertriglyceridemia, hypercholesterolemia, hypertension and cigarette smoking, in the pathogenesis of DPN. 26 In a seemingly paradoxical relationship, both poor glucose control and rapid treatment of hyperglycaemia can be associated with an increased risk of neuropathy. The diagnosis of DPN is most often made on clinical grounds with a suggestive clinical history and neurologic examination. Peripheral neuropathy can be demonstrated by a variety of bedside clinical techniques, including the 10 g monofilament to assess sensation on the sole of the feet, tendon hammer for assessment of ankle jerk reflexes, and the assessment of vibration sense using a tuning fork or a vibrometer. Vibration perception threshold (VPT) is considered as a gold standard for the diagnosis of DPN. However, the data are sparse using VPT to assess frequency of DPN in Nigeria. This cross-sectional study investigated the prevalence and clinical characteristics of diabetic peripheral neuropathy using a vibrometer in adults with T2DM treated at hospital in northeast Nigeria.

Methods

The study was approved by the Health Research Ethics Committee of Federal Medical Centre Yola. Each patient provided written informed consent according to institutional guidelines. Two hundred and fifty adult T2DM patients on treatment were recruited from the general outpatient clinics and Endocrinology Diabetes and Metabolic (EDM) clinic of Federal Medical Centre Yola, Nigeria. The study was conducted between November 2017 and January 2018. Inclusion criteria included black Nigerian Africans of 18 years or above with a clinically confirmed diagnosis of T2DM based on the criteria of the American Diabetes Association and receiving any form of treatment for diabetes. We excluded patients with T1DM, gestational diabetes, patients with other causes of peripheral polyneuropathy. In a standardized questionnaire data was recorded on diabetes duration, waist circumference, height and weight and history of hypertension and smoking. All participants had fasting blood glucose, glycated hemoglobin (HbA1c), fasting triglycerides and cholesterol determined. Body Mass Index (BMI) was calculated as weight divided by height square. Blood pressure of the participants was measured at the time of recruitment in the sitting position in the right arm to the nearest 2 mmHg with a mercury sphygmomanometer. Hypertension was defined as an average systolic blood pressure of > 140 mmHg or diastolic blood pressure > 90 mmHg or self-reported use of blood pressure lowering drugs. Hyperlipidaemia was defined as either a cholesterol level >5.2 mmol/l, triglycerides (TG) >3.9 mmol/l, low-density lipoprotein (LDL) cholesterol >3.4 mmol/l, or high-density lipoprotein (HDL) cholesterol <1.04 mmol/l.

A vibrometer (Diabetik Foot Care Pvt Limited, India) was used to determine the vibration perception threshold in both feet for each study participant. The study participants were asked to remove their shoes, socks or stockings and lie in a supine position. Testing was done in an air conditioned room at 22 to 24o C. The participants were supine throughout the testing procedure and could not see the biothesiometer controls. The probe was held at 90o to the skin with constant pressure. A trial run with the biothesiometer was initially conducted at a site (palm) other than the soles of the feet in order to demonstrate to the participant the expected sensation. The methods of limits were applied whereby the voltage was slowly increased from 0 volt at a rate of 1 Volt/sec to each limb consecutively. VPT was the recorded voltage at the moment the participant indicated he or she first felt the vibration. The average of vibration perception and the vibration disappearance threshold was taken as the vibration threshold. A value below 15 volts indicated no neuropathy (normal study), between 16 and 20 volts indicated mild loss of vibration perception, between 21 and 25 Volts indicated moderate loss of vibratory perception and above 25 Volts indicated severe loss of vibratory perception.

We used the software package SPSS for Windows version 14 (SPSS Inc., Chicago, IL, USA) for all statistical analyses. Data are presented as the mean with standard deviation (SD)) and numbers or frequency with percentages. Logistic regression analysis was used to determine the independent predictors of peripheral neuropathy while Pearson's correlation was used to determine the relationship between the various quantitative variables and VPT readings. In these analyses, a value of $p < 0.05$ was considered significant.

Results

There were 82 (4%) males and 168 (68%) females in the study population. Table 1 shows the demographic and metabolic characteristics of the participants of the study. One hundred and ninety-nine (80%) had tertiary

Table 2: Predictors or Determinants of left foot and right foot VPT readings

Variable	Correlation co-efficient (r)	F	p-value
Age vs VPT (left foot)	0.258	17.76	0.000
Age vs VPT (right foot)	0.258	17.69	0.000
Diabetes duration vs VPT (left foot)	0.279	20.90	0.000
Diabetes duration vs VPT (right foot)	0.264	18.62	0.000
Waist circumference vs VPT (left foot)	0.004	0.004	0.95
Waist circumference vs VPT (right foot)	0.047	0.55	0.47
Total cholesterol vs VPT (left foot)	0.001	0.00	0.98
Total cholesterol vs VPT (right foot)	0.007	0.12	0.91
Triglyceride vs VPT (left foot)	0.006	0.008	0.93
Triglyceride vs VPT (right foot)	0.015	0.053	0.82
BMI vs VPT (left foot)	0.010	0.026	0.87
BMI vs VPT (right foot)	0.002	0.001	0.97
SBP vs VPT (left foot)	0.145	5.343	0.022
SBP vs VPT (right foot)	0.154	6.018	0.015
DBP vs VPT (left foot)	0.137	4.743	0.030
DBP vs VPT (right foot)	0.143	5.154	0.024
FBS vs VPT (left foot)	0.009	0.019	0.891
FBS vs VPT (right foot)	0.081	1.656	0.199
HbA1c vs VPT (left foot)	0.039	0.387	0.534
HbA1c vs VPT (right foot)	0.045	0.511	0.475

Note: VPT = vibration perception threshold; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; FBG = fasting blood glucose.

education, while 150 (64%) resided in urban settlement. Peripheral neuropathy was present in 217 (87%) of the study population; 40 (16%) were classified as mild neuropathy, 37(15%) as moderate and 140 (56%) had severe neuropathy. Females had a higher prevalence of DPN than males – (72[33%] and 145[67%] respectively. The age of the patients, diabetes duration, systolic blood pressure and diastolic blood pressure were statistically significant factors in the development of DPN. No statistically significant difference was found between smoking history, body mass index, waist circumference, total cholesterol, triglyceride, glycated hemoglobin and presence of diabetic peripheral neuropathy (Table 2).

Discussion

The findings of this study indicate our population of black Nigerian T2DM patients hitherto on oral antidiabetic drugs had a high prevalence of diabetic peripheral neuropathy. This is in agreement with a previous report from northcentral Nigeria with similar experimental deign. Uwakwe et al 27 reported a prevalence of 75% among 100 adults with T2DM in Jos, Nigeria. However, Ugoya et al 28 also reported a prevalence of 75% among Nigerians with T2DM using the Michigan Neuropathy Screening Instrument which involved the use of tuning fork, Semmes-Weinstein monofilament as well as Achilles tendon reflex. Phulpoto and colleagues 29 reported a prevalence of 35% using VPT among 1044 patients with both T1DM and T2DM in Pakistan. However, a VPT recording greater than 25 Volts was used by these investigators. 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. 30 This has been further supported by a large epidemiological prospective study reporting a VPT of greater than 25 Volts had a sensitivity of 83%, specificity of 63%, positive likelihood ratio of 2.2 (95% CI, 1.8-2.5), a negative likelihood ratio of 0.27 (95% CI, 0.14-0.48) for predicting a foot ulceration over 4 years. Jayaprakash and colleagues 32 reported a prevalence of peripheral neuropathy of 35% with VPT among 1044 patients with diabetes in India. Albeit, these authors used a VPT greater or equal to 25 Volts as cut-off for the diagnosis of neuropathy. Bansal et al 33 reported a prevalence of 29% among 1637 with known diabetes and 369 newly diagnosed diabetes mellitus. A higher prevalence of 34% was observed in known diabetes compared with 9% newly diagnosed diabetics. They reported a prevalence of 8%, 15% and 7% as mild, moderate and severe neuropathies respectively.

The estimates of DPN prevalence vary widely from 10% to 78% in different populations. 34, 35 This could be attributed to different types of diabetes, i.e., type 1 and 2, genetic predisposition, age at onset of diabetes, methodological differences, sample selection and different diagnostic criteria used. The present study used VPT greater than 15 Volts as standard for diagnosing neuropathy in accordance with the guidelines for the vibrometer we used (Diabetic Foot Care India, PVT). Most of our study population (n = 140) had severe neuropathy, which is similar to the findings by Bansal and colleagues 33 where most of their study subjects had moderate and severe neuropathy. This group of patients are at a greater risk of foot ulcers and amputation in future.

This present study found a significant positive linear trend between age of patient, diabetes duration, systolic blood pressure and diastolic blood pressure and the odds of developing DPN. Bansal and colleagues 33 reported increasing age, longer duration of diabetes, dyslipidaemia and presence of other microvascular complications to be significantly associated with DPN. Neuropathy was evidently related to diabetes duration and HbA1c from previous studies that showed that chronic exposure to hyperglycaemia is a key factor in the development of neuropathy. 33, 41 In our T2DM patient population

determinants of peripheral neuropathy differed with regards to glycated haemoglobin, dyslipidaemia, body mass index and waist circumference. Many studies have shown age as risk factor 34, 35, 37, 39, 40, 42-44 whereas few studies have shown no association. 45 Sex-specific predispositions to DPN has been observed with female preponderance in a study by Katulanda et al, 46 with males being at higher risk in the Diabetes Control and Complications Trial. 47

Our data revealed that a huge percentage of black Nigerians with T2DM had severe neuropathy, and this is alarming in view of the colossal proportion of limb amputation among Nigerians with poorly controlled diabetes with complications. Overall, our patients had higher than normal fasting blood glucose and glycated haemoglobin (Table 1) in spite of being on oral antidiabetic drugs. The relatively large sample size, multiethnic composition of the cohort and use of a non-invasive, simple and validated instrument to assess DPN are among the strengths of our study. This hospital based study to assess the burden of DPN in an ethnically diverse cohort of black Nigerians with T2DM is first in northeast Nigeria.

The alarmingly high rates of DPN, coupled with poor glycaemic control, systolic and diastolic blood pressure, in this cohort reinforces the need for clinicians improving care for T2DM patients, and to be vigilant in screening for DPN, as symptoms may not be present. Our findings have several clinical implications for DPN prevention in patients with T2DM, and suggests that clinicians should pursue not only achieving the glycaemic target but also stability of glycaemic control.

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Author declaration

The authors confirm that they have no competing interests to declare; that no animals were used in the research, and that informed consent was obtained from patients (documentary evidence on this provided to the publisher).

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