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Original Research Article

Vascular Abnormalities in Stable Type 2 Diabetes Patients Attending a Teaching Hospital in South-Eastern Nigeria: Trends of the Burden and Associations with Conventional Cardiovascular Risk Factors

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Abstract: Vascular abnormalities are very prevalent in type 2 diabetes mellitus (T2DM) and are the major causes of morbidity and mortality in this setting. This study aimed at determining the prevalence and associated risk factors for diabetic peripheral neuropathy (DPN) and peripheral artery disease (PAD) in T2DM subjects at NAUTH, Nigeria. This was a cross-sectional study that evaluated 142 stable T2DM out-patients. Anthropometric and blood pressure measurements were done. Glycated haemoglobin and fasting lipid profile were assayed. Biothesiometry of the feet and Doppler ultrasonography of the brachial and pedal arteries were done for diagnosis of vascular complications. Data was analysed using SPSS version 25. Results of categorical variables were presented in tables as frequencies and percentages. The mean values and standard deviation for the continuous variables were calculated. Chi-square test was used to determine the association between the vascular abnormalities and the categorical variables. The level of significance was set at $p < 0.05$. The prevalence rate of DPN and PAD was 50.7% and 18.3%, respectively. DPN showed significant association with age ($X^2 = 14.059$; $p = 0.001$), sex ($X^2 = 6.630$; $p = 0.010$), education level ($X^2 = 12.286$; $p = 0.006$), duration of DM ($X^2 = 5.246$; $p = 0.022$), global obesity ($X^2 = 5.494$; $p = 0.019$), DM treatment ($X^2 = 11.821$; $p = 0.003$), dyslipidaemia ($X^2 = 9.767$; $p = 0.002$), lipid-lowering drugs use ($X^2 = 4.036$; $p = 0.045$) and PAD ($X^2 = 8.158$; $p = 0.004$). Similarly, PAD showed significant association with systolic hypertension ($X^2 = 10.942$; $p = 0.001$), diastolic hypertension ($X^2 = 24.026$; $p = 0.000$), DM treatment ($X^2 = 7.262$; $p = 0.026$) and DPN ($X^2 = 8.753$; $p = 0.003$). The prevalence of DPN and PAD from the study was high and depicted a high burden of vascular abnormalities in T2DM subjects.

Keywords: Associations, Artery, Neuropathy, Peripheral Vascular Disease, Type 2 Diabetes, Southeast.

INTRODUCTION

Diabetes mellitus (DM) is defined as a group of metabolic disorders of multiple aetiologies, characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both [1]. Type 2 diabetes mellitus (T2DM) is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, increased glucose production and constitute up to about 90% of the cases of diabetes mellitus [1].

Current statistics show that 9.3% of adults aged between 20 and 79 years all around the world are living with diabetes [2]. Nigeria as a country has her own big share of the growing global burden of diabetes. A systematic review and meta-analysis done in 2018 placed the overall pooled prevalence of DM in Nigeria at 5.77% [3].

Type 2 DM is viewed as a chronic inflammatory disease resulting in altered vascular dynamics and vascular dysfunction in both the micro and macro vessels [4]. The systemic inflammatory state in T2DM causes haemodynamic disruption with alteration of vascular

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thrombus formation and an increase in the risk for atherosclerosis development [5]. The predisposing molecular cascades and cellular mechanisms for diabetic vasculopathy include: inappropriate activation of the rennin-angiotensin-aldosterone system, mitochondrial dysfunction, excessive oxidative stress, inflammation, dyslipidaemia and thrombosis [6].

The micro-vascular complications of DM include the diabetic peripheral neuropathy (DPN), diabetic retinopathy (DR) and diabetic nephropathy (DN), while the macro-vascular abnormalities include peripheral artery disease (PAD), coronary artery disease (CAD) and cerebrovascular diseases (stroke) [6].

Ankle brachial pressure index (ABPI) and vibration perception threshold (VPT), could be considered as surrogate markers for macrovascular and microvascular complications in type 2 diabetes mellitus [7, 8]. Peripheral artery disease (PAD) denotes a complete or partial occlusion of one or more of the non-cardiac, non-intracranial, peripheral arteries of the upper and lower limbs, which may lead to reduced blood flow or tissue loss [9]. Several investigations play important roles in the diagnosis of PAD and these include: contrast angiography, which is widely regarded as the gold standard, but is limited by its inability to image the vessel walls or the dynamics of blood flow in the lumen, the simple noninvasive tests with an accuracy close to that of angiography; like Color duplex sonography and additionally, the inexpensive and bed side procedure; the ABPI that is suited for screening for and diagnosing PAD in the primary care setting [10, 11]. Studies have found that ABPI is a reliable surrogate to Color Doppler Ultrasonogram for the effective screening for and the diagnosis of PAD, in places where Duplex Ultrasonography is unavailable [12, 13]. The ABPI demonstrated a good reliability for diagnosis of PAD which is a macrovascular complication prevalent in T2DM. The sensitivity of ABPI improves with increasing severity of arterial stenosis in the lower limbs, reaching 100% in severe cases [12]. PAD is usually viewed as a manifestation of macrovascular disease, but recent studies have shown the potential involvement of microvascular disease in its progression [14].

Diabetic peripheral neuropathy (DPN) is defined as presence of symptoms and, or signs of peripheral nerve dysfunction in subjects with DM, after exclusion of other causes [15]. It is a common complication of Type 2 DM that affects both the somatic and autonomic nerves and equally has a complex pathophysiology [16]. Chronic hyperglycaemia results in metabolic disruptions in the peripheral nerve system, including altered protein kinase C activity, and increased polyol pathway activity in neurons and Schwann cells that play key roles in the development and progression of diabetic peripheral neuropathy [16].

Diabetic peripheral neuropathy can be assessed using several symptoms scores and measurements that include the Diabetic neuropathy symptom score (DNS), Nerve conduction studies (NCS) and Vibration perception threshold (VPT) [17, 18]. Nerve conduction studies is considered the gold standard for the diagnosis of DPN, while VPT is its practical, simple, reliable and inexpensive surrogate which also doubles as a quick bed side procedure and hence is suited for use in resource poor and rural settings typical of the sub-Saharan Africa [17, 18]. High VPT values are associated with DPN symptoms and predictive of foot abnormalities such as foot ulcers or of foot at the risk of ulceration or amputation [19].

The prevalence of DPN was 40.3% and 42.2% among T1DM and T2DM subjects, respectively [15]. They are both independent risk factors for foot ulcer and the resultant amputation. About 25% to 90% of lower limb amputations are associated with diabetes and the risk is attributable to a combination of PN, PAD and infection caused by diabetes [20]. The prevalence rate of peripheral artery disease (PAD) in the South-eastern Nigeria was 59.5% and 31.1%, respectively [21, 22]. The prevalence rate of PAD in Northern Nigeria was 38.5%, while that in Western Nigeria was 40.0% [23, 24]. A systematic review and meta-analysis found that the prevalence rate of PAD in sub-Saharan Africa was 32.97% [25]. The significant predictors of PAD were duration of DM, abdominal obesity, hypertension, triglyceride (TG) and high density lipoprotein cholesterol (HDL-C) [21]. In Northern Nigeria PAD was associated with female sex, age greater than 50 years, body mass index (BMI) $\geq$ 25Kg/m^2 and low HDL-C levels [23]. In Western Nigeria, older age > 60 years and poor glycaemic control were potential predictors of neuropathy [24].

The prevalence rate of DPN in Nigeria is dependent on the modality for the diagnosis. The overall prevalence rate of DPN in Nigeria was 31.2% – 97.5%, while the modality-dependent prevalence rates were 37% - 97.5% by biothesiometery, 41.7% - 75% by Michigan Neuropathy Screening Instrument, 31.2% - 43.3% by United Kingdom screening test and 43.3% - 69.9% by diabetic neuropathy examination score [26]. The associated factors were diabetes duration and control, the age of the patients, presence of hypertension, dyslipidaemia and other microvascular complications (diabetic retinopathy and nephropathy) [26].

The prevalence of DPN in T2DM subjects in Southeastern Nigeria was 66.7% with tuning fork and 38.5% with biothesiometry [27]. Significant predictors of DPN using biothesiometry were hypertension and triglyceride levels [27]. The prevalence rate of DPN in T2DM subjects without neuropathic symptoms in Southeastern Nigeria was 71.5% with tuning fork and 14.8% with biothesiometry, respectively [28]. The prevalence rate of DPN diagnosed based on a

combination of tuning fork, 10 G Semmes-Weinstein monofilament and presence of symptoms, in Western Nigeria was 82.0% [29]. In Northern Nigeria, the prevalence rate of DPN 39.7% using biothesiometry [30].

The burden of vascular abnormalities in T2DM subjects in Nigeria, typified by high prevalence rates of PAD and DPN is high and is still underappreciated and underreported by both the health care professionals and patients alike. There is still a paucity of published data on the macrovascular and microvascular complications of diabetes among the people living with T2DM in the sub-Saharan Africa. This study evaluated the prevalence and associated risk factors of macrovascular and microvascular complications, typified by DPN and PAD, respectively in persons living with T2DM in NAUTH, Nnewi in South-eastern Nigeria.

MATERIALS AND METHODS

This study was a cross-sectional study that was carried out at the diabetes clinic of the Medical Out-patient Department of Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi in Anambra State, Nigeria. A total of 142 consenting T2DM subjects of the age of 18 years and above, recruited from the diabetes clinic had complete results and were evaluated. The study was carried out from June to December, 2022. Ethical clearance for the study was obtained from the Research Ethics Committee of the Nnamdi Azikiwe University Teaching Hospital, Nnewi before the commencement of the study with the ethical code: NAUTH/CS/66/VOL.15/VER.3/077/2022/038.

All the T2DM subjects aged 18 years and above, who gave their consent to participate in the study and had none of the exclusion criteria, were included in the study. The exclusion criteria included age of less than 18 years, type 1 DM, gestational diabetes mellitus (GDM) or very sick or unstable patients. Subjects' recruitment for the study was by a simple random sampling method. During each clinic consultation all the subjects that qualified for the study were made to pick a card randomly from a pool of cards written "Yes" and "No", that were folded and put in a pot. All the subjects that picked "Yes" were Recruited consecutively into the study. The study was carried out in two stages and the researcher interacted with the subjects on two separate clinic days.

At the first meeting, informed consent was obtained, relevant medical history was taken, anthropometric and blood pressure measurements were done. Then, doppler ultrasonogram and biothesiometry of both lower limbs were done to determine ankle brachial pressure index (ABPI) and vibration perception threshold (VPT), respectively.

The subjects were then given another clinic appointment that was convenient for them and instructed to come between 8 – 9 a.m and to observe a 10 – 12 hours over night fast, prior to the scheduled clinic visit which was for blood sample collection.

Laboratory Procedure

A total of 5ml of venous blood was collected from each subject during the second meeting; 1 ml of blood was for glycated haemoglobin (HbA1c) assay and was stored in ethylenediaminetetraacetic acid (EDTA) bottle. The remaining 4 ml of blood was for fasting lipid profile assay and was stored in plain bottle, until analysed. HbA_{1C} was measured using the boronate affinity chromatography method using the automated CLOVER A1c Analyzer (Infopia, Korea) and CLOVER A1c Self-Test Cartridge [31].

High density lipoprotein (HDL-C) was obtained by a precipitation technique [32].

Total cholesterol level was determined using the kit employing the enzymatic and the 4-hydroxybenzoate/4-aminophenazone systems (BioSystems) [33].

Triglyceride level was determined using a kit employing enzymatic hydrolysis of triglyceride with lipases (Randox) [34].

Low density lipoprotein cholesterol (LDL-C) was measured using a kit employing a precipitation technique (MyBioSource – MBS023682 kit. San Diego, California) [35].

Clinical Procedure

Doppler ultrasonography assessment of the brachial, dorsalis pedis and posterior tibial arteries was done using EDAN SONTRAX Ultrasonic Pocket Doppler version 1.2 (CE 0123) with 8.0 MHz probe and an Accoson mercury Sphygmomanometer [36, 37]. Ankle brachial pressure index (ABPI) was calculated using the formular: ABPI for a leg = Higher pressure obtained from the ankle vessel in that leg / Higher systolic brachial pressure of the arms [38].

Peripheral artery disease (PAD) was taken as ABPI $\leq$0.9 [39].

The Biothesiometer objectively measures vibration perception threshold (VPT) and this was used for determining the presence of diabetic peripheral neuropathy (DPN) in this study. With the patient lying supine in a couch, testing was commenced by applying the vibrator of the Biothesiometer to the pulp of the big toe of each foot. The vibrator was steadily held, such that, its weight delivered a standard pressure on the vibrator button with the probe balanced vertically on the pulp of the great toe. The subject was instructed to concentrate fully on the procedure and to verbally report the first feeling of the vibration [27, 28]. The amplitude of the vibrator button was set as low as possible at the start of

the testing and steadily increased until the subject perceived the vibration. The voltage that the Biothesiometer displayed at the instant of the vibration was recorded. The process was repeated thrice on the pulp of each of the big toes and the mean taken as the VPT for each of the lower limbs [27, 28]. Diabetic peripheral neuropathy was defined by a mean vibration perception threshold of > 25 Volts measured with the biothesiometer [40].

Weight and height were measured using Stadiometer (RGZ-120), waist circumference, measured with a measuring tape and blood pressure measured using Accoson mercury Sphygmomanometer in accordance with the WHO STEPS instruments [37].

DEFINITION OF TERMS AND CRITERIA

Hypertension was defined as systolic BP ≥ 140mmHg and or diastolic BP ≥ 90 mmHg, measured on at least 2 separate occasions or if a patient is already on anti-hypertensive medications [41].

Diabetes mellitus was defined by fasting plasma glucose of ≥ 7.0 mmol/l (126 mg/dl) measured on at least 2 separate occasions or the patient is already on glucose lowering agents [1].

Type 1 DM was defined as subjects with DM who are dependent on insulin for survival and are at risk for ketoacidosis [1].

Type 2 DM was defined as patients with DM on diet therapy either alone or in combination with oral glucose lowering agent(s) for glycaemic control [1].

Dyslipidaemia was taken as HDL-C <1.04 mmol/L(males) or < 1.3 mmol/L or TG ≥ 1.7 mmol/L or LDL-C ≥ 2.6 mmol/L or total cholesterol (TC) ≥ 5.2 mmol/L or if the patient is on lipid lowering agents [42].

Young age was taken as 18-44 years, middle age as 45-64 years and old age as 65 years and above [43].
Poor glycaemic control was taken as $HbA_{1C} \geq 7.0\%$ [1].
Global obesity was defined by body mass index (BMI) >30 (kg/M^2) [1].
Central obesity was defined by waist to hip ratio (WHR) > 0.9 [1].

Diabetic peripheral neuropathy (DPN) was defined by a vibration perception threshold (VPT) > 25 Volts measured with the biothesiometer [40].

Peripheral artery disease (PAD) was defined by an ankle brachial pressure index (ABPI) value of ≤ 0.9; normal ABPI was 0.9 – 1.29; mild PAD was ABPI of 0.8 – 8.9; moderate PAD was ABPI of 0.5 – 7.9; severe PAD was ABPI of < 0.5 while calcification of the arteries was defined by ABPI of ≥ 1.3 [36-44].

Statistical Analysis

Data collected was analysed using Statistical Package for Social Sciences (SPSS) version 25. Results of categorical variables were presented in tables as frequencies and percentages. The mean values and standard deviation for the continuous variables were calculated. Chi-square test was used to determine the association between the vascular complications (PAD/DPN) and the categorical variables. The level of significance was set at $p < 0.05$.

RESULTS

A total of 142 subjects had complete results and were analysed.

1. The mean age of the subjects was 59.15 ± 11.37 years, and varied from 32 to 80 years. Majority of the participants were of middle age (54.9%) and had tertiary education (40.8%) and the male to female ratio was 1.00 : 1.36 (details in Table 1).

Table 1: Socio-demographic characteristics of the study subjects

Variable	Frequency	Percentage
Age (years)		
18-44	14	9.9
45-64	78	54.9
≥65	50	35.2
Mean = 59.15 ± 11.37		
Sex		
Male	60	42.3
Female	82	57.7
Educational level		
No formal	2	1.4
Primary	56	39.4
Secondary	26	18.3
Tertiary	58	40.8

2. The clinical characteristics of study subjects showed the mean values of the following variables: duration of diabetes mellitus (11.34 ± 8.72 years); waist circumference (99.54 ± 12.48cm); hip circumference (105.52 ± 11.25 cm); body mass index (27.74 ± 5.42 kg/m^2),

glycated haemoglobin (HbA1c) (8.30 ± 2.26 %); systolic blood pressure (128.73 ± 22.66 mmHg); diastolic blood pressure (82.39 ± 16.28 mmHg); total cholesterol (4.45 ± 0.94 mmol/L); triglyceride (1.24 ± 0.83 mmol/L); high density lipoprotein (1.12 ± 0.36 mmol/L); low density lipoprotein (2.72 ± 0.81 mmol/L) (details in Table 2).

Table 2: Clinical characteristics of the study subjects

Variable	Minimum	Maximum	Mean	SD
Duration of DM (years)	0.50	38.00	11.34	8.72
Waist circumference (cm)	70.00	144.00	99.54	12.49
Hip circumference (cm)	84.00	143.00	105.52	11.25
Body mass index (kg/m^2)	19.20	41.82	27.74	5.42
HbA1c (%)	4.50	15.50	8.30	2.26
Systolic blood pressure (mmHg)	70.00	200.00	128.73	22.66
Diastolic blood pressure (mmHg)	60.00	170.00	82.39	16.28
Total cholesterol (mmol/L)	2.60	7.11	4.45	0.94
Triglyceride (mmol/L)	0.40	4.79	1.24	0.83
High density lipoprotein (mmol/L)	0.24	3.09	1.12	0.36
Low density lipoprotein (mmol/L)	0.56	4.76	2.72	0.81

DM = diabetes mellitus: HbA1c = glycated haemoglobin

3. The prevalence rate of diabetic peripheral neuropathy (DPN), a surrogate for microvascular abnormality was 50.7%, while that of peripheral artery disease (PAD), a surrogate for macrovascular abnormality was 18.3% (details in Table 3).

Table 3: Prevalence and pattern of vascular (microvascular & macrovascular) abnormalities among the subjects

Variable	Frequency	Percentage (%)
Diabetic peripheral neuropathy (DPN)		
Present	72	50.7
Absent	70	49.3
Peripheral artery disease (PAD)		
Present	26	18.3
Mild	6	4.2
Moderate	14	9.9
Severe	4	2.8
Absent	116	81.7
Calcification	54	38.0
No calcification	62	43.7

4. The result of the association between diabetic peripheral neuropathy (DPN) and the socio-demographic cardiovascular risk factors showed that there was a statistically significant association with age (X^2 = 14.059; p = 0.001), sex (X^2 = 6.630; p = 0.010) and education level (X^2 = 12.286; p = 0.006). A higher prevalence rate of DPN was found among the subjects aged 65 years and above (68.0%), male subjects (63.3%), the subjects that had primary education (64.3%) and secondary education (53.8%), respectively. (details in Table 4).

Table 4: Association between Diabetic peripheral neuropathy (DPN) and socio-demographic cardiovascular risk factors

Factor	DPN		X^2	p-value
	Present	Absent		
Age (years)				
18-44	2 (14.3)	12 (85.7)	14.059	0.001
45-64	36 (46.2)	42 (53.8)		
≥65	34 (68.0)	16 (32.0)		
Sex				
Male	38 (63.3)	22 (36.7)	6.630	0.010
Female	34 (41.5)	48 (58.5)		
Educational level				
No formal	2 (100)	0	12.286	0.006
Primary	36 (64.3)	20 (35.7)		

Secondary	14 (53.8)	12 (46.2)		
Tertiary	20 (34.5)	38 (65.5)		

5. The association between diabetic peripheral neuropathy (DPN) and clinical/laboratory cardiovascular risk factors, showed that there was a statistically significant association with the duration of diabetes mellitus ($X^2 = 5.246$; $p = 0.022$), global obesity ($X^2 = 5.494$; $p = 0.019$), treatment for diabetes mellitus ($X^2 = 11.821$; $p = 0.003$), dyslipidaemia ($X^2 = 9.767$; $p = 0.002$), the use of lipid-lowering drugs ($X^2 = 4.036$; $p = 0.045$) and peripheral artery disease ($X^2 = 8.158$; $p = 0.004$). A higher prevalence of DPN was found among the subjects that had a long duration of diabetes mellitus (57.1%), global obesity (56.9%), were on insulin (75.0%) or both insulin and OADs (70.0%), had no dyslipidaemia (87.5%), were not on lipid-lowering drugs (62.5%) and had peripheral artery disease (62.9%). There were no statistically significant association between DPN and abdominal obesity, glycaemic control, hypertension, exercise level and anti-hypertensive medications use ($p > 0.05$ in these cases) (details in Table 5)

Table 5: Association between Diabetic peripheral neuropathy (DPN) and clinical/laboratory cardiovascular risk factors

Factor	**DPN**		**X^2**	**p-value**
	Present	**Absent**		
Duration of Diabetes mellitus				
Short	16 (36.4)	28 (63.6)	5.246	0.022
Long	56 (57.1)	42 (42.9)		
Abdominal obesity (males)				
Present	18 (64.3)	10 (35.7)	0.021	0.886
Absent	20 (62.5)	12 (37.5)		
Abdominal obesity (females)				
Present	26 (37.1)	44 (62.9)	3.679	0.055
Absent	8 (66.7)	4 (33.3)		
Global obesity				
Present	14 (35.0)	26 (65.0)	5.494	0.019
Absent	58 (56.9)	44 (43.1)		
Glycaemic control				
Good	18 (45.0)	22 (55.0)	0.725	0.395
Poor	54 (52.9)	48 (47.1)		
Systolic hypertension				
Present	28 (58.3)	20 (41.7)	1.688	0.194
Absent	44 (46.8)	50 (53.2)		
Diastolic hypertension				
Present	22 (52.4)	20 (47.6)	0.067	0.796
Absent	50 (50.0)	50 (50.0)		
Treatment for Diabetes				
Diet alone	0	0	11.821	0.003
OADs	38 (40.0)	56 (59.6)		
Insulin	6 (75.0)	2 (25.0)		
Both	28 (70.0)	12 (30.0)		
Dyslipidaemia				
Present	58 (46.0)	68 (54.0)	9.767	0.002
Absent	14 (87.5)	2 (12.5)		
Exercise				
Yes	10 (38.5)	16 (61.5)	1.909	0.167
No	62 (53.4)	54 (46.6)		
Anti-hypertensive therapy				
Yes	40 (50.0)	40 (50.0)	0.036	0.849
No	32 (51.6)	30 (48.4)		
Lipid-lowering therapy				
Yes	42 (44.7)	52 (55.3)	4.036	0.045
No	30 (62.5)	18 (37.5)		

Peripheral artery disease (PAD)				
Present	44 (62.9)	26 (37.1)	8.158	0.004
Absent	28 (38.9)	44 (61.1)		

OADs = oral anti-diabetic drugs

6. Peripheral artery disease (PAD) showed no significant association with any of the socio-demographic cardiovascular risk factors evaluated ($p > 0.05$) (details in Table 6).

Table 6: Association between peripheral artery disease (PAD) and socio-demographic cardiovascular risk factors

Factor	**PAD**		**X^2**	**p-value**
	Present	**Absent**		
Age (years)				
18-44	4 (28.6)	10 (71.4)	2.570	0.277
45-64	16 (20.5)	62 (79.5)		
≥65	6 (12.0)	44 (88.0)		
Sex				
Male	10 (16.7)	50 (83.3)	0.188	0.665
Female	16 (19.5)	66 (80.5)		
Educational level				
No formal	0	2 (100)	5.971	0.113
Primary	12 (21.4)	44 (78.6)		
Secondary	8 (30.8)	18 (69.2)		
Tertiary	6 (10.3)	52 (89.7)		

7. The association between peripheral artery disease (PAD) and the clinical/laboratory risk factors showed that there was a statistically significant association with systolic hypertension ($X^2 = 10.942$; $p = 0.001$), diastolic hypertension ($X^2 = 24.026$; $p = 0.000$), treatment for diabetes mellitus ($X^2 = 7.262$; $p = 0.026$) and diabetic peripheral neuropathy ($X^2 = 8.753$; $p = 0.003$). A higher prevalence of PAD was found among the subjects that had systolic (33.3%) and diastolic hypertension (42.9%); the subjects that were on insulin for DM treatment (50%) and subjects that had diabetic peripheral neuropathy (27.8%). No significant association was found between PAD and duration of DM, obesity (both abdominal and global), glycaemic control, dyslipidaemia, exercise level, anti-hypertensive drugs use and lipid-lowering drugs use ($p > 0.05$ in these cases) (details in Table 7).

Table 7: Association between peripheral artery disease (PAD) and the clinical/laboratory cardiovascular risk factors

Factor	**PAD**		**X^2**	**p-value**
	Present	**Absent**		
Duration of Diabetes mellitus				
Short	6 (13.6)	38 (86.4)	0.931	0.335
Long	20 (20.4)	78 (79.6)		
Abdominal obesity (males)				
Present	2 (7.1)	26 (92.9)	3.429	0.064
Absent	8 (25.0)	24 (75.0)		
Abdominal obesity (females)				
Present	16 (22.9)	54 (77.1)	3.408	0.065
Absent	0	12 (100)		
Global obesity				
Present	8 (20.0)	32 (80.0)	0.106	0.744
Absent	18 (17.6)	84 (82.4)		
Glycaemic control				
Good	10 (25.0)	30 (75.0)	1.666	0.197
Poor	16 (15.7)	86 (84.3)		
Systolic hypertension				
Present	16 (33.3)	32 (66.7)	10.942	0.001
Absent	10 (10.6)	84 (89.4)		
Diastolic hypertension				
Present	18 (42.9)	24 (57.1)	24.026	0.000

Absent	8 (8.0)	92 (92.0)		
Treatment for Diabetes				
Diet alone OADs Insulin Both	0 18 (19.1) 4 (50.0) 4 (10.0)	0 76 (80.9) 4 (50.0) 36 (90.0)	7.262	0.026
Dyslipidaemia				
Present Absent	24 (19.0) 2 (12.5)	102 (81.0) 14 (87.5)	0.407	0.524
Exercise				
Yes No	2 (7.7) 24 (20.7)	24 (92.3) 92 (79.3)	2.399	0.121
Anti-hypertensive Therapy				
Yes No	16 (20.0) 10 (16.1)	64 (80.0) 52 (83.9)	0.350	0.554
Lipid-lowering Therapy				
Yes No	14 (14.9) 12 (25.0)	80 (85.1) 36 (75.0)	2.170	0.141
Diabetic peripheral neuropathy (DPN)				
Present Absent	20 (27.8) 6 (8.6)	52 (72.2) 64 (91.4)	8.753	0.003

OADs = oral anti-diabetic drugs

DISCUSSIONS

The mean age of the 142 T2DM subjects studied was 59.15 ± 11.37 years. This study found that the prevalence rate of DPN diagnosed using biothesiometry was 50.7% among the subjects. Oguejiofor *et al*., had found the prevalence rate of 38.5% also using biothesiometry, in T2DM patients in the same area almost a decade ago [27]. Oguejiofor *et al*., studied 106 T2DM subjects, a number that is smaller than the 142 T2DM subjects evaluated by the index study and this and the improvements in the effective diabetes management over the years could account for the difference in the finding from both works [27]. Oguejiofor *et al*., equally got the prevalence rate of DPN of 71.5% with tuning fork and 14.8% with biothesiometry, respectively in T2DM subjects without neuropathic symptoms [28]. Again the index study unlike Oguejiofor et al's work did not differentiate between the type 2 diabetic patients with and without neuropathic symptoms. The prevalence rate of DPN from the index study was also lower than the 82.0% found by Ikem *et al*., [29]. Their diagnosis of DPN was based on presence of the triad of symptoms, examination with tuning fork and 10 g Semmes-Weinstein monofilament and not by biothesiometry [29]. Kaoje *et al*., found a prevalence rate of DPN of 39.7% using biothesiometry among their type 2 diabetic cohort [30]. Their figure is less than that found by the index study and the reasons could be traced to the fact that Kaoje *et al*., studied a larger sample size of 330 T2DM subjects and their subjects were younger, with mean age of 49.60 ± 9.81 years when compared with the mean age of this study's subjects which was 59.15 ± 11.37 years [30]. Increasing age has been found to be significantly associated with DPN [26-45].

This study found a statistically significant association between DPN and the age, sex and educational level of the subjects. Equally found was a significant association of between DPN and the duration of diabetes mellitus, global obesity, treatment for diabetes mellitus, dyslipidaemia, anti-lipid drugs use and peripheral artery disease. The finding by this study that DPN is significantly associated with age of the subjects fell in line with what is expected from literatures. Diabetic peripheral neuropathy is viewed as a common age-related degenerative disorder of unkown aetiology that has been studied both in mice and humans [46, 47]. It has been suggested that the mechanisms underlying chronic nociceptive pain-processing differ in relation to gender and gonadal hormone status [48]. Hormonal differences between male and female subjects may play a role. Estrogen, for instance has been shown to influence nerve function and contribute to the development and progression of neuropathy [49]. Female subjects tend to have more of painful DPN compared with male subjects [50]. Studies have found that sex and gender differences influence DPN; male subjects have a higher frequency for DPN generally, but female subjects have a higher frequency of severe neuropathic symptoms. Female subjects reported greater pain intensity than the male subjects [51-53]. Education, more especially structured supportive-education can decrease the symptoms and severity of diabetic peripheral neuropathy [54]. There is potential association between educational levels and increased risk of diabetic peripheral neuropathy [15]. Lower educational attainment can be associated with other socioeconomic factors, like lower income or limited access to healthcare which can impact on DPN risk. [15]. The common practice in our clime is that educated subjects adopt western Lifestyles that include sedentary living and consumption of high calorie diets, which are risk factors for micro- and microvascular

complications. Our subjects were no exceptions to this misconceived common trend.

Long duration of diabetes, obesity, dyslipidaemia and peripheral artery disease are all known risk factors for microvascular and macrovascular complications of DM and the finding of significant association between DPN and these cardiovascular risks by the index study is in agreement with other studies. Diabetic peripheral neuropathy was independently associated with cardiovascular disease and risk factors [18,55]. While insulin undoubtedly plays a beneficial role in DM management, it has a complex relationship with DPN. It can indirectly benefit DPN by its glucose-lowering effects or directly by its neurotrophic role in supporting peripheral neurons [20]. Insulin deficiency, excess or resistance however can contribute to the development and progression of DPN by impacting peripheral nerve function directly [56, 57]. A combination of insulin and oral anti-diabetic drugs could predispose diabetic subjects to recurrent hypoglycaemia and hence to Diabetic peripheral neuropathy [57]. Severe hypoglycaemia was an independent risk factor of DPN [58]. Also the risk of DPN increased with the frequency of hypoglycaemic events [58].

There were conflicting reports on the association between DPN and use of lipid-lowering medications. The index study found that dyslipidaemia and the use of lipid-lowering drugs were significantly associated with increase in prevalence of diabetic peripheral neuropathy and this agrees with the finding of Pasha *et al*., while Chang *et al*., found that neither hyperlipidaemia nor lipid-lowering medications were associated with diabetic peripheral neuropathy [59, 60].

The overall prevalence rate of PAD found by this study was 18.3%, out of which 4.2%, 9.9% and 2.8% of the subjects had mild, moderate and severe PAD, respectively. The prevalence rate of PAD is by far lower than the 52.5% found by Oyelade *et al*., over a decade ago [61]. The improvement in the holistic management of T2DM and in the quality and coverage of diabetes education that had taken place in the sub-Saharan Africa over the last decade could explain the drop in the Prevalence rate of PAD observed in the index study. A recent systematic literature review reported that four large multinational randomized controlled trials found that 12.5% - 22.0% of people with type 2 DM had co-morbid PAD [62]. This prevalence rate of PAD found by this study is very comparable to that reported by Verma *et al*. A systematic review on PAD in sub-Saharan Africa and India found that pooled prevalence rate of PAD in T2DM subjects was 32.97% and 18%, respectively [25-63]. The result from the sub-Saharan Africa is almost twice as high as that of this study while that from India is very comparable to that of the index study [25-63].

Lastly, Akalu *et al*., found that the prevalence rate of PAD among their type 2 DM cohort was 30.7% [64]. Their sample size was almost double that of the index study (280) and their subjects were more elderly with a mean age of 61.2 ± 7.3 years [64]. Literature review had shown that increasing age was significantly associated with PAD in T2DM subjects [23-64].

This study equally found that PAD was significantly more in subjects with elevated blood pressure, subjects on insulin therapy for their DM control and subjects who had diabetic peripheral neuropathy and this is as expected because hypertension and diabetic peripheral neuropathy are both risk factors for peripheral artery disease. Moreover, it was found that insulin use had a complex relationship with PAD. In as much as insulin is very vital in managing high blood glucose levels, it is also linked to the development and progression of peripheral artery disease. Poorly controlled DM, usually requiring insulin administration and insulin resistance with the resultant hyperinsulinaemia common in T2DM were strongly associated with peripheral artery disease [65, 66]. In contrast to the findings of the index study, some literatures have shown that age, higher HbA1c levels (poor glycaemic control), female sex, overweight and obesity (BMI $\geq$ 25 Kg/m^2) and dyslipidaemia (low HDL-C levels) were significantly associated with higher prevalence of PAD in subjects with type 2 diabetes mellitus [23-64]. Equally, contrastingly to the index study, Haile *et al*., found that increasing age, increases in the level of low density lipoprotein cholesterol (LDL-C) and diabetes duration of more than 10 years were significant predictors of PAD in subjects with T2DM [25]. Lastly, Stein *et al*., found that physical activity intensity frequency was associated with lower PAD, while Metsushita *et al*., found that low educational level was associated with increased PAD in type 2 diabetes mellitus subjects [67, 68].

CONCLUSION AND RECOMMENDATIONS

This study found that the prevalence rates of DPN and PAD, which are surrogate markers for microvacular and macrovascular abnormalities in subjects with T2DM at Nnamdi Azikiwe University Teaching Hospital (NAUTH) in Southeastern Nigeria were high (50.7% and 18.3%, respectively). This depicts the huge burden of cardiovascular morbidity and mortality in this cohort of patients. Furthermore, there was a significant association between DPN and age, sex, educational status, duration of DM, global obesity, DM treatment, dyslipidaemia, lipid-lowering medications use and peripheral artery disease. Equally, PAD had significant association with hypertension, diabetes treatment and diabetic peripheral neuropathy. These findings still under- represent the enormous scourge of vascular complications in T2DM subjects and this is because these abnormalities are under-screened for and under-reported and under-appreciated. These underscore the need for a proactive approach towards tackling these vasculopathies in This group of subjects both by attending physicians and other stake holders in the health

sector. Early and scheduled screening for and treatment of vascular abnormalities in T2DM subjects is highly advocated. Lastly, holistic tackling of the cardio-metabolic sequalae and risk factors of T2DM via life style modifications and drug treatment will go a long way towards reducing the burden of the vascular complications of type 2 diabetes mellitus.

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