Asymptomatic Cardiovascular Disorders in a Cohort of Clinically Stable Type 2 Diabetes Mellitus Patients in South Eastern Nigeria: A Cross Sectional Study

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Authors' contributions

This work was carried out in collaboration among all authors. Authors EEY and CME designed the study. Data was collected by all the authors. Authors UNI and CBN performed the literature search. Author EEY managed the data analyses and wrote the initial draft. All the authors read and approved the manuscript.

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ABSTRACT

Introduction: Coronary artery disease (CAD), stroke and peripheral artery disease (PAD) are commonly referred to as cardiovascular disorders (CVD) due to a common underlying pathophysiology of atherosclerosis and are more common in diabetic patients. This study was carried out to determine the pattern and associated factors of CAD and PAD in asymptomatic patients with type 2 diabetes mellitus in South east Nigeria.

Materials and Methods: One hundred and twenty stable adults with type 2 diabetes mellitus were recruited consecutively from two out-patient clinics in two tertiary hospitals in South east Nigeria at Nnewi and Enugu. They were assessed for risk factors for CVD including hypertension, obesity and dyslipidaemia. Their ankle-brachial index (ABI) was measured using a hand-held doppler and they also had a 12 lead ECG. Results were analyzed using SPSS V23; p value of < 0.05 considered significant.

Results: There were 60 males and 60 females, with a mean age of 61.7(11.2) years and mean diabetes duration of 127.7(99.9) months. Dyslipidaemia was present in 73.3%, 70% had hypertension, PAD was present in 55.8%, while 16.5% had CAD. PAD was more common in those with higher BMI (p = 0.04), higher diastolic BP (p = 0.03) and higher mean arterial pressure (p = 0.03). On further multivariate stepwise regression analysis, there was no significant predictor of PAD. None of the clinical factors were associated with CAD.

Conclusion: PAD and CAD are common in patients with type2 DM even in the absence of symptoms. Obesity, high diastolic and high mean arterial pressure are more common in patients with PAD.

1. INTRODUCTION

Cardiovascular disorders include coronary artery disease (CAD), peripheral arterial disease (PAD) and stroke. These disorders share a common underlying pathogenesis of atherosclerosis and result in increased morbidity and mortality. Cardiovascular disorders are common in patients with type2 DM and have been reported to be the commonest cause of mortality in them [1]. Patients with DM are two to threetimes at risk of developing cardiovascular disease when compared to the normal population [2].

Risk factors for cardiovascular diseases include obesity, hypertension, dyslipidaemia, smoking, sedentary lifestyle among others. A clustering of these risk factors have been described as the metabolic syndrome and is found in over half of patients with diabetes mellitus [3]. Diabetes mellitus is regarded as a coronary artery disease equivalent [4]. Coronary artery disease in DM patients is usually extensive and multi-vessel in nature, however associated with episodes of silent myocardial ischemia, infarction and sudden death. [5] In addition, studies have reported worse outcomes from cardiovascular disease such as myocardial infarction in patients with DM compared to non-diabetic patients [5]. Peripheral arterial disease in diabetic patients also contributes to diabetic foot ulcers, gangrene and increased amputation rates.

In the management of patients with diabetes mellitus, routine screening for cardiovascular disease can easily be missed in stable patients without symptoms. Screening for PAD with ABI is recommended in patients with symptoms or reduced peripheral pulses [6]. The patient is assessed for symptoms such as reduced walking speed, leg fatigue and claudication. Duplex ultrasound scan may also be done when available either for screening or in the presence of symptoms. In resource-constrained settings, these may not be available routinely. Resting ECG assessment may not be sufficient to diagnose silent CAD, however the use of coding systems such as the Minnesota coding system may improve its utility. ECG abnormalities are common in diabetic patients, ischemic heart disease features occurring in as many as 20%, while 1.5% had evidence of left ventricular hypertrophy. [7] Silent myocardial ischemia in diabetic patients has been attributed to cardiac autonomic neuropathy. [8] Furthermore, various forms of CVD may occur simultaneously in a patient leading to poor outcome.

This study was done to estimate the burden of asymptomatic cardiovascular disease in stable outpatients with type 2 diabetes mellitus attending two tertiary hospitals in south-eastern Nigeria.

2. MATERIALS AND METHODS

This was a cross sectional observational study among clinically stable asymptomatic patients with DM who were evaluated for the presence of clinically silent CAD and PAD. The study was conducted in the diabetes clinics of NnamdiAzikiwe University Teaching Hospital (NAUTH), Nnewi, Anambra and the University of Nigeria Teaching Hospital (UNTH), Enugu, Enugu state, both in south eastern Nigeria. The study population consisted of subjects from Enugu and Anambra states as well as the neighboring south eastern states of Imo, Delta, Ebonyi and Abia. A convenient sampling method was used whereby all consecutive patients with T2DM presenting to the diabetes clinics in both centers, who met the inclusion criteria and had none of the exclusion criteria were recruited for the study.

Coronary artery disease (CAD) and peripheral artery disease (PAD). Type 2 DM patients were patients with DM on diet therapy in combination with oral glucose lowering agent(s) with or without insulin for glycaemic control[9].

Subjects were excluded if they were aged less than 30 years, had T1DM, had past history of stroke, CAD or PAD or presented with neurological signs, chest pain, dyspnoea, body swelling, intermittent claudication or rest pain.

Focused medical history was taken and other relevant data extracted using a researcher structured and administered study protocol. Next a resting ECG was done, followed by a detailed physical examination, anthropometric measurements and vascular assessment with Doppler ultrasound.

Doppler ultrasound assessment of the brachial, dorsalispedis and posterior tibial arteries was done using EDAN SONOTRAX Utrasonic Pocket Doppler version 1.2 (CE 0123) with 8.0 MHz probe and an Accoson mercury Sphygmomanometer. Ankle brachial pressure index (ABPI) was calculated using the formula:

ABPI for a leg = Higher pressure obtained from the ankle vessel in that leg [10]/Higher systolic brachial pressure of the 2 arms

Peripheral artery disease (PAD) is taken as ABPI ≤ 0.9[11]. Electrocardiography (ECG) was done using Schiller AT-102 Plus 12 lead resting ECG. Ten electrodes were placed in the specific anatomic positions to obtain quality tracings. The four limb leads were applied to the upper and lower extremities; the right leg, left leg, right arm and left arm. The six chest leads were applied at the precordial locations (V1-V6). The recording was over a period of about 10 seconds after the connections were made. The interpretation of the ECG recordings was done by a cardiologist and CAD diagnosed using the University of Minnesota Codes for Resting Electrocardiograms [12].

Major ECG abnormality was defined as pathological Q waves (codes 1-1 and 1-2), marked ST depression (codes 4-1 and 4-2) and/or T wave inversion (codes 5-1 and 5-2), bundle branch block (codes 7-1 and 7-2) or some significant arrhythmias. Minor ECG abnormalities were defined as high voltage, axis deviation and lesser degrees of ST-T wave abnormality (4-3, 5-3) according to the Minnesota Code. A different form of classification of "ischaemic ECG" was defined as pathological Q waves (any code 1), ST and/or T wave inversion of any degree (any code 4 or 5) or left bundle branch block (code 7-1-1). Left ventricular hypertrophy was defined as a combination of high voltage and either ST depression or T wave inversion, again on the basis of appropriate Minnesota Codes.

The participants were told to come on another clinic day between 8a.m and 9a.m after an overnight fast of about 10-12 hours for biochemical tests which included fasting lipid profile (FLP), fasting blood sugar (FBG) and glycatedhaemoglobin (HbA1c). A total of 7 mL of blood was collected from each subject via venopuncture of the cubital vein, 1 mL for HbA1c, 2 mL for FBS and 4 mL for FLP. Samples for HbA1c were collected in EDTA bottles and measured with automated CLOVER A1c Analyzer (Infopia, Korea) and CLOVER A1c Self-Test Cartridge using the boronate affinity method [13]. Samples for FBS were collected in fluoride oxalate bottles and analyzed by the Trinder glucose oxidase method [14] while samples for FLP were collected in plain bottles. High density lipoprotein (HDL-C) was obtained by a precipitation technique [15], Total cholesterol (TC) level was determined using the kit employing the enzymatic and 4-hydroxybenzoate/4- aminophenazone systems (Bio Systems)[16,17], Triglyceride level (TG) level was determined by enzymatic hydrolysis of triglyceride with lipases (Randox)[18] and Low density lipoprotein cholesterol (LDL-C) was measured by precipitation technique [19].

Weight and height were measured using a Stadiometer (RGZ - 120) and body mass index (BMI) calculated using the ratio of weight (Kg) to the square of the height (M).

Hypertension was taken as systolic BP ≥ 140 mmHg and / or diastolic BP ≥ 90 mmHg or if patient was already on antihypertensive medications [20]. Poor glycaemic control was taken as HbA1c ≥ 7.0%[21]. Global obesity was defined by BMI > 30 (Kg/M^2)[20]. Central obesity was defined by waist circumference (WC) > 102 cm for men and > 88 cm for women[21]. Dyslipidaemia was taken as HDL-C < 40 mg/dl for men and < 50 mg/dl women or TG ≥ 150 mg/dl or LDL-C ≥ 100 mg/dl or TC ≥ 200 mg/dl or if patient was on lipid lowering agents [21]. Statistical analysis was doneusing Statistical Package for Social Sciences (SPSS) version 23 (Chicago, IL, USA).

Continuous variables were expressed as mean (SD) while categorical variables were expressed as percentages. Comparison of means was done using independent t-test, while comparison between categorical variables was done using Chi-square test p < 0.05 was considered statistically significant.

3. RESULTS

A total of 123 patients were recruited into the study; 3 of them had a prior history of stroke and were excluded from the final analysis. The remaining 120 patients were made up of 60 males and 60 females; 60 from NAUTH (40 males and 20 females) and 60 from UNTH (20 males and 40 females). Only 79 patients had an ECG assessment. The mean age of all the patients was 61.7(11.2) years. They had a mean diabetes duration of 127.7(99.9) months. Diabetes treatment was with both oral medications and insulin in 31(25.8%) patients, insulin only in 6(5.0%) and oral medication only in 83(69.2%).

3.1 Clinical Features

Dyslipidaemia was present in 88(73.3%) patients. The mean systolic BP in the patients was 136.8(20.2) mmHg, while the mean diastolic BP was 84.7(12.3) mmHg. Hypertension was present in 84(70.0%) patients. The mean HbA1c was 8.5(2.7) %. The mean FBG was 8.1(3.7) mmol/l. Poor glycaemic control was present in 68(56.7%) patients.

The mean BMI was 29.3(5.8) kg/m2. The mean waist circumference for the females was 97.0(10.5) cm, while for the males, the mean was 96.6(12.0) cm.

The patients had a mean total cholesterol of 4.84(1.11) mmol/l, triglycerides 1.32(0.78), LDL 3.02(1.05) and HDL 1.20(0.38). The mean right ABI was 1.04(0.3) ad for the left was 1.03(0.29).Other clinical characteristics are outlined in Table 1.

3.2 Coronary Artery Disease and Peripheral Arterial Disease in the Patients

Coronary artery disease was detected in 13 patients out of 79(16.5%) who had ECG done. The common ECG abnormalities were ST-T changes in 7(53.8%), arrhythmias in 3(23.1%) and chamber hypertrophy in 5(38.5%). None of them had pathological Q wave. The mean ABI was 1.04(0.32) on the right leg and 1.04(0.29) on the left leg. Peripheral arterial disease was present in 67(55.8%) patients. Of the 13 patients with CAD, 10(76.9%) of them also had PAD.

3.3 Factors Associated with Peripheral Arterial Disease

Peripheral arterial disease was noted in 30.3% of the women and 26.1% of the men (p = 0.34). The mean duration of DM in those with PAD was 114.9(92.2) months, while those without PAD had mean DM duration of 140.1(105.2) months (p = 0.14). There was no difference in the mean age of those with PAD; 61.9(11.9) years and those without PAD; 61.4(10.5) years (p = 0.79). The mean HbA1c of patients with PAD was 8.4(2.5) %, while it was 8.8(2.8)% in those without (p = 0.47). Other clinical characteristics of patients with PAD are outlined in Table 2.

3.4 Factors Associated with Coronary Artery Disease

Coronary artery disease was present in 5.1% of the women and 11.4% of the men (p = 0.20). The mean duration of DM in those with CAD was 161.8(131.4) months, while those without CAD had mean DM duration of 125.2(97.7) months (p = 0.25). There was no difference in the mean age of those with CAD; 62.2(11.8) years and those without CAD; 66.2(12.0) years (p = 0.27). The mean HbA1c of patients with CAD was 9.4(2.9)%, while it was 8.3(2.4)% in those without (p = 0.14). Other factors associated with coronary artery disease are outlined in Table 3.

Table 1. Clinical features of the study population

Clinical Features	Male (n = 60)	Female (n = 60)	Total (N = 120)	p
Age	64.6(10.8)	59.2(10.8)	61.7(11.2)	0.008*
Duration of DM	137.6(108.3)	119.9(90.5)	127.7(99.9)	0.34
Systolic BP	135.5(17.1)	138.4(22.8)	136.8(20.2)	0.43
Diastolic BP	85.1(11.5)	84.4(13.1)	84.7(12.3)	0.77
BMI	28.2(4.9)	30.5(6.4)	29.3(5.8)	0.03*
Waist circumference	96.6(12.0)	97.0(10.5)	96.9(11.2)	0.84
HBA1c	9.0(2.8)	8.0(2.5)	8.5(2.7)	0.05
Total cholesterol	4.6(1.1)	5.2(1.1)	4.9(1.1)	0.007*
Triglycerides	1.4(0.9)	1.3(0.5)	1.3(0.8)	0.59
LDL	2.8(0.9)	3.3(1.1)	3.0(1.1)	0.03*
HDL	1.1(0.4)	1.3(0.3)	1.2(0.4)	0.01*
Pulse pressure	50.4(14.8)	53.9(16.4)	52.1(15.6)	0.22
Mean arterial pressure	101.9(11.7)	102.4(15.1)	102.1(13.5)	0.83

significant values

Table 2. Factors associated with peripheral arterial disease

Clinical features	PAD absent (n = 52)	PAD present (n = 68)	p	95% Confidence Interval
Age	61.4(10.5)	61.9(11.9)	0.79	-4.61 to 3.61
DM duration	140.1(105.2)	114.9(92.2)	0.17	-10.69 to 61.09
HBA1c	8.8(2.8)	8.4(2.5)	0.47	-13.30 to 1.41
BMI	28.1(5.4)	30.3(5.9)	0.04*	-9.39 to -0.59
Waist Circumference	96.3(12.6)	87.0(13.6)	0.62	-5.17 to 3.08
Total Cholesterol	4.8(1.1)	4.9(1.1)	0.39	-4.31 to -0.10
LDL	2.9(1.1)	3.2(1.1)	0.11	-6.7 to 1.45
HDL	1.2(0.4)	1.2(0.4)	0.70	-0.59 to 0.24
Systolic BP	133.4(17.3)	139.4(21.9)	0.11	-0.72 to -0.07
Diastolic BP	82.0(9.6)	87.0(13.6)	0.03*	-0.11 to -0.17
Pulse pressure	51.4(14.8)	52.4(16.3)	0.74	-6.69 to 4.79
Mean arterial pressure	99.2(10.6)	104.5(15.0)	0.03*	-10.17 to -0.45

significant values

Table 3. Factors associated with coronary artery disease

Clinical features	CAD absent n = 66	CAD present n = 13	p	95% Confidence interval
Age	62.2(11.8)	66.2(12.0)	0.27	-11.14 to 3.14
DM duration	125.2(97.7)	161.8(131.4)	0.25	-99.2 to 26.07
HBA1c	8.3(2.4)	9.4(2.9)	0.14	-15.82 to 9.07
BMI	29.9(6.4)	28.2(5.5)	0.70	-7.61 to 7.62
Waist circumference	97.2(11.5)	99.0(10.8)	0.61	-8.64 to 5.11
Total cholesterol	5.0(1.2)	4.7(0.9)	0.38	-3.08 to 4.54
LDL	3.2(1.1)	2.9(0.8)	0.49	-2.73 to 0.39
HDL	1.3(0.4)	1.1(0.4)	0.07	-0.38 to 0.98
Systolic BP	137.4(20.9)	140.8(18.9)	0.59	-0.42 to 0.87
Diastolic BP	84.6(11.8)	84.6(16.1)	0.99	-0.02 to 0.47
Pulse pressure	52.8(16.4)	56.2(11.2)	0.48	-12.86 to 6.09
Mean arterial pressure	102.2(13.4)	103.3(16.3)	0.79	-9.51 to 7.27

3.5 Logistic Regression to Determine Factors Associated with Peripheral Artery Disease

Logistic regression was used to ascertain factors associated with peripheral artery disease in the patients. Factors that had p value < 0.1 on univariate analysis were entered into a stepwise forward regression model as shown in Table 4. None of the variables was significantly associated with the occurrence of PAD in the patients.

Table 4. Logistic regression to determine factors associated with peripheral artery disease

Variable	p	Exp B	95% confidence interval for Exp B
DM Duration (months)	0.81	0.999	0.995 to 1.004
Systolic BP	0.87	1.002	0.98 to 1.08
Diastolic BP	0.14	1.033	0.99 to 1.08
Waist circumference	0.18	0.961	0.91 to 1.02
BMI	0.09	1.117	0.98 to 1.27
LDL	0.14	1.343	0.91 to 1.99

4. DISCUSSION

Cardiovascular diseases are common in patients with diabetes mellitus and are a major risk of morbidity and mortality. Coronary artery disease in these patients tend to be multi-vessel in nature[10] and patients tend to have worse outcomes following intervention than their non-diabetic counterparts[4]. Subclinical episodes of myocardial infarction or ischemia may occur; referred to as "silent ischaemia" and these may often times only be detected retrospectively following routine ECG. The presence of ECG abnormalities has been reported to significantly predict future cardiovascular events in them [21].Smoking and diabetes mellitus are regarded as the major risk factors for PAD [22]. In this study, stable asymptomatic patients with DM were evaluated for the presence of clinically silent coronary artery disease and peripheral artery disease.

Peripheral artery disease was common and was noted in slightly more than half of the patients (55.8%). The mean ABI was similar in both lower limbs. The prevalence of PAD in our patients was much higher than the prevalence of 22% obtained in another study in South West Nigeria, however in their study, the patients were younger with a mean age of 56 years [23]. There was also no significant gender difference in the prevalence of PAD in this study as previously reported [23]. Patients with PAD in our study had significantly higher mean BMI than those without PAD. Obesity is associated with a pro-inflammatory state, with high levels of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor [24].No significant correlation between BMI and peripheral arterial disease using the ABI have been reported [25]. In the general population, SBP has been found to be the most significant predictor of CVD [26]. We did not obtain a statistical significance although higher SBP was observed in the PAD sub-group. Aside from the small patient population, this parameter could also be affected by whitecoat phenomenon. Furthermore, we found DBP and

MAP were significantly higher. Higher MAP reflects a higher average vascular pressure which can contribute to PAD formation. This is in line with the ADVANCE study in which MAP was found to have a correlation with CVD [27]. In our study, mean HbA1c appeared slightly higher in patients with PAD than those without, though not significant. This was an unexpected finding, as hyperglycemia is a known risk factor for PAD. A few studies have also reported no significant correlations between HbA1c and PAD [28,29]. However, a single measurement of HbA1c being a snapshot of glycaemia over a period of 2-3 months may not capture the glycaemic state of the patient over a longer period, which would more accurately predict the risk of developing PAD, which is a chronic complication of diabetes. Further analysis of the factors that contributed to the presence of PAD using multiple regression did not identify any of them as significant predictors. This suggests that the interactions between clinical characteristics and PAD is complex. Prospective studies, rather than cross-sectional studies will be more useful to clearly define these relationships.

In our study, we detected evidence of CAD on resting ECG in about 16.5% of the patients, with no significant gender bias. ECG abnormalities were present in 20% of diabetic patients in Northern Nigeria [7] with the most common abnormalities being ST-T changes, left atrial enlargement and left ventricular hypertrophy. In the present study, ST-T changes were also common and a few patients had arrhythmia. As many as 25% of asymptomatic patients with type 2 diabetes in North India also had ECG changes consisting mainly of non-specific ST-T changes, LVH and LAE [30], while a prevalence of 23% of ECG abnormalities using the Minnesota coding system was reported among African-American patients with diabetes mellitus [31].

We also reported that males had a higher prevalence of CAD than females, though this did not attain statistical significance. Males have been found to have higher prevalence rates in all

CVD outcomes than females [32]. The male patients in our study were significantly older than the females, and this may in part explain their higher incidence of CAD. None of the clinical factors examined in the study appeared to significantly differ between patients with and without CAD. However, patients with CAD tended towards higher levels of glycatedhaemoglobin, longer duration of diabetes mellitus and lower HDL cholesterol levels. Resting ECG and ABI have been found to be poor predictors of coronary artery calcium scores, which are a reliable index of atherosclerosis, suggesting that they are not very useful in the detection of subclinical atherosclerosis in patients [33]. This may explain why despite the long duration of diabetes in patients in the present study, features of CAD were not very common in them as would have been expected. The use of coronary artery calcium score may have resulted in a higher prevalence.

The major limitation of our study is its cross-sectional nature. In addition, the authors did not evaluate other risk factors such as smoking history and drug adherence. The authors used very basic tools with low sensitivity i.e. ECG and ABI to assess for PAD and CAD. The use of techniques such as cardiac CT, coronary artery calcium scores and doppler ultrasonography of the lower limbs may have improved the results. The authors recommend larger prospective studies in order to properly categorize patients with type 2 diabetes in our own environment. In addition, more sensitive tests such as coronary artery calcium score, stress ECG etc. may be better to identify persons with CAD, rather than ECG alone. This could not however be done due to financial constraints.

5. CONCLUSION

In conclusion, there was a high prevalence of PAD in this cohort of diabetic patients, though CAD was uncommon. This buttresses the importance of regular screening and prevention of cardiovascular diseases in our patients to reduce the morbidity and mortality arising from living with diabetes mellitus.

CONSENT

All the participants were met individually by the researchers at the diabetes clinics. Informed consent was obtained from each participant before recruitment into the study. Inclusion criteria included all consenting subjects with T2DM aged 30 years and above who had no past history of cerebrovascular disease (stroke),

ETHICAL APPROVAL

Ethical clearance was obtained from the Research ethics committee of the NnamdiAzikiweTeaching Hospital, Nnewi.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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