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Original article

The Carotid Intima Medial Thickness Among Type 2 Diabetes Mellitus and Controls: A Cross Sectional Study

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Abstract

Introduction: In Nigeria, the prevalence of diabetes mellitus has been on increasing steadily. With the increasing prevalence of diabetes mellitus, one expects higher rate of its complications including carotid atherosclerosis (which may present with silent infarct, transient ischemic attack, or ischemic stroke) and coronary artery disease. The common link between carotid atherosclerosis and coronary artery disease is atherosclerotic cardiovascular disease with increase intimal medial thickness. This study evaluated medial intima thickness of among Diabetes at the University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria. ***Methods and Materials:*** The study was a descriptive cross-sectional, to assess relationship between peripheral artery disease and carotid atherosclerosis among type 2 diabetic subjects in UPTH using the ankle brachial pressure index and carotid intima-medial thickness. 110 diabetic subjects, and 110 age and gender matched non-diabetic, controls were recruited for the study. Type 2 diabetic subjects and controls that met the inclusion criteria and consented were recruited consecutively as they met the inclusion criteria.

Demographic data, anthropometric measures were taken and recorded. Using a structured questionnaire, information on medical history, physical examination and examination of carotid intima-medial thickness were measured and documented. Confidentiality was maintained throughout the 13 months period of the study. Data obtained were checked for errors and corrected before being analyzed using the statistical package for social sciences software 20.0 (SPSS 20.0).

Results: There were 67 females and 43 males with type 2 diabetes, while 61 Females and 49 males served as controls. The mean age for the diabetic subjects was 54.85 ± 10.09, while that for the controls was 52.86 ± 10.31. The mean duration of diabetes mellitus was 6.24 ± 4.53. The patient with CIMT more than 1mm account for 19.1% of the subjects, while the controls had 7.3% Th is statistically significant with a p-vale of <0.001.

Increased thickness of the carotid intima-medial was found to be significantly associated, increasing duration of diabetes.

Conclusion: CIMT is more common in diabetic patients compared to age and gender-match controls. Most subjects with increased CIMT are asymptomatic.

Keywords: ***Type 2 diabetes mellitus, Carotid intima medial thickness'***

Introduction

Cardiovascular disease (CVD) refers to diseases that involved the heart and the blood vessels [1]. These include coronary artery disease, stroke, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathies, arrhythmia, congenital heart disease, valvular heart disease, carditis, aortic aneurysms, peripheral artery disease (PAD), thromboembolic disease, and venous thrombosis. CVDs prevalence increase with age [2-4]. cardiovascular diseases are major the complications of Diabetes Mellitus. About 50 percent of people with diabetes die from heart disease and stroke [3].

CIMT is a surrogate marker of generalized atherosclerosis and is a risk factor for ischemic stroke and coronary artery disease [5,6]. CIMT is a non-invasive means of assessing early atherosclerosis in the carotid arteries. Its advantage over coronary calcium scoring and coronary CT angiography is the lack of ionizing radiation and the ability to detect disease at an earlier stage when coronary calcium score is often zero. Hence this study cross sectional looked at CIMT among patients with type 2 diabetes mellitus as compared with age and sex control.

Methods and Materials

This was a descriptive cross-sectional study designed to assess the carotid intima media thickness among type 2 diabetic patients at UPTH, Port Harcourt. The CIMT was assessed using carotid ultrasound. The study enrolled 110 confirmed diabetic patients who were on lifestyle modification in combination with oral anti-diabetic agents. The study was carried out in the Medical Out-patient Clinic (MOPC) and Medical Wards of the University of Port Harcourt Teaching Hospital (UPTH). The study population consisted of patients with T2DM who presented to the medical out-patient department.

Inclusion criteria for patients

1. All type 2 diabetic subjects on lifestyle modification or oral antidiabetic agents, who gave written informed consent or thumb printed consent. A patient was classified as having T2DM if he or she had been diagnosed with DM for at least 1 year on lifestyle modification and oral antidiabetic agent(s).
2. Patients between 30 and 70 years of age.

Exclusion criteria for patients

1. Subjects classified as Type 1 Diabetes Mellitus based on dependence on insulin for survival at onset of illness.
2. T2DM patients on insulin.
3. Hypertension: patients on antihypertensive medication or blood pressure equal or greater than 140/90 mmHg
4. Pregnant women with Diabetes mellitus
5. Severe (critical) medical illness (including diabetic foot ulcers) that would interfere with the ability to carry out the study.
6. History of tobacco use (past or current smokers, active or passive smokers)
7. Patients with estimated glomerular filtration rate ≤ 60 ml/min/1.73m3

Inclusion criteria for control

1. Apparently healthy age and sex matched individuals without diabetes mellitus were selected from hospital staff and patient relatives.

Exclusion criteria for controls

1. Patients with impaired fasting glucose tolerance. This refers to FBG of 6.1 to 6.9 mmol/l [7]
2. All the exclusion criteria for the subjects listed above equally applied for the controls.

Informed written consents were obtained from all the subjects and controls before recruitment into the study. Ethical approval for the study was sought and obtained from the Ethics Committee of the University of Port Harcourt Teaching Hospital before commencement of the study.

Carotid intima-media thickness (CIMT) measurement

The procedure was explained to the patient. The patient was in supine position, comfortable, relaxed and rested with the neck slightly hyper-extended and turned at 45 degrees for better exposure of the landmark of the carotid artery. Imaging of both carotid arteries was performed in all subjects using General Electronic (GE) LOGIQ e ultrasound Machine (GE medical system, 2007, Jiangsu, China) equipped with a 7.5-MHz imaging transducer.

The transducer was lubricated with gel and applied on the lower aspect of the neck transversely with the orientation marker pointing posteriorly. The common carotid artery was identified, and the course was followed until the bifurcation and the external and internal carotid arteries were visualized. The transducer was subsequently positioned longitudinally with the marker orientation pointing towards the patient head. This was displayed in longitudinal axis and measurement was taken from far and near walls, each about 1cm proximal to the bulb of the common carotid artery. The carotid wall was seen as two parallel echogenic lines separated by a hypo-echoic line. The inner hypo-echoic line was the lumen-media interface and the outer line was the media-adventitia interface. The distance between the two lines is the combined intima-medial thickness. Two measurements (the far and near wall) was made in each common carotid artery. The mean of the four readings was used to calculate the CIMT [8]. Plaque was defined as a focal protrusion of more than or equal to 1.5mm or 50% IMT of the surrounding wall [8].

For the study, measurements were made on frozen images, and each measurement was repeated two times and the mean of the left and right CCA IMT taken for analysis. For the purpose of this study; values > 1.0 mm was considered significant since no Nigerian normative values were available.

Data analysis

Statistical analysis was performed using the 20th version of Statistical Package for Social Sciences (SPSS), IBM cooperation 2011, Armonk, New York, USA [9]. The results were presented in tabular or graphical forms, as were appropriate. Mean CIMT for subjects and controls was compared for difference in mean using independent sample t-test. The aged, related intima media thickness were compared among the study group using Chi square.

Definitions

Normal CIMT ≤1.0mm, Significant Carotid intima media thickness was defined as CIMT >1 -1.5mm; carotid intima plaque was defined > 1.5 mm [8-13]. Age was categorized as <55 years and ≥ 55 years for the assessment of CIMT risk factor.

Results

This study was conducted over a period of 13 months, between May 2016 and May 2017. A total of 220 subjects comprising 110 subjects and 110 controls were recruited after they satisfied the inclusion and exclusion criteria for the study. The male/female ratio among the subjects and controls was 1:1.5 and 1:1.3 respectively. The age distribution and socio-demographic characteristics of the entire study population was summarized in Table 1.0.

The ages of the diabetic subjects ranged from 34 - 70 years, while those of controls ranged from 32 - 70 years. The mean age for the diabetic subjects was 54.85 ± 10.09, while that for the controls was 52.86 ± 10.31. There was no statistically significant difference in the mean ages between the diabetic subjects and the controls (t test = 1.447, p-value= 0.150). The female were more than male in both subjects and controls. There was no statistically significant difference between the genders for subjects and controls (X2 = 0.019, p-value= 0.890).

The participants in this study were mostly civil servants. Of the 110 subjects and 110 controls, 95.5% and 94.5% respectively were married, while 2.7% of cases and 3.6% of controls were singles. Subjects who had been widowed comprised 0.9% of subjects and 1.8% of controls. 0.9% of the subjects had divorced.

Table 1. Demographic characteristics of the entire study population

Variable	Diabetic subjects N=110 n (%)	Controls N=110 n (%)	Total N=220 n (%)	X^2	p-value
Age (year)					
1.<40 years	9 (8.2)	9 (8.2)	18 (8.2)		
2.40 - 49 years	28 (25.5)	27 (24.5)	55 (25.0)	2.427	0.331
3.50 - 59 years	33 (30.0)	29 (26.4)	62 (28.2)		
4. ≥60 years	40 (36.4)	45 (40.9)	85 (38.6)		

Gender 1.Male 2.Female	 43 (39.1) 67 (60.9)	 49 (44.5) 61 (55.5)	 2 (41.8) 128 (58.2)	 0.019	 0.890
Education 1.None 2.Primary 3.Secondary 4.Tertiary	 18 (16.4) 23 (20.9) 28 (25.5) 41 (37.3)	 18 (16.4) 24 (21.8) 24 (21.8) 44 (40.0)	 36 (16.4) 47 (21.4) 52 (23.6) 85 (38.6)	 5.162	 0.890
Occupation 1.Civil servants 2.Farmers 3.Students 4.Business 5.Unemployed 6.Others	 46 (41.8) 19 (17.3) 10 (9.1) 20 (18.2) 5 (4.5) 10 (9.1)	 44 (40.0) 14 (12.7) 11 (10.0) 23 (20.9) 6 (5.5) 12 (10.9)	 90 (40.9) 33 (15.0) 21 (9.5) 43 (19.5) 11 (5.2) 22 (10.0)	 1.028	 0.149

Thickened Carotid Intima Medial Thickness [CIMT] among subjects

CIMT was thickened in 19.1% (17 had thickened CIMT and 4 had plaques) among subjects, with a male-female ratio of 1.3:1.0. (**See Figure 1**). Among the controls, CIMT is thickened in 7.3% (7 had thickened CIMT and 1 had plaque). The five plaques seen in this study are homogenous with smooth surface (Gray-Wale class 4). The risk of developing thickened CIMT [carotid atherosclerosis] in the diabetic subject is 3.0 times higher when compared to the age and gender matched control. The average CIMT among subjects is 0.84 ± 0.23 and controls is 0.77 ± 0. This is statistically significant with a P-value of 0.012. In both subjects and control, the CIMT increase with age as seen in Table 2.

Table 3 showed increasing the duration of diabetes mellitus was associated with higher CIMT values and this was statistically significant (p-value <0.001).

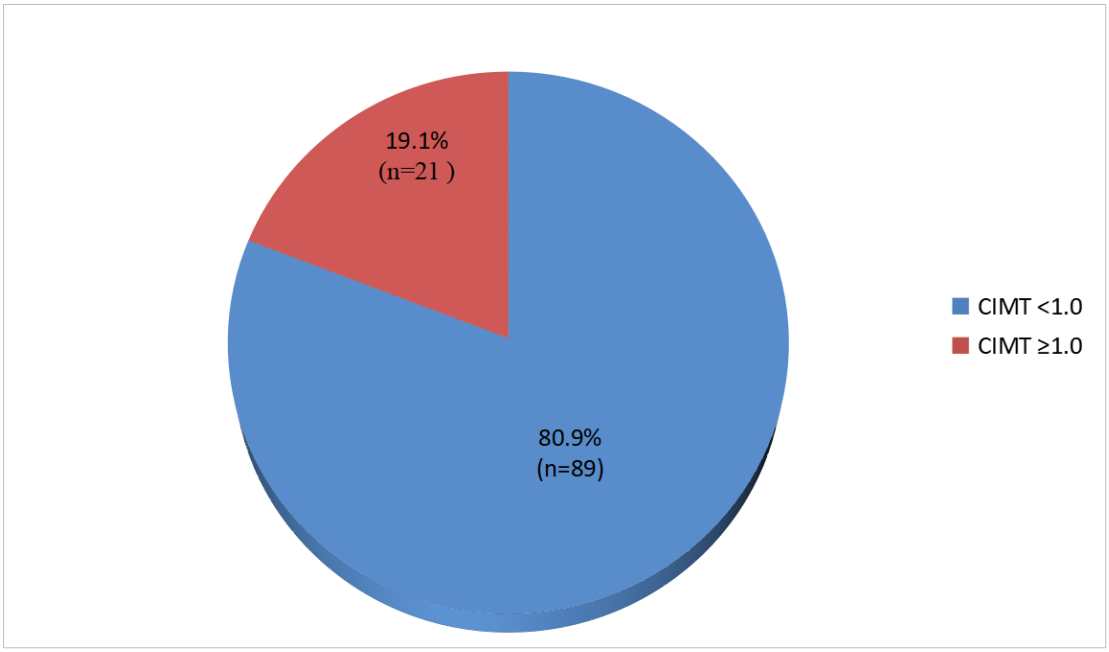

Figure 1: Pie chart showing distribution of carotid intima media thickness among T2DM patients. CIMT≥1 mm (carotid atherosclerosis); CIMT<1mm (no carotid atherosclerosis).

Table 2. Age grouping distribution of carotid intima medial thickness among subjects

Age (years)	CIMT ≤ 1mm n [%]	CIMT >1mm n [%]	P-value
<40	8 (88.9)	1 (11.1)	
40-49	25 (89.3)	3 (10.7)	
50-59	26 (78.8)	7 (21.2)	
≥60	30 (75.0)	10 (25.0)	
Total	89 (80.8)	21 (19.1)	0.042

Table 3: Duration of T2DM and CIMT

Variable	CIMT1mm n [%]	CIMT>1mm n [%]	X^2 Chi square	p-value	95% CI
Duration of DM (yr) < 5 5-10 >10	 51(94.4) 33(86.8) 5(27.8)	 3(5.6) 5(13.2) 13(72.2)	 32.221	 <0.001*	 0.000, 0.027

Discussion

CITM is a marker used to diagnose the extent of carotid atherosclerotic vascular disease. The test measures the thickness of the inner two layers of the carotid artery the intima and the media layers and alerts physicians to any thickening when patients are still asymptomatic [14]. The measurement is usually made by external ultrasound and occasionally by internal invasive ultrasound catheters. It is a marker of subclinical atherosclerosis (asymptomatic organ damage) and should be evaluated in every asymptomatic adult or hypertensive patient at moderate risk for cardiovascular disease [14]. Intima-media thickness values of more than 0.9 mm (European Society of Cardiology) or over the 75th percentile (American Society of Echocardiography) should be considered abnormal [15]. Normal mean carotid intima-media thickness values of 0.5 mm - 0.9 mm have been reported for the young (20 - 30 years) and for older (>60 years) age group respectively [16-18]. While values between 0.9 mm - 1.4 mm are considered as thickening, values higher than 1.4 mm are indicative of atheromatous plaque [19]. In this study however, thickness was classified into 2 broad classes, >1 mm (carotid atherosclerosis) and ≤1mm (normal with no carotid atherosclerosis).

The findings of this study demonstrated that there is an increase in CIMT in patients with Type II DM when compared to the control group. This has been well documented in previous studies such as Kumar *et al* [19] where average CIMT was significantly higher in Diabetic cases than Control with 25% of the Diabetics having abnormal CIMT while none of the control group had abnormal CIMT [19]. The results of Temelkova - Kurktschiev *et al* show that the diabetic subjects, both men and women, displayed carotid intimal-medial thickening, even in the subgroup with fasting plasma glucose between 7.0 and 7.8 mmol/l (i.e., lower FPG levels) [20]. Another study by Folsom *et al* which analyzed the relationship between increase in CIMT and some risk factors including DM found that in both sexes, diabetic subjects had carotid artery walls about 0.07 mm thicker than the control group and subjects with fasting glucose equal to 6.4 to 7.7 mmol/L had artery walls about 0.02 mm thicker than subjects with fasting glucose <6.4 [21]. These findings are in conformity with the results of this study which showed a statistically significant increase in the risk of developing carotid atherosclerosis in Type II DM patients with a P-value of 0.012. Other studies have demonstrated similar results such as Charvat *et al*, L.E Wagenknecht *et al*, van Mil *et al* Okafor *et al* [22-25].

The study also found a positive correlation between the duration of type II DM and CIMT. It was discovered that there is an increase in CIMT with increase in duration of Type II DM. Essentially, the longer the duration of Type II DM, the more likely there is to be an increased CIMT. This is in line with findings of similar studies such as Okafor *et al* which attributed the positive association to continued post prandial hyperglycemia resulting in oxidative stress, impaired endothelial function and facilitating monocyte adhesion to endothelial cells and thickening of intima - media which eventually contributes to the development of atherosclerosis [25]. Similarly in Kota *et al* it was discovered that subjects with duration of T2DM >10 years had a higher prevalence of increased CIMT [26]. Noor *et al* indicates that with respect to duration of diabetes the carotid intimal thickness showed a linear relationship [27]. As the duration of diabetes increased the value of carotid intimal thickness progressively increased. This finding was also in consonance with the findings of other studies such as Butt *et al*, Gayathri *et al*. [28,29].

The prevalence of the carotid atherosclerosis from the results of this study is 19.1% among subjects. Most of these patients are asymptomatic. This prevalence is significantly lower when compared to similar studies such as Baba *et al* in which the diabetic group had a significantly higher mean CIMT compared to control at all levels. Seventy-nine (90.8%) of the patients with diabetes in this particular study had CIMT greater than 0.9 mm, while sixty-nine (79.3%) had CIMT greater than 1.0 mm [30]. This discrepancy in prevalence size may be due to inclusion of hypertensive patients, patients with elevated cholesterol which resulted in a broader sample size as opposed to this study which excluded patients with elevated blood pressure, stroke, elevated cholesterol levels resulting in a much smaller sample size which in turn resulted in a smaller prevalence. This is also seen in other studies such Okeahialam *et al*. in which the prevalence of carotid atherosclerosis was 47.5% for diabetics and this prevalence was much higher than what was observed in the study due to the inclusion of hypertensive patients in their study population [18].

Conversely, Zhou *et al* which analyzed the risk factors for carotid intima-media thickness in patients with type 2 diabetes mellitus had a prevalence rate 29.7% from a total of 1372 patients [31]. The exclusion criteria of the study were similar to that of this study which could account for the lower prevalence seen here. The prevalence (19.1%) of carotid atherosclerosis among subjects in this study was similar to the 20% reported by Argawal *et al* in a study of 140 T2DM in Chennai, India [32]. The reason for this similarity was not clear because the Indian study did not exclude current smokers and hypertension, but race differences could account for it. We studied blacked Population in Africa while Argawal *et al* studied Indian Asian population. The two studies were carried out in different racial population background, ours was a hospital based cross sectional among blacks living in Port Harcourt, while theirs was a community cross sectional among Asian living in Chennai, India.

However, the prevalence in this study was lower than the prevalence of 47.5% among T2DM reported by Okeahialam *et al* at the Jos University Teaching Hospital (JUTH) [18]. The reasons for the low prevalence in this study compared to the JUTH study is not clear. However, the two studies differed in CIMT cut off; ≥ 1.0mm was used to defined carotid atherosclerosis in this study, while ≥ 0.91mm was used to defined it in JUTH study. Total numbers of participants in the JUTH study were 70, while this study included 110 participants. The mean duration of DM in this study was 6.24 ± 4.53. The mean duration of DM in the JUTH study was not stated.

The prevalence in this study was much lower than 69.5% reported by Brasileiro *et al* in Brazil [33]. Their study involved smokers, and advanced atherosclerotic subjects and different ethnic background compare to this study. Thus, our findings emphasize screening for atherosclerosis at the time of diagnosis of diabetes not only for early detection but also to prevent the progression to end-stage disease, which is in line with the recommendations of international guidelines to screen for peripheral vascular disease in patients with diabetes.177 The difference in the two studies may also be related to the CIMT value considered to be abnormal, >0.9mm was used as the cut off in their study, while ours used ≥1.0mm [34]. This study prevalence was much lower than the prevalence of 58.18% reported by Wu *et al* in China [34]. The reasons might be different clinical setting and racial background, inclusion of current smokers and ex-smokers, longer mean duration of DM (8.23 years for male, and 10.10 years for females) and higher mean HbA1c (9.54±2.39 for males and 9.54 ± 2.39 for females).

Conclusion

The results of this study indicate that there is a strong correlation between the presence of type II diabetes mellitus and increased CIMT. This correlation is one of note as it shows that presence of Type II DM significantly increases the risk of cerebrovascular events.

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Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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