INFLUENCE OF DIABETES MELLITUS ON CAROTID INTIMA-MEDIA THICKNESS OF NON-OBESE, NORMOTENSIVE DIABETIC PATIENTS

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ABSTRACT

Background*: Diabetes mellitus is a chronic metabolic disease of great public health importance. Macrovascular complications like stroke and myocardial infarction initially manifest as atherosclerosis which is seen as thickened arterial wall. Direct determination of the progression of atherosclerosis can be undertaken through serial ultrasound measurement of the common carotid artery (CCA) intima media thickness (IMT).*

Aim: *The objective of the study was to compare the IMT of the CCA in diabetic patients and healthy subjects within the same age, sex and geographic distribution.*

Method: *This prospective study was conducted on 100 diabetic patients and 100 non-diabetic subjects aged 21years and above. The CCAs were scanned using GE Logic 5 color Doppler scanner (2007) with 7.5MHz linear probe. Two measurements of the IMT were obtained at 1cm proximal to the right and left carotid bulbs and the mean value of the two measurements was recorded.*

Results: *The age range of the 200 participants comprising of 65 males and 135 females was 21-70 years with a mean age of 46.60 ±12 years. Mean CIMT was significantly higher in diabetic patients compared to normal patients (0.81±0.25mm and 0.61±0.12mm, p= 0.001). Age has significant influence on the CIMT on both groups of participants. However, male and overweight subjects had significantly higher CIMT values than female and underweight subjects respectively only among non-diabetic subjects. The overall right and left mean CIMT in the diabetic patients and control respectively were 0.78±0.21mm, 0.83±0.37mm, 0.61±0.12mm and 0.61±0.13mm. In each group, there was no significant difference between the two sides.*

Conclusion: *CIMT values were higher among non-obese normotensive diabetic patients compared to normal subjects. Age, sex, and BMI have effects on CIMT of non-diabetic subjects, whereas only age has significant effect on the CIMT of diabetic patients.*

Keywords: *Diabetes Mellitus, Carotid Intima-Media Thickness, Non-Obese, Normotensive*

Introduction

Diabetes mellitus is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both[1]. In Nigeria, diabetes had a prevalence rate of 2.2% in 1997[2]. The case fatality rate among patients with diabetes was estimated as 11.1% of total medical deaths[3]. Early predictor of cardiovascular event is atherosclerosis which is a systemic condition primarily affecting elastic arteries (carotid, iliac arteries, aorta) as well as large and medium sized muscular arteries. Its presence is a sinister pointer to cerebro-vascular diseases and myocardial infarction[4]. It initially manifests as thickened arterial wall, progressing to atheroma formation especially of the carotid and coronary arteries.

Ultrasound scan permits us to accurately quantify the carotid intima media thickness (CIMT) which is generally considered an early marker of atherosclerosis sonographically. This assessment has been proposed as a noninvasive measure of cardiovascular disease burden in adults[5]. Several studies have been carried out to underscore the causes of thickened carotid intima media complex. The roles of hypertension, cigarette smoking, obesity, hyperlipidaemia and ageing have been investigated and documented. There is paucity of knowledge on the role of isolated hyperglycemia as an index of thickened carotid artery intima media complex. This study compared the carotid artery intima media thickness among non-hypertensive, non-obese diabetic patients with the normal healthy volunteers. The outcome of this study is expected to be useful in the diagnosis, management and follow up of patients with diabetes mellitus.

Methodology

This hospital-based cross-sectional study was carried out at the Jos University Teaching Hospital (JUTH) within a 5-month period, between May and December, 2015. Diabetic patients were recruited from the endocrinology unit of the hospital. Ethical clearance was obtained from the Ethical committee of the hospital.

The examination was performed using high resolution real time ultrasound scanner GE Logic 5 color Doppler scanner (2007) with 7.5MHz linear probe. Using a high frequency transducer ensures greater resolution for superficial structures like the carotid artery.

Subject's study area was adequately exposed and jewelry around the area was requested to be removed. In the absence of dyspnea or back pain, carotid arteries were examined with the patient in supine position. Hyperextension was achieved by placing a small pillow under the neck. To enhance the neck exposure, the head was turned away from the examined side at about 45^0 angles from the midline. The CCA was located lateral to the thyroid gland, medial to the internal jugular vein (IJV). Multiple transverse and longitudinal views of the artery were undertaken. The IMT was taken in the longitudinal plane at the point of maximal thickness on the far wall of the CCA, at a point 1cm proximal to the bifurcation. The machine was frozen and using its caliper markers the IMT was measured as the distance between the inner echogenic line representing the intima-blood interface and the outer echogenic line representing the media-adventitia junction. Magnification of the image was used to improve accuracy of the caliper placement. The average value of two different measurements was recorded for both left and right CCAs respectively.

Results

A total of 200 subjects made up of 100 diabetic patients and 100 non diabetic controls participated in the study. Participants were between 21 and 70 years with mean age of 47.8±11.61 and 45.26±12.95 years for the diabetics and control respectively. Among the diabetes, 33 were males and 66 were female, while in the control, 32 were male and 68 were female, giving approximate male-to-female ratio of 1:2 in each subject group. The predominant age group in diabetics and control was 41-50 years accounting for 34% and 31% respectively, followed closely by 31-40 years group comprising 29% and 28% for diabetics and control respectively (Table 1)

In diabetic subjects, overall right and left mean CIMT was 0.78±0.21 mm and 0.83± 0.37mm respectively, while in control, corresponding values were 0.61± 0.12mm and 0.61±0.13mm. On each side, a statistically significant difference (p=0.001) existed in the mean CIMT between the diabetic and control groups (Table 3). However, there was no statistically significant difference between the right and left CIMT in both groups (Table 2).

The mean carotid intima-media thickness (CIMT) for diabetic group in this study was 0.81±0.25mm and 0.61±0.12mm for the control (p= 0.001). The mean CIMT for male and female diabetics were 0.83±0.29mm and 0.79±0.22mm respectively while for the control, the values were 0.66±0.12mm and 0.58±0.09mm respectively. Males IMT values were higher than females IMT value in both groups. However, the difference between male and female IMT was significant only among the control (P=0.498 Vs P = 0.002, Table 3).

Statistically significant increase in CIMT occurred in both subject groups with age (p=0.001) (Table 4). Also, CIMT was significantly higher in all age groups among diabetics compared with age-graded control ($p < 0.05$ across all age groups) (Table 4).

Weighing CIMT with BMI in non-obese diabetic and control subjects revealed increasing CIMT values from underweight to overweight participants in both groups. This increase was significant only in the control group (p= 0.003 vs 0.250). In each BMI group, there was a significant difference between diabetic patients and control (Table 5).

Table 1: **Age Distribution of Participants**

Age group	**Diabetics**		**Control**	
(Years)	**Frequency**	**Percent (%)**	**Frequency**	**Percent (%)**
21 – 30	5	5.0	8	8.0
31 – 40	29	29.0	28	28.0
41 – 50	34	34.0	31	31.0
51 – 60	16	16.0	17	17.0
61 – 70	16	16.5	16	16.0
Total	**100**	**100.0**	**100**	**100.0**

Table 2: **Comparison between Right and Left Mean CIMT of participants**

Group	**Right CIMT Mean±SD(mm)**	**Left CIMT Mean±SD(mm)**	**t-test**	**P**
Diabetic	0.78±0.21	0.83±0.37	1.544	0.126
Control	0.61±0.12	0.61±0.13	0.250	0.803
Total	**0.69±0.19**	**0.72±0.30**		
t= 7.043	p = 0.001	t= 5.768	p = 0.001	

Table 3: **Relationship between gender and CIMT of participants**

Gender	**Diabetic Frequency**	**CIMT Mean±SD(mm)**	**Control Frequency**	**CIMT Mean±SD(mm)**	**t-test**	**P**
Male	33	0.83±0.29	32	0.66±0.12	3.063	0.003
Female	67	0.79±0.22	68	0.58±0.11	6.957	0.001
Total	**100**	**0.81±0.25**	**100**	**0.61±0.12**	**9.240**	**0.001**
t = 0.680	p= 0.498t = 3.157		p= 0.002			

Table 4: **Relationship between age group of participants and CIMT**

Age group (Years)	Diabetic Frequency	CIMT Mean±SD(mm)	Control Frequency	CIMT Mean±SD(mm)	t-test	P
21-30	5	0.66±0.07	8	0.49±0.09	3.581	0.004
31-40	29	0.70±0.01	28	0.53±0.08	7.269	0.001
41-50	34	0.82±0.29	31	0.59±0.07	4.176	0.001
51-60	16	0.82±0.10	17	0.61±0.07	6.850	0.001
61-70	16	1.01±0.34*	16	0.82±0.05*	2.278	0.030
Total	**100**	**0.81±0.25**	**100**	**0.61±0.12**	**7.240**	**0.001**

F = 3.436 P = 0.001F = 47.555 P = 0.001

*Age group 61-70 is significantly higher than the others at p = 0.05

Table 5: **Relationship between BMI of participants and CIMT**

BMI (Kg/m^2)	Diabetic Frequency	CIMT Mean±SD(mm)	Control Frequency	CIMT Mean±SD(mm)	t-test	P
<18.5	4	0.66±0.01	6	0.47±0.08	4.494	0.002
18.5-24.9	37	0.77±0.01	44	0.59±0.12	6.223	0.001
25.0-29.9	59	0.84±0.30	50	0.63±0.11	4.480	0.001
Total	**100**	**0.81±0.25**	**100**	**0.61±0.12**	**7.240**	**0.001**

F = 1.408P = 0.250 F = 6.178P = 0.003

Discussion

Diabetes mellitus is the most common chronic metabolic disorder in Nigeria[2]. Thickness of the carotid intima-media complex is a surrogate marker of atherosclerosis. Stensland-Bugge *et al* regarded ultrasound measurement of carotid artery intima-media thickness (IMT) as a valid index of atherosclerosis[6]. The objectives of this study were to compare the carotid intima-media thickness (CIMT) in non-obese, non hypertensive diabetic patients and normal healthy control across age, sex and BMI status.

A total of 200 subjects (made up of 100 each of diabetic and control groups) were studied which revealed majority of the patients to be females with male to female ratio of 1:2 in each category. This study size was higher than those recruited in some previous studies[7,8] but less in some[9,10]. This variation results from difference in prevalence of diabetes in the different research environments. Majority of the participants (63% and 59% for diabetics and control respectively) were between 31–50 years of age. This probably represented the population of hospital attendees in a developing world like ours (with little family and institutional support for the elderly), as diabetes mellitus is essentially a disease

of middle age and elderly[11]. The finding of female preponderance in this study could be due to the fact that females access health care more and that there is a slightly higher prevalence of diabetes mellitus in female[2].

The overall CIMT value was significantly higher in diabetic patients investigated than in the control (0.81±0.25mm Vs 0.61±0.12mm) (p= 0.001). This was consistent with previous studies [7,9,12]. None of the reviewed previous studies had a contrary finding. These differences in the overall CIMT in the two cohort groups was due to persistent hyperglycemia in the diabetic group not present in the control. Endothelial dysfunction and increased oxidative stress are present in diabetic individuals and are known pathogenetic mechanisms for atherosclerosis in them[13,14]. Also, persistent hyperglycemia is an established cause of endothelial damage with abnormalities of platelet aggregation[14]. This effect is not seen in non-diabetic patients whose blood levels are essentially normal, and thus normal CIMT is present in this group.

The mean CIMT value in diabetic subjects in this study (0.81±0.25mm) is comparable to other studies reviewed which recorded 0.79mm, and 0.84mm[7,9]. While Folsom *et al* [10] in United States, had lower values in diabetic patients between 45-65 year age group (0.75mm), a Swedish study arrived at a higher value (0.83mm)[15]. This most probably suggests genetic and environmental variation in CIMT. Inter-racial variation in the values of CIMT in diabetic and non-diabetic patients was established by Brohall *et al* in a review of 21 published studies across four continents[16]. Toumilehto *et al* found higher CIMT value in the non-diabetic elderly men compared with a diabetic group (1.36mm and 1.28mm respectively)[17]. However, this study differed from our study as the patients were all older men, aged 70-89 years.

This study showed greater, but insignificant (p= 0.126) difference in mean CIMT in the left CCA than in the right in patients with diabetes (0.78±0.21mm Vs 0.83±0.37mm on the right and left respectively). No difference was recorded regarding non-diabetic control (0.61±0.12mm Vs 0.61±0.13mm respectively, p= 0.803). These findings were supported by previous studies [8,18,19,20]. This is not surprising as apart from different anatomic origin, the right and left CCA are exposed to the same hemodynamic changes and hyperglycaemic stress.

There was a progressive increase in CIMT from age 21 to 70 years in diabetic patients and control. Age has a very strong association with carotid IMT in both subject groups. The CIMT values in diabetic subjects were higher than in the control for each age group. Most of the studies reviewed were consistent with increased CIMT with age [8,10,16,19]. These studies also showed that age has a strong correlation with CIMT values recorded. The increase in mean CIMT with age in normal healthy subjects could probably be due to specific effects of aging on the arterial wall or probably be due to exposure to risk factors not measured or captured in this work. Age, directly influencing the duration of diabetes and metabolic consequences of diabetes, modifies atherosclerotic process. A sharp rise in CIMT after age 60 years is observed in both diabetic and control groups depicting the overall greater effects of ageing over glycaemic status on CIMT in the elderly.

The mean CIMT values of male and female diabetics were higher than the mean CIMT values of male and female control (0.83±0.29mm and 0.79±0.22mm Vs 0.66±0.12mm and 0.58±0.11mm). In diabetic subjects and control, males had a higher CIMT value than females. These differences were significant between diabetic and control groups in each sex group (p< 0.005), and between male and female control (p=0.002). Other studies supported this finding [7,12,15,19]. This may be explained by the sex variation in the development of atherosclerosis. Males have a higher predisposition to atherosclerosis more often than women, although the reasons are not known but may be due to the fact that males are more prone to psychological and environmental stress than females[21]. However, in patients with diabetes mellitus, the effects of hyperglycaemia on CIMT override these gender variations.

This study evaluates the effects of BMI on the CIMT of non-obese diabetic and non- diabetic subjects and shows a progressive increase in mean CIMT in both categories. This was statistically significant only in the control (diabetic, p= 0.250; control, p= 0.003). Nilgun *et al* observed that apart from age, BMI is the most influential independent determinant of increased IMT of the CCA in normal patients[8]. Why hyperglycaemia overrides the effects of BMI in non-obese diabetes mellitus patients is unknown. BMI has been shown to influence the CIMT but the role of BMI of non-obese subjects in arterial wall thickening is poorly understood and its influence is probably independent of age[8]

Conclusion

This study showed thickened carotid intima-media complex among non-hypertensive, non-obese diabetic patients compared with control. Gender and BMI differences have no significant effects on CIMT of diabetic patients. Higher values of CIMT were seen with increasing age, in the male gender and with increased BMI status in normal subjects.

Conflict of Interest: None

REFERENCES

1. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complication. Report of a WHO Consultation Part 1: Diagnosis and Classification of Diabetes Mellitus.AccessedJuly8,2014.Available:http: //www.staff.ncl.ac.uk/philip.home/who_dcm /htm.
2. Akinkugbe O. Non-Communicable Diseases in Nigeria- Final Report of a National Survey; Lagos: Fed Ministry of Health-National Expert Committee on NCD, 1997:1-12.
3 Unachukwu C, Ofori S. Diabetes Mellitus and Cardiovascular Risk. The *Internet J of Endocrinology*. 2012; 7(1):83-87.
4 O' Leary DH, Polark JF, Richard AK. Carotid Artery Intima Media Thickness as a Risk Factor for Myocardial Infarction and Stroke in Older Adult. *N Engl J Med* 1999; 340:14-22
5 Lee EJ, Kim HJ, Bee JM. Relevance of common Carotid Intima Media Thickness and Carotid Plaque as Risk factors for Ischaemic Stroke in Patients with type 2 Diabetes Mellitus. *America J of Neuroradiology* 2007;28:916-919
6 Stensland-Bugge E, Bønaa KH, Joakimsen O, Diamond J. Sex Differences in the Relationship of Risk Factors to Subclinical Carotid Atherosclerosis Measured 15 Years Later. Stroke 2000;31:574
7 El-Barghouti N, Elkeles R, Nicolaides A, Geroulakos G, Dhanjil S. The ultrasonic evaluation of the carotid intima-media thickness and its relation to risk factors of atherosclerosis in normal and diabetic population. Int Angiol 1997; 16: 50–54
8 Nilgun G, Neslihan B, Aytekin O, Tomris E. Major Determinants of the Carotid Intima-Media Thickness in Type 2 Diabetic Patients: Age and Body Mass Index. *Endocrine J* 2000, 47(5), 525-533
9 Manuel AG, José IR, Emiliano RS, Maria CP, Rosa M, *et al*. Carotid Intima-Media Thickness in Diabetics and Hypertensive Patients. *Rev Esp Cardiol*. 2011;64(7):622-625
10 Folsom AR, Eckfeldt JH, Weitzman S. Relation of carotid artery wall thickness to diabetes mellitus, fasting glucose and insulin, body size and physical activity. Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Stroke* 1994;25(1):66-73
11 Backman JA, Creager MA, Libby P. Diabetes and Atherosclerosis. Epidemiology, Pathophysiology and Management. JAMA 2002; 287: 2570.
12 Okeahialam BN, Alonge BA, Pam SD, Puepet FH. Carotid Intima Media Thickness as a Measure of Cardiovascular Disease Burden in Nigerian Africans with Hypertension and Diabetes. *Int J Vasc Med*. 2011. Published 2011 doi: 10.1155/2011/321717
13 John AC, Maria-Lopez V, Perry VH. Pathogenesis of Atherosclerosis in Diabetes Mellitus. *Diabetes Care* 1981; 4:121-133 Mellitus. *International Journal of Vascular Medicine*. 2011 Article ID 327171.
14 Doron A, Elliot R. How Hyperglycemia promotes Atherosclerosis: Molecular Mechanism. *Cardiovascular Diabetology* 2002, 1(1) 1475- 2840.
15 Hedblad B, Nilsson P, Janzon L, Berglund G. Relation between insulin resistance and carotid intima-media thickness and stenosis in non-diabetic subjects. Results from a cross-sectional study in Malmo, Sweden. Diabet Med 2000; 17: 299–307
16 Brohall G, Odén A, Fagerberg B. Carotid artery intima-media thickness in patients with type 2 diabetes mellitus and impaired glucose tolerance: a systematic review. *Diabet Med*. 2006;23:609-616
17 Tuomilehto J, Qiao Q, Salonen R, Nissinen A, Salonen JT. Ultrasonographic manifestations of carotid atherosclerosis and glucose intolerance in elderly eastern Finnish men. *Diabetes Care*. 1998; 21(8):1349-1352
18 Niskanen L, Rauramaa R, Miettinen H, Haffner MS, Mercuri M. Carotid artery intima-media thickness in elderly patients with NIDDM and in non-diabetic subjects.

Stroke 1996;27: 1986-1992

19 Kolade-Yunusa HO, Haruna AS. Sonographic Measurement of Common Carotid Artery intima media thickness among healthy Adults in Jos, Nigeria. *J. Harmoniz. Res. Med. And Hlth. Sci*. 2015;2(4):156-162

20 Rosfors S, Hallerstam S, Jensen-Urstard K. Relationship between intima-media thickness in the common carotid artery and atherosclerosis in the carotid bifurcation. *Stroke* 2004;29(7):1378-1382

21 Bosevski M, Georgievska L, Tosev S, Borozanov V. Risk factors for development of peripheral artery disease among Type 2 diabetic patients. *Prilozi*. 2009;30(1):81-90