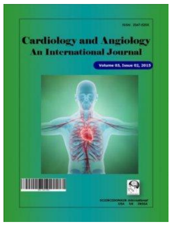

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Carotid Intima-media Thickness and Risk of Cardiovascular Disease among Healthy Adult Volunteers in North Eastern Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MAT, MMB, POI and HA designed the study and wrote the protocol. Authors MAT, MMB and FB performed the statistical analysis and wrote the first draft of the manuscript. Authors MMB, POI and HA managed the analyses of the study. Author FB managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Assessment of carotid intima media thickness (CIMT) have evolved over the years to assume a key role in assessment of cardiovascular risk. However, there is paucity of data on CIMT among Nigerian. We assessed CIMT and its association with cardiovascular risk factors among apparently healthy individuals.
Methods: Apparently healthy adults were consecutively recruited from July 2013 through March 2014 at the Federal Medical Centre Nguru. Anthropometric variables were measured and blood samples collected. CIMT was determined at the common carotid, carotid bifurcation, and proximal internal carotid artery levels using a high-resolution 2-D USS scanner, and values above 0.9mm

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considered abnormal. Means of continuous variables were compared using Student t-test or Mann-Whitney *U* test, while between groups mean was compared using one-way ANOVA. Association of CIMT other continuous variable was assessed using bivariate correlation and multivariable linear regression models. A p value of <0.05 was considered significant for all statistical analysis.
Results: Ninety nine apparently healthy consenting adults comprising 63(63.6%) males and 36(36.4%) females were consecutively recruited. Their median (interquartile range) age was 34(27) years. Mean left CIMT at common carotid, carotid bifurcation and internal carotid artery levels were 0.82(0.22), 0.91(0.23) and 0.85(0.21) respectively (F=3.57, p=0.029). There was no difference in CIMT between the left and the right sides. Thirty one (31.3%) had CIMT above 0.9mm. Significant correlation was found between CIMT and age (r^2=0.33, p<0.001), body mass index (BMI) (r^2=0.06, p<0.001), systolic blood pressure (r^2=0.11, p=0.001), glycated haemoglobin (r^2=0.34, p<0.001), total cholesterol (r^2=0.42, p<0.001), LDL-c (r^2=0.47, p<0.001) and HDL-c (r^2=-0.14, p<0.001). Age, BMI, blood pressures, total cholesterol, LDL-c and HDL-c independently predicted CIMT.
Conclusion: The prevalence of increased CIMT is high among healthy adults, and CIMT correlated positively with other cardiovascular risk factors. Routine assessment of CIMT may identify individuals with increased risk for cardiovascular diseases and result in more targeted preventive measures.

Keywords: Carotid-intima-media-thickness; healthy adults; cardiovascular risk.

1. INTRODUCTION

Cardiovascular disease is an important cause of morbidity and mortality in the developing world, Nigeria inclusive [1,2]. This has featured prominently as a leading cause non-communicable disease (NCD) death, followed by malignancies/other neoplasms, respiratory diseases and diabetes mellitus [2]. Although hypertensive heart disease, rheumatic heart disease (RHD) and dilated cardiomyopathy (DCM) including peripartum cardiomyopathy (PPCM) remains the dominant aetiologies for heart related death in sub-Saharan Africa, the region is faced with high burden of atherosclerotic cardiovascular diseases including stroke and myocardial infarction [3,4].

Assessment of carotid intima media thickness (CIMT) using ultrasound (USS) have evolved over the years to assume a key role in the assessment of cardiovascular risk [5,6]. It combines the unparalleled advantages of being a sensitive, non-invasive and a reproducible test for assessing atherosclerotic vascular diseases and risk of CVD. The predictive and prognostic roles of CIMT for CVD has been validated in a number of landmark studies [7,8], leading to its inclusion in the list of diagnostic tools for global cardiovascular risk assessment [9]. Its impact is mainly in individuals with intermediate 10-year risk for cardiovascular events, allowing for reclassification to either the low-risk or high-risk category [10]. This has an enormous implication for the implementation of cost effective preventive measures.

There are a number of published researches on CIMT from different regions of Nigeria, but most of the studies centred on people with defined cardiovascular risk factors [11-14]. We sought to determine CIMT and its association with other cardiovascular risk factors among apparently healthy individuals from the northeast sub-region of Nigeria. This, we believe will add to the scanty pool of information on CIMT among healthy Nigerians, and allow for a more representative national reference to be generated.

2. METHODS

Apparently healthy consenting adults from all works of life were consecutively recruited from July 2013 to March 2014 at the Federal Medical Centre (FMC) Nguru. People with history or findings consistent with cardiovascular diseases or its treatment, smoking (current and past), substance abuse as well as pregnant women were excluded from the study. Anthropometric variables were measured using standard protocols, and blood samples collected for determination of blood sugar, cholesterol and BUN. Body mass index (BMI) was classified using the WHO guideline [15], while cholesterol levels were classified according to the NCTP III guideline [16]. Blood pressure was classified using the JNC 8 guideline [17].

Assessment of CIMT was done by a single radiologist with expertise in vascular USS, using a high-resolution 2-D USS scanner. Carotid USS was performed with the participants lying supine and the neck slightly extended. The head was directed away from the side of interest, and images systematically obtained at the common carotid, carotid bifurcation, and proximal internal carotid artery levels in both longitudinal and short axis planes. Images of the far wall of carotid artery was used in assessing CIMT. The intima-media interface was recognised in zoomed images, and CIMT determined using the leading-edge to leading edge method. Carotid plaques, where present were classified according to modified Gray-Weale classification [18]. Increased CIMT was defined as values greater than 0.9 mm at the left internal carotid artery.

Data was analysed using SPSS software (22.0). Normally distributed continuous variables were expressed as means (SD), while those not consistent with parametric distribution were expressed as median (interquartile range). Categorical variables were expressed as proportions and percentages. Means of continuous variables were compared using Student t-test or Mann-Whitney *U* test as appropriate, while between groups mean was compared using one-way ANOVA with Turkey's post-hoc analysis. Paired-sample t-test was used in comparing CIMT of the right and left side. Categorical variables were compared using Fischer exact Chi-square test. Association of CIMT other continuous variable was assessed using bivariate correlation and multivariable linear regression analysis. A p value of <0.05 was considered significant for all statistical analysis.

3. RESULTS

Ninety nine apparently healthy consenting adults comprising 63 (63.6%) males and 36 (36.4%) females were consecutively recruited. Their median (interquartile range) age was 34(27) years. The females are significantly older than the males (p<0.001). Their clinical characteristics are illustrated in Table 1.

The mean BMI was 22.1(2.12) kg/m^2, with 86(86.9%) having normal weight, 4 (4%) being overweight, and 9 (9.1%) being underweight. Pre-hypertensive systolic blood pressure (SBP) was documented in 57 (57.6%), while 2(2%) had SBP of 140 mm Hg. Twenty one (21.2%) had a diastolic blood pressure (DBP) of 90 mm Hg (with SBP less than 140 mm Hg), while 23 (23.2%) had a pre-hypertensive DBP.

One (1.3%) subject had a fasting blood glucose of 8.6 mmol/L, but none had impaired fasting glucose. The mean glycated haemoglobin (HbA1c) was 4.8(0.82) %. Total cholesterol was elevated in 26(26.3%), while elevated low density lipoprotein cholesterol (LDL-c) was documented in 24 (24.2%). Ten (10.1%), comprising of two males and eight females had low levels of high density lipoprotein cholesterol (HDL-c).

Table 1. Clinical characteristics of the participants

Variable	Male (n=63)	Female (n=36)	*p*
Age (years)	29 [24]*	45.5[29]*	<0.001†
BMI (kg/m^2)	21.6(2.07)	22.79(2.02	0.008
Blood pressure (mmHg)			
Systolic	114.9(8.96)	120.8(10.79)	0.004
Diastolic	72.9(9.91)	78.6(9.61)	0.006
FBS (mmol/l)	4.5(0.79)	4.3(0.50)	0.118
HbA1c (%)	4.8(0.83)	5.0(0.78)	0.187
Total cholesterol (mmol/l)	4.1(1.11)	4.7(0.98)	0.002
LDL-c (mmol/l)	2.8(0.81)	3.2(0.81)	0.012
HDL-c (mmol/l)	1.7(0.46)	1.6(0.47)	0.296
Triglycerides (mmol/l)	2.1(0.28)	2.2(0.35)	0.340
Intima-media thickness (mm)			
Right CC	0.81(0.24)	0.90(0.27)	0.068
Left CC	0.82(0.22)	0.90(0.27)	0.135
Right CB	0.90(0.25)	0.98(0.28)	0.117
Left CB	0.91(0.23)	0.98(0.28)	0.152
Right ICA	0.85(0.22	0.88(0.26)	0.443
Left ICA	0.85(0.21)	0.89(0.28)	0.431

*BMI=Body mass index; FBS=Fasting blood sugar; HbA1c=Glycated haemoglobin; LDL-c=Low density lipoprotein cholesterol; HDL-c=High density lipoprotein cholesterol; CC=Common carotid; CB= carotid bifurcation; ICA=Internal carotid artery; *=Median [interquartile range]; †=Mann-Whitney U test. Values expressed as mean (SD)*

The mean right and left CIMT were 0.84(0.25) mm and 0.85(0.24) mm at the common carotid artery (p=0.456), 0.93(0.26) mm and 0.94(0.25) mm at the carotid bifurcation (p=0.567), and 0.86(0.23) mm and 0.86(0.24) mm at the internal carotid (p=0.712) respectively. However, CIMT differed at the various levels (F=3.57, p=0.029), being highest at the level of carotid bifurcation. Males and females had comparable CIMT at all levels. However, there was a significant difference in mean CIMT between the various age groups (F=12.92, p<0.001). Individuals in the age groups 45 years and above had a significantly higher CIMT at similar levels than those 44 years and below in whom measured CIMT were also similar (Table 2). Participants with SBP of 120 mm Hg and above, glycated haemoglobin greater than 6% and total cholesterol greater than 5.2 mmol/L had significantly higher CIMT (Table 3). Thirty one (31.3%) of the participants had CIMT above 0.9 mm.

Table 2. Mean left internal carotid intima-media thickness by age group

Age group	Number (%)	Mean CIMT (mm)
<24	30(30.3)	0.78(0.106)
25 – 34	20(20.2)	0.69(0.189)
35 – 44	12(12.1)	0.775(0.277)
45 – 54	17(17.2)	1.053(0.223)
55 – 64	14(14.1)	1.056(0.201)
>64	6(6.1)	1.050(0.105)

CIMT=Carotid intima-media thickness. Values expressed as mean (SD)

Significant correlation was found between left internal carotid artery CIMT and age (r^2=0.33, p<0.001), BMI (r^2=0.06, p<0.001), SBP (r^2=0.11, p=0.001), HbA1c (r^2=0.34, p<0.001), total cholesterol (r^2=0.42, p<0.001), LDL-c (r^2=0.47, p<0.001) and HDL-c (r^2=-0.14, p<0.001). Using a threshold of 0.9 mm (Table 4), individuals having higher left internal carotid artery CIMT had significantly increased age (p<0.001), SBP (p<0.001), DBP (p=0.003), BMI (p<0.001), HbA1c (p<0.001), total cholesterol (p=<0.001), LDL-c (p<0.001) and lower HDL-c (p<0.001). Age, BMI, blood pressures, total cholesterol, LDL-c and HDL-c independently predicted CIMT (Table 5).

4. DISCUSSION

This is the first time CIMT is being evaluated among apparently healthy adults aged 18 years and above in north-eastern part of Nigeria. The average CIMT in our study is comparable to what was reported in Jos [11], although their patients were relatively older. Even though our female cohorts were significantly older than the males, there was no difference in CIMT between the two groups, a finding in contrast with reports from other parts of the world.

Table 3. Comparison of left internal carotid intima-media thickness based on levels of various cardiovascular risk factors

Variable	CIMT (mm)	*P*
SBP (mmHg)		0.032
≥120	0.91(0.23)	
<120	0.80(0.23)	
DBP (mmHg)		0.111
≥80	0.91(0.26)	
<80	0.83(0.21)	
FBS (mmol/l)		0.457
>5.6	0.86(0.24)	
≤5.6	0.95(0.24)	
HbA1c (%)		<0.001
>6.0	1.08(0.17)	
≤6.0	0.83(0.23)	
Total cholesterol (mmol/l)		<0.001
>5.2	1.16(0.11)	
≤5.2	0.75(0.17)	
LDL-c (mmol/l)		<0.001
>4.0	1.74(0.07)	
≤4.0	0.79(0.20)	
Triglyceride (mmol/l)		0.464
≥1.7	0.87(0.24)	
<1.7	0.66(0.13)	

CIMT=Carotid intima-media thickness; SBP=systolic blood pressure; DBP=diastolic blood pressure; FBS=fasting blood sugar; HbA1c=glycated haemoglobin; LDL-c=low density lipoprotein cholesterol. Values expressed as mean (SD)

Similar to what was earlier reported from north-central Nigeria [11], our measured CIMT is higher than what was documented from other regions of the world [19-21]. Whether this is indicative of higher CIMT among apparently healthy Nigerians compared Caucasians will require a larger, multi-centre study to establish. The atherosclerosis in communities (ARIC) and the multi-ethnic study of atherosclerosis (MESA) study reported comparable CIMT in Caucasians and African-Americans [22,23]. Most of the recent studies employed the use of semi-automated quantitative edge detection technique for measuring CIMT as opposed to the manual method used in our study. However, the manual method has been validated to have comparable reproducibility to the semi-automated method

[24]. In addition to variation in technique, differences in burden of atherosclerotic risk factors, sample size as well as ethnic and geographic diversity might also contribute to the observed differences in measured CIMT. Blacks are known to have higher blood pressures and left ventricular mass compared to Caucasians. Whether these differences in cardiovascular profile applies to CIMT remains to be established.

The high prevalence of traditional cardiovascular risk factors among the apparently healthy participants studied might be responsible for the high prevalence of increased mean CIMT observed. This has reflected in the significant correlations observed between the various atherosclerotic risk factors and CIMT. Several studies had previously established the roles of these various atherosclerotic risk factors in the development of vasculopathy [25,26]. Many of the traditional risk factors independently predicted CIMT, a finding similar to what was previously reported [7,8]. The rather weak predictive value of age (r^2=0.33, p=0.048) in our study might be explained by the fact that the 62 (62.6%) of the participants studied were younger than 45 years.

Measurement of carotid intima-media thickness is increasingly becoming a valuable tool in assessing cardiovascular risk factors by providing information beyond that provided by traditional risk factors. This is particularly important in the setting of intermediate cardiovascular risk where CIMT may result in reclassification into either higher or lower risk category, allowing for a more cost-effective management of patients. The atherosclerosis risk in communities (ARIC) study showed an increase in risk for coronary heart disease of 17% in men and 38% in women for every 0.19mm increase in CIMT over a follow-up period ranging from 4 to 7 years [27]. The risk for stroke and myocardial

Table 4. Comparison of cardiovascular risk factors based on left internal carotid intima-media thickness

Variable	Left CIMT (mm) >0.9 (n=31)	Left CIMT (mm) ≤0.9 (n=68)	*P*
Age (years)	53.74(9.95)	30.24(11.51)	<0.001
SBP (mmHg)	122.26(8.84)	114.71(9.69)	<0.001
DBP (mmHg)	79.35(8.14)	72.44(10.38)	0.003
BMI (kg/m^2)	23.32(1.05)	21.48(2.24)	<0.001
FBS (mmol/l)	4.60(0.49)	4.13(0.96)	0.001
HbA1c (%)	5.67(0.58)	4.46(0.60)	<0.001
Total cholesterol (mmol/l)	5.62(0.63)	3.70(0.68)	<0.001
LDL-c (mmol/l)	3.95(0.65)	2.45(0.35)	<0.001
HDL-c (mmol/l)	1.33(0.32)	1.75(0.46)	<0.001
Triglycerides (mmol/l)	2.14(0.28)	2.16(0.32)	0.762

CIMT=Carotid intima-media thickness; SBP=systolic blood pressure; DBP=diastolic blood pressure; BMI=body mass index; FBS=fasting blood sugar; HbA1c=glycated haemoglobin; LDL-c=low density lipoprotein cholesterol. Values expressed as mean (SD)

Table 5. Association of some risk factors with intima-media thickness in multivariable regression analysis

	Standardised β	95% CI	*p*
R^2=0.67			
Age	0.210	0.000 – 0.006	0.006
BMI	-0.411	-0.065 - -0.027	<0.001
Systolic blood pressure	0.401	0.005 – 0.014	<0.001
Diastolic blood pressure	-0.378	-0.013 - -0.005	<0.001
Fasting blood glucose	0.117	-0.017 – 0.096	0.172
HbA1c	0.003	-0.056 – 0.057	0.975
Total cholesterol	0.376	0.015 – 0.145	0.017
LDL-c	0.435	0.052 – 0.194	0.001
HDL-c	-0.173	-0.165 - -0.012	0.023
Triglyceride	0.106	-0.015 – 0.177	0.098

BMI=Body mass index; HbA1c=Glycated haemoglobin; LDL-c=Low density lipoprotein cholesterol; HDL-c=High density lipoprotein cholesterol infarction were similarly reported to increase by up to 28% for every 0.20 mm increase in CIMT over 6 years of follow-up [23]. Our study is not designed or powered to determine whether the increased CIMT in our apparently healthy cohorts translates into higher cardiovascular event rate. There are no studies on the prognostic implications of increased CIMT among Nigerians.

Our study has a few limitations. Most of the participants are younger than 45 years of age with fewer proportions of females, making comparison with other studies difficult. Because of the substantial number that are not eligible for assessment of risk using the Framingham risk score, we were unable to assess its association with CIMT. All CIMT measurement were carried out one radiologist and intra-observer variability was not established. Finally, we used manual method for measuring CIMT, rather than the semi-automated edge detection method.

5. CONCLUSION

The prevalence of increased CIMT is high among apparently healthy adult Nigerians, and CIMT correlated positively with other cardiovascular risk factors. This finding, along with the high prevalence of traditional cardiovascular risk factors is a harbinger for increased cardiovascular disease morbidity and mortality in the future. There is the need to assess these factors in a community wide study so that the looming epidemic of cardiovascular diseases can be averted. In addition, larger cohorts devoid of cardiovascular risk factors will be required to establish normal CIMT in our population.

CONSENT

All authors declare that written informed consent was obtained from the participants for the conduct of the study and for the publication of the findings.

ETHICAL APPROVAL

Approval for the conduct of this study was duly granted by the research and ethics committee of the Federal Medical Centre Nguru. The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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