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Research Article

Carotid Intima Media Thickness as a Surrogate Marker of Atherosclerosis and Cardiovascular Burden in Hypertensive Subjects: Relevance and Implications

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Abstract

Background: The availability of surrogate markers of severity of atherosclerosis is essential to monitor and prevent cardiovascular morbidity associated with atherosclerosis. Carotid intima media thickness (c-IMT)) is a marker of atherosclerosis. We aimed to compare the c-IMT of hypertensive subjects with their normotensive counterparts and associated demographic and echocardiographic correlates.

Methods: We studied 122 hypertensive and fifty controls. Their demographic and clinical parameters were obtained. All participants had echocardiography. Statistical analysis was done using SPSS 18.0.

Results: The hypertensive subjects were well matched in age and gender distribution with their normotensive counterparts. Maximum CIMT was significantly higher among hypertensive subjects than controls right (11.1 ± 5.1 vs. 6.1 ± 1.6, $p<0.05$), Left coronary artery (11.4 ± 4.7 vs. 6.0 ± 2.2, $p<0.05$). The mean CIMT was also significantly higher in the RCA of hypertensive subjects (9.01 ± 3.8 vs. 7.6 ± 2.62, $p<0.05$) although that of the LCA did not achieve statistical significance. CIMT was well correlated to age, blood pressure, left ventricular wall dimensions and mass index.

Conclusion: Carotid intima media thickness measurements are mostly significantly higher among hypertensive Nigerian subjects than normotensive counterparts. C-IMT measurements were also well correlated with many cardiovascular risk factors. Left ventricular mass, age and major echocardiographic risk parameters such as ejection fraction, left ventricular wall dimensions and relative wall thickness are the major determinants of the maximum carotid intima media thickness measurements. Therefore c-IMT has a good potential for evaluating cardiovascular burden of hypertensive Nigerian subjects.

Keywords: Carotid intima media thickness; Hypertension; Nigeria; Echocardiography; Marker; Atherosclerosis

Introduction

Atherosclerosis is a chronic multifactorial disorder [1,2]. Although its consequences can be very sudden such as development of stroke and acute myocardial infarction, the processes leading to it may take decades [3-5]. Atherosclerosis is generally related to cardiovascular risk factors and diseases [4,6]. While some receive treatment for acute event such as stroke and AMI, others receive risk factor based interventions, the success of which is to prevent development of acute events [5]. Others however prevent with sudden death as their first presentation [7,8]. Surrogate markers to determine the course of disease and evaluate the response to the treatment of multiple risk factors that contribute to development of atherosclerosis are therefore invaluable [1,2,8]. Cardiovascular disease (CVD) is the number one cause of death worldwide [6]. Developing countries are beginning to experience a high prevalence of CVD [6]. In a three year review of hospital medical admission in Nigeria recently, stroke and hypertension related disorders were the two leading causes of medical admission [9].

The carotid intima media thickness (c-IMT) is defined as the distance between the lumen-intima interface and the media-adventitia interface, which corresponds to the inner and outer echogenic lines seen on the B-mode ultrasound image [10]. This measurement serves a non-invasive marker of arterial wall atherosclerotic disease. Studies have been found that the intima-media thickness on average, based on gender and age, will increase 0.01-0.03mm per year [10,11].

The CIMT measurement is a widely acceptable marker of atherosclerosis and has gained considerable influence in prognosticating, risk stratification and evaluation of cardiovascular disease burden [12,13]. Some authors shows that in normotensive subjects, an increase of 0.1 mm in CIMT will lead to a 10-15% increased risk for having myocardial infarction and a 13-18% risk for having a stroke [14]. The c-IMT measurement has been shown to directly correlate with many cardiovascular risk factors [3,5,11,15,16]. Over the years, clinical trials have provided outcomes that support the role of c-IMT measurements for predicting cardiovascular events (i.e., the thicker the c-IMT, the higher the rate of myocardial infarction or stroke) [17,18].

Despite its wide use as a surrogate marker of CV risk worldwide, there is a great dearth of information on the relevance and usefulness of c-IMT among Africans. This study therefore aimed at determining the relevance and implications of c-IMT as CV surrogate marker in Nigerian hypertensive subjects.

Materials and Methods

This was a cross sectional descriptive study performed at the

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Ladoke Akintola University of Technology Teaching Hospital, Ogbomoso. The study period was between March 2012 and January 2013. One hundred and twenty two hypertensive and fifty normotensive control subjects were randomly selected for this study.

Demographic and clinical parameters were obtained. Information obtained includes age, gender, weight, height, systolic and diastolic blood pressure. The body mass index was calculated as weight/height^2 (kg/m^2). The participants had Echocardiography performed according to the American Society of Echocardiography guideline [19]. Hypertension was diagnosed according to standardized protocols when blood pressure was >140/90 mmHg or when patients were already on antihypertensive regimen [20].

Echocardiography and B Mode Carotid Doppler were done using a general Electric Ultrasound Machine with 3.5MHz and 9 MHz probes respectively. The parameters obtained in the echocardiography included posterior wall thickness in diastole (PWTd), interventricular septal thickness in diastole (IVSd), left ventricular end diastolic dimension (LVDD), left ventricular end systolic dimension (LVSD) and right ventricular dimension. Doppler echocardiography was done to assess the trans-mitral and trans-tricuspid Doppler flow velocity.

The left ventricular mass was calculated using the equation [21]

$$LVM(g) = 0.81[1.04(IVSd + PWTd + LVDD)^3 - LVDD^3] + 0.6.$$

Left ventricular mass index (LVMI) was calculated as LVM/ht (m)$^{2.7}$. This correction has been shown to minimize the effect of gender, race, age and obesity on the validity of various parameters for the diagnosis of left ventricular hypertrophy (LVH). LVH was defined as LVMI > 51 g/m$^{2.7}$. Relative wall thickness was defined as 2 ×PWTd/LVDD. Abnormal RWT was defined as RWT ≥ 0.45.

The measurements for the c-IMT were carried out in common carotid artery, with the subject lying down, neck extended and head slightly turned in the direction opposite to the carotid artery being examined. A 10-mm longitudinal section located at a distance of 1-2 cm from the bifurcation was studied and measurements were performed in the distal walls along an axis perpendicular to the artery, to establish two lines: the intima-media interface and the media-adventitia interface. A total of six measurements were obtained in each carotid artery, and the average mean and maximum values were recorded.

Statistical analysis was done using the Statistical Package for Social Sciences SPSS 18.0 (Chicago Ill.) Quantitative data were summarized as means ± standard deviation while qualitative data were summarized with frequency and percentages. Group comparism was done with the student's t test and chi square. P < 0.05 was taken as statistically significant. Correlation of maximum c-IMT with clinical and echocardiographic parameters was done. Multiple Regression analysis was done to determine the significance of clinical and echocardiographic parameters to the c-IMT measurement. Informed consent was obtained from all participants of the study. Institutional Ethical clearance was also obtained.

Results

The hypertensive subjects were well matched in age and gender distribution with the control subjects. The mean age of hypertensive subjects was not significantly different from that of normotensive control subjects (57.3 ± 14.3 vs. 53.9 ± 12.0 years). Male gender constituted 63.1% of the hypertensive population while it constituted 58% of the normotensive controls. Expectedly, the mean systolic and diastolic blood pressures of hypertensive subjects were significantly higher than their normotensive counterparts. Mean body mass index was similar between the two groups (26.62 ± 6.33 kg/m^2 vs. 25.58 ± 5.92 kg/m^2, p>0.05). Left ventricular wall dimensions, left ventricular internal diastolic dimension and left atrial dimension were significantly higher hypertensive subjects compared to normotensive controls. The maximum c-IMT on the right and left coronary artery were significantly higher among hypertensive subjects compared to controls. The mean right and left c-IMT was also higher hypertensive subjects than normotensive subjects although only that of the right achieved statistical significance. This is shown in Table 1.

Table 2 shows the correlation statistics of some demographic and

Table 1: Demograhic and echocardiographic parameters of study participants.

Variable	Hypertensive Subjects	Controls	P Value
AGE (years)	57.3 ± 14.7	53.9 ± 12.0	0.343
MALE GENDER (n)	77/122 (63.1%)	29/50 (58.0%)	0.061
SBP(mmHg)	137.3 ± 29.1	126.2 ± 7.83	0.014*
DBP (mmHg)	78.0 ± 13.8	75.6 ± 4.9	0.284
BMI (kg/m2)	26.62 ± 6.33	25.58 ± 5.92	0.364
LVDD (mm)	48.1 ± 8.7	43.4 ± 5.0	0.000**
EF (%)	60.8 ± 15.4	66.0 ± 6.7	0.000**
IVSd (mm)	12.1 ± 2.7	10.3 ± 1.4	0.011*
PWTd (mm)	11.5 ± 3.8	9.8 ± 1.5	0.003*
AOD (mm)	31.5 ± 4.4	30.4 ± 1.93	0.082
LAD (mm)	39.7 ± 7.7	35.7 ± 3.5	0.001*
RT CIMT 1 (mm)	11.1 ± 5.1	6.1 ± 1.6	0.000**
RT CIMT 2 (mm)	9.01 ± 3.8	7.6 ± 2.62	0.018*
LT CIMT 1 (mm)	11.4 ± 4.7	6.0 ± 2.2	0.000*
LT CIMT 2 (mm)	9.5 ± 3.3	8.64 ± 2.82	0.115
LVMI (g/m2.7)	61.7 ± 32.1	42.6 ±13.2	0.000**

*- statistically significant

Key to table: SBP: Systolic Blood Pressure, DBP: Diastolic blood pressure, LVDD: Left Ventricular End Diastolic Dimension, EF: Ejection Fraction, PWTd: Posterior Wall Thickness in Diastole, IVSd: Interventricular Septal Thickness In Diastole, ME: MA ratio – ME/MA ratio, TE_TA ratio-TE/TA ratio, RWT: Relative Wall Thickness, LVMI: Left Ventricular Mass Index, BMI: Body Mass Index, RT CIMT 1: Maximum right carotid intima media thickness , RT CIMT 2: Mean Right Carotid Intima Media Thickness, LT CIMT 1: Maximum Left Carotid Intima Media Thickness , LT CIMT 2: Mean Left Carotid Intima Media Thickness.

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echocardiographic parameters with the c-IMT measurements. Age, systolic blood pressure, diastolic blood pressure, Interventricular septal thickness in diastole posterior wall thickness in diastole and left ventricular mass index were significantly and well correlated with all c-IMT parameters. Body mass index was only significantly correlated with the right c-IMT.

To determine the contribution of various parameters to the c-IMT using the right carotid intima media thickness, all parameters with significant correlations statistics were entered into a multivariate Logistic regression analysis. Left ventricular mass index, relative wall thickness, age were the highest determinant of c-IMT measurements among the study participants. Other parameters with significant contribution include ejection fraction and body mass index. This is as shown in Table 3.

Discussion

Carotid intima media thickness has been extensively studied among Caucasians as a surrogate marker for evaluating the burden of atherosclerosis in CVD. However, reports are very scarce on its usefulness and implications among African hypertensive subjects. This study revealed that carotid intima media thickness measurements were significantly higher among Nigerian hypertensive subjects than their normotensive controls. This is in agreement with similar study in other hypertensive population [14,18]. Okeihalam in Jos Nigeria also showed that carotid atherosclerosis using the CIMT value was similar among hypertensive and diabetic subjects [22]. The rise in c-IMT from the normotensive subjects to hypertensive subjects was far more significant in our study than that reported by Okeihalam. The dietary pattern of the population in that study which has been said to be pro-inflammatory might have supposedly accounted for the far less significant rise in their own study. The hypertensive subjects therefore theoretically have a higher burden of atherosclerosis than their normotensive subjects. The increased atherosclerosis parallels the increasing burden of other cardiovascular risk factors as shown by other authors [20,23,24]. Atherosclerosis is the underlying factor for many complications of hypertension. It progresses over a long time before acute complications with potential consequences can occur [6,10]. Therefore, the presence of a surrogate marker to identify carotid intima media thickness has been shown to correlate with the severity of many cardiovascular risk factors [25-27]. Intervention studies have also shown its regression with effective management [28]. All c-IMT measurements were well correlated with many important CV risk factors in this study such as age, systolic blood pressure, left ventricular mass index and body mass index as shown in Table 2.

The factors associated with the increased c-IMT as shown in the multivariate regression included age, left ventricular mass index, body mass index, ejection fraction, posterior wall thickness in diastole and interventricular septal thickness. These were the major determinants of the carotid intima media thickness among the study participants. These echocardiographic and clinical parameters have been associated

Table 2: Correlation of maximum right CIMT with clinical and echocardiographic parameters.

Variable	Right CIMT 1	RT CIMT 2	Left CIMT 1	LT CIMT 2
AGE (years)	0.567**	0.510**	0.538 **	0.435 **
SBP (mmHg)	0.314 **	0.423 **	0.278*	0.328 **
DBP (mmHg)	0.256*	0.362 **	0.204*	0.323 **
IVSd (cm)	0.402 **	0.403 **	0.368 **	0.279 *
PWTd (cm)	0.322 **	0.238*	0.364 **	0.226 *
LVMI (g/m2.7)	0.320 **	0.705 **	0.371 **	0.200*
BMI	0.179	0.358 **	0.137	0.121

*- statistically significant
Key to table: SBP: systolic blood pressure, LVDD: Left Ventricular End Diastolic Dimension, EF: Ejection Fraction, PWTd- Posterior Wall Thickness in Diastole, IVSd: Interventricular Septal Thickness In Diastole, ME-MA ratio – ME/MA ratio, TE_TA ratio-TE/TA ratio, RWT: Relative Wall Thickness, LVMI: Left Ventricular Mass Index, BMI: Body Mass Index.

Table 3: Regression analysis of maximum right carotid intima media thickness.

Variable	Standardized B Coefficient	T Value	Significance
Konstant	20.682		
Age(years)	0.630	3.774	0.001*
Gender	-0.096	-0.823	0.416
SBP (mmHg)	-0.157	-1.164	0.252
LVDD (mmHg)	-1.325	-2.034	0.049*
EF (%)	0.486	4.577	0.000**
IVSd (mm)	-1.552	-3.002	0.005*
PWTd (mm)	-4.336	-2.555	0.015*
ME_MA ratio	0.343	1.830	0.075
TE_TA ratio	0.286	1.938	0.060
RWT	2.980	2.355	0.024*
LVMI (g/$m^{2.7}$)	5.008	3.466	0.001*
BMI (kg/m^2)	-4.819	-2.959	0.005*

*- statistically significant
Key to table: SBP: Systolic Blood Pressure, LVDD: Left Ventricular End Diastolic Dimension, EF: Ejection Fraction, PWTd: Posterior Wall Thickness in Diastole, IVSd: Interventricular Septal Thickness In Diastole, ME: MA ratio – ME/MA ratio, TE_TA ratio-TE/TA ratio, RWT: Relative Wall Thickness, LVMI: Left Ventricular Mass Index, BMI: Body Mass Index.

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with cardiovascular risk from many studies [20,26]. It is therefore relevant to use c-IMT as a surrogate marker of CV injury since they correlate well with many conventional cardiovascular risk factors.

Although Africans have been suggested to have a higher c-IMT than their Caucasian counterpart as it follows similar adaptive response to left ventricular hypertrophy, we found that the maximum and mean c-IMT among hypertensive subjects in this study was similar to that reported in South America by Gomez-Marcos [29]. Other reasons that have been adduced for the relative increase in c-IMT among Africans include increase prevalence of hepatitis, HIV and other infections, etc [29-31]. Hypertensive subjects with cluster of multiple CV risk factors are common in Nigeria [32,33] and the availability of surrogate markers to identify them for early management is therefore invaluable. A higher c-IMT indicative of carotid atherosclerosis is therefore another indication of the high CV burden as shown in this study.

Therefore, one can safely infer that CIMT is a very useful risk stratification index of CV disease among Nigerians with hypertension as it correlates with major cardiovascular risk factors. It can therefore be used in identifying those with significant CV risk for which institution of appropriate management will reduce the cardiovascular burden.

Conclusion

Carotid intima media thickness measurements are mostly significantly higher among hypertensive Nigerian subjects than normotensive counterparts. C-IMT measurements were also well correlated with many cardiovascular risk factors. Left ventricular mass, age and major echocardiographic risk parameters such as ejection fraction, left ventricular wall dimensions and relative wall thickness are the major determinants of the maximum carotid intima media thickness measurements. Therefore c-IMT has a good potential for evaluating cardiovascular burden of hypertensive Nigerian subjects.

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