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Carotid Intima Media Thickness In Metabolic Syndrome – An Indian Perpective

KEYWORDS: Carotid Intima Media Thickness (CIMT), Metabolic syndrome

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ABSTRACT *BACKGROUND: Carotid Intima Media Thickness (CIMT) is a surrogate marker for atherosclerosis. It correlates well with incident heart disease or stroke. In this study we used CIMT as a marker of atherosclerosis to identify individuals at high risk of cardiovascular disease in a group of subjects with Metabolic syndrome in a tertiary care hospital in South India*

METHODS: 116 subjects in the age group of 45to 60 years were enrolled to look at the CIMT. A cut off value of 0.8 mm or more was used to identify the high risk group, in an observational study design. Measurement was taken at 6 sites of the carotid. The results were analysed using chi square tests and multivariate logistic regression analysis to control for traditional risk factors.

RESULTS: We found that the prevalence of high CIMT was 10.34%. CIMT was found to be significantly associated with Metabolic syndrome (p value of ‹0.001). Other traditional risk factors like diabetes, hypertension, and dyslipidemia were not significantly associated with elevated CIMT.

The best site for measurement of CIMT was the internal carotid.

CONCLUSIONS: Metabolic syndrome is significantly associated with CIMT. The risk attributable to Metabolic syndrome is over and above the risk conferred by individual risk factors or combinations of them. The site which gives the best pick up rate of high CIMT is the internal carotid.

Introduction

Myocardial infarction and stroke are todays leading killers globally. The incidence of these events has only increased over the past years and now contributes to about 14 million deaths worldwide.1 In India alone, as per the National Registry, circulatory causes of death were the highest contributors to mortality accounting for 29.8 million deaths in 2010 alone. Hence prevention and early screening to prevent myocardial infraction and stroke has become a necessity.

There are several screening methods for heart disease available today in the form of risk scores such as Framingham risk score, and several individual screening tests for atherosclerotic heart disease such as CT for coronary calcium scoring. There are several newer markers also available such as lipoprotein a, CRP, Homocysteine which contribute significantly to coronary artery disease and stroke. Hence the question arose as to whether there was a single test which would prove better, cheaper and easier to perform with a good correlation with atherosclerosis than these individual tests and scoring systems.

CIMT is an ultrasound of the carotid which measures the thickness of the carotid wall as a surrogate marker of atherosclerosis. Carotid Intima Thickness (CIMT) measurement gets a class2a recommendation from the AHA/ACC guidelines for cardiovascular risk assessment.2 In a review of 8

studies with more than 1000 subjects with follow up suggested that CIMT was significantly associated with myocardial infarction or stroke or both. 3 Metabolic syndrome (MetS) was described as early as the 1980's by Reaven. Metabolic syndrome or syndrome X consists of a constellation of clinical and laboratory information that has shown to be associated with future cardiovascular risk. What is the relevance of metabolic syndrome in today's world when so many newer markers of assessing cardiovascular risk exist? What is the prevalence of a high CIMT in an Indian tertiary care center? What is the best site for measuring CIMT. These were some of the questions this study was designed to answer.

Methods

Study design:

Observational cross-sectional study done in a tertiary care hospital.

Study Participants

All individuals between the age of 45-65 presenting to the outpatient departments of General medicine and Cardiology who met the eligibility criteria.

Inclusion criteria

Individuals between the age of 45-65 who gave informed consent for the study

Exclusion criteria

1. Previous history of Coronary artery disease - as ascertained by clinical history, examination, previous re-

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cords, ECG evidence, or ECHO, treadmill test or angiogram.
2. Previous history of cerebrovascular disease - as ascertained by clinical history of TIA or stroke , examination findings of focal deficits, previous records or CT or MRI evidence of the same.

Study procedure
All patients coming to the medical and cardiology OPD were screened to fit eligibility criteria. Informed consent was obtained. They were then administered a questionnaire which was filled by the principal investigator about their lipid levels, duration and control of diabetes and hypertension. MetS was identified using the IDF criteria 2005.4 Height and weight were determined with subjects in light clothing and without shoes, and body mass index (BMI) was calculated by dividing weight (kilograms) by height (meter squared). Waist circumference was measured using the National Health and Nutrition Examination Survey III protocol during normal minimal respiration by placing a measuring tape around the waist just above the uppermost lateral border of the iliac crest. Blood pressure was measured with an automatic blood pressure recorder, using an adult sized cuff, with subjects sitting in a chair with feet on the floor and arm supported at heart level (Figure 1: study procedure)

CIMT measurement
The study patients were then subject to measurement of the carotid intima media thickness by ultrasonography. The measurements were taken with the use of border detection technology at 3 sites in both right and left carotid artery. The 3 sites were the common carotid, carotid bifurcation and internal carotid. At each level 3 measures were taken and the mean of the 3 were chosen as value at that level.

Outcomes
The primary outcome was to estimate the prevalence of a high CIMT (value more than 0.8mm) in individuals with and without metabolic syndrome.

Secondary outcomes were to evaluate the correlation between select risk factors with CIMT and to identify the best site for measurement of CIMT in terms of pick up rate for atherosclerosis

Statistical methods
The sample size required to show a prevalence of CIMT > 0.8 mm was found to be 95 subjects with 5% level of significance and a precision of 10% with an expected prevalence of 40%. Descriptive statistics was used, such as number and percentage for categorical variables, mean and standard for continuous variables. Two independent sample t-test was used to compare the means of CIMT with following continuous variables, which were normally distributed. The association of metabolic and no metabolic syndrome with CIMT chi-square test/Fisher Exact test were used. Relations of all continuous variables were analysed using Pearson correlation coefficient. Multiple linear regressions were used to predict the risk factors.

Results
A total of 296 subjects were screened and 133 were included as per our criteria. 3 persons did not give consent and 17 persons did not show up for CIMT measurement. Hence 116 patients were enrolled into the study (Figure 2: consort diagram)

The study population were divided into 2 groups based on the presence or absence of metabolic syndrome as defined by the IDF criteria. Hence there were significant differences between the 2 groups in terms of age and presence of diabetes and hypertension. However their lipid levels were not significantly different. These results are summarized in table 1.

Primary outcome
Overall 10.34% had CIMT more than 0.8mm or more. In the group with metabolic syndrome the prevalence was 17%. No individuals without metabolic syndrome had high CIMT defined as more than 0.8 or more.

Secondary outcomes
Metabolic syndrome at all sites of measurement was found to be very strongly associated with CIMT p value <0.05. (Table 2)

The results also show that although all site of measurement show statistical significance in their association with CIMT (table 3), difference exists between pick up rates of high CIMT at different sites of measurement of CIMT. There is not much significant difference between the right and left measurement while the other measurements such as between the common carotid and internal carotid and bifurcation all have statistically significant differences. The site with the increased pick up rate for high CIMT being the internal carotid (table 4)

Multivariate logistic regression analysis of various risk factors with CIMT
Since many traditional risk factors are known to affect atherosclerosis, a multivariate regression analysis of various risk factors with CIMT to assess the role of MetS was done. (See table 3) When all the traditional risk factors that were evaluated in the study were put through the multivariate regression analysis, it was found that only age and metabolic syndrome were significantly related to CIMT independent of the presence of other risk factors.

DISCUSSION
In this observational study we found that CIMT was significantly associated with Metabolic syndrome independent of the presence of other risk factors for disease. We also found that the risk of atherosclerosis attributable to metabolic syndrome does not seem to be conferred to it by the combination of various risk factors since these combinations themselves were not significantly associated with atherosclerosis. Other than metabolic syndrome, age also stood out as one of the risk factors for atherosclerosis that was independent of the presence of other confounding variables like diabetes, hypertension or dyslipidaemia.

Our results are similar to the results of other studies that have evaluated metabolic syndrome and CIMT. In an observational study done by Scuteri at al6, it was found that presence of MetS significantly increased the odds of having both thicker and stiffer large arteries. Another study from Finland in a group of 1766 individuals with MetS also noted higher CIMT values than in controls.7

Many reasons have been put forward to explain the strong association between MetS and cardiovascular morbidity. MetS is known to adversely affect both the structural and functional properties of the vasculature resulting in change in shear stress.8. Another postulated mechanism is that of formation of AGEPs' - Advanced Glycation End Products, within the blood vessel which causes carotid dysfunction9. These are formed by non-enyzmatic cross links between

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glucose and 5amino acids in proteins that line the vessel wall. These gradually accumulate on long standing proteins like collagen and elastin and increased stiffness and wall thickness in both the blood vessels and well as the heart.

In our study the prevalence of high CIMT was found to be approximately 10%. All the high values were in those with metabolic syndrome. In studies done by Sunita Dodani et al10 among South Asian US immigrants, the prevalence of high CIMT was found to be about 41%. Our study found a much lower prevalence of high CIMT in Metabolic syndrome. This is possibly because the study was done in a tertiary level care hospital where risk factors are being identified and modified. They actual population based prevalence of the same maybe very different.

We used a cut off of 0.8mm to identify those at high risk of coronary artery disease and stroke. This cut-off point has been tried and stood the test of time in other studies also. The cardiovascular health study11 was done among 5858 subjects 65 years or older who were followed up for a median of 6.2 years to watch for incidence of myocardial infarction or stroke. They compared those at a lowest quartile and highest quartile of CIMT. They found that CIMT was independently associated with an increase incidence of new cardiovascular events even when other traditional risk factors were accounted for. They also found that the cut-off point for the highest quintile was 0.8mm. In another study done in UK by Gerloukos et al12 the cut off of 0.85mm was found to be predictive of cardiovascular disease. Using this cut-off point, only 12 patients in our study were at risk for incident cardiovascular events. This estimate is lower than the population expected norm. The accuracy of this cut off point for the Indian population is yet to be determined and maybe good scope for future studies. In a study from south India, they noted that CIMT can be used as a screening tool for CAD in patients with ESRD and found that if the CIMT was less than 0.75 mm then there is no need for coronary angiogram.13

The ASE (American Society of Echocardiography) has recommended the common carotid far wall as the standard site of measurement of CIMT. Theoretically, CIMT should be more at the bifurcation since atherosclerosis should start at the site where turbulence is maximum. Hence in this study we decided to measure CIMT at 3 different points along the carotid and assess where the pickup rate was maximum. We found that CIMT was maximum at the internal carotid artery level and the difference between CIMT as measured at these different sites was statistically significant. The left side seemed to have a trend toward higher CIMT than the right but this difference was not statistically significant. In fact it has been shown that ICA – CIMT predicts cardiac events better than the common carotid ones. 14 Quantitative measures of plaques such as plaque number, plaque thickness, plaque area and 3 dimensional volume of the same have been suggested to add to the value of the assessment of CIMT.15

CIMT provides a cheap and convenient method to estimate the effect of atherosclerosis. Hence it can be used with ease to identify high risk individuals with Metabolic Syndrome.

CONCLUSIONS

High CIMT is not as common as earlier thought with a prevalence of only about 10% within the population presenting to tertiary care hospital in India. Secondly, metabolic syndrome is positively associated with CIMT. The risk conferred by metabolic syndrome is more than the risk of its individual components. CIMT is positively associated with age and metabolic syndrome. Thirdly, the site with the best pick up of high CIMT appears to be the internal carotid. Earlier detection of atherosclerosis using CIMT in asymptomatic individuals will go a long way in preventing atherosclerotic diseases.16

LIMITATIONS

This study was done in a hospital based population which may not be generalizable in the population. The sample size included is small and a larger study to look at the cut off value for in a population based subjects may be worth studying.

Figure 1: Study procedure

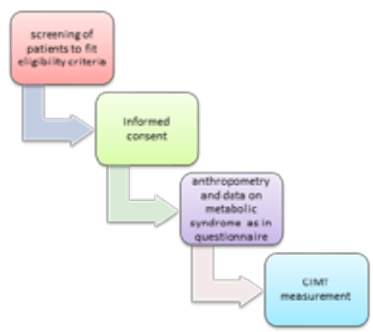

Figure 2: Consort Diagnram

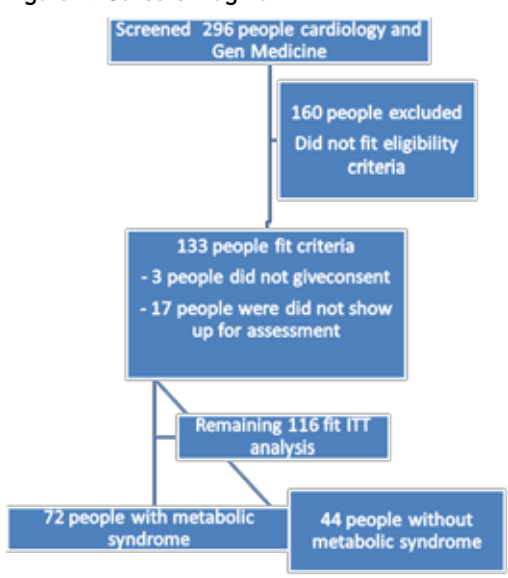

Table 1: Baseline characteristics

Variable	No Metabolic syndrome (second standard deviation) n =44	Metabolic syndrome (second standard deviation) n = 72	P value
Age – mean	47.07 (9.23)	52.44 (8.39)	0.002
Sex - males	86.36%	87.5%	0.860
Waist circumference mean	95.455cm (8.87)	99.676cm(7.53)	0.009
BMI mean	26.11 (4.474)	26.48 (4.448)	0.661

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Variable	No Metabolic syndrome (second standard deviation) n =44	Metabolic syndrome (second standard deviation) n = 72	P value
Diabetes mellitus	15.9%	56.94%	‹0.001
HbA1c	6.03 (0.66)	6.94 (1.46)	‹0.001
Hypertensive	22.7%	68.05%	‹0.001
Lipidprofile			
Cholesterol mean	176.7 (±35.78)	0165.97 (±43.53)	0.172
Triglycerides mean	156.41 (±92.49)	151.39 (±68.46)	0.738
HDL – mean value	42.16 (±8.49)	38.86 (±9.76)	0.066
LDL – mean value	106.59 (±31.27)	101.85 (±33.41)	0.461

Table 2: Relationship between CIMT and Metabolic syndrome

CIMT measurements at various sites	Metabolic syndrome N=72		Without metabolic Syndrome N= 44		Pvalue
	Mean	SD	Mean	SD	
Right Common Carotid	0.675	0.135	0.580	0.111	‹0.001
Right Bifurcation	0.794	0.290	0.634	0.122	0.001
Right Internal Carotid	0.586	0.117	0.527	0.083	0.002
Left Common Carotid	0.699	0.176	0.601	0.133	0.002
Left Bifurcation	0.824	0.183	0.653	0.133	‹0.001
Left Internal Carotid	0.616	0.107	0.522	0.096	‹0.001
OVERALL CIMT	0.699	0.108	0.586	0.083	‹0.001

Table 4: Site of measurement of CIMT

Site	P value
Right mean CIMT vs. Left side mean CIMT	0.055
Common carotid vs. internal carotid CIMT	<0.001
Common carotid vs. bifurcation	<0.001
Internal carotid vs. bifurcation	<0.001

Table 5 shows the percentage of people according to site measured who had a CIMT above 0.8mm (the cut-off point for high CIMT).

Site	Right		Left	
	n	%	n	%
Common carotid	18	15.51	23	19.82
Internal carotid CIMT	35	30.17	43	37.06
bifurcation	3	2.6	3	2.6

Table 3: Multivariate logistic regression analysis of various risk factors with CIMT

Variable	CIMT					
	β coefficient	95%CI	P Value	β coefficient	95%CI	P Value
Age	0.006	(0.004-0.008)	0.000	0.004	(0.003-0.006)	0.000
Sex	0.055	(-0.007-0.117)	0.079	-		
HTN	0.041	(0.000-0.082)	0.053	-0.008	(-0.045-0.029)	0.674
DM	0.050	(0.008-0.091)	0.020	-0.011	(-0.052-0.031)	0.612
HDL	0.000	(-0.002-0.003)	0.693	-	-	-
TG	0.000	(0.000-0.001)	0.391	-	-	-
Waist	0.004	(0.001-0.006)	0.005	0.001	(0.000-0.003)	0.269
HBAIC	0.020	(-0.002-0.041)	0.074	-	-	-
FBS	0.001	(0.000-0.001)	0.001	0.000	(0.000-0.001	0.127
BMI	-0.003	(-0.007-0.002)	0.288	-	-	-
Creat	-0.010	(-0.096-0.076)	0.817	-	-	-
Mets	0.113	(0.075-0.151)	0.000	0.079	(0.036-0.123)	0.000

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