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Carotid Intima-media Thickness as a Surrogate Marker of Atherosclerosis and its Correlation with Coronary Risk Factors and Angiographic Severity of Coronary Artery Disease.

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Abstract : Carotid arterial intima-media thickness (CIMT) has been a good indicator of the presence and extent of coronary artery disease(CAD) in observational studies. Since treadmill testing and stress echocardiography can have limited specificity in diagnosing CAD, other surrogate markers of CAD and Atherosclerosis are required. Biochemical investigations for risk factor's and B-mode ultrasound examinations were performed to calculate CIMT. All the patients were catheterized percutaneously via the femoral vessels with standard Judkins technique and angiographic scoring of CAD was performed. CIMT was higher in subjects with hypertension, diabetes mellitus, smoking, dyslipidaemia, and males. The extent and severity scores for CAD were all positively correlated with CIMT ($p<0.0001$). A significant, nearly linear correlation between CIMT and advancing CAD ($p<0.0001$) was found. Patients with one, two and three vessel CAD had significantly higher CIMT than the patients without CAD. The univariate logistic regression analysis showed that increased CIMT levels were associated with severity of atherosclerosis. There is a strong correlation between carotid atherosclerosis and coronary atherosclerosis, and CIMT is a good predictor of presence and extent of CAD, hence it can be used as a surrogate marker in the prediction of pre-clinical atherosclerosis and CAD.

Key words : Myocardial infarction, Coronary artery Byepass graft, Cerebrovascular accident, Triglycerides, Highdensity lipoprotein, Lowdensity lipoprotein.

Imtroduction

The quantitative assessment of atherosclerosis in populations is essential for a better understanding of the pathophysiology of this disease and for the consequent development of optimal disease prevention stratergies. Thickening of the intima-media at any local site is generally considered to be an early marker of generalized atherosclerosis. (Mohan *et al.*, 2000). Most epidemiological and clinical studies in progress are based on measurement of the carotid arteries intima-media studies have shown that the extent of extra cranial carotid and coronary atherosclerosis is correlated with Pearson's correlation coefficient values of r = 0.4-0.6 (Holme I *et al.*, 1981). For these reasons, CIMT has been suggested as a surrogate marker for coronary atherosclerosis (O'Leary, 1999; Hodis *et al.*, 1998) In adults, CIMT ranges from 0.25 to 1.5 mm and value above 0.9 mm is often regarded as abnormal as suggested by Zwiebel I 2000. CIMT has been proposed as a quantitative index of atherosclerosis and is of value in guiding disease progression and the effects of treatment. Age is one of the most powerful determinants of CIMT with increases of 0.01-0.02 mm per year (Howard *et al.*,1993). CIMT is used as a non-invasive surrogate end point to measure progression of atherosclerosis; furthermore, carotid arterial CIMT has been a good indicator of the presence and extent of coronary artery disease (CAD) in observational studies(Geroulakos *et al.*, 1994; Crouse III JR, *et a*l., 1995). Despite methodological differences with previous studies, the association found between CIMT and known risk factors for atherosclerosis such as age, hypertension, lipid abnormalities, smoking and diabetes are in good agreement. Age and hypertension appeared to be the strongest determinants of the presence of plaque and increased CIMT(O'Leary *et al.*, 1992)

Materials and Methods

We retrospectively reviewed the association between carotid artery atherosclerosis, valued from the CIMT and the presence of atherogenic plaques, and CAD in 100 patients who were subjected for coronary angiography. Subjects were excluded if they had a past history of coronary artery bypass graft surgery (CABG), coronary angioplasty, carotid surgery and cerebrovascular accident (CVA).

Ultrasound

B-mode ultrasound examinations were performed using a 7.0 MHz linear array transducer. Three scanning angles were used in each case: anterior oblique, lateral and posterior oblique (Wofford *et al.*, 1991).

Three segments were identified on each side: (1)

the distal 1.0 cm of the common carotid proximal to the bifurcation; (2) the bifurcation itself and (3) the proximal 1.0 cm of the internal carotid artery[Howard G et al ;1993]At each of the three segments for both near and far wall in the left and right carotid arteries, 2 interfaces were identified: (1) **on the near wall** - the first interface is the adventitial-medial boundary and the second is the intimal lumen boundary, (2) **on the far wall** - the first interface is the lumen-intima and the second is medial-adventitial. These define the CIMT on the near and far walls, respectively. After measuring all twelve areas the maximum value was taken. The maximum CIMT and not the mean value was taken into consideration for calculating the results.

Laboratory methods

Blood samples were taken after a fasting period of 12 hours in all subjects. Baseline biochemistry included lipid profile and liver function tests to rule out any other systemic illness or a secondary cause of dyslipidemia. Total cholesterol (TC), triglycerides (TG) and high density lipoprotein (HDL) cholesterol were analyzed using enzymatic methods. Low density lipoprotein (LDL) cholesterol was computed (Friedewald *et al.*,1972). The reports were retrospectively analysed and correlated with CIMT and angiographic severity of CAD.

Coronary angiography and scoring

All the patients were catheterized percutaneously via the femoral vessels with standard Judkins technique (Judkin, 1976). Angiographic scoring was performed. Coronary angiograms were interpreted visually and always analyzed in two orthogonal views and scored.

With the severity score, the number of coronary vessels with luminal stenosis more than 70% was scored from 0 to 3 (for right, left anterior descending and circumflex arteries). Left main stenosis more than 70% was scored as one-vessel disease (Rohani *et al;* 2005).

Statistical analysis

Continuous variables were expressed in mean ± standard deviation and categorical variables in numbers with percentage. Continuous variables were compared using Student t-test and categorical variables using chi-square test. Association of CIMT with other variables was ascertained using regression analysis.

Results

We retrospectively analyzed and correlated CIMT and angiographic extent and severity of CAD in 100 patients who underwent elective coronary angiography to assess the strength of any relation between CIMT and CAD. There were 89 (89%) men and 11 (11%) women in the study with mean age of 37 ±17 years. The baseline characteristics of the study cohort are summarized in Table 1.

Overall mean CIMT for 100 subjects was 1.05 ± 0.32 mm. The mean CIMT was more in men (1.40 mm),

Table 1 : Risk factor profiles and variable of the patients.

PATIENTS VARIABLE	N%
Mean age(years)	37±17
Males	89(89%)
Females	11(11%)
Smoking	56(56%)
Hypertension	68(68%)
Diabetes mellitus	34(34%)
Total Cholestrol(mg/dl)	196±34
LDL-cholestrol(mg/dl)	134±36
HDL-cholestrol(mg/dl)	32.6±5
Triglycerides(mg/dl)	169±89
Mean CIMT(mm)	1.05±0.32
LDL = low density lipoprotein; HDL= high density lipoprotein; CIMT = carotid intima-media thickness; MI= myocardial infarction; UA = unstable angina. Data is expressed as mean and standard deviation for continuous variables and as percentage for categorical variables.	

subjects with hypertension (1.37 mm), smoking (1.25 mm), diabetes (1.39 mm), total cholesterol >200 mg/dl (1.37 mm), LDL-cholesterol >100 mg/dl (1.48 mm), triglycerides > 150 mg/dl (1.12 mm), HDL-cholesterol <40 mg/dl (1.28 mm) and patients with lower left ventricular ejection fraction (1.47mm) when compared with women (1.31mm), non-hypertensive subjects (0.9mm), non-smokers (0.93mm), nondiabetics (1.05mm), total cholesterol <200 mg/dl (0.98 mm). LDL-cholesterol <100 mg/dl (0.85 mm), triglycerides <150 mg/dl (0.85mm). HDL-cholesterol >40 mg/dl (0.89mm) and patients with normal left ventricular ejection fraction (0.89 mm) (Table 2).

The p-value was significant in correlation of mean CIMT and hypertension ($p < 0.05$), smoking ($p < 0.05$), diabetes mellitus ($p < 0.05$), total cholesterol ($p< 0.05$), LDL-cholesterol ($p < 0.05$), HDL-cholesterol ($p < 0.05$), left ventricular ejection fraction ($p < 0.05$). Even though there was a significant difference in correlation of the mean CIMT with triglyceride levels the p-value was statistically not significant ($p > 0.05$).

Total cholesterol (TC), LDL-cholesterol (LDLC), HDL cholesterol (HDLC) levels were

Table 2 : Correlation of variables of Risk factor with mean CIMT

VARIABLE	MEAN CIMT (mm)	P-VALUE
HYPERTENSION		
Hypertensives	1.37	$p < 0.05$
Non-hypertensives	0.9	
SMOKING		
Smokers	1.25	$p < 0.05$
Non-smokers	0.93	
DIABETES MELLITUS		
Diabetics	1.39	$p < 0.05$
Non-diabetics	1.05	
TOTAL CHOLESTEROL		
TC > 200 mg/dl	1.37	$p < 0.05$
TC < 200 mg/dl	0.98	
LDL-CHOLESTEROL		
LDLC > 100 mg/dl	1.48	$p < 0.05$
LDLC < 100 mg/dl	0.85	
TRIGLYCERIDES		
TG > 150 mg/dl	1.12	$p > 0.05$
TG < 150 mg/dl	0.85	
HDL-CHOLESTEROL		
HDLC < 40 mg/dl	1.28	$p < 0.05$
HDLC> 4 mg/dl	0.89	
LVEF		
Lower LVEF	1.47	$P < 0.05$
Normal LVEF	0.89	
SEX		
Male	1.40	P>0.005
Female	1.31	

CIMT= carotid intima-media thickness; TC = total cholesterol; LDLC = low density lipoprotein cholesterol; HDLC = high density lipoprotein cholesterol; TG - triglycerides; LVEF = left ventricular ejection fraction. (a Indicates significant p-value.)

compared in patients with normal and elevated levels of CIMT. In subjects having high CIMT (>0.9 mm) the TC, LDLC and HDLC levels were 210±14 mg/dl, 146.13 mg/dl and 30.40 mg/dl respectively, whereas in subjects having normal CIMT (<0.9 mm) the TC, LDLC and HDLC levels were 170.30± 10mg/dl, 104.4± 12 mg/dl and 40.04± 6 mg/dl respectively. In all the 3 cases p-value was significant ($p < 0.05$). Univariate analysis showed that increased CIMT levels were associated with hypertension, smoking, and triglycerides (Table 3). Multivariate logistic regression analysis showed that an increased level of CIMT was associated with hypertension and triglycerides (Table 4).

A comparison between CIMT and risk factors was done and from this statistically significant elevated CIMT was found in multiple risk factors when compared with single and double risk factors respectively. Patients with three or more risk factors had higher CIMT (1.26 mm) then patients with two or less risk factors (0.86 mm) and p-value was found significant ($p < 0.05$) (Fig. 1).

Table 3 : Univariate logistic regression for association of CIMT with risk factors

Independent variable	Coefficient	S.E	Odd ratio	95% CI	p-Value
Hypertension	0.824	0.335	2.281	(1.18-4.40)	0.01[a]
Smoking	0.999	0.339	2.715	(1.39-5.28)	0.003[a]
Total cholesterol	0.988	0.397	2.687	(1.23-5.85)	0.01[a]
LDL-cholesterol	0.538	0.275	1.712	(0.99 -2.93)	0.05[a]
Triglycerides	0.505	0.185	1.65	(1.15-2.38)	0.01[a]

CIMT as dependent variable and other variables as independent variable.
S.E = standard error; LDL = low density lipoprotein.
(a Indicates significant p-value (p < 0.05).)

Table 4 : Associations of CIMT with risk factors in multivariate logistics regression

Independent variable	Coefficient	S.E	Odd ratio	95%CI	p-value
Hypertension	0.643	0.581	1.93	(0.62-2.60)	0.005[a]
Triglycerides	0.803	0.387	2.233	(1.046-4.40)	0.05[a]

CIMT as dependent variable and other variables as independent variable
SE-Standard error
(a indicates significant p value (P<0.05))

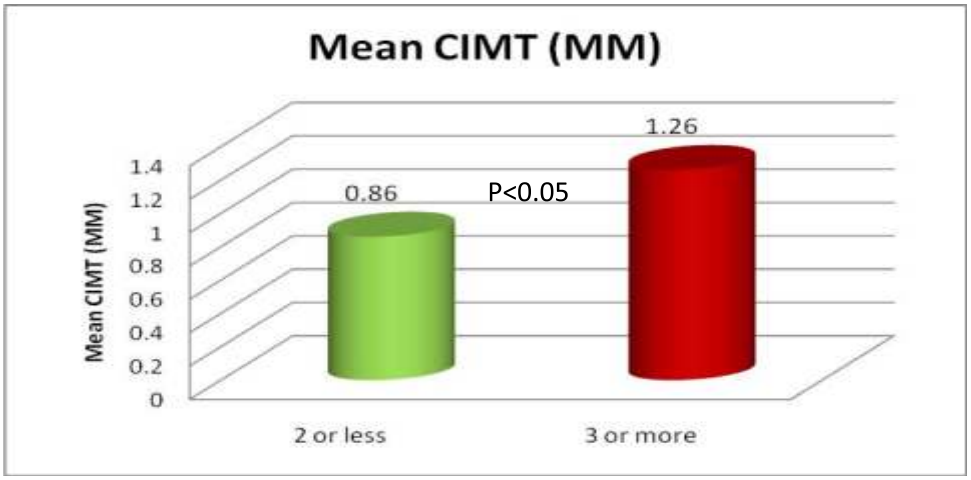

Fig. 1. CIMT correlated with number of risk factor for CAD

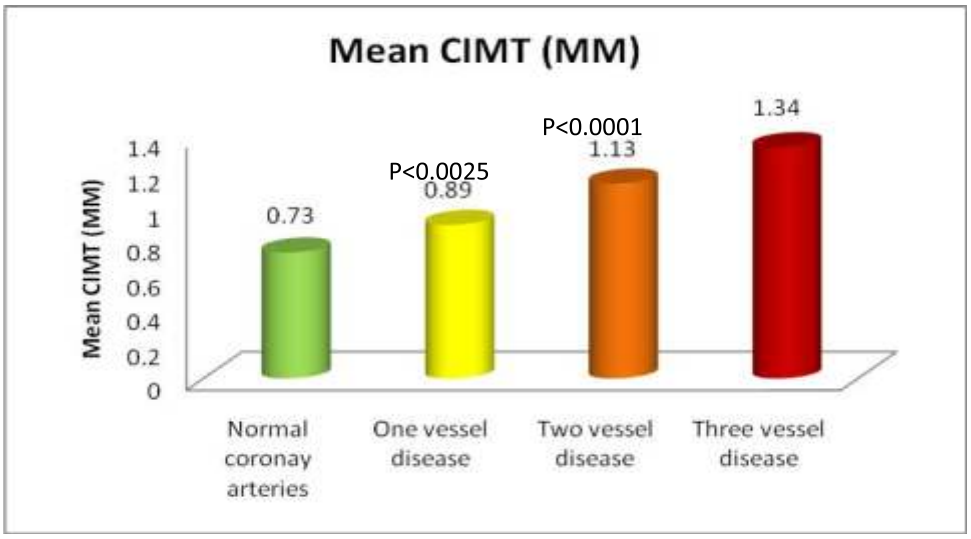

Fig.2. Correlation of CIMT with extent of CAD.

The severity scores for CAD were all positively correlated ($p < 0.0001$ in every case). The mean measured CIMT calculated for patients with normal coronary arteries was 0.73 mm and in patients with angiographic proven CAD was 1.32 mm. The mean CIMT was found to be 0.89 mm. 1.13 mm and 1.34 mm in patients with one-vessel CAD, two vessel CAD and three-vessel CAD respectively. A significant, nearly linear correlation between CIMT and advancing CAD ($p < 0.0001$) was found. Patients with one, two and three vessel CAD had significantly higher CIMT than the patients without CAD (Fig. 2).

We observed significant differences in CIMT between patients with one and two-vessel CAD ($P < 0.0025$) as well as between two and three-vessel CAD ($p < 0.0001$) (Fig. 2).

The correlation between CIMT and vessel score showed that elevated CIMT was seen in three vessel disease or two vessel disease group, when compared with normal CIMT seen in normal coronaries or one vessel disease group. The univariate analysis showed that increased CIMT levels were associated with severity and extent of CAD.

Discussion

In this study we evaluated the relationship between carotid disease and the presence and severity of CAD by coronary angiography in patients with risk factors subjected to coronary angiography. The present study showed strong correlation between CIMT and conventional atherosclerotic risk factors. Patients particularly with multiple risk factors were having elevated CIMT. In this study our main finding was that CIMT and carotid disease was significantly related to the presence of severe CAD. Furthermore, in patients with impaired left ventricular systolic performance, the presence of higher CIMT and carotid disease reflects the presence of severe CAD.

Autopsy studies have demonstrated a strong correlation between the extent of extra cranial carotid and coronary atherosclerosis (Mitchell *et al*., 1962). Non-invasive measurements that relate to the severity of coronary atherosclerosis have been sought for clinical screening of patients with chest pain syndromes (Admas *et al.*, 1995). Thus CIMT has been suggested as a surrogate marker for coronary atherosclerosis for use in clinical trials. Craven *et al.* (1990) have suggested that B-mode score is strongly and independently associated with CAD in patients aged >50 years and is at least as useful as well-known risk factors for identifying patients with CAD; Salonen *et al.* (1991) reported that greater common carotid CIMT values in middle-aged men may be independently associated with higher subsequent risk of acute coronary events.

However, possible additional associations between carotid disease and the severity of CAD have not been well addressed. To investigate this issue further, we extended our attention to the exact relationship between carotid disease and CAD. We found that increased CIMT and carotid disease could indicate the presence of severe CAD in patients undergoing coronary angiography for chest pain. Moreover, the combination of carotid disease with impaired left ventricular systolic performance could predict the presence of severe CAD. Also, the absence of carotid disease in a patient with normal left ventricular systolic performance may reflect the absence of severe CAD.

In concordance with the above, Hertzer *et al.* (1985) studied patients with asymptomatic carotid

bruits or transient ischemic attacks and revealed severe CAD in 37% of patients without suspected CAD.

Our study correlated well with the study conducted by Kablak *et al* (2004) which showed that CIMT increases with advancing CAD, significant increase in CIMT was observed among patients with one, two and three-vessel disease and patients with mean CIMT over 1.15 mm have a 94% likelihood of having CAD. CIMT also showed a positive association with traditional risk factors like male sex, age, obesity, hypertension, serum cholesterol, smoking and diabetes (Howard *et al.*,1993; Kitamura *et al.*,2004)]

Hence it is concluded that CIMT is a simple, non invasive and reproducible clinical tool to evaluate atherosclerosis. There was a strong correlation between carotid atherosclerosis and coronary atherosclerosis, and CIMT is a good predictor of presence and extent of CAD, hence it can be used as a marker for prediction of pre-clinical artherosclerosis and CAD.

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