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SIGNIFICANCE OF THE CAROTID INTIMA MEDIA THICKNESS IN THE EVALUATION OF CORONARY ARTERY DISEASE PATIENTS WITH AGE < 40 YEARS

Cardiology

Dr. Venkatalakshmi Gowthami. R Senior Resident, Department of Cardiology, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad

Dr. O. Adikesava Naidu Professor, Department of Cardiology, Osmania Medical College/General Hospital, Hyderabad

Dr. Nagula Praveen* Assistant Professor, Department of Cardiology, Osmania Medical College/General Hospital, Hyderabad *Corresponding Author

Dr. Ravi Srinivas Associate Professor, Department of Cardiology, Osmania Medical College/General Hospital, Hyderabad

Dr. KMK Reddy. P Professor and Head, Department of Cardiology, Osmania Medical College/General Hospital, Hyderabad

ABSTRACT

Introduction: Carotid Intimal Media Thickness (CIMT) is a surrogate marker of atherosclerosis. There is limited evidence regarding the relationship with coronary artery disease (CAD) in the young (<40 years).
Aims: To describe the clinical and demographic profile of the young CAD subjects. To assess the relationship between individual lipid fraction, risk factors with CIMT and its correlation with the severity of CAD.
Settings and Design: Hospital based observational study (June 2017 –November 2018)
Methods and Material: Patient aged more than 18 years and less than 40 years being evaluated for CAD were included. Patients aged more than 40 yrs, with the history of coronary artery bypass graft surgery, coronary angioplasty, significant valvular heart disease, cardiomyopathy, cardiac rhythm abnormalities, congenital heart diseases, pregnancy, acute illnesses were excluded. CIMT and coronary angiography apart from the biochemical profile and demographic data were studied.
Results: The male and female ratio was 2.12:1. The mean age of presentation was 35.89 ± 4.09 years (n=100). The CIMT in patients with and without CAD was (0.87 ± 0.38 vs 0.56 ± 0.35, P =0.001). It had positive correlation with syntax score (r = 0.45, P = 0.029). Abnormal CIMT correlated with increased body mass index, total cholesterol and low-density cholesterol on subgroup analysis.
Conclusions: CIMT can be used in risk stratification of patients being evaluated for CAD in the young.

KEYWORDS

Atherosclerosis, carotid intima medial thickness, syntax score

INTRODUCTION:

Atherosclerotic Cardiovascular disease (ASCVD) is a major health burden worldwide with the occurrence of disease at an early age over the last decade.[1] Coronary artery disease (CAD) occurring below the age of 40 years is termed as Young Coronary artery disease (yCAD) with a prevalence of 1.2% as per the existing literature.[1]

Carotid Intimal Medial Thickness (CIMT) evaluation has been recommended as a screening tool for ASCVD occurrence in Intermediate to high -risk population, as it correlated with the severity of CAD.[2] There is limited evidence regarding the relationship between CIMT and severity of CAD, individual lipid fraction in the yCAD.[3]

Atherosclerosis, quiescent until significant obstruction of the arteries or an acute event needs early recognition by noninvasive methods. Current cardiovascular risk assessment is by risk scores and algorithms which were shown to be inaccurate in both high risk and low-risk population.[2] Coronary angiography, a direct measure of disease is invasive and risk-prone when considered for the evaluation of patients at low risk of ASCVD. There is a high need for a noninvasive method (CIMT assessment) which can predict significant CAD on screening.[3] In 2010, ACC/AHA guidelines for the assessment of cardiovascular risk in asymptomatic individuals, it is recommended that CIMT could be measured for risk stratification in individuals at intermediate risk of CAD (Class IIa).[4]

Measuring the thickness of the complex CIMT than the luminal narrowing can be an accurate representation of atherosclerosis.[5] CIMT has graded association with CAD visualized on angiography, thereby helps in early detection of atherosclerosis.[6,7] In small subset, it could be secondary to shear stress as a result of hypertension.[8] Salonen et al, showed for the first time that in vivo use of ultrasound imaging of the carotid arteries demonstrated a close histological relationship between coronary, cerebral, and carotid atherosclerotic diseases.[9]

The Kuopio Ischaemic Heart Disease (KIHD) study was the first study to demonstrate an association of CIMT with future coronary events. Every 0.1mm increment of IMT was associated with an 11% increased risk of myocardial infarction (MI) during follow-up.[9] The ARIC investigators showed that CIMT and plaque information had an incremental value in atherosclerotic risk prediction over the traditional risk factors.[10]

In 2002, Belhassen et al. demonstrated the values of CIMT (< 0.55) and Aortic IMT (<3 mm) predicted the absence of CAD respectively. Besides, the NPV of CIMT and Aortic IMT were reported as 100% and 99% respectively, and the specificity as 50% and 65% respectively, for ruling out of CAD.[11]

The relationship of IMT with cardiovascular risk is continuous hence determining a threshold IMT value would be incorrect. As per the American Society of Echocardiography (ASE) and the Society of Atherosclerosis Imaging and Prevention (SAIP) appropriate use criteria (AUC), CIMT and plaque presence are recommended for the initial detection of CAD in asymptomatic patients at intermediate risk, in the setting of 2 or more National cholesterol education program (NCEP) risk factors, with metabolic syndrome, in the setting of a family history of premature CHD, with a known CAC score of zero and Framingham Risk Score (FRS) of 11–20%.[12]

The American Society of Echography (ASE) Taskforce recommends that IMT ≥ 75th percentile is considered as high and indicative of increased cardiovascular risk. Values from the 25th to the 75th percentile are considered as average and indicative of unchanged cardiovascular risk. Values ≤ 25th percentile are considered as low and indicate lower than the expected cardiovascular risk. There are also more conservative cut-off suggestions: IMT values ≥ age-adjusted

97.5th percentile to be defined as abnormal (and predictive of increased vascular risk).[12] Nevertheless, it should be noted that in the latest ESH/ESC hypertension guidelines (2013) carotid IMT ≥0.9 mm has been re-confirmed as a marker of asymptomatic organ damage, although it has been proven that in middle-aged and elderly patients the threshold values indicating high cardiovascular risk are higher.[13]

Aims and objectives:
To describe the clinical and demographic profile of the yCAD subjects (≤40years). Assess the relationship between individual lipid fraction, risk factors and the CIMT in them. To assess whether CIMT is predictive of coronary atherosclerosis and know its correlation with the severity of CAD.

MATERIALS AND METHODS
The present study is a hospital based, cross-sectional and observational study conducted from June 2017 to November 2018. The ethical committee of the institute approved the study. A total of 100 patients with a diagnosis of CAD, willing to undergo invasive coronary angiography were enrolled.

Inclusion criteria
Patient with age > 18 years and ≤40 years (both male and female), with the chest pain to rule out the CAD, were included.

Exclusion criteria
Patients with age > 40 yrs, who have not given consent, with the history of coronary artery bypass graft surgery, previous coronary angioplasty, significant valvular heart disease, cardiomyopathy, cardiac rhythm abnormalities, congenital heart diseases, previous carotid surgery, congenital heart disease, pregnancy, acute and systemic illnesses were excluded.

Study design:
Written Informed consent was obtained from all the subjects. In all subjects, demographic and anthropometric characteristics (age, sex, height, weight, BMI, and waist hip ratio), laboratory parameters including fasting plasma glucose, low-density cholesterol (LDL), high- density cholesterol (HDL), Total cholesterol (TC), Very low-density cholesterol(VLDL), triglycerides (TG) were assessed. The CIMT of the distal common carotid artery (CCA), a mean of the three readings (in millimeters) was measured.

Diagnosis of CAD was done according to the ACC/AHA criteria with clinical features, Electrocardiography (ECG) changes, two-dimensional echocardiography (2D echo), cardiac biomarkers. Later patients were subjected to conventional coronary angiography to look for the extent of the disease.

Biochemical Assessment:
Blood specimens were obtained after a 12 hour fast (8 pm– 8 am) to reduce the influence of circadian variation. The concentrations of Triglycerides were measured using standard enzyme methods (Liquixx Triglycerides GPO-Trinder Method). Total Cholesterol (CHOD-PAP) and High-density lipoprotein (HDL) cholesterol were assessed after Very low-density cholesterol (VLDL) with phosphotungstic acid precipitation, and Low-density cholesterol (LDL) was calculated using the Friedewald formula. Fasting glucose levels were enzymatically examined by the hexokinase method.

Carotid Ultrasound
Carotid arterial imaging was performed in a dark room by a trained radiologist who was blinded to all the clinical information and study. Patients were examined in the supine position with slight hyperextension and rotation of the neck to the contralateral side. High-resolution B-mode color Doppler and pulse Doppler ultrasonography of both carotid arteries was performed with an ultrasound machine (Philips) equipped with a 7.5 MHz linear array transducer. To optimize the image quality, the depth control was fixed at 4 cm, with an axial resolution of 0.2mm. All the measurements were acquired at the end-diastole phase (defined as the R wave of an electrocardiogram) avoiding thinning of CIMT due to systolic expansion of the lumen. Both CCAs and internal and external carotid arteries were first identified through longitudinal images. CIMT was defined as the distance between the leading edges of the intima-lumen echo and of the media-adventitia echo. CIMT was measured at the distal common carotid artery (CCA) 1 cm proximal to dilation of the carotid bulb at the far wall in a plaque-free region by placing the calipers for individual measurements three times and then an average value of both right and left carotid arteries was taken as mCIMT. Three scanning angles were used in each case: anterior oblique, lateral, and posterior oblique. The image was focused on the posterior (far) wall, and images of the distal 10 mm of the CCA were recorded from the angle showing the greatest distance between the lumen-intima interface and the media-adventitia interface (IMT). Manual measurements were taken and the value of both the right and the left side were obtained for analysis. A thickness of ≥0.9 mm was considered as increased mCIMT.[14]

Coronary angiography and scoring:
Coronary angiography was performed through the femoral or radial artery using the standard technique. Significant CAD was defined as a >50% reduction of the internal diameter of epicardial coronary arteries and side branches with a diameter >1.5 mm. The Syntax Score(SS) was used to quantify the severity of CAD, low SS with the value of <21, Intermediate as between 22-32, and high SS as >33.[15] Coronary angiography was performed in the catheterization laboratory (Siemens AXIOM-Artis, Munich, Germany), equipped with Quantitative coronary analysis software.

Statistical analysis
Data entry was done using Microsoft Excel 2007 and analyses were performed using SPSS for Windows version 24.0(SPSS, Chicago, USA). Data were expressed as mean ± standard deviation(continuous variables) or number and percentages(categorical variables). Comparison of quantitative variables between the groups has been done using Student's t test, and chi-square test has been applied for categorical variables. $P \leq 0.05$ has been considered statistically significant to determine the association between variables. Correlation of the parameters was assessed with Pearson's ® correlation test.

Results:
The present study included 100 subjects. The mean age of presentation of the whole group of participants was 35.89 ± 4.09 years. Males were more than the females with a ratio of 2.125:1. Table 1 shows the baseline characteristics of the study population.

Table 1: Baseline characteristics of the study participants Characteristic Number (Male, Female)

Characteristic		Number (Male, Female)	
Age group (years)	25-30	17 (15,2)	
	31-35	32 (18,14)	
	36-40	51 (35,16)	
	Mean ± SD, years	35.89 ± 4.09	
Sex ratio	Male: Female 2.125: 1		
Presenting complaints	Chest pain	90	
	Shortness of breath	67	
	Orthopnea	03	
	Cough	10	
	Palpitations	12	
	Syncope	02	
Risk factors	Diabetes	35	
	Hypertension	26	
	Smoking	30	
	Tobacco chewing	48	
	Alcohol	35	
	Family history of CAD	10	
Body Mass Index(BMI) (kg/m2)	< 18.5	3	
	18.5 -24.99	69	
	≥ 25.0	28	
Lipid profile		abnormal	Normal
	Total cholesterol (mg/dl)	38	7
	LDL (mg/dl)	45	14
	VLDL (mg/dl)	36	09
	HDL (mg/dl)	50	19
	TG (mg/dl)	47	15
Waist Hip ratio	< 0.9 (males),< 0.85 (females)	03,04	
	> 0.9(males), > 0.85 (females)	65,28	
Angiography	Normal	17	
	Minimal	13	
	SVD	29	
	DVD	28	
	TVD	13	

VLDL – very low-density cholesterol, HDL – high-density cholesterol, TG – triglycerides, CAD – coronary artery disease

Total cholesterol was elevated in 38 patients compared to 7 patients who had normal cholesterol levels. Elevated LDL and TG was found in 45 and 47 patients respectively.

Table 02: Comparison of risk factors and biochemical profile in the significant CAD and no angiographic CAD groups

Risk factor	CAD (n=70)	No CAD (n=30)	P
Age (years)*	36.04 ± 3.86	35.53 ± 4.62	0.57
Hypertension, n (%)	20 (28.57)	6 (20)	0.37
Diabetes mellitus, n (%)	27 (38.6)	8 (26.7)	0.25
Family History, n (%)	8 (11.4)	2 (6.7)	0.47
Smoking, n (%)	26 (37.14)	4 (13.3)	0.02
BMI (kg/m2) *	23.20 ± 3.48	24.84 ± 4.11	0.44
WHR	0.961	0.964	0.10
FBS (mg/dl)*	113.2 ± 40.8	104.5 ± 34.2	0.31
TC (mg/dl)*	200 ± 60.8	176 ± 50.6	0.06
LDL (mg/dl)*	122 ± 51.9	99.4 ± 40.3	0.07
HDL (mg/dl)*	35.85 ± 9.8	37.8 ± 9.3	0.35
VLDL(mg/dl)*	42.2 ± 22.2	35.4 ± 19.3	
TG (mg/dl)*	210.9 ±110.9	177.2 ± 96.7	0.13

* data is expressed in mean ± SD (corrected to two decimals) or n(%), CAD – coronary artery disease, BMI- body mass index, WHR – waist-hip ratio, FBS – fasting blood sugar, TC – total cholesterol, LDL – low density cholesterol, HDL – high density cholesterol, VLDL – very low density cholesterol, TG - triglycerides

In Table 2 comparison of risk factors and biochemical profile between participants with CAD and without CAD showed no statistical significance except for the smoking (P =0.017). The m CIMT of Right CCA and left CCA was found to be 0.78 ± 0.21 mm (range 0.38 – 1.25) and 0.79 ± 0.22 (range 0.48-1.30) respectively. There was significant correlation of CCA with presence or absence of angigoraghic CAD (Table 3). The correlation of m CIMT CCA with different risk factors showed a significant positive correlation with smoking, total cholesterol and LDL cholesterol with P values of 0.001, 0.003, 0.024 respectively. The negative correlation with HDL was found to be statistically insignificant (Table 4).

The mCIMT had a positive correlation with Syntax score (r =0.45, P =0.029) thereby with the severity of coronary artery disease.

Table 03: Correlation of Carotid Intima medial thickness of CCA with CAD

Categorization of patients		Mean ± SD, mm	P	R
m CIMT CCA	CAD	0.87 ± 0.38	0.001	0.7
	No CAD	0.56 ± 0.35		

m CIMT – mean carotid intima-media thickness, CCA – common carotid artery , CAD – coronary artery disease, SD – standard deviation

Table 04: Comparison of variables between the groups based on m CIMT

Variable	mCIMT of CCA ,mm		P	R
	< 0.9	≥0.9		
BMI (Kg/m^2)	23.70 ± 4.03	23.7 ± 3.02	0.048	0.62
Waist Hip ratio	0.957 ± 0.06	0.97 ± 0.04	0.317	0.4
FBS (mg/dl)	111.07 ± 35.06	107.26± 47.40	0.582	0.29
TC (mg/dl)	180.10 ± 52.57	218.66 ± 66.68	0.011	0.65
LDL (mg/dl)	101.61 ± 41.95	142.87 ± 57.38	0.001	0.35
HDL (mg/dl)	37.89 ± 8.65	33.51 ± 11.39	0.072	-0.22
VLDL (mg/dl)	40.59 ± 23.20	39.24 ± 17.07	0.529	0.19
TG (mg/dl)	202.98 ± 116	196.21 ± 85.37	0.45	0.35

Data is expressed in mean ± SD, mCIMT – mean Carotid intima medial thickness; mm - millimetre, CCA – common carotid artery; BMI – body mass index; FBS – fasting blood sugar; TC – total cholesterol; LDL – low-density cholesterol; HDL – high-density cholesterol; VLDL – very low-density cholesterol; TG - triglycerides

DISCUSSION:

The present study focused on CAD patients aged < 40 years, who were subjected to CIMT measurement on Ultrasonography before conventional angiography. We found that patients with CAD had more number of risk factors, abnormal lipid profile and abnormal CIMT. We found that CIMT can be used in risk stratification of patients being evaluated for CAD and had positive correlation with elevated LDL cholesterol and total cholesterol.

Conventional CAD accounts for about 80% of CAD in young adults. Obesity and current smoking are the two important conventional risk factors associated with adverse outcomes (two times higher in women than in men <50 years of age).[14,15]

The prevalence of normal coronaries in yCAD varies from 8-22% compared to 3-4% in general CAD population. Spontaneous lysis of an occlusive thrombosis secondary to a plaque rupture, or prolonged vasospasm can be the cause of CAD in them.[14] The arteries show positive remodeling which indicates plaque instability (vulnerable plaque). Lipid core plaques, in contrast to the severely calcified plaques, show positive vascular remodeling, thus early plaques are more prone for CAD.[14,15]

High CRP and serum fibrinogen have been associated with recurrence of future acute coronary events and increased mortality.[16] They have higher rates of normal coronary vessels, mild luminal irregularities and single-vessel disease on angiography compared to the older CAD patients.[17]

Family history of premature CAD is an important risk factor for y CAD. Myers et al, [19] reported that among men at low risk for CAD by risk factor profile (non-smoking, non-hypertensive), more than two-thirds of those who experienced CAD, had a positive parental history of CAD. The present study has only 10 (10%) patients with a family history of Premature CAD out of which 11.4% had significant CAD.

Obesity and overweight have been associated with a harmful effect on the cardiovascular system and increased cardiovascular mortality in various epidemiological and clinical studies. In the Jaipur Heart Watch study, Gupta et al.[1] found a high prevalence of obesity in urban men and women of Jaipur and reported that obesity was a significant risk factor for CAD. The association of BMI and WHR with CAD and CIMT was not significant in the present study.

The Indians have low HDL and high triglycerides level compared to the western population as shown in INTERHEART study.[20] There was a negative correlation between HDL and CAD while others were not significant. The present study was compared with Aggarwal et al [17] (Table 5).The total number of patients were more in number (156 vs 100).The CIMT and lipid profile values are lower in the study compared to our observation, probably secondary to increased number of participants in Aggarwal et al.[17]

Table5: Comparison of the present study with the previous study

	Agarwal et al [17]	Present study
Number of patients, n	156	100
CIMT(mm)	0.6 ± 0.13	0.84 ± 0.7
TC (mg/dl)	160.4 ± 45 *	192.83 ± 58.7*
LDL (mg/dl)	94.2 ± 38.0	115.23 ± 49.6*
HDL (mg/dl)	35.6 ± 7.75	36.45 ± 9.6
TG (mg/dl)	144.1 ± 87.6*	200.75 ± 10.8

Data is expressed in Mean ± SD, * - was found to be statistically significant in correlation with the severity of CAD, CIMT – carotid intima medial thickness, TC- total cholesterol, LDL – low-density cholesterol, HDL – high-density cholesterol, TG – triglycerides.

The purpose of our study was to perform imaging to measure the CIMT in young individuals being evaluated for CAD. This type of screening strategies can emphasize abnormal lipid profile has an increased risk of CAD and can improve long term health outcomes by optimal medical management by use of statins. CIMT provides additional information over the conventional risk factors in the diagnosis of subclinical atherosclerosis.

Limitations:

This is a single-center, small group of yCAD patients, not a randomized study. There is selection bias, extrapolating the findings regarding the relationship of various risk factors with mCIMT relevant to the group of patients to the general population is not applicable. The method used to measure CIMT was manual, and therefore was subject

to intra- and inter-observer variability. Non significant association of some conventional risk factors like Diabetes and Hypertension with CAD could be because of the lesser age and lesser duration of the illness as a whole in the study population.

CONCLUSION

Male gender, Smoking, and low HDL cholesterol are risk factors for Young CAD. Smoking, elevated Total Cholesterol, LDL cholesterol and high BMI cause abnormal m CIMT in y CAD. Elevated m CIMT is associated with significant CAD on CAG in y CAD.

In conclusion, CIMT can be used in risk stratification of patients being evaluated for CAD in young.

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