# **Original Research Article**

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# Association between carotid intima media thickness and metabolic syndrome

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# **ABSTRACT**

**Background:** Metabolic syndrome and its individual criteria pose a risk for atherosclerosis and cardiovascular disease (CVD). Carotid intima media thickness (CIMT) is a well-known marker of subclinical atherosclerosis. This study was aimed to assess CIMT in patients with metabolic syndrome.

**Methods:** This one year cross-sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2016 to December 2016. A total of 100 patients diagnosed to have metabolic syndrome based on national cholesterol education program adult treatment panel III (NCEP ATP III) criteria were studied. All the patients were subjected to carotid B mode ultrasonography.

**Results:** The most common age group was 51 to 60years (29%). Out of 100 individuals who were diagnosed to have metabolic syndrome, 60% had five criteria, 29% had four criteria and 3% had three criteria. Most of the of the individuals (61.00%) had normal ( $\leq$ 0.10cms) CIMT while high (>0.10cm) levels were noted in 39.00% of the individuals. The mean CIMT was noted as  $0.13\pm0.16$ cms. The mean SBP ( $150.15\pm10.39$  vs  $142.98\pm20.09$ mmHg; p=0.042), DBP ( $94.51\pm6.53$  vs  $90.16\pm9.91$  mmHg; p=0.017), total cholesterol levels ( $243.53\pm65.74$  vs  $195.95\pm29.8$  mg/dL; p<0.001) and triglyceride levels ( $221.07\pm48.44$  vs  $180.85\pm24.74$ mg/dL; p<0.001) were noted in individuals with raised CIMT compared to individuals with normal CIMT. Majority of the individuals had abnormal HDL (93.00%) and 41.94% of the individuals with abnormal HDL had raised CIMT (p=0.027).

**Conclusions:** Some individuals with metabolic syndrome are likely to have raised CIMT. The rise in CIMT among the patients with metabolic syndrome is associated with raised SBP, DBP, abnormal HDL (specifically in males), total cholesterol and triglycerides.

**Keywords:** Atherosclerosis, Carotid intima media thickness, Metabolic syndrome

# INTRODUCTION

Metabolic syndrome has affected approximately one quarter of the population in developed world. In India, studies have reported prevalence of metabolic syndrome ranging from 24.9% in northern India to 41% in Southern India using different definitions.<sup>1</sup>

Approximately one fourth of the adult European population was estimated to have metabolic syndrome,

with a similar prevalence in Latin America.<sup>2</sup> Metabolic syndrome is considered as an emerging epidemic in developing East Asian countries like China, Japan, and Korea.

The prevalence of metabolic syndrome ranges from 8 to 13% in men and 2 to 18% in women depending on the population and definitions used.<sup>3-5</sup> Metabolic syndrome has now been recognized as a highly prevalent problem in many other countries worldwide.<sup>6</sup>

Clinical definitions of metabolic syndrome by National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP-III) or International Diabetes Federation (IDF) have gained enormous value in the diagnosis, management and research on the cluster of metabolic risk factors.<sup>7,8</sup> Yet, there is an increasing recognition that other atherogenic, pro-thrombotic and inflammatory aspects of this syndrome are still not captured by these practical clinical definitions which warrant further investigation, particularly for valuable clinical markers.<sup>9</sup>

Presence of metabolic syndrome poses a major risk for development of both type 2 diabetes mellitus and atherosclerosis. The prevalence of cardiovascular disease increases to two to three times higher in individuals with metabolic syndrome than in age-matched controls. <sup>10</sup>

In addition, metabolic syndrome is also associated with carotid intima-media thickness (CIMT), which is a surrogate marker of preclinical atherosclerosis. CIMT is a strong predictor of future cardiovascular morbidity and mortality, in particular myocardial infarction and stroke.<sup>11</sup>

In various studies, increased carotid intima media thickness (CIMT) has been shown to be a good indicator of atherosclerosis. CIMT has been reported to correlate with myocardial infarction, stroke, and peripheral artery disease.<sup>11</sup>

Metabolic syndrome is a disorder characterized by a cooccurrence of three out of five of the following medical conditions: abdominal obesity, elevated blood pressure, high serum triglycerides, low high-density lipoprotein cholesterol levels, and elevated fasting plasma glucose. Some studies showed that increased numbers of metabolic syndrome risk components lead to worsening cardiovascular disease outcomes and risk factors. Although CIMT is related to metabolic parameters, only a few studies have investigated the relationship between numbers of metabolic syndrome risk parameters and CIMT.<sup>12</sup> Hence the present study was undertaken to assess carotid intima media thickness in patients with metabolic syndrome.

#### **METHODS**

This a one year cross sectional study was undertaken under the Department of Medicine, of a 1800 bedded tertiary care teaching hospital situated in north Karnataka, India attached to Jawaharlal Nehru Medical College, Belgaum, Karnataka, India from January 2016 to December 2016.

A total of 100 Patients diagnosed to have metabolic syndrome based on NCEP ATP III criteria who fulfilled the selection criteria during the study period were enrolled. Patients who fulfil the National Cholesterol Education Program-ATP-III criteria for metabolic syndrome that is, three or more of the five components viz.<sup>7</sup>

#### Inclusion criteria

- Abdominal obesity (waist circumference >102cm in men, >88 cm in women),
- Triglycerides ≥ 150mg/dL
- HDL-cholesterol <40mg/dL in men, <50mg/dL in women,
- Systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85mm Hg and
- Fasting plasma glucose ≥110 mg/dL.

#### Exclusion criteria

- Patients with liver disorders, renal disorders, congestive cardiac failure, hypothyroidism, rheumatoid arthritis, psoriasis,
- under treatment of any thyroid related disorder,
- Pregnant women, women on oral contraceptive pills,
- Stroke and transient ischemic attack patients and patients on statins and other medications that alter thyroid functions, lipid levels.

The ethical clearance was obtained from the Institutional Ethical committee, Jawaharlal Nehru Medical College, Belgaum.

#### Procedure

Patients fulfilling selection criteria were explained about the nature of the study and a written informed consent was obtained prior to the enrolment. Demographic data like gender and age were collected and the patients were interviewed for the relevant history such as diabetes mellitus, hypertension and heart disease.

A thorough general physical examination was conducted to assess vital parameters followed by systemic examination. Under strict aseptic precautions fasting blood samples were drawn and subjected to investigations including fasting blood sugar, glycosylated haemoglobin (HbA1c) and fasting lipid profile (total cholesterol, triglycerides, HDL and LDL). Patient's HDL, LDL and Triglycerides level were obtained from enzymatic method in Biochemistry Laboratory. The fasting blood sugar and glycosylated haemoglobin levels were interpreted based on ADA 2018 guidelines and lipid profile was interpreted based on NCEP ATP III criteria.<sup>7,13</sup> The carotid intima media thickness was determined by imaging of common carotid artery using a high frequency B-mode ultrasonography. High resolution mode, colour Doppler, and pulse Doppler ultrasonography of both carotid arteries were performed with ultrasound machine, PHILIPS HD-11 equipped with a 7.5 MHz linear array transducer. Patients were examined in supine position with head tilted backwards. After the carotid arteries were located by transverse scans the probe was rotated 90° to obtain and record a longitudinal image of the anterior and posterior walls. The maximum IMT was measured at near and far walls of the common carotid artery, the bifurcation, and the internal carotid arteries and was expressed as a mean aggregate value. CIMT values of >0.1cm were considered abnormal and confer increased absolute risk of CHD. 14,15

# Statistical analysis

The data thus obtained was tabulated on Microsoft Excel spreadsheet. The categorical data was expressed as ratios and percentages. Chi-square test was used to assess the association. Continuous data was expressed as mean±standard deviation (SD) and then the comparison was done using independent sample 't' test. A probability value ('p' value) of less than or equal to 0.050 was considered to be statistically significant.

#### **RESULTS**

The clinical, biochemical and lipid profile of the study population is as depicted in Table 1. Majority of the individuals were males (78%). Most of the patients were aged between 51 to 60 years (29%) and next common age group was 61 to 70 years (28%).

The mean age was 57.14±11.10years. All the individuals had history of hypertension and diabetes mellitus. Abnormal waist circumference and HDL was noted in 72% and 93% of the patients respectively. The total cholesterol and LDL levels were high in 52% and 34% of the individuals respectively. In the present study, HbA1c levels were >8.5 percent in most of the patients (32%) (Table 2). High (>0.10cms) CIMT levels were noted in 39.00% of the individuals, the mean CIMT level were 0.13±0.16cms and median CIMT levels were 0.09cms and ranged between 0.05 to 1.30cms (Table 1). Out of

100 individuals diagnosed to have metabolic syndrome, 68.00% had five criteria. No association was found between CIMT and metabolic syndrome criteria (p=0.532).

The mean CIMT levels in males  $(0.12\pm0.16\text{cms})$  and females  $(0.13\pm0.13\text{cms})$  was comparable (p=0.931). Most of the individuals were aged between 51 to 60 years (29.00%), 61 to 70 years (28.00%), and 41 to 50 years (26.00%). Among them 37.93%, 39.29% and 30.77% of the individuals had raised CIMT respectively. However, no association was found between age and CIMT (p=0.535) (Table 3).

All the individuals with normal HDL had normal CIMT (100%) and 41.94% of the individuals with abnormal HDL (58.06%) had raised CIMT (p=0.027). No association was found between CIMT total cholesterols, HbA1c, waist circumference (p>0.050) (Table 3). Significantly higher mean SBP (150.15±10.39 142.98±20.09mmHg; p=0.042), DBP (94.51±6.53 vs 90.16±9.91mmHg; p=0.017), total cholesterol (243.53±65.74 vs 195.95±29.8mg/dL; p<0.001) and triglyceride levels (221.07±48.44 vs 180.85±24.74mg/dL; p<0.001) were noted with raised CIMT. Also, significantly lower HDL levels (30.55±5.86 vs 27.69±4.52 mg/dL; p=0.018) were noted in males with raised CIMT.

# **DISCUSSION**

In the present study, the CIMT levels were raised and suggest that, a considerable subset of individuals with metabolic syndrome are likely to have higher CIMT levels.

Table 1: Characteristics of the study population.

Wawiahlas	Distribution (n=100)		M - 1!	Range	
Variables	Mean	SD	Median	Minimum	Maximum
Age (years)	57.14	11.10	57.00	28.00	86.00
Systolic BP (mm Hg)	145.78	17.28	150.00	110.00	200.00
Diastolic BP (mm Hg)	91.86	8.97	90.00	70.00	120.00
Weight (kgs)	96.47	8.34	96.00	80.00	118.00
Height (cms)	168.11	6.09	169.50	150.00	178.00
WC (cm) - males	103.78	2.70	103	100	119
WC (cm) - females	99.81	2.10	100	98	106
BMI (Kg/m²)	34.09	2.45	33.60	29.10	41.90
FBS (mg/dL)	161.18	44.48	146.00	120.00	400.00
HbA1C (%)	8.04	1.96	7.50	5.40	13.30
Total cholesterol (mg/dL)	214.51	52.36	200.00	154.00	394.00
LDL (mg/dL)	87.46	25.39	78.00	60.00	160.00
HDL (mg/dL) - males	29.49	5.54	29.00	20.00	45.00
HDL (mg/dL) - females	27.82	5.10	25.00	20.00	40.00
Triglycerides (mg/dL)	196.54	40.75	188.00	154.00	346.00
CIMT (in cms)	0.13	0.16	0.09	0.05	1.30

Table 2: Metabolic and lipid profile.

		Distribution (	Distribution (n=100)		
Criteria	Observations	Number	Percentage		
	Present	100	100.00		
History of hypertension	Absent	0	0.00		
	Total	100	100.00		
TT' C	Present	100	100.00		
History of diabetes mellitus	Absent	0	0.00		
	Total	100	100.00		
	Normal (> 40 M; > 50 F)	7	7.00		
HDL (mg/dL)	Abnormal (≤40 M; ≤50 F)	93	93.00		
= (8,)	Total	100	100.00		
	Normal (< 100)	66	66.00		
LDL (mg/dL)	High (100 or more)	34	34.00		
(8,)	Total	100	100.00		
	Normal (0 to 200)	48	48.00		
Total cholesterol	High (> 200)	52	52.00		
(mg/dL)	Total	100	100.00		
Waist circumference (cms)	Normal (<90 M; <80 F)	28	28.00		
	Abnormal (≥90 M; ≥80 F)	72	72.00		
	Total	100	100.00		
Triglycerides (mg/dL)	Normal (0 to 150)	0	0.00		
	High (> 150)	100	100.00		
	Total	100	100.00		
	Optimal (≤5.50)	3	3.00		
	Prediabetes (5.51-6.50)	19	19.00		
Glycemic control (%)	Good control (6.51-7.0)	17	17.00		
	Moderate control (7.01-8.50)	29	29.00		
	Poor control (> 8.5)	32	32.00		
	Total	100	100.00		
	Underweight (<18.5)	0	0.00		
	Normal (18.5 -22.99)	0	0.00		
Body mass index	At risk (23.00-24.99)	0	0.00		
(Kg/m²)	Overweight (25.00-29.99)	1	1.00		
(right)	Obese (≥30)	99	99.00		
	Total	100	100.00		

These findings were consistent with a study by Koskinen J et al, who found that, metabolic syndrome was significantly associated with accelerated CIMT progression.<sup>15</sup>

The mean CIMT noted in the present study corroborates with the result of the study by Timoteo AT et al, who reported mean CIMT as  $0.88\pm0.33$ cms. <sup>16</sup> In the European Lacidipine Study on Atherosclerosis (ELSA), metabolic syndrome was associated in a bivariate model with a 4-year change in CIMT among 1734 hypertensive subjects aged 45 to 75 years at baseline. <sup>17</sup>

Ispessimento Medio Intimale e Rischio cardiovascolare media-intima thickness and cardiovascular risk] (ISMIR) study, showed an association between metabolic syndrome and CIMT. The prevalence of an increased CIMT (defined as common carotid artery CIMT >0.80cms) was significantly higher in patients with

metabolic syndrome than in patients without it, and mean CIMT was also significantly higher.

In this study, the mean SBP in individuals with raised CIMT was significantly high compared to those with normal CIMT (150.15±10.39 vs 142.98±20.09mmHg; p=0.042). Similar findings were noted with respect to DBP that is, mean DBP in individuals with raised CIMT was significantly high compared to those with normal CIMT (94.51±6.53 vs 90.16±9.91 mm Hg; p=0.017). These findings hypothesize relationship between blood pressure and CIMT.

In contrast to these observations, a study by Liu CP et al, reported no significant association between systolic blood pressure and CIMT.<sup>19</sup> This lack of relationship reported by Liu CP et al, was in accordance with the several other studies in hypertensive patients by Myung Y et al, and Catena C et al.<sup>20,21</sup> Systolic blood pressure seems to be an

important risk factor of early arterial structural changes. In this study no association was found between triglycerides and CIMT. However, the mean triglyceride levels were significantly high in individuals with raised

CIMT (221.07±48.44 mg/dL) compared to those who had normal CIMT (180.85±24.74mg/dL) and the difference observed was statistically significant (p<0.001).

Table 3: Association of CIMT with metabolic syndrome components.

		CIM	CIMT (Cms)			
Variables	HDL (mg/dL)	≤ 0.1				'p' value
		%	No.	%	No.	•
Sex	Male	49	62.82	29	37.18	0.482
	Female	12	54.55	10	45.45	
	Total	61	61.00	39	39.00	
	18 to 30	0	0.00	1	100.00	0.535
	31 to 40	3	75.00	1	25.00	
	41 to 50	18	69.23	8	30.77	
Age	51 to 60	18	62.07	11	37.93	
(years)	61 to 70	17	60.71	11	39.29	
	71 to 80	5	45.45	6	54.55	
	81 to 90	0	0.00	1	100.00	
	Total	61	61.00	39	39.00	
HDL	Normal (> 40 males; > 50 females)	7	100.00	0	0.00	0.027
	Abnormal (≤40 males; ≤50 females)	54	58.06	39	41.94	
(mg/dL)	Total	61	61.00	39	39.00	
LDI	Normal (<100)	41	62.12	25	37.88	0.749
LDL (ma/dL)	High (≥100)	20	58.82	14	41.18	
(mg/dL)	Total	61	61.00	39	39.00	
Total	Normal (0 to 200)	33	68.75	15	31.25	0.127
cholesterol	High (≥ 200)	28	53.85	24	46.15	
(mg/dL)	Total	61	61.00	39	39.00	
Waist	Normal (<90 male; <80 Females)	16	57.14	12	42.86	0.622
circumference (cms)	Abnormal (≥102 male; ≥88 females)	45	62.50	27	37.50	
	Total	61	61.00	39	39.00	
HbA1c (%)	Optimal (≤5.50)	1	33.33	2	66.67	0.567
	Prediabetes (5.51-6.50)	13	68.42	6	31.58	
	Good control (6.51-7.0)	9	52.94	8	47.06	
	Moderate control (7.01-8.50)	20	68.97	9	31.03	
	Poor control (> 8.5)	18	56.25	14	43.75	
	Total	61	61.00	39	39.00	
BMI (Kg/m²)	Underweight (<18.5)	0	0.00	0	0.00	
	Normal (18.5 -22.99)	0	0.00	0	0.00	
	At risk (23.00-24.99)	0	0.00	0	0.00	
	Overweight (25.00-29.99)	0	0.00	1	100.00	
	Obese (≥30)	61	61.62	38	38.38	
	Total	61	61.00	39	39.00	
Triglycerides (mg/dL)	Normal (0 to 150)	0	0.00	0	0.00	-
	High (> 150)	61	61.00	39	39.00	
	Total	61	61.00	39	39.00	

These findings propose relationship between hypertriglyceridemia and CIMT in patients with metabolic syndrome. These findings were in concordance with a study by Sipla K et al, who found statistically significant correlations between triglycerides and CIMT in univariable models for both sexes.<sup>22</sup> In this study,

significantly higher number of individuals (41.94%) with abnormal HDL had raised CIMT (p=0.027). However, gender wise comparison of HDL levels revealed significantly higher mean HDL levels among males with normal CIMT (30.55±5.86), compared to those with raised CIMT (27.69±4.52mg/dL) (p=0.018). But HDL

levels among females with normal CIMT (27.25±4.18) and raised CIMT (28.50±6.20mg/dL) were statistically almost similar (p=0.595). In contrast to these observations, a study by Sipla K et al, found statistically significant correlations between HDL and CIMT in univariable models for both sexes.<sup>22</sup> The lack of relationship between HDL and CIMT among females can be explained by a smaller subset of females in the present study.

In this study, 37.50% of the individuals had raised CIMT while 62.50% of the individuals with abnormal waist circumference had normal CIMT. This difference was statistically not significant (p=0.622) suggesting lack of relationship between waist circumference and raised CIMT. The mean waist circumference among males (103.82±1.98 vs 103.72±3.66cms; p=0.901) and females (99.33±1.30 vs 100.40±2.76cms; p=0.901) with normal and raised CIMT levels were statistically comparable suggesting lack of association between raised CIMT and waist circumference. In contrast to these observations, Koskinen J et al, in their study found that, waist circumference had a strong association with CIMT progression.<sup>15</sup> This observation may suggest that increased waist circumference is a risk factor that reflects long-term deviations in several metabolic risk variables. Central obesity predisposes to metabolic syndrome, hypertension, development of insulin resistance, and cardiovascular diseases. It is also possible that a part of the risk factor associated with increased waist circumference is mediated by some unmeasured factors. Potential candidates may include increased oxidative stress and inflammatory cytokines secreted by adipose tissue.

Overall in nutshell, a considerable subset of patients with metabolic syndrome are likely to have raised CIMT. However, the rise in CIMT among the patients with metabolic syndrome was independent of the number of components of metabolic syndrome criteria. Furthermore, the raised CIMT is associated with hypertension, abnormal HDL (especially in males), total cholesterol and triglyceride levels. CIMT is independent of body mass index, fasting blood sugar, glycosylated haemoglobin, LDL and waist circumference. These finding need further validations due to potential limitations of this study, namely single centre study, smaller sample size, smaller subset of female participation, age distribution was not uniform, majority of the patients had all five abnormalities and almost all the patients presented with history of hypertension and diabetes mellitus whose duration of disease was not considered in the assessment. The treatment history and treatment compliance were not analyzed.

Present study is a cross-sectional study, and as such, it is not possible to establish a causal relationship since no information from the follow-up was analyzed and patients underwent only a single evaluation of CIMT. Authors did not account for the potential difference

between plaque presence in a single artery vs in multiple arteries. It is possible that plaque presence in multiple carotid artery segments may be associated with higher risk. The present scanning protocol for CIMT measurement focuses primarily on the common carotid artery due to difficulties in an adequate evaluation of CIMT of the bulb and internal carotid arteries. However, scanning of the remaining segments of the carotid arteries for plaques might be important to avoid missing "upstream" advanced atherosclerosis. Manual assessment of CIMT is not optimally reproducible. There has been rapid advancement in ultrasound technology resulting in greater consistency and resolution of images.

Further multicentric studies addressing these limitations may focus the true CIMT profile in patients with metabolic syndrome.

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Institutional Ethics Committee

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