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Original Research Article

The impact of insulin resistance, dyslipidemia and high sensitivity C-reactivity protein on carotid intima-media thickness in metabolic syndrome

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ABSTRACT

Background: Carotid intima-media thickness (CIMT) is a strong predictor of cardiovascular events and associated with metabolic syndrome (MetS). The CIMT has been widely used as one of the parameters of atherosclerosis. The aim of the study was to evaluate the impact of insulin resistance, dyslipidemia and high sensitivity C-reactive protein on carotid intima-media thickness in metabolic syndrome patients of Western Maharashtra as very sparse data is available.
Methods: It was a cross-sectional study of 400 adults (200 cases and 200 control), 18-50 years of age, both the sexes randomly selected from diabetes and obesity OPD at tertiary care hospital. Diagnosis of metabolic syndrome was done according to modified NCEP adult treatment panel III criteria. CIMT was measured by B mode ultrasound (Philips HT-11, Color Doppler), hs-CRP by ELISA method (Cal biotech). Insulin resistance by HOMA-IR (Homeostatic model assessment of insulin resistance). The predictors of CIMT with various variables were studied by multiple linear regression analysis.
Results: We found significant increase in CIMT (0.7895±0.110, $p<0.001$) in MetS and a positive correlation of CIMT with age, waist to hip ratio, triglyceride levels and systolic blood pressure ($p<0.001$).
Conclusions: Increased carotid intima-media thickness in metabolic syndrome may increase the risk of having a stroke and cardiovascular mortality. It was considered an early deterioration in the arterial intima and is a preclinical stage of atherosclerosis. Early diagnosis and prevention may help to reduce the risk of stroke and cardiovascular mortality.

Keywords: Metabolic syndrome, Insulin resistance, Cardiovascular risk markers, CIMT, hs-CRP

INTRODUCTION

The metabolic syndrome (syndrome X, insulin resistance syndrome) consists of a constellation of metabolic abnormalities that confer an increased risk of cardiovascular disease (CVD) and diabetes mellitus. Individuals with the metabolic syndrome are twice as likely to die of cardiovascular disease as those who do not and their risk of acute myocardial infarction or stroke is three-fold higher.[1] The approximate prevalence of metabolic syndrome among patients with coronary heart disease (CHD) is 50%, with a prevalence of ~35% among patients with premature coronary artery disease (before or at age 45 years).[1] Obesity is the driving force behind metabolic syndrome. Data also indicate that atherogenic dyslipidemia, glucose intolerance, thrombotic tendency, subclinical inflammation, and endothelial dysfunction are proportionately higher in metabolic syndrome.[2,3] Atherogenic dyslipidemia is an integral component of metabolic syndrome and is a major contributor to cardiovascular risk in these patients. Carotid intima-media thickness (CIMT) is a marker of atherosclerosis development and predictor of cardiovascular events in daily clinical practice.

It alerts physicians to any thickening when patients are still asymptomatic. Early detection may indicate the need for a more aggressive approach to managing the risk factors associated with heart disease and stroke. There has been an increasing interest in the involvement of low-grade inflammation in the pathogenesis of metabolic syndrome.[4] Recently hs-CRP has received the most attention as a marker of inflammation in metabolic syndrome responsible for cardiovascular diseases. For more than 30 years, cardiovascular risk prediction algorithms have relied on blood pressure, smoking status, hyperlipidemia, and the presence or absence of diabetes. The time has come for careful consideration of adding CIMT as an atherosclerosis index as a clinical criterion for metabolic syndrome.[5] The aim of the study was to evaluate the CIMT in metabolic syndrome patients and to assess its correlation with insulin resistance, hs-CRP and dyslipidemia.

METHODS

Study design

This was a cross-sectional analytic study.

Study type

The study type was comparative and correlation study.

Study period

The study period was December 2018 to May 2020.

Sample size

Sample size was calculated by using WinPepi software. Assuming an increase in CIMT of 7 mm with a standard deviation 0.35, it was estimated to be 200 participants in each group would provide 90% power at an α-level of 0.05.

Participants

200 diagnosed cases of metabolic syndrome attending diabetes and obesity OPD in the age group of 18 to 50 (100 males and 100 females) were studied and compared with 200 age and sex-matched control group (100 males and 100 females).

Source

The study was conducted in the physiology department in collaboration with medicine (obesity, diabetes) OPD, CCL- biochemistry, radiology and microbiology serology laboratory of tertiary care hospital of western Maharashtra.

Ethical approval

Institutional ethical committee approval was obtained before the start of the study and informed consent was taken from all subjects.

Inclusion criteria

Diagnosis of metabolic syndrome was done according to modified NCEP National Cholesterol Education Program, Adult Treatment Panel III criteria (2004).[1] The individuals who meet at least three of the five clinical criteria were included. Central obesity- waist circumference >90 cm in men and >80 cm in female, BSL >100 mg/dl or T2DM or specific medication, BP >130/85 mmHg or specific medication, triglycerides >150 mg/dl or specific medication, HDL <40 mg/dl in men <50 in women.

Exclusion criteria

Non-obese and obese patients that do not meet criteria for metabolic syndrome, acute infections, chronic infections like rheumatoid arthritis, autoimmune disorders, patients with a previous history of coronary artery disease, hepatic and kidney disease, malignancy, chronic obstructive pulmonary disease and endocrinal disorder like hypothyroidism, PCOS, acromegaly, Cushing syndrome.

Data collection

Demographic, socioeconomic, and self-reported behavioral information (smoking, alcohol, physical activity, and diet), objective measures of anthropometry (height, weight, BMI, waist circumferences, waist to hip ratio) and vital parameters heart rate, blood pressure and thorough clinical examination was done.

Biochemical parameters

Blood sugar

Fasting, postprandial glucose by using glucose GOD-PAP method (Biolab diagnostics) was done.

Lipid profile

Triglycerides- GPO-PAP method (Pathozyme diagnostics) and HDL- direct method (Pathozyme diagnostics) was done.

Insulin

Fasting by electro-chemiluminescence immune assay, ECLIA-Roche (Cobas kit).

High sensitivity C-reactive proteins (hs-CRP)

By enzyme-linked immunosorbent assay- ELISA method (Cal biotech) was done.

Insulin resistance

By HOMA-IR, for estimation of insulin sensitivity. Way to reveal the dynamic between your baseline (fasting) blood sugar and the responsive hormone insulin.[1]

$$\frac{\text{Fasting glucose (mg/dl) x Fasting insulin (µU/ml)}}{405}$$

Carotid intima-media thickness test

CIMT by B mode ultrasound (Philips HT-11, Color Doppler).

The test measures the thickness of the inner two layers of the carotid artery, the intima, and media at the internal carotid artery. CIMT above 1.0 mm is regarded as abnormal and above 1.2 mm considered high risk.

Procedure

The ultrasound probe is placed on the skin overlying carotid arteries in the neck. The technique used to measure and calculate CIMT was to measure a double line with the definition of the light-intima and media-adventitia interfaces of the vessel. The distance between the two acoustic interfaces was considered the CIMT measure. The intima-media thickness IMT was defined as the distance between the leading edges of the 2 echogenic lines separated by a hypo echogenic space; the first line represented luminal-intimal transition and the second medial-adventitial. Three determinations of IMT were conducted at the site of the thickest and two adjacent points (1 cm up and downstream from the thickest point) and were averaged (mean IMT).

Statistical analysis

Statistical Package for Social Science (SPSS) program version 15 was used for the analysis of data. Data were presented as mean±SD. Pearson correlation coefficient was used for detection of the correlation between HOMA-IR and CIMT variables. P value<0.05 was considered significant. The multiple linear regression analysis was done to reveal a predictive model of CIMT.

RESULTS

This was a cross-sectional analytic, tertiary care hospital-based study on 200 metabolic syndrome patients attending obesity and diabetic OPD with an equal number of age and sex-matched controls. 200 out of these, there were 100 males and 100 females in each group. The mean age in both groups was 42.5±0.49 with an age range from 18 to 50 years. All subjects were evaluated for components of metabolic syndrome, adiposity markers, insulin resistance and atherosclerotic markers like hs-CRP and carotid intima-media thickness. The weight and adiposity parameters like BMI (26.89±0.4089), WC (103.3±14.9), and WHR (0.96±0.0057) were significantly (p<0.0001) higher in metabolic syndrome patients as compared to BMI (22.59±0.2611), WC (70.57±7.6), and WHR (0.96±0.0057) control group (Table 1).

The individual components of MetS were significantly higher and low HDL levels were found in MetS patients when compared with control (p<0.0001). Fasting blood sugar (158.2±2.92 vs 96.94±0.97), systolic blood pressure (135±0.93 vs 114.9±0.63), diastolic blood pressure (86.61±0.69 vs 74.52±0.42), triglycerides (160.7±1.41 vs 105.1±1.15) and HDL (38.05±0.44 **vs** 50.88±0.45). High insulin resistance HOMA-IR (6.836±0.086 vs 1.36±0.0412) and high levels of fasting insulin (18.24±0.258 vs 5.836±0.1745), p<0.001 were found in MetS (Table 1). Atherosclerotic markers like hs-CRP (6.5±0.9881), triglyceride were significantly higher (p<0.0001) and low HDL levels were found in MetS as compared to controls (0.65±0.4927) (Table 1).

Carotid intimal thickness was higher in MetS as compared to control. CIMT right side-0.7854±0.112 vs 0.4251±0.082 (p<0.0001) and CIMT left side-0.7937±0.109 vs 0.4292±0.085 (p<0.0001). Left-sided carotid artery thickness was found greater than the right side. There was no significant correlation of CIMT with insulin resistance and hs-CRP (p>0.05) but there is a positive association with lipids.

An increase in CIMT is not associated with insulin resistance (Table 2). The multiple linear regression analysis revealed a predictive model, the predictors of left-sided CIMT are age, WHR, hs-CRP, triglyceride, HDL and systolic blood pressure (Figure 1). It revealed systolic blood pressure as a significant predictor of left-sided CIMT (Table 3). The predictors of right-sided CIMT are age, WHR, hs-CRP, triglyceride, HDL, fasting insulin (Figure 2) (Table 4).

Table 1: Demographic, clinical and metabolic characteristics of patients with metabolic syndrome (N=200) and healthy controls (N=200).

Parameters	Control (mean±SD)	Case (mean±SD)	P value
Age (years)	41.5±0.56	42.5±0.49	p>0.05
BMI	22.59±0.2611	26.89±0.4089	p<0.0001
Waist circumference	70.57±7.6	103.3±14.9	p<0.0001
WHR	0.79±0.0049	0.96±0.0057	p<0.0001
Systolic BP	114.9±0.63	135±0.93	p<0.0001
Diastolic BP	74.52±0.42	86.61±0.69	p<0.0001
Heart rate	82.91±8.46	114.6±9.12	p<0.0001
Fasting sugar	96.94±0.97	158.2±2.92	p<0.0001
PP sugar	119.2±1.46	236.6±54	p<0.0001
Triglyceride	105.1±1.15	160.7±1.41	p<0.0001

Continued.

Parameters	Control (mean±SD)	Case (mean±SD)	P value
HDL	50.88±0.45	38.05±0.44	p<0.0001
Fasting insulin	5.836±0.1745	18.24±0.258	p<0.0001
HOMA- IR	1.36±0.0412	6.836±0.086	p<0.0001
hs-CRP	0.65±0.4927	6.5±0.9881	p<0.0001
CIMT-RT	0.4251±0.082	0.7854±0.112	p<0.0001
CIMT-LT	0.4292±0.085	0.7937±0.109	p<0.0001
CIMT (mean)	0.4271± 0.083	0.7895±0.110	p<0.0001

Note: p<0.05 significant, p<0.0001 highly significant.

Table 2: Pearson correlation coefficient between CIMT with HOMA-IR, hs-CRP and lipid levels.

Correlation coefficient	R value	P value
hs-CRP	0.24	p>0.05
HOMA-IR	0.13	p>0.05
Triglycerides	0.37	p<0.001
HDL	0.30	p<0.001

Note: p<0.05 significant, p<0.001 highly significant.

Table 3: Multiple linear regression analysis of CIMT-LT with all variables.

Variables	F	R2	P value
Age (years)	5.43	0.0267	p<0.05
hs-CRP	15.8	0.074	p<0.001
HOMA-IR	0.122	0.0006	p>0.05
F insulin	2.84	0.014	p>0.05
Triglyceride	23.72	0.107	p<0.001
HDL	16.39	0.76	p<0.0001
SBP	4.28	0.021	p<0.05
DBP	0.45	0.0022	p>0.05
AC	1.60	0.008	p>0.05
WHR	5.34	0.026	p<0.05

Table 4: Multiple linear regression analysis of CIMT-RT with all variables.

Variables	F	R2	P value
Age	5.7	0.02	p<0.05
hs-CRP	9.4	0.04	p<0.05
HOMA-IR	0.0006	0.0000033	p>0.05
F insulin	4.36	0.021	p<0.05
Triglycerides	23.6	0.1069	p<0.05
HDL	16.72	0.077	p<0.05
SBP	5.6	0.02	p>0.05
DBP	0.28	0.0014	p>0.05
AC	1.2	0.0060	p>0.05
WHR	6.3	0.03	p<0.05

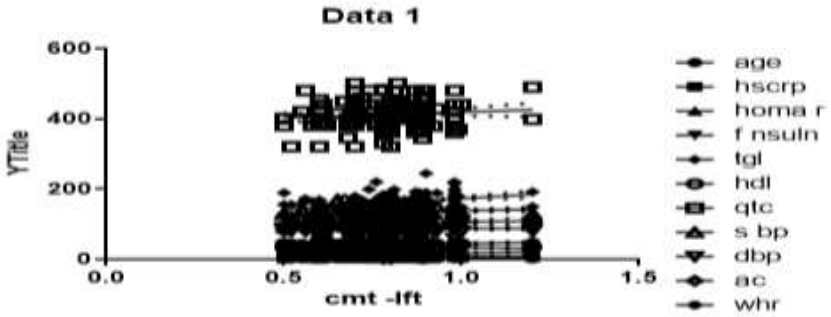

Figure 1: Multiple linear regression analysis of CIMT-LT with all variables.

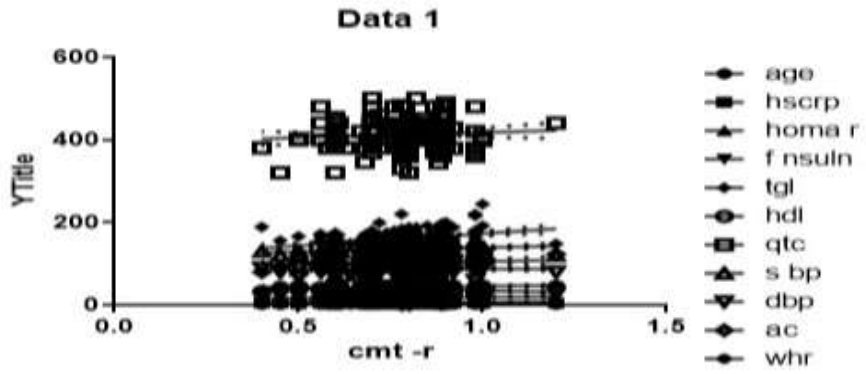

Figure 2: Multiple linear regression analysis of CIMT-RT with all variables.

DISCUSSION

There was a growing body of evidence that among risk factors that promote atherosclerosis, metabolic syndrome is a powerful and prevalent predictor of cardiovascular events. The systemic inflammatory process associated with metabolic syndrome has numerous deleterious effects that promote plaque activation, which is responsible for clinical events. Interactions between the innate immune system with lipid-derived products seem to play a major role in the pathophysiology of atherosclerosis about the metabolic syndrome

Increase carotid intima-media thickness was considered an early deterioration in the arterial intima and is a preclinical stage of atherosclerosis.[8,9] Despite controversial results, the majority of studies have recommended measuring CIMT in clinical practice for the assessment of cardiovascular risk.[10-15] Carotid intima-media thickness is an index of atherosclerosis in the vascular bed and is highly predictive of the development of atherosclerosis; incident metabolic syndrome provides additional information regarding the progression of preclinical atherosclerosis beyond conventional risk factors and can therefore improve the prediction of clinical CVD. In this study, among the various components of metabolic syndrome triglycerides and HDL levels have shown a positive correlation with CIMT.

CIMT measures the thickness of the 2 innermost layers (intima and media) of the walls of the carotid arteries (located within the neck). These layers tend to get thicker with dyslipidemia. Abnormal thickening of the artery wall is the first sign of plaque formation. Clinical studies over the previous few decades have shown that after factoring for age, gender, and ethnicity, individuals with increased CIMT values have a greater risk of coronary failure and stroke than those with CIMT values that are judged to be normal for the comparable group.There was no correlation between hs-CRP and CIMT in this study.

The measurement of markers of inflammation has been proposed as a method to improve global cardiovascular risk prediction hs-CRP serves as a marker of inflammation and predicts the risk of adverse cardiovascular events. Moreover, chronic subclinical inflammation was associated with cardiovascular risk and a significant linear increase in CIMT with increasing quartiles of hs-CRP.16

When determined with a high sensitivity test, hs-CRP is an independent predictor of future cardiovascular events and adds prognostic information to lipid screening. After having analyzed the results of the 200 MetS, we found that the combination of MetS components affects CIMT. Amongst the components of MetS, the factors that had the strongest associations with CIMT were arterial hypertension and lipid levels.

We did not find any relation between CIMT and HOMA-IR. Insulin resistance does not affect increased CIMT. It was necessary to spot the relevant risk factors for CIMT to facilitate the first comprehensive prevention and treatment of macroangiopathy. According to previous studies, CIMT can be affected by many factors, including age, sex, smoking, blood pressure, blood lipid levels, thyroid function, blood glucose levels, blood glucose level fluctuations and C-peptide levels.[16-26] The present results support the findings of studies in middle-aged individuals that have reported an instantaneous relationship of metabolic risk factors.

Bilateral CIMTs became thicker with age ($p<0.001$). In addition to this, the left CIMT in Figure 1 was thicker than the right Figure 2 and associate positively with systolic blood pressure in this study. Of the components, increased waist to hip ratio and triglyceride levels contribute to the association between metabolic syndrome and the change in carotid IMT. These data suggest that emphasis should be focused on multiple metabolic risk factors rather than on each risk factor separately. With this approach, it would be possible to identify a large number of individuals who are at an increased risk for clinical CVD.

Limitations

The limitations of the study were that CHD prediction by ultrasonography-assessed carotid plaque may be more representative of atherosclerosis than CIMT. So,

measurement of carotid plaque would have added more value for the assessment of cardiovascular risk factors in metabolic syndrome.

CONCLUSION

Increased CIMT is associated with age, dyslipidemia, high waist to hip ratio, raised systolic blood pressure. Increased CIMT is a worthwhile predictor of subsequent CHD and stroke, the two leading causes of cardiovascular death. CIMT may provide additional prognostic information to that of conventional risk factors is pivotal in discussing its clinical utility in primary prevention.

Recommendations

Authors recommend evaluation of CIMT in metabolic syndrome patients as a routine test to get an insight into vascular changes associated with age, hypertension and dyslipidemia.

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