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STUDY OF ASSOCIATION BETWEEN HIGH SENSITIVITY C REACTIVE PROTEIN (CRP) AND METABOLIC SYNDROME

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Abstract

Background: Metabolic syndrome is an accretion of numerous disorders, which composed advance the risk of an individual emerging atherosclerotic cardiovascular disease, insulin resistance, and diabetes mellitus, and vascular and neurological complications. MetS has been associated with a pro-inflammatory state branded by raised plasma concentrations of several markers of inflammation. Present study was aimed to study association between high sensitivity C reactive protein (CRP) and metabolic syndrome. **Material and Methods:** Present study was cross-sectional observational study, conducted in patients diagnosed with Metabolic Syndrome according to the NCEP ATP III criteria. Serum hs-CRP levels were to be determined by immuno-turbidometric assay using with dedicated reagents. **Results:** In present study, among 78 subjects mean age of the study population was 49.24 ± 10.45 years. 70(92.1%) of study subjects were females and 6(7.9%) were males. Among 76 study subjects, 48(63.2%) of subjects had Diabetes Mellitus and 67(88.2%) had Hypertension. There is positive correlation between waist circumference (r value= 0.43, p-0.034), BMI (r value= .74, p 0.02), FBS (r value= .36, p 0.04), SBP (r value= .34, p 0.045) and DBP (r value=.47, p value-.047) and hs-CRP. This showed that patients with elevated hs-CRP has higher waist circumference, high Body Mass Index, high FBS, high SBP and DBP (HTN). There is a negative correlation between hs-CRP and HDL, showing that an elevated hs-CRP is associated with lower values of HDL (r value= -0.56, p-0.03). This shows that there is an inverse relationship between HDL an hs-CRP showing that when hs-CRP increases, HDL decreases. 50(71.4%) of females had hs-CRP of high-risk category, 68.8% of Hypertensives had hs-CRP of high-risk category, 74.6% of Diabetics had hs-CRP of high risk category. These association were statistically

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significant. **Conclusion:** There was positive correlation between waist circumference, BMI, FBS, SBP and DBP (components of metabolic syndrome) and hs-CRP.
Keywords: waist circumference, metabolic syndrome, hs-CRP, diabetes mellites, hypertension

Introduction

Metabolic syndrome is an accretion of numerous disorders, which composed advance the risk of an individual emerging atherosclerotic cardiovascular disease, insulin resistance, and diabetes mellitus, and vascular and neurological complications such as a cerebrovascular accident.[1,2] Metabolic syndrome (MS) is a pre-morbid condition that advances in the setting of insulin resistance and factors such as poor diet, physical inactivity, obesity, and genetics play a contributing role. Metabolic syndrome rises the hazard for development of type 2 diabetes mellitus, coronary artery disease (CAD), and other cardiovascular diseases and has been shown to independently increase all-cause mortality.[3,4]

MetS has been associated with a pro-inflammatory state branded by raised plasma concentrations of several markers of inflammation.[5] Leptin, a cytokine-like molecule secreted by adipose tissue, controls adipose mass and body weight by constraining food intake and stimulating energy expenditure. Leptin upsurges obesity, type 2 diabetes mellitus, hypertension and MetS. Leptin is also considered as a biomarker for obesity, insulin resistance and MetS.

A proinflammatory state, as indicated by amplified circulating TNF-α and high-sensitivity C-reactive protein levels, and a prothrombotic state, evidenced by increased PAI-1 levels, are often detected in MetS patients. [6] Many studies demonstrated that high-sensitivity C-reactive protein is an autonomous predictor for myocardial infarction, stroke, peripheral artery disease and sudden cardiac death. [7,8] Present study was aimed to study association between high sensitivity C reactive protein (CRP) and metabolic syndrome

Material And Methods

Present study was cross-sectional observational study, conducted in department of General medicine, Viswa Bharathi medical college and general hospital, a Tertiary Care hospital, Penchikalapadu, India. Study duration was of 12 months (January 2021 to January 2022). Study approval was obtained from institutional ethical committee.

Inclusion criteria

- Patients diagnosed with Metabolic Syndrome according to the NCEP ATP III criteria considering abdominal obesity as per World Health Organization (WHO) guidelines for South Asians aged 20 to 85 years, willing to participate in present study.

Exclusion criteria

- Patients less than 20 years and more than 85 years.
- Patients takings statins, aspirin, thiazolidinediones, steroids, synthetic oestrogens, heparin, calcium channel blockers, amiodarone, valproic acid, antiviral agents.
- Patients with acute infections.
- Patients with chronic inflammatory conditions like inflammatory bowel disease, osteoarthritis, rheumatoid arthritis, gout, bronchial asthma and chronic hepatits
- Patients with acute myocardial infarction, cerebral infarction
- Patients with chronic kidney disease.

Study was explained to patients in local language & written consent was taken for participation & study. The data were recorded from each subject with an in-person interview by administering a specific questionnaire. The components of metabolic syndrome were defined according to the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria considering abdominal obesity as per World Health Organization (WHO) guidelines for South Asians.

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Waist circumference was measured at midpoint between lower costal margin and highest point of iliac bone in mainly around the widened region of gluteus using a measurement tape which is circled over the abdomen without any wrinkles and stretching. Systolic and diastolic blood pressure was measured by sphygmomanometer. Diabetes mellitus was diagnosed as per the American Diabetic Association (ADA) diagnostic criteria and/or concomitant anti-diabetic treatment, regardless of the measured glucose values.

In all the patients, a peripheral venous blood sample was to be drawn in the morning after 8 - 10 hours of fasting, to measure venous plasma glucose, serum total cholesterol, serum high density lipoprotein (HDL) cholesterol, and serum triglyceride levels. Serum glucose was to be measured by the glucose oxidase method; plasma triglycerides, total cholesterol and HDL-cholesterol were to be measured by enzymatic colorimetric assay using auto-analyzer. Serum hs-CRP levels were to be determined by immuno-turbidometric assay using with dedicated reagents. We used CRP cut-off values of 3.0 mg/l, as recommended by the Centers for Disease Control and the American Heart Association.[9]

Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi-square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

Results

In present study, among 78 subjects mean age of the study population was 49.24 ± 10.45 years. 27(35.5%) of study subjects belong to 41-50 years, 22(28.9%) belonged to 51-60 years and 19(25%) belonged to 21-40 years. 70(92.1%) of study subjects were females and 6(7.9%) were males. Among 76 study subjects, 48(63.2%) of subjects had Diabetes Mellitus and 67(88.2%) had Hypertension.

The mean Pulse Rate, SBP, DBP among study population were 74.72 ±8.05, 143.58±9.72, 89.34±7.08 respectively. The mean Waist Circumference, Body Mass Index, Fasting Blood Sugar among study population were 107.5±9.36, 28.36±2.13, 152.97±29.24 respectively.

Table 1: General characteristics

	No. of patients	**Percentage**
Age groups (in years)		
21-40	19	25.0
41-50	27	35.5
51-60	22	28.9
>60	8	10.5
Mean age (mean ± SD)	49.24 ± 10.45	
Gender		
Female	70	92.1
Male	6	7.9
Co-morbidities		
Diabetes Mellitus	48	63.2
Hypertension	67	88.2
vital statistics		
Pulse rate (Beats per min)	74.72 ± 8.05	
Systolic Blood Pressure (mm of Hg)	143.58 ± 9.72	
Diastolic Blood Pressure (mm of Hg)	89.34 ± 7.08	

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Waist Circumference in cm	107.5 ± 9.36	
BMI Kg/m^2	28.36 ± 2.134	
FBS (mg/dl)	152.97 ± 29.24	

The mean Total Cholesterol, Triglycerides, HDL, LDL, VLDL among study population were 170.07±19.65, 177.97±17.06, 37.8±7.61, 102.58±11.26, 31.17±5.87 mg/dl respectively. The minimum Total Cholesterol, Triglycerides, HDL, LDL, VLDL were 144, 109, 28, 84, 22 mg/dl and maximum values were 220, 208, 92, 128, 44 mg/dl respectively.

Table 2: Lipid profile

Study Population (N=76)-mg/dl	Total Cholesterol	Triglycerides	HDL	LDL	VLDL
Mean	170.07	177.97	37.8	102.58	31.17
SD	19.65	17.06	7.61	11.26	5.87
Median	168	178	38	102	28
Mode	168	168	38	96	28
Minimum	144	109	28	84	22
Maximum	220	208	92	128	44

The mean Albumin, Globulin, Total Bilirubin, Direct Bilirubin, SGOT, SGPT, Total Protein among study population were 3.41±.398 g/dl, 2.72±.4 g/dl, .824±.159 mg/dl, 243±.11 mg/dl, 56.01±12.08 units/l, 68.83±13.36 units/l, 6.06±.314 g/dl respectively. The minimum Albumin, Globulin, Total Bilirubin, Direct Bilirubin, SGOT, SGPT, Total Protein were 2.8 g/dl, 0.3 g/dl, 0.5 mg/dl, 0.1 mg/dl,34 units/l, 38 units/l, 5.2 g/dl and maximum values were 4.2 g/dl, 3.4 g/dl, 1.2 mg/dl, 0.6 mg/dl, 85 units/l, 92 units/l, 7 g/dl respectively.

Table 3: Liver Function test

Study Population (N=76)	Albumin g/dl	Globulin g/dl	Total Bilirubin mg/dl	Direct Bilirubin mg/dl	SGOT units/L	SGPT units/L	Total Protein g/dl
Mean	3.41	2.72	.824	.243	56.01	68.83	6.06
SD	.398	.400	.159	.11	12.08	13.36	.314
Median	3.4	2.8	.80	.20	56	67	6
Mode	3.8	2.8	.80	.20	56	67	5.9
Minimum	2.8	0.3	0.5	0.1	34	38	5.2
Maximum	4.2	3.4	1.2	0.6	85	92	7

The mean Haemoglobin, ESR, S. urea and S. creatinine were 11.432±1.49 g%, 22.71±8.86, 28.3±6.78 mg/dl, .976±.23mg/dl. The minimum Haemoglobin, ESR, S. urea and S. creatinine were 7.8 g%, 10, 17 mg/dl, 1.5 mg/dl. The maximum Haemoglobin, ESR, S. urea and S. creatinine were 14.2 g%, 60, 44 mg/dl, 1.5 mg/dl.

Table 4: Haemoglobin, ESR and Renal Function test

Study Population (N=76)	Haemoglobin g/dl	ESR	Serum Urea mg/dl	Serum Creatinine mg/dl
Mean	11.432	22.71	28.3	.976
SD	1.49	8.86	6.78	.23
Median	11.8	22	26	.95
Mode	12.6	18	23	.8
Minimum	7.8	10	17	0.6
Maximum	14.2	60	44	1.5

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The mean hs-CRP was 3.81±1.28 with a minimum of 1.2 and maximum 6.3. According to AD/CDC definition, 56(73.7%) had high risk and 20(26.3%) had moderate risk of development of cardio vascular disease.

Table 5: Categorisation of hs-CRP

hs-CRP	Frequency	Percentage
MODERATE RISK (1 to 3mg/dL)	20	26.3
HIGH RISK (> 3mg/dL)	56	73.7
Total	76	100.0

Pearson's correlation was done between high sensitivity CRP and components of metabolic syndrome like waist circumference, BMI, FBS, SBP, DBP, HDL. There is positive correlation between waist circumference (r value= 0.43, p-0.034), BMI (r value= .74, p 0.02), FBS (r value= .36, p 0.04), SBP (r value= .34, p 0.045) and DBP (r value=.47, p value-.047) and hs-CRP. This showed that patients with elevated hs-CRP has higher waist circumference, high Body Mass Index, high FBS, high SBP and DBP (HTN). There is a negative correlation between hs-CRP and HDL, showing that an elevated hs-CRP is associated with lower values of HDL (r value= -0.56, p-0.03). This shows that there is an inverse relationship between HDL an hs-CRP showing that when hs-CRP increases, HDL decreases.

Table 6: Correlation of components of metabolic syndrome and high sensitivity CRP

hs-CRP	WC	BMI	FBS	SBP	DBP	HDL
Correlation coefficient	.43	.74	.36	.34	.47	-.56
p value	.034*	.02*	0.04*	0.045*	0.047*	0.03*

*Pearson's correlation, p value<0.05 was significant

Pearson correlation was done between hs-CRP and Liver function tests like Albumin, Globulin, Total and Direct Bilirubin, SGOT, SGPT, Total protein. Positive correlation present between SGOT (r =0.23, p value: .03), SGPT (r value= 0.3, p value- 0.03), Direct bilirubin (r= 0.24, p value: 0.04) and hs-CRP. Elevated hs-CRP is associated with elevated SGOT, SGPT and Direct bilirubin.

Table 7: Correlation of hs CRP and liver function tests

hs-CRP	ALBUMIN	GLOBULIN	TOTAL BILIRUBIN	DIRECT BILIRUBIN	SGOT	SGPT	TOTAL PROTEIN
Correlation coefficient	.122	.02	.09	.24	.23	0.3	.05
p value	.294	.83	0.4	0.034*	0.04*	0.03*	0.64

*Pearson's correlation p value<0.05 was significant

Pearson correlation was done between hs-CRP and VLDL, LDL, Hb, ESR, Serum creatinine, Serum urea. Positive correlation present between LDL (r =0.20, p value: .024), VLDL (r value= 0.212, p value- 0.031) and hs-CRP. Elevated hs-CRP is associated with elevated LDL and VLDL.

Table 8: Correlation of hs-CRP and LDL, VLDL, Hb, ESR, RFT (Serum creatinine and urea)

hs-CRP	LDL	VLDL	Hb	ESR	Creatinine	Urea
Correlation coefficient	.20	.212	.178	.035	.041	.028
p value	.024*	.031*	0.12	.76	.81	.73

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*Pearson's correlation, p value<0.05 was significant

50(71.4%) of females had hs-CRP of high-risk category, 68.8% of Hypertensives had hs-CRP of high-risk category, 74.6% of Diabetics had hs-CRP of high risk category. These association were statistically significant.

Table 9: Crosstabulation between levels of hs-CRP and HTN, DM, gender

Variables		**hs-CRP Moderate risk**	**hs-CRP High risk**	**table value**	**p value**
Gender	**Female**	**20(28.6%)**	**50(71.4%)**	**2.33**	**0.046***
	Male	0	6(100%)		
Hypertension	Yes	15(31.2%)	33(68.8%)	1.64	0.04*
	No	5(17.9%)	23(82.1%)		
Diabetes Mellitus	Yes	17(25.4%)	50(74.6%)	2.3	0.04*
	No	3(33.3%)	6(66.7%)		

Discussion

Metabolic syndrome refers to a bunch of several interconnected cardiometabolic risk factors that endorse the occurrence of atherosclerotic cardiovascular disease (CVD) and Type 2 diabetes mellitus (T2DM). Now a day's metabolic syndrome gained its name as a vital risk factor for increased cardiovascular mortality and morbidity. Recent definitions of metabolic syndrome vary and cardiovascular risk seems to vary according to which component risk factors present. The prevalence of obesity and metabolic syndrome is swiftly growing in India and other South Asian countries, leading to bigger mortality and morbidity due to CVD and T2DM.[10]

The mean age of the study population in this study was 49.24 ± 10.45 years. The mean age in the participants in another study by den Engelsen *et al.*,[11] was 48.4 (SD 10.7) years. The mean age was 46.7±0.37 years in another study done by Hyemin Jeong *et al.*,[12] 70 (92.1%) of study subjects were females and 6(7.9%) were males in our study showing the female preponderance for metabolic syndrome. Another study showed that among cross-sectional sample of subjects with a normal BMI, male gender was an independent risk factor for all components of the MetS.[13]

Among 76 study subjects, 48(63.2%) of subjects had Diabetes Mellitus and 67(88.2%) had Hypertension. The mean hs-CRP was 3.81±1.28 with a minimum of 1.2 and maximum 6.3. This was higher than the median hs-CRP levels in individuals with central obesity with the metabolic syndrome (2.2 mg/L (IQR 1.2-4.0).[11] Another study had higher mean value of hs-CRP (8.3±1.04 mg/l).[14] According to AD/CDC definition, 56(73.7%) had high risk and 20(26.3%) had moderate risk of development of cardio vascular disease. This was similar to another study done by Gowdaiah *et al.*,[14] among 50 patients with metabolic syndrome.[65]

Pearson's correlation was done between high sensitivity CRP and components of metabolic syndrome like waist circumference, BMI, FBS, SBP, DBP, HDL. There is positive correlation between waist circumference (r value= 0.43, p-0.034), BMI (r value= .74, p 0.02), FBS (r value= .36, p 0.04), SBP (r value= .34, p 0.045) and DBP (r value=.47, p value-.047) and hs-CRP. This showed that patients with elevated hs-CRP has higher waist circumference, high Body Mass Index, high FBS, high SBP and DBP (HTN). There is a negative correlation between hs-CRP and HDL, showing that an elevated hs-CRP is associated with lower values of HDL (r value= -0.56, p-0.03). This was similar to another study done by Mahajan *et al.*,[15] and Bo *et al.*,[16] showing the strong association between CRP and components of metabolic syndrome. Similar results were shown by Bang-Gee *et al.*,[17] concluding that body weight, body

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mass index and body fat mass were positively correlated with serum CRP levels, while high-density lipoprotein cholesterol (HDL-C) was negatively correlated with fasting serum CRP levels in CAD patients. Ravi *et al.*,[18] showed that a highly positive correlation was established between hS-CRP and all the components of metabolic syndrome except for HDL cholesterol which showed a negative correlation.

BMI and hs-CRP has a higher positive correlation showing increased obesity can be a predictor of metabolic syndrome similar to other studies. Adipose tissue also secrete cytokines that excite the production of hs-CRP in the liver, but adipose tissue itself may also secrete hs-CRP and thereby raise hs-CRP levels.[11,19] Santosh Kumar Sah *et al.*,[20] showed that hs-CRP had positive correlation with blood glucose ($r = 0.2$, $p = 0.026$) and negative with HDL cholesterol ($r = -0.361$, $p < 0.001$). Patients with elevated hs-CRP had higher waist circumference ($p = 0.03$), diastolic BP ($p = 0.002$) and lower HDL cholesterol ($p = 0.004$) than others. Elevated hs-CRP were individually associated with higher odds for low HDL cholesterol and hyperglycaemia.

Pearson correlation was done between hs-CRP and VLDL, LDL, Hb, ESR, Serum creatinine, Serum urea. Positive correlation present between LDL ($r = 0.20$, p value: .024), VLDL (r value= 0.212, p value- 0.031) and hs-CRP. Elevated hs-CRP is associated with elevated LDL and VLDL. Anit Lamichanne *et al.*,[21] showed that hs-CRP was positively correlated with BMI, WC, HOMA-IR and triglycerides and highly significant ($p<0.001$). Using the cut-off value of 2.5 µg/ml hs-CRP can be used for predicting metabolic syndrome with sensitivity of 97% and specificity of 96%.

50(71.4%) of females had hs-CRP of high-risk category, 68.8% of Hypertensives had hs-CRP of high-risk category, 74.6% of Diabetics had hs-CRP of high-risk category. These association were statistically significant. This was similar to another study done by Mirhafez *et al.*[22] This was similar to other studies showing increased association of hs-CRP with Diabetics, hypertensives. [23-25]

Limitations of present study were, confounding factors like smoking, alcohol intake, fatty food intake, liver and kidney diseases were not considered leading to bias. Smaller sample size might have reduced the generalisability of the study. Hospital based study in a tertiary care setting might have increased the number of patients with severe Hypertension, Diabetes Mellitus, Dyslipidaemia, Impaired liver function and renal function leading to the increased association

Further studies with increased sample size matched for confounding factors done also in other settings such as primary and secondary care will represent the true nature of association. Higher values of high sensitivity C- reactive protein (hs-CRP) are linked with metabolic syndrome and its components and provides additional prognostic information on future progress of cardiovascular events in them. Hs-CRP has limited capacity to predict the presence of the metabolic syndrome in a population but it can be used as a prognostic marker of metabolic syndrome.

Conclusion

There was positive correlation between waist circumference, BMI, FBS, SBP and DBP (components of metabolic syndrome) and hs-CRP. This showed that patients with elevated hs-CRP has higher waist circumference, high Body Mass Index, high FBS, high SBP and DBP (HTN). There is a negative correlation between hs-CRP and HDL, showing that an elevated hs-CRP is associated with lower values of HDL

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