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A STUDY OF CORRELATION OF HIGH SENSITIVITY C-REACTIVE PROTEIN WITH VARIOUS COMPONENTS OF METABOLIC SYNDROME AT A TERTIARY CENTRE

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ABSTRACT: BACKGROUND: The metabolic syndrome (MetS) is a cluster of cardiovascular risk factors, which includes abdominal obesity, hypertension, hyperglycemia, dyslipidemia, and insulin resistance. Recent evidence implicates inflammation in the development of insulin resistance and MetS. Evidence has emerged demonstrating that high concentrations of high-sensitive C-reactive protein (hsCRP) are associated with MetS and may predict diabetes and cardiovascular events, independent of traditional risk factors. It has also been suggested that hsCRP may be included in the criteria for MetS. **OBJECTIVES OF THE STUDY:** To study the significance of high sensitivity C- reactive protein as a biochemical marker in metabolic syndrome. To correlate high sensitivity C-reactive protein titres with fasting plasma glucose, body mass index, blood pressure, waist circumference, triglyceride and high density cholesterol levels. **MATERIALS AND METHODS:** 50 cases and 50 controls were taken into the study. Cases were selected according to new IDF criteria. **RESULTS:** In the present study, there were 23 males & 27 females in each study group with mean Age distribution of 48.32±14.2 among cases and 48.12±14.1 among controls. Mean BMI in our study was 30.48±1.76 among cases and 23.42±1.52 among controls, with all cases meeting criteria for metabolic syndrome according to new IDF criteria. In our study 84% of cases were hypertensives, 10% of controls had systolic Blood. Pressure >130mmHg. 82% of cases were known diabetics on treatment. 82.6% of cases (Males) had HDL <40. All cases (females) had HDL<50. All cases had hsCRP >3, 88% of controls had hsCRP <3. Age, waist, circumference, BMI, SBP, DBP, FBS, TG levels correlated positively whereas HDL levels correlated negatively with hsCRP levels. **CONCLUSIONS:** There is a positive association between increasing age and the increase in prevalence of metabolic syndrome. Waist circumference and BMI correlated positively with hsCRP values, implying that obesity plays an important role in inflammation and pathogenesis of metabolic syndrome. There is a positive correlation between individual components of metabolic syndrome with increasing hsCRP titres. hsCRP titres increased significantly with increasing values of FBS, SBP, DBP, TG levels. hsCRP titres increased significantly with decreasing values of HDL.

KEYWORDS: Metabolic Syndrome, high sensitivity C reactive protein, Waist circumference, Obesity, Diabetes, Hypertension, Dyslipidemia.

INTRODUCTION: The metabolic syndrome (MetS) is a cluster of cardiovascular risk factors, which includes. abdominal obesity, hypertension, hyperglycemia, dyslipidemia, and insulin resistance.[1] Recently, several lines of evidence implicate inflammation in the development of insulin resistance and MetS.[2] Furthermore, abundant evidence has emerged demonstrating that high concentrations of high-sensitive C-reactive protein (hsCRP) are associated with MetS and may predict diabetes and cardiovascular events, independent of traditional risk factors.

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It has also been suggested that CRP may be included in the criteria for MetS.[3] Concentrations of CRP predict increased cardiovascular events in MetS and diabetes.[4-7] In addition, CRP concentrations correlate strongly with adiposity and insulin resistance.[8-10]

Developing a robust biomarker that can predict MetS instead of examining individual features will be important from a population standpoint in screening, monitoring the natural history of the disease, and measuring the response to therapeutic interventions. MetS seems to be a proinflammatory state characterized by increased concentrations of CRP. Several earlier studies have shown that high CRP concentrations predict the development of diabetes. Although increased CRP concentrations correlate most strongly with adiposity and insulin resistance, it also correlates significantly with the other features of MetS. Furthermore, CRP concentrations predict increased cardiovascular events in MetS and in diabetes.

AIMS AND OBJECTIVES:
1. To study the significance of high sensitivity C- reactive protein as a biochemical marker in metabolic syndrome.
2. To correlate high sensitivity C-reactive protein titres with fasting plasma glucose, body mass index, blood pressure, waist circumference, triglyceride and high density cholesterol levels.

MATERIALS AND METHODS: This study was conducted in Employees State Insurance Corporation Medical College and Post Graduate Institute of Medical Sciences and Research, Rajajinagar, Bangalore.

Duration: The study was conducted in the Department of General Medicine for duration of 18 months.

Study Design: Case- Control study.

Sample Size: 50 cases and 50 controls.

Patients presenting to the outpatient department, diabetic clinic and in the wards were taken for the study. Equal number of healthy people were taken as controls.

Method of Collection of Data: Patients presenting to OPD, diabetic clinic and in-patients of our hospital were included in the study. Informed consent was taken. Patients satisfying the inclusion criteria underwent relevant investigations which includes, fasting blood sugars, fasting lipid profile, high sensitivity C-reactive protein levels. To measure waist circumference, top of right iliac crest was located. A measuring tape was placed in a horizontal plane around abdomen at level of iliac crest.

Before reading measurement, it is estimated that the tape is snug but does not compress the skin and is parallel to floor. Measurement was at the end of normal expiration.

Blood samples for fasting blood glucose were taken after eight hours overnight fast. Blood samples for lipid profile were taken after 12 hours overnight fast. Blood pressure was recorded in right upper limb with patient in sitting posture. The high sensitivity C-reactive protein was measured quantitatively using particle enhanced. turbidimetric assay. Human C-reactive protein agglutinated with latex particle coated with monoclonal anti-C-reactive protein antibody, this precipitate was determined turbidimetrically at 552nm in Autoanalyser (ROCHE COBAS INTERGRA 400PLUS).

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Inclusion Criteria: According to the new IDF (International Diabetic Federation) definition of metabolic syndrome patients meeting the following criteria were taken as cases: Central obesity (Defined as waist circumference ≥90cm for asian men and ≥80cm for Asian women, with ethnicity specific values for other groups) plus any two of the following four factors:

- **Raised Triglyceride (TG) level:** ≥150mg/dL (1.7mmol/L), or specific treatment for this lipid abnormality.
- **Reduced High Density cholesterol (HDL):** <40mg/dL (1.03mmol/L*) in males and <50mg/dL (1.29mmol/L*) in females, or specific treatment for this lipid abnormality.
- **Raised blood pressure(BP):** Systolic BP ≥130 or diastolic BP ≥85mmHg, or treatment of previously diagnosed hypertension,
- **Raised fasting plasma glucose (FPG):** ≥100mg/dL (5.6mmol/L), or previously diagnosed type 2 diabetes.

If above 5.6mmol/L or 100mg/dL, Oral Glucose Tolerance Test (OGTT) is strongly recommended but is not necessary to define presence of the syndrome. Equal number of age and sex matched healthy volunteers were taken as controls.

Exclusion Criteria:
- Patients with chronic inflammatory conditions like.
- Malignancy.
- Myocardial Infarction.
- Connective tissue disease.
- Infectious diseases.
- Inflammatory bowel disease.
- Rheumatoid arthritis.
- Rheumatic fever.
- Tuberculosis.

STATISTICAL ANALYSIS: Data was analyzed using Statistical Package for Social Sciences (SPSS) version 17.0. Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean and SD. (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Student t test (Two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis) on metric parameters. Leven1s test for homogeneity of variance has been performed to assess the homogeneity of variance.

RESULTS AND ANALYSIS: Table 1 shows the age distribution of subjects. In our study 72% of cases were >40 years of age. Age distribution of 48.32±14.2 among cases and 48.12±14.1 among controls.

Table 2 shows sex distribution, there were 23 males & 27 females in each study group. Both cases and controls were matched for age and sex. 46% of cases and controls were males and 54% were females. Table 3 shows BMI distribution, all cases had BMI > 25.98% of controls had BMI <25. Figure 1 shows the waist circumference in men and fig 2 in females.

All cases (Males) had waist circumference > 90 cm, controls (males) had waist circumference <90cm. All cases (Females) had waist circumference > 80cm.

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All controls had waist circumference <80cm. Table 4 shows systolic blood pressures- 84% of cases were hypertensives. Only 10% of controls had systolic blood pressure >130mmHg. Table 5 shows diastolic blood pressure-In our study 38% of cases had Diastolic Blood Pressure of >90mmHg. 58% of cases had DBP between 80-90mmHg. Only 4% of cases had DBP <80mmHg. Whereas 50% of controls had DBP <80mmHg and 50% had DBP of 80- 90mmHg. Table 6 shows fasting blood sugars, 82% of cases had FBS >100mg%.

All controls had FBS <100mg%. 82.6% of cases (males) had HDL <40 whereas all controls had HDL >40. All cases (Females) had HDL <50 whereas 88.8% of controls had HDL > 50. In our study all cases had TG >150. All controls had TG<150. Table 7 shows hsCRP values -100% cases had hsCRP >3. 88% of controls had hsCRP <3. Table 8 shows comparison between variables and statistical significance.

Figure 3 shows correlation between age and hsCRP, as seen from the graph as age increases hsCRP value rises significantly. Figure 4 plots correlation between BMI and hsCRP levels, as BMI increases, hsCRP levels rise significantly. Figure 5 shows correlation between Triglycerides and hsCRP levels, as Triglycerides increase, hsCRP levels rise significantly. This was also observed with systolic, diastolic and fasting blood sugar levels.

DISCUSSION: Of novel risk factors for cardiovascular disease currently under investigation, high-sensitivity C-reactive protein (hsCRP) is the most promising. To date, more than 20 prospective epidemiologic studies have demonstrated that hsCRP independently predicts vascular risk, 6 cohort studies have confirmed that hsCRP evaluation adds prognostic information beyond that available from the Framingham Risk Score, and 8 cohort studies have demonstrated additive prognostic value at all levels of metabolic syndrome or in the prediction of type 2 diabetes.

In contrast to several other biomarkers that also reflect biological aspects of inflammation, hypofibrinolysis, and insulin resistance, hsCRP measurement is inexpensive, standardized, widely available, and has a decade-to-decade variation similar to that of cholesterol. Given the consistency of prognostic data for hsCRP and the practicality of its use in outpatient clinical settings, the time has come for a careful consideration of adding hsCRP as a clinical criterion for metabolic syndrome and for the creation of an hsCRP-modified coronary risk score useful for global risk prediction in both men and women.

This is a study designed to find out the utility of hsCRP as a biochemical marker in patients with metabolic syndrome. In this study, the sample population had a representation of males (46%) and females (54%) respectively. Various studies have been presented regarding the prevalence of metabolic syndrome in our population and the association of various risk factors. However, there are not many studies that have considered the role of hsCRP as a marker of metabolic syndrome.

AGE DISTRIBUTION: In this study, 72% of the patients with metabolic syndrome are above 40yrs of age. In this study, it was observed that prevalence of metabolic syndrome increases as the age advances. Various risk factors and components of metabolic syndrome increase with age and this could be one main reason for the higher incidence of metabolic syndrome in elderly people. The low prevalence of metabolic syndrome in younger population possibly may be due to an active life style and less obesity. This observation is supported by: Gupta et al.[11] and Ramachandran et al.[12]

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Sex & Metabolic Syndrome: 46% of the patients in my study having metabolic syndrome were male & 54% were females. This is in accordance with previous studies which show a higher female prevalence of metabolic syndrome.

BMI and Metabolic syndrome: In a study done by Bilgilli Sebel et al,[13] all subjects of metabolic syndrome had BMI >25Kg/m2. Mean BMI in our study was 30.48±1.76, with all of patients meeting criteria for central obesity according to new IDF criteria. All the patients had BMI >25Kg/m2.

Diabetes & Metabolic Syndrome: In this study, 82% of metabolic syndrome patients were having type 2 diabetes. The recent studies done in Delhi and Jaipur in general population by Wasir JS,[14] et al where a subgroup included the diabetics showed a prevalence of MS as 73.5%. The prevalence of metabolic syndrome is higher in diabetics.

Hypertension & Metabolic Syndrome: In this study, 84% of the metabolic syndrome patients were having hypertension. Metabolic syndrome is highly prevalent in hypertensives and hypertension is an important factor that may predispose for the development of metabolic syndrome. This observation is supported by: Kjeldsen et al.[15]

Obesity, Dyslipidemia and Metabolic syndrome: The increased focus on the metabolic syndrome has drawn attention to the identification and treatment of the dyslipidemia associated with abdominal fat accumulation. The changes in lipid metabolism seen with abdominal fat accumulation have been well characterized and include hypertriglyceridemia, reduced HDL cholesterol, and increased numbers of small, dense LDL particles. In our study, all patients with metabolic syndrome had decreased HDL, increased TG levels. HDL showed inverse relationship with waist circumference and hsCRP levels (p<0.001). Triglyceride levels correlated positively with waist circumference and hsCRP levels (p<0.001).

Metabolic syndrome and hsCRP: Inflammation has been associated with metabolic syndrome and its individual components. We found that participants with metabolic syndrome had significantly higher hs-CRP and greater prevalence of elevated hs-CRP >3mg/L than did those without metabolic syndrome. In addition, hs-CRP levels increased as the number of components of metabolic syndrome increased. Our findings agree with results from previous studies, although in some of them CRP levels were not adjusted for meaningful covariates. Of all the individual components of metabolic syndrome, abdominal obesity was more significantly associated with elevated levels of hs-CRP. Among 628 healthy Japanese participants (aged 19–85 years), waist circumference was the strongest determinant of high CRP levels. Several mechanisms have been suggested for the association between metabolic syndrome and CRP levels. Festa et al.[8] showed that hsCRP was positively correlated with BMI, waist circumference, BP, triglycerides, cholesterol, LDL cholesterol, plasma glucose, and fasting insulin, and inversely correlated with HDL cholesterol and insulin sensitivity index.

A recent study evaluated the correlations between adiposity, tumor necrosis factor alpha (TNF-a), IL-6, adiponectin, and CRP levels in obese and nonobese healthy participants and obese and nonobese type 2 diabetic patients. The authors found that TNF-a, IL-6, and CRP levels were positively associated with adipocyte size, whereas adiponectin was negatively correlated.

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We did not determine cytokine or adiponectin levels in our study. In addition, most of our participants were overweight or obese, and we could not determine whether abdominal obesity or overall obesity mediated elevation of hs-CRP. Future studies to determine possible associations between cytokine production and hs-CRP levels in obese people are warranted.

Limitations of the Study:
1. Sample size was small 50 cases and 50 controls. The study group may not be a representation of general population.
2. We did not measure other inflammatory markers such as IL6, which may be playing an important role in metabolic syndrome.
3. The causal role of hsCRP in metabolic syndrome could not be established.

CONCLUSION:
1. There is a positive association between increasing age and the increase in prevalence of metabolic syndrome
2. Waist circumference and BMI correlated positively with hsCRP values, implying that obesity plays an important role in inflammation and pathogenesis of metabolic syndrome.
3. There is a positive correlation between individual components of metabolic syndrome with increasing hsCRP titres.
4. HsCRP titres increased significantly with increasing values of FBS, SBP, DBP, TG levels.
5. HsCRP titres increased significantly with decreasing values of HDL.

Age Group	Case	Control	Total
20-40	14	14	28
41-60	25	25	50
61-80	11	11	22
Total	50	50	100
Table 1: Age distribution of subjects studied			

Sex	Cases	Control
Male	23	23
Female	27	27
Table 2: Sex distribution		

BMI	Cases	Control	Total
<25	0	49	49
25-30	23	1	24
30-35	27	0	27
Total	50	50	100
Table 3: BMI			

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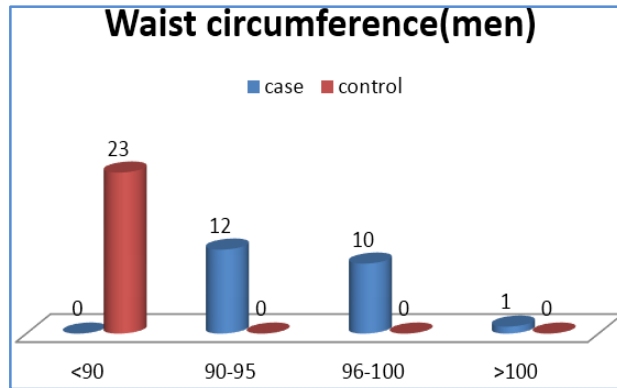
Fig. 1
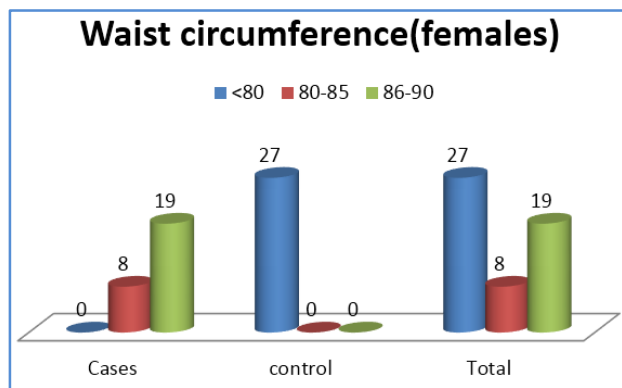
Fig. 2

Systolic blood Pressure	Cases	Control	Total
<130	8	45	53
130-140	3	5	8
141-150	21	0	21
151-160	18	0	18
Total	**50**	**50**	**100**
Table 4: Systolic Blood Pressure			

Diastolic blood Pressure	Cases	Control	Total
<80	2	25	27
80-90	29	25	54
>90	19	0	19
Total	**50**	**50**	**100**
Table 5: Diastolic blood Pressure			

Fasting Blood Sugar	Cases	Control	Total
<100	9	50	59
100-125	5	0	5
>125	36	0	36
Total	**50**	**50**	**100**
Table 6: Fasting blood sugar			

hsCRP values	Cases	Control	Total
<1	0	8	8
1 to 3	0	36	36
3 to 5	23	6	29
5 to 7	25	0	25
>7	2	0	2
Total	**50**	**50**	**100**
Table 7: hsCRP values			

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| Variable	Cases	Control	P value
Age	48.32±14.2	48.12±14.1	0.944
Sex (Males/females)	23/27	23/27	NA
Waist circumference	90.12± 5.24	79.36±5.29	<0.001
BMI	30.48±1.76	23.42±1.52	<0.001
SBP	145.24±9.68	124.56±5.92	<0.001
DBP	88.36±5.86	78.84±5.24	<0.001
FBS	134.64±26.92	85.68±6.73	<0.001
TC	207.24±31.86	189.48±22.65	0.002
LDL	127.6±21.02	102.08±17.15	<0.001
HDL	41.36±4.78	49.5±5.22	<0.001
TG	178.32±23.56	137.24±10.41	<0.001
hsCRP	5.09±1.04	2.13±0.79	<0.001
Table 8: Comparison between case and control groups			
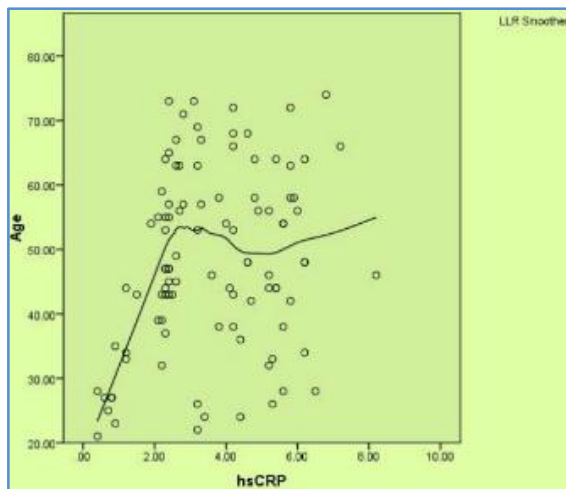
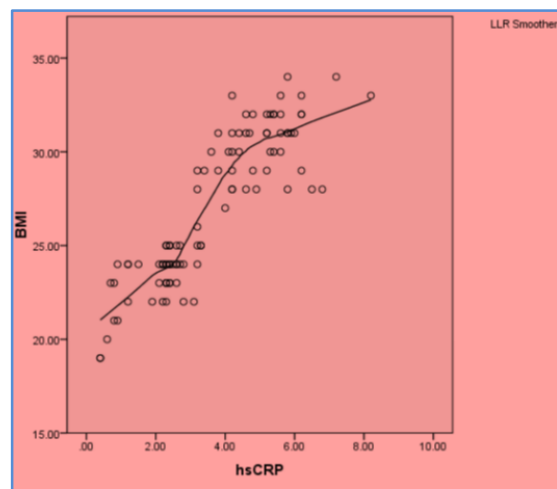*Fig. 3: Correlation between age and hsCRP Levels*

Fig. 4: Correlation between BMI and hsCRP levels
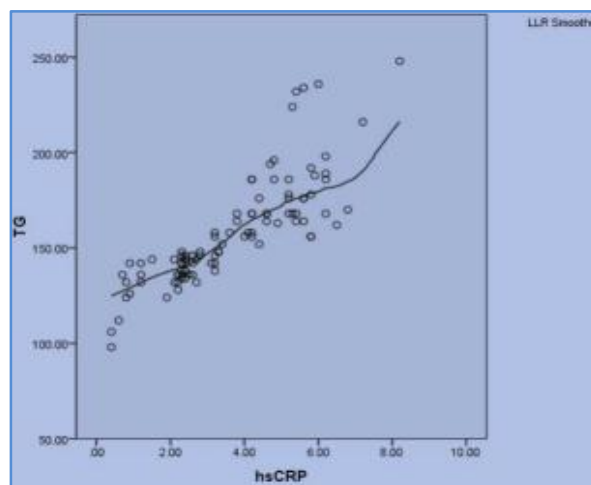

Fig. 5: correlation between Triglycerides and hsCRP levels

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