# Original Research Paper

## General Medicine

## ASSOCIATION OF HSCRP LEVELS IN EARLY DIAGNOSIS OF METABOLIC SYNDROME

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**KEYWORDS :**

## INTRODUCTION

Industrialisation and sedentary lifestyle have increased the prevalence of obesity, type 2 diabetes and hypertension in human population which increases the risk of developing metabolic syndrome. Metabolic syndrome also known as Syndrome X, Insulin resistance syndrome, consists of a constellation of a metabolic abnormalities and proinflammatory conditions that confer increased risk of Coronary vascular disease and diabetes mellitus 2[1]. The major features include central obesity, hypertriglyceridemia, low levels of HDL cholesterol, hyperglycemia and hypertension[3].

C-reactive protein (CRP) was discovered by Tillett and Francis in 1930. The name CRP arose because it was first identified as a substance in the serum of patients with acute inflammation that reacted with the "c" carbohydrate antigen of the capsule of pneumococcus. C-Reactive protein is an acute phase reactant protein that the liver makes when there is inflammation in the body and is a sensitive marker of systemic inflammation[4].

Various studies have emerged demonstrating that high concentrations of highly sensitive C reactive protein are associated with metabolic syndrome and may predict diabetes and cardiovascular events independent of traditional risk factors5,6. Frohlich M et al7 found an association between CRP and features of metabolic syndrome,CRP levels correspond with individual components of the metabolic syndrome and had hypothesized the role of inflammation in several processes critical to the development of both diabetes and atherothrombosis.

The hsCRP test is a highly sensitive quantification of C-reactive protein which was released as early response to inflammation8. Early diagnosis and treatment of metabolic syndrome is necessary to prevent the chance of developing various complications.This study was aimed at estimating the hsCRP levels in subjects with metabolic syndrome and its importance in early diagnosis and treatment.

## MATERIALS AND METHODS:

The study was conducted in Department of General Medicine, Rajarajeshwari medical college and Hospital,Bangalore. Patients attending Outpatient clinics or Inpatients in the department of medicine of Rajarajeswari medical college and hospital,who fit in  the criteria for metabolic syndrome were taken as cases.International diabetes federation(2005)criteria were used to define metabolic syndrome in the study group. Ethical clearance for the study was obtained from the Institutional Review Committee  The patients were selected on the basis of inclusion and exclusion criteria.In all those patients,high Sensitivity C-reactive protein was estimated and analysed. The study included 50 cases with metabolic syndrome.

## Inclusion criteria:

International Diabetes Federation definition (IDF)[9]

1)Central obesity defined as waist circumference in South Asian population male>/= 90cm and female>/=80 cm

Plus any two of the following four factors

2)Triglycerides >/= 150mg/dL(1.7 mmol/L)

3)HDL<40mg/dL(1.03mmol/L) in males, <50mg/dL(1.29 mmol/L) in females

4) Blood pressure >/= 130mmhg systolic and >/= 85mmhgdiastolic or treatment of previously diagnosed hypertension

5) Fasting plasma glucose >/= 100mg/mg/dL(5.6mmol/L) or previously diagnosed type 2 diabetes.

6) If BMI is >30kg/m2, central obesity can be assumed and waist circumference need not be measured.

## Exclusion criteria:
- Acute and chronic Infectious diseases.
- Chronic inflammatory conditions such as ulcerative colitis or crohns disease, rheumatoid arthritis or lupus.
- Chronic liver disease and renal disease.
- Pregnancy.
- Acute stroke and Acute Myocardial infarction.
- Woman on HRT.
- Thyroid disorders.

A proforma was drafted including details about the patient and specifically related to known risk factors and factors that can elevate hs-CRP.

## Assessment of biomarkers:
Levels of fasting glucose,HDL-C and triglycerides were determined by enzymatic methods using an auto analyzer,whereas hs-CRP levels were measured using Rapid Quantitative test.It is a fluorescence immunoassay test measuring range between 0.5 to 200mg/L. The CRP rapid quantitative test uses sandwich immunodetection method.

When the blood sample is added to the sample well of the test cartridge,the fluorescence labeled detector CRP antibodies on the sample pad bind to CRP antigens in blood specimen and they form immune complexes.As the complexes migrate on the nitrocellulose matrix of the test strip by capillary action,the complexes of detector antibodies and CRP are captured to CRP antibodies that have been immobilized on test strip.Thus, the more CRP antigens in blood specimen,the more complexes accumulated on the test strip. The signal intensity of fluorescence of detector antibodies reflected the amount of captured CRP.

The American Heart Association and US center for Diabetes Control and Prevention have defined risk group as follows based on hsCRP levels:

<1.0mg/L-Low CVD risk

1-3mg/L-Moderate CVD risk
>3mg/L-High CVD risk
<0.5mg/L-Taken as NORMAL.

**RESULTS:**
In the study 50 subjects were taken, 3 cases were excluded from study as they showed very high hsCRP levels suggesting an ongoing infection. Hence data was analysed among 47 cases.

In our study, among the cases, the youngest was of 29 years and the oldest was of 80 years. The mean age among cases were 55+/-11 years (Table 1). Among the 47cases, 31 were female and 16 were male.

The mean triglyceride levels among cases was 194+/-87.62mg/dL and the mean HDL-C was 40+/- 6mg/dl. The mean systolic blood pressure was 137.34+/-16.49 mm hg and the mean diastolic blood pressure was 93.51+/-8.51 mm hg. The mean fasting blood sugar level was 176.22+/-59.75 mg/dL.

In this study, out of the included 47 cases, 34 patients (72%) showed high hsCRP level(>3mg/L) and mean hsCRP level in cases were 7.94mg/L. P value was <0.001, significant by Fisher Exact test. As observed in our study, hsCRP was significantly higher among the cases with metabolic syndrome.

| hsCRP | Cases |
|---|---|
| <0.5mg/L | 3(6.4%) |
| 0.6-0.9mg/L | 1(2.1%) |
| 1-3mg/L | 9(19.1%) |
| >3mg/L | 34(72.3%) |
| Total | 47(100%) |

In 47 cases studied ,5 cases were below 40 years and 60%(3) of these cases showed high values of hsCRP (>3mg/L).11 cases were between 40-50 years and 72%(8) of these cases showed high hsCRP levels(>3mg/L).31 cases were above 50 years and 74%(23) of these cases showed high hsCRP levels.

Hence the study conducted suggested that hsCRP levels increase with increase in age.

In 47 cases studied ,31 cases were female and 16 cases were male. 77% of the female cases showed high hsCRP levels(>3mg/L) and 62.5% of male cases showed high hsCRP levels. Thus, hsCRP levels were increased in females when compared to males.

| Variables | hs CRP <0.5mg/L normal | 0.6-0.9mg/L low risk | 1-3mg/L moderate risk | >3 mg/L high risk | Total | P Value |
|---|---|---|---|---|---|---|
| **Age in years** | | | | | | |
| • <40 | 1(33.3%) | 0(0%) | 1(11.1%) | 3(8.8%) | 5(10.6%) | |
| • 40-50 | 1(33.3%) | 0(0%) | 2(22.2%) | 8(23.5%) | 11(23.4%) | 0.716 |
| • >50 | 1(33.3%) | 1(100%) | 6(66.7%) | 23(67.6%) | 31(66%) | |
| **Gender** | | | | | | |
| • Female | 0(0%) | 1(100%) | 6(66.7%) | 24(70.6%) | 31(66%) | |
| • Male | 3(100%) | 0(0%) | 3(33.3%) | 10(29.4%) | 16(34%) | 0.074+ |

Chi Square Test/Fisher Exact Test

On comparing the waist circumference with hsCRP levels, in 31 female cases, 5 cases had waist circumference between 80-90cm of which 20% of the patients had high hsCRP levels ,13 patients had waist circumferencebetween 91-99cm of which 76.9% of cases had high hsCRP levels and 13 cases had waist circumference >/= 100cm of which 100% patients had high hsCRP levels. In the 16 male cases, 6 cases had waist circumference between 90-99cm of which 50% of cases had high hsCRP levels and 10 cases had waist circumference >/= 100cm of which 70% of cases had high hsCRP levels. This showed that as waist circumference increases, patients are at risk for increased levels of hsCRP

| Variables | hs CRP <0.5mg/L normal | 0.6-0.9mg/L low risk | 1-3mg/L moderate risk | >3 mg/L high risk | Total |
|---|---|---|---|---|---|
| **Female (waist circumference)** | | | | | |
| • 80-90cm | 0(0%) | 1(20%) | 3(60%) | 1(20%) | 5 |
| • 91-99cm | 0(0%) | 0(0%) | 3(23.07%) | 10(76.9%) | 13 |
| • >/=100cm | 0(0%) | 0(0%) | 0(0%) | 13(100%) | 13 |
| • Total | 0(0%) | 1(3.2%) | 6(19.3%) | 24(77.4%) | 31(100%) |
| **Male (waist circumference)** | | | | | |
| • 90-99cm | 1(16.6%) | 0(0%) | 2(33.3%) | 3(50%) | 6 |
| • >/=100cm | 2(20%) | 0(0%) | 1(10%) | 7(70%) | 10 |
| • Total | 3(18.75%) | 0(0%) | 3(18.75%) | 10(62.5%) | 16(100%) |

On comparing type 2 diabetes and hypertension with hsCRP levels, 44 cases were diabetic and 94.1% of diabetic patients studied showed high hsCRP levels(>3mg/L). Nearly 34 cases were hypertensive and 79.4% of hypertensive patients studied showed high hsCRP levels(>3mg/L). Thus more positive correlation was found between diabetes and hsCRP levels.

| Variables | hs CRP <0.5mg/L normal | 0.6-0.9mg/L low risk | 1-3mg/L moderate risk | >3 mg/L high risk | Total | P Value |
|---|---|---|---|---|---|---|
| **K/C DM** | | | | | | |
| • No | 0(0%) | 0(0%) | 1(11.1%) | 2(5.9%) | 3(6.4%) | 0.631 |
| • Yes | 3(100%) | 1(100%) | 8(88.9%) | 32(94.1%) | 44(93.6%) | |
| **K/C HTN** | | | | | | |
| • No | 0(0%) | 1(100%) | 5(55.6%) | 7(20.6%) | 13(27.7%) | 0.048* |
| • Yes | 3(100%) | 0(0%) | 4(44.4%) | 27(79.4%) | 34(72.3%) | |
| Total | 3(100%) | 1(100%) | 9(100%) | 34(100%) | 47(100%) | |

Chi-Square Test/Fisher Exact Test

On comparing lipid profile with hsCRP levels, 18 cases had triglyceride levels between 150-199 mg/dL and 66.6% had high hsCRP level(>3mg/L).16 cases had triglyceride level more than 199mg/dL and 93.7% showed high hsCRP levels(>3mg/dL). Hence in our study, as triglyceride levels increased hsCRP levels also increased. 23 cases had HDL level <40mg/dL.82.6 % of these cases had high hsCRP levels(>3mg/L).

| Variables | hs CRP <0.5mg/L normal | 0.6-0.9mg/L low risk | 1-3mg/L moderate risk | >3 mg/L high risk | Total | P Value |
|---|---|---|---|---|---|---|
| **TGL** | | | | | | |
| • <150 | 3(100%) | 0(0%) | 3(33.3%) | 7(20.6%) | 13(27.7%) | |
| • 150-199 | 0(0%) | 1(100%) | 5(55.6%) | 12(35.3%) | 18(38.3%) | 0.033* |
| • >199 | 0(0%) | 0(0%) | 1(11.1%) | 15(44.1%) | 16(34%) | |
| **HDL-C** | | | | | | |
| • <40 | 1(33.3%) | 0(0%) | 3(33.3%) | 19(55.9%) | 23(48.9%) | 0.445 |
| • >40 | 2(66.7%) | 1(100%) | 6(66.7%) | 15(44.1%) | 24(51.1%) | |
| Total | 3(100%) | 1(100%) | 9(100%) | 34(100%) | 47(100%) | |

Chi-Square Test/Fisher Exact Test

**DISCUSSION:**
Among the novel risk factors for cardiovascular disease currently under investigation, high sensitivity C-reactive protein(hsCRP) is the most promising. Many studies have demonstrated that hsCRP independently predict the cardiovascular risk and also has an additive prognostic value for diagnosis of metabolic syndrome. There is a linear increase in hs-CRP with increasing number of components of metabolic syndrome. Hence, hs-CRP may be used as a surrogate marker of chronic inflammation in patients with metabolic syndrome.

Elevation of hsCRP is associated with increased risk of type 2 diabetes development in patients with metabolic syndrome. Measurement of hsCRP is inexpensive and widely available and can also be done in outpatient clinical settings. This study was conducted to know the importance of hsCRP as a biochemical marker of chronic inflammation in diagnosing metabolic syndrome patients.

In this study, 72% cases showed high hsCRP level(>3mg/L) and the mean hsCRP level in cases were 7.94mg/L. In a study by Ravi Arulantham et al10 on hsCRP as a proinflammatory marker for components of metabolic syndrome ,42 of the 50 cases with metabolic syndrome had high hsCRP level and it falls outside the confidence interval of 0.95.

On comparing the individual components of metabolic syndrome with hsCRP levels, our study showed increase in hsCRP levels with increase in waist circumference. Diabetic and hypertensive patients showed elevated levels of hsCRP levels. AlsohsCRP level increased with increase in triglyceride levels. In a study by Nazar S.Haddad11, High sensitivity c-reactive protein (hs-CRP) and metabolic syndrome: correlation with number and type of metabolic syndrome components ,48 cases with metabolic syndrome and 30 controls healthy individuals were recruited. hsCRP among cases was 2.13+/- 1.8mg/L and among controls was 0.30+/- 0.21mg/L.

In our study,as the age increases hsCRP level increases. The hsCRP levels in females were more than males. The hsCRP levels were found to be higher in diabetic patients. In a study conducted by Koziarska-Ro et al12, a positive correlation was found between hsCRP and age suggesting strong significance. A study by Kawamoto et al13 also showed that the age was significantly associated with high hsCRP levels with p value <0.001.

In our study, high hsCRP levels were seen in females more than males. In a study conducted by Vinicius Pacheco Garcia et al13,which included 70 men and 48 women and women with MetS risk factors presented higher hsCRP levels when compared with men (p < 0.01). A study conducted by Koziarska-Ro et al12also proved that females with metabolic syndrome had higher hsCRP levels and p value of 0.0173 suggesting strong significance.

**CONCLUSION:**

From the present study it can be concluded that patients with metabolic syndrome have significantly high hsCRP levels.Hence hsCRP levels can be used as a surrogate marker for chronic inflammation in patients with metabolic syndrome.

Among Metabolic syndrome patients, elder patients and female patients showed significantly high hsCRP levels. Diabetic and hypertensive patients showed elevated levels of hsCRP levels and also hsCRP level increase with increase in triglyceride levels.and hsCRP levels increased with increase in waist Circumference.

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