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HIGH SENSITIVITY- C REACTIVE PROTEIN AS CARDIOVASCULAR RISK MARKER IN METABOLIC SYNDROME PATIENTS.

Dr. Sangeeta M Gawali* MBBS MD (Physiology), Associate professor, Department of Physiology, B J Govt Medical College, Pune. *Corresponding Author

Dr Mahesh S Karandikar MSc Ph.D. (Physiology), Professor, Department of Physiology, Dr. D.Y. Patil Medical College, Pune.

ABSTRACT

Background & Objectives: 20-25% of the world's adult population have metabolic syndrome (MetS); mortality of these people is double, and the morbidity of heart attack or stroke is three times higher than in the healthy population. Recent research has focused on the use of high-sensitivity C-reactive protein (hs-CRP), a marker of inflammation, in the detection of patients at increased risk for cardiovascular disease. The study was conducted to evaluate for the evidence of the association between baseline hs-CRP levels and the metabolic syndrome.

Methods: It was a cross-sectional study of 200 adults, 18–50 years of age, both the sexes randomly selected from diabetes & obesity OPD at tertiary care hospital & compared with 200 age & sex-matched controls. Diagnosis of Metabolic syndrome was done according to Modified National Cholesterol Education Program ATP III criteria (2004).

High Sensitivity -C Reactive Proteins -hs-CRP was done by ELISA method (CAL BIOTECH). Statistical Analysis was done by Pearson correlation coefficient to study the correlation between hs-CRP & various components of metabolic syndrome.

Results: We found significantly increased hs-CRP levels ($P<0.001$) in metabolic syndrome, 60% of patients with metabolic syndrome belonged to the high-risk group with a mean hs-CRP value >3 mg/L & a positive correlation of hs-CRP with abdominal circumference & triglyceride & HDL levels

Conclusion: increased hs- CRP levels in metabolic syndrome may increase the risk of having cardiovascular mortality. These prospective data suggest that measurement of hs-CRP adds clinically important prognostic information to the metabolic syndrome.

KEYWORDS : Metabolic syndrome, insulin resistance, cardiovascular risk markers, hs-CRP.

INTRODUCTION

Cardiovascular diseases comprise the most prevalent serious disorders in industrialized nations and are a rapidly growing problem in developing nations. Cardiovascular diseases remain the most common cause of death, responsible for 35% of all deaths, almost 1 million deaths each year. Approximately one-fourth of these deaths are sudden.[1] In the industrialized world, physical activity continues to decline while total caloric intake increases. The resulting epidemic of overweight and obesity may signal the start of the age of inactivity and obesity. Rates of type 2 diabetes mellitus, hypertension, and lipid abnormalities are on the rise, trends that are particularly evident in children. If these risk factor trends continue, age-adjusted CVD mortality rates could increase in the coming years.[1]

The metabolic syndrome (syndrome X, insulin resistance syndrome) consists of a constellation of metabolic abnormalities that confer increased risk of cardiovascular disease (CVD) and diabetes mellitus.[2] The strong association between metabolic syndrome & cardiovascular disease emphasizes the need for a better understanding of pathophysiologic mechanisms responsible for this relationship.

Visceral obesity is a form of obesity most strongly associated with metabolic syndrome & cardiovascular risk factors. Early detection of CVD may well prove to be instrumental in introducing effective treatment & may contribute to reducing mortality. Examination of trends in metabolic risk factors like lipid levels, obesity, hypertension, and diabetes mellitus provides insight into changes in the CVD burden globally.[3]

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.[5]

The proinflammatory state, the enhanced secretion of interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) produced by adipocytes and Cytokines and FFAs also increases the hepatic production of fibrinogen and adipocyte production of plasminogen activator inhibitor 1 (PAI-1), resulting in a prothrombotic state contributing to cardiovascular mortality.[6,7] The proinflammatory state is superimposed and contributory to the insulin resistance produced by excessive FFAs[7].

Higher levels of circulating cytokines stimulate hepatic production of C-reactive protein (CRP) is also associated with metabolic syndrome. It affects the process of athero-thrombosis, hence has emerged as a powerful risk marker for cardiovascular disease[7].

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 hs-CRP as a clinical criterion for metabolic syndrome. It is highly recommended to study this sensitive inflammatory marker in metabolic syndrome as cardiovascular risks factor in addition to traditional other risk factors. Therefore, this study was conducted to evaluate & find the association of hs-CRP with various components of metabolic syndrome.

METHODS

Study design & participants

A Cross-sectional study was conducted in the department of physiology in collaboration with the medicine, Biochemistry, and Microbiology department at the tertiary care hospital of western Maharashtra. The study was approved by the local ethical committee & written informed consent was taken. 200 diagnosed cases of metabolic syndrome attending diabetes & obesity OPD in the age group of 18 to 50 (100 male & 100 female) were studied & compared with 200 age & sex-matched control group (100 male & 100 female).

The presence of MetS was defined by the criteria of the NCEP ATP III. The diagnosis was made when at least three of the five following criteria were present[(1)]: Central obesity ---Waist circumference >90 cm in men & >80 cm in female, BSL > 100mg/dl or T2DM or specific medication BP >130/85 mmHg or specific medication, Triglycerides > 150mg/dl or specific medication ,HDL < 40 mg/dl in men < 50 in women. Individuals like smokers, alcoholics, inflammatory diseases like rheumatoid arthritis, recent acute infections & taking drugs that have been shown to reduce hs-CRP concentrations include aspirin, statins, cyclooxygenase-2 inhibitors, and fibrates were excluded.

Measurements

In a physical examination, anthropometric parameters like body weight, height, BMI, waist circumference (WC), waist to hip ratio (WHR), and vital parameters like heart rate, blood pressure were measured. Venous blood samples were drawn after an overnight fast to determine fasting blood glucose, lipids (Triglycerides and HDL cholesterol), insulin, and hs-CRP.

Blood sugar—Fasting, Postprandial glucose done by using glucose GOD-PAP method (BIOLAB DIAGNOSTICS)

Lipid profile--- Triglycerides: GPO-PAP method (PATHOZYME DIAGNOSTICS) & The HDL- Direct method (PATHOZYME DIAGNOSTIC) was used.

Insulin--fasting insulin was done by Electro-chemiluminescence immune assay, ECLIA--ROCHE (COBAS KIT). Hs-CRP was analyzed by ELISA METHOD using CALBIOTECH KIT.

Insulin resistance: by HOMA – IR –Homeostatic Model Assessment of Insulin Resistance[1]. (Fasting glucose (mg/dl) x Fasting insulin (μU/ml)/405) for estimation of insulin sensitivity. It is the way to reveal the dynamic between baseline (fasting) blood sugar and the responsive hormone insulin.

Data collection: The participants completed a questionnaire to determine lifestyle factors (smoking habits, alcohol use, and physical activity), relevant medical history, socio-economic and demographic variables.

The hs-CRP was divided into three categories based on the cut-off points for risk stratification for cardiovascular risk [14]. A level below 1.0 mg/l is considered the low cardiovascular risk, between 1.0 and 3.0 mg/l, moderate risk, and between 3.0 and 10.0 mg/l a high risk. A level above 10.0 mg/l is associated with active infection and therefore not applicable in the risk estimation [15]. Individuals with a hs-CRP level above 10.0 mg/L were excluded from the analyses.

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 hs-CRP & Mets variables. P-value <0.05 was considered significant.

RESULTS :

This was a cross-sectional analytic, tertiary care hospital-based study on 200 metabolic syndrome patients attending obesity & diabetic OPD with an equal number of age & sex-matched controls. (200) .Out of these, there was 100 males and 100 females in each group.

The mean age in both the groups was 42.5 +0.49 with an age range from18 to 50 years.

All subjects were evaluated for components of metabolic syndrome, adiposity markers, and atherosclerotic marker like hs-CRP.

After comparison of various demographic, clinical & metabolic characteristics between two groups, we found 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 (0.79+0.0049) of the control group (p<0.0001) . Table1

The individual components of MetS were significantly higher & low HDL levels were found in MetS patients when compared with control (P<0.001). Fasting blood sugar (158.2+2.92 **vs** 96.94+0.97), postprandial blood sugar (236.6+54 vs 119.2+1.46) 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) & HDL (38.05+0.44 **vs** 50.88+0.45) respectively. Table 1.

High insulin resistance HOMA- IR (6.836+0.086 vs 1.36+0.0412) & high levels of fasting insulin (18.24+0.258 vs5.836+0.1745) p <0.001 were found in MetS. Table 1

Table I: Demographic, clinical & metabolic characteristics of patients with Metabolic Syndrome (n=200) & healthy controls (n=200)

Parameters	MetS (n200) Mean ± SD	Control (n200) Mean ± SD	P value
Age (yrs)	42.5 ±0.49	41.5 ±0.56	> 0.05
BMI (kg/m2)	26.89 ± 0.41	22.59 ±0.26	<0.001
Waist circumference (cm)	103.3+14.9	70.57+7.6	<0.001
Waist to hip ratio	0.96+0.0057	0.79+0.0049	<0.001
Fasting blood Sugar (mg/dl)	158.2 ±2.92	96.94 ±0.97	< 0.001
Postprandial sugar mg/dl	236.6±0.54	119.2±1.46	< 0.001
Triglycerides(mg/dl)	160.7 ± 1.41	105.1 ±1.15	< 0.001
HDL(mg/dl)	38.05+0.44	50.88+0.45	< 0.001
Fasting Insulin	18.24+0.258	5.836+0.174	< 0.001
HOMA- IR	6.836+0.086	1.36+0.0412	< 0.001
Heart rate	114.6±9.12	82.91± 8.46	< 0.001
Systolic Blood Pressure	135.5 ± 0.93	114.9 ±0.42	< 0.001
Diastolic Blood Pressure	86.61 ± 0.69	74.52 ± 3.13	< 0.001

P<0.05 Significant P<0.001 Highly significant

Inflammatory marker in MetS.

hs-CRP -- Inflammatory marker like hs-CRP (6.5+0.9881) was significantly higher (p<0.0001) in MetS as compared to controls (0.65+0.4927).Table 2

Table II : Shows hs-CRP levels in Metabolic Syndrome (MetS) patients & control group.

Parameters	MetS (n=150) Mean ± SD	Control (n150) Mean ± SD	P value
hs-CRP	6.5+0.9881	0.65+0.4927	< 0.001

P<0.05 Significant P<0.001 Highly significant

Pearson correlation coefficients of hs-CRP with various components of MetS show a positive correlation with abdominal circumference, triglycerides, HDL levels.(p<0.001) Table 3

Table III: Shows Pearson Correlation coefficient between demographic, clinical & metabolic syndrome components and hs-CRP

Parameters	MetS (n=200) (r value)	P value
Age	0.07	>0.05
Gender	0.03	>0.05
BMI	0.03	>0.05
Abdominal circumference	**0.523**	**<0.001**
Systolic blood pressure	0.15	>0.05
Diastolic blood pressure	0.01	>0.05
Triglycerides	**0.33**	**<0.001**
HDL	**0.499**	**< 0.001**
Fasting blood glucose	-0.06	>0.05
Postprandial sugar	0.04	>0.05
HOMA-IR	0.08	>0.05
Fasting Insulin	0.13	>0.05

P<0.05 Significant P<0.001 Highly significant

On subgroup analysis, 120 (60%) patients with metabolic syndrome belonged to the high-risk group with a mean hs-CRP value >3 mg/L compared to 20 (10%) controls. Whereas, the low to moderate risk category was composed of a majority of 180 (90%) controls Vs 80 (40%) cases as given in Table 4 and Figure 1

TABLE IV: Distribution of hs-CRP values among different risk groups of MetS and controls.

Risk category	MetS	Control	Total
hs-CRP <1.0 Low risk	20	150	170
hs-CRP >1.0 <3.0 moderate risk	60	30	90
hs-CRP >3.0 <10.0 High risk	120	20	140
Total	200	200	400

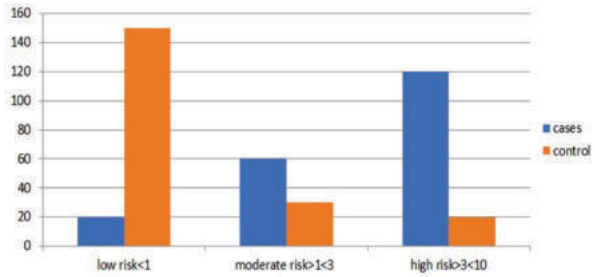

Figure I. hs-CRP values among cases and controls.

DISCUSSION.

We found high hs-CRP levels in MetS patients as compared to the control group & hs-CRP strongly associated with abdominal circumference & triglyceride levels. The relationship between central obesity and increased levels of hs-CRP has been well studied. Adipose

tissue is known to secrete cytokines that stimulate the production of hs-CRP in the liver, but adipose tissue itself may also secrete hs-CRP and thereby raise hs-CRP levels [8]. It indicates central obesity is the major determinant of elevated hs-CRP levels in individuals with the Mets. The other MetS components do not, or only marginally, increase the hs-CRP level.

Many South Asians who appear to be inherently insulin resistant a condition that is exacerbated by mild abdominal obesity than western counterpart [9]. There is increased production of inflammatory cytokines plasminogen activator inhibitor and other bioactive products but at the same time, the potentially protective adipokine, adiponectin, is reduced[8].

The CDC/AHA report also endorsed hsCRP as the only inflammatory biomarker currently available with adequate standardization and predictive value to justify use in outpatient clinical settings[10]. Based on data from available investigations, levels of hsCRP <1, 1 to 3, and >3 mg/L have been defined as lower, moderate, and higher cardiovascular risk[10].

60% of metabolic syndrome patients belonged to the high-risk group with a mean hs-CRP value >3 mg/L compared to 10% controls.

Whereas, the low to moderate risk category was composed of the majority 90% controls vs 40% cases. A significant linear trend over increasing hs-CRP categories was seen for the presence of the Mets.

Cardiovascular disease (CVD) is multifactorial in etiology. Recently, a better understanding of the role of inflammation in atherosclerosis has prompted many to propose the measurement of various inflammatory markers to better identify those who are at increased risk[11,12]

Inflammatory processes play a pivotal role within the pathogenesis of atherosclerosis and mediate many of the stages of atheroma development from initial leukocyte recruitment to eventual rupture of the unstable atherosclerotic plaque. Traditionally, hs- CRP has been thought of as a bystander marker of vascular inflammation, without playing a direct role in CVD. More recently, accumulating evidence suggests that hs-CRP may have direct pro-inflammatory effects, which are associated with all stages of atherosclerosis[13].

C-reactive protein (CRP) is found in endothelial atherosclerotic lesions, and evidence suggests that it play a role in atherogenesis. Of candidate serum markers that might add information to clinical risk assessment, high-sensitivity C-reactive protein (hs-CRP) measurement has the most potential for clinical use for multiple reasons [14]: (a) high hs-CRP is associated with a twofold to a threefold increase in the prevalence of myocardial infarction, stroke, and peripheral vascular disease, and it predicts incident cardiovascular events in those with and without preexisting CVD; (b) the increased risk associated with high hs-CRP is independent of other established risk factors; (c) hs-CRP assays are standardized and this analysis is biologically stable over time; (d) various risk-reducing interventions also reduce hsCRP, and research is underway to assess whether specifically targeting hs-CRP reduces CVD risk. National guidelines regarding the clinical utility of hs-CRP in primary and secondary prevention settings have been recently issued [14].

It has been suggested that treatment with a single high-dose or a short-term common dose of simvastatin could rapidly reduce CRP level. Those data indicated that the benefit to the vascular endothelium might occur quickly in patients with CVD, which is a critical issue for the high-risk subgroup.[15]

In contrast to several other biomarkers that also reflect biological aspects of inflammation and insulin resistance, hs-CRP measurement is relatively inexpensive, standardized, and widely available. Given the consistency of prognostic data for hs-CRP and the practicality of its use in outpatient clinical settings, the time has come for careful consideration of adding hsCRP as a laboratory criterion for diagnosing metabolic syndrome and for the creation of a hs-CRP-modified coronary risk score useful for global risk prediction[14].

CONCLUSIONS

Approximately one-third of urban South Asians have evidence of metabolic syndrome.

Visceral obesity is a form of obesity most strongly associated with metabolic syndrome & cardiovascular risk factors.

High hs-CRP is associated with a twofold to a threefold increase in the prevalence of myocardial infarction, stroke, and peripheral vascular disease and it predicts incident cardiovascular events in those with and without preexisting CVD.

Early detection of CVD may well prove to be instrumental in introducing effective treatment & may contribute to reducing mortality.

The other interventions, such as lifestyle changes, weight loss, and stop smoking are also warranted attention.

Recommendations

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

Authors recommend evaluation of hs-CRP in metabolic syndrome patients as a routine test to get an insight into atherosclerotic changes associated with waist circumference, hypertension & dyslipidemia.

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