C -Reactive Protein an inflammatory marker in Metabolic Syndrome

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ABSTRACT:

Background: Most individuals who develop cardiovascular disease (CVD) have multiple risk factors. Some risk factors that commonly cluster together like dyslipidaemia, hypertension and hyperglycaemia have been termed the metabolic syndrome. It is well known that the prevalence of obesity, diabetes and Metabolic syndrome all increase with age and have shown convincing evidence linking to oxidative stress markers. Very few studies have been done to show the role of inflammatory marker in metabolic syndrome. Hence in present study we aim to evaluate inflammatory marker in these patients which may help in predicting the prognostic outcome of metabolic syndrome cases.

Methodology: A prospective randomized double blinded case control study was undertaken on 30 Metabolic syndrome patients and 30 non-Metabolic syndrome controls in the age group of 40-70 years of either sex admitted to the respective specialty unit. The study protocol was approved by the institutional ethical committee. Aseptically 3ml of venous blood was collected with due consent from the patients and the controls for estimating: FBS, lipid profile and C reactive protein.

Result: The statistical significant differences were observed in the mean values of FBS, lipid profile and C reactive protein between study groups. It shows a direct correlation with the syndrome.

Conclusion: Hence, by periodically estimating the above said parameter with regular treatment protocols in diagnosed or suspected metabolic syndrome patients it will predict early and better outcome.

Keywords: chronic inflammation, metabolic syndrome, lipid profile, CRP

I. INTRODUCTION

Most individuals who develop cardiovascular disease (CVD) have multiple risk factors. Some risk factors that commonly cluster together (like dyslipidaemia, hypertension and hyperglycaemia) have been termed the metabolic syndrome. Most people with this syndrome have insulin resistance, which confers an increased risk of type 2 diabetes. When diabetes becomes clinically apparent, CVD risk rises sharply. Apart from CVD and type 2 diabetes, individuals with metabolic syndrome are susceptible to other conditions, notably polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma etc.

ATP (Adult Treatment Panel) III defined the metabolic syndrome essentially as a clustering of metabolic complications of obesity. The criteria listed include abdominal obesity, determined by increased waist circumference, raised triglycerides, reduced HDL, elevated blood pressure, and raised plasma glucose. Patients having at least three of the following five criteria were considered to have Metabolic Syndrome: (i) fasting blood glucose ≥110 mg/dl; (ii) serum triglyceride ≥150 mg/dl or being on lipid lowering therapy; (iii) serum HDL <40 mg/dl in men and <50 mg/dl in women or being on anti-lipidemic therapy; (iv) blood pressure ≥130 mmHg systolic and/or ≥85 mmHg diastolic or being on antihypertensive therapy; and (v) waist circumference >102 cm in men and >88 cm in women.

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WHO Clinical Criteria for Metabolic Syndrome\\nInsulin resistance, identified by one of the following:
\- Type 2 diabetes
\- Impaired fasting glucose
\- Impaired glucose tolerance
\- or for those with normal fasting glucose levels (<6.1 mmol/L), glucose uptake below the lowest quartile for the background population under investigation under hyperinsulinemic, euglycemic conditions,

Plus any two of the following:
\- Antihypertensive medication and/or high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic)
\- Plasma triglycerides ≥1.7 mmol/L
\- HDL cholesterol <0.9 mmol/L in men or <1.0 mmol/L in women
\- BMI >30 kg/m² and/or waist: hip ratio >0.9 in men, >0.85 in women
\- Urinary albumin excretion rate ≥20 μg/min or albumin: creatinine ratio ≥3.4 mg/mmol

C-reactive protein (CRP) is an acute phase protein found in the blood, the levels of which rise in response to inflammation. This acute phase response develops in a wide range of acute and chronic inflammatory conditions like bacterial, viral or fungal infections; rheumatic, metabolic syndrome and other inflammatory diseases, malignancy and tissue injury or necrosis.

Very few studies have been done to show the role of inflammatory marker in metabolic syndrome. Hence in the present study we aim to evaluate inflammatory marker in these patients which may help in predicting the prognostic outcome of metabolic syndrome cases.

**Inclusion Criteria**

Metabolic syndrome patients aged between 40-70 years of either sex. And non metabolic syndrome patients (control) aged between 40-70 years of either sex, admitted to the respective specialty units/OPD in JSS medical college and hospital.

**Exclusion criteria**

1) Critical ill patients.
2) Patients aged either <18 years and >60 years of either sex.
3) Female patients with menstruation/pregnancy.

**II. METHODOLOGY**

The sample size will consist of around 30 metabolic syndrome patients in the age group of 40-70 years of either sex admitted to the respective speciality unit/OPD, and around 30 non-metabolic syndrome patients aged between 40-70 years of either sex admitted to the respective speciality unit/OPD.

Three milliliter of venous blood will be collected under all aseptic precaution and used for estimation of inflammatory marker C reactive protein.

The methodologies for the above parameters are mentioned below:

- Glucose is estimated by GOD-PAP method.
- Total cholesterol is estimated by CHOD-PAP method.
- HDL cholesterol is estimated by immunoinhibition method.
- Triglycerides is estimated by GPO-PAP method.
- LDL cholesterol is estimated by enzyme selective protection method.
- VLDL is estimated by calculation method
- CRP is estimated by immunoturbidimetric method by RANDOX IMOLA autoanalyser.

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Statistical methods to be employed
Mean and standard deviation will be estimated to assess the level of C-reactive protein in the study and control groups. Student-t test will be applied to test the significance of difference in the parameters between the study and the control groups. Data entry and statistical analysis will be carried out using Microsoft excel and EPI-INFO. Package version 3.5.1. Pearson's co-relation will be applied among various parameters under study.

All the above mentioned statistical methods will be performed through software SPSS (Statistical Package for Social Sciences) version 16 for windows.

III. RESULTS
The present study analyzes the correlation between the inflammatory marker and metabolic syndrome patients with healthy controls.
The study was compared between 30 metabolic syndrome patients with 30 non-metabolic syndrome patients. The cases and controls were age and sex matched.
The age group was between 40 years to 70 years. The mean age in metabolic syndrome patients was 54.7 ± 9.2 years and in controls was 52.8 ± 8.310 years. The cases and controls were age matched with p > 0.05. This is also shown graphically in terms of mean ± SD as bar diagrams in Fig 1.

Table 1: Mean values of age distribution between the study groups

<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>Metabolic syndrome</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-55 years</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>56-70 years</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>54.7±9.2</td>
<td>52.8 ± 8.310</td>
</tr>
</tbody>
</table>

Figure 1: Mean values of age distribution between the study groups.

Table no 2 shows gender distribution in the study groups. Patients with metabolic syndrome consisted of 10 males and 20 females. In the control group there were 9 males and 21 females. The cases and controls were sex matched with p > 0.05. This is also shown graphically as pie charts in Fig 2.

Table 2: Mean values of gender distribution between the study groups

<table>
<thead>
<tr>
<th>Gender</th>
<th>Cases</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
<td>Number</td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>33.3</td>
<td>9</td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>66.6</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>100.0</td>
<td>30</td>
</tr>
</tbody>
</table>

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Fasting Blood Sugar:
The mean and standard deviation (SD) of fasting blood sugar in metabolic syndrome and in non-metabolic syndrome were 171.7±51.269 mg/dl, and 77.63±4.730 respectively. These are represented in the following table.

<table>
<thead>
<tr>
<th>Parameters (FBS)</th>
<th>Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td>Mean</td>
<td>171.7</td>
<td>77.63</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>51.269</td>
<td>4.730</td>
</tr>
</tbody>
</table>

The above table shows that mean fasting blood glucose levels were significantly increased in metabolic syndrome patients when compared to controls. The statistical significant difference in the mean values of the above parameters between study groups was < 0.001. This is also shown graphically in terms of mean as bar diagrams in Fig 3.
Lipid Profile

The mean and standard deviation (SD) of lipid profile parameters in metabolic syndrome patients and in controls respectively are represented in the following table.

Table 4: Mean values and SD with significance of lipid profile between the study groups.

<table>
<thead>
<tr>
<th>Lipid parameters</th>
<th>Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td>CHOL (mg/dl)</td>
<td>191.76±54.23</td>
<td>146.60±9.61</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>38.33±10.40</td>
<td>47.63±4.74</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>112.9±44.34</td>
<td>83.16±10.47</td>
</tr>
<tr>
<td>VLDL (mg/dl)</td>
<td>46.4±35.28</td>
<td>18.53±4.98</td>
</tr>
<tr>
<td>TGL (mg/dl)</td>
<td>241.53±171.91</td>
<td>86.93±14.85</td>
</tr>
</tbody>
</table>

The above table also shows that mean levels of lipid profile parameters were significantly increased in metabolic syndrome patients when compared to controls. The statistical significant difference in the mean values of the above parameters between study groups was < 0.01. This is also shown graphically in terms of mean as bar diagrams in Fig 4.1, 4.2, 4.3, 4.4 and 4.5.

Figure 4.1: Mean values of cholesterol levels in the study groups
Figure 4.2: Mean values of HDL levels in the study groups

Figure 4.3: Mean values of LDL levels in the study groups

Figure 4.4: Mean values of VLDL levels in the study groups
C-reactive Protein

The mean and standard deviation (SD) of C-reactive protein levels in metabolic syndrome patients and in controls respectively are represented in the following table.

Table 5: Mean values and SD with significance of CRP between the study groups.

<table>
<thead>
<tr>
<th>C-reactive Protein</th>
<th>Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td>Mean</td>
<td>36.58</td>
<td>1.77</td>
</tr>
<tr>
<td>Stand deviation</td>
<td>18.84</td>
<td>0.64</td>
</tr>
</tbody>
</table>

The above table shows that mean levels of CRP were significantly increased in metabolic syndrome patients when compared to controls. The statistical significant difference in the mean values of the above parameters between study groups was < 0.001. This is also shown graphically in terms of mean as bar diagrams in Fig 5.
IV. DISCUSSION

Metabolic syndrome is a complex condition that is characterized by a cluster of closely related clinical features linked to obesity, including insulin resistance, dyslipidaemia and hypertension. Using data from NHANES IV, the age-adjusted prevalence of metabolic syndrome in Americans is 27%.[17] Metabolic syndrome is associated with an increased risk of cardiovascular disease, which is ultimately responsible for a considerable proportion of diabetic mortality. The most accepted and unifying hypothesis to describe the pathophysiology of the metabolic syndrome is insulin resistance.

Obesity is the most common and important risk factor for the development of type 2 diabetes mellitus (T2DM). Obesity leads to the reduction in the sensitivity to the biological actions of insulin, a pathophysiological state known as insulin resistance.[6]

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.[7] The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.

Hypertension is a very common condition which frequently remains undiagnosed until relatively late in its course, leading to a variety of other life-threatening conditions like kidney damage and heart failure. It is a very prominent feature of the metabolic syndrome, present in up to 85% of patients. In the context of global cardiovascular risk, metabolic syndrome is indeed a high risk condition, involving obesity, dyslipidaemia, hypertension and diabetes. In spite of controversy surrounding its definition and etiology, metabolic syndrome represents a useful and simple clinical concept which allows for earlier detection of type 2 diabetes and cardiovascular disease. The establishment of hypertension as a component of the syndrome has enabled better insight into the condition and allowed for earlier detection and treatment.[18]

In the present study it was observed that the gender distribution in metabolic syndrome patients was 10 males and 20 females respectively which suggests that metabolic syndrome is more prevalent in women when compared to men. Many previous studies state that women are more likely to develop metabolic syndrome when compared to men.[5]

The table shows that mean fasting blood glucose levels were significantly increased in metabolic syndrome patients when compared to controls. The mean and standard deviation (SD) of fasting blood sugar in metabolic syndrome and in non-metabolic syndrome were 171.7±51.269 mg/dl, and 77.633±4.730 respectively. Many previous studies will conCURS with our study.[8-13] Insulin resistance plays a critical role in the development of type 2 diabetes.[11] Insulin resistance is a decrease in the ability of insulin to metabolize glucose, and it is characterized by glucose intolerance and hyperglycemia followed by an increase in plasma concentrations of insulin, dyslipidaemia (elevated levels of triglycerides and diminished HDL cholesterol), elevation of blood pressure, abdominal obesity, and elevated tendency for thrombosis.[12,13]

In the present study it was observed that the mean values of lipid profile parameters including cholesterol, LDL, VLDL and triglycerides were significantly increased in cases when compared with controls, whereas HDL was significantly decreased in cases when compared with controls. Many previous studies oblige with our findings.[14-16] The changes in lipid profile components in the present study are common abnormalities of lipoprotein metabolism associated with metabolic syndrome patients. The elevation in cholesterol, triglyceride and LDL is accounted for by the effect of insulin resistance on lipoprotein lipase activity and the expression of LDL receptor, and these changes probably play an important role in atherogenesis in untreated metabolic syndrome. Low HDL cholesterol has been shown to be an independent risk factor for CAD and premature atherosclerosis, independent of serum LDL or triglyceride levels. The primary mechanism by which HDL exerts its atheroprotective efficacy is reverse cholesterol transport, a process by which cholesterol is extracted from macrophages, foam cells, and atherosclerotic plaque, and delivered back to the liver for elimination as bile salts or biliary cholesterol. However, several other anti-inflammatory, antithrombotic, and antiproliferative functions for HDL have also been identified.[19]

Hypertriglyceridemia may lead to decreased high density lipoprotein, enhancing HDL clearance from the circulation and in turn leading to atherogenic lipid profile.[20] Resistance to the suppressive effect of insulin on the production of VLDL in the liver is another postulated defect in insulin-resistant states.[21] This may additionally lead to increased production of apolipoprotein B-containing very low density lipoprotein (VLDL), IDL and LDL in MetS and insulin resistance.

In our present study, the C-reactive protein levels in the metabolic syndrome patients group showed significantly higher values than compared to the control group: 36.58±18.84 and 1.77±0.64 respectively. Many previous studies showed a similar results which concurs with our study. C-reactive protein is a well-known unspecific marker of inflammation and tissue damage. It is a part of a molecular family called acute phase reactants made by the liver cells. A cross sectional study on was done by Yudkin et al.showed that levels of

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CRP were related to all measures of obesity. CRP-levels were also related to insulin resistance, blood pressure, HDL, and triglycerides and markers of endothelial dysfunction. The authors concluded that these research data suggested that adipose tissue is an important determinant of low-grade chronic inflammation, and that chronic low-grade inflammation may induce insulin resistance and endothelial dysfunction. They also stated that this could be a possible link between insulin resistance and endothelial dysfunction and obesity & cardiovascular disease.[22]

V. CONCLUSION

ATP (Adult Treatment Panel) III defined the metabolic syndrome essentially as a clustering of metabolic complications of obesity. Based on the present study and data available from the literature, it is implied that there is association between lipid profile parameters, inflammatory marker with their increased risk for insulin resistance disorders, such as Type-2 diabetes, metabolic syndrome and cardiovascular disease. There is also an association between inflammatory marker and metabolic syndrome. Given the high prevalence of the metabolic syndrome, it is essential that patients with this syndrome are to be identified as early as possible and followed regularly so as to prevent the development of various lethal complications emerging from the pathogenesis of this syndrome. Thus estimation of the above said parameters regularly will help in the better management of the metabolic syndrome patients and proves as better prognostic markers in such patients.

Competing interests: The authors declared that they have no competing interests. All the authors have read and approved the final manuscript.

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