Serum Concentration of High-sensitivity CRP in Metabolic Syndrome
A Case-control Study
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Abstract

Background: Metabolic Syndrome is an aggregation of conditions that together increases the risk of cardiovascular disease in individuals that would not otherwise be recognized to be at risk. The lack of a consensus definition of Metabolic Syndrome, debate about its etiology and pathogenesis and lack of a consensus document for its treatment contribute to this confusion. Chronic, sub-clinical inflammation and its association with Metabolic Syndrome is well documented. Inflammatory mediators have been recognized as factors that increase the risk of cardiovascular disease.

Objectives: to assess the status of high sensitive C reactive protein (hs-CRP) in patients with Metabolic Syndrome.

Methods: This study is a case-control study based on New National Cholesterol Education Programme Adult Treatment Panel III which approved the criteria of metabolic syndrome, The patients included in this study were 48 patients (of both sexes) attending the Diabetic Consultant Clinic for follow up and monitoring therapy during the period from January, 2010 till the end of September, 2010. The study included another 48 apparently healthy volunteer that were comparable to patients group with respect to age and sex and serve as a control group. They were screened for Metabolic Syndrome criteria: namely, high blood pressure, high body mass index, high fasting blood sugar, high triglyceride, low high density lipoprotein; a significant difference was found between patients and controls with respect to FBS, BML, TG, HDL and BP (P<0.05). For the two groups high sensitivity C - reactive protein was measured using ELISA kit.

Results: BMI and BP were significantly higher in the MetS than the control. MetS group had significantly higher (hs-CRP) levels than control group, (p < 0.001) and significantly higher LDL-C, triglyceride (TG), and lower HDL-C than the control group. Also (hs-CRP) showed a positive correlation with BMI (p < 0.001), blood pressure, TG, and LDL size index which are the criteria involved in definition of metabolic syndrome. Mean concentrations of (hs-CRP) were higher among patients who had the MetS.

Conclusion, high sensitive C Reactive Protein can thus be simple, powerful markers of Metabolic Syndrome.

Key words: metabolic syndrome, hs-CRP

Introduction

Metabolic Syndrome (MetS) is an aggregation of conditions that together increases the risk of cardiovascular disease in individuals that would not otherwise be recognized to be at risk [1]. This phenomenon is associated with a rapidly increasing trend in cases of type 2 diabetes. Obesity also seems to harbor a number of risk factors for (CVD) in adult life, but is not yet clear whether these are determined by glycemia, degree of obesity, or other demographic, clinical, or biochemical features of the obese [2]. Additionally, Metabolic Syndrome increases the risk of developing diabetes mellitus and chronic kidney disease and is associated with a number of other disorders [3]. Obesity seems to contribute to the development of vascular inflammation and the progression of arterial wall changes. (hs-CRP) has recently emerged as a useful biomarker for vascular inflammation associated with atherosclerosis [3].

Chronic, sub-clinical inflammation and its association with Metabolic Syndrome is well documented inflammatory mediators have been recognized as factors that increase the risk of cardiovascular disease, but also are one cause of insulin resistance [4]. Increased concentrations of inflammatory mediators, such as, CRP, tumor necrosis factor-alpha, interleukin-6 and others have been found in the obese. Adipose tissue has been found to express most of these inflammatory markers [5]. The MetS has been defined as a cluster of risk factors for atherosclerotic cardiovascular disease that includes insulin resistance, dyslipidemia, abdominal adiposity, and often hypertension [6].

The metabolic syndrome has generated a great deal of interest in recent years. Comprised of a constellation of anthropometric, physiologic, and biochemical abnormalities, the MetS is a risk factor for CVD and diabetes among adults. [7] CRP is a major inflammatory cytokine that functions as a nonspecific defense mechanism in response to tissue injury or infection. Synthesized mainly in the liver, CRP activity is stimulated by other cytokines, especially interleukin (IL)-6, IL-1β, and tumor necrosis factor-α (TNF-α). Accumulating evidence suggests that CRP, which is also found within macrophages of atheromatous plaques, is causally or mechanistically related to atherothrombosis [8].

To date, more than 20 prospective epidemiologic studies have demonstrated that (hs-CRP) independently predicts vascular risk [8]. This study was conducted to assess the status of (hs-CRP) in patients with Met-S.

Patients and methods

This study is a case-control study based on New National Cholesterol Education Programme (NCEP),
Adult Treatment Panel III which approved the criteria of metabolic syndrome

The patients included in this study were 14 patients (of both sexes) aged 20-65 years; attending the Diabetic Consultant Clinic at Al-Kadhimiya Teaching Hospital for follow up and monitoring therapy during the period from January, 2010 till the end of September, 2010.

They were screened for Met S. criteria:

The study included another 48 apparently healthy volunteer that were matched to patients group with respect to age and sex and serve as a control group.

Inclusion and Exclusion Criteria:- The following inclusion criteria were used:
1- Adults (≥ 20 years)
2- Only type 2 diabetes.

While exclusion criteria were the following:
1- Type 1 diabetes.
2- Age less than 20
3- Gestational diabetes.
4- Presence of fatty liver on abdominal ultra sound.
5- Presence of chronic hepatitis B or C on serology.

Five milliliters of fasting venous blood were withdrawn from each patient, in supine position, without application of tourniquet. Samples were transferred into clean new plane tube, left at room temperature for 15 minutes for clotting, centrifuged, and the separated serum was stored at -20°C until analysis of hs-CRP, which was done within one month after collection.[9]

Serum high sensitivity CRP was measured using ELISA kit DRG CRP, HS (C - reactive protein) (EIA-3954).[9]

Statistical analysis was done using Excel system version 2003. When P-value was less than 0.05, the difference is considered statistically significant.

Results:

For Met S group: the fasting blood sugar (FBS) ranges between 5.7-22 mmol/L (mean FBS ± SD = 10.99±4.47 mmol/L); the triglyceride ranges between 1.4-5 mmol/L (mean TG ± SD = 3.48±1.02 mmol/L); the high-density lipoprotein (HDL) ranges between 0.56-1.1 mmol/L (mean HDL ± SD = 0.94±0.18 mmol/L); the LDL size Index (LDL-SI) (molar ratio between TG: HDL) ranges between (2-8.56) (Mean LDL-SI ± SD = 3.84±1.49); the body mass index (BMI) ranges between 27-41 kg/m² (mean BMI ± SD = 33.75±4.86kg/m²); the systolic blood pressure ranges between (120-170) mmHg (mean BP ± SD = 147.9 ± 11.5 mmHg); the diastolic blood pressure ranges between (80-100) mmHg (mean BP ± SD = 89.4 ± 6.4mmHg) as in Table 1.

For control group: the fasting blood sugar (FBS) ranges between 4.2-6 mmol/L (mean FBS ± SD = 5.03±0.47mmol/L); the triglyceride ranges between(0.4-2.5 )mmol/L (mean TG ± SD = 1.56±0.74 mmol/L); the high-density lipoprotein (HDL) ranges between 4.03±0.47 mmol/L (mean HDL ± SD = 1.32±0.33 mmol/L); The LDL size Index (LDL-SI) (ratio between TG : HDL) ranges between (0.4-3.4 ) (mean LDL-SI ± SD = 1.34±0.80);the body mass index (BMI) ranges between 20-23 kg/m² (mean BMI ± SD = 21.68±0.74kg/m²); the systolic blood pressure ranges between(110-120) mmHg (mean BP ± SD = 111.6 ± 5.7 mmHg); the diastolic blood pressure ranges between 70-80 mmHg (mean BP ± SD = 75.1 ± 4.1mmHg) as in Table 1.

A significant difference was found between patients and controls with respect to FBS, BMI, TG, HDL and BP (P<0.001) as in Table 1.

Table (1): Criteria for studied groups (patients vs control) presented as mean ± SD.

<table>
<thead>
<tr>
<th>Variable</th>
<th>G1</th>
<th>G2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI(Kg/m²)</td>
<td>33.5±5.1</td>
<td>21.7±0.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>SBP(mmHg)</td>
<td>147.9±11.9</td>
<td>111.6±5.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>DBP(mmHg)</td>
<td>89.4±6.4</td>
<td>75.1±4.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>FBS(mmol/L)</td>
<td>11±4.5</td>
<td>5.03±0.47</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>TG(mmol/L)</td>
<td>3.48±1.02</td>
<td>1.56±0.74</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HDL(mmol/L)</td>
<td>0.94±0.18</td>
<td>1.32±0.33</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LDL-SI</td>
<td>3.84±1.49</td>
<td>1.3±0.8</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Serum hs-CRP was significantly elevated in patients with MetS compared with controls [P < 0.001].

Significant positive correlation was found between hs-CRP and BMI, BP (systolic & diastolic), FBS, LDL size index in patients with MS as in Figure 1, 2, 3, and 4; however, this correlation was lost in control group.
Discussion:
Systemic inflammation is closely involved in the pathogenesis of MetS. Several clinical studies have demonstrated that CRP was increased in subjects with MetS [10, 11, 12].

While there have been many previous studies relating CRP and cardiovascular risk factors, the association of CRP with subclinical cardiovascular...
complication has been examined primarily in adults, with few studies in obese patients. Kerner et al. [11] demonstrated, in a general population, an association between increased plasma levels of CRP in subjects with one or more components of MetS, and they proposed that hepatic inflammation related to non-alcoholic fatty liver disease might be involved in the systemic inflammation associated with MetS [11].

In order to prevent the incidence of cardiovascular events, it is important to weigh the influence of each risk factor on the cardiovascular system [12]. In this respect, we investigated the relationship of inflammatory markers with other risk factors.

In our study, we found that BMI was significantly higher in the MetS group than in the control group. Also, MetS group had significantly higher hs-CRP, LDL-C, TG and significantly lower HDLC than the control group.

These findings were in concordance with Quijada et al. who stated that, Systolic, diastolic, and mean blood pressures (MBP), low-density lipoprotein cholesterol (LDL-C), TG/HDL-C, TC/HDL-C, LDL-C/ HDL-C ratios, CRP, and leptin were significantly higher in the obese group [13].

Our study showed elevated serum Hs-CRP levels were positively associated with elevated BMI, confirming previous observations in adults [12,13].

The mechanisms underlying this association with BMI or obesity might be as follows; the adipose tissue is a source of cytokines such as tumor necrosis factor-a (TNF-a) and interleukin-6 (IL-6), and these cytokines stimulate the production of acute-phase proteins such as CRP in the liver. Not unexpectedly, then, we found that serum hs-CRP levels were positively associated with BMI [14].

Our results are in agreement of Martos et al. (2009) who reported that (CRP) levels were significantly (P < 0.001) higher in obese than in controls. In addition to BMI, hs-CRP was also found to be closely correlated with SBP, DBP, and TG concentrations. Previous studies reported that CRP levels are significantly positively correlated with TG, total ratio of serum cholesterol to serum HDL cholesterol, fibrinogen levels, heart rate, SBP, smoking, and white blood cell count and negatively correlated with HDL-C levels [15].

Atherosclerosis and insulin resistance were found to share a common inflammatory basis when it was shown that CRP exerts directly harmful effects on vessel walls. Obesity-mediated cytokine production is presumed to be a central mechanism for systemic elevations of CRP. Cytokines produced by adipocytes, such as IL-1, IL-6, and TNF-α, stimulate the hepatic synthesis of CRP, and modify the glucose and lipid metabolism. Thus, the systemic acute-phase response may mediate systemic metabolic impairments. In addition, it was suggested that CRP has proatherogenic and prothrombic properties.

Interestingly, a recent report demonstrated that atorvastatin, a lipid-lowering agent, directly reduces CRP levels and consequently reduces the incidence of cardiovascular events. A Japanese study found a mean CRP of 1.0 mg/L for men (mean 69.0 years) and 0.8 mg/L for women (mean 67.6 years), with their CRP values associated with obesity. In this study Mean concentrations of hs-CRP were significantly higher among patients who had the metabolic syndrome than among those who did not. Among patients with the metabolic syndrome, 42 % had a concentration of hs-CRP > 3.0 mg/L, a concentration considered to place adults at high risk for cardiovascular disease [17], the comments of Dr. Kholeif regarding the utility of (CRP) measurement in stratifying cardiovascular disease (CVD) risk as it relates to our results of patients with the metabolic syndrome into hs-CRP and high-risk (<3 mg/l) levels are appropriate for stratifying patient risk in combination with other risk factor [27]. Dr. Kholeif reported that a single CRP measurement, given its intra individual biological variability, is not suitable and that the use of multiple measures would establish the certainty of a given level [18].

Our findings are consistent with those of Ridker et al. showing MetS patients with elevated (hs CRP) levels to have optimistic prognosis than those with normal (hs-CRP) levels [19].

The metabolic syndrome has generated a great deal of interest in recent years. Among adults and adolescents, components of the metabolic syndrome and the metabolic syndrome itself are associated with measures of inflammation, such as concentrations of (CRP).

This low-grade inflammation, which has been associated with an increased risk for cardiovascular disease and diabetes may provide a mechanism for the increased risk of these conditions experienced by individuals who have the metabolic syndrome, however, abdominal obesity was the component that was responsible for much of the difference in concentrations of (hs-CRP). The present study showed association between obesity and elevated concentrations of (hs CRP) [14].

Concentrations of (hs CRP) have also been significantly associated with the other four components of the metabolic syndrome. Our results suggest that the presence of the metabolic syndrome and abdominal obesity among adult may be laying the foundation for the emergence of cardiovascular disease and diabetes later in life through early low-grade inflammation. Unfortunately, the sample size was inadequate to provide results separately for males and females, similar results were obtained by Cizmecioglu et al. (2009) as they found that Waist circumference had the highest sensitivity and specificity for predicting MS in their patients. [20].

**Serum Concentration of high-sensitivity CRP in Metabolic Syndrome**

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Recently, the Centers for Disease Control (CDC)/American Heart Association (AHA) workshop on markers of inflammation and cardiovascular disease did recommend that the mean of only two measures taken 2 weeks apart could be averaged to provide a clinically useful value. The studies above demonstrate that vascular risk prediction and the prediction of type 2 diabetes can be improved by knowledge of (hs CRP) levels, even among those with metabolic syndrome. Recent studies relating (hs CRP) to incident hypertension serving to reinforce the importance of blood pressure in the metabolic syndrome complex. Although ultrasonography allows visualization of early subclinical stages of atherosclerosis in obese children, the measurement of the serum (hs CRP) level is simpler and cheaper than ultrasonography, is highly reproducible, and well correlates with carotid intima-media wall thickness (IMT)21.

Thus, (hs CRP) would be a useful screening marker for evaluating and estimating the degree of atherosclerosis.

References:


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