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Correlation Of Serum C-Reactive Protein with the Features of Metabolic Syndrome and Associated Microangiopathy in Egyptian Population

KEYWORDS: C- reactive protein, metabolic syndrome, microangiopathy

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ABSTRACT *Low-grade inflammation is characteristic of the metabolic syndrome (MetS), The aim of this study to investigate the relationship between serum CRP with metabolic syndrome and associated microvascular complications.The present study provides evidence that CRP levels are elevated in MetS subjects. In addition, it could be predictor for development of microvascular complications in MetS patients.*

Introduction:
Metabolic syndrome is a cluster of metabolic and physiological abnormalities, the US National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) requires at least three of the following: [1]

- Central obesity: waist circumference ≥ 102 cm or 40 inches (male), ≥ 88 cm or 36 inches(female)
- Dyslipidemia: TG ≥ 1.7 mmol/L (150 mg/dl)
- Dyslipidemia: HDL-C < 40 mg/dL (male), < 50 mg/dL (female)
- Blood pressure ≥ 130/85 mmHg
- Fasting plasma glucose ≥ 6.1 mmol/L (110 mg/dl)

There is mounting interest in the role of inflammation in the pathogenesis of obesity, metabolic disturbances, diabetes, and cardiovascular disease. Among the various biomarkers of inflammation that are associated with increased risk for these disorders, C-reactive protein (CRP) has attracted the most attention [2]. It is well established that the individual components of the MetS are related to endothelial dysfunction [3]. CRP is an inflammatory biomarker, involved in endothelial dysfunction and atherogensis [4]. Inflammation as measured by serum C-reactive protein has been shown to be increased in people with diabetes who have macro vascular complications [5] and microangiopathy [6]. To date, studies largely in endothelial cells, but also in monocyte-macrophages and vascular smooth muscle cells, support a role for CRP in atherogenesis. The proinflammatory, proatherogenic effects of CRP that have been documented in endothelial cells include the following: decreased nitric oxide and prostacyclin and increased endothelin-1, cell adhesion molecules, monocyte chemoattractant protein-1 and interleukin-8, and increased plasminogen activator inhibitor-1. In monocyte-macrophages, CRP induces tissue factor secretion, increases reactive oxygen species and proinflammatory cytokine release, promotes monocyte chemotaxis and adhesion, and increases oxidized low-density lipoprotein uptake. Also, CRP has been shown in vascular smooth muscle cells to increase inducible nitric oxide production, increase mitogen-activated protein kinase activities, and, most importantly, upregulate angiotensin type-1 receptor resulting in increased reactive oxygen species and vascular smooth muscle cell proliferation [7]. In view of this, we investigated the correlation between serum CRP level and MetS components and associated microvascular complications in two hundred Egyptian subjects.

Materials and methods
Our study was conducted on two hundreds unrelated Egyptian subjects divided into four groups, group1: fifty non obese healthy individuals, group 2: fifty obese individuals without MetS, group3: fifty obese subjects with MetS and group 4: fifty subjects the same like group3, but developed microvascular complications. All subjects were informed of the purpose of the study and their consent was obtained. Physical data for each subject, including weight, height, waist and hip circumferences were recorded.

Group 1 subjects were judged to be in good health according to their medical history and their fasting blood glucose (<110mg/dL). Group 2 were ensured to have BMI >30 kg/m2 . Subjects in group 3 were diagnosed as MetS according to NCEP-ATPIII report .Subjects in group 4 were subjected to fundus examination for detection of the presence of retinopathy and urine analysis to detect the presence of nephropathy , neuropathy was defined as the typical subjective symptom of symmetrical distal neuropathy with the bilateral decrease of the Achilles tendon reflex or deep sensory capacity. laboratory investigations including, fasting blood glucose level by colorimetric method and fasting serum insulin level [8]. Insulin resistance was measured using the homeostasis model assessment of insulin resistance (HOMA-IR) [9]. Subjects were assayed for CRP [10], and Lipid profile [11].

Statistical analysis:
The collected data were tabulated and analyzed using SPSS version 16 software. Comparison of variables among groups of the study was made by one way analysis of variance (ANOVA). Correlation between serum CRP and other parameters of the subjects was determined by Pearson's correlation coefficient (r). Bonferroni's correction was also applied to analyses. Differences were considered statistically significant at $P < 0.05$ and highly significant at $P < 0.01$. The receiver operating characteristic (ROC) curve was used to evaluate the performance of fasting serum CRP level as an indicator of developing microvascular complications in MetS subjects.

Results : The serum CRP levels (table1) showed high significant difference between non metabolic syndrome groups (G 1 & G2) and groups with metabolic syndrome (G3 & G4) ($p<0.01$).

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Table(1): Mean± S.D of serum CRP in the study groups.

	CRP	F	P
G 1 n=50	3.5 ±0.45	121.16	<0.01
G 2 n=50	4.2 ± 0.8	Bonferroni test Group 1 & group 3 <0.005 Group 1& group 4 <0.005 Group 2& group 3 <0.005 Group 2 & group 4 <0.005 Group 3 & group 4 <0.005	
G 3 n=50	8.9±1.9		
G 4 n=50	12.3±1.9		

Serum CRP was significantly correlated with the number of MetS components (table2).

Table (2):Simple regression analysis, in patients of MetS:(three components= 0, four components = 1 and five components =2), was involved as dependent variable, and serum CRP as an independent variable. CRP concentration is significantly positively correlated with the number of the components of the MetS.

Dependent variable	Components Of MetS
Unstandardized regression Coefficient	0.1541
standadized regression coefficientt	0.1238
Standard error	0.03
P	0.0319

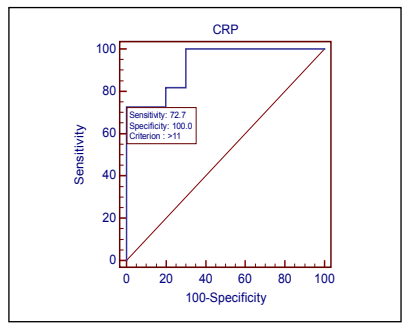
Serum CRP concentrations were not correlated with LDL –C levels, whereas there was a highly significant positive correlation between serum CRP concentrations and triglycerides, BMI and FBG. Serum CRP is significantly positively correlated with waist circumferences and W/ H ratio, while it is significantly negatively correlated with HDL-C (table3).

Table (3): Correlations between serum CRP level and other parameters in all studied groups.

Variables	r	P
Age (years)	0.501	<0.01
BMI(kg/m2)	0.5051	<0.01
Waist (cm)	0.3863	<0.05
Waist/hip ratio (cm)	0.4963	<0.01
FBG(mg/dl)	0.5086	<0.01
HOMA–R (µU/mL-mmol/L)	0.5908	<0.01
HDL Cholesterol(mg/dl)	- 0.3958	<0.05
LDL Cholesterol(mg/dl)	0.0579	>0.05
Triglycerides (mg/dl)	0.6614	<0.01
Systolic blood pressure	0.5	<0.01
Diastolic blood pressure	0.39	<0.05

ROC curve analysis was performed in order to establish a threshold serum CRP concentration for the existence of microvascular complications associated with metabolic syndrome, the cut-off value of 11mg/ dl shows sensitivity 72.7%, specificity 100%, positive predictive value 100% and negative predictive value 76.9% (figure 1)

Figure (1): ROC curve analysis of CRP values in MetS patients with and without microangiopathy.



Discussion

Our results showed that circulating levels of CRP were significantly elevated in MetS groups as compared to non MetS groups. This was in agreement with Zhao et al [5] who stated that inflammation as measured by serum C-reactive protein have been shown to be increased in people with diabetes and MetS and the study of Belfki et al on Tunisian population [12] also showed concomitant results. There is a linear relationship between the number of metabolic features and increasing levels of CRP. Furthermore, Festa et al [13] in the Insulin Resistance and Atherosclerosis Study (IRAS) showed that CRP 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. The strongest associations are observed between CRP levels, central adiposity, and insulin resistance. The largest study to date that examined the association between inflammation and the MetS was the NHANES III study [14]. In a representative sample of the US population (8570 participants >20 years of age), patients with the MetS, defined using ATPIII criteria, were more likely than those without the syndrome to have elevated levels of markers of inflammation such as CRP, fibrinogen as well as leukocyte count. A specific complication of diabetes and MetS is microangiopathy, including retinopathy, nephropathy, and neuropathy. Hyperglycemia increases polyol pathway flux, protein kinase C (PKC) activity, and the production of advanced glycation end products (AGE), and reactive oxygen species (ROS) [15]. So the development or progression of diabetic microangiopathy could be affected by serum CRP. The MetS subjects with microvascular complications had the highest serum CRP levels, also Matsumoto et al [6] concluded that CRP increased in diabetic and MetS patients with microangiopathy, however, the associations of CRP with the microvascular complications of diabetes and MetS, have been inconsistent from the few studies that examined this association. In the European diabetes study [16]. CRP was found to be positively associated with microangiopathy severity, but when BMI was added to the model, the association was no longer significant. Similarly, in a longitudinal study of patients with type 2 diabetes, Spijkerman et al [17] reported that CRP was cross-sectionally associated with baseline prevalence of diabetic microangiopathy, but this association was not independent of HbA1c levels and BMI and there were also no associations between CRP levels and microangiopathy progression.

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