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Inflammation in Metabolic Syndrome: Relationship to Circulating Chemerin

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Abstract

Objectives: We hypothesized that increased chemerin levels may contribute to the development of insulin resistance, and hence metabolic syndrome. Thus, we aimed to investigate whether body fat measures, insulin resistant and serum high sensitivity-C Reactive Protein (hs-CRP) levels in metabolic syndrome are correlated with circulating chemerin levels.
Methods: Case-control study of 83 patients with metabolic syndrome matched for age and gender with 83 apparently healthy controls. Demographic, anthropometric, and biochemical variables were estimated in all subjects.
Results: Serum levels of chemerin and hs-CRP were significantly higher among subjects with metabolic syndrome versus their matched controls ($p<0.05$). After adjusting for systolic and diastolic blood pressure and insulin resistance index (HOMA-IR), chemerin levels were independently associated with serum levels of triglycerides and hs-CRP.
Conclusion: Elevated serum hs-CRP and triglycerides levels are suggested to be independent predictors of serum chemerin levels in patients with metabolic syndrome. However, its role in cardiovascular diseases needs to be fully elucidated.

Keywords: Chemerin; Metabolic syndrome; Inflammation; hs-CRP

Introduction

Metabolic syndrome is known to be a cluster of interrelated risk factors of metabolic origin such as elevated blood pressures, glucose metabolism disturbances, dyslipidemia, and obesity, which are linked to the development of atherosclerotic cardiovascular diseases and type 2 diabetes mellitus [1]. Furthermore, metabolic syndrome has evolved to attain a greater role in the pathogenesis of many other conditions [2, 3]. Insulin resistance has been extensively reported in patients with metabolic syndrome [4]. Nevertheless, metabolic syndrome cannot be solely interpreted by the concept of insulin resistance.

Growing prevalence of obesity and sedentary lifestyles contributes to the high prevalence of metabolic syndrome [5]. Obesity is a multi-factorial disease caused by a complex interplay between genetic predisposition and the environment. In particular, abdominal obesity has been recognized as a causal factor for the origin of metabolic disorders prevalent in obesity-related health risks [6].

Adipose tissue is an active endocrine secretory organ which secretes a number of adipokines, such as leptin, tumor necrosis factor alpha, interleukin 6, and adiponectin, which are involved in the regulation of lipid and glucose metabolism through systemic actions in the brain, liver and muscle.

They are dysregulated in obesity and contribute to metabolic and vascular complications. Adipokines have been shown to be associated with insulin resistance; some adipokines have shown to decrease insulin sensitivity whereas other adipokines have shown the opposite [7, 8]. Nevertheless, insulin resistance relationship with the dysregulation of adipokines in metabolic syndrome is not fully explained [9], but their serum levels have emerged as important biomarkers for prediction, diagnosis, and risk stratification for patients with obesity related comorbidities [10].

Chemerin is a novel adipocytokine that plays a role in the inflammatory responses of immune cells [11]. Main functions of chemerin are to regulate adipogenesis, metabolic homeostasis in adipocytes and it may play an important role in macrophage infiltration into the adipose tissue [12]. It is suspected to have an important role in the pathophysiology of obesity and metabolic syndrome [13]. Therefore, chemerin could be a marker of adiposity and may have a key role in the development of cardiovascular diseases.

We hypothesized that increased chemerin levels may contribute to the development of insulin resistance, and hence metabolic syndrome. Thus, we examined whether body fat measures, insulin resistant and serum high sensitivity-C reactive protein (hs-CRP) levels in metabolic syndrome are correlated with circulating chemerin levels.

Methods

Subjects

Subjects' enrollment was performed consecutively in a case-control study design from the outpatient clinics of the internal medicine department at King Abdulaziz University Hospital located in Jeddah, KSA. The Ethics Committee in KAUH approved the study protocol and all subjects gave informed consent to participate in the study. All subjects were screened through a detailed questionnaire, medical history and physical examination. The following exclusion criteria were used: 1) the known presence of diabetes mellitus type 2, hypertension, or hyperlipidemias; 2) a history of inflammatory, infectious, malignancy, thyroid, renal, or liver diseases; and 3) receiving treatment (e.g., aspirin, statins, diuretics, or β-blockers).

There were 83 patients diagnosed with metabolic syndrome based on clinical symptoms. The control group consisted of 83 apparently healthy participants matched by age and gender. The International Diabetes Federation (IDF) criteria [14] were used to classify the study subjects as being with or without metabolic syndrome on the basis of the presence or absence of central obesity (waist circumference ≥80 cm in women and ≥94cm in men) plus any 2 of the following factors: (1) elevated fasting triglycerides ≥150 mg/dl (1.7mmol/L), (2) reduced HDL cholesterol <50mg/dl (1.3mmol/L) in women and <40 mg/dl (1mmol/L) in men, (3) elevated blood pressure (systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg), and (4) elevated fasting glucose ≥110mg/dl (5.6mmol/L).

Anthropometric and Clinical Measurements

Height and weight were measured with participants wearing lightweight clothing without shoes (Seca 200, Hamburg, Germany). Body Mass Index (BMI) was calculated in Kg/m^2 as an estimate of overall adiposity. Waist circumference was measured to the nearest centimeter using a non-stretchable tailors' measuring tape at the midpoint between the bottom of the rib cage and above the top of the iliac crest during minimal respiration. Hip circumference was measured to the nearest centimeter as the largest girth below the waist. Waist Hip Ratio (WHR) is the ratio of the circumference of the waist to that of the hips.

Blood pressure was measured in the supine position on the right arm after a 10 min rest; a standard mercury sphygmomanometer of appropriate cuff size was used and the first and fifth phases were recorded. Values used in the analysis are the average of three readings taken at 5 min intervals.

Biochemical Tests

Venous blood samples were drawn from the forearm before coronary angiography with the use of standard venipuncture. Collected samples were immediately stored at -80°C until further use.

Fasting lipid profile and fasting blood glucose were determined by enzymatic colorimetric methods (Dimension Vista System, Siemens, Germany). Dextran-magnesium precipitation was used for HDL-C separation, while LDL-C was calculated using the Friedewald formula when serum triglyceride level is <4mmol/L [15].

Fasting insulin was measured by a chemiluminescence method (Modular E170 immunoassay analyzer, Roche, USA). To estimate insulin resistance, the HOMA index was calculated as fasting insulin concentration (μU/mL) × fasting glucose concentration (mmol/L)/22.5 [16]. Quantitative insulin sensitivity check index (QUICKI) was calculated by (QUICKI= 1/ [log (fasting insulin) + log (fasting glucose)] [17].

Serum high-sensitivity CRP was measured with the use of a latex-enhanced immunonephelometric assay by BN II analyzer (Siemens Healthcare Diagnostics, Deerfield, Ill). Serum chemerin was measured by enzyme-linked immunosorbent assay according to procedures recommended by the manufacturer (Calbiochem). Intra- and inter-assay coefficients of variation were between 5% and 10%.

Statistical Analysis

Results are reported as the mean ±standard deviation. Frequencies and proportions were reported for categorical variables. Data normality was analyzed using the Kolmogorov-Smirnov test. All not normally distributed parameters were logarithmic transformed for further analysis. The difference between subjects with and without metabolic syndrome was evaluated using Mann-Whitney test for continuous variables and $\chi 2$ for categorical variables. The associations between chemerin levels and the all measured parameters were examined by Pearson's and/or Spearman correlation coefficient analysis as appropriate. A stepwise multiple regression analysis was performed to assess which parameters were independently associated with chemerin. All analyses used a 5%, 2-sided significance level. SPSS 15.0 software was used for statistical analysis. (SPSS for Windows, SPSS, Chicago, Illinois, USA).

Results

A total of 166 subjects (48 men and 118 women), with a mean age of 57.2±0.6 years were included in this case control study.

Anthropometric measurements are outlines in Table 1. Although mean values of adiposity measures namely, BMI and WHR, showed non-significant difference between the groups but the prevalence of obesity was significantly higher among patients with metabolic syndrome as compared to the control subjects ($p<0.05$).

Table 1: Clinical characteristics of the study population

	Subjects without MetS (n=83)	**Subjects with MetS (n=83)**	***p***
SBP (mmHg)	130.6±2.1	138.9±2.5	<0.05
DBP (mmHg)	75.2±1.2	80.1±1.6	<0.05
Body weight (Kg)	78.9±2.0	84.2±2.1	<0.05
Body height (cm)	159.6±1.0	160.1±0.9	NS
BMI(Kg/m^2)	30.9±0.7	32.7±0.7	NS
BMI classes			
Normal (18.5-24.9) Overweight (25-29.9) Obese (≥30)	18(22) 25(30) 40(48)	8(10) 22(27) 53(64)	<0.05
Waist circumference (cm)	103.3±1.4	108.5±1.3	<0.05
Hip circumference (cm)	112.3±1.7	114.5±1.4	NS
WHR	0.92±0.0	0.95±0.0	NS

Data are given as the mean ± SD or as the number of subjects with percentages given in parentheses, as appropriate. Categorical data are compared by $\chi 2$ test, continuous variables are compared by Mann-Whitney U test. BMI: Body mass index, DBP: Diastolic blood pressure, NS: non-significant, SBP: Systolic blood pressure, WHR: waist-hip ratio.

Biochemical parameters are depicted in Table 2. As expected, all measures of insulin resistance show significant difference between both groups ($p<0.05$). Serum levels of chemerin and hs-CRP were significantly higher among subjects with metabolic syndrome versus their matched controls ($p<0.05$).

Table 2: Biochemical characteristics of the study population

	Subjects without MetS (n=83)	**Subjects with MetS (n=83)**	***p***
FBG (mmol/L)	6.14±0.19	7.94±0.28	<0.05
Fasting insulin (μU/ml)	14.9±1.44	16.6±1.45	NS
HOMA-IR	4.13±0.41	6.06±0.69	<0.05
HOMA-IS	145.7±16.3	92.58±8.14	<0.05
QUICK-I	0.33±0.0	0.31±0.0	<0.05
TC (mmol/L)	4.75±0.11	4.74±0.11	NS
TG (mmol/L)	1.23±0.06	1.90±0.08	<0.05
HDL-C (mmol/L)	1.40±0.03	1.10±0.03	<0.05
LDL-C (mmol/L)	2.77±0.09	2.91±0.09	NS
Chemerin (ng/ml)	361.1±12.6	400.3±12.4	<0.05

hs-CRP (mg/L)	0.65±0.06	0.74±0.06	<0.05

Data are given as the mean ± SD or as the number of subjects with percentages given in parentheses, as appropriate. Continuous variables are compared by Mann-Whitney U test. FBG: fasting blood glucose, HDL-C: high density lipoprotein cholesterol, HOMA-IR: Homeostasis model assessment insulin resistance index, HOMA-IS: homeostasis model assessment of β-cell insulin secretion, hs-CRP: high sensitivity-C reactive protein, LDL-C: low density lipoprotein cholesterol, NS: non-significant, QUICK-I: Quantitative insulin sensitivity check index, TC: total cholesterol, TG: triglycerides.

Table 3 summarizes correlation study between serum chemerin levels and other studied parameters. Additionally, positive correlation was shown between serum levels of hs-CRP and waist circumference (Figure 1). Serum hs-CRP levels also showed positive correlation with BMI values (Figure 2).

Table 3: Correlation analysis of serum chemerin levels with all studied parameters in the study participants. Significant correlations are shown in bold font.

	All (N=166)		**Subjects without MetS (n=83)**		**Subjects with MetS (n=83)**	
	r	***p***	**r**	***p***	**r**	***p***
Age (years)	**0.243**	**0.033**	0.208	0.059	0.156	0.158
SBP (mmHg)	0.058	0.461	**0.239**	**0.039**	-0.096	0.389
DBP (mmHg)	-0.080	0.314	**-0.225**	**0.045**	**-0.278**	**0.012**
hs-CRP (mg/L)	**0.235**	**0.003**	0.148	0.096	**0.255**	**0.02**
TG (mmol/L)	**0.173**	**0.031**	0.122	0.270	0.084	0.448
HOMA-IR	**-0.228**	**0.031**	-0.182	0.102	-0.213	0.054

DBP: Diastolic blood pressure, HOMA-IR: Homeostasis model assessment insulin resistance index, hs-CRP: high sensitivity-C reactive protein, SBP: Systolic blood pressure, TG: triglycerides.

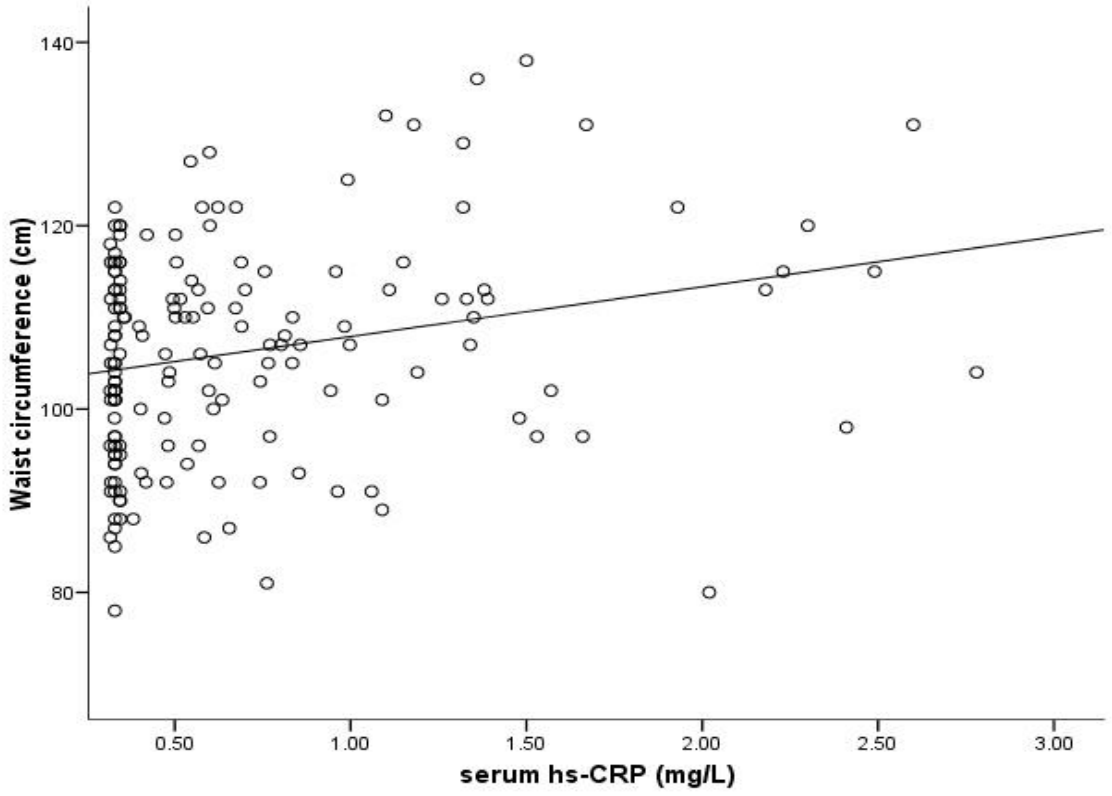

Figure 1: Scatter plot showing correlation between serum levels of high sensitivity-C reactive protein and waist circumference among the 166 study participants (r=0.218, p<0.01).

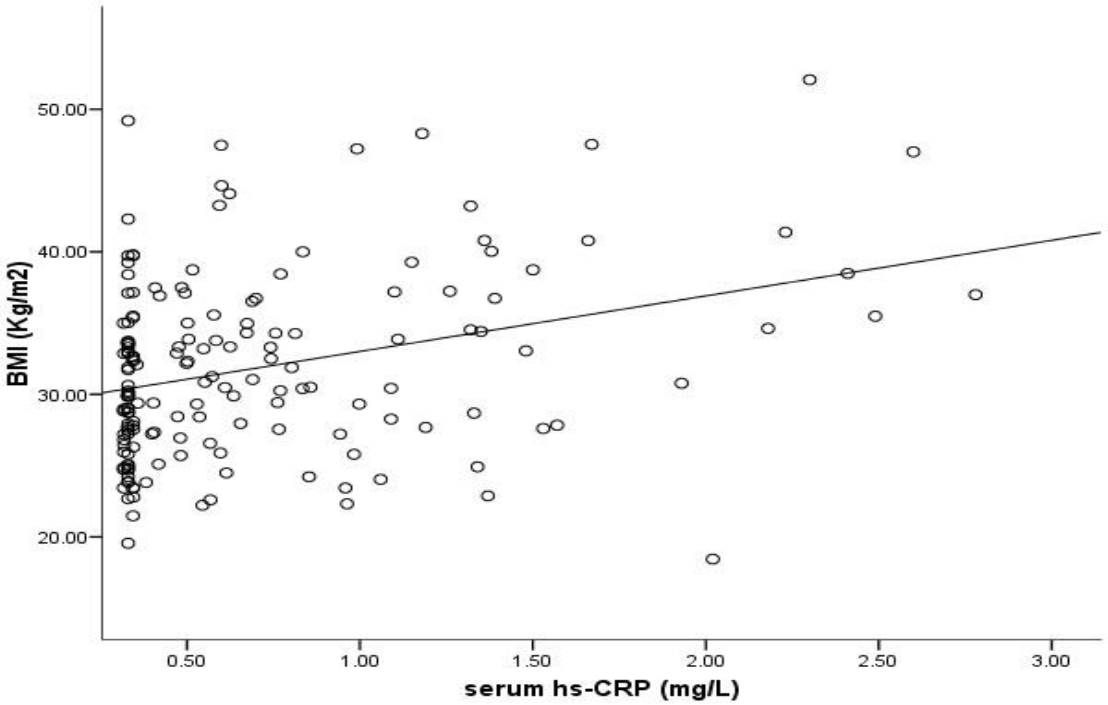

Figure 2: Scatter plot showing correlation between serum high sensitivity-C reactive protein levels and body mass index values among the 166 study participants (r= 0.320, p<0.0001)

After adjusting for SBP, DBP, and HOMA-IR, chemerin levels were independently associated with serum levels of TG and hs-CRP as shown in Table 4.

Table 4: Stepwise multiple regression analysis of serum chemerin level with all Variables with p value up to 0.1 entered into the model among the study population (N=166).

Independent variables	**β**	**95% CI limit of β**		***p***
Total R^2= 9.4%				
hs-CRP (mg/L)	0.216	27.1	154.5	0.005
TG (mmol/L)	0.164	1.94	48.6	0.034

95% CI: 95% confidence interval, hs-CRP: high sensitivity C reactive protein, TG: triglycerides

Discussion

Metabolic syndrome is known to be a constellation of abnormalities, including hypertension, hyperglycemia, hyperlipidemia, and abdominal obesity [1]. It is well established that visceral fat accumulation causes chronic low grade inflammation, which contributes to the initiation and progression of metabolic disorders [18]. This was clearly shown by positive associations between circulating levels of hs-CRP, as a low-grade inflammatory marker, with adiposity measures in the study population, namely BMI (r= 0.320, p<0.0001) and waist circumference (r=0.218, p<0.01).

Adipokine secretion and blood level is mostly affected by the degree of adiposity, leading to the hypothesis that dysregulation of pro-inflammatory and anti-inflammatory adipokines secretion in obesity may serve as a pathogenic link between obesity, insulin resistance and cardiovascular diseases [7, 8]. Elevated levels of chemerin were significantly associated with the presence of metabolic syndrome (Table 2).

It was demonstrated that blood concentration of chemerin is associated with the parameters of obesity and type II diabetes such as BMI, serum TG level, and blood pressure, implicating its roles in the pathogenesis of diabetes complications and metabolic syndrome [12, 19]. Univariate and multivariate analysis results indicated that high

chemerin levels were correlated with key metabolic syndrome markers such as blood pressure, insulin resistance, and serum TG (Tables 3 and 4).

These findings indicate that chemerin may be involved in the development and progression of metabolic syndrome. Predicting coronary risk in patients with metabolic syndrome at the early stages is important for targeting prevention strategies. Chemerin is clearly altered in patients with metabolic syndrome, but whether such alterations significantly increase cardiovascular risk remains unknown [20].

Previous studies have suggested that elevated serum chemerin levels are strongly related to inflammatory markers such as hs- CRP, IL-6, and TNF-α [21]. Similar results were found in the present study ($r=0.235$, $p<0.01$). Also, after adjustment for confounding variables, serum hs-CRP levels were an independent marker of serum chemerin concentrations ($\beta=0.216$, $p<0.01$, 95%CI: 27.1-154.5). This is in accordance with the hypothesis that increased chemerin and hs-CRP levels might predispose to increased coronary risk [7, 18, 22].

Potential limitations of this study design are worth consideration. The cross-sectional design of the current study requires further in long-term prospective studies before a causal relationship between chemerin and hs-CRP in metabolic syndrome patients can be established. Also, our sample size was relatively small. Therefore, our findings require more investigation in prospective studies with larger sample sizes.

Conclusion

In conclusion, this study showed that serum levels of chemerin and hs-CRP were elevated in patients with metabolic syndrome as compared with age and gender matched controls. Elevated serum hs-CRP and TG levels are suggested to be independent predictors of serum chemerin levels in patients with metabolic syndrome. However, its role in cardiovascular diseases needs to be fully elucidated.

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