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Original Article

Association of serum chemerin levels with the severity of coronary artery disease in patients with metabolic syndrome

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Abstract: Objectives: The newly identified adipokine chemerin has been shown to be associated with the components of MetS, inflammation and insulin resistance. In this study, the relationship between serum chemerin levels and the presence and severity of coronary artery disease (CAD) was evaluated in patients with MetS. Methods: The study population consisted of 84 MetS patients (43 patients with CAD and 41 without CAD), who had coronary angiography for suspected coronary artery disease, and 46 healthy individuals as a control group. Angiographic CAD was defined as ≥ 50% luminal diameter stenosis of at least one major epicardial coronary artery. The severity of CAD was determined by the Gensini score. Serum chemerin levels were measured with enzyme linked immunosorbent assay (ELISA). Results: Serum chemerin levels were significantly higher in patients with MetS (n=84) than those in the control group (120.47±25.32 vs. 90.4±11.4 ng/ml P < 0.001). In addition, MetS patients with CAD had higher chemerin levels than MetS patients without CAD (128.7±26.6 vs. 115.7±15.2 ng/ml, P < 0.001). Serum chemerin levels had a significant positive correlation with the Gensini score (r=0.58, P < 0.001). Multivariate logistic regression demonstrated that serum high-density lipoprotein cholesterol (HDL-C) and chemerin levels were significant and independent predictors for determining the presence of angiographic CAD (OR=1.009, 95% CI: 0.972-1.057; P=0.003 and OR=0.925, 95% CI: 0.896-0.922; P < 0.001, respectively). Conclusion: This study demonstrated that in patients with MetS, chemerin levels were higher in patients with CAD than patients without CAD and also showed a significant positive correlation with CAD severity.

Keywords: Chemerin, metabolic syndrome, coronary artery disease, Gensini score

Introduction

Metabolic syndrome (MetS) is characterized by multiple risk factors, which are related to cardiovascular diseases. Factors include abdominal obesity, insulin resistance, high triglyceride (TG) levels, high blood pressure, impaired glucose tolerance and low levels of high density lipoprotein (HDL-C). Patients with MetS are at risk for CAD and related morbidity and mortality [1, 2]. For this reason, they must be carefully evaluated with regard to CAD.

Adipose tissue is not merely a lipid store but also an endocrine organ that secretes cytokines and adipokines, such as leptin, adiponectin, tumor necrosis factor-alpha (TNF-α) and resistin [3-5]. Adipokines have several systemic effects on brain, liver, muscle, lymphoid organs and vasculature [6]. Adipokines affect the functions of endothelial cells, arterial smooth muscle cells and macrophages in the atherosclerotic process related to obesity [7-9]. Previous studies have demonstrated that adipokines released from adipose tissue play a significant role in the development of CAD in patients with MetS [10-13].

Chemerin is a newly discovered adipokine, which is released from liver and white fat tissue [14]. Chemerin also helps to regulate expression of adipocyte genes, such as glucose transporter-4, adiponectin and leptin, which play a role in the differentiation of adipocytes, and

Table 1. Baseline clinical characteristics

Variables	Controls (n=46)	MetS patients		*P* value
		Without CAD (n=41)	With CAD (n=43)	
Age (years)	52.6±9.1	53.7±9.2	53.1±9.5	0.792
Male sex n (%)	21 (46)	20 (49)	19 (45)	0.452
Smoking n (%)	25 (55)	22 (54)	24 (56)	0.243
Waist circumference (cm)	84.7±8.4	89.8±9.8[a]	90.1±10.5[a]	0.009
BMI (kg/m^2)	27.6±3.7	29.5±1.8[a]	30.9±1.5[a]	0.032
SBP (mmHg)	118.8±12.9	125.8±20.8[a]	133.2±19.4[a]	0.048
DBP (mmHg)	70.5±11.1	78.3±13.9[a]	82.7±12.5[a]	0.044
Fasting glucose (mg/dL)	91.12±10.4	107.54±12.43[a]	111.67±13.11[a]	0.009
TC (mg/dL)	172.1±28.1	174.2±39.2	181.6±38.4	0.377
TG (mg/dL)	150.9±56.1	166.2±72.3	178.1±137.7	0.527
LDL-C (mg/dL)	95.7±23.7	102.3±37.1	107.3±26.9	0.370
HDL-C (mg/dL)	38.1±10.2	37.8±7.1	35.1±10.2[a,b]	0.007
Chemerin (ng/ml)	90.4±11.4	115.7±15.2[a]	128.7±26.6[a,b]	< 0.001
Gensini score			34.41±11.9	
Cardiovacular medication				
Statins n (%)		12 (29)	14 (32)	0.342
ACEI/ARB n (%)		14 (34)	15 (35)	0.568

Abbreviations: CAD, coronary artery disease; MetS, metabolic syndrome; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; T, total cholesterol; TG, triglycerides; LDL-C, low-density cholesterol; HDL-C, high-density lipoprotein cholesterol; ACEI, anjiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker. Data are presented as means ± SD. [a]P < 0.017 compared with control subjects. [b]P < 0.017 compared with MetS patients without CAD.

also lipid and glucose metabolism [15]. Previous studies have demonstrated the relationship between chemerin and MetS components, insulin resistance and inflammation [16-18]. The relationship between chemerin levels and the development of coronary atherosclerosis in MetS patients has not yet been investigated.

The purpose of this study was to assess the relationship between chemerin levels and the presence and extent of CAD in patients with MetS.

Methods

Study population

Randomly selected patients, who underwent diagnostic coronary angiography (CAG) for suspected coronary artery disease (CAD) at Ondokuz Mayıs University Hospital between February 1, 2012 and March 1, 2014, were enrolled in this prospective study. Among the subjects, 84 had MetS [43 with CAD (19 men and 24 women; mean age 53.1±9.5 years) and 41 without CAD (20 men and 21 women; mean age 53.7±9.2 years)], and 46 were healthy (21 men and 25 women; mean age 52.6±9.1 years).

All subjects were classified according to the modified National Cholesterol Education Program (NCEP) criteria for MetS (19) and were diagnosed as MetS patients if three or more of the following criteria were met: (1) waist circumference (WC) over 90 cm in men and over 80 cm in women, (2) systolic blood pressure ≥ 130 mmHg or diastolic pressure ≥ 85 mmHg, (3) triglyceride ≥ 150 mg/dl, (4) HDL-C < 40 mg/dl for men and < 50 mg/dl for women, and (5) fasting glucose ≥ 110 mg/dl.

Patients with acute coronary syndrome (ACS), diabetes mellitus, previously documented CAD, suspected myocarditis or pericarditis, advanced renal and liver disease, known malignant disease, systemic inflammatory disease or autoimmune disease were excluded. This study was approved by the institutional ethics committee, and informed consents were obtained from all the participants.

Coronary angiography analysis

All of the patients had coronary angiography using the Judkins technique with a femoral approach. Images were stored in a digital angiographic system (ACOM.PC; Siemens AG, Germany) and collected at a rate of 15 frame/s. Iopromide was used as a contrast agent (Ultravist 370, Schering AG, Berlin Germany). Recordings were analyzed by two independent

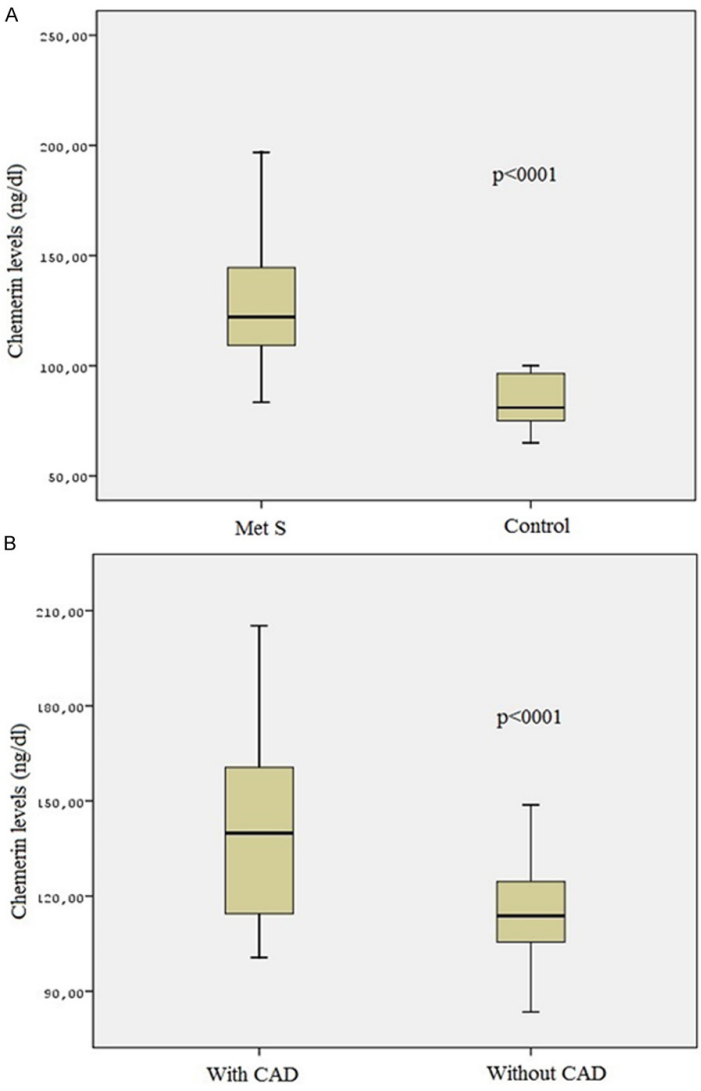

Figure 1. A: The levels of chemerin in the metabolic syndrome and the control group. B: The levels of chemerin in the metabolic syndrome patients with CAD and without CAD.

cardiologists, and angiographic CAD was defined as ≥ 50% luminal diameter stenosis of at least one major epicardial coronary artery. The severity of CAD was determined using the Gensini score, which is a measure of the extent of coronary stenosis according to degree and location. In the Gensini scoring system, larger segments are more heavily weighted with scores ranging from 0.5 to 5.0. The narrowing of the coronary artery lumen is rated 2 for 0% to 25% stenosis, 4 for 26% to 50%, 8 for 51% to 75%, 16 for 76% to 90%, 32 for 91% to 99%, and 64 for 100%. The Gensini index is the sum of the total weights for each segment [20].

Standard echocardiography

Echocardiographic examinations were done while patients were lying in the left lateral decubitus position using a GE Vingmed Vivid 7 (GE Vingmed Ultrasound, Horten, Norway) by an experienced cardiologist. Parasternal long axis, short axis, apical four chamber and two chamber views were obtained and measured with M-Mode, 2-D and continuous wave Doppler and pulsed wave Doppler. Measurements were performed according to recommendations by the American Society of Echocardiography [21]. Values were measured on three separate beats and then averaged for all parameters.

Biochemical measurements

Anthropometric (height, weight and blood pressures), clinical and laboratory analyses were performed. Peripheral venous blood samples were collected, after a 12-h fasting period, from all the subjects. Biochemical parameters were measured using an Abbott ARCHITECT c8000 (Abbott Laboratories, USA) auto-analyzer with commercial kits. Hematologic parameters were obtained using an Abbott CellDyn 3700 (Abbott Laboratories, USA) device with laser and impedance methods. Serum chemerin levels were measured using a Human Chemerin (CHEMERIN) ELISA kit (Hangzhou Eastbiopharm Co. Hangzou, CHINA), a Multiwash (Tri-Continent Scientific, USA) microplate washer and Synergy 4 Microplate Reader (Biotek, USA), according to standard procedures. Standard curves were generated using a four-parameter curve fitting equation, and chemerin levels were calculated according to this curve, with values given as ng/ml.

Statistical analysis

Statistical analyses were based on the SPSS 15.0 (Statistical Package for Social Sciences) program. The Kolmogorov-Smirnov test was used to check normal distribution of all parameters. Categorical variables were expressed in

Table 2. Correlation analyses between serum chemerin levels and various parameters in metabolic syndrome patients with coronary artery disease

Variables	r value	*P* value
Age	0.05	0.634
Sex (Male)	0.11	0.108
BMI	0.32	< 0.001
SBP	0.29	0.015
DBP	0.08	0.322
Fasting glucose	0.22	0.012
TG	0.21	0.042
TC	0.05	0.522
HDL	-0.35	< 0.001
LDL	0.07	0.436
Gensini score	0.58	< 0.001

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density cholesterol.

percentage, whereas numerical variables were presented as mean values ± standard deviation (SD). For statistical analysis, the background data were analyzed by the Kruskal-Wallis Test and the chi-square test to examine the overall balance among the three groups. If the Kruskal-Wallis test was statistically significant, the Wilcoxon rank-sum test was performed to assess which differences were significant. Multivariate logistic-regression analysis was also performed and the model included potential confounders (age, sex, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), HDL-C, fasting glucose, and chemerin) for CAD. Inclusion of variables into final models was based on both clinical and statistical considerations. A value of $P < 0.05$ was considered significant. We employed a Bonferroni approach for assessing the significance of group differences and declared a significant difference between control and MetS groups only when the associated *P*-value was less 0.017.

Results

Baseline clinical characteristics

Basal and laboratory findings of the patients are shown in **Table 1**. Patients with MetS had significantly higher waist circumference, BMI, SBP, DBP and fasting blood glucose, levels than those of the control group ($P < 0.017$). At the same time, HDL-C levels were significantly lower in MetS patients who had CAD than those of the control group and MetS patients who did not have CAD ($P < 0.017$). No significant differences were found regarding statin, angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) usage in MetS patients, regardless of their CAD status.

Serum chemerin levels

Serum chemerin levels were significantly higher in MetS patients (n=84) than those in the control group (120.47±25.32 vs. 90.4±11.4 ng/ml, $P < 0.001$, **Figure 1A**). In addition, MetS patients with CAD had higher chemerin levels compared to patients without CAD (128.7±26.6 vs. 115.7±15.2 ng/ml, $P < 0.001$, **Figure 1B**).

Association of serum chemerin levels with clinical characteristics and angiographic risk score

Chemerin levels in MetS patients showed a significant positive correlation with BMI, SBP, serum TG levels, fasting blood glucose and showed a significant negative correlation with HDL-C levels (**Table 2**). Moreover, chemerin levels had a significant positive correlation with the Gensini score ($r=0.58$, $P < 0.001$, **Figure 2**).

Association of serum chemerin levels with CAD in MetS patients

In MetS patients, simple logistic regression analysis revealed that HDL-C (OR=1.114, 95% CI: 1.031-1.203, P=0.006), BMI (OR=0.750, 95% CI: 0.554-1.015, P=0.034) and serum chemerin levels (OR=0.941, 95% CI: 0.906-0.976; $P < 0.001$) were associated with the presence of angiographic CAD ($P < 0.05$, **Table 3**). These variables were then entered into a backward, stepwise, multivariate logistic regression model. Multivariate logistic regression demonstrated that serum HDL-C and chemerin levels were significant and independent predictors for determining the presence of angiographic CAD (OR=1.009, 95% CI: 0.972-1.057, P=0.003 and OR=0.925, 95% CI: 0.896-0.922; $P < 0.001$, respectively, **Table 3**).

Discussion

Results from our study demonstrated that in MetS patients, chemerin levels were higher in patients with CAD than those in patients with-

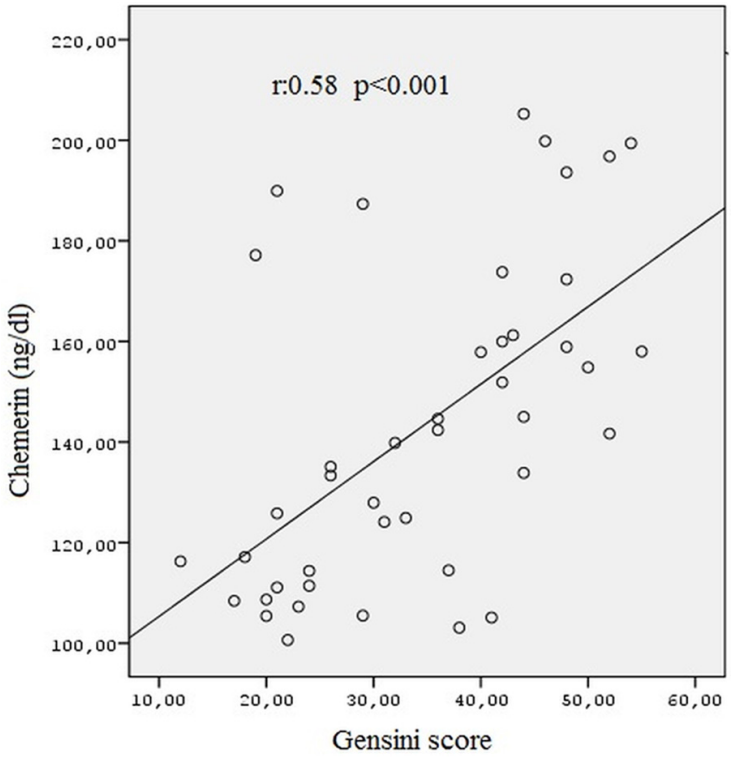

Figure 2. The correlation analysis of chemerin levels and Gensini score.

out CAD and showed a significant positive correlation with CAD severity.

Metabolic syndrome patients have a higher risk for the development of cardiovascular diseases and related mortality than that of the general population [2]. Adipokines released from adipose tissue and related to inflammation in obesity have been previously demonstrated to play a role in the pathogenesis of CAD in metabolic syndrome patients [10-13].

Previous studies have demonstrated that chemerin, a newly identified adipokine, is related to glucose and lipid metabolism, insulin resistance, and inflammation [15-18, 22]. Studies also reported that serum chemerin levels are increased in MetS patients and correlate with components of MetS [23, 24]. The correlation of chemerin with inflammation and MetS components, which are also CAD risk factors, led us to determine the relationship between chemerin levels and development of coronary atherosclerosis.

Studies that have attempted to determine the relationship between chemerin levels and development of coronary atherosclerosis have provided conflicting results. Two studies have demonstrated that chemerin levels were significantly higher in Chinese individuals with CAD than those in a Chinese control group [25, 26]. In addition, Dong *et al.* [24] reported that chemerin levels were higher in MetS patients who had CAD than those in MetS patients who did not have CAD. In another study, which enrolled 131 Korean patients, serum chemerin levels were found to have a significant correlation with cardiometabolic parameters and percentage of coronary artery narrowing [27]. In our study, we also found that serum chemerin levels were higher in MetS patients who had CAD than those in MetS patients who did not have CAD. On the other hand, Lehrke *et al.* [17] demonstrated no relationship between serum chemerin levels and coronary atherosclerosis development when comparing the extent of coronary atherosclerosis using multi-slice CT angiography in 303 Caucasian patients and adjusting for other cardiovascular risk factors. Several reasons can explain the conflicting results, such as the use of multi-slice CT angiography to evaluate coronary atherosclerosis index and enrollment of patient populations with different ethical backgrounds and basal characteristics. Variability could also arise when measuring total chemerin levels, because chemerin ELISA kits can detect prochemerin as well as some proteolytically processed short forms of chemerin in their study. In addition, the adipokine chemerin may play a role in the pathogenesis of CAD in MetS patients.

Chemerin is accepted as a chemokine that plays a role in the inflammatory process, induces leukocyte migration and modulates chemotaxis and activation of macrophages and dendritic cells [22]. Strong correlations between atherosclerosis and inflammation are well known and led to the evaluation of the contribution of chemerin to the atherosclerotic process. In a study done by Kostopoulos *et al.* [28] in which the correlation between chemerin and the development of atherosclerotic lesion was

Table 3. Logistic regression analysis for the presence of CAD in patients with MetS (n=84)

	Univariate Logistic Regression			Multivarite Logistic Regression Analysis		
	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
Age (years)	0.979	0.915-1.048	0.538			
Sex (Male)	5.260	0.812-34.077	0.482			
BMI (kg/m^2)	0.750	0.554-1.015	0.034	0.718	0.512-1.003	0.056
SBP (mm Hg)	1.095	1.011-1.186	0.266			
DBP (mm Hg)	0.866	0.788-0.996	0.431			
TG (mg/dL)	1.002	0.994-1.011	0.594			
TC (mg/dL)	0.985	0.946-1.025	0.465			
LDL-C (mg/dL)	1.009	0.969-1.051	0.594			
HDL-C (mg/dL)	1.114	1.031-1.203	0.006	1.009	0.972-1.057	0.003
Fasting glucose (mg/dL)	0.991	0.982-1.000	0.057			
Chemerin (ng/ml)	0.941	0.906-0.976	< 0.001	0.925	0.896-0.922	< 0.001

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; LDL-C, low-density cholesterol; HDL-C, high-density lipoprotein cholesterol.

evaluated, chemerin levels were found to be high in atherosclerotic lesions, periadventitial adipose tissue, foam cells and vascular smooth muscle cells (VSMC). Moreover, a significant correlation was found between the severity of the atherosclerotic lesion and chemerin levels released from cells within the lesions. Likewise, Spiroglou *et al*. [29] confirmed the correlation between epicardial chemerin levels and coronary atherosclerosis. In a study done by Hart *et al.* [30], chemerin was shown to stimulate the adhesion of macrophages to extracellular matrix protein fibronectin and vascular cell adhesion molecule 1 (VCAM-1). This process was proposed to contribute to the progression of atherosclerosis. In addition, previous studies have demonstrated that chemerin activates MMP-2 and MMP-9 that belong to the matrix metalloproteinase (MMP) class which plays a key role in plaque instability [31] and induce the expression of adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and E-selectin [32]. Also it was hypothesized that chemerin could be a new biomarker for coronary atherosclerosis [25]. In light of this information, a significant correlation can be assumed between chemerin, which plays a role in the inflammatory response during the atherosclerotic process, and the Gensini score. This may be related to intensive plaque burden, possibly reflecting the intensive inflammatory process. Accordingly, the increased Gensini score in our study may be related to an intensive inflammatory state. To our knowledge, our study is the first one that demonstrates the correlation between chemerin levels and extent of CAD.

Bozaoğlu *et al.* [18, 33] have demonstrated that serum chemerin levels are higher in MetS patients than those in the control group and showed a significant correlation between chemerin levels and BMI, blood pressure, fasting blood glucose, and TG and HDL-C levels in different patient populations. Similarly, in our study, chemerin levels were higher in MetS patients than those in the control group and showed a significant positive correlation with BMI, SBP, serum TG levels, fasting blood glucose and significant negative correlation with HDL-C levels. It can be proposed that chemerin, which has a significant correlation with MetS components that contribute to the atherosclerotic process, may play a role MetS-related atherosclerosis.

Study limitations

The main limitation of our study is the low number of the patients. It is also incapable, up to certain extent, to explain the effect of the chemerin on clinical events and plaque stability. Further studies are needed in order to explicate the role of chemerin in the atherosclerotic process.

Conclusion

Results from our study have demonstrated that in MetS patients, chemerin levels were higher in the subjects with CAD than those in without

CAD and showed a significant positive correlation with CAD severity. Chemerin could be used as a biomarker to identify high risk patients, such as MetS or diabetic patients, who could develop atherosclerotic heart disease. Because serum chemerin levels also correlate with the extent of the disease, it may also be helpful in guiding the treatment strategy.

Disclosure of conflict of interest

None.

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