Serum Chemerin and Adiponectin Levels in Metabolic Syndrome Patients with or without Coronary Artery Diseases

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Abstract: Objective :Obesity and metabolic syndrome (MS) are considered chronic inflammatory condition. Patients with metabolic syndrome are at high risk for developing atherosclerosis and cardiovascular diseases (CVD). Serum levels of chemerin have been found to be elevated in patients with MS and are associated with several risk factors for CVD. Hypoadiponectinemia are found in obese individuals and have been associated with increases incidence of MS and developing of CVD . We studied the adipokines – chemerin and adiponectin serum levels in MS subjects with or without coronary artery diseases (CAD). **Patients and Methods**:The current study included 64 subjects with MS diagnosed according to International Diabetes Federation (IDF) criteria (24 patients with coronary artery disease, CAD and 40 patients without CAD) and 36 healthy age and sex matched subjects as controls. Patients with MS underwent coronary angiography for evaluation of CAD. Body mass index (BMI), fasting plasma glucose, fasting serum insulin, triglyceride, LDL, HDL, highly sensitive C-reactive protein, chemerin and adiponectin were measured for all participants . **Results** :MS patients had higher serum chemerin and lower serum adiponectin levels compared with healthy subjects. Level of serum chemerin was significantly elevated in MS patients with CAD compared with those without CAD and healthy controls. Furthermore, MS patients without CAD also showed higher levels of serum chemerin than did healthy subjects. Serum chemerin was positively while adiponectin was negatively associated with BMI, and all parameters of MS except HDL, HOMA-IS where the pattern reversed. **Conclusions** :Among apparent healthy adults, individuals with high chemerin levels coupled with low circulating adiponectin are at a significantly increased risk of dyslipidemia , metabolic syndrome and coronary artery diseases.
[Abdelhaleem A.A. and Alsayed M. Alsalamony **Serum Chemerin and Adiponectin Levels in Metabolic Syndrome Patients with or without Coronary Artery Diseases.** Journal of American Science 2012;8(9):387-394]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 56

Keywords: Chemerin, Adiponectin, Metabolic Syndrome, Coronary Artery Diseases.

1. Introduction

Obesity, the most common nutritional disorder, has reached epidemic proportions worldwide, particularly in the highly industrialized Western societies (1). Obese individuals are at increased risk for hypertension, dyslipidemia, cardiovascular disease, and type 2 diabetes [2– 4]. Insulin resistance is a major factor underlying the adverse metabolic consequences of obesity [5, 6].

Metabolic syndrome (MS) is a clustering of cardiovascular risk factors such as abdominal obesity, insulin resistance, elevated plasma triglyceride (TG) levels, low high density lipoprotein cholesterol (HDL-c) levels, high blood pressure and altered glucose homeostasis [7]. Obesity and metabolic syndrome (MS) are considered to be chronic inflammatory states in which macrophages accumulate in adipose tissue and secrete inflammatory cytokines. The adipokines are shifted towards the proinflammatory spectrum in obesity, and these hormonal changes may be used as early markers of energy metabolism [8].

Persons with metabolic syndrome have at least a 5-fold increase in risk for type 2 diabetes compared with those without. Once a patient develops type 2 diabetes, risk for CVD is enhanced [9]. Not only is relative risk for coronary artery disease (CAD) raised by 2- to 3-fold, but once CAD becomes manifest in a patient with diabetes, the prognosis for survival is greatly reduced [10]. Follow-up of CAD patients with MS reveals that these patients are at increased risk of cardiovascular morbidity [11]. Therefore, the early risk assessment of CAD in MS patients and the development of strategies for preventing CAD are important.

In addition to an important energy storage function, adipose tissue serves as an active endocrine organ that secretes a number of hormone-like compounds, adipokines [12].

Chemerin is a novel adipokine, that highly expressed in liver and adipose tissue, is secreted as an 18-kDa inactive proprotein that can be rapidly converted by C-terminal proteolytic cleavage into its active 16-kDa form, which is found in plasma, serum, and hemofiltrate [13]. Chemerin serum level is associated with the degree of adiposity, insulin resistance and MS risk factors [14]. Clinical studies have demonstrated that serum chemerin levels are

elevated in obese patients compared with healthy individuals [15]. Recent studies have associated chemerin with several inflammatory markers in obesity and type-2 diabetes [16,17]. Thus, chemerin is considered a candidate in linking inflammation to obesity-related diseases. A strong relationship between chemerin and key parameters of MS has been reported [18].

Adiponectin is an adipokine, produced almost exclusively in adipose tissue and is expressed at high levels by lean, healthy individuals. It exerts anti-inflammatory properties directly affecting the vasculature [19]. An anti-atherogenic role of adiponectin was supposed by the ability to modulate the expression of endothelial adhesion molecules [20] and to influence key mechanisms of atherogenesis via an adventitia-AMPK iNOS pathway [21].

In obese subjects, adiponectin levels are decreased, and the ability of adiponectin to inhibit the inflammatory processes is limited. Low adiponectin levels are inversely related to high levels of C-reactive protein (CRP) in patients with obesity, type 2 diabetes, and CAD [22]. Hypoadiponectinemia is associated with CAD [23]. Moreover, adiponectin plasma levels correlate with various atherosclerotic risk factors, such as low-density lipoproteins and triglycerides [24].

Therefore, it has been proposed that chemerin and adiponectin contribute to the pathology of insulin resistance, metabolic syndrome and CAD. The present study was undertaken to determine the association of serum chemerin and adiponectin with the presence or absence of CAD in MS patients.

2. Material and Methods

The current study was conducted from May 2010 to November 2011 in Diabetic Center, Al Noor Specialist Hospital (Tertiary Hospital), holy Makkah, Saudi Arabia, and was approved by the ethics committee of Al Noor Specialist Hospital. all subjects gave written informed consent.

The study included 64 subjects with MS (35 males and 29 females), their ages were ranged from 35 to 70 years. They were divided into two groups according to the presence or absence of coronary artery disease (CAD)

A) Group-I included 24 MS patients with CAD (14 males and 10 females).
B) Group-II included 40 MS patients without CAD (21 males and 19 females).

They were screened for the presence of MS according to International Diabetes Federation (IDF) [25] criteria as follows: *central obesity* (waist circumference - males >90 cm, females >80 cm) plus any two of the following: *raised triglycerides* (>150 mg/dl), *reduced HDL-C* (<40 mg/dl in men and <50 mg/dl in women), *raised blood pressure* (systolic ≥130 mm Hg or diastolic ≥85 mm Hg), *raised fasting plasma glucose (FPG)* (≥100 mg/dl).

Coronary angiography was conducted and films were separately reviewed by two cardiologists and if they agreed about more than 50% stenosis of at least one vessel, subjects were considered as patients with CAD.

The control group, consisted of 36 age- and sex-matched healthy subjects, who had none of the 5 criteria of MS described above and no history of obesity, dyslipidemia, hypertension and diabetes mellitus. They have never been diagnosed with diabetes mellitus, impaired glucose tolerance or any other systemic diseases.

Exclusion criteria

Chronic renal failure, chronic or acute hepatitis, malignant disease, active inflammatory disease , pregnant women, Patients with acute coronary syndromes, previously documented CAD, suspected myocarditis or pericarditis, congenital and valvular heart disease and also those with the history of myocardial infarction, heart failure .endocrine diseases, infectious diseases, alcoholism.

Anthropometric measures like weight, height and blood pressure were taken. Body mass index (BMI) was calculated as weight in kilogram divided by square of height in meters. Venous blood was collected after overnight fasting for estimation of FPG, renal and hepatic parameters, HbA1c, lipid profile, and high sensitive C-reactive protein (hs-CRP) were tested using an auto biochemistry instrument (Hitachi 7170, Tokyo, Japan). One aliquot of the sample was frozen at −80°C for the measurement of serum insulin, adiponectin and chemerin.

Fasting serum insulin was measured by Electro-chemiluminescence method using Cobas e 601 module (Roche Diagnostics R&D, USA).

The HOMA model was used to calculate insulin resistance and insulin secretion. The formulae are as follows:

Insulin resistance = $\frac{FI \times G}{20 \times FI}$ Insulin secretion = $\frac{22.5}{G - 3.5}$

where FI = fasting insulin in µIU/ml and G = fasting glucose in mmol/l.

Serum Chemerin levels were determined using a commercially available Human Chemerin ELISA, Biotin-labelled antibody Kits (Cat. No.: RD 1911-36200R, manufactured by BioVendor R&D–Laboratorní medicína a.s**.**) as the manufacturer's instructions. The inter-assay coefficient of variation was 7.6 %, and the within-assay coefficient of variation was less than 6.0%. The lowest detectable concentration of human chemerin was 0.1 ng/ml.

Serum Adiponectin was measured with AviBion Human Adiponectin ELISA commercial kits (supplied by Orgenium Laboratories Business Unit, Finland) as manufacturer's instructions. The assay range of 0.185-15 ng/ml and a sensitivity of <0.3 ng/ml. Intra-assay precision was ≤10% and inter-assay precision was ≤12%.

Statistical analysis was carried out using Graphpad Prism-5 (*San Diego, California*; USA). Data were presented as mean ± SD. All parametric data were analyzed by Student's *t*-test. Pearson correlation coefficients were used to ascertain the association between various parameters. A *P*-value of <0.05 was considered statistically significant.

3. Result

Sixty-four subjects aged 35-70 years were recruited in the present study, thirty five of them were males (54.7%). Mean age of the study population was 50.5 ± 7.0. Table 1 shows the basic characteristics of the study population.

MS subjects showed higher levels of BMI, systolic blood pressure (SBP), fasting plasma glucose (FPG), fasting serum insulin (FSI), HOMA-IR, serum TG , LDL-c, and CRP as well as lowered HDL-c levels and HOMA-IS levels than did controls. There were no significant differences in age, and DBP levels between the two groups.

There were significantly higher levels of BMI, TG, LDL, hs-CRP in the MS patients with CAD compared with those without CAD. There was a significantly lower level of HDL in the MS patients with CAD compared with those without CAD. There were no significant differences of HOMA-IR between the two groups of MS patients (Table-1).

The current study demonstrated that MS patients had higher serum chemerin levels compared with healthy subjects. Moreover, levels of serum chemerin were significantly elevated in MS patients with CAD compared with those without CAD and healthy controls. Furthermore, MS patients without CAD also showed higher levels of serum chemerin than healthy controls . Subjects with MS had significantly lower adiponectin levels than controls. MS patients with CAD had a non-significant higher adiponectin levels compared with those without CAD (Table 1).

Serum chemerin was positively correlated with BMI, SBP, FPG, FSI, HOMA-IR, serum TG , LDL and hs-CRP while it was negatively correlated with HOMA-IS, HDL, and serum adiponectin. Also, Serum adiponectin was negatively correlated with BMI, SBP, FPG, FSI, HOMA-IR, serum TG , LDL and hs-CRP while it was positively correlated with HOMA-IS, and HDL (Table-2).

Table-1. Clinical and Biochemical Characteristics of MS Patients with or without CAD and Healthy Controls

	Control	MS patients	
		Without CAD	With CAD
N	36	40	24
Age (years)	48.7 + 11.8	50.5 ± 8.9	49.6 ± 9.9
BMI (kg/m^2)	21.9 ± 1.83	32.7 ±2.5 a	35.6 ± 3 a,b
SBP (mmHg)	124.62 ± 15.27	140.98 ± 11.19 a	142.92 ± 13.75 a
DBP (mmHg)	82.62 ± 11.40	82.35 ± 9.64	83.47 ± 12.82
FPG (mg/dL)	81.8 ± 6.9	144.0 ± 16.5 a	145.0 ± 17.4 a
HbA1c (%)	5.0 ± 0.3	7.9 ± 0.9 a	8.1 ± 0.7 a
FSI (uIU/mL)	14.6 ± 2.6	19.2 ± 2.5 a	20.9 ± 2.8 a
HOMA-IR	1.52 ± 0.28	2.4 ± 0.24 a	2.5 ± 0.27 a
HOMA-IS	129.2 + 42	64.4 + 27 a	65.0 + 28 a
TG (mg/dL)	91.9 ± 20	196.0 ± 26 a	258.0 ± 44 a,b
HDL-C (mg/dL)	54.5 + 5.5	35.0 + 4.0 a	31.8 + 7.0 a,b
LDL-C (mg/dL)	102 + 13	130 + 25 a	158 + 33 a,b
hs-CRP (mg/L)	1.76 ± 0.435	2.57 ± 0.37 a	3.28 ± 0.57 a,b
Chemerin (µg/L)	94.06 ± 27.7	111.03 ± 21.3 a	137.04 ± 18.6 a,b
Adiponectin (µg/ml)	8.85 ± 0.98	4.84 ± 1.33 a	5.38 + 1.44 a

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; FSI, fasting serum insulin ; HOMA-IR, homeostasis model assessment of insulin

resistance; HOMA-IS, homeostasis model assessment of insulin secretion ; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hs-CRP, highly sensitive C-reactive protein.
Data are presented as means ± SD.
a significant versus control group
b significant versus MS without CAD group

Table-2. Pearson correlation coefficients between parameters

	AGE	BMI	FPG	FSI	HOMA-IR	HOMA-IS	TG.	LDL	HDL	hs-CRP	CHEM.
BMI	0.031										
FPG	0.007	0.872*									
FSI	0.101	0.705*	0.698*								
HOMA-IR	0.064	0.816*	0.819*	0.656*							
HOMA-IS	-0.067	-0.592*	-0.604*	-0.491*	-0.603*						
TG	-0.022	0.889*	0.746*	0.610*	0.750*	-0.586*					
LDL-C	-0.003	0.785*	0.631*	0.548*	0.576*	-0.366*	0.729*				
HDL-C	0.010	-0.879*	-0.832*	-0.685*	-0.719*	0.578*	-0.816*	-0.712*			
hs-CRP	0.108	0.827*	0.720*	0.585*	0.694*	-0.445*	0.799*	0.754*	-0.715*		
CHEM.	0.123	0.656*	0.515*	0.503*	0.486*	-0.278*	0.561*	0.690*	-0.493*	0.706*	
ADIPO.	0.034	-0.885*	-0.821*	-0.572*	-0.726*	0.495*	-0.709*	-0.660*	0.803*	-0.702*	-0.544*

BMI, body mass index; FPG, fasting plasma glucose ; FSI, fasting serum insulin ; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-IS, homeostasis model assessment of insulin secretion; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol ; HDL-C, high-density lipoprotein cholesterol; hs-CRP, highly sensitive C-reactive protein; CHEM, chemerin ; ADIPO., adiponectin.
* There is a significant correlation (P<0.05)

4. Discussion

Obesity and metabolic syndrome (MS) are considered to be chronic inflammatory states in which macrophages accumulate in adipose tissue and secrete inflammatory cytokines. Adipocytes synthesize pro-inflammatory, pro-atherogenic molecules like IL-6 and mononocyte chemoattractant protein-1 (MCP-1), and also potentially anti-inflammatory, antiatherogenic proteins such as adiponectin. Adipokines are shifted towards the proinflammatory spectrum in obesity [8]. Chemerin is a novel adipokine, that highly expressed in liver and adipose tissue. The present study demonstrated that MS patients had higher serum chemerin levels compared with healthy subjects with agreement of Stejskal and his coworkers [18]. These findings indicate that chemerin may be involved in the development and progression of MS. Chemerin is clearly altered in patients with MS, but whether such alterations significantly increase cardio-vascular risk remains unknown.

The current study, also, revealed that MS patients with CAD had significantly higher serum chemerin levels than those without CAD. This result, however, is contradicted by another study in which no correlation of chemerin levels with the presence of coronary atherosclerotic plaques was found [26]. A possible explanation for the present results is that elevated chemerin levels may be a consequence of impaired cardiovascular function in patients with MS. Chemerin may play a role in the pathogenesis of CAD in MS patients. However, future investigations will be needed to explain the exact role of chemerin in the presence of CAD.

Serum chemerin levels were positively correlated with key MS markers such as elevated levels of BMI, FPG, FSI, HOMA-IR, serum TG, LDL and blood pressure. This is consistent with other studies that also reported a significant association of serum chemerin levels with multiple compounding factors of MS [27,28]. These findings indicate that chemerin may play an important role in the mechanism of MS and might be a potential independent adipocytokine marker of MS.

A growing body of evidence supports the idea that inflammation is involved in the initiation and progression of CAD [29,30]. Previous studies have suggested that elevated serum chemerin levels were strongly related to inflammatory markers such as high sensitivity CRP [26,31], similar results were found in the present study.

Adiponectin is a cytokine, “adipokine”, produced almost exclusively in adipose tissue and is expressed at high levels by lean, healthy individuals. However, it has been reported that in pathological conditions such as coronary artery disease (CAD), diabetes mellitus, and hypertension that adiponectin levels decline [23,32,33]. Moreover, adiponectin plasma levels correlate with various atherosclerotic risk factors, such as low-density lipoproteins [24].

Obesity-related hypoadiponectinemia might also contribute to impaired endothelial function, increased vascular ROS production and overall proatherogenic effects [34]. Finally, increased release of proinflammatory cytokines by adipose tissues, including IL-6, IL-1, and TNF-α, sustains vascular wall inflammation and promotes pro-atherogenic gene expression [35].Therefore, it is generally believed that by acting as an anti-inflammatory, antioxidant and vasodilator agent, adiponectin prevents endothelial dysfunction and the progression of atherosclerosis.

In the current study, subjects with MS had significantly lower adiponectin levels than controls; moreover, MS patients with CAD had non-significant higher adiponectin levels compared with those without CAD. Low adiponectin levels have been reported in most of the studies on MS among people of various age groups, ethnicity and gender [36-43]. This result, however, is in agreement with the study of Antonopoulos and his coworkers [44], who found that serum adiponectin was higher in CAD compared to healthy individuals. However, one study reported higher adiponectin levels in MS [45] and another found low adiponectin level which was statistically not significant [46].

Serum adiponectin levels were negatively correlated with BMI, FPG, hypertension, TG, LDL, hsCRP, and HOMA-IR and positively related to HDL and HOMA-S in the present study. Similar associations have been reported in many literatures [47-52). In our study, adiponectin showed negative correlation with fasting insulin levels, as also observed by two studies [48,53], whereas in one study from South India there were no relation between serum adiponectin levels and fasting insulin level [54]. Vikram *et al*., [55] did not observe any relation between adiponectin and hsCRP in Indian adolescents.

In conclusion, this study showed that serum chemerin were elevated in metabolic syndrome patients with CAD compared with those without CAD. Elevated serum chemerin levels are suggested to be an independent predictive markers of the presence of CAD in patients with MS. And some therapy targeted for chemerin may reduce the incidence of CAD and mortality in MS patients Thus, among apparently healthy adults, individuals with high chemerin levels coupled with low circulating adiponectin are at a significantly increased risk of dyslipidemia, metabolic syndrome and coronary artery diseases.

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