

Serum HMW Adiponectin is a Better than Chemerin Biomarker of Insulin Resistance and Metabolic Syndrome in Overweight and Obese Patients

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Abstract

Objective: Disturbances induced by obesity in the secretion of adipokines have an influence on the development of metabolic complications such as insulin resistance and inflammation. Recently, chemerin was suggested to be an independent biomarker of the metabolic syndrome. So, the aim of this study was to compare chemerin and other cytokine levels between healthy normal-weight people and people with high BMI, and also with metabolic syndrome.

Materials and Methods: 55 adult patients with BMI ≥ 25 kg/m² (among them 38 with metabolic syndrome) and 23 healthy controls with normal BMI without MS were studied. All individuals underwent anthropometrical examination (body composition) and biochemical analysis such as: concentrations of glucose, insulin, chemerin, HMW adiponectin, leptin, TNF- α , IL-6, hs-CRP, PAI-1, total cholesterol, HDL and triglycerides.

Results: The chemerin levels were significantly higher in overweight and obese patients in the comparison to normal weight subjects; and correlated with BMI, body fat, waist circumference, blood pressure, PAI-1, HDL cholesterol and TG levels. A significantly lower HMW adiponectin level was found in patients with MS in comparison to non-MS persons with BMI ≥ 25 kg/m². The HMW adiponectin level negatively correlated with hs-CRP. The analysis of logistic regression showed that a decreased HMW adiponectin level was a factor associated with the presence of MS.

Conclusions: Serum HMW adiponectin may be a better than chemerin biomarker of insulin resistance and MS in overweight and obese patients.

Keywords: Metabolic syndrome; Chemerin; Adiposity; HMW adiponectin; Leptin

Introduction

Adipose tissue is an important component of the human endocrine system [1,2,3]. Endocrine activity of adipose tissue is not only restricted to the fat cells. It also concerns the rest of components of adipose tissue, for example macrophages [4]. Adipokines, which are secreted by adipose tissue are involved in maintaining the energy balance, blood pressure, immune processes, angiogenesis, lipid and glucose homeostasis [2,5,6,7]. They are the major regulators of insulin sensitivity and thus constitute a potential link between obesity, insulin resistance and metabolic syndrome (MS) [8,9]. Leptin and adiponectin

are adipokines that promote insulin sensitivity. Resistin, TNF- α and IL-6 are insulin antagonists, and increased levels of these adipokines induce insulin resistance [6,7,10].

Chemerin is a novel adipokine that is produced by both adipose tissue and the liver. Moreover, it is a chemoattractant for immune cells such as macrophages and promotes adipocyte differentiation [11]. Sell et al. showed that adipose tissue chemerin secretion was higher in obese patients than that in non-obese control subjects, which proved that chemerin secretion is associated with fat volume [12]. However, the role of chemerin in pathogenesis of obesity and MS is not yet established [13,14]. It was proposed by some authors to be an independent biomarker of MS [4] and increased cardiovascular risk [15]. But still the link between chemerin and insulin resistance connected with the metabolic syndrome is not well-known [13,14,16,17]. So the aim of this study was to compare levels of chemerin and other cytokines in patients with MS and healthy normal-weight controls.

Materials and Methods

The study was performed in a group of 38 adult patients (21F, 17 M) with MS, and 17 persons with BMI ≥ 25 kg/m² without MS. The mean age of the MS patients was 38.8 ± 10.2 years.

Patients thought to have secondary obesity, as judged by interviews and examination, were excluded from the study. Also excluded, women taking oral contraceptives, hormonal replacement therapy, within 6 months after giving birth, or breastfeeding; patients with endocrine, mental, malignant or serious medical diseases were excluded.

The control group consisted of 23 healthy people with BMI < 25 kg/m² (17 F, 6 M) in the mean age 36.3 ± 9.1 years. The scheme of the study is presented in Table 1 and characteristics of all studied groups in Table 2.

All participants underwent anthropometric and laboratory measurements and blood-pressure examination. All subjects gave their informed consent for inclusion before they participated in the study. The study was approved by the Medical University Ethics Committee.

Anthropometric Measurements

The following parameters were measured:

- body mass (kg), waist circumference (cm), hip circumference (cm)
- BMI - body mass index – was calculated as the ratio of the current body mass/height² [kg/m²]. BMI values in the range of 25-30 kg/m² were termed overweight, BMI ≥ 30 kg/m² was called obesity;
- WHR - waist to hip ratio estimated based on waist to hip circumferences ratio;
- body composition: the body fat content (%F) and lean body mass (LBM) were obtained by the near-infrared spectroscopy

Table 1: Scheme of the study.

Study group 55 subjects with BMI ≥ 25 ↓ Metabolic Syndrome according IDF criteria	Control group 23 subjects with BMI < 25 ↓ Metabolic Syndrome according IDF criteria
↓ (+) n=38	↓ (-) n=17
↓ (-) n=23	

Table 2: The anthropometric measurements, SBP, DBP and markers of insulin resistance in studied groups.

Parameters	MS (n= 38)	Non-MS (n=17)	Controls (n=23)	p MS /non-MS vs. Controls	p MS vs. non-MS
F/M	21/17	7/10	17/6	ns	ns
Age (years)	39.2 ± 9.2	37.3 ± 10.5	36.3 ± 9.10	ns	ns
BMI (kg/m ²)	35.6 ± 6.1	29.8 ± 3.7	22.2 ± 1.9	0.001	0.001
Waist circumference (cm)	117.2 ± 17.2	103.8 ± 12.2	76.9 ± 6.9	0.001	0.05
WHR	0.93 ± 0.03	0.9 ± 0.01	0.79 ± 0.07	< 0.001	0.04
Body fat (F %)	43.1 ± 7.5	37.9 ± 5.7	26.3 ± 5.0	0.001	0.003
SBP (mmHg)	134.7 ± 17.3	104.1 ± 8.3	101.7 ± 10.4	0.001	0.001
DBP (mmHg)	85.5 ± 10.7	71.2 ± 6	67.3 ± 6.9	0.001	0.001
Insulin (μIU/ml)	26.4 ± 18.7	14.7 ± 9.1	10.1 ± 2.9	0.001	0.005
HOMA-IR	6.1 ± 4.4	3.1 ± 1.9	2.4 ± 0.74	0.001	0.04
Glucose (mg/dl)	90.7 ± 10.8	97.1 ± 13.1	86.6 ± 8.8	ns	0.002
Total cholesterol (mg/dl)	227 ± 55.9	206.2 ± 33.2	196.3 ± 35.2	0.04	0.18
LDL (mg/dl)	144.8 ± 49.8	130.2 ± 29.4	109.2 ± 29.7	0.04	0.67
HDL (mg/dl)	40.3 ± 8.1	56.4 ± 8.6	57.4 ± 17.4	0.003	0.01
Triglycerides (mg/dl)	203 ± 94.1	97.8 ± 44.7	99 ± 45.7	< 0.001	0.09

Data is presented as means ± SD

method (NIR) using a Futrex 5000A unit (Gatesburg Inc., USA).

Body mass and height were measured with an attested electronic scales with a body-height measuring device.

Blood pressure (DBP - diastolic blood pressure, SBP - systolic blood pressure) was checked twice; sitting and after at least 15 minutes rest using a proper sleeve. In this study an average from the two measurements is given.

Laboratory Assay

Blood samples were collected after an overnight fast of 12 hours and the levels of the following compounds were measured in plasma:

- Glucose by enzymatic-calorimetric method, (EMAPOL);
- Insulin by MEIA method (microparticle enzyme immunoassay), using units and IMX by Abbott USA;
- Chemerin by ELISA method Biovendor R & D (Slovakia);
- HMW Adiponectin (high molecular weight adiponectin) by ELISA method, Linco (USA);
- Leptin by ELISA method, DRG (Germany);
- TNF (tumor necrosis factor) by ELISA method, Bender MedSystem (Austria);
- hs-CRP (high sensitivity C-reactive protein), DRG (Germany);
- IL-6 (interleukin -6), Bender MedSystem (Austria);
- PAI-1 (plasminogen activator inhibitor 1) by ELISA method, Roche (France);
- total cholesterol (TC), triglycerides (TG), HDL-cholesterol (HDL) by the routine methods using Hitachi 911.

The Criteria for Metabolic Syndrome (MS)

Metabolic syndrome was recognized according to the IDF proposition. Essential criteria to recognize MS is:

- abdominal obesity (recognized in the European population with waist circumference ≥ 94 cm in men, and ≥ 80 cm in women);

and two of the following criteria:

- triglycerides ≥ 150 mg/dl or hypertriglyceridemia treatment;
- HDL cholesterol <40 mg/dl in men and <50 mg/dl in women or dyslipidemia treatment;

- systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or high blood pressure treatment;

- plasma glucose fasting ≥ 100 mg/dl or diagnosed diabetes mellitus type 2.

Insulin Resistance (HOMA-IR)

Insulin resistance HOMA-IR (Homeostatic Model Assessment) index has been calculated using the following formula:

$$HOMA-IR = (FPI (mU/L) \times FPG (mmol/L)) / 22.5$$

where: FPI - fasting plasma insulin; FBG - fasting plasma glucose.

HOMA-IR index demonstrates a high correlation with the hyperinsulinemic-euglycemic clamp method [19].

Statistical Analysis

Each of the continuous variables was assessed for compliance with the normal distribution. Variables with normal distribution were analyzed using parametric methods. To evaluate the differences between the two groups, Student's t-test and variances analysis (ANOVA) with post-hoc tests have been performed. Univariate correlations were assessed by the Pearson correlation test. Multivariate regression analysis and logistic regression tests were used.

Variables whose distribution has diverged from a normal distribution were logarithmically transformed and analyzed by nonparametric methods. P value < 0.05 was considered statistically significant for all analyses. Statistical analysis was performed using Statistica 11.0 version for Windows (Krakow, Poland).

Results

Anthropometric parameters, blood pressure and lipids profile

Metabolic syndrome according to IDF criteria was diagnosed in 69.1% of the subjects with BMI ≥ 25 kg/m². Among MS patients 21% were overweight, 58% had obesity grade I or II, and 21% were severely obese. All people with severe obesity were diagnosed with MS (Figure 1). In the MS and non-MS groups a higher content of body fat and increased waist circumference, blood pressure, fasting insulinaemia and HOMA-IR were observed in comparison to controls. Both groups differed with regard to all lipid parameters. Data is presented in Table 2.

Adipokines profile

The levels of adipokines and inflammatory markers are presented in Table 3.

In the MS and non-MS groups elevated levels of chemerin, TNF- α , hs-CRP, PAI-1, and IL 6 were noticed in comparison with the control group. Serum HMW adiponectin level was higher in the non-MS than in the MS group ($p=0.04$), but there were no statistical differences when the control group was compared to MS and non-MS patients ($p=0.51$). Leptin level did not differ significantly between the studied groups. However, in both MS and non-MS, an elevated concentration of hs-CRP was noticed.

The chemerin levels positively correlated with BMI ($r=0.36$), body fat ($r=0.22$), PAI-1 ($r=0.33$), TG ($r=0.3$), SBP and DBP ($r=0.27$), waist circumference ($r=0.38$; $p<0.05$) and negatively correlated with HDL cholesterol ($r= -0.25$; $p<0.05$). The correlation between BMI and chemerin level is presented in Figure 2 and between PAI-1 and chemerin level in Figure 3.

The HMW adiponectin level negatively correlated with hs-CRP ($r=-0.29$; $p<0.05$) and leptin level correlated with BMI and body fat ($r=0.31$, $p<0.05$).

Regression analysis

The analysis of logistic regression showed that increased BMI and decreased HMW adiponectin levels were factors associated with the occurrence of MS defined according to the IDF criteria (Table 4).

Discussion and Conclusion

Obesity, MS, diabetes and cardiovascular diseases are more and more prevalent. A clearer understanding of the role played by cytokines in the pathogenesis of insulin resistance and vascular diseases is important to search for novel useful biomarkers which are able to indicate high cardiovascular risk patients [19]. It might help also to create new therapeutic options. A recently discovered adipokine named chemerin, which is produced by both adipose tissue and the liver, was suggested to be associated with lipid metabolism, obesity-induced insulin resistance and metabolic complications [1].

We have confirmed abnormally high serum chemerin levels in

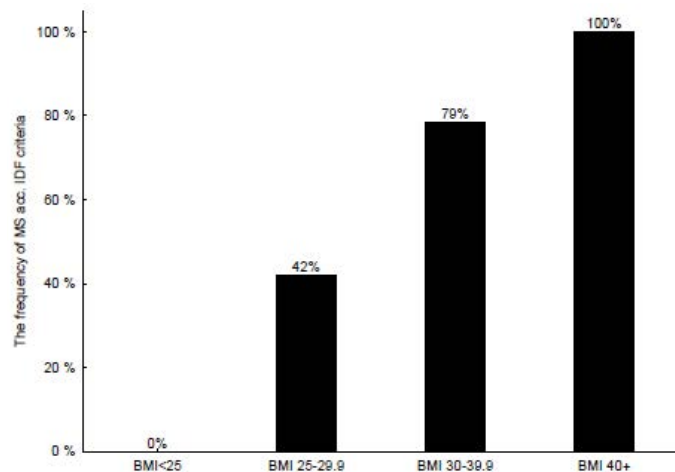


Figure 1: The frequency of MS according to IDF depending on BMI.

Table 3: The adipokines and inflammatory parameters in studied groups.

Parameter	MS (n= 38)	Non-MS (n=17)	Control group (n=23)	p MS /non-MS vs Control	MS vs non-MS
Chemerin ($\mu\text{g/ml}$)	207.5 \pm 187	188.2 \pm 125	71.8 \pm 76.5	0.01	0.7
HMW Adiponectin($\mu\text{g/ml}$)	703.3 \pm 452	1145.3 \pm 766	994.2 \pm 741	0.51	0.04
Leptin (ng/ml)	9.97 \pm 12.9	7.2 \pm 11.1	6.6 \pm 10.9	0.3	0.49
TNF- α (pg/ml)	20.1 \pm 16.6	15.1 \pm 7.6	14.3 \pm 8.5	0.03	0.13
Interleukin 6 (pg/ml)	3.2 \pm 0.4	2.8 \pm 0.7	2.5 \pm 0.4	0.03	0.13
hs-CRP (mg/l)	9.14 \pm 2.3	7.2 \pm 4.4	4.8 \pm 3.4	0.002	0.11
PAI-1 (ng/ml)	69.1 \pm 27.8	56.1 \pm 31.7	21.8 \pm 13.4	0.001	0.28

Data is presented as means \pm SD

subjects with obesity and overweight. The role of the chemerin in the pathogenesis of obesity and MS is not established yet. Some authors suggest that chemerin appears to induce insulin resistance in skeletal muscle, which is the major site of peripheral insulin resistance [20]. Other authors observed that levels of chemerin are higher in subjects with nascent MS, suggesting that chemerin could be involved early in the pathogenesis of the syndrome [21].

In our study, we did not find a correlation between the indicator of insulin resistance HOMA-IR and the chemerin level. The other authors similarly did not find obvious correlation between IR and chemerin concentration [14,16,17,22,23]. Stejskal et al. [4] have found that chemerin level correlated with waist circumference and BMI after adjustment for age, gender, blood pressure and blood lipids. Our results are consistent with the findings of these studies, showing that chemerin is correlated with central obesity.

In our study, chemerin as well leptin levels did not differ in the

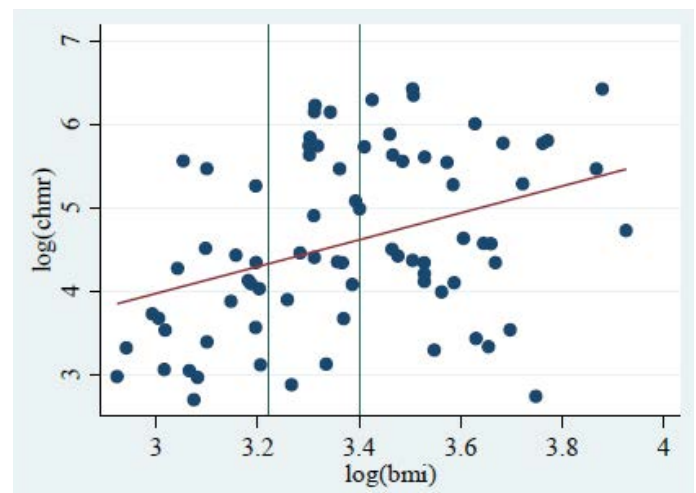


Figure 2: The correlation between BMI and chemerin levels.

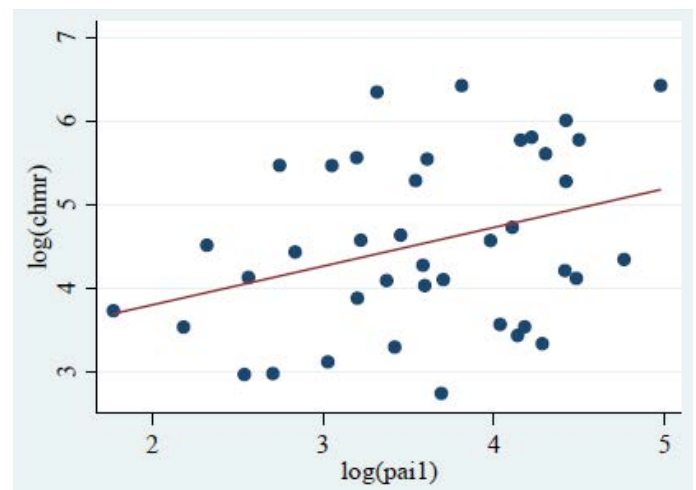


Figure 3: The correlation between PAI-1 and chemerin levels.

Table 4: The results of logistic regression. The dependent variable: occurrence of MS according to IDF.

The dependent variable:	P
BMI (kg/m ²)	0.006
HMW Adiponectin (µg/ml)	0.017
Leptin (mg/dl)	0.673
Chemerin (µg/ml)	0.922
HOMA-IR *	0.034
Insulina (µIU/ml)*	0.039

* - log

MS group in the comparison to non-MS subjects with BMI \geq 25 kg/m². These results were different from those obtained by Wang et al. [24]. The reasons for the differences may be variations in genetic background, lifestyle habits, research protocols, different diagnostic criteria for MS and our limited sample size. MS is a combination syndrome with multiple dysfunctions. Our control subjects had an uncomplicated medical status without abnormalities in blood lipids, blood glucose, and blood pressure. Whether single-component or multiple-component abnormalities lead to changes in chemerin levels remains to be studied further.

Some studies have reported that chemerin is related to blood pressure after adjustment for age and gender in subjects with normal glucose tolerance [25,26]. We observed also that plasma chemerin was positively correlated with systolic and diastolic blood pressure. We found as well that the chemerin level was negatively correlated with the HDL-C level and positively with the PAI-1 level. HDLs provide a vascular protective effect by reducing the damage of vascular lesions, by lowering high blood pressure caused by vasospasm and vascular wall cell proliferation, for example. Results of our study suggest a relationship between the chemerin level and dyslipidemia and in consequence in vascular damage. It was already suggested by Neves et al. that chemerin may be important in obesity-related vascular injury and development of coronary artery disease [27] and some authors postulated that chemerin may be a biomarker used to identify patients with plague vulnerability [28].

We would like to emphasize that in our study the only adipokine that was significantly lower in MS vs. non-MS group was HMW adiponectin. Also, statistical analysis by regression showed association between the HWM adiponectin (apart from BMI, HOMA-IR and insulin) and occurrence of MS.

Adiponectin, discovered in 1995 by Scherer and Lodish, is a relatively well-known adipokine. Among various adipocytokines it is considered as an important factor which plays a crucial role in glucose and lipid metabolism. It has also anti-inflammatory properties [29]. Adiponectin is secreted exclusively by adipocytes and is abundantly present in human serum. Its levels are negatively regulated by the visceral fat amount. Many studies concluded that hypo adipokinaemia may be a very important pathogenetic factor in the development of insulin resistance, and consequently diabetes type 2 [30,31,32], and it was proposed already some time ago that a decreased adiponectin level may be a good biomarker of metabolic syndrome [33,34]. Clinical improvement in adiponectin concentration might play an important protective role against MS as administration of adiponectin improves insulin action in mice and humans [35,36]. Currently adiponectin is being tested as a new therapeutic agent for metabolic syndrome [22,35].

In our study we concluded that serum HMW adiponectin may be a better than chemerin biomarker of insulin resistance and MS in overweight and obese patients. The results of our study are consistent with the observations of other authors that an excess of chemerin related with hypertension, dyslipidemia and high PAI-1 levels may play a role in vascular injury [27,28], and low adiponectin levels may be a primary link to inflammation and insulin resistance which is a culprit of the

MS [33,34]. There are many mechanisms leading to the development of diabetes and vascular injury in obesity and MS. Some may depend mainly on adiponectin, and others on chemerin [37]. Further studies should assess precisely how chemerin and adiponectin can contribute to the development of MS and its complications like vascular injury.

Finally, we would like to postulate that, not chemerin and leptin, but the serum HMW adiponectin level might be a single valuable biomarker of insulin resistance and MS in overweight and obese patients.

Abbreviations

%F: Body Fat Percentage; BMI: Body Mass Index; BP: Blood Pressure; DBP: Diastolic Blood Pressure; HDL: High Density Lipoprotein; HMW adiponectin: High Molecular Weight Adiponectin; HOMA: IR Insulin Resistance Homeostatic Model Assessment; hs-CRP: High Sensitivity C reactive protein; IDF: International Diabetes Federation; IL-6: Interleukin 6; LBM: Lean body mass; MS: Metabolic Syndrome; NIR: Near Infrared; PAI-1: Plasminogen Activator Inhibitor 1; SBP: Systolic Blood Pressure; TG: Triglycerides; TNF: Tumor Necrosis Factor; WHR: Waist to Hip Ratio.

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