

Chemerin Serum Level and Insulin Resistance in Hypertensive Patients with Obesity

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Abstract

The article presents data on serum chemerin levels and its relation to insulin resistance in hypertensive patients with obesity. The results show the increase in serum chemerin levels in patients with hypertension compared healthy subjects with the highest levels in early stages of obesity that may contribute to development of insulin resistance. Advanced grades of obesity that are characterized by already established hyperinsulinemia are characterized by lower serum chemerin levels compared to grade I obesity.

Keywords: hypertension, obesity, chemerin, insulin resistance

1. Introduction

Cardiovascular disease is the main cause of disability and premature mortality worldwide, which necessitates a detailed study of the risk factors for cardiovascular pathology. Insulin resistance (IR) is one of the most common metabolic disorders that contributes to the development of multiple hemodynamic disturbances and leads to the progression of cardiovascular disease. It was shown that excessive body weight and obesity are the most important factors that reduce tissue sensitivity to insulin [1, 2]. To even greater extent, it concerns visceral type of obesity that is considered to be metabolically active. Visceral adipose tissue (AT), unlike subcutaneous fat, has special morphological and functional properties that determine its high sensitivity to the lipolytic action of catecholamines and low sensitivity to the anti-lipolytic effect of insulin, which leads to the development of IR and secondary hyperinsulinemia (HI) According to

modern concepts, visceral AT is a source of variety of adipokins, including chemerin. The latter is a newly identified molecule with pleiotropic properties, which, according to some studies [3, 4], may be involved in the regulation of adipogenesis and the formation of chronic inflammatory reaction in AT. The potential role of chemerin in the regulation of carbohydrate metabolism and formation of insulin resistance is also poorly studied.

The purpose of our research was to investigate the relation between serum chemerin level and insulin resistance in patients with hypertension, depending on the presence and grade of obesity.

2. Materials and methods

82 patients (34 male and 48 female) with hypertension, aged 38 to 76 have been examined. Verification of the diagnosis was performed according to the criteria recommended by the European Society of Hypertension (ESH) / European Society of Cardiology (ESC) (2013). The diagnosis of obesity was established according to the WHO classification (1997).

The patients were divided into 5 groups: the first one included patients with hypertension and normal body weight, $n = 17$ (9 male and 8 female), mean age 62 (56; 72) years, mean values of the body mass index (BMI) 22,8 (21,5; 24,0) kg/m^2 (group 1); the second one – patients with hypertension and overweight, $n = 26$ (9 male and 17 female), mean age 60 (56; 64) years, BMI 26,9 (25,8, 27,6) kg/m^2 (group 2); the third – patients with hypertension and I gr. obesity, $n = 16$ (6 male and 10 female), mean age 61 (55; 67) years, BMI 32,4 (31,8; 33,4) kg/m^2 (group 3); the fourth – patients with hypertension and II gr. obesity, $n = 13$ (3 male and 10 female), mean age 61 (55, 66) years, BMI 36,3 (35,0; 37,4) kg/m^2 (group 4); the fifth – patients with hypertension and III gr. obesity, $n = 10$ (7 male and 3 female), mean age 56 (51; 61) years, BMI 43,0 (40,8; 46,6) kg/m^2 (group 5). The control group included 12 healthy, gender- and age-matched individuals.

The study did not involve patients with cancer, atrial fibrillation, acute and chronic inflammatory processes, diffuse connective tissue diseases, concomitant diseases of the thyroid gland, those symptomatic hypertension and advanced congestive chronic heart failure.

Patients were examined according to the standard protocol. Anthropometric measurements included height, body mass, waist and hips circumference with the calculation of waist to hips (W/H) ratio. Body mass index (BMI) was calculated as $(\text{body mass (kg)} / \text{height (m)}^2)$. Abdominal obesity (AO) criteria used were waist > 94 cm in men, > 80 cm in women. The W/H value $> 0,90$ in males and $> 0,85$ in females was considered a sign of the visceral or abdominal type of adipose tissue distribution [5]. Additionally, fasting chemerin and insulin serum levels were estimated by ELISA using Human Chemerin ELISA Kit (Kono Biotech Co., Ltd.) and DRG® Insulin (DRG Instruments GmbH, Germany, Marburg) reagent kits. The standard oral glucose tolerance test (OGTT) was also performed. For the quantitative evaluation of IR, the HOMA-IR, Caro and FIRI indices were used.

The HOMA-IR index was calculated using the formula: $\text{HOMA-IR} = \text{Fasting glucose (mmol/l)} \times \text{Fasting insulin } (\mu\text{M/ml}) / 22,5$. In HOMA-IR values $> 2,77$, the patients were considered insulin-resistant. The Caro index was calculated using the formula: $\text{Caro} = \text{Fasting glucose (mmol/l)} / \text{Fasting insulin } (\mu\text{M/ml})$, with the IR criterion of $\text{Caro} < 0,33$. The FIRI (Fasting Insulin Resistance Index) index was calculated according to the formula: $\text{FIRI} = \text{Fasting insulin } (\mu\text{M/ml}) \times \text{Fasting glucose (mmol/l)} / 25$, with normal values $\leq 5,5$.

The statistical analysis of the data was performed using Statistica for Windows 6.1 software package (Statsoft Inc., USA). For independent samples comparison, due to non-Gaussian distribution, Mann-Whitney U test and Spearman rank correlation were used. Quantitative characteristics are presented as median (Me), upper (UQ) and lower (LQ) quartiles. The critical level of significance in checking statistical hypotheses was $p < 0,05$.

3. Results and discussion

The visceral type of AT distribution was detected in 34,5% (6 patients) of hypertensive patients without obesity. For the overweight group, the figure was 69,2% (18 patients), $p = 0,02$. With the progression of obesity, the rate of patients with AO unreliably increased: 83,4% (13 patients), 69,2% (9 patients) and 90% (9 patients) in the group of patients with hypertension and I, II and III gr. of obesity, respectively, $p > 0,05$ (see Table 1).

Table 1.
Anthropometrical data in hypertensive patients depending on grade of obesity

Parameters	Hypertensi on without obesity	Hypertensi on with overweight	Hypertensi on with I gr. obesity	Hypertensi on with II gr. obesity	Hypertensi on with III gr. obesity
Height, cm	170 (169;178)	164 (158;171)	170 (163; 180)	162 (160;168)	164 (159;170)
Weight, kg	71 (63;73)	80 (70;85)	94,8 (82; 102,5)	98 (88;112)	106,4 (98; 122)
BMI, kg/m ²	22,75 (21,5; 24,0)	26,9 (25,8; 27,6)	32,4 (31,8; 33,4)	36,3 (35,0; 37,4)	43,0 (40,8; 46,6)
Waist, cm	79 (76;88)	95 (92;100)	112,5 (106; 115,5)	116 (104;125)	121 (116; 136)

Table 1. (Continued):
Anthropometrical data in hypertensive patients depending on grade of obesity

Hips, cm	97 (90;100)	103 (101;107)	113,5 (109; 120)	122 (117;134)	128 (122;138)
W/H ratio	0,84 (0,79;0,89)	0,93 (0,91;0,95)	0,96 (0,91; 1,02)	0,90 (0,86;0,97)	0,94 (0,91; 1,04)

Our attention was also drawn to the decrease of W/H ratio (the classical marker of AO), as well as lower prevalence of abdominal type of AT distribution in the group of patients with the II gr. of obesity. The possible explanation for this, as well as the lower height in the named group, is the above-mentioned prevalence of female patients in it, who, in comparison to male, are more prone to the accumulation of AT in the hips area.

According to the purpose of our study, an analysis of the glycemic response to OGTT and the indexes of IR (Table 2) was performed.

Table 2.
Comparative characteristics of carbohydrate metabolism markers in hypertensive patients depending on the presence and grade of obesity

Parameters	Hypertensi on without obesity	Hypertensi on with overweight	Hypertensi on with I gr. obesity	Hypertensi on with II gr. obesity	Hypertensi on with III gr. obesity
1	2	3	4	5	6
Fasting glucose, mmol/l	4,42 (3,89; 4,62)	4,57 (3,99; 5,29)	4,74 (4,20; 5,24)	5,10 (4,86; 5,67) p*=0,04	6,32 (5,24; 7,40) p*=0,01 p^=0,02 p#=0,03

Table 2. (Continued):
Comparative characteristics of carbohydrate metabolism markers in hypertensive patients depending on the presence and grade of obesity

OGTT glucose, mmol/l	4,34 (3,81; 6,46)	4,25 (3,45; 5,53)	7,10 (5,57; 7,66) p*=0,04 p^=0,03	7,68 (5,2; 8,63) p*^=0,03	6,86 (5,84; 8,63) p*^=0,05
Fasting insulin, µM/ml	20,6 (15,9; 31,4)	28,2 (20,6; 35,6)	37,8 (22,6; 29,2) p*=0,006 p^=0,04	39,2 (29,7; 49,5) p*=0,01 p^=0,02	45,3 (38,6; 56,1) p*=0,001 p^=0,001 p#=0,04
1	2	3	4	5	6
HOMA-IR	4,11 (3,57; 5,57)	5,43 (3,91; 7,50)	7,97 (4,46; 10,47) p*^=0,03	9,43 (6,00; 10,67) p*=0,01 p^=0,04	10,70 (7,66; 16,90) p*=0,001 p^=0,0005 p#=0,04
Caro index	0,24 (0,19; 0,27)	0,16 (0,14; 0,28)	0,13 (0,10; 0,20) p*=0,01	0,13 (0,12; 0,18) p*=0,05	0,12 (0,12; 0,16) p*=0,01
FIRI	3,70 (3,20; 5,01)	4,89 (3,52; 6,76)	7,18 (4,01; 9,43) p*=0,03	8,49 (5,37; 9,60) p*=0,01 p^=0,04	9,65 (6,90; 15,20) p*=0,002 p^=0,001

Notes: p* = vs group 1; p^ = vs group 2; p# = vs group 3.

The results showed a significantly higher level of blood glucose in patients with hypertension and the III gr. of obesity compared to other groups. For patients with the II gr. of obesity, there was a significant difference compared with patients without obesity. In OGTT, glucose tolerance was impaired in 75% (12 patients) in the group of gr. I obesity (p* = 0,01, p^ = 0,001), in 62,8% (8 patients)

in the group of gr. II obesity ($p^* = 0.04$, $p^{\wedge} = 0.01$) and in 60% (6 patients) in the group of patients with the III gr. of obesity ($p^{\wedge} = 0.02$). For groups of patients with hypertension with normal and overweight, the rate was 29,4% (5 patients) and 22,7% (6 patients), respectively. The presence of obesity in patients with hypertension was significantly associated with an increase in the fasting serum insulin level and with the presence of IR in comparison with the groups of patients with normal and overweight

Intra-group analysis has revealed the presence of IR-HI in 35,3% of patients with hypertension with normal weight and in 30,4% of patients with overweight. Development of obesity significantly increased the rate to 68,8% ($p^{\wedge} = 0,03$) in the group of patients with gr. I obesity and to 76,7% ($p^* = 0,05$, $p^{\wedge} = 0,02$) in the group of gr. II obesity. Among the patients with hypertension and the III gr. of obesity, IR-HI was revealed in 100% of subjects ($p^{\wedge} = 0,001$, $p\# = 0,03$).

The potential role of chemerin in the regulation of carbohydrate metabolism and in the formation of insulin resistance is quite controversial and poorly studied. Analyzing the literature, we have found the publications, the authors of which obtained results with positive correlations between the serum chemerin levels, fasting insulin and the HOMA-IR index, as well as the opposite data. In a study by Adriana F. et al., 2014 [6], high levels of serum chemerin, which positively correlated with IR and oxidative stress markers ($r = 0,6$), were obtained in patients with high grades of obesity. In an in vitro experiment by Huang Z., Xie X., 2015 [7] it was shown that 24h treatment of the C2C12 myoblast cell line in mice with different concentrations of chemerin followed by 30-minute insulin stimulation induced insulin resistance in these cells due to an inflammatory reaction mediated by NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) by. According to Ernst M. et al., 2010 [8], the introduction of exogenous chemerin to mice with diet-induced obesity and type 2 diabetes exacerbated glucose intolerance, reduced serum insulin levels, and reduced glucose uptake in tissues, but this effect was not obtained in the normoglycemic mice. In contrast, in the clinical study by Erifili H. et al., 2015 [9], there was no significant relation between obesity and non-alcoholic fatty liver disease ($r > 0.18$), although there is data suggesting the probable relation of chemerin with increased beta cell function. The role of chemerin in beta cell regulation was also the subject of the study by Takahashi M. et al., 2011 [10], which investigated disorders of glucose homeostasis in genetically engineered chemerin deficient mice. According to the authors, the lack of chemerin synthesis in animals increased glucose uptake in the muscular system and gluconeogenesis in the liver, which in turn was associated with a decrease in insulin secretion in beta cells. The authors suggest this is the predominant cause of glucose intolerance in chemerin deficient mice was the reduction of insulin synthesis, and not the IR.

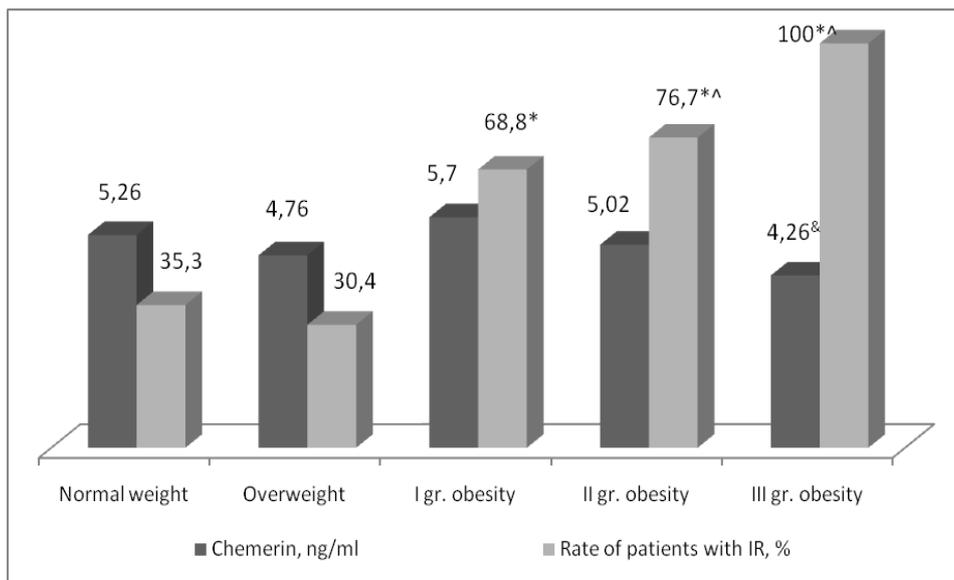
In our study, serum chemerin was 5,26 (4,56; 6,52) ng/ml in the group of patients with hypertension and normal weight; 4,76 (4,42; 6,29) ng/ml in those with overweight; 5,70 (4,67; 6,64) ng/ml in hypertensive patients with the I gr. of obesity; 5,02 (4,20; 7,39) ng/ml in the II gr. obesity ; 4,26 (3,80, 4,70) ng/ml in the III gr. obesity, which was significantly higher compared to healthy individuals:

3,92 (3,75; 4,29) ng/ml, ($p = 0,001$ with all clinical groups). Intergroup analysis has shown statistically significant differences in the serum chemerin levels in the patients with the III gr. obesity compared to other groups: ($p = 0,03$) vs normal and overweight; ($p = 0,02$) vs I gr. obesity; ($p = 0,05$) vs II gr. obesity. Other inter-groups differences were statistically insignificant. A medium strength positive correlation has been revealed ($r = 0,34$) between serum chemerin level and presence / grade of obesity in rank correlation analysis ($p = 0,05$).

In the analysis of the relations between the serum chemerin level and the carbohydrate metabolism indices in the general cohort of the examined patients, no significant correlations have been found. At the same time, a sub-analysis among patients with concomitant obesity has shown a reliable correlation between serum chemerin and both fasting and postprandial glycemia ($r = -0,43$ and $r = -0,37$, respectively). Correlation with postprandial glycemia level was the strongest among patients with gr. II-III obesity ($r = -0,80$); in this subgroup, the absent in lower BMI values correlation with type 2 diabetes presence has been also found ($r = 0,46$).

The revealed relations between serum chemerin levels and carbohydrate metabolism indices in patients with hypertension on the background of the highest chemerin levels in patients with concomitant obesity of the I gr. with subsequent decrease in higher grades of obesity, as well as significant increase in the rate of patients with IR (Fig.1) in groups with morbid obesity can be explained by the data presented in [11].

Figure 1.
Serum chemerin and rate of IR in hypertensive patients



Notes: $p < 0,05$; * - vs group 1; p^{\wedge} - vs group 2; $p^{\#}$ - vs group 3, $p^{\&}$ - vs all groups.

It is known that macrophages play a decisive role in the formation of IR [12]. Along with an increase in the expression of adipokines, chemokines and proinflammatory cytokines that are associated with an equivalent increase in hyperplastic and hypertrophic adipocytes, macrophages at the same time are a source of proinflammatory markers, in particular, chemerin [12]. According to the previous research [13, 14], chemerin has several isoforms that may have opposite, pro- as well as anti-inflammatory effects, depending on the type of proteases that have activated pre-chemerin molecule. In the context of obesity, the increase in the circulating chemerin level contributes both to chronic inflammation and development of dysmetabolic phenotype. Thus, at the initial stages of IR formation, an increase in the level of chemerin contributes to the development of the dysmetabolic profile that occurs as a result of an adipose tissue dysfunction. Development and progression of hyperinsulinemia in patients with high grades of obesity is associated with a decrease in the level of circulating chemerin in patients with advanced metabolic disorders and established IR.

4. Conclusions

1. The presence of obesity in patients with hypertension is reliably associated with an increase in fasting insulin levels and the presence of IR in comparison with the groups of patients with normal and overweight.
2. The level of serum chemerin in patients with hypertension is reliably associated with the presence and grade of concomitant obesity and is the highest in patients with gr. I obesity.
3. The level of serum chemerin is linked to the state of carbohydrate metabolism, with an increase in the hyperinsulinemia incidence in patients with gr. II-III obesity being associated with a decrease in serum chemerin compared with groups of gr. I obesity, overweight and normal body mass.

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