Circulating Chemerin Levels, Anthropometric Indices and Metabolic Profile in Morbid Obesity

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Recent data suggest that chemerin could be important for the pathophysiology of obesity. However, its relation with clinical indices of obesity and metabolic parameters is controversial and less studied in metabolic healthy patients with morbid obesity. Our study demonstrated that circulating chemerin is related to anthropometric indices, it is an independent predictor for waist to hip circumference ratio as well as for decreased insulin sensitivity, but not for other metabolic changes. Chemerin/adiponectin ratio is also a useful parameter, but not superior to chemerin levels.

Keywords: chemerin, chemerin/adiponectin ratio, morbid obesity, anthropometric indices, metabolic health

Over the recent decades, the prevalence of obesity has increased dramatically, leading to a high rate of cardiovascular and metabolic diseases and also an excess of mortality [1]. Abdominal perivascular fat tissue (PVAT) is recognized as an important player in obesity-mediated disorders, being a wide source of biologically active molecules termed adipokines, that can act in both autocrine and paracrine fashion [2]. On the other hand, obesity could cause PVAT dysfunction, an emerging paradigm highlighting its deleterious effects. PVAT dysfunction is induced by complex and not fully elucidated mechanisms involving adipocyte and hypoxia, insulin resistance, oxidative stress, vascular inflammation, and macrophage activation as early stages of atherosclerosis [3-5]. Chemerin is a novel adipokine with controversial role in obesity [6]. Since chemerin is a pro-inflammatory cytokine it may link obesity to vascular inflammation, metabolic changes and atherosclerosis [7]. On the other hand the relation of chemerin with clinical indices of obesity is conflictual [8-11]. Bozaouglu et al [9] first demonstrated that circulating chemerin levels correlate with the components of metabolic syndrome such as body mass index (BMI), triglycerides and blood pressure. A very recent meta-analysis also confirms that chemerin is related to BMI and insulin resistance, so it could be important for the pathophysiology of obesity [12]. However, the role of chemerin in morbid obesity, particularly in metabolic healthy subjects, is less studied. Thus, our study aimed to investigate the relationship of plasma chemerin levels with anthropometric indices and metabolic parameters in morbidly obese individuals.

Experimental part

Material and methods

We conducted a cross-sectional study including 50 subjects, i.e. 25 morbidly obese patients (BMI ≥40 kg/m^2) who were admitted for bariatric surgery and 25 age- and gender matched non-obese control patients (BMI < 30 kg/m^2). The enrollment started after the study protocol was approved by the University and the Hospital Local Ethics Committees and the patients signed the informed consent. None of the enrolled patients had more than two criteria for defining metabolic syndrome [13]. The exclusion criteria were strictly respected, i.e. subjects with diagnosed or treated cardiovascular disease or diabetes, enrolled in concurrent studies. We used the classical anthropometric indices such as BMI (kg/m^2), waist circumference and waist to hip circumference ratio (WHR), and also the index of central obesity defined as waist circumference to height ratio. Waist circumference was measured midway between the lowest ribs and the iliac crest. Systolic and diastolic blood pressure, as components of metabolic syndrome, were also determined according to the rules of office blood pressure measurement. Venous blood samples were collected after 12 hours fasting for the assessment of biochemical parameters linked to metabolic syndrome (plasma cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, fasting plasma glucose, uric acid, insulinemia). Fasting plasma glucose, total cholesterol and triglycerides were determined using enzymatic colorimetry, while imunoturbidimetry was used for HDL-cholesterol measuring. LDL-cholesterol was calculated by Friedewald equation, as described elsewhere [14]. Fasting insulinemia was assessed using chemiluminiscence immunoassay kits (Siemens Healthcare GmbH., Germany) automated by Immulite 1000 analyzer. Insulin sensitivity (IS) and insulin resistance (IR) were also performed as parameters of metabolic health. IS was calculated using quantitative check index (QUICKI) and IR by Homeostasis Model Assessment (HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mg/dl)/225 × 18; reference normal values < 2.5) [15]. The venous blood samples collected for assessment of chemerin and adiponectin levels were stored at -20°C for processing.

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Serum chemerin and adiponectin were measured quantitatively by specific Human ELISA (enzyme-linked immunosorbent assay) kits (ab155430, ab99968, respectively) supplied by Abcam Cambridge, U.K., for research use only. Chemerin (known as retinoic acid receptor responder protein 2 - RARRES2) is a 14 kDa protein that becomes functional after activating by different proteases. Chemerin has an established role in adipocyte differentiation and glucose uptake [6]. Adiponectin is an antiatherogenic adipokine, involved in carbohydrate and lipid metabolism. Although is mainly secreted by adipose tissue, a negative relation between circulating adiponectin and the amount of visceral adiposity is described [16]. Adiponectin is also considered a marker of IS with controversial metabolic protection [16].

Statistical analysis

Data analysis was performed using IBM SPSS Statistics Version 22.0. The variables were described using mean values ± standard deviation (SD). Independent two-sample test was used to study the differences between the obese and non-obese samples. A natural logarithmic transformation was performed for the variables without a normal distribution. Thus, Pearson coefficient was used to analyze the linear correlation between circulating chemerin, adiponectin, and the studied variables. Multiple linear regression models were created to analyze the factors that determine anthropometric indices, levels of HDL-cholesterol, triglycerides, fasting plasma glucose, uric acid, insulinemia, IS and IR in the obese group. The most important condition when creating these models was for circulating chemerin to be an independent variable.

Results and discussions

The baseline clinical and biochemical characteristics of the study population are presented in Table 1. The obese and non-obese patients didn't fulfill the criteria for defining metabolic syndrome, the mean age was comparable between the groups, and females accounted for over 2/3 of all patients in both samples. Similar to other studies [8-9, 17-19], chemerin levels were significantly higher in obese patients compared to the non-obese group (11.56 (10.39–13.10) vs 9.10 (8.13–10.60) ng/mL, p = 0.0001). However, in our studied obese group chemerin was significantly lower compared to other reported series [8, 20, 21], possibly related to the status of metabolic health. Adiponectin levels were also significantly different between the two samples (18.05 ± 1.55 vs 16.36 ± 1.49 ng/mL, p = 0.0003). It is worth mentioning that unlike other studies [22], we report higher values in the obese subjects. This finding could sustain that not circulating adiponectin, but the local expression in perivisceral fat and also the

	Non-obese (control group) n = 25	Obese n = 25	p-value
Age (years)	43.36 ± 13.9 (37.62-49.10)	39.24 ± 8.74 (35.63-42.85)	**0.021**
Female sex (%)	68	84	-
Systolic blood pressure	118.04 ± 11.72	129.36 ± 13.03	**0.0022**
Diastolic blood pressure	67.08 ± 7.89	75.28 ± 11.12	**0.0044**
BMI (kg/m^2)	24.24 ± 3.15 (22.36-24.96)	43.9 ± 6.07 (40.49-45.50)	**0.0001**
Waist circumference (cm)	83.04 ± 8.75 (79.43-86.65)	125.5 ± 18.68 (117.79-133.21)	**0.0001**
WHR	0.83 ± 0.08 (0.80-0.86)	0.96 ± 0.10 (0.92-1)	**0.0001**
Index of central obesity	0.50 ± 0.06 (0.48-0.52)	0.75 ± 0.08 (0.71-0.78)	**0.0001**
Cholesterol (mg/dL)	197.80 ± 41.39 (180.71-214.89)	201.4 ± 27.17 (190.18-212.62)	0.718
HDL-cholesterol (mg/dL)	50.36 ± 14.94 (44.19-56.53)	50 ± 9.98 (45.88-54.12)	0.92
LDL-cholesterol (mg/dL)	125.04 ± 39.97 (109.37-140.71)	127.68 ± 23.48 (117.98-137.37)	0.76
Triglycerides (mg/dL)	121.24 ± 25.74 (100.29-142-19)	124.32 ± 17.96 (94.61-154.03)	0.86
Plasma glucose (mg/dL)	88.32 ± 8.80 (84.69-91.95)	99.28 ± 14.62 (93.24-105.32)	**0.0026**
Insulinemia (μU/mL)	5.98 (2.81–12)	18.80 (13.50–30.10)	**0.0004**
Insulin sensitivity	0.16 ± 0.02 (0.15-0.17)	0.13 ± 0.02 (0.13-0.14)	**0.0001**
HOMA-IR	1.28 (0.63–2.87)	4.91 (3.38–6.62)	**0.0012**
Uric acid (mg/dL)	5.29 ± 1.48 (4.68-5.90)	6.79 ± 2.19 (5.88-7.69)	**0.0067**
Adiponectin (ng/mL)	16.36 ± 1.49	18.05 ± 1.55	**0.0003**
Chemerin (ng/mL)	9.10 (8.13–10.60)	11.56 (10.39–13.10)	**0.0001**
Chemerin/adiponectin x 10^{-3}	0.55 ± 0.12	0.67 ± 0.18	**0.0052**
Data are presented as means ± standard deviations and confidence interval or median and interquartile range 25%-75% according to the normality of distribution5			

Table 1
BASELINE CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF THE STUDY POPULATION

distribution of adipose tissue, are related with its metabolic functions [23, 24]. An alternative explanation could be the adiponectin resistance phenomena, recently described by Engin [25], as a compensatory response caused by adiponectin unresponsiveness to IR at different stages of obesity.

Taking into account the suggested clinical significance of the chemerin/adiponectin ratio for the assessment of metabolic health [26], we also studied the parameter. In our study the mean value was significantly higher in obese group (0.67 ± 0.18 vs 0.55 ± 0.12, p = 0.0052). Regarding the status of metabolic health, all biochemical parameters were within the normal range in the two groups (plasma fasting glucose 88.32 ± 8.80 vs 99.28 ± 14.62 mg/dL, uric acid 5.29 ± 1.48 vs 7.9 ± 2.19 mg/dL, cholesterol 197.80 ± 41.39 vs 201.4 ± 27.17 mg/dL, HDL-cholesterol 50.36 ± 14.94 vs 50 ± 9.98 mg/dL, LDL-cholesterol 125.04 ± 39.97 vs 127.68 ± 23.48 mg/dL, triglycerides 121.24 ± 25.74 vs 124.32 ± 17.96 mg/dL). Only for plasma fasting glucose and uric acid there were significant differences between groups ($p < 0.05$). All anthropometric indices were within the normal range in the non-obese group, including the mean value of 0.50 admitted for index of central obesity [27]. Also, the same indices were significantly higher in obese group (BMI 24.24 ± 3.15 vs 43.9 ± 6.07 kg/m^2; waist circumference 83.04 ± 8.75 vs 125.5 ± 18.68 cm; WHR 0.83 ± 0.08 vs 0.96 ± 0.10; index of central obesity 0.50 ± 0.06 vs 0.75 ± 0.08; p = 0.0001). Similar findings were documented for insulinemia (0.16 ± 0.02 vs 0.13 ± 0.02, p = 0.0004) and the derived parameters of metabolic health (IS 0.16 ± 0.02 vs 0.13 ± 0.02, p = 0.0001; HOMA-IR 1.28 vs 4.91, p = 0.0012). Systolic (SBP) and diastolic (DBP) blood pressures, as components of metabolic syndrome, had also normal mean values in both groups (SBP 118.04 ± 11.72 vs 129.36 ± 13.03 mmHg, p = 0.0022; DBP 67.08 ± 7.89 vs 75.28 ± 11.12 mmHg, p = 0.0044).

In our study circulating chemerin was not correlated with BMI (r =0.25, p =0.08) as other reports demonstrate in obesity [8-10, 12, 19, 26, 28]. On the other hand, the reported data in morbid obesity are controversial, mainly based on results after bariatric surgery [8, 20, 21, 29]. According to other clinical studies [9-12, 19] our results demonstrate the correlation between circulating chemerin and waist circumference (r =0.37, p = 0.012) and WHR (r = 0.36, p = 0.012). Also, our study is the first to report the correlation of serum chemerin with index of central obesity (r = 0.47, p = 0.003). It is worth mentioning that chemerin/adioponectin ratio offers similar findings when relation with anthropometric indices is studied, in contrast to serum adiponectin which was not related to any clinical or biochemical parameter. So, chemerin/adiponectin ratio was not related to BMI (r = 0.23, p = 0.11), but a positive correlation was found with waist circumference (r = 0.39, p = 0.008), WHR (r = 0.41, p = 0.005) and index of central obesity (r = 0.45, p = 0.002). Our results suggest that chemerin/adiponectin ratio is superior to circulating adiponectin levels when relation with anthropometric parameters is assessed. Another finding of our study is that chemerin and chemerin/adiponectin ratio are not related with parameters of glucose metabolism homeostasis, including fasting plasma glucose, insulinemia, IS or IR, and also with HDL-cholesterol, triglycerides (p > 0.05). Taken together and considering that our obese patients are metabolic healthy, these results cannot be extrapolated to the whole spectrum of obesity. In fact, Li et al. [12] underline this point due to the heterogeneity of design between studies, while Chu et al. highlight the importance of bias factors [26]. All the mentioned correlations are detalied in table 2.

Regarding the hemodynamic parameters related to metabolic health, our study demonstrates that serum chemerin and chemerin/adiponectin ratio are related to systolic blood pressure (r = 0.33, p = 0.022; r = 0.29, p = 0.044, respectively). Also, serum chemerin is related to mean arterial pressure (r = 0.3, p = 0.041), a parameter representative to peripheral resistance and estimated using the formula: [(2 x DBP) + SBP]/3. This finding suggests the role of chemerin in modulating vascular tone. In fact, in a previous report we demonstrated that chemerin is an independent predictor for several parameters of arterial

Parameter	Chemerin		Chemerin/adiponectin ratio	
	r	p	r	p
BMI (kg/m^2)	0.25	0.08	0.23	0.11
Waist circumference	0.37	**0.012**	0.39	**0.008**
Waist to hip circumference ratio (WHR)	0.36	**0.012**	0.41	**0.005**
Index of central obesity	0.47	**0.003**	0.45	**0.002**
Fasting plasma glucose (mg/dL)	0.24	0.095	0.23	0.11
Insulinemia (μU/mL)	0.21	0.143	0.21	0.150
IS	-0.25	0.082	-0.25	0.087
HOMA-IR	0.27	0.08	0.29	0.08
HDL-cholesterol (mg/dL)	0.03	0.8	0.05	0.7
Triglycerides (mg/dL)	0.03	0.8	0.004	0.98
Systolic blood pressure (mmHg)	0.33	**0.022**	0.29	**0.044**
Diastolic blood pressure (mmHg)	0.27	0.06	0.21	0.13
Mean arterial pressure (mmHg)	0.3	**0.041**	0.26	0.07

Table 2
CORRELATIONS OF CHEMERIN AND CHEMERIN/ADIPONECTIN RATIO WITH PARAMETERS OF METABOLIC HEALTH

Dependent variables	Independent variable - Chemerin			
	Coefficient	p-value coefficient	p-value Model	R^2adjusted
BMI (kg/m²)	-0.23	0.21	0.946	0.0001
Waist circumference (cm)	0.992	0.24	0.858	0.0001
WHR	0.016	**0.013**	0.642	0.0001
Index of central obesity	0.005	0.21	0.862	0.0001
Insulinemia (µU/mL)	1.019	0.066	0.874	0.0001
IS	-0.00269	**0.003**	0.0001	0.845
HOMA-IR	0.231	0.13	0.0001	0.894

Table 3
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VARIABLE

stiffness in metabolic healthy subjects with morbid obesity [30].

When multiple linear regression models were created to analyze chemerin as an independent variable that determine anthropometric indices and glucose homeostasis in obese group, we found that circulating levels still correlated with WHR (p = 0.013), but also with IS (p = 0.003) (table 3). As we previously reported in a separate linear regression model where chemerin was a dependent variable, fasting plasma glucose determined the circulating chemerin level [31]. Despite the presence of IR in our obese group, chemerin was not related with this parameter. Our results are concordant with the previous report of Bozaoglu et al [19]. The authors concluded that chemerin is not a predictor for IR in patients with normal glucose tolerance. Corona-Meraz et al. also reported that serum chemerin levels are higher in obesity without IR versus obesity with IR [32]. This could explain the levels of chemerin much lower in our study in comparison with similar clinical studies. The properties of perivisceral fat in our obese sample could be also determinant of chemerin and adiponectin profiles [6, 33, 34].

Although we demonstrated that serum chemerin levels were related to anthropometric indices, our study has several limitations. First of all, we didn't study the expression of CMKLR1 receptor, mentioned to better characterize the role of chemerin in obesity-related metabolic and clinical changes [6, 32, 33]. Secondly, we didn't use other relevant indices for morbid obesity such as body fat percentage, the subcutaneous fat mass amount and distribution [32]. Finally, due to the small size of samples and the method of chemerin measurement, not specifically addressed to the different isoforms, our results should be confirmed by further research.

Conclusions

The relation between circulating chemerin and anthropometric indices in metabolic healthy morbidly obese patients is suggestive for the potential role of this adipokine in the pathophysiology of obesity. In morbidly obese patients without criteria for defining metabolic syndrome, chemerin is an independent predictor for WHR and decreased insulin sensitivity, but not for other metabolic changes. Chemerin/adiponectin ratio is also a useful parameter, but not superior to chemerin levels.

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