Circulating Chemerin, Oxidative Stress, Inflammation and Insulin Resistance in Morbid Obesity

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Chemerin is a relatively novel adipokine with controversial pathophysiological role in obesity. Our study aimed to investigate the relationship of serum chemerin level with inflammation, oxidative stress and insulin resistance in morbidly obese subjects. Circulating chemerin was an independent predictor of TNF-Q level, superoxide dismutase activity and lipid peroxidation, but no relation with insulin resistance could be sustained. Taken together chemerin could be a marker of dysfunctional adipose tissue, but its serum level does not reflect properly the metabolic phenotype in morbid obesity.

Keywords: chemerin, oxidative stress, inflammation, insulin resistance

Adipose tissue is now recognized as a huge endocrine organ, highly active metabolic. It is not only a passive reservoir for energy storage, but also secretes numerous biologically active molecules, known as adipokines, and expresses specific receptors involved in neuro-endocrine responses. Adipokines act in both autocrine/paracrine and endocrine fashion, thus coordinating energy, glucose and lipid metabolisms, and regulating immune function, insulin sensitivity (IS), inflammation [1]. In obesity, adipose tissue is both expanded and dysfunctional, causing adverse metabolic consequences. On the other hand, not all fat depots have similar properties. Visceral adipose tissue activity is the determinant of metabolic risk and is characterized by preferentially secretion of pro-inflammatory adipokines. Actually, obesity *per se* induces oxidative stress that triggers the release of pro-inflammatory cytokines, which in turn enhance reactive oxygen species production [2]. Thus, it is generated a chronic low-grade inflammation as well as insulin resistance (IR) [3].

Chemerin is a relatively novel adipokine with controversial pathophysiological role in obesity [4]. Clinical studies report conflicting results regarding its relationship with obesity and metabolic syndrome [5,6], but a recent meta-analysis confirms that the circulating levels correlate with clinical indices of obesity, high-sensitive reactive C protein (hs-CRP) and IR [7]. Also, human studies demonstrate high circulating levels in morbidly obese patients that decrease after bariatric surgery [8,9]. Chemerin is a multifunctional protein, acting as a chemokine and adipokine through its specific receptor (chemokine-like receptor 1-CMKLR1) and possibly as growth factor [10]. There are many clinical and experimental studies that support association of chemerin with markers of inflammation (i.e. hs-CRP, tumor necrosis factor alpha – TNF- α, interleukin-6 etc.) and oxidative stress [11-16]. However, our knowledge about its direct influence on inflammation is still unclear [17], because it has been demonstrated that chemerin also appears to exert anti-inflammatory effect in human vascular endothelial cells [18]. The mechanisms are incompletely understood and seem to involve nitric oxide synthesis and TNF-α production, another cytokine that mediate obesity-induced inflammation and IR [19-20]. Considering all these conflicting data, our study was designed to investigate the relationship of chemerin with markers of inflammation, oxidative stress and insulin resistance in apparently healthy morbidly obese subjects.

Experimental part

Material and methods

Our study enrolled 25 consecutive morbidly obese patients (BMI > 40 kg/m^2) who were referred to the Department of Cardiology for preoperative assessment, and 25 age- and gender matched non-obese control participants (BMI < 30 kg/m^2). Patients with documented cardiovascular or metabolic risk factors and/or disease, medical or surgical comorbidities generating inflammation, or treated with drugs interfering inflammation were excluded. All subjects who presented any 3 of 5 criteria for defining metabolic syndrome [21] or had concurrent enrollment in another study were also excluded. The study protocol was approved by the University- and the Hospital Local Ethics Committees. The protocol has been explained in detail and the informed consent was signed before enrollment. Anthropometric measurements included body mass index (BMI) (kg/m^2), waist circumference, waist to hip circumference ratio (WHR) and index of central obesity (waist circumference to height ratio). All venous blood samples were collected after overnight fast. The assessment of biochemical parameters related to obesity (plasma cholesterol, high-density lipoprotein-cholesterol – HDL-cholesterol, low-density lipoprotein-cholesterol – LDL-cholesterol, triglycerides, plasma glucose, uric acid, insulinemia) and hs-CRP, as marker of inflammation, was performed within two hours. Fasting plasma glucose, total cholesterol and triglycerides were determined applying enzymatic colorimetric method, while HDL-cholesterol and hs-CRP were measured using imunoturbidimetry. LDL-cholesterol levels were calculated by Friedewald equation as described elsewhere [22]. Fasting insulinemia and

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serum TNF-α - as marker of inflammation were assessed using chemiluminiscence immunoassay kits (Siemens Healthcare GmbH., Germany) automated by Immulite 1000 analyzer. IR and IS completed the assessment of metabolic health. IR is defined as the inability of cells to use insulin effectively. IR and IS were calculated applying Homeostasis Model Assessment (HOMA) and quantitative check index (QUICKI), respectively, as recently described elsewhere [23]. The complete blood cell count was measured by use of an automated analyzer. The venous blood samples collected for assessment of chemerin, TNF-á and oxidative stress were stored at -20°C and processed after completing the enrollment of patients. Serum chemerin was measured using quantitative Human ELISA (enzyme-linked immunosorbent assay) kit (ab155430) 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, 131-137 amino acids long, resulted from proteolytic cleavage of the inactive molecule [4]. The activities of superoxide dismutase-SOD, glutathione peroxidase-GPx (Randox assay kits) and malondialdehyde-MDA (Sigma-Aldrich Co. LLC., assay kit) were used as oxidative stress markers and determined by spectrophotometry. The activity of SOD was evaluated by its ability to inhibit the photochemical reduction of nitroblue tetrazolium (NBT). Each 1.5 mL reaction mixture contained 100 mM TRIS/HCl (*p*H 7.8), 75 mM NBT, 2μM riboflavin, 6 mM EDTA, and 200μL of supernatant. One unit of SOD was defined as thequantity required for inhibiting the rate of NBT reduction by 50%. GPx activity was analyzed using a reaction mixture (1mL of 0.4M phosphate buffer (*p*H 7.0) containing 0.4mM EDTA, 1mL of 5mM NaN3, 1mL of 4mM GSH, and 0.2 mL of supernatant) preincubated at 37°C for 5 min. Then 1ml of 4mM H_2O_2 was added and incubated at 37°C for further 5 min. The excess amount of GSH was quantified by the DTNB method. One unit of GPX was defined as the amount of enzyme required to oxidize 1 nmol GSH/min. Lipid peroxidation (MDA) was measured applying the thiobarbituric acid assay. 200 μL of supernatant wass added and briefly mixed with 1 mL of 50% trichloroacetic acid in 0.1M HCl and 1 mL of 26 mM thiobarbituric acid. The samples were maintained at 95°C for 20 min and then were centrifuged at 3000 rpm for 10 min. The supernatants were read at 532 nm. A calibration curve was constructed using MDA as standard and the results were expressed as μmol/L.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics Version 22.0. The variables were described using mean values ± standard deviation and confidence interval or median and inter-quartile range 25%-75% according to the normality of distribution. Independent two-sample test was used to study the differences between the obese and non-obese groups. A natural logarithmic transformation was performed for the variables without a normal distribution and Pearson coefficient was used to determine if there were linear correlations between chemerin and the studied variables. Kendall tau coefficient was used to determine the correlations between chemerin and the variables without a normal distribution. Multiple linear regression models were created to analyze the factors that determine inflammation, oxidative stress and IR in the obese subgroup. The most important condition when creating these models was for serum chemerin to be an independent variable. Also, a separate linear regression model was created to analyze the factors that determined the level of chemerin.

Results and discussions

The characteristics of study population are described in table 1.

Table 1
BASELINE CHARACTERISTICS OF THE STUDY POPULATION

	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	-
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-cholesteol (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	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**
Insulin resistance	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**
hs-CRP (mg/L)	0.24 (0.09–044)	0.67 (0.22–0.28)	**0.0422**
TNF-α (pg/mL)	7.77 (6.22–9.58)	6.49 (5.56–7.92)	0.1167
Chemerin (ng/mL)	9.10 (8.13–10.60)	11.56 (10.39–13.10)	**0.0001**
SOD (U/gHb)	1015 (840.50–1155)	1065 (923–1110)	0.228
GPx (U/gHb)	65 (51–67.50)	35 (33–45)	**0.0001**
MDA (μmol/L)	1.19 (1.06–1.30)	1.79 (1.51-2.29)	**0.005**
White blood cell count (/mm^3)	7194 ± 2374.75 (6602.1-8617.8)	7450 ± 2374.75 (7248.7-8634.8)	0.32

Data are presented as mean value ± standard deviation and confidence interval or median and inter-quartile range 25%-75% according to the normality of distribution

Both subgroups didn't fulfill the criteria for defining metabolic syndrome [21], but decreased IS (0.13 ± 0.02, p = 0.0001) and presence of IR – 4.91 (3.38–6.62) (p = 0.0012) were documented in morbidly obese patients. Similar to other clinical studies that refer to morbid obesity [6-9,12,24], plasma chemerin levels were significantly higher when BMI > 40 kg/m^2 – 11.56 (10.39–13.10) vs 9.10 (8.13–10.60) ng/mL (p = 0.0001). Yet, our study didn't find a significant correlation between serum chemerin levels and BMI (r =0.25, p =0.08) as other reports sustain [5,7,9,25-28]. On the other hand, our results are difficult to interpret, as there are scarce and conflicting data on morbid obesity [8,9,12]. Similar to other clinical studies [5-7] we found a positive correlation of serum chemerin with waist circumference (r =0.37, p = 0.012) and WHR (r = 0.36, p = 0.012) [5,25,26]. Our study is the first to report the correlation of chemerin with index of central obesity (r = 0.47, p = 0.003). Regarding the parameters of glucose metabolism homeostasis, chemerin level was correlated with fasting plasma glucose (r = 0.45, p = 0.027), but not with IS or IR (p > 0.05). All these correlations are presented in table 2.

Table 2
CORRELATIONS OF CHEMERIN WITH OTHER STUDIED VARIABLES IN MORBID OBESITY

Parameter	Chemerin	
	r	p
BMI (kg/m^2)	0.25	0.08
Waist circumference	0.37	**0.012**
Waist to hip circumference ratio (WHR)	0.36	**0.012**
Index of central obesity	0.47	**0.003**
TNF-α (pg/mL/)	0.445	**0.002**
hs-CRP (mg/L)	0.22	0.1
SOD (U/gHb)	-0.11	0.9
GPx (U/gHb)	0.1	0.47
MDA (µmol/l)	0.14	0.3
Fasting plasma glucose (mg/dL)	0.45	**0.027**
IS	-0.33	0.19
IR	0.334	0.1

Experimental and clinical studies have suggested that chemerin may be an independent mechanism linking obesity to IR markers [5,12,25-29]. On the other hand, Li et al. recommend the results to be interpreted with caution due to the heterogeneity of design between studies [7]. Chu et al. highlight the importance of bias factors [28], while Bozaoglu et al. report that chemerin is an independent predictor for metabolic syndrome components, but not for IR markers in patients with normal glucose tolerance [25]. The markers of inflammation – hs-CRP and TNF-Q had normal median values in both subgroups, as shown in table 1. Similar to recent data [12] we found that hs-CRP was not related to chemerin levels (p > 0.05), but our results are inconsistent with most studies in obesity [5,11,13,15,27-30]. TNF-Q, the other marker of inflammation, was significantly related to serum chemerin levels in obese subgroup (r = 0.44, p = 0.002). We noticed that our results are in discrepancy with another study in morbid obesity [12], but confirm the relation demonstrated by most experimental and clinical data [3,8,16,31]. Regarding the markers of oxidative stress, activity of GPx and MDA were statistically significant different in obese patients when compared to the control group (p < 0.05) as described in table 1. GPx, catalase and SOD activities reflect the antioxidant defense and it has been reported that are inversely related to BMI [32-34]. In our study, SOD had normal values, while GPx activity was slightly under the normal range in obese patients (< 40 U/gHb). The results are difficult to interpret, but it has been demonstrated elsewhere that GPx activity is higher in morbid obesity associated with IR [35]. It could be assumed that the current values of GTx reflect this process. We also found malonyldialdehyde (MDA) – an indicator of lipid peroxidation to have statistically significant increased levels in obese patients. The most important finding is that chemerin was not related to oxidative stress (p > 0.05) as shown in table 2. When multiple linear regression models were created to analyze chemerin as an independent variable that determine inflammation, oxidative stress and glucose homeostasis in obese subgroup, we observed that its levels still correlated with TNF-Q (p = 0.003), but also with SOD activity (p = 0.03) and MDA (p = 0.005), as described in table 3. In these models GPx activity was also an independent predictor of IS and IR (p=0.0001).

Also, in a separate linear regression model where chemerin was a dependent variable, hs-CRP, MDA, WBC count and fasting plasma glucose determined its serum level as shown in table 4.

Taken together, our findings could have several explanations. Firstly, our study was addressed to morbidly obese patients, with no criteria for defining metabolic syndrome [21]. Most studies focus on obese patients with metabolic syndrome or diabetes. Taking into account the heterogeneity of metabolic phenotypes between reports, the data cannot be extrapolated to our study. Secondly, the profile of adipokines secretion is closely linked to early

Dependent variables	Independent variable - Chemerin			
	Coefficient	p-value coefficient	p-value Model	R^2adjusted
TNF-α (pg/mL/)	0.78	0.003	0.0001	0.706
hs-CRP (mg/L)	-0.18	0.15	0.04	0.33
SOD (U/gHb)	-0.33	0.033	0.012	0.41
GPx (U/gHb)	-0.37	0.52	0.001	0.525
MDA (µmol/l)	0.121	0.005	0.0001	0.555
IS	-0.00269	0.003	0.0001	0.845
IR	0.231	0.13	0.0001	0.894

Table 3
MULTIPLE LINEAR REGRESSION MODELS USING CHEMERIN AS AN INDEPENDENT VARIABLE IN MORBID OBESITY

Independent variables	Dependent variable - Chemerin			
	Coefficient	p-value coefficient	p-value Model	R^2 adjusted
hs-CRP (mg/L)	-0.643	0.013	0.0001	0.774
MDA (µmol/l)	2.639	0.0001		
Fasting plasma glucose	0.077	0.018		
WBC count (/mm^3)	-0.0003	0.021		

Table 4
LINEAR REGRESSION MODEL USING CHEMERIN AS DEPENDENT VARIABLE IN MORBID OBESITY

metabolic changes in obesity. Our study noticed decreased IS and presence of IR. Recently, Corona-Meraz et al. demonstrated increased levels of circulating chemerin in obesity without IR compared to obesity with IR and non-obese patients [36]. This could be a good explanation for the levels of chemerin much lower in our study when compared to other studies. Another important experimental finding is that the relation of chemerin with IR, inflammation and clinical metabolic parameters is better characterized when expression of CMKLR1 receptor is also measured [3,4,36]. Thirdly, the study of Corona-Meraz et al. highlights the significance of using multiple indices of adiposity when the role of chemerin is discussed [36]. This could be a limitation of our study, as we didn't determine body fat percentage and the subcutaneous fat mass amount and distribution. In morbid obesity the amount of subcutaneous fat is increasing, so the indices of abdominal obesity should be interpret in a different manner. Finally, the properties of perivisceral fat are determinant of pro-inflammatory adipokines secretion and could explain the variance in serum chemerin levels [2-4]. It was suggested that chemerin has a critical role in adipogenesis and its expression may reflect the adypocites size, the grade of differentiation or body mass fat [10,25]. For this reason, it would be more relevant to study the contribution of local chemerin expression compared to local adiponectin, when influence on inflammation and oxidative stress is measured. It is worth mentioning that the studied markers of inflammation were within the normal range in our study. However, we found that chemerin was related independently with TNF-Q levels, while hs-CRP is determinant of serum chemerin level. Also, circulating chemerin was an independent determinant of SOD activity and level of lipid peroxidation. Thus, serum chemerin might participate in adipose tissue-induced inflammation and oxidative stress.

Conclusions

Chemerin could be considered a predictor of inflammation and oxidative stress in apparently healthy morbidly obese patients, but the circulating level does not reflect properly the metabolic health. The measurement of visceral local secretion or the study of chemerin level coupled with expression of CMKLR1 receptor could better characterize the dymetabolic phenotype.

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