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ORIGINAL ARTICLE

# Chemerin serum levels in girls with anorexia nervosa

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**Abstract**

**BACKGROUND:** The regulatory function of chemerin (CHEM) in the process of adipogenesis and the metabolism of adipocytes has been confirmed. Data from several studies have shown higher serum CHEM in obesity. To date, there are no available studies on serum CHEM concentrations in patients with anorexia nervosa (AN), which is recognized as a good biological model of the chronic atrophy of adipose tissue and energy metabolism disorders in humans.

**OBJECTIVES:** The aim of the study was to assess serum CHEM concentrations in girls with AN in comparison to healthy and obese subjects and determine its relationship with body mass, BMI and insulin.

**METHODS**: CHEM serum concentrations were evaluated using commercially available ELISA kit in 65 Polish girls with restrictive AN, in 39 healthy controls (H) and 64 girls with simple obesity (OB).

**RESULTS:** The mean serum CHEM concentration in the AN group was significantly lower than in the H and OB groups. After adjusting for BMI, CHEM concentrations in the AN group were significantly lower than in the H group, but statistically higher than in the OB group. Significant correlations between serum CHEM and body mass (r=0.77), BMI (r=0.82), Cole index (r=0.81) and serum insulin (r=0.78) were observed.

**CONCLUSIONS:** Serum chemerin concentrations in female adolescents are strongly associated with nutritional status. After adjustment for BMI, lower CHEM may result from the loss of body mass caused by nutrition restrictions and/or intensive physical effort in AN and compensatory mechanisms preventing further adipose tissue expansion, metabolic dysfunction and insulin resistance in obesity.

## INTRODUCTION

Chemerin (CHEM), initially known as TIG2 (tazarotene-induced gene 2 protein) or RARRES2 (retinoid acid receptor responder 2), subsequently described as a chemotactic factor, is one of the newly recognized adipokines (Nagpal *et al.* 1997; Wittamer *et al.* 2003; Cash *et al.* 2008). Active CHEM, which contains 137 amino acids (16-kDa), generated from prochemerin (18-kDa) under the impact of serine or cysteine protease, acts as a secretion ligand for chemokine receptors: CMKLR1 (chemokine-like receptor1), also referred to as Chem23 or DEZ, and CCRL2 (chemokine C-C motif receptor-like 2) (Zabel *et al.* 2005; Wittamer *et al.* 2005).

Intensive mRNA expression of CHEM in white adipose tissue, liver, and placenta in mice has been demonstrated; the most intense expression of CMKLR1 mRNA has been detected in adipocytes and the stroma of white adipose tissue, in lungs, heart, and placenta. The expression of CMKLR1 mRNA depends on the differentiation degree of adipocytes, which may suggest its autocrine activity on fat cells (Goralski *et al.* 2007). Roh *et al.* (2007) and Rhee (2011) have detected intensive expression of mRNA CHEM and its receptor in adipose tissue and the increase of the level of this expression in mice fed with a high-fat diet. The regulatory function of CHEM in the process of adipogenesis and the metabolism of adipocytes has been confirmed (Goralski *et al.* 2007; Muruganandan *et al.* 2010). During the differentiation of adipocytes from mesenchymal stem cells of the stroma, the system CHEM/CMKLR1 cooperates with the transcription factor PPRγ, the main regulator of fat cell differentiation (Muruganandan *et al.* 2011).

It is suggested that CHEM is included in the liver–adipose tissue–skeletal muscles system (Becker *et al.* 2010). There is also some evidence that it plays a role in the metabolism of carbohydrates and fats (Takahashi *et al.* 2008; Kralisch *et al.* 2009; Sell *et al.* 2009; Ernst *et al.* 2010). Data from several studies have shown higher concentrations of CHEM in serum of obese persons compared with nonobese persons (Bozaglou *et al.* 2007; Bozaoglu *et al.* 2009; Catalán *et al.* 2013), as well as a positive correlation between the serum CHEM concentration and body mass index (BMI) (Bozaglou *et al.* 2007; Bozaoglu *et al.* 2009; Sell *et al.* 2010; Chakaroun *et al.* 2012; Shin *et al.* 2012). A review of the literature yielded no research on the expression of CHEM in adipose tissue or its serum concentrations in humans with body mass deficit.

Anorexia nervosa (AN), a chronic psychosomatic syndrome, most frequently occurs in young girls and is characterized by inappropriate nutrition habits leading to a drastic loss of the body mass and frequently to severe malnutrition (Nogal & Lewiński 2008). AN is recognized as a good biological model of the chronic atrophy of adipose tissue and energy metabolism disorders in humans. To date, there are no available studies on serum CHEM concentrations in patients with AN.

Our previous research demonstrated significantly lower serum concentrations of leptin, apelin, resistin, and visfatin, but higher concentrations of adiponectin in girls with AN than in healthy girls with the normal body mass as well as in obese girls (Ziora *et al.* 2010a; Ziora *et al.* 2010b; Ziora *et al.* 2010c; Ziora et al.,2012a; Ziora *et al.* 2012b). However, after adjusting for BMI and the absolute values of these adipokines, we found no linear correlations between the total content of leptin, resistin, and visfatin in blood and in the mass of adipose tissue (Ziora *et al.* 2010a; Ziora *et al.* 2012a; Ziora *et al.* 2012b).

As previous reports indicated a positive correlation between serum CHEM and BMI, we hypothesized that CHEM concentrations in persons with AN were significantly lower than in subjects with a normal body mass and in the obese. Thus, the objective of this study was to evaluate serum CHEM concentrations in girls with AN in comparison to healthy as well as obese girls and determine its relationship with BMI and insulin.

## MATERIALS AND METHODS

*Subjects*

This study involved 158 girls aged 10.9 to 18.6 years. BMI (body weight [kg]/height [$m^2$]), standard deviation score (SDS) for BMI, and Cole Index (patient's BMI expressed as a percentage of the median BMI for age and sex) were calculated for all participants according to current Polish populational normal ranges (Palczewska & Niedźwiedzka 2001). The examined group consisted of 65 girls with the restrictive form of AN according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (*DSM-IV*) (1994) classification (mean age, 15.2±0.2 years). Restrictive AN includes an intense fear of gaining weight, a refusal to maintain body weight >85% of the expected weight for a given age and height, three consecutive missed periods, and either refusal to admit the seriousness of the weight loss, or undue influence of shape or weight on one's self image, or a disturbed experience in one's shape or weight (Czekalski *et al.* 2001). The control group included 39 healthy (H), regularly menstruating female volunteers with BMI-SDS between –2.0 and +2.0 who were recruited from secondary schools (mean age, 16.0±0.4 years). We also examined a group of 54 girls with simple obesity (OB)

defined as BMI-SDS >2.0 (mean age, 14.6±0.3 years) with normal glucose tolerance.

All examined girls were at the pubertal stage of Tanner IV-V. Clinical characteristics of the examined participants are shown in Table 1.

Participants in the AN were examined during the first 2 days of hospitalization before therapy was started. Eligibility criteria consisted of a stable general medical condition and the absence of clinical signs of dehydration. The initial results of additional laboratory tests (serum electrolytes, aspartate and alanine aminotransferases, and creatinine) excluded those with hepatic and renal dysfunction. Girls with any organic or psychiatric disorders, other than eating disorders that could cause cachexia, were excluded from the study. None of the participants took any medications, including hormonal drugs within the past 3 months or had infections within the last month before the study. All participants were non-smokers.

This study was approved by the Bioethics Committee at the Medical University of Silesia in Katowice (No. L. dz. KNW/0022/KB1/2/I/11), and written informed consent was obtained from all examined participants and their parents or legal guardians before participation.

*Laboratory analyses*

To determine hormone concentrations, blood was drawn between 7:00 AM and 8:30 AM after at least a 12-hour fast. Serum was frozen at –70 °C until the time of assay. Serum CHEM concentrations were determined using the immunoenzymatic method with the application of the Human Chemerin ELISA kit (BioVendor, Czech Republic) according to the manufacturer's protocol. Concentrations were determined on the basis of the standard curve made for a series of dilutions of the standards available in the kit (recombinant human CHEM [Glu21-Ser157]. The absorbance of the samples was determined by Universal Microplate Spectrophotometer (μQUANT, Biotek Inc. Winooski, VT, USA), using the wavelength of 450 nm. The sensitivity of the kit was 0.1 ng/mL. The intra- and inter-assay coefficient of variations were 6.1% and 7.5%, respectively. The determination of insulin concentration was performed by IRMA (immunoradiometric assay), using the kit by Immunotech (Germany).

*Statistical analysis*

MedCalc software v. 12.4.0.0 (Ostend, Belgium) was used for statistical calculations. The level of statistical significance was set at $\alpha$=0.05. The normality of the data was verified by Shapiro-Wilk test. The homogeneity of variance was checked Levene's test. Non-normal distribution of data was evaluated using the using Kruskal-Wallis and median tests. Correlations were analyzed by Spearman's test.

## RESULTS

The mean age of the girls in the AN group was similar to the age of girls in the H and OB groups. The mean body mass and the BMI of participants with AN was statistically significantly lower ($P$<.0001) than participants in the H and OB groups. The mean BMI-SDS and Cole index of participants in the AN group was significantly lower ($p$<0.0001) compared with the H and OB groups (Table 1).

In the AN group, the mean duration of illness before admittance to the hospital was 12.24±2.95 months (3.0–48.0), the mean maximum body mass before the disease onset was 52.01±2.22 kg (33.0–72.00), the mean loss of the body mass was 12.03±1.71 kg (3.0–27.0), and the mean percentage loss of body mass was 22.6±2.61% (7.2–40.82).

The mean serum CHEM concentration in the AN group (128.70±1.01 ng/mL) was significantly lower ($p$<0.0001) than in the H (188.66±3.72 ng/mL) and OB groups (229.84±4.89 ng/mL) (Figure 1).

**Tab. 1.** Clinical characteristics of the examined groups of girls.

| | AN (n= 65) | H (n= 39) | OB (n= 54) |
|---|---|---|---|
| | | *mean±1.96 SE (range)* | |
| Age (years) | 15.21±0.21 (11.0–17.70) | 16.02±0.35 (11.5–18.50) | 14.58±0.32 (10.9–18.60) |
| Body weight (kg) | 40.21±0.71 (28.0–50.40)* | 55.44±1.45 (40.6–75.0) | 88.31±2.53 (42.10–133.80) |
| Height (cm) | 162.02±0.83 (143.0–176.5) | 164.18±1.20 (148.9–179.0) | 163.36±1.30 (133.0–182.0) |
| BMI (kg/m$^2$) | 15.31±0.22 (11.4–19.30)* | 20.47±0.33 (16.75–24.65) | 32.94±0.71 (23.46–52.0) |
| BMI-SDS | 2.51±0.13 (–5.31 to –0.44)* | 0.18±0.17 (- 1.74–1.99) | 7.54±0.39 (2.95–17.83) |
| Cole Index (%) | 78.40±1.20 (57.36–96.56)* | 103.63±1.77 (86.8–124.44) | 172.33±3.27 (130.25–222.54) |
| Insulin (mIU/L) | 2.32±0.04 (1.8–3.1)* | 4.21±0.08 (3.2–5.2) | 4.47±0.07 (3.6–5.8) |

AN, anorexia nervosa group; OB, simple obesity group; H, healthy group; SE, standard error; SDS, standard deviation score; BMI, body mass index; BMI-SDS, BMI standard deviation score for age and sex, according to the normal ranges for Polish population of children; Cole Index, patient's BMI expressed as a percentage of the median BMI for age and sex in Polish population of children: <75%=emaciation, 75–85%=undernutrition, 85–90%=mild undernutrition, 90–100%= normal range; >110%=overnutrition. *$p$<0.0001, AN vs H and AN vs. OB

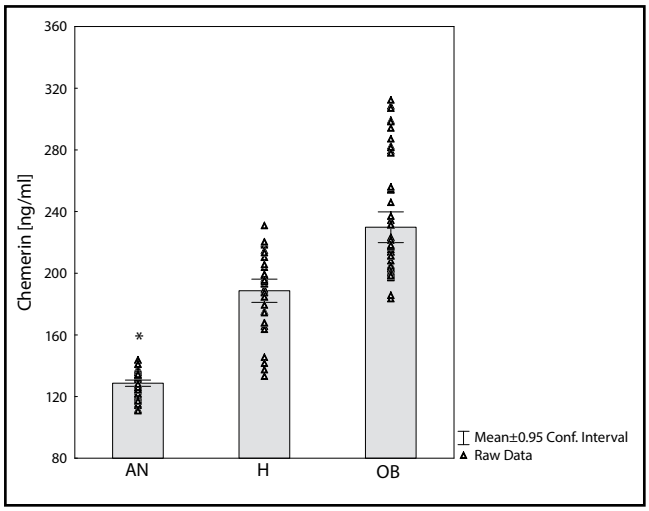


**Fig. 1.** Mean chemerin serum concentrations (ng/mL) in the examined groups. *$p$<0.0001 vs. H and OB group.

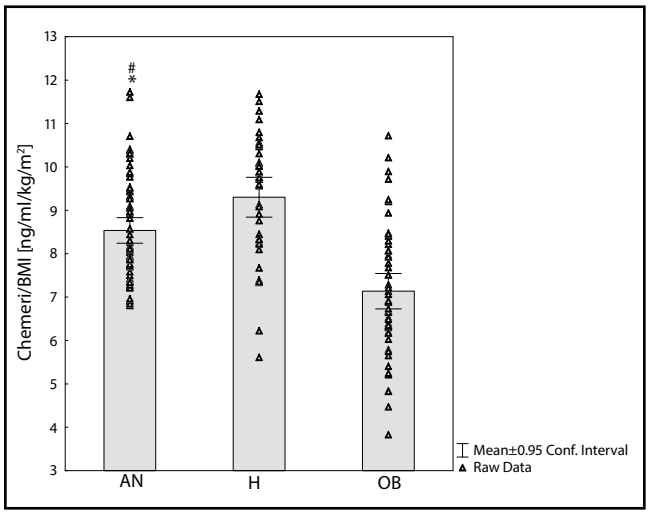


**Fig. 2.** Mean chemerin/BMI (ng/mL/kg/m$^2$) values in the examined groups. *$p$<0.05 vs. H group; #$P$<.0001 vs. OB group.

After adjusting for BMI, the mean CHEM concentrations in the AN group (8.54±0.15 ng/mL/kg/m$^2$) were significantly lower than in the H group (9.30±0.23 ng/mL/kg/m$^2$; $p$<0.05), but statistically higher than in the OB group (7.14±0.20 ng/mL/kg/m$^2$; $p$<0.0001) (Figure 2).

In the AN group, no statistically significant relationships between serum CHEM and the following were observed: illness duration, maximum body mass before the onset of the disease, loss of body mass, or percentage loss of the body mass.

The mean concentration of serum insulin in the AN group was significantly lower (2.32±0.04 mIU/L; $p$<0.0001) compared with the H (4.21±0.08 mIU/L) and the OB groups (4.47±0.07 mIU/L). There were no statistically significant differences in mean insulin between the H and OB subjects (Table 1).

Significant correlations between serum CHEM and body mass were observed (r=0.77; $p$<0.0001) (Figure 3), BMI (r=0.82; $p$<0.0001) (Figure 4), and Cole index (r=0.81; $p$<0.0001) in all examined subjects (AN, H, OB). Conversely, there were no significant correlations between these parameters in the individual groups. A positive correlation between serum CHEM and insulin concentrations was found in all examined subjects (r=0.78; $p$<0.001) (Figure 5).

## DISCUSSION

To the best of our knowledge, this is the first report on serum CHEM concentrations in girls with AN. The essence of AN is the patient's striving to obtain a slim silhouette by deliberately limiting the amount of ingested foods, participating in strenuous physical exercise, and inducing vomiting or using laxatives and/or diuretics to lose weight. AN leads to a significant decrease of the overall adipose tissue mass, which is manifested by emaciation or even severe wasting (Nogal & Lewiński

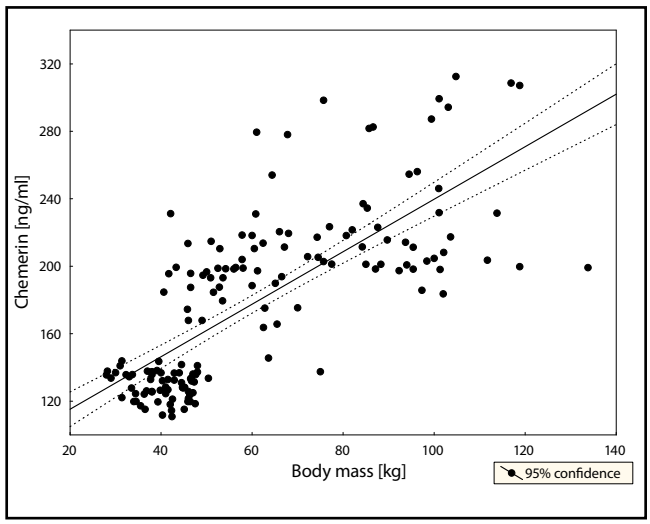


**Fig. 3.** Correlation between body weight (kg) and serum chemerin (r=0.77; $p$<0.0001) concentrations (ng/mL) in all examined girls.

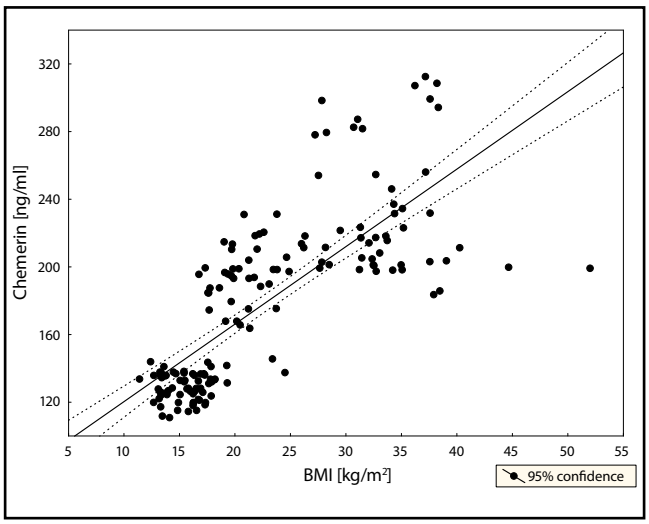


**Fig. 4.** Correlation between BMI (kg/m$^2$) and serum chemerin (r=0.82; $p$<0.0001) concentrations (ng/mL) in all examined girls.

2008). Numerous hormone disorders observed in AN, such as those that pertain to secretion and metabolism of thyroid hormones ("euthyroid sick syndrome"), adrenal cortex hormones, growth hormone, insulin, and sex hormones, is the effect of the organism's adaptation to the condition of chronic starvation aimed at maintaining energy and homeostasis (Nogal & Lewiński 2008). There are two subtypes of AN: (1) restrictive, without regular episodes of binge eating and purging behaviors; and (2) binge-purge, in which binge eating and purging behaviors, such as inducing vomiting, overusing laxatives and/or diuretics occur. To maintain the homogeneity of the group we recruited only patients with the restrictive type of AN to participate in this study.

There have been preliminary reports that serum CHEM concentrations may depend on age and sex. In their extensive epidemiological research, Bozaglou *et al.* (2007) observed higher concentrations of CHEM in women than in men and in older persons than in younger persons.

Our study demonstrated significantly lower concentrations of CHEM in girls with AN compared with concentrations seen in healthy (between –2.0 and +2.0 SDS), as well as those in obese girls. However, after adjusting serum CHEM for BMI, values in the AN group were significantly lower than in the healthy group, but significantly higher than in the obesity group. CHEM concentrations were positively correlated with body mass, BMI, and Cole index in all examined subjects (AN, H, OB), but not in the individual subgroups.

BMI, which has a strong correlation with the total mass of adipose tissue (Bozaoglu *et al.* 2010) and additionally with Cole index, is also recognized as a good parameter for evaluating the conditions of being underweight or overweight. Therefore, it could be assumed that in cases of body mass disorders, i.e., extreme emaciation or significant excess of adipose tissue, there are certain adaptive mechanisms of the human organism leading to the increased or decreased production and/or secretion of the adipocytokines.

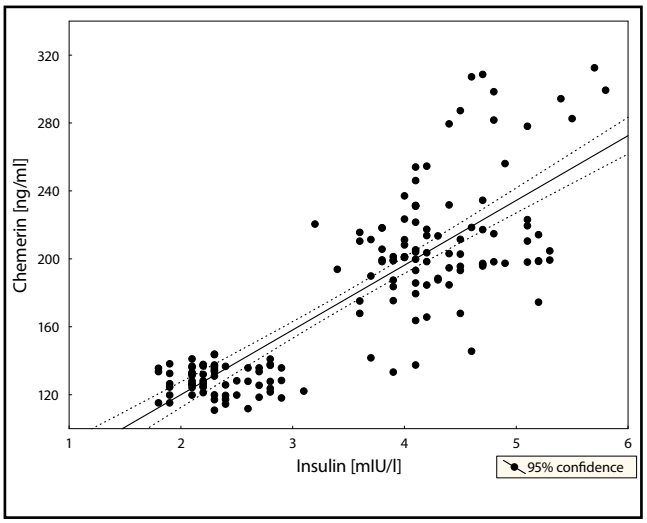


**Fig. 5.** Correlation between serum insulin (mIU/L and chemerin (ng/mL) and (r=0.78; $p<0.0001$) concentrations in all examined girls.

In our previous studies, we reported similar observations with reference to serum resistin, leptin and visfatin concentrations in AN (Ziora *et al.* 2010a; Ziora *et al.* 2010b; Ziora *et al.* 2010c; Ziora et al.,2012a; Ziora *et al.* 2012b). Although published data on serum CHEM in AN is lacking, there have been studies conducted in obese patients. Studies on CHEM expression in adipose tissue and its serum concentration in adult patients (Bozaglou *et al.* 2007; Bozaoglu *et al.* 2009; Sell *et al.* 2010; Catalán *et al.* 2013) have demonstrated significantly higher concentrations serum CHEM in obese patients with BMI >30 kg/m$^2$ compared with subjects with BMI <25 kg/m$^2$ and showed positive correlations with BMI, fat body mass, and the waist-hip ratio. In the San Antonio Family Heart Study (Bozaoglu *et al.* 2009), among 1431 people of Mexican origin, higher CHEM concentrations were observed in obese adult patients than in lean subjects. In addition, the existence of significant relationships between serum CHEM and the characteristics of the metabolic syndrome (elevated BMI, fasting insulin concentration, triglycerides and HDL concentrations in blood), irrespective of sex and age, was confirmed.

According to Bozaglou *et al.* (2010) serum CHEM concentrations also could be influenced by genetic factors, and CHEM could play a role in the occurrence of obesity by stimulating angiogenesis in the area of the expanding mass of adipose tissue.

CHEM can also play a role in food intake regulation. Brunetti *et al.* (2011) demonstrated that injections of CHEM in the area of the arcuate nucleus of the hypothalamus in rats increased the expression levels of agouti-related peptide and pro-opiomelanocortin in this region of the brain.

Our results are consistent with other researchers (Catalán *et al.* 2013) who confirmed higher serum CHEM concentrations as well as increased expression of CHEM and the CMKLR1 receptor in visceral fat tissue obtained during the Roux-en-Y gastric bypass in obese women. The amount of CHEM measured before bariatric surgeries significantly correlated with BMI as well as with homeostasis model assessment-estimated of insulin resistance (HOMA-IR) (Sell *et al.* 2010; Chakaroun *et al.* 2013). Three months after bariatric surgery (Roux-en-Y gastric bypass), decreased glycemia, HOMA-IR (Sell *et al.* 2010), and C-reactive protein (CRP) were seen (Tönjes *et al.* 2010). Moreover, a significant decrease in serum CHEM concentrations was documented 1 and 2 years after bariatric surgery (Sell *et al.* 2010).

Decreased CHEM expression in subcutaneous and visceral fat tissue and its serum concentrations results not only from the bariatric procedure, but also from the reduction of body mass due to the 12-week intensive preoperative physical workout (Chakaroun *et al.* 2012).

A low-calorie restrictive diet also has a significant impact on serum CHEM concentrations (Chakaroun *et al.* 2012). Perhaps the observed lower absolute as well as adjusted for BMI concentrations of serum CHEM in girls with AN compared with healthy and obese girls in our study may result from the loss of body mass caused by nutrition restrictions and/or intensive physical effort.

Decreased serum CHEM concentrations in obese patients after bariatric procedures is associated with improvement of glucose tolerance and lower CRP, and is irrespective of BMI changes. It is possible that insulin resistance and low-grade inflammation observed in obesity are predictors of increased serum CHEM concentrations independent from BMI (Chakaroun *et al.* 2012).

Our results demonstrated significantly lower mean serum insulin concentrations in girls with AN than in healthy and in obese girls. The concentrations of insulin did not differ significantly in healthy and obese groups because we only included girls with simple obesity to participate in our study, and excluded disorders of carbohydrate metabolism. We observed a strong positive correlation between serum concentrations of CHEM and insulin in all examined girls.

Data from experimental studies indicated that CHEM is involved in the regulation of carbohydrate metabolism. Some authors have demonstrated that CHEM increases the glucose uptake in cell lines 3T3-L1 of adipocytes (Takahashi *et al.* 2008). Conversely, studies by Becker *et al.* (2010) examining low-density lipoprotein cholesterol receptor knockout mice subjected to a high-fat diet showed that CHEM evoked insulin resistance in skeletal muscles in vivo, and thus suggests that CHEM is included in the liver–adipose tissue–skeletal muscles system.

Kralish *et al.* (2009) proved CHEM increases the insulin-stimulated transport of glucose to adipose tissue in the lines 3Yr-L1 of adipocytes, whereas Sell *et al.* (2009) showed that it reduced the glucose uptake in human skeletal muscle cells and at the level of the insulin receptor and Akt. Administration of recombinant human CHEM intensified glucose intolerance and decreased the glucose uptake in obese mice mutants (*ob/ob, db/db*) and in mice with diet-induced obesity (Ernst *et al.* 2010).

Tönjes *et al.* (2010) demonstrated that serum CHEM concentrations were significantly different in patients with impaired glucose tolerance compared with patients with elevated fasting glycemia (227.3±42.5 ng/mL vs 193.3 36.9 ng/mL; $p$=0.002). Therefore, changes in CHEM concentrations detected in early pre-diabetic stages may reflect the dysfunction of adipose tissue as an early pathogenic factor in the development of type 2 diabetes .

Results from a mice model of obesity and on pre-adipocytes cell lines 3T3-L1 indicated that in dysfunctional hypertrophic adipocytes, the activation of sterol regulatory element-binding protein 2, which is a transcriptional factor involved in regulation of cholesterol synthesis, induced the u-regulation of CHEM. A higher expression of CMKLR1 was also observed and may reflect an increased number of adipose tissue-resident macrophages in obesity. These findings indicate that adipocyte hypertrophy and chronic inflammation are equally important in inducing CHEM synthesis (Bauer *et al.* 2011).

Shin *et al.* (2001), evaluated body composition with the application of computerized tomography in 173 persons and demonstrated that CHEM concentration in serum positively correlated with the visceral fat, triglycerides, blood cholesterol, fasting glycemia, and HOMA-IR. Thus, CHEM may be a link between the presence of obesity and cardiovascular risk factors.

In a pilot study involving Caucasians, Stejskal *et al.* (2008) found that CHEM may be a marker of the metabolic syndrome. Among 181 persons exhibiting metabolic syndrome risk factors, they observed higher serum CHEM concentrations than in 55 lean healthy persons (266.0 μg/L vs. 192.5μg/L; $p$<0.01). The CHEM concentration correlated positively with patients' age, systolic and diastolic blood pressure, glycemia, triglycerides, and negatively with serum high-density lipoprotein cholesterol concentration. In this study, the established cut-off point for the CHEM concentration that was significant for metabolic syndrome was >240 μg/L (75% sensitivity and 67% specificity).

We identified at least three potential limitations to this study. The first was its cross-sectional design. The second limitation was the lack of data on fasting glycaemia and insulin sensitivity/resistance in our patients, which could have been used to better characterize study participants. Another limitation was that body composition was not analyzed using bioimpedance or other methods.

We conclude that serum chemerin concentrations in female adolescents are strongly associated with nutritional status. After adjustment for BMI, lower CHEM may result from the loss of body mass caused by nutrition restrictions and/or intensive physical effort in AN and compensatory mechanisms preventing further adipose tissue expansion, metabolic dysfunction and insulin resistancy in obesity.

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