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Low Complement C1q/TNF-related Protein-13 Levels are Associated with Childhood Obesity But not Binge Eating Disorder

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What is already known on this topic?

C1q/tumor necrosis factor-related proteins (CTRPs) play an important role in energy metabolism in humans. CTRP-13, a new member of this family, has been shown to increase insulin sensitivity and had an anorexigenic effect.

What this study adds?

We demonstrated significantly lower CTRP-13 levels in children with obesity compared with healthy weight children. A positive correlation between CTRP-13 and high-density lipoprotein-cholesterol levels suggested a possible effect of this adipokine on lipid metabolism.

Abstract

Objective: C1q/tumor necrosis factor-related proteins (CTRPs) are recently described members of the adipokine family. CTRP-13, a new member of this family, has been shown to increase insulin sensitivity and had an anorexigenic effect on food intake in experimental studies. The aim was to investigate serum CTRP-13 levels in children with obesity, and its relationship with other adipokines, metabolic parameters, or binge eating disorder (BED).

Methods: A cross-sectional study was conducted with 105 pubertal children attending a single center. Clinical (metabolic syndrome, BED) and biochemical (glucose, insulin, lipids, leptin, adiponectin, CTRP-13 levels) parameters were assessed.

Results: Sixty children with obesity [24 males (40%); median age 14.7 (13.0-16.4) years] and 45 healthy controls [15 males (33.3%); median age 15.2 (14.1-16.5) years] were included. Serum adiponectin and CTRP-13 levels were significantly lower in children with obesity than controls (7.1 vs 20.1 µg/mL, $p < 0.001$; 64.7 vs 103.8 ng/mL, $p < 0.001$, respectively). CTRP-13 levels correlated negatively with body mass index (Spearman rho = -0.230, $p = 0.018$) and positively with high-density lipoprotein-cholesterol levels (Spearman rho = 0.218, $p = 0.026$). There was no significant difference in serum CTRP-13 concentrations in terms of the presence of metabolic syndrome or BED.

Conclusion: Childhood obesity seems to be causing dysregulation in adipokine production and function, including the down-regulation of CTRP-13. The positive correlation between CTRP-13 and HDL-C levels suggested a possible effect of this adipokine on lipid metabolism. Thus CTRP-13 may be a novel biomarker for dyslipidemia in childhood obesity.

Keywords: C1q/TNF-related proteins, adipocyte, binge eating disorder, metabolic syndrome, pediatrics

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Introduction

Obesity has become an important public health problem for children and adolescents in the last few decades. Obesity is characterized by an increase in body fat mass, developing when energy intake is greater than energy consumption. In other words, obesity is a complex and multifactorial disease that is accompanied by endocrine and metabolic changes as a result of enhanced body fat tissue (1). Since childhood obesity is associated with metabolic and cardiovascular diseases in both children and later adulthood, diagnostic and preventive approaches are essential (2,3).

Appetite regulators play a significant role in ensuring the balance between energy intake and consumption. Among them, insulin and leptin are the major hormones that control dietary intake and the feeling of satiety (4). Adiponectin is one of the main hormones released from adipose tissue and regulates cardiovascular and metabolic functions (5). It has been shown in several studies that decreased adiponectin serum levels were associated with obesity, insulin resistance, metabolic syndrome, and type 2 diabetes mellitus (DM) in pediatric patients (6,7). Binge eating disorder (BED) is characterized by loss of control in food intake and presentes as recurrent episodes of eating large amounts of food until feeling uncomfortably full. BED has an increasing prevalence of 1-5% among children and adolescents, and obesity is one of the main physical results of BED (8).

C1q/tumor necrosis factor-related proteins (CTRPs) are recently described members of the adipokine family, secreted from adipose tissue, like adiponectin. Some types of CTRPs play an important role in energy metabolism in humans (9,10). CTRP-13, a new member of this family, has been shown to increase insulin sensitivity and had an anorexigenic effect on food intake in experimental studies (11,12). Clinical studies have also shown that a decrease in the serum level of CTRP-13 was a risk factor for the development of type 2 DM, coronary artery disease, and non-alcoholic fatty liver disease in adults with obesity (13,14,15).

In this study, we aimed to investigate whether serum CTRP-13 levels were altered by children with a diagnosis of obesity or BED and how CTRP-13 levels were related to other adipokines or metabolic parameters. To our knowledge, this is the first study in children to evaluate CTRP-13 levels in the context of obesity.

Methods

This was a single-center, cross-sectional study and we recruited the study participants from amongst individuals from the same geographic region, aged 12-18 years, who attended our department between May 2020 and April 2021. Before participating in the present study, a comprehensive physical examination was performed for all subjects. Also, laboratory tests, including thyroid function and serum cortisol were performed for children with obesity to diagnose possible endocrine disorders. Children with any acute or chronic systemic diseases, a history of drug use (such as anti-epileptics, anti-psychotics, and steroids), obesity-related syndromes, and endocrine disorders (hypothyroidism and Cushing syndrome) were excluded. In addition, prepubertal subjects or those under 12 years of age were not included in the study. Children without obesity and attending for routine check-up were recruited as a healthy control cohort.

Anthropometric Measurements

Height was measured using a Harpenden stadiometer with an accuracy of 0.1 cm without shoes, and body weight was measured using a scale (SECA, Hamburg, Germany) with a sensitivity of 0.1 kg while wearing light clothing. Body mass index (BMI) was calculated by dividing body weight (kg) by height in metres squared (m^2). Standard deviation (SD) scores for weight, height and BMI were calculated with the online calculator for pediatric endocrinologists (Child Metrics) (16), using the reference created for the Turkish population by Neyzi et al (17). Obesity was defined as BMI >2 SD score, according to the criteria of the World Health Organization (18).

Waist circumference (WC) was measured at the end of a gentle expiration using a non-stretchable tape with a sensitivity of 0.1 cm, at the midpoint between the lowest extent of the rib cage and the iliac crest, without clothing (19). WC percentiles and SD scores were calculated according to the age and gender, using reference data for Turkish children (20). The pubertal stage of each participant was assessed according to Tanner and Whitehouse (21). Breast development of stage 2 and above in girls or testicular volume of ≥4 mL in boys was accepted as pubertal findings. Blood pressure measurements were performed using a calibrated sphygmomanometer by a single investigator using a validated protocol. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice on the right arm after 10 minutes of rest in a seated position. Blood pressure percentile and SD scores were calculated according to age, gender, and height (16).

Metabolic Syndrome

Homeostasis model assessment of insulin resistance (HOMA-IR) was used to evaluate the status of insulin

resistance. A cut-off value of >4.0 for pubertal patients was defined as insulin resistance (22). Metabolic syndrome was described according to the criteria of the International Diabetes Federation Consensus (23):

- For patients between the ages of 10-16, metabolic syndrome was defined as the presence of central obesity (WC ≥90th percentile or adult cut-off if lower) plus any two of the following factors: triglyceride level of ≥150 mg/dL; high-density lipoprotein-cholesterol (HDL-C) level of <40 mg/dL; SBP ≥130 or DBP ≥85 mmHg; fasting serum glucose level of ≥100 mg/dL and/or known type 2 DM.

- For patients ≥16 years old, metabolic syndrome was defined as: Presence of central obesity (WC ≥94 cm for males and ≥80 cm for females) plus any two of the following factors: triglyceride level of ≥150 mg/dL; HDL-C level of <40 mg/dL in males and <50 mg/dL in females; SBP ≥130 or DBP ≥85 mmHg or treatment of previously diagnosed hypertension; fasting serum glucose level of ≥100 mg/dL; or known type 2 DM.

Binge Eating Disorder

A trained psychiatrist determined the diagnosis of BED using a survey, based upon the criteria of the Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V). Binge-eating episodes at least one day a week for three months accompanied by marked distress and a lack of inappropriate compensatory behaviors and additional questions regarding the DSM-V criteria were assessed for diagnosis, such as (i) eating much more rapidly than normal, (ii) eating large amounts of food when not feeling physically hungry, (iii) eating until feeling uncomfortably full, (iv) eating alone because of being embarrassed by how much one is eating, and (v) feeling disgusted with oneself, depressed, or very guilty after overeating. An episode was described as follows; eating an amount of food in a discrete period of time that is definitely larger than most people would eat under similar circumstances and with the sense of lack of control over eating during this time (24).

Sample Collection and Storage

Blood samples for analyzing glucose, insulin, lipid profile, leptin, adiponectin, and CTRP-13 levels were obtained via venepuncture from the antecubital vein, after 10-12 hours of overnight fasting. To avoid run-to-run difference, all the samples were analyzed in the same run. Therefore, no correction or calibration factor was required. After allowing 60 minutes for spontaneous blood clotting, the plain tubes were centrifuged at 1200 x g for 10 minutes, and the serum samples were collected into tubes using plastic Pasteur pipettes and stored at -80 °C until analysis. Serum samples were diluted prior to analysis according to the manufacturer's instructions.

Biochemical Analysis

Fasting serum glucose, triglyceride, total cholesterol, and HDL-C levels were measured enzymatically using DP Modular Systems (Roche Diagnostic Corp., Indianapolis, IN, USA). Low-density lipoprotein-cholesterol (LDL-C) levels were calculated using the Friedewald formula when triglyceride levels were <400 mg/dL. Serum insulin level was measured by an electrochemiluminescence immunoassay method using an automated immunoassay analyzer (Immulite 2500, Diagnostic Products Corporation, Los Angeles, CA, USA).

Serum leptin (Catalog number: EK0437, Boster Biological Technology Co. Ltd., Wuhan, China) and adiponectin (Catalog number: EK0595, Boster Biological Technology Co. Ltd., Wuhan, China) levels were measured by commercial enzyme-linked immunosorbent assay (ELISA) kits based on the principle of solid-phase enzyme immunoassay. CTRP-13 (Catalog number: SK00333-06, Aviscera Bioscience Inc., Santa Clara, CA, USA) level was measured by a commercial ELISA kit employing the sandwich phase enzyme immunoassay technique. The ELISA tests for leptin, adiponectin and CTRP-13 had a sensitivity of <10 pg/mL, <60 pg/mL and 2 ng/mL, with a detection range of 62.5-4000 pg/mL, 1.56-100 ng/mL and 3.9-250 ng/mL, respectively. Intra- and inter-assay coefficients of variation were <7.6% and <8.4% for leptin, <7.8% and <9% for adiponectin, 4-6% and 8-12% for CTRP-13, respectively.

This study was approved by the Dokuz Eylül University Local Ethics Committee (ethics approval number: 2020/01-26, date: 06.01.2020) and performed in accordance with the principles of the Declaration of Helsinki. An informed written consent form was obtained from the children and their parents before the study.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences application for Windows, version 24.0 (IBM Co., Armonk, NY, USA). The distribution of data was evaluated using the Kolmogorov-Smirnov test. Clinical data are presented as number (%) for categorical variables and median (25th-75th percentiles) for continuous variables. Comparisons of categorical and continuous variables were performed with the Pearson chi-square test and the Mann-Whitney U test, respectively. The Spearman correlation test was applied for correlations between CTRP-13 and continuous variables. Then, any correlation was investigated among the identified significant variables after

adjusting for age, gender, and BMI. A two-sided p value of < 0.05 was considered statistically significant.

Results

A total of 105 pubertal children [39 males (37.1%); median age 14.9 (13.5-16.5) years] were enrolled in this study. The group with obesity consisted of 60 children [24 males (40%); median age 14.7 (13.0-16.4) years] and the control group included 45 healthy children [15 males (33.3%); median age 15.2 (14.1-16.5) years]. There was no significant difference between the two groups in terms of age and gender (p = 0.154 and p = 0.484, respectively) (Table 1).

Significant differences were observed between children with obesity and children of healthy weight in terms of BMI, BMI SD scores, serum insulin, HOMA-IR, triglyceride, HDL-C, leptin, and adiponectin levels, whereas serum glucose, total cholesterol, and LDL-C concentrations were similar (Table 1). Individuals with obesity had significantly lower CTRP-13 levels than the control group (p = 0.013) (Table 1).

Eighteen of the subjects with obesity (30%) had metabolic syndrome and among children with and without metabolic syndrome, statistically significant differences were observed in terms of hypertension, serum insulin, HOMA-IR, triglyceride, and HDL-C levels (Table 2). Among children with obesity, although adiponectin was found to be significantly lower in those with metabolic syndrome (p = 0.021), no significant difference was observed in leptin or CTRP-13 levels (Table 2). When subgroup analysis was performed regarding gender, there was no significant difference in circulating CTRP-13 levels in boys (p = 0.655) or girls (p = 0.596).

Thirty-two of the patients with obesity (53.3%) had insulin resistance. When individuals with obesity were compared according to the presence of insulin resistance, serum adiponectin concentration was significantly lower in the insulin resistance-positive group [4.2 (1.9-10.9) vs 9.9 (6.1-18.3) µg/mL, p = 0.008]. However, serum leptin and CTRP-13 levels were found to be similar in both groups, with or without insulin resistance [40.1 (30.3-58.9) vs 55.3 (35.4-99.8) ng/mL, p = 0.093 and 64.7 (29.5-109.0) vs 63.5 (36.3-100.6) ng/mL, p = 0.717, respectively].

Twenty-three (38.3%) of the patients with obesity were diagnosed with BED. Among groups with and without BED, significant differences were observed in BMI and BMI SD scores (p = 0.033 and p = 0.029, respectively). However, metabolic and biochemical parameters, including CTRP-13 levels, were similar in both groups (Table 3). Moreover, there was no significant difference found when conducting subgroup analyzes according to gender, in boys (p = 0.976) or girls (p = 0.427).

CTRP-13 correlated negatively with BMI (Spearman rho = -0.230, p = 0.018), BMI SD score (Spearman rho = -0.237, p = 0.015) and positively with HDL-C (Spearman rho = 0.218, p = 0.026) in all participants (Figure 1). After adjustment for age, gender, and BMI, serum CTRP-13 levels showed a positive correlation with HDL-C levels in subjects with obesity (Spearman rho = 0.313, p = 0.018).

Table 1. The clinical and laboratory characteristics of children with obesity and healthy controls

	Children with obesity (n = 60)	Controls (n = 45)	p
Age (year)	14.7 (13.0-16.4)	15.2 (14.1-16.5)	0.154[a]
Gender (male) [n (%)]	24 (37.1)	15 (40%)	0.484[b]
BMI (kg/m²)	32.0 (30.0-35.6)	20.5 (18.2-22.3)	**< 0.001[a]**
BMI SD score	2.7 (2.3-3.1)	-0.5 [(-1.2)-0.6]	**< 0.001[a]**
Glucose (mg/dL)	85.5 (80.3-91)	85 (81-92)	0.766[a]
Insulin (uIU/mL)	19.3 (15.8-25.9)	10.9 (7.7-14.6)	**< 0.001[a]**
HOMA-IR	4.1 (3.3-5.8)	2.3 (1.5-3.3)	**< 0.001[a]**
TG (mg/dL)	90.5 (77.8-140.3)	82 (59.5-101.5)	**0.017[a]**
TC (mg/dL)	171 (155-195)	166 (152.5-192)	0.524[a]
LDL-C (mg/dL)	103.9 (86.1-123.7)	95.4 (83.1-110.3)	0.138[a]
HDL-C (mg/dL)	53 (47.5-64)	48 (41-54.8)	**0.004[a]**
Leptin (ng/mL)	46.4 (31.1-80.5)	7.2 (2.5-13.4)	**< 0.001[a]**
Adiponectin (µg/mL)	7.1 (3.1-13.1)	20.1 (7.3-46.4)	**< 0.001[a]**
CTRP-13 (ng/mL)	64.7 (35.7-103.9)	103.8 (42.9-167.8)	**0.013[a]**

Data are given as mean ± standard deviation or median (25^{th}-75^{th} percentile). [a]Mann-Whitney U test, [b]Pearson chi-square test, $p < 0.05$.
BMI: body mass index, BMI SD score: standard deviation score of BMI, HOMA-IR: homeostasis model assessment-insulin resistance, TG: triglyceride, TC: total cholesterol, LDL-C: low-density lipoprotein-cholesterol, HDL-C: high-density lipoprotein-cholesterol, CTRP-13: C1q/tumor necrosis factor-related protein-13

Discussion

CTRPs are new members of the adipokine family, which are secreted from adipose tissue, like adiponectin and leptin. It has been suggested that CTRPs play an important role in energy metabolism. CTRPs also have significant and distinct effects on the immune, endocrine, vascular, skeletal, and sensory systems (9,10). Fifteen types of CTRPs have been identified so far, some of which have metabolic functions

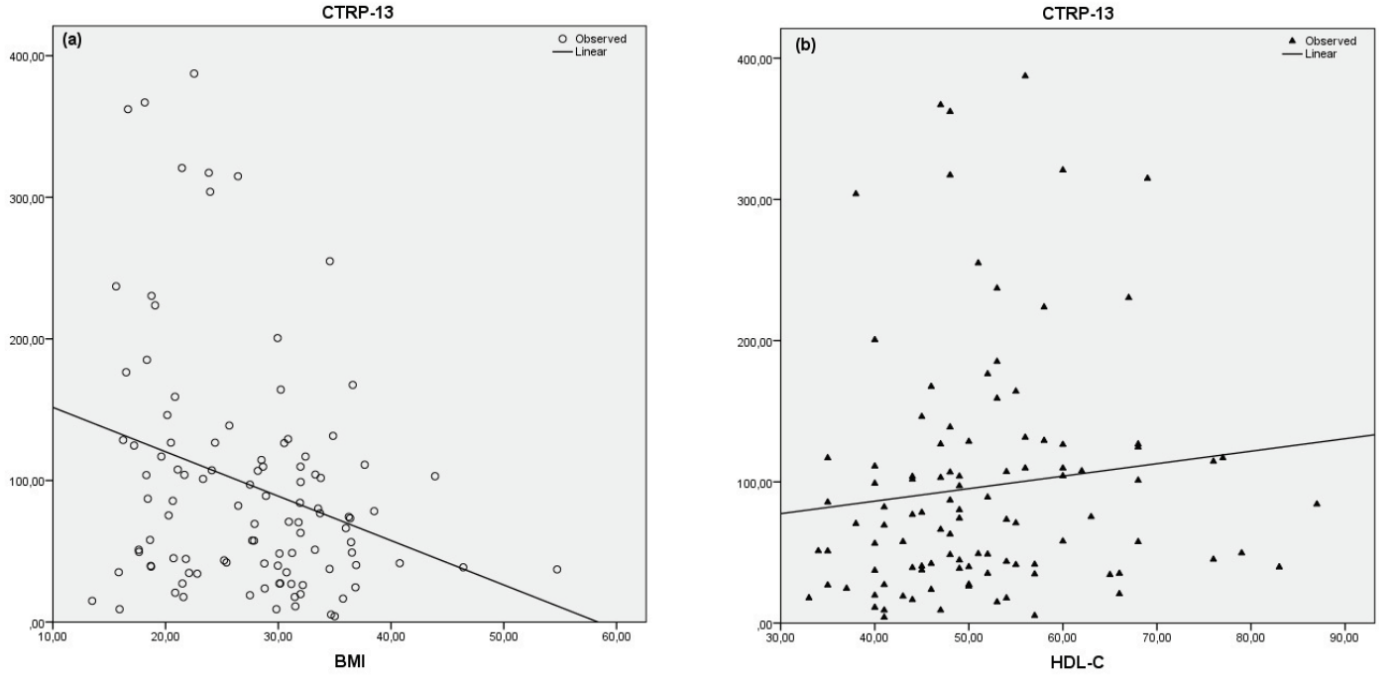

Figure 1. The correlation between serum C1q/tumor necrosis factor-related protein-13 levels and (a) BMI, (b) HDL-C

HDL-C: high-density lipoprotein-cholesterol, BMI: body mass index

Table 2. The clinical and laboratory characteristics of children with obesity according to the presence of metabolic syndrome or not

	MS (+) group (n = 18)	MS (-) group (n = 42)	p
BMI (kg/m²)	32.3 (31.5-34.6)	31.1 (29.6-36.3)	0.233
BMI SD score	2.7 (2.4-3.1)	2.6 (2.3-3.3)	0.411
WC (cm)	3.6 (3.0-4.0)	3.6 (3.1-4.0)	0.974
SBP SD score	2.2 (1.8-2.3)	1.2 (0.6-2.3)	**0.011**
DBP SD score	1.6 (0.7-2.1)	0.7 (0.4-1.6)	0.051
Hypertension, n (%)	15 (83.3)	20 (47.6)	**0.010**
Glucose (mg/dL)	89.5 (80.5-100)	85 (80-90.3)	0.320
Insulin (uIU/mL)	24.7 (16.3-32.6)	17.9 (14.8-24.4)	**0.044**
HOMA-IR	5.7 (3.4-6.9)	3.8 (3.2-5.0)	**0.025**
TG (mg/dL)	156.5 (86.8-181.5)	87 (68.5-107.3)	**0.001**
TC (mg/dL)	188 (143.8-202.8)	168.5 (155-186)	0.266
LDL-C (mg/dL)	114.2 (87.3-127.1)	97.8 (85.7-122.8)	0.287
HDL-C (mg/dL)	44.5 (37.3-50.3)	49 (43.8-55.3)	**0.025**
Leptin (ng/mL)	38.2 (23.8-63.0)	51.2 (22.9-98.0)	0.129
Adiponectin (µg/mL)	4.6 (1.7-7.6)	9.9 (3.3-17.6)	**0.021**
CTRP-13 (ng/mL)	64.7 (34.6-105.9)	63.5 (33.2-104.9)	1.000

Data are given as median (25^{th}-75^{th} percentile). Mann-Whitney U test was used to determine the differences of variables between the two groups, $p < 0.05$.
MS: metabolic syndrome, BMI: body mass index, BMI SD score: standard deviation score of BMI, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA-IR: homeostasis model assessment-insulin resistance, TG: triglyceride, TC: total cholesterol, LDL-C: low-density lipoprotein-cholesterol, HDL-C: high-density lipoprotein-cholesterol, CTRP-13: C1q/tumor necrosis factor-related protein-13

(9,10). CTRP-13 is one of the members of this family, mostly expressed from adipose tissue and brain in mice and predominantly from adipose tissue in humans (11). The CTRP family has homologous effects on energy homeostasis and may prove to be novel pharmacological targets for diseases secondary to obesity. CTRPs can dynamically adjust the response to changes in short-term nutritional or long-term metabolic status. Excess caloric uptake in obesity and related inflammatory disorders usually disrupt the signaling pathways regulated by CTRPs, with changes in structural configurations and post-translational modifications of these molecules (9). Previous studies demonstrated reduced levels of CTRP-3, CTRP-6, CTRP-7, CTRP-9, CTRP-12, and CTRP-15 in mice or humans with obesity (25,26,27,28). In a childhood study, Chen et al (29) found that CTRP-3 concentrations significantly decreased in children with obesity, demonstrating a negative correlation with BMI. They indicated that the circulating level of CTRP-3 was down-regulated in the pro-inflammatory state of obesity, but the exact mechanism has not been clarified. Adiponectin and CTRPs share similar structures and functions, like organizing anti-inflammatory responses and regulating energy metabolism by improving insulin sensitivity (30). As an example for the relationship between CTRPs and adiponectin, CTRP-9 was shown to associate with adiponectin to form a heterotrimeric structure and to share the same receptor (31). Shanaki et al (32) showed that CTRP-13 and adiponectin inversely correlated with BMI in women, and CTRP-13 positively correlated with adiponectin, too. They also found that decreased serum levels of CTRP-13 may be related to visceral fatness, but no pathophysiological explanation was suggested (14). On the other hand, Omidifar et al (33) found no significant association between mRNA expression levels of CTRP-13 in subcutaneous or visceral adipose tissue in women with obesity and normal weight women. There was no relevant data concerning CTRP-13 in pediatric patients in the existing literature with which to compare our findings. We found that obesity in pubertal children was associated with lower serum CTRP-13 concentrations compared to healthy weight children. As a sign of visceral adiposity, CTRP-13 was negatively correlated with BMI in those individuals. However, in contrast with adult studies, we could not find any correlation between CTRP-13 and adiponectin levels. Although the exact molecular mechanism is not understood, our results suggested that childhood obesity disrupts metabolic homeostasis and causes dysregulation in adipokine production and function, including CTRP-13.

Adipokine dysregulation and inflammatory disorders in obesity result in metabolic problems, such as insulin resistance and type 2 DM (9,34,35). Experimental studies have shown that CTRP-13 has an insulin-sensitizing effect by promoting glucose uptake in adipocytes, myotubes, and hepatocytes, via the adenosine monophosphate-activated protein kinase signalling pathway. It also inhibits the c-Jun

Table 3. The clinical and laboratory characteristics of children with obesity according to the presence of binge eating disorder or not

	BED (+) group (n = 23)	BED (-) group (n = 37)	p
BMI (kg/m²)	33.3 (31.5-36.8)	31.2 (29.4-34.6)	**0.033**
BMI SD score	2.9 (2.6-3.6)	2.5 (2.3-3.0)	**0.029**
WC (cm)	3.6 (3.0-4.3)	3.6 (3.1-3.9)	0.563
SBP SD score	1.9 (0.9-2.3)	1.6 (0.8-2.3)	0.502
DBP SD score	1.4 (0.3-2.1)	0.8 (0.5-1.6)	0.784
Hypertension [n (%)]	15 (65.2)	20 (54.1)	0.394
Glucose (mg/dL)	85 (79-91)	87 (81-92)	0.428
Insulin (uIU/mL)	18.0 (15.8-23.2)	21.0 (15.4-29.4)	0.261
HOMA-IR	3.8 (3.2-5.7)	4.5 (3.4-6.5)	0.334
TG (mg/dL)	92 (81-165)	89 (75.5-126.5)	0.503
TC (mg/dL)	171 (148-195)	170 (156-197.5)	0.773
LDL-C (mg/dL)	104 (84.4-123.8)	103.8 (87.7-124.6)	0.429
HDL-C (mg/dL)	47 (40-56)	48 (41-52)	0.927
Leptin (ng/mL)	49.5 (32.4-98.9)	42.1 (30.7-78.2)	0.538
Adiponectin (µg/mL)	6.6 (3.5-13.2)	7.7 (2.6-14.1)	0.855
CTRP-13 (ng/mL)	73.3 (40.2-103.0)	57.5 (27.1-105.5)	0.447

Data were given as median (25^{th}-75^{th} percentile). Mann-Whitney U test was used to determine the differences of variables between the two groups, $p < 0.05$.
BED: binge eating disorder, BMI: body mass index, BMI SD score: standard deviation score of BMI, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA-IR: homeostasis model assessment-insulin resistance, TG: triglyceride, TC: total cholesterol, LDL-C: low-density lipoprotein-cholesterol, HDL-C: high-density lipoprotein-cholesterol, CTRP-13: C1q/tumor necrosis factor-related protein-13

N-terminal kinase (JNK) signal pathway, which is activated by fatty acids and ameliorates lipid-induced insulin resistance in hepatocytes (11). In addition, CTRP-13 has significant impact on gluconeogenic enzymes to reduce glucose output in hepatocytes (11). All these literature data, gained from experimental studies, support a significant effect of CTRP-13 on glucose homeostasis. In several clinical studies, a decrease in the serum level of CTRP-13 was found to be a risk factor for the development of type 2 DM or coronary artery disease in adult patients (13,15). Shanaki et al (14) found that CTRP-13 had a negative correlation with insulin, triglyceride levels, and HOMA-IR. They also observed lower CTRP-13 levels in patients with type 2 DM and non-alcoholic fatty liver disease, suggesting CTRP-13 as a potential marker for these clinical conditions (14). An et al (36) demonstrated significant differences in CTRP-13 levels in adults with non-alcoholic fatty liver disease when compared to the control group, and a correlation between CTRP-13 and triglyceride levels in those patients. However, the exact mechanism of CTRP-13 effects on glucose and lipid metabolism in humans has not yet been established. However, Bai et al (37) showed no difference in CTRP-13 levels among age- and BMI-matched adults with or without type 2 DM. They observed similar concentrations at 0 and 2 hours of the oral glucose tolerance test (37). Fadaei et al (15) reported that circulating levels of CTRP-13 did not correlate with lipid profiles in adults. We observed a positive correlation between CTRP-13 and HDL-C levels, which might be a result of the possible effect of this novel adipokine on lipid metabolism, as recently shown with CTRP-3 levels in pediatric patients (38). This alteration was thought to be caused by the modulatory effects of CTRP-13 through signaling pathways, including JNK in hepatocytes, as a defence mechanism against the metabolic complications of obesity. Nevertheless, we did not find any significant difference in CTRP-13 levels according to the presence of metabolic syndrome in children with obesity, as well as insulin resistance. In light of the conflicting literature data and our results, questions still need to be answered about the molecular and functional role of CTRP-13 in inflammatory pathways leading to metabolic complications secondary to obesity. Although CTRP-13 levels were decreased in our patients with obesity, we hypothesized that the metabolic dysregulating consequences of this decrease take some time and hence may present in adulthood. Therefore, a novel therapeutic approach on correcting CTRP-13 levels in childhood may be protective against metabolic complications of obesity seen in later life.

BED is defined by the loss of control of food intake, which results in eating large amounts of food and therefore obesity (8). Insulin and leptin are the main hormones that control food intake and feeling of satiety, which play an important role in maintaining the balance between energy intake and consumption (4). Leptin is an adipokine produced from adipose tissue that controls food intake in the brain through leptin receptors in the arcuate nucleus. It suppresses the release of hypothalamic peptides, such as neuropeptide-Y, resulting in decreased appetite (39). While leptin acts as a "satiety signal" to prevent excess food intake and links adipose tissue to hypothalamic centers regulating energy homeostasis, we could not find any relationship between serum leptin levels and BED. In an experimental study with mice, CTRP-13 was found to be an anorexigenic factor and its secretion from the hypothalamus increased after high-fat feeding and reduced after food restriction. Also in the same study, it was observed that appetite was suppressed and weight loss was achieved in mice given CTRP-13 exogenously (12). Therefore, a hypothalamic feedback loop including orexigenic neuropeptides, such as neuropeptide-Y and agouti-related protein, together with CTRP-13, was thought to be modulating food intake in mice (12). Although the underlying pathophysiology of BED is unclear, we investigated the role of CTRP-13 in this psychiatric disorder based on the data from experimental studies. However, we could not find any evidence of a relationship between a diagnosis of BED and circulating CTRP-13 levels in subjects with obesity. This result may be related to the complex etiopathogenesis of BED.

Study Limitations

To the best of our knowledge, this is the first study evaluating CTRP-13 levels in children with obesity. However, our study has some limitations. First of all, we could not reach the targeted sample size due to the COVID-19 pandemic and the time-limited nature of the study. Therefore, we performed a post-hoc power analysis using G*Power software (version 3.1.9.4, http://www.gpower.hhu.de/en.html) with values of mean and SD gained from the results of this study, and found power at 0.90, with an effect size (d) of 0.60 and type I error at 0.05. Secondly, the limited number of participants in subgroup analyzes might have a negative impact on the accuracy of these results. Therefore, prospective clinical and molecular studies with larger sample sizes are required in this field to elucidate the exact mechanism of the relationship between CTRP-13 and obesity. Finally, BED diagnosis was determined according to a clinical survey, which may be affected by the subjective responses of the individuals with obesity. Nevertheless, a trained psychiatrist performed the surveys and this method was compatible with the daily clinical practice to determine the diagnosis of BED.

Conclusion

We demonstrated significantly lower CTRP-13 levels in children with obesity than in age-matched children with healthy weight. The positive correlation between CTRP-13 and HDL-C levels suggested a possible effect of this adipokine on lipid metabolism and it can be used as a marker for dyslipidemia in childhood obesity. However, unlike adult studies, we could not find any difference in CTRP-13 levels in regard to obese children with or without metabolic syndrome or insulin resistance. A novel therapeutic approach may be to optimize CTRP-13 levels in childhood which may be protective against metabolic complications of obesity seen in later life but much more evidence is required to support this hypothesis.

Ethics

Ethics Committee Approval: This study was approved by the Dokuz Eylül University Local Ethics Committee (ethics approval number: 2020/01-26, date: 06.01.2020) and performed in accordance with the principles of the Declaration of Helsinki.

Informed Consent: An informed written consent form was obtained from the children and their parents before participating the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İbrahim Mert Erbaş, Ahu Paketçi, Serkan Turan, Ali Rıza Şişman, Korcan Demir, Ece Böber, Ayhan Abacı, Concept: İbrahim Mert Erbaş, Ayhan Abacı, Design: İbrahim Mert Erbaş, Ayhan Abacı, Data Collection or Processing: İbrahim Mert Erbaş, Ahu Paketçi, Serkan Turan, Ali Rıza Şişman, Korcan Demir, Ece Böber, Ayhan Abacı, Analysis or Interpretation: İbrahim Mert Erbaş, Ahu Paketçi, Serkan Turan, Ali Rıza Şişman, Korcan Demir, Ece Böber, Ayhan Abacı, Literature Search: İbrahim Mert Erbaş, Ahu Paketçi, Serkan Turan, Ali Rıza Şişman, Korcan Demir, Ece Böber, Ayhan Abacı, Writing: İbrahim Mert Erbaş.

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