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Effects of weight intervention-induced changes in pathological fat mass of patients with extreme obesity and anorexia nervosa on adipokines and visceral adipocyte functions: a prospective, comparative, observational study

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Abstract. – OBJECTIVE: Adipose tissue is the largest endocrine organ in the human body, and as its mass changes, the serum levels of the molecules it secretes also change. Visceral adipose tissue index (VAI) is a simple surrogate marker of visceral adipose tissue dysfunction. This study evaluated the effects of changes in fat mass on adipocytokine behavior and VAI in patients with anorexia nervosa (AN) and extreme obesity (EO).

PATIENTS AND METHODS: The study group consisted of three subgroups: Group 1, patients with EO who were candidates for obesity surgery with BMI≥50 kg/m² (n=20). Group 2, newly diagnosed patients with AN (n=12). Group 3 controls with BMI 20-25 kg/m² (n=20). The AN and EO groups were followed until at least a 10% weight change before and after the intervention.

RESULTS: Prior to the intervention, EO patients exhibited the lowest levels of apelin, omentin, and adiponectin, while AN patients demonstrated the highest levels of these markers. Leptin and IL-6 were elevated in EO and reduced in AN patients. After treatment, all adipokines and VAI increased in AN patients, and omentin, adiponectin, and IL-6 increased in EO patients, while apelin, leptin, and VAI decreased. The change in each adipocytokine (Δ) was positively correlated with the other adipocytokines ($p<0.050$) and negatively correlated with metabolic and VAI changes ($p<0.050$). The regression analysis determined that the following variables were associated with the change in adipose tissue mass: Δapelin (OR: 1.061; $p=0.028$) and Δadiponectin (OR: 1.057; $p=0.036$).

CONCLUSIONS: In individuals with pathological adipocyte mass, the change in adipocytokine levels in response to weight change is not as expected. The fact that these changes are not seen in the early period of the weight intervention treatment indicates that these patients have compensatory physiological mechanisms to protect them. In addition, using VAI instead of BMI, whose reliability is increasingly questioned because it does not reflect body fat mass, can be considered an alternative. However, there may be modeling errors in the early stages of weight change and in AN and EO patients where metabolic parameters reach extreme values. Therefore, it should be tested in studies where larger patient groups are followed for a more extended period. ClinicalTrials gov ID: NCT04663919.

Key Words:
Extreme obesity, Anorexia nervosa, Roux-en-Y Gastric bypass, Adipokines, Visceral adiposity index, Fat mass changes.

Introduction

Adipose tissue is the largest endocrine organ in the human body[1]. The increase in adipose tissue mass, especially in the visceral region, releases various adipokines, causing changes in metabolic and endocrine functions in different organs and systems[2]. Body fat distribution is an essential factor for cardiovascular disease risk

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assessment and the prevention and treatment of obesity-related metabolic disorders[3].

Adiponectin is one of the most studied molecules secreted from adipose tissue[1]. Low adiponectin levels are associated with insulin resistance (IR), type-2 diabetes (T2D), metabolic syndrome (MetS), and hypertension, and its circulating levels increase as patients lose weight. Treatment of these diseases with adiponectin is among the research subjects[4-8].

Other relatively new molecules include omentin and apelin. Omentin has been suggested[9,10] as a biomarker of obesity and has protective effects against atherosclerosis. *In vitro* studies[11] have determined that omentin has an insulin-sensitizing effect on adipocytes in all compartments through insulin signaling and increases insulin-stimulated glucose uptake. It has been shown[12] that its expression is not only in visceral adipocytes but also in mesothelial cells, vascular smooth muscle cells and endothelial cells, epicardial fat, small intestine, colon, thymus, ovary, and testes, as well as intestinal Paneth and Goblet cells and airways. Serum levels decrease in patients with MetS, T2D, and atherosclerosis[13]. Despite the absence of a specific receptor, weight loss can increase serum omentin concentration[14].

Another marker of interest in obesity is apelin, which promotes glucose uptake, improves insulin sensitivity and regulates lipolysis and fatty acid oxidation[15]. It is known[15] that insulin stimulates apelin expression in adipocytes by inhibiting glucose-induced insulin secretion. Its beneficial effects have been tested in sarcopenia and atherosclerotic heart disease[16,17]. In experimental studies[18-22], it has been shown to reduce blood pressure, increase drinking behavior, decrease food intake, and inhibit insulin response to intravenous glucose after a high-fat meal due to endothelium-dependent nitric oxide-mediated vasodilation. In addition to studies showing that apelin increases significantly, especially in obese patients with hyperinsulinemia, other studies[22] show no relationship between plasma apelin levels and insulin secretion when intravenous glucose is overloaded after bariatric surgery (BS).

Leptin, another adipokine produced in adipocytes, acts on the hypothalamus to affect energy intake/expenditure to decrease or increase food intake[23]. It is not known whether plasma leptin levels directly affect food intake, but it is determined via adipose tissue mass. Increased fat mass is associated with increased leptin levels to reduce food intake. Leptin levels are high in obese patients, and serum levels decrease with weight loss[23]. On the other hand, obesity is one of the health disorders linked with leptin resistance.

It has been shown[24] that in obesity, there is an increase in the expression of proinflammatory markers with macrophage infiltration in adipose tissue, and in parallel with this process, the release of inflammatory markers such as interleukin-6 (IL-6) from adipose tissue increases. Studies[25] conducted mainly in adult patients with anorexia nervosa (AN) indicate a low-grade proinflammatory state and increased IL-6 levels compared to healthy controls.

The visceral adiposity index (VAI) can be considered a simple surrogate marker of visceral adipose tissue dysfunction[3,26]. Its formula includes biomarkers that better reflect metabolic status than body mass index (BMI)[27]. However, it has not been clarified whether situations in which metabolic parameters reach extreme values may lead to errors in modeling. Therefore, it is worth testing VAI in patients with very low (i.e., AN) or very high (i.e., extreme obesity, EO) adipose tissue mass.

There are many studies[28-30] in the literature on the effects of a low-calorie diet and exercise interventions on fat tissue and serum adipocytokine levels. However, the number of studies on the changes in fat mass on adipocytokines in individuals diagnosed with AN who gained weight with a hypercaloric diet and in individuals with extreme obesity who lost weight with a hypocaloric diet after BS was applied is very limited. In particular, data obtained from patients diagnosed with AN differ significantly from healthy individuals. On the other hand, the fact that structurally weak individuals have similar findings to healthy individuals is a situation that the literature cannot explain. From this point of view, this study primarily aims to evaluate and compare the relationship between changes in fat mass and changes in adipocytokine levels of patients at both ends of the nutritional spectrum before and after treatment interventions. Thus, it sheds light on how abnormalities in body fat mass change after treatment and the adaptation mechanisms. The secondary aim is to test how accurately VAI, a marker reflecting functional pathology in visceral adipose tissue, reflects the metabolic status in patients with very low and very high adipose tissue mass and to evaluate its relationship with adipocytokines.

Patients and Methods

Ethics

This study is designed as a prospective, comparative before-after study. The study was approved

by the Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 14.08.2015, No.: 13) and was conducted following the Declaration of Helsinki Principles[31]. A brief explanation was given to all participants, and the treatment and follow-up process was explained. All subjects provided written informed consent for inclusion before they participated in the study. The trial was registered on the ClinicalTrials.gov PRS website (ID: NCT04663919).

Subjects

Group-1 (extreme obesity group-EO)

Patients who were followed up at the Obesity Outpatient Clinic of Istanbul University, Istanbul Faculty of Medicine, Department of Endocrinology and Metabolism, between 2020 and 2022 were evaluated. Among these patients, those with a BMI ≥50 kg/m^2 had EO. Those who were operated on for bariatric surgery (Roux en-Y-gastric bypass; RYGB) by the same team at the Department of Surgery of the university were re-evaluated. Patients with cancer, chronic kidney disease, chronic liver disease, heart failure, symptomatic atherosclerotic disease, autoimmune or auto-inflammatory disease; those who are under chronic steroid treatment, immune suppressant agents, or hormone replacement therapy; and women currently pregnant or planning pregnancy were excluded from the study. In line with these criteria, the study was explained to eligible patients, and those who agreed to participate were included in the study and were followed within the scope of the study until they lost 10% of their post-operative body weight.

Group-2 (anorexia nervosa group-AN)

Within the scope of this study, patients who applied to Istanbul University, Istanbul Faculty of Medicine, the Outpatient Clinic of Eating Disorders at the Department of Psychiatry between 2020 and 2022 and were newly diagnosed with AN (According to the Fifth Diagnostic and Statistical Manual of Mental Disorders; DSM-V[29]) and followed and treated were evaluated. These patients were simultaneously consulted with the Nutrition Outpatient Clinic of Istanbul University, Istanbul Faculty of Medicine, Department of Endocrinology and Metabolism for follow-up and treatment of their metabolic status. The study included patients who did not have other medical or psychiatric diagnoses in addition to anorexia nervosa, whose physical examination findings were normal, who did not use medications that could affect their body composition and hormones, and who were followed up in the outpatient clinic. Parents of minor patients were also informed about the study, and their informed consent was obtained. Those who agreed to participate in the study were followed until they gained 10% weight.

Group-3 (healthy control group-HC)

Among the patient companions and hospital staff, those without any history of disease or medication use and with a BMI of 20-25 kg/m^2 were invited to participate after the study was explained. Those who agreed to participate were included in the study as healthy control (HC) individuals.

Anthropometric Parameters and Body Fat

Waist circumference (WC) was measured with a non-stretchable tape measure and repeated three times at the level of the umbilicus, in expiration, while the patient was standing upright in a position with equal weight on both feet, and the average value was recorded in "cm". BMI was calculated by dividing the kg body weight by square meters of height. Body fat mass was assessed in "kg" by bioimpedance analysis (BIA; Tanita, body-fat analyzer TBF-300, Tokyo, Japan).

Biochemical Analysis

All participants were asked to fast overnight (approximately 12 hours), and then, on the following morning, blood samples from the antecubital vein were collected into 4 mL EDTA tubes and centrifuged immediately. Plasma/serum samples were then separated and transferred to Eppendorf tubes and stored at -80°C until the day of testing. After sample collection from all participants was completed, apelin, omentin, adiponectin, leptin, and IL-6 levels were evaluated with tests performed on the same day. All biochemical analyses, including high-density lipoprotein-cholesterol (HDL-c) and triglycerides (TG) concentrations, were performed at the Central Biochemistry Laboratory with an oxidase-based technique, measured by an autoanalyzer with a colorimetric assay (Roche Diagnostics, Mannheim, Germany). Low-density lipoprotein-cholesterol (LDL-c) levels were calculated using Friedewald's formula, or if TG was over 400 mg/dL, it was measured using the direct method.

Omentin (Human Omentin-1, Cat.#EZH0MNTN1-29K, Millipore®, MO, USA), adiponectin (Human Adiponectin, Cat.#EZHADP-61K, Linco Research, St. Charles Millipore®, MO, USA), apelin (Human Apelin-12, Cat.YHB0363Hu, YH

Biosearch Lab. China), leptin (Human Leptin, Cat.#EZHL-80SK, Millipore®, MO, USA), and IL-6 (IL-6 HS, Cat.950.035.096, Diaclone SAS, France) were measured using ELISA before the weight intervention program and when patients reached their target intervention weight.

Intervention

For extreme obesity group

All patients with extreme obesity underwent Roux en-Y-gastric bypass by the same surgeon. In laparoscopic RYGB surgery, the standard gastric pouch is prepared as 20-25 cc. In classical RYGB surgery, the alimentary tract length is 150 cm. The length of the biliopancreatic tract is 50-70 cm.

Postoperative meal plans of EO patients were made according to the gradual dietary recommendations in the guidelines prepared by the American Association of Clinical Endocrinologists, the Obesity Society, and the American Society of Metabolic and Bariatric Surgery (AACE/TOS/ASMBS)[32]. Patients were administered a clear liquid diet from the first to the third postoperative days, followed by a liquid diet from the third to the fourteenth days (60-80 g/d protein, each meal contained <20 g protein and <15 g carbohydrate). Subsequently, they underwent three weeks of a puree diet (60-80 g/d protein), three weeks of a soft diet (frequent meals with 60-80 g/d protein), and three weeks of a standard diet (50-55% CH, 15-20% protein and 25-30% fat). After at least 10% weight loss, adipose tissue-derived parameters were re-evaluated.

For anorexia nervosa group

The American Psychiatric Association[33] recommends that patients with AN requiring nutritional rehabilitation and weight restoration have individualized goals for weight gain and target weight. In this regard, individual calorie requirements of AN patients receiving outpatient psychiatric treatment at the eating disorder clinic were calculated in the nutrition clinic. The daily energy requirement of each patient was calculated as 30-40 kcal/kg/d, and the total requirement was increased by 100-150 kcal/day during weekly meetings. The fat rate of the prepared diet is determined as approximately 30% of the total calories with 15-20% protein and 50-55% carbohydrate[34]. Patients were monitored within the scope of the study until they gained at least 10% of their initial body weight. The fat tissue-related parameters were assessed at baseline and after weight gain.

Calculation of the Visceral Adiposity Index

The VAI scores were calculated using the participants' BMI (kg/m^2), WC (cm), TG (mmol/L), and HDL-c (mmol/L) levels, with the equations different by gender, as described below[35]:

$$Males: VAI = \left(\frac{WC}{39.68 + (1.88 \times BMI)}\right) \times \left(\frac{TG}{1.03}\right) \times \left(\frac{1.31}{HDL}\right)$$

$$Females: VAI = \left(\frac{WC}{36.58 + (1.89 \times BMI)}\right) \times \left(\frac{TG}{0.81}\right) \times \left(\frac{1.52}{HDL}\right)$$

Statistical Analysis

Statistical analysis was performed with the SPSS software version 22.0 (IBM Corp., Armonk, NY, USA). The normality of the variables was tested with visual (histogram) and analytic methods (Shapiro-Wilk's test) to analyze distribution. Since serum levels of apelin, omentin, adiponectin, leptin, and IL-6 were not normally distributed, these parameters were corrected according to body fat mass (fm). Accordingly, the corrected adipokine levels [apelin (apelin:fm), omentin (omentin:fm), adiponectin (adiponectin:fm), leptin (leptin:fm), and IL-6 (IL-6:fm)] were calculated by dividing their raw levels to fat mass in "kg". Kruskal-Wallis and Mann-Whitney U tests were conducted to compare parameters among groups. Comparisons during baseline and 10% weight change for AN and EO were determined by the Wilcoxon signed-rank test. Spearman correlation was used to test correlations between variables. A p-value lower than 0.05 was accepted as statistically significant. We used logistic regression analyses to assess independent factors associated with the change in adipose tissue mass. Variables with a p-value <0.20 were included in the model. Statistical significance was accepted at two-sided $p<0.05$. The homeostasis model of assessment insulin resistance (HOMA-IR) was calculated using fasting plasma glucose (FPG) and fasting plasma insulin (FPI) via the following formula:

$$HOMA\text{-}IR=[(FPG\ (mg/dL) \times FPI\ (\mu U/mL)]/405.$$

Results

Since the COVID-19 lockdown period coincided with the patient recruitment period for the study, the number of patients applying for treatment was lower than in previous years. A total of 71 volunteers (16 AN, 25 EO, and 20 HC) were included in the study. However, some participants

were excluded from the study because their treatment and follow-up process was interrupted due to quarantine (2 AN and 2 EO). Some patients also wanted to leave the study because they did not want to visit the hospital due to the pandemic (2 AN and 3 EO). The data of these patients were not included in the statistical calculation. The study was completed with 52 patients: 12 AN, 20 EO, and 20 HC (mean age: 30.54±11.97 years, 38 female; 73%). The study flow is summarized in Figure 1, and the anthropometric characteristics of the participants are summarized in Table I.

Considering the whole group, a logistic regression model showed that the variables associated with the change in adipose tissue mass with the intervention were: Δapelin (OR: 1.061; 95% CI: 1.006-1.119; p=0.028); Δadiponectin (OR: 1.057; 95% CI: 1.004-1.114; p=0.036), (Table II).

Extreme Obesity Group

The mean age of participants (women/men: 13/7) included in the EO group was 37.70±11.63 years. The anthropometric characteristics of the patients are presented in Table I.

The follow-up period of the EO group was 108.75±12.41 days, during which the weight decreased by 28.63±9.90 kg (18.7%), and their fat mass decreased by 21.32±7.61 kg (28.3%). After weight loss with serum levels of fasting plasma insulin (FPI) (p=0.000), HOMA-IR (p=0.000), HbA1c (%) (p=0.000), triglyceride (p=0.015), and LDL-c (p=0.002) levels decreased significantly (Table III).

At baseline, the EO group had the lowest apelin:fm, omentin:fm, adiponectin:fm, and IL-6:fm values. VAI value was the highest in the EO group. The EO group's initial leptin:fm value was lower than the AN group and higher than the HC group. The values are presented in Table III. The changes in the patient's serum apelin, omentin, adiponectin, leptin, and IL-6 levels are shown in Figure 2.

Apelin:fm (p=0.004), omentin:fm (p=0.005), adiponectin:fm (p=0.005), leptin:fm (p=0.005), and IL-6:fm (p=0.008) values after weight gain decreased, while VAI value (p>0.050) increased. The values are presented in Table III.

At the beginning of treatment, a moderately significant positive relationship was observed between apelin:fm and HOMA-IR, and a moderately significant negative relationship was observed between apelin:fm and waist circumference

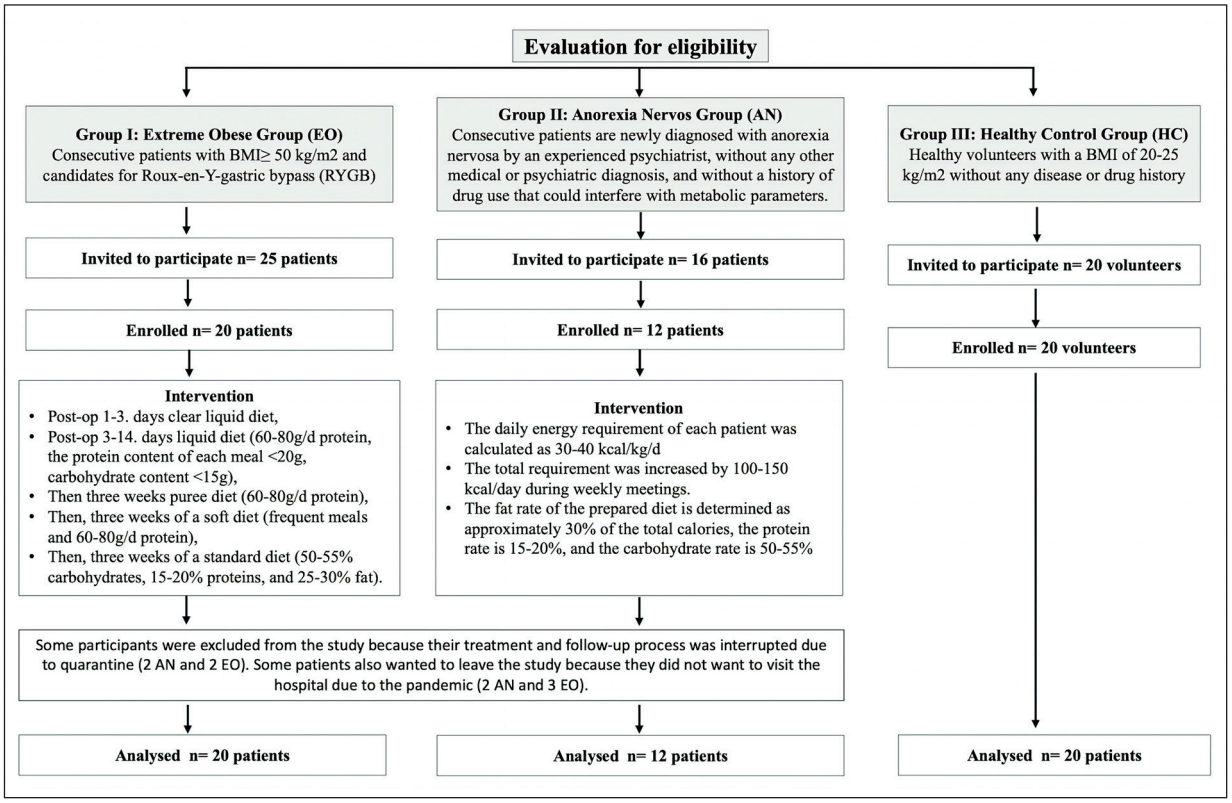

Figure 1. Study flow chart.

Table I. General characteristics of the study groups.

Variables (mean±SD)	Anorexia nervosa (n=12)			Extremely obese (n=20)			Healthy control (n=20)	
	Pre-treatment	Post-treatment	*p* (intra-group)	Pre-treatment	Post-treatment	*p* (intra-group)		*p* (inter-group)
Women/Men	11/1			13/7			14/6	
Age (year)	19.08±7.30		-	37.70±11.63		-	31.33±9.47	**0.000**
WC (cm)	58.75±5.25	61.58±4.20	0.000	140.83±13.44	127.05±13.04	0.002	76.55±12.15	**0.000/0.000**
Hip (cm)	76.08±11.83	79.41±11.55	0.000	142.38±10.51	129.22±11.91	0.011	94.88±5.18	**0.000/0.000**
BMI (kg/m²)	14.60±1.70	17.16±1.74	0.000	53.63±7.48	43.55±5.87	0.002	23.77±2.12	**0.000/0.000**
Weight (kg)	37.81±5.47	44.37±4.99	0.000	150.71±28.77	122.08±20.88	0.002	65.25±9.67	**0.000/0.000**
Height (cm)	160.75±5.15			167.30±10.33			165.33±6.80	0.097
Fat mass (%)	2.72±5.88	5.96±5.84	0.000	50.21±5.97	43.89±6.24	0.003	23.84±6.41	**0.000/0.000**
Fat mass (kg)	1.23±2.73	3.26±2.83	0.000	75.22±16.41	53.89±12.70	0.002	15.36±4.17	**0.000/0.000**

BMI, body mass index; WC, waist circumference.

Table II. Variables associated with the change in adipose tissue mass (including the entire study group).

	Variables in the equation							
	B	S.E.	Wald	df	Sig.	Exp (B)	95% CI for EXP (B) Lower	Upper
ΔApelin	**0.059**	**0.027**	**4.808**	**1**	**0.028**	**1.061**	**1.006**	**1.119**
ΔOmentin	0.039	0.025	2.575	1	0.109	1.040	0.991	1.092
ΔIL-6	0.001	0.003	0.202	1	0.653	1.001	0.995	1.007
ΔLeptin	0.002	0.007	0.076	1	0.783	1.002	0.989	1.015
ΔAdiponectin	**0.056**	**0.027**	**4.376**	**1**	**0.036**	**1.057**	**1.004**	**1.114**
Constant	-0.213	0.408	0.273	1	0.601	0.808		

B, coefficient; S.E., standard errors; df, degrees of freedom; Sig., *p*-value; Exp (B), odds ratios; CI, confidence interval.

Table III. Change in biomarkers after weight interventions in anorexia nervosa and extreme obese groups.

	Anorexia nervosa (n=12)			Extremely obese (n=20)			Healthy control (n=20)	Intergroup analysis *p*-values (EO *vs.* AN)	
Variables (mean±SD)	Pre-treatment	Post-treatment	*p* (intra-group)	Pre-treatment	Post-treatment	*p* (intra-group)	Present	Pre-treatment	Post-treatment
FPG (mg/dl)	72.30±8.50	78.41±9.08	**0.032**	100.30±29.06	90.85±14.62	0.061	82.83±7.68	**0.000**	**0.001**
FPI (mIU/L)	4.15±1.43	4.95±1.24	0.158	32.62±14.11	14.13±8.03	**0.000**	6.65±2.69	**0.000**	**0.000**
HOMA-IR	0.74±0.29	0.95±0.24	0.051	8.32±5.20	3.26±2.21	**0.000**	1.36±0.54	**0.000**	**0.000**
HbA1c (%)	5.15±0.18	5.34±0.28	**0.004**	6.13±0.79	5.48±0.29	**0.000**	5.02±0.34	**0.000**	0.088
TG (mg/dL)	91.07±31.59	114.75±27.33	**0.034**	154.65±57.88	115.00±32.28	**0.015**	83.00±46.81	**0.001**	0.953
LDL-c (mg/dL)	122.72±25.02	130.91±18.97	0.638	122.50±26.00	98.30±29.64	**0.002**	103.00±19.52	0.985	**0.001**
HDL-c (mg/dL)	65.19±14.73	67.75±18.09	0.432	43.05±8.68	40.25±5.05	0.131	56.88±20.44	**0.000**	**0.000**
Apelin (ng/mL)	1.28±0.96	1.44±0.99	**0.034**	0.91±0.83	0.85±0.61	0.391	1.67±1.27	0.613	0.192
Apelin:fm (ng/mL/kg)	52.64±59.09	0.88±0.64	**0.004**	0.01±0.1	0.02±0.01	**0.001**	0.11±0.08	**0.000**	**0.000**
Omentin (ng/mL)	90.90±18.62	122.78±50.97	**0.041**	46.66±15.89	51.65±13.17	0.204	47.10±14.10	**0.000**	**0.000**
Omentin:fm (ng/mL/kg)	4,433.21±3,829.80	125.51±159.81	**0.005**	0.65±0.29	0.99±0.33	**0.000**	3.15±0.86	**0.000**	**0.000**
IL-6 (pg/mL)	0.90±1.00	1.07±1.11	0.424	3.93±2.68	4.00±3.87	0.247	1.36±1.73	**0.000**	**0.000**
IL-6:fm (pg/mL/kg)	27.46±38.59	0.94±1.43	**0.008**	0.05±0.03	0.08±0.09	0.478	1.10±0.16	**0.000**	**0.047**
Leptin (ng/mL)	2.81±2.35	5.58±3.95	**0.005**	66.35±17.45	36.26±22.82	**0.000**	5.95±7.10	**0.000**	**0.000**
Leptin:fm (pg/mL/kg)	130.21±237.85	4.73±5.47	**0.005**	0.90±0.22	0.80±0.46	0.526	0.38±0.49	**0.000**	**0.003**
Adiponectin (ng/mL)	28.01±5.67	38.38±16.12	**0.041**	14.76±6.90	16.95±6.85	**0.025**	18.50±15.44	**0.000**	**0.000**
Adiponectin:fm (pg/mL/kg)	1,279.00±1,047.23	32.44±31.96	**0.005**	0.20±0.10	0.32±0.15	**0.001**	1.22±1.02	**0.000**	**0.000**
VAI	2.45±1.06	2.87±0.96	0.209	6.33±3.38	4.76±1.34	0.062	2.72±2.09	**0.000**	**0.002**

FPG, fasting plasma glucose; FPI, fasting plasma insulin, HOMA-IR, homeostasis model of assessment insulin resistance; HbA1c, glycated hemoglobin A1c; TG, triglycerides; LDL-c, low-density lipoprotein-cholesterol; HDL-c, high-density lipoprotein-cholesterol; apelin:fm, apelin corrected for fat mass; omentin:fm, omentin corrected for fat mass; IL-6, interleukin 6; IL-6:fm, IL-6 corrected for fat mass; leptin:fm, leptin corrected for fat mass; adiponectin:fm, adiponectin corrected for fat mass; VAI, visceral adiposity index.

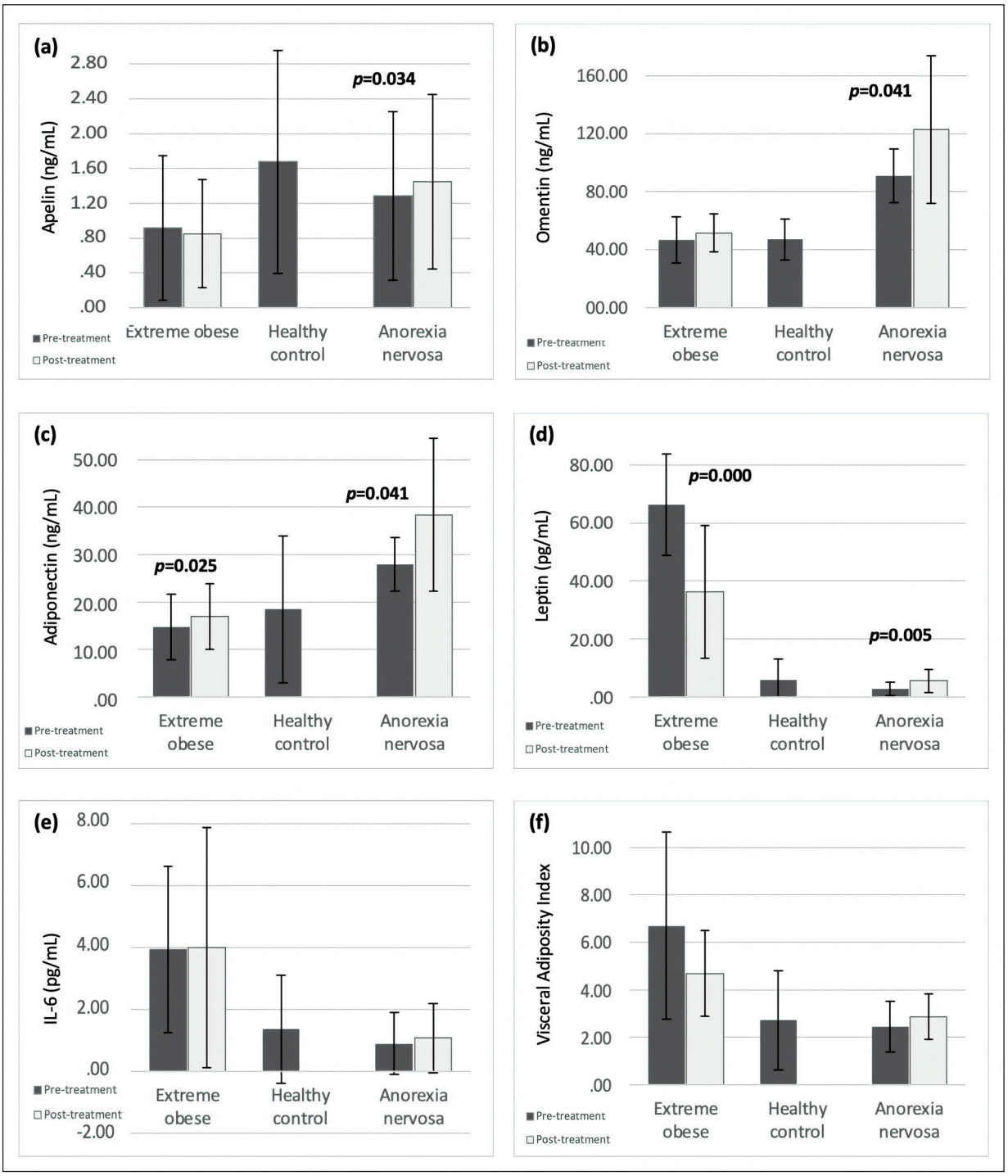

Figure 2. Change in apelin (**a**), omentin (**b**), adiponectin (**c**), leptin (**d**), interleukin-6 (**e**), and visceral adiposity index (**f**) after weight interventions in anorexia nervosa and extremely obese groups.

and BMI. A moderate significant negative relationship was found between omentin:fm and VAI. A moderately significant positive relationship was observed between adiponectin:fm and IL-6:fm. It was observed that there was a moderately significant negative relationship between IL-6:fm and LDL-c. A moderately significant negative relationship was observed between leptin:fm and waist circumference. The relationships between the changes in adipocytokines, anthropometric measurements, and

biochemical parameters at baseline and after weight loss with treatment are presented in Table IV.

Anorexia Nervosa Group

The mean age of participants (women/men: 11/1) in the AN group was 19.08±7.30 years. The anthropometric characteristics of the patients are presented in Table I.

The follow-up period of the AN group was 115.43±81.19 days, during which the average weight of the patients with AN increased by 6.55±3.39 kg (18.1%), and the fat mass increased by 2.03±1.83 kg (165.1%).

After weight gain with treatment, serum fasting plasma glucose (FPG) (p=0.032), glycosylated hemoglobin A1c (HbA1c) (p=0.004), and triglyceride (p=0.034) levels of the patients significantly increased (Table III).

At baseline, apelin:fm, omentin:fm, adiponectin:fm, leptin:fm, and IL-6:fm values were higher and the VAI was lower than the HC and EO groups. The values are presented in Table III.

After 10% weight gain, apelin:fm (p=0.004), omentin:fm (p=0.005), adiponectin:fm (p=0.005), leptin:fm (p=0.005), and IL-6:fm (p=0.008) values decreased (Table III). However, the VAI did not change significantly. The alterations in serum levels of apelin, omentin, adiponectin, leptin, and IL-6 are shown in Figure 2.

At the beginning of the treatment, a moderately to highly significant positive relationship was observed between apelin:fm and omentin:fm, adiponectin:fm, IL-6:fm, leptin:fm, FPG, and HOMA-IR. A highly significant positive relationship was found between omentin:fm and adiponectin:fm, IL-6:fm, leptin:fm, VAI, and HDL-c. A high to very high significant positive relationship was observed between adiponectin:fm and IL-6:fm, leptin:fm, VAI, and HDL-c. It was observed that there was a highly significant positive relationship between IL-6:fm and only leptin:fm, a highly significant positive relationship between leptin:fm and HDL-c, and a highly significant negative relationship between leptin:fm and VAI. The relationships between the changes in adipocytokines, anthropometric measurements, and biochemical parameters at baseline and after weight loss with treatment are presented in Table V.

Healthy Control Group

The average age of participants (women/men: 14/6) included in the HC group was 31.33±9.47 years. The anthropometric characteristics of the participants are presented in Table I.

A highly significant positive relationship was found between adiponectin:fm and leptin:fm (p=0.006, r=.618). A highly significant positive relationship was observed between IL-6:fm and HOMA-IR (p=0.009, r=.646), and FPI (p=0.004, r=.702). It was observed that there was a moderately significant positive relationship between VAI and BMI (p=0.024, r=.529).

Compared to baseline levels of AN and EO groups, in the HC group, apelin:fm, omentin:fm, adiponectin:fm, and IL-6:fm values were lower than the AN group but higher than the EO group. Whereas the leptin value was lowest in the HC group, the VAI was lower than the EO group but higher than the AN group (Table III).

Discussion

Excessive deviations in body weight are problems that disrupt the interactions between the immune system (i.e., low-grade inflammation) and metabolism and predispose to several additional health disorders. However, it is unclear how the relationships between cytokines released from adipocytes and metabolism are regulated with interventions that improve body weight.

Targeting a 10% change in body weight, as in this study, is a rational approach that will make it possible to examine the interactions between cytokines released from adipocytes and alterations in glucose and lipid metabolism in both very thin (AN) and very obese (EO) individuals. We corrected the serum levels according to the body fat mass to better assess the adipose tissue-derived biomarkers (adipokines) more accurately. We compared the adipokines in EO and AN groups before and after the weight intervention. In addition, we tested how VAI, a marker that reasonably reflects the functional pathology in visceral adipose tissue in individuals with MetS and obesity, changes with weight gain or loss in individuals with very low or very high-fat mass and its relationship with metabolic status and adipokines after interventions.

Apelin is a molecule known to play a role in the pathophysiology of obesity and carbohydrate metabolism. It is high in obese individuals, and its levels decrease when weight is lost with a hypocaloric diet or BS[36]. This has been explained[37] by the decrease in mRNA expression of adipocytes and the production of less apelin with weight loss. Although calorie restriction is the main reason for improving metabolic status, especially after BS,

Table IV. Spearman correlation coefficients and *p* values between basal biomarkers and metabolic parameters in patients with extreme obesity.

	Apelin:fm	Omentin:fm	Adiponectin:fm	IL-6:fm	Leptin:fm	VAI	FPG	FPI	HOMA-IR	TG	LDL	HDL	Age	WC	BMI
Apelin:fm	r=1.00								r=.486 *p*=0.030					r=-.541 *p*=0.014	r=-.508 *p*=0.022
Omentin:fm		r=1.00				r=-.520 *p*=0.019									
Adiponectin:fm			r=1.00	r=.489 *p*=0.029											
IL-6:fm				r=1.00							r=-.464 *p*=0.040				
Leptin:fm					r=1.00									r=-.551 *p*=0.012	
VAI						r=1.00				--		--		--	

After weight intervention,

- **No correlation was found between Δapelin:fm and changes in other parameters.**
- **No correlation was found between Δomentin:fm and changes in other parameters.**
- **There was a negative correlation between Δadiponectin:fm and ΔFPG (*p*=0.003, *r*=-.632), ΔFPI (*p*=0.036, *r*=-.472), and ΔHOMA-IR (*p*=0.013, *r*=-.543).**
- **A positive correlation was observed with Δleptin:fm, ΔBMI (*p*=0.016; *r*=.532), and ΔVAI (*p*=0.019; *r*=.520).**
- **ΔIL-6:fm was negatively correlated with, ΔHOMA-IR (*p*=0.033; *r*=-.478), and ΔFPG (*p*=0.020; *r*=-.515).**
- **No correlation was found between ΔVAI and changes in other parameters.**

Apelin:fm, apelin corrected for fat mass; omentin:fm, omentin corrected for fat mass; adiponectin:fm, adiponectin corrected for fat mass; IL-6:fm, interleukin-6 corrected for fat mass; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HOMA-IR, homeostasis model of assessment insulin resistance; TG, triglycerides; LDL-c, low-density lipoprotein-cholesterol; HDL-c, high-density lipoprotein-cholesterol; WC, waist circumference; BMI, body mass index; VAI, visceral adiposity index.

Table V. Spearman correlation coefficients and *p*-values between baseline biomarkers and metabolic parameters in patients with anorexia nervosa.

	Apelin:fm	Omentin:fm	Adiponectin:fm	IL-6:fm	Leptin:fm	VAI	FPG	FPI	HOMA-IR	TG	LDL-c	HDL-c	Age	WC	BMI
Apelin:fm	*r*=1.00	*r*=.622 *p*=0.031	*r*=.671 *p*=0.017	*r*=.573 *p*=0.050	*r*=.636 *p*=0.026		*r*=.627 *p*=0.029		*r*=.622 *p*=0.031						
Omentin:fm		*r*=1.00	*r*=.916 *p*=0.000	*r*=.580 *p*=0.048	*r*=.972 *p*=0.000	r=-.706 *p*=0.010						*r*=.897 *p*=0.000			
Adiponectin:fm			*r*=1.00	*r*=.671 *p*=0.017	*r*=.895 *p*=0.000	*r*=-.727 *p*=0.007						*r*=.855 *p*=0.000			
IL-6:fm				*r*=1.00	*r*=.636 *p*=0.026										
Leptin:fm					*r*=1.00	*r*=-.650 *p*=0.022						*r*=.890 *p*=0.000			
VAI						*r*=1.00				--		--		--	

After weight intervention,

- **Δapelin:fm was positively correlated with Δomentin:fm (*p*=0.017, *r*=.671), Δadiponectin:fm (*p*=0.008, *r*=.720), and Δleptin:fm (*p*=0.022, *r*=.650).**
- **Δomentin:fm was positively correlated with Δadiponectin:fm (*p*=0.000, *r*=.867), ΔIL-6 (*p*=0.045, *r*=.587), and Δleptin:fm (*p*=0.000, *r*=.972), and negative ΔVAI (*p*=0.050, *r*=-.559).**
- **Δadiponectin:fm and Δomentin:fm (*p*=0.000, *r*=.867), Δ IL-6 (*p*=0.000, *r*=.540), Δleptin:fm (*p*=0.000, *r*=.538) continued to be positively correlated, and ΔVAI (*p*=0.035, *r*=-.299) remained negative.**
- **Δleptin:fm was positively correlated with ΔIL-6:fm (*p*=0.042, *r*=.594).**
- **All correlations with ΔIL-6 disappeared.**
- **ΔVAI was negatively correlated with Δweight (*p*=0.039; *r*=-.601), ΔHbA1c (*p*=0.035; *r*=-.610), and ΔLDL-c (*p*=0.010; *r*=-.705).**

Apelin:fm, apelin corrected for fat mass; omentin:fm, omentin corrected for fat mass; adiponectin:fm, adiponectin corrected for fat mass; IL-6:fm, interleukin-6 corrected for fat mass; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HOMA-IR, homeostasis model of assessment insulin resistance; TG, triglycerides; LDL-c, low-density lipoprotein-cholesterol; HDL-c, high-density lipoprotein-cholesterol; WC, waist circumference; BMI, body mass index; VAI, visceral adiposity index.

this alone cannot explain the serum apelin levels, which decreased three days after BS[38]. Soriguer et al[36] showed that apelin levels decreased after surgery, especially in patients with diabetes. At the same time, there was no change in patients with normal glucose tolerance. They[36] suggested that decreased apelin levels with BS were associated with improved blood glucose and insulin sensitivity, as we found in our study. However, we found that there was no significant difference between the apelin levels of our patients with and without a diagnosis of diabetes, that the change in apelin level was related to the anthropometric values of the participants before and after their treatment, and that every 1-unit change in fat mass changed apelin levels by 1.006 times.

It is thought[37] that the change in apelin levels is affected not only by the decrease in weight and fat mass due to diet but also by negative energy balance. An experimental study[39] observed that the food intake and weight of rats increased with a long-term intracerebroventricular infusion of apelin. In our study, we thought that the fact that the basal apelin levels of patients with anorexia were higher than those of extremely obese patients was related to a compensatory mechanism that increases appetite and encourages weight gain. The high serum apelin levels detected in individuals with AN despite low-fat tissue mass can be explained by establishing a compensatory balance by producing it from other organs such as the stomach and central nervous system[40]. Studies[36,41-44] in the literature examining apelin behavior after BS generally show that serum apelin levels decrease between 3 and 6 months after surgery and begin to rise again after the 6th month. This increase continues gradually until the 2nd year after surgery. This may be due to the decrease in calorie intake due to the shrinkage of stomach capacity in the early period after BS and the increase in calorie intake due to increased stomach volume as time progresses. We could have seen it increase if we had extended the follow-up period in our study.

Similar to apelin, serum omentin levels are low in patients with obesity and T2D, and serum levels increase when weight is lost through a hypocaloric diet or BS or when insulin sensitivity increases, as we saw in our study[29,45,46]. There is very limited information about the behavior of omentin, whose levels begin to increase only 24 hours after BS, in AN patients. In studies[47,48], serum omentin levels and omentin:fm ratios in patients with AN were found to be higher than in healthy and obese individuals, similar to our results, and as we saw in our study, they showed a negative correlation with BMI and HOMA-IR. At this point, the following question comes to our mind: could changes in omentin levels in patients with AN be due to compensatory mechanisms affecting appetite? In an *in vitro* study by Burnetti et al[49], it was shown that chronic omentin infusion in rats increased appetite, just like apelin.

As with apelin and omentin, serum adiponectin levels are higher in obese individuals than in healthy individuals, and serum levels have been shown[50-52] to increase with a 10% weight loss induced by both diet and BS, as in our study. This increase has been associated with a decrease in insulin resistance and inflammation. Serum adiponectin levels are also higher in patients with AN than in healthy individuals. We found that this increase was associated with changes in TG, LDL-c, and IL-6 levels, as in the study of Tural and Iosifescu[53]. In addition, we found that in both patient groups, every 1-unit change in the participants' fat mass caused a 1,057-fold change in serum adiponectin levels. The literature underscores a crucial observation[54]: adiponectin levels, which are higher in patients with AN than healthy controls, were found to be similar to healthy controls in constitutional thin individuals with similar weights. Altered physiological functions in anorexic patients[54] have explained this difference. At this point, adiponectin levels, negatively related to BMI in EO patients, display a behavior independent of BMI in AN. These findings were interpreted in Tural and Iosifescu[53] meta-analysis as a mechanism that compensates for the severe impairment in the metabolism of patients with anorexia.

In our study, leptin levels of obese patients decreased as expected after surgery, and studies[55] have shown that this decrease, as in other adipocytokines, begins in the early period after surgery, before significant weight loss, and continues for at least a year. However, some studies[2] associate this decrease with a decrease in fat mass, regardless of the type of surgery. On the other hand, it has been shown[55] that serum leptin levels, which begin to decrease two weeks after gastric band application without any anatomical changes and continue to decrease until the 6th month, do not change in the future, although weight loss continues. Experimental studies[55] have shown that the change in leptin level in response to rapid weight gain or rapid weight loss becomes independent of fat tissue. In the study of Stroe-Kunold et al[56], similar to ours, it was observed that leptin increased with weight gain in AN patients treated with a

high-calorie diet but decreased again near the completion of the treatment, reaching initial levels[56]. Post-treatment high leptin levels in patients with AN are a predictive factor for patients losing weight again[57]. Therefore, while there is a significant increase in BMI during the refeeding period, the lesser increase in leptin levels can be interpreted as a protective adaptive response against the disease. As a matter of fact, in the study of Kubat Uzum et al[58], it was observed that leptin levels decreased at the end of treatment in people with AN who gained weight. On the other hand, it has been shown[58] that the serum leptin levels of individuals who have been treated for AN in the past, who have fully recovered, and whose condition is stable are up to two times higher than those of patients who are just at the beginning of their treatment.

Since obesity is currently explained as a low-grade inflammatory disease, serum IL-6 levels are high, and it has been shown[59] that both tissue and serum IL-6 levels decrease with a weight loss of approximately 10% of body weight. However, as seen in Rao's meta-analysis[59], unlike adipocytokines, there is no change in serum leptin levels in the 1st month after surgery, while a significant decrease is observed starting from the 6th month. In our study, where we continued follow-up until approximately the 3rd month after surgery, the fact that IL-6 levels did not change in the postoperative period is consistent with this finding[59].

It has been reported[60] that individuals with AN have a low-grade proinflammatory state similar to obesity and elevated IL-6. Although studies on this subject are few and contradictory, it has been shown[60] that serum IL-6 levels are low in newly diagnosed AN patients and continue to decrease even after weight gain but are still higher than in healthy controls. Similar to these findings, in our study, IL-6 levels, which were lower in newly diagnosed patients than in HC, increased slightly after weight intervention and reached similar levels.

It is known that VAI is positively associated with HOMA-IR, FPI, and FPG, as we confirmed in our study. In addition, to our knowledge, this is the first study in which VAI was evaluated in AN patients, and its relationship with adipocytokines was revealed. It is known that in adolescent AN patients, fat mass loss occurs predominantly in the visceral region and that weight restoration causes fat accumulation, especially in the trunk region[61]. Restoring fat mass, especially truncal fat, is a critical strategy in treating AN and an essential element of recovery[61]. This fat accumulation leads to the development of insulin resistance, which does not negatively affect the psychopathology of the eating disorder and disappears in the long term with the normalization of central fat mass distribution[61]. We found that the VAI values of anorexic patients after gaining weight were higher than the VAI values of healthy individuals. This increase reflects the metabolic effects of the change in the fatty tissues of patients with AN during the early recovery period. However, their HOMA-IR, FPG, and FPI did not reach pathological values and were lower than in the control group. In AN patients, the strong negative relationship between VAI and omentin:fm, adiponectin:fm, and leptin:fm disappeared after weight gain. Similarly, in the EO group, the inverse relationship with preoperative omentin:fm disappeared as the patients lost weight. In both cases, it indicates that the reliability of the relationship between VAI and adipocytokines in the early period when fat mass and metabolic parameters begin to change with treatment intervention should be tested in new studies in which more patients are followed for a more extended period of time.

To the best of our knowledge, this is the first study to evaluate the changes in serum levels of adipokines (i.e., apelin, omentin, adiponectin, and leptin) and their relationship with clinical and biochemical parameters through weight interventions in patients at the two edges of the spectrum of eating disorders such as EO or AN. The most striking finding of this study is that while significant increases were detected in corrected apelin, omentin, adiponectin, and leptin levels with weight loss in the EO group, a significant decrease in all of these parameters was observed with weight gain in the AN group. In addition, there was no significant change in VAI values with the weight intervention in both groups. In the EO group, weight loss improved glycemia (FPG, HbA1c), insulin resistance (FPI, HOMA-IR), and lipid profile (TG, LDL-c). On the other hand, weight gain intervention in the AN group led to an increase in glycemic parameters (FPG and HbA1c) and TG levels, but there was no significant change in HOMA-IR.

On the other hand, this is the first study comparing the change of VAI, which reveals visceral adipocyte pathology and provides more reliable information about patients than BMI after weight loss in individuals with the most severe obesity, with adipocytokines. It is also the first known study to evaluate the changes before and after weight gain and its relationship with adipocytokines in patients with AN.

Conclusions

Adipocytokines secreted from adipocytes are closely related to insulin and glucose metabolism parameters. In this study, it is noteworthy that the expected change in adipocytokine levels due to weight gain and weight loss was not observed in the early post-treatment period, especially in patients with pathologically low or high adipocyte mass. The fact that these changes are not seen in the early stages of weight intervention treatments indicates that there are compensatory physiological mechanisms to protect the patient in these patients with a chronic process. On the other hand, BMI, which was invented by Keys et al[62] in the 1970s and gives an idea about the body composition of individuals, is losing its reliability as the importance of the functional effects of fat tissue is understood more and more each day[62]. Instead, VAI, which better reflects the functional impairment of visceral fat tissue, may be a good alternative. However, VAI may cause modeling errors, especially in patients with extreme obesity and anorexia nervosa, where metabolic parameters reach extreme values. Although it showed parallel behavior with adipocytokines in our study in terms of reflecting the current pathology, its reliability is controversial, especially in the early period when the fat tissue mass changes. Therefore, it needs to be tested in studies where larger patient groups are followed for a more extended period.

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Authors declare no conflict of interest.

Authors' Contributions
Substantial contributions to the conception and design of the study: Bedia Fulya Calikoglu, Ayse Kubat Uzum, Ozge Telci Caklili, Umut Barbaros, Ilhan Satman. Acquisition of data, or analysis and interpretation of data: Bedia Fulya Calikoglu, Ozge Telci Caklili, Ayse Kubat Uzum, Basak Yucel, Yildiz Tutuncu, Ayse Merve Kurt, Umut Barbaros, Ilhan Satman. Drafting the article or making critical revisions related to the relevant intellectual content of the manuscript: Bedia Fulya Calikoglu, Ozge Telci Caklili, Ayse Kubat Uzum, Umut Barbaros, Ilhan Satman. Supervision: Umut Barbaros, Ilhan Satman. Validation: Bedia Fulya Calikoğlu, Ozge Telci Caklili, Umut Barbaros, Ilhan Satman. Final approval of the version of the article to be published: Bedia Fulya Calikoğlu, Umut Barbaros, Ilhan Satman.

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Data Availability
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval
This study was approved by the Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 14.08.2015, No.: 13) and was conducted following the Declaration of Helsinki Principles.

Informed Consent
A brief explanation was given to all participants, and the treatment and follow-up process was explained. All subjects provided written informed consent for inclusion before participating in the study.

Trial Registration
The trial was registered on the ClinicalTrials.gov PRS website (ID: NCT04663919).

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